RESEARCH ARTICLE

Association between trace elements in cancerous and non-cancerous tissues with the risk of breast cancers in western Iran

Borhan Mansouri[1] · Zana Ramezani[2] · Vahid Yousefinejad[3] · Samaneh Nakhaee[4] · Namamali Azadi[5] · Peyman Khaledi[2] · Bahram Nikkhoo[6] · Kambiz Hassanzadeh[7] · Azin Rahimi[6]

Abstract

This study aimed to assess the tissue content of essential and toxic metals including lead (Pb), cadmium (Cd), arsenic (As), silver (Ag), aluminum (Al), chromium (Cr), copper (Cu), iron (Fe), selenium (Se), and zinc (Zn) in the breast cancerous tissues compared to the non-cancerous tissue. The biopsy specimens of 63 breast cancers along with 63 adjacent healthy tissues in Kurdistan Province, Iran, were collected from 2019 to 2020 and assayed using ICP-MS (Agilent 7900). The results of the Mann-Whitney test illustrated that the concentration of Pb, Cd, As, Cr, Cu, and Se were significantly elevated in cancerous tissue ($p < 0.05$), while Zn was the only trace element with higher levels in healthy subjects ($p < 0.05$). Moreover, weak to moderate correlations between elements were observed in the cancerous group including Al-Cr ($r=0.60$), As-Cu ($r=0.52$), and Cu-Se ($r=0.56$). In contrast, no correlation over 0.50 was found between trace elements in the non-cancerous group. Raw risk differences (RDs) accounted for a significant effect for Pb, Cd, As, Ag, Cr, Se, and Zn on the development of breast cancer. In conclusion, elevated levels of As, Cd, Cu, Pb, and Se may contribute to enhancing the risk of breast cancer.

Keywords Breast cancer · Environmental exposure · Trace elements · Arsenic · Cadmium

Introduction

Global mortality due to various types of cancer is increasing and expecting to surge over 13.1 million casualties by 2030 (IARC 2008). Cancer is the third cause of mortality in Iran with an annual death toll of over 30,000 cases. After skin cancer, breast cancer is the most common type of cancer among women and the second leading cause of death after lung cancer (Bray et al. 2004). Breast cancer affects mainly women (99% of cases are women). Generally speaking, breast cancer is the most common cancer in the world in terms of mortality (Barnes and Newman 2007).

In 2016, the WHO reported 519,000 casualties due to breast cancer globally (Szkutnik-Fiedler et al. 2016). In Iran, the number of breast cancer cases was estimated to be 40,000 with 6,000 new cases annually (Otaghvar et al. 2015; Jafari et al. 2018). In recent years, the surge of breast cancer incidence in Iran has led to this cancer as the most common cancer type among women so that more than 30% of cases were under 30 years old (Mousavi et al. 2007). Moreover, in

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✉ Borhan Mansouri
borhanmansouri@yahoo.com

✉ Zana Ramezani
zana.ramezani@muk.ac.ir

[1] Substance Abuse Prevention Research Centre, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

[2] Student Research Committee, Kurdistan University of Medical Sciences, Sanandaj, Iran

[3] Liver and Digestive Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran

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

[5] Biostatistics Department, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

[6] Department of Pathology, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran

[7] Cellular and Molecular Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran

Kurdistan Province, located in the west of Iran, the rate of breast cancer has boosted from 13 new cases in 2000 to 103 cases by 2009, so that is ranked as the fifth common cancer among women.

Several factors including age, family history of breast and uterine cancer, colon and rectum cancer, previous history of breast abnormalities, not getting pregnant or having the first pregnancy after the age of 30, alcohol consumption, smoking, and obesity have been reported to associate with the risk of developing breast cancer (Land et al. 2014; Miller et al. 2018). Environmental pollutants such as trace elements are also suspected to accelerate the incidence of breast cancer. Mortality and morbidity due to air, soil, and water pollution have been reported in the literature (Mohammadi et al. 2020; Hajizadeh et al. 2020; Malakootian et al. 2020; Rehman et al. 2018; Lu et al. 2015). One explanation for these findings could be due to the existence of trace elements and their inextricable association with unhealthy impacts.

Trace elements are the environmental pollutants that play a key role in the occurrence of many diseases among animal and human societies (Mansouri et al. 2012a, b; Rezaei et al. 2021; Farnia et al. 2021). Increasing amounts of trace elements followed by human activities in our environment have had far-reaching clinical effects (Burguera et al. 2002; Rautray et al. 2010). Trace elements and metalloids such as Hg, As, Pb, Cd, and Cr can interfere with human metabolomics, leading to morbidity and even mortality (Rai et al. 2019). They can disturb metabolic functions of the body in different ways. Trace elements may accumulate in various organs (e.g., liver, heart, kidney, and brain) disturbing normal biological functions. Moreover, trace elements can enter the body via the consumption of contaminated food, water, and air (Rajaei et al. 2012; Mansouri et al. 2012c; Rehman et al. 2018). Diseases due to the aforementioned elements include principally respiratory problems, cardiovascular events, kidney diseases, and central nervous system dysfunctions (Manisalidis et al. 2020). Environmental pollutions are linked as an important factor in the occurrence of many cancer types (Lu et al. 2015).

Trace elements are divided into two groups: essential and non-essential metals for the metabolic activities of the human body. Trace elements such as copper (Cu), iron (Fe), and zinc (Zn) are essential elements that play an important role in the body's metabolic and physiological activities, but in order to avoid their negative side effects, their amounts intake must be controlled (Norouzi et al. 2012; Majnoni et al. 2013; Maleki et al. 2015). For example, Fe can react with peroxides and generate free radicals. The excessive amount of these free radicals can cause damage to DNA, lipids, proteins, and carbohydrates in tissues, leading to oxidative stress (Kawanishi et al. 2002; Leonard et al. 2004). Geraki et al. (2002) found higher iron concentrations in breast cancer patients compared to their controls. Also, Ionescu et al. (2006) obtained

significant concentrations of nickel (Ni) in the breast cancer tissue compared to healthy samples.

Metals such as cadmium (Cd), lead (Pb), and chromium (Cr) are non-essential metals that do not play a role in the body's metabolic activities, and their presence has adverse effects on human health (Rezaei et al. 2019). Some metals (i.e., Cd and Pb) have been reported to be associated with some diseases including breast, cardiovascular, renal, gestational diabetes, hypothyroidism, and thyroid cancer as well as skeletal tissue diseases (Järup 2003; Rezaei et al. 2019, 2021). Since Cd stimulates cell growth, short-term exposure to low concentrations of Cd can damage breast tissue DNA (Roy et al. 2004).

Although the effect of trace elements on breast cancer has been well documented (Roy et al. 2004; Ionescu et al. 2006; Romaniuk et al. 2017; Chanihoon et al. 2021), research on the effect of trace elements on breast cancer in Iran has been largely ignored. Therefore, the main objective of this study was to compare the accumulation of essential and toxic metals (Pb, As, Cd, Ag, Al, Cr, Cu, Fe, Se, and Zn) in breast cancer and non-cancerous breast tissue samples in an Iranian population.

Materials and methods

Study population

This research was a case-control study. The study area of the present study was Kurdistan Province. Kurdistan, also known as Persian Kurdistan, is located at the west of Iran and shares a border with the Arabic Kurdistan region in Iraq. Persian Kurdistan consists of three provinces; one of them is Kurdistan Province with Sanandaj City as its capital. The current population of Kurdistan Province is 1,600,000 (66% in urban versus 34% in rural areas) with an annual rainfall of 500 mm.

Biopsy samples

This study was designed to measure trace elements in breast tissue samples in both cancerous ($n = 63$) and non-cancerous ($n = 63$) groups. Initially, individuals attending Kowsar Hospital and its pathology clinics in Sanandaj City during 2019 and 2020 were invited to enroll in the study. Informed consent was obtained before collecting breast tissue samples from participants. The biopsy specimens were then put away in formaldehyde solution with the endorsement of a pathologist. Cancerous patients were selected from 25 to 40 years old women who are at the highest risk of breast cancer development. All patients were newly diagnosed with no specific treatment history. Patients with kidney dysfunctions, anemia, pregnancy, historical gastric surgery, and consumption of

zinc, iron, calcium, and selenium supplements were excluded from the study. Controls were selected from women visited by a physician and diagnosed as healthy after pathology examination of breast tissue. Like cancerous tissues, specimens from control tissues were frozen at −20 °C.

Determination of heavy metals

We applied the nitric-perchloric acid digestion method to prepare samples for measuring heavy metals. Approximately 1 g of samples was mixed with 2 mL of ultrapure (HNO_3, 65%, Merck, Germany) and 1 mL of perchloric acid ($HClO_4$, 70%, Merck, Germany). The mixture was kept in a water bath (TW12, JULABO GmbH, Germany) at 100°C. After cooling, a mixture was obtained by adding double-distilled water up to 25 mL (18.2 MΩ-cm at 25 °C, Fistreem, WSC044, UK). The prepared solution was measured for Pb, As, Cd, Cr, Ag, Al, Cu, Fe, Se, and Zn using inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7900)(Nozadi et al. 2021). After every four analyses, spikes and control samples were implemented. The recovery of Ag, Al, As, Cd, Cr, Cu, Fe, Pb, Se, and Zn were 98%, 97%, 98%, 96%, 102%, 97%, 101%, and 99%, respectively. The detection of limits for all the elements fell between 0.5 and 2 µg L^{-1}.

Statistical analysis

Descriptive statistics including median and interquartile range were used to report summaries for numerical variables and numbers and percentages for nominal or categorical covariates. Since metal concentrations were usually right-skewed, to tackle this issue, it is a routine practice to standardize concentration levels. Concentrations were log-transformed and then standardized using the mean and interquartile range. To compare the concentrations between the cancer and healthy group, the Mann-Whitney test was used. Potential relationships between trace element concentrations were checked using the Spearman correlation coefficient. Additionally, clustering analysis and principal component analysis (PCA) were used on standardized concentration levels to discover the grouping behavior of trace elements. The results of PCA were used by linear discriminant analysis (LDA) to verify the PCA classification merit in allocating subjects into cancerous or non-cancerous groups. Classification accuracy of subjects was evaluated using the area under the ROC curve (AUC), the true positive rate, and the true negative rate. The effect of studied trace elements on the individual's risk of breast cancer was evaluated using logistic regression analysis to calculate adjusted and unadjusted risk differences (RDs) between cancerous or non-cancerous groups. RDs were adjusted for age, size of the tumor, and the direction of surgery.

Results

In this study, 126 female participants were recruited and organized in two groups; 63 with breast cancer and 63 served as their controls. The mean age of cancerous patients was 52.29 ± 11.18 (30 to 76 years) and the mean age of controls was 35.02 ± 14.25 (17 to 66 years). Mann-Whitney test revealed a significant mean age difference between the two groups ($p < 0.001$).

Concentrations of elements

In cancerous group, the general pattern of increasing trace element concentrations was Al < Cu < Zn < Se < Fe < Cr <Pb< As < Cd < Ag. The pattern in non-cancerous group was Al < Zn < Cu < Se < Fe < Cr <Pb< Ag < Cd < As (Table 1). Mann-Whitney test revealed that the levels of As (1.25 vs. 0.30 µg kg^{-1}), Cd (1.1 vs. 0.2 µg kg^{-1}), Cr (17.05 vs. 13.7 µg kg^{-1}), Cu (87.7 vs. 68.6 µg kg^{-1}), Pb (13.1 vs. 6.4 µg kg^{-1}), and Se (58.2 vs. 39.2 µg/L) were significantly higher in cancerous subjects. Zn (102.5 vs 64.55 µg kg^{-1}) was the only trace element with higher levels in healthy subjects. There were no significant differences in Ag (0.55 vs. 0.66 µg kg^{-1}), Al (117 vs. 126.9 µg kg^{-1}), and Fe (28.8 vs. 28.2 µg kg^{-1}) levels between two groups.

Relationships between elements

Association between 10 trace elements was investigated using Spearman correlation analysis. Figures 1 and 2 provides a matrix of useful information about trace elements including pairwise scatter plots (lower diagonal), histogram plots (diagonal), and also a measure of association between trace elements (upper diagonal) for both cancerous (Figure 1) and control subjects (Figure 2). Spearman correlation was used to measure the association. Significant correlations were marked with stars: three stars if it was significant at 0.001 ($p < 0.001$), two stars if it was significant at 0.01 ($p < 0.01$), and one star if the correlation was significant at nominal 0.05 level. In the cancerous group, correlations between elements were positive but mostly non-significant. Moderate correlations were observed between Al-Cr ($r=0.60$), As-Cu ($r=0.52$), and Cu-Se, ($r=0.56$). In the non-cancerous group, no correlation over 50% ($r > 0.50$) was observed between elements.

Cluster 1 consists of As and Fe, cluster 2 Cd-Pb, cluster 3 Zn-Se, cluster 4 Cu, and cluster 5 consists of Ag-Ai-Cr (Figure 3A). For the non-cancerous group, a totally different grouping of elements was observed. There were five clusters but with different elements as those clusters we observed for cancerous patients. Cluster 1 consisted of Ag-Cd, cluster 2 Cu-As, cluster 3 AI-Cr, cluster 4 Pb-Se-Zn, and cluster 5 Fe alone (Figure 3B).

Table 1 The levels of trace elements in cancerous and healthy subjects. Data presented as median (25th–75th percentile)

	Cancerous	Healthy	Total	*p*-value
Ag	0.554 (0.312–1.04)	0.657 (0.324–1.42)	0.62 (0.32–1.12)	0.195
Al	117 (108.8–143.3)	126.9 (99.8–162. 6)	120.5 (103.5–156.3)	0.465
As	1.25 (0.6–2.2)	0.30 (0.2–0. 5)	0.5 (0.3–1.3)	**< 0.001**
Cd	1.1 (0.4–2.17)	0.2 (0.2–0.3)	0.3 (0.2–1.1)	**< 0.001**
Cr	17.05 (12.57–26.07)	13.7 (9.5–20.4)	16.3 (11.6–23.4)	**0.022**
Cu	87.7 (76.8–121.4)	68.6 (51.8–109.3)	80.3 (66.7–119.2)	**0.002**
Fe	28.8 (22.3–37.9)	28.2 (23.2–36.8)	28.4 (22.5–36.9)	0.626
Pb	13.1 (7.15–15.25)	6.4 (5.10–7.80)	7.7 (5.7–13.2)	**< 0.001**
Se	58.2 (36.9–70.2)	39.2 (24.8–60.1)	53.6 (28.7–66.6)	**0.007**
Zn	64.55 (50.2–93.1)	102.6 (58.2–108.2)	77.5 (52.9–108.1)	**0.003**

Moreover, to reduce dimensionality, PCA analysis was used to combine trace elements with similar behavior in one component to evaluate whether it can be used for the classification of individuals as either cancerous or non-cancerous based on their levels of trace elements. PCA revealed that the first five components accounted for 73.4% of the variance (Figure 4). For instance, the first components included 23.7% of the variance and comprise Cd, As, Pb, and Se. Five PCA components were used by LDA to classify subjects into cancerous or non-cancerous groups. LDA showed that AUC was 0.979 with a true positive rate of 93% and a true negative rate of 8%.
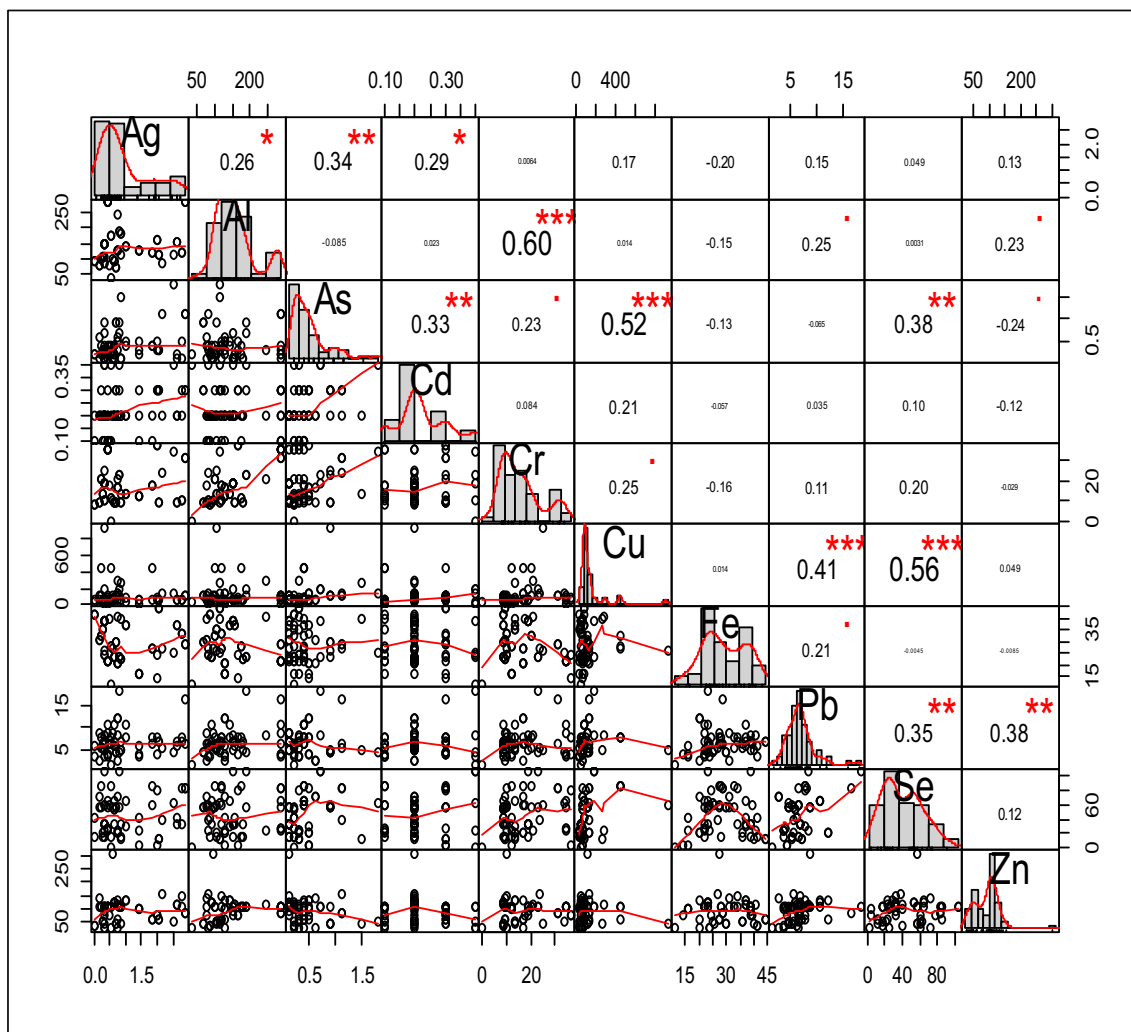
Fig. 1 Pairwise correlation analysis of trace elements for cancerous subjects; * significant at 0.05, ** significant at 0.01, ***significant at 0.001
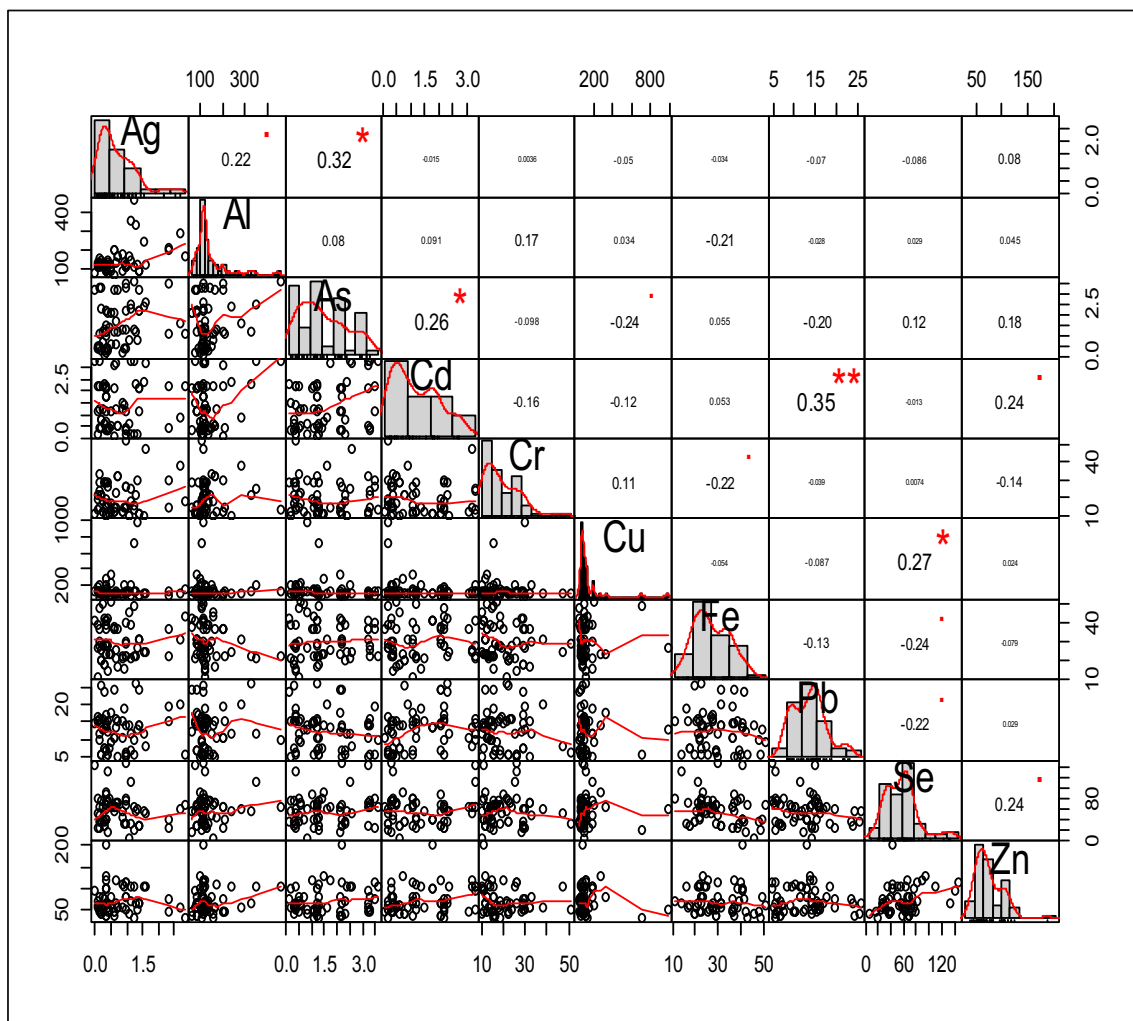
Fig. 2 Pairwise correlation analysis of 10 trace elements for non-cancerous subjects; * significant at 0.05, ** significant at 0.01, *** significant at 0.001

Relationships between elements and breast cancer

Table 2 reports the adjusted and unadjusted risk differences (RDs) for each of the 10 trace elements. Raw RDs show significant effect of the levels of Ag (RD = −0.082; 95% CI, −0.206, −0.041), As (RD = 0.560; 95% CI, 0.419, 0.701), Cd (RD = 0.855; 95% CI, 0.733, 0.977), Cr (RD = 0.144; 95% CI, 0.009, 0.279), Pb (RD = 0.557; 95% CI, 0.408, 0.707), Se (RD = 0.172; 95% CI, 0.047, 0.297), and Zn (RD = −0.175; 95% CI, −0.332, −0.017) on the development to breast cancer in women. The positive sign of RD value denotes that compared to controls, the risk of breast cancer increases if the levels of element are increased. The negative sign of RD indicates that compared to controls, in the case of patients, higher levels of elements are contributed to a lower risk of breast cancer. For example, for trace element Ag, the RD value (−0.082) was negative and significant (95% CI does not include zero), which means in cancerous women, the levels of Ag were lower than controls. In other words, elevated

levels of Ag contribute to lowering the risk of breast cancer. When the raw RDs adjusted for age, the size of the tumor, and also the direction of surgery, the levels of Ag, Cr, and Zn were no longer significant, but the levels of Cu turned into a significant factor (RD = 0.082; 95% CI, 0.005, 0.159).

Discussion

The concentration of trace elements in biological samples and tissues can provide the normal/optimal level of the elements that may be variable depending on age, gender, dietary status, geographic conditions, or genetic characteristics. The results of our study showed an elevated concentration of As, Pb, Cr, Cd, Cu, and Se and lowered levels of Zn in tissues with breast cancer compared to non-cancerous breast tissues. The significant function of trace elements in physiological and metabolic status is well documented. However, the role of these elements in cancer has long been speculated, and many types of

Fig. 3 The dendrogram of trace elements resulting for cluster analysis for both cancerous (top panel) and non-cancerous group (bottom panel)
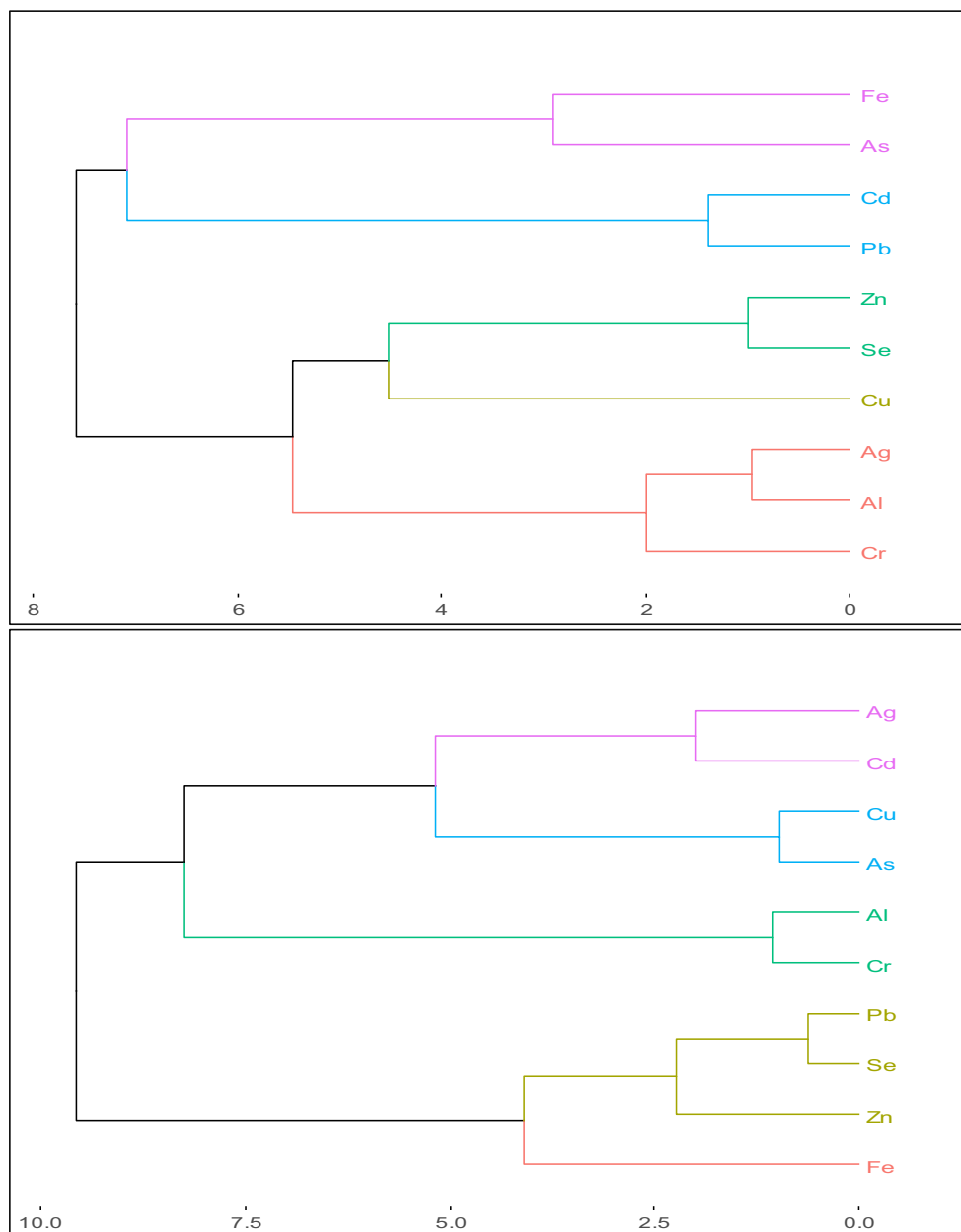

research have yielded conflicting results (Kuo et al. 2002). The changes in the concentration of essential trace elements including Fe, Cu, Zn, and Se have been studied in patients with various forms of cancers including breast cancer. However, such investigations are limited in the Iranian populations. Siddiqui et al. (2006) found that compared to healthy subjects, the concentration of Cu, Zn, Fe, and Ca was higher in benign and malignant breast tumor tissues with the significant increase in Cu, Fe, and Ca concentrations in benign tissue and Zn, Fe, and Ca concentrations in the malignant tissue. Ebrahim et al. (2007) reported similar findings for higher levels of Se, Cr, and Zn in breast cancer tissues. Some studies suggest monitoring concentration levels of Cu, Zn, and Se for breast cancer diagnosis,

prognosis, and management (Florea and Büsselberg 2011; Riesop et al. 2015). Kuo et al. (2002) proposed a prognostic value of the Zn/Cu ratio for breast cancer diagnosis (Kuo et al. 2002).

Some studies reported a lower blood or serum concentration level of selenium in patients with breast cancer, though Se levels were higher in cancerous tissues compared to normal tissues (Borella et al. 1997; Kuo et al. 2002). The elevated concentration of Se in cancerous tissues is due to this fact that Se can bind easily to proteins and absorb rapidly by growing cells. Ebrahim et al. (2007) in vitro study suggest that selenium can affect endothelial and tumor cells, reducing the main molecules required for angiogenesis (Choi et al. 2019). It has been shown that Se can reinforce strong junctions and

Fig. 4 ROC curves for predicting cancerous patients and healthy women
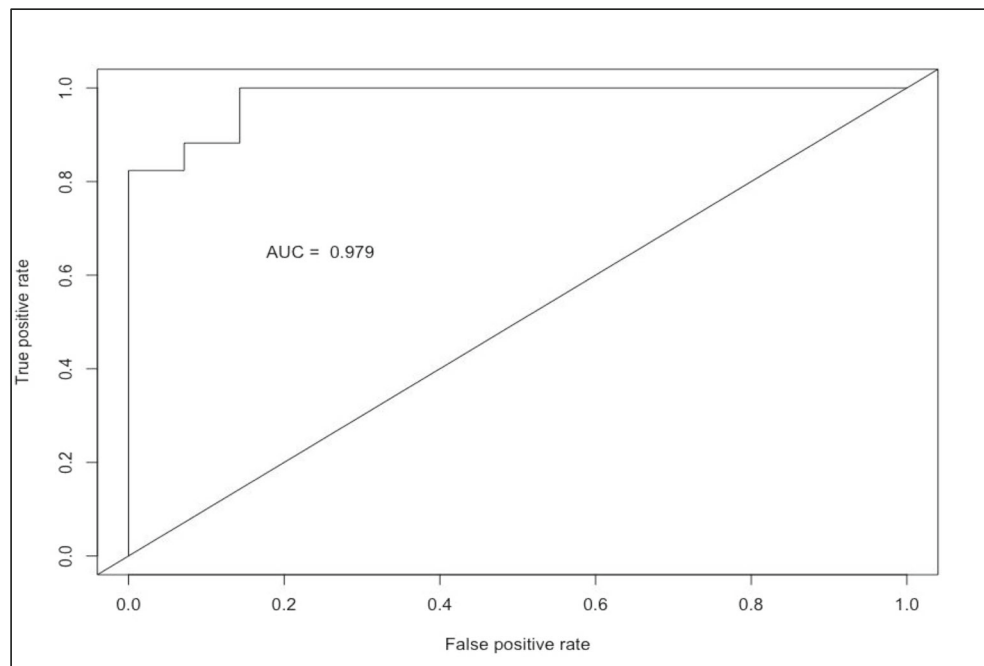
strengthen cell-cell attachments in tissues with breast cancer, which is in line with anti-proliferative results of selenium (Chen et al. 2013).

Elevated levels of Cu were detected in cancerous breast tissues compared to non-cancerous tissues (Silva et al. 2009; Raju et al. 2006). Kuo et al. (2002) also found that Cu levels in the serum and tissues of patients with malignant breast cancer were significantly elevated than in benign and normal cases, likely due to being Cu as an effective factor for angiogenesis (Silva et al. 2009). Since Cu can be observed in all living cells and it is an important element in many essential enzymes, it requires some specific events including angiogenesis, immortality, and metastasis (Choi et al. 2019). Although Cu is

important for a variety of biochemical functions, it has a potential toxic nature too. Tissue and DNA injury due to oxygen free radicals can play important role in neoplastic formation due to copper accumulation (Raju et al. 2006).

In contrast to our study, some studies have reported elevated concentration levels of Zn in breast cancer tissues (Tapiero and Tew 2003; Ebrahim et al. 2007; Silva et al. 2009) as a result of destroying the protecting effect of Se against cancer progression causing an increase of cancer growth rate. Moreover, Cu accumulation can limit Zn absorption (Kuo et al. 2002). The potential differences between metastases, heterogeneity in treatment protocols, dietary status, and geographic conditions can also affect the trace elements levels in patients with breast cancer.

In this study, we found an elevated concentration of Cr in breast cancer tissues compared to non-cancerous ones. Similar findings have been reported elsewhere (Ionescu et al. 2006; Byrne et al. 2013; Ragab et al. 2014). Despite the metabolic necessity, Cr has been known as a carcinogenic agent. Cr (VI) exposure can lead to phenotypes abnormality due to reactive oxygen species formation and DNA damages. Another possible mechanism for the carcinogenicity of this element is through the suppressing of p53, a protein for tumor suppression (Raju et al. 2006).

In agreement with our study, escalation of lead (Pb) concentration in breast cancer tissues has been reported by other studies (Ionescu et al. 2006; Siddiqui et al. 2006; Ragab et al. 2014; Alatise and Schrauzer 2010). The impaired antioxidant-oxidant balance in patients with breast cancer and tumorous tissue can provide a potential link between oxidative stress and breast cancer pathogenesis (Feng et al. 2012; Gönenç et al. 2006).

Table 2 Risk difference (RD) estimation for elements under logistic regression model

Element	Unadjusted)		Adjusted	
	RD	95% CI	RD	95% CI
Ag	**−0.082**	**−0.206, −0.041**	−0.02	−0.141, 0.101
Al	−0.017	−0.112, 0.076	−0.010	−0.083, 0.063
As	**0.560**	**0.419, 0.701**	**0.395**	**0.276, 0.514**
Cd	**0.855**	**0.733,0.977**	**0.748**	**0.534, 0.961**
Cr	**0.144**	**0.009, 0.279**	0.118	−0.011, 0.246
Cu	0.089	−0.009, 0.188	**0.082**	**0.005, 0.159**
Fe	0.031	−0.107, 0.169	−0.008	−0.125, 0.109
Pb	**0.557**	**0.408, 0.707**	**0.443**	**0.311, 0.575**
Se	**0.172**	**0.047, 0.297**	**0.151**	**0.021, 0.282**
Zn	**−0.175**	**−0.332, −0.017**	−0.096	−0.218, 0.026

Findings of the Cd effects on breast cancer disease are paradoxical; it may potentiate the progression of breast cancer, and also it may inhibit the development of tumors by preventing angiogenesis. Jablonska et al. (2017) reported that elevated concentrations of this metal were more pronounced in small or low-grade tumors. Pacini et al. also showed that exposure of MCF-7 cell line to sub-toxic concentrations of cadmium can lead to a reduction in production and release of anti-cancer factors (Pacini et al. 2009). In contrast, Strumylaitė et al. (2008) showed that Cd concentrations were significantly elevated in malignant breast tissue compared to tumor-free breast tissue. Such contradictory results may partly explain the inconsistency in the epidemiological studies for the association of cadmium exposure and breast cancer risk, emphasizing the need for further studies.

In our study, the focus was to study the distribution as well as the interaction of toxic and essential trace elements. There is good evidence to show that many trace elements have an important role in different biological processes using activation or inhibition of enzymes or using competition with other trace elements for binding sites. Thereby, it is sensible to assume trace elements can affect the carcinogenic process by using complex interactions (Siddiqui et al. 2006).

By clustering analysis, we found several clusters of trace elements in cancerous patients; cluster 1 consists of As and Fe, cluster 2 Cd-Pb, cluster 3 Zn-Se, cluster 4 Cu, and cluster 5 consists of Ag-Al-Cr. Studies to cluster trace elements concentration levels in breast cancer patients are limited. By using hair samples of patients who were at stage III of breast cancer; Cihan et al. (2011) obtained eight clusters of 34 elements which were different clusters of trace elements to what we found in this study. However, there was a similarity in the grouping of Fe and As. We also used PCA to identify potential sources and the grouping of trace elements in normal and cancerous breast tissues. In breast cancer tissues, PC1 showed higher loading for Cd, As, Pb, and Se. These trace elements are mainly associated with environmental exposure, contaminated food, and dietary habits. As expected, PCA results were different for cancerous and normal tissues; therefore, it highlights the main role of certain elements in each group. Pasha et al. (2008) showed higher loadings of Cd, Pb, Co, Cu, Fe, Mg, Mn, and Ni in the benign breast tissues.

The incidence of cancer can be associated with living in polluted areas. Environmental pollution may insert individuals at higher risk of heavy metal exposure. Some studies report the excessive number of heavy metals in the soil, water, and foods of polluted areas (Maleki et al. 2014; Ebrahimi and Ebrahimzadeh 2015; Maleki et al. 2015; Karimyan et al. 2020). For instance, Maleki and Jari (2021) reported that the amount of As and nitrate in the drinking water of Sanandaj city (the capital of Kurdistan province) exceeded the standard limit, suggesting a carcinogenic risk of As. Another study reports high concentration levels of Cr and Pb in vegetables from farms in Sanandaj city that were above the standards threshold limit of the Food and Agriculture Organization (FAO) and also the World Health Organization (WHO) (Maleki et al. 2014). Ebrahimi and Ebrahimzadeh (2015) study also found high levels of Pb, Cr, As, and Hg in 79 (out of the 96) drinking water resources across Kurdistan Province.

The strength of the current study is the application of the ICP-MS method to assess several essential and toxic elements simultaneously in cancerous and non-cancerous breast tissues. This investigation can provide basic information on supporting the effects of essential and toxic elements in breast cancer etiology. However, our study had several limitations. Dietary intake information of patients was not available in our study. Further studies with larger sample sizes are necessary to study more types of tissues and lymph nodes. The involvement of cancerous patients with lymph node metastasis is helpful to assess the potential links between different metals and the involvement of lymph nodes. Also, further studies are needed to establish a relationship between heavy metal concentrations in serum and tissue with nutrient supplementation and patient outcomes with different stages of breast cancer.

Conclusion

In this study, the concentration of different essential and toxic elements in the breast tissue was investigated. The results of our study showed an elevated concentration of As, Cd, Cr, Cu, Pb, and Se and lowered levels of Zn in breast cancer tissues compared to normal ones in the Iranian context. Also, moderate correlations were observed between Al-Cr, As-Cu, and Cu-Se in the cancerous group. In the case of the breast cancer tissues, PC1 showed higher loading for Cd, As, Pb, and Se. Our study provides insights into the possible roles and effects of different elements in breast cancer.

Declarations

Ethics approval and consent to participate This study was approved by the Research and Ethics Committee of Kurdistan University of Medical Sciences (IR.MUK.REC.1397.122), 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

Alatise OI, Schrauzer GN (2010) Lead exposure: a contributing cause of the current breast cancer epidemic in Nigerian women. Biol Trace Elem Res 136(2):127–139

Barnes DM, Newman LA (2007)Pregnancy-associated breast cancer: a literature review. Surg Clin North Am 87(2):417–430

Borella P, Bargellini A, Caselgrandi E, Piccinini L (1997) Observations on the use of plasma, hair, and tissue to evaluate trace element status in cancer. J Trace Elem Med Biol 11(3):162–165

Bray F, McCarron P, Parkin DM (2004) The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res 6: 229–239

Burguera E, Romero Z, Burguera M, Burguera JL, de Arenas H, Rondon C (2002) Determination of some cationic species in temporary teeth. J Trace Elem Med Biol 16(2):103–112

Byrne C, Divekar SD, Storchan GB, Parodi DA, Martin MB (2013) Metals and breast cancer. J Mammary Gland Biol Neoplasia 18 (1):63–73

Chanihoon GQ, Afridi HI, Talpur FN, Kazi TG, Baig AJ (2021) Interaction between essential (Zn) and toxic (Cd) elements in different stages of female breast cancer patients, resident in different cities of Sindh, Pakistan. Biol Trace Elem Res. https://doi.org/10.1007/s12011-021-02757-4

Chen YC, Prabhu KS, Mastro AM (2013) Is selenium a potential treatment for cancer metastasis? Nutrients 5(4):1149–1168

Choi R, Kim MJ, Sohn I, Kim S, Kim I, Ryu JM (2019) Serum trace elements and their associations with breast cancer subgroups in Korean breast cancer patients. Nutrients 11(1):37

Cihan YB, Sözen S, Yıldırım SÖ (2011) Trace elements and heavy metals in hair of stage III breast cancer patients. Biol Trace Elem Res 144 (1):360–379

Ebrahim AM, Eltayeb M, Shaat M, Mohmed NM, Eltayeb E, Ahmed AY (2007) Study of selected trace elements in cancerous and noncancerous human breast tissues from Sudanese subjects using instrumental neutron activation analysis. Sci Total Environ 383(1-3):52–58

Ebrahimi SJ, Ebrahimzadeh L (2015) Evaluation of heavy metals concentration in drinking water resources in the cities of Kurdistan province. Adv Biores 6:55–61

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

Feng JF, Lu L, Zeng P, Yang YH, Luo J, Yang YW (2012) Serum total oxidant/antioxidant status and trace element levels in breast cancer patients. Int J Clin Oncol 17(6):575–583

Florea AM, Büsselberg D (2011) Metals, and breast cancer: risk factors or healing agents? J Toxicol 2011:2011–2018

Geraki K, Farquharson M, Bradley D (2002) Concentrations of Fe, Cu and Zn in breast tissue: a synchrotron XRF study. Phys Med Biol 47 (13):2327–2339

Gönenç A, Erten D, Aslan S, Akıncı M, Şimşek B, Torun M (2006) Lipid peroxidation and antioxidant status in blood and tissue of malignant breast tumor and benign breast disease. Cell Biol Int 30(4):376–380

Hajizadeh Y, Jafari N, Mohammadi A, Momtaz SM, Fanaei F, Abdolahnejad A (2020) Concentrations and mortality due to short- and long-term exposure to PM 2.5 in a megacity of Iran (2014–2019). Environ Sci Pollut Res 27(30):38004–38014

International Agency for Research on Cancer (2008). GLOBOCAN 2008 (IARC), Section of Cancer Information. available at: http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=900. 2013. Accessed 12 Feb 2021.

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

Jafari A, Goudarzian AH, Nesami MB (2018) Depression in women with breast cancer: a systematic review of cross-sectional studies in Iran. Asian Pac J Cancer Prev 19(1):1

Jablonska E, Socha K, Reszka E, Wieczorek E, Skokowski J, Kalinowski L (2017) Cadmium, arsenic, selenium and iron–implications for tumor progression in breast cancer. Environ Toxicol Pharmacol 53:151–157

Järup L (2003) Hazards of heavy metal contamination. Br Med Bull 68 (1):167–182

Karimyan K, Alimohammadi M, Maleki A, Yunesian M, Nodehi RN, Foroushani AR (2020) Human health and ecological risk assessment of heavy metal (loid) s in agricultural soils of rural areas: a case study in Kurdistan Province, Iran. J Environ Health Sci Eng 18(2):469–481

Kawanishi S, Hiraku Y, Murata M, Oikawa S (2002) The role of metals in site-specific DNA damage with reference to carcinogenesis. Free Radic Biol Med 32(9):822–832

Kuo HW, Chen SF, Wu CC, Chen DR, Lee JH (2002) Serum and tissue trace elements in patients with breast cancer in Taiwan. Biol Trace Elem Res 89(1):1–11

Leonard SS, Bower JJ, Shi X (2004)Metal-induced toxicity, carcinogenesis, mechanisms and cellular responses. Mol Cell Biochem 255(1): 3–10

Land SR, Liu Q, Wickerham DL, Costantino JP, Ganz PA (2014) Cigarette smoking, physical activity, and alcohol consumption as predictors of cancer incidence among women at high risk of breast cancer in the NSABP P-1 trial. Cancer Epidemiol Biomark Prev 23: 823–832

Lu Y, Song S, Wang R, Liu Z, Meng J, Sweetman AJ, Jenkins A, Ferrier RC, Li H, Luo W, Wang T (2015) Impacts of soil and water pollution on food safety and health risks in China. Environ Int 1(77):5–15

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

Malakootian M, Mohammadi A, Faraji M (2020) Investigation of physicochemical parameters in drinking water resources and health risk assessment: a case study in NW Iran. Environ Earth Sci 79(9):1–1

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

Maleki A, Jari H (2021) Evaluation of drinking water quality and non-carcinogenic and carcinogenic risk assessment of heavy metals in rural areas of Kurdistan. Iran Environ Technol Inn 23:101668

Maleki A, Amini H, Nazmara S, Zandi S, Mahvi AH (2014) Spatial distribution of heavy metals in soil, water, and vegetables of farms in Sanandaj, Kurdistan, Iran. J Environ Health Sci Eng 12(1):136

Manisalidis I, Stavropoulou E, Stavropoulos A, Bezirtzoglou E (2020) Environmental and health impacts of air pollution: a review. Front Public Health 8:14

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

Mansouri B, Salehi JEtebari B, Moghaddam HK (2012c) Metal concentrations in the groundwater in Birjand flood plain, Iran. Bull Environ Contam Toxicol 89:138–142

Miller ER, Wilson C, Chapman J, Flight I, Nguyen A-M, Fletcher C, Ramsey IJ (2018) Connecting the dots between breast cancer, obesity and alcohol consumption in middle-aged women: ecological and case control studies. BMC Public Health 18(1):460

Mohammadi A, Faraji M, Nemati Mansour S, Abdolahnejad A, Miri M (2020) Spatial analysis of heavy metals in surface soil, NW Iran. Int J Environ Anal Chem 1-0.

Mousavi SM, Montazeri A, Mohagheghi MA, Jarrahi AM, Harirchi I, Najafi M (2007) Breast cancer in Iran: an epidemiological review. Breast J 13(4):383–391

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

Nozadi F, Azadi N, Mansouri B, Tavakoli T, Mehrpour O (2021) Association between trace element concentrations in cancerous and non-cancerous tissues with the risk of gastrointestinal cancers in Eastern Iran. Environ Sci Pollut Res. https://doi.org/10.1007/s11356-021-15224-3

Otaghvar HA, Hosseini M, Tizmaghz A, Shabestanipour G, Noori H (2015) A review on metastatic breast cancer in Iran. Asian Pac J Trop Biomed 5(6):429–433

Pacini S, Punzi T, Morucci G, Gulisano M, Ruggiero M (2009) A paradox of cadmium: a carcinogen that impairs the capability of human breast cancer cells to induce angiogenesis. J EnvironPathol Toxicol Oncol 28(1):85–88

Pasha Q, Malik SA, Iqbal J, Shaheen N, Shah MH (2008) Comparative evaluation of trace metal distribution and correlation in human malignant and benign breast tissues. Biol Trace Elem Res 125(1):30–40

Ragab AR, Farouk O, Afify MM, Attia AM, El Samanoudy A, Taalab YM (2014) The role of oxidative stress in carcinogenesis induced by metals in breast cancer Egyptian females sample at Dakahlia Governorate. J Environ Anal Toxicol 4(2):207–211

Rai PK, Lee SS, Zhang M, Tsang YF, Kim KH (2019) Heavy metals in food crops: health risks, fate, mechanisms, and management. Environ Int 1(125):365–385

Rajaei G, Mansouri B, Jahantigh H, Hamidian AH (2012) Metal concentrations in the water of Chah Nimeh reservoirs in Zabol, Iran. Bull Environ Contam Toxicol 89(3):495–500

Raju GN, Sarita P, Kumar MR, Murty GR, Reddy BS, Lakshminarayana S (2006) Trace elemental correlation study in malignant and normal breast tissue by PIXE technique. Nucl Inst Methods Phys Res B 247(2):361–367

Rautray TR, Das S, Rautray AC (2010) In situ analysis of human teeth by external PIXE. Nucl Inst Methods Phys Res B 268(14):2371–2374

Rehman K, Fatima F, Waheed I, Akash MS (2018) Prevalence of exposure of heavy metals and their impact on health consequences. J Cell Biochem 119(1):157–184

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 28:45230–45239

Riesop D, Hirner AV, Rusch P, Bankfalvi A (2015) Zinc distribution within breast cancer tissue: a possible marker for histological grading? J Cancer Res Clin Oncol 141(7):1321–1331

Romaniuk A, Lyndin M, Sikora V, Lyndina Y, Romaniuk S, Sikora K (2017) Heavy metals effect on breast cancer progression. J Occup Med Toxicol 12:32

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 Therap 3(2):199–204

Siddiqui M, Singh S, Mehrotra P, Singh K, Sarangi R (2006) Comparison of some trace elements concentration in blood, tumor free breast and tumor tissues of women with benign and malignant breast lesions: an Indian study. Environ Int 32(5):630–637

Silva M, Tomal A, Perez C, Ribeiro-Silva A, Poletti M (2009) Determination of Ca, Fe, Cu and Zn and their correlations in breast cancer and normal adjacent tissues. X-Ray Spect Int J 38(2):103–111

Strumylaitė L, Boguševičius A, Ryselis S, Pranys D, Poškienė L, Kregždytė R (2008) Association between cadmium and breast cancer. Medicina 44(6):415

Szkutnik-Fiedler D, Kus K, Ratajczak P, Antoniów M, Nowakowska E, Grześkowiak E (2016) Coadministration of tramadol with aripiprazole and venlafaxine—The effect on spatial memory functions in male rats. Pharmacol Rep 68(2):451–456

Tapiero H, Tew KD (2003) Trace elements in human physiology and pathology: zinc and metallothioneins. Biomed Pharmacother 57(9):399–411