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Trace Elements Homeostasis in Biological Samples as New Candidate Biomarkers for Early Diagnosis and Prognosis of Female Breast Cancer and Therapeutic Response: Systematic Review

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ABSTRACT

Background: Female breast cancer (BC) remains the most common cause of total cancer deaths around the world. Several studies have investigated BC biomarkers, but vital circulating biomarkers for early diagnosis of malignancy are still scarce. Thus, finding sensitive, selective and accurate biomarkers is required to get better BC outcome and to prolong patients' survival. Therefore, this review investigated the feasibility of using circulating trace elements (TEs) as the new promising biological biomarkers for BC diagnosis and prevention.

Methods: We systematically searched EMBASE, Medline, Google Scholar, PubMed, SciELO, Scopus databases or Web of Science for original studies presenting the significant changes in the concentrations of circulating TEs in terms of serum, plasma or blood from female breast cancer patients.

Results: The search yielded 2697 articles, of which 39 were considered for this review. The study showed that four essential TEs (Se, Cu, Zn and Mn) significantly decreased when only one essential trace element (Fe) increased consistently, while five toxics circulating TEs (Cd, Cr, Pb, Co, Mo) increased significantly with a significant difference compared to healthy groups. The essential TEs, Se and Cu were reported to decrease the most in fifteen and twenty-one studies, respectively. However, regarding the toxic circulating TEs, Cd and Pb were found to increase most significantly in seven studies. Among the essential TEs, Se and Zn were reported to have the most potential, with Cd and Pb having the most potential for use as new promising biomarkers to diagnose or prevent BC.

Conclusion: The findings provide an insight into the TEs circulating biomarkers for early BC diagnosis and prevention. Due to its high heterogeneity, meta-analysis was not assessed; hence, further investigation may be required on their clinical outcomes in BC with high sensitivity and specificity for accurate therapeutic response.

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INTRODUCTION

Breast cancer (BC) affects millions of women worldwide and is ranked in the second position among the causes leading to mortality of women each year. Its incidence is increasing in developing and developed countries due to western dietary habits and improper lifestyles amplified by genetic factors.[1,2]

Since the last two decades, numerous efforts have been made by researchers throughout the world in order to develop new circulating blood methods beyond the classical biomarkers for early diagnosis in benign form as well as in all clinical stages (I, II, III and IV) in order to reduce the number of deaths. Among the classical biomarkers we have ER, PR and HER2, exosomes, Ki-67, miRNAs and many other protein biomarkers which have been used to diagnose BC; however, these biomarkers show limitations due to heterogeneity of tumor (such as tumor size, tumor grade, and lymph node metastases), and inaccuracy of clinical evidence linked with multifactorial aspects (genetic, hormonal and environmental) of the disease.[3,4]

Additionally, there are factors like age and the involvement of genes affecting BC patients. For this reason, finding other biomarkers for early detection is indispensable. Exploring other biomarkers that are involved in biological samples may be more important in order to increase patients' survival. In fact, some nutrients such as vitamins, fatty acids and micro-minerals or trace elements (TEs) are essential for homeostasis in the human body. These micronutrients play an important role in the development of various diseases such as neurodegenerative and other non-communicable diseases including cancer.[5,6] The circulating TEs such as zinc (Zn), copper (Cu), selenium (Se), manganese (Mn), and iron (Fe) play an important role in carcinogenesis of BC.[5,6,7,8] Hence, deficiency of these essential TEs may contribute to BC disease.[7] The circulating TEs may act as catalytic or functional and structural components in human body because each of them may serve specific biological functions after the activation of specific enzymes and hormones. These can lead to specific signaling pathways of tumor growth.[9] Other TEs act as co-factors for activation of catalytic enzymes that lead to the development of cancers after any disorders in the human body.

For example, Zn is a cofactor for proteins which can mediate DNA repair and protect the integrity and stability of DNA and a cofactor of Cu/Zn superoxide dismutase (SOD).[8,10] It was reported that Cd, Cu, Fe, Zn, Co, Cr, Pb, Al, Hg, Sn, As and Ni can activate estrogen receptors and induce the estrogen target genes and the proliferation of BC.[11,12] Thus, the imbalance of TEs in female BC patients can be used as a vital biomarker for early diagnosis of malignancy because of their role in many biochemical processes such as protein synthesis including DNA, immune function, antioxidant defense and inhibition of cell proliferation or apoptosis.[13,14]

Accordingly, a reduction in circulating TEs was associated with chronic oxidative stress which characterized the BC invasion, metastasis, angiogenesis or progression as well as its early phase[15,16,17,18], suggesting that reductions in concentrations of these specific TEs in blood, plasma or serum can be used as a potential emerging biomarker to diagnose BC. Numerous researchers have reported changes in blood plasma Zn concentration as a biomarker affecting BC growth.[19,20,21]

In addition, Silva *et al.*[22] found that circulating TEs can be a relevant tumor biomarker for predicting BC. The biomarkers are any type of measurable elements which demonstrate the presence of malignancy or malignant potential, or predict the behavior of the tumor, the prognosis or the treatment response.[23] However, some other studies found inconsistent results which may be due to the methodologies used to analyze TEs, size of patients, types of instruments, chemical exposure, stage of disease, the status, age, lifestyle as well as race of BC patients.

The circulating TEs can be the emerging biomarkers in biological samples including serum, plasma and blood. These circulating TEs are measured by different analytical methods. Some of these methods are more sensitive, and selective and have higher accuracy than others. These methods include X-ray fluorescence spectroscopy, atomic absorption spectroscopy (AAS) (flame atomic absorption spectrometry, inductively coupled plasma mass spectrometry (ICP-MS), and inductively coupled plasma atomic emission spectroscopy (ICP-AES), Total Reflection X-Ray Fluorescence (TXRF), Wavelength Dispersive X-Ray Fluorescence (WDXRF) or Energy Dispersive XRay Fluorescence (EDXRF, Synchrotron radiation-based X-ray fluorescence (SRXRF) and Particle-Induced X-Ray Emission (PIXE).

However, when compared to conventional method such as AAS, XRF with less intensity of the photon beam, poor detection limits and energy tunability depending on X-ray tube, SRXRF offers the advantages of high intensity beam, superior detection limits and wide range of energy tunability. However, these methods use very expensive equipment and are not available in many laboratories. For this reason, assessing the circulating TEs homeostasis (upregulation and downregulation) in biological samples including whole blood, serum and plasma might be a potential emerging prognostic and diagnostic biomarker for BC patients.

The present systematic review aimed to investigate some of the essential and toxic TEs (Zn, Cu, Fe, Zn, Mn, Se) and (Cd, Co, Cr, Pb, Mo) in biological samples including the terms blood, serum and plasma as new promising diagnostic/predictive biomarkers of BC for better survival outcomes in patients with BC.

METHODS

The systematic review was designed and conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (HSRI). This study followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) described by Page *et al.*[24] presented in Figure 1.

Search Strategy

We systematically searched EMBASE, Medline, Google Scholar, PubMed, SciELO, Scopus databases or Web of Science to identify the studies using the terms blood, serum and plasma concentrations of TEs in BC patients. We also searched some articles from American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and American Urological Association (AUA).

We conducted our search strategically by including the following terms: "serum levels of trace elements and breast cancer", "trace elements as predictive biomarkers for breast cancer", "Trace elements to diagnose breast cancer", "level of trace elements in breast cancer as new biomarkers", "breast cancer and level of trace elements in plasma", " trace elements in blood of breast cancer patients as predictive biomarkers", " trace elements in plasma and breast cancer disease", "Serum/plasma levels of trace elements in female patients with breast cancer", "whole blood concentrations of trace elements in female patients with breast cancer as circulating biomarkers," "serum levels in breast cancer", "role of some trace elements in female breast cancer", "serum selenium concentration in women with breast cancer", "trace elements in serum levels of breast cancer patients as a circulating biomarker", "micronutrients levels in female with breast cancer as a biomarker," "trace element levels and female breast cancer" and " trace elements as a biomarker or a marker".

The literature research was conducted from November 2021 to April 2022 by reviewing all citations of the articles eligible for the systematic review.

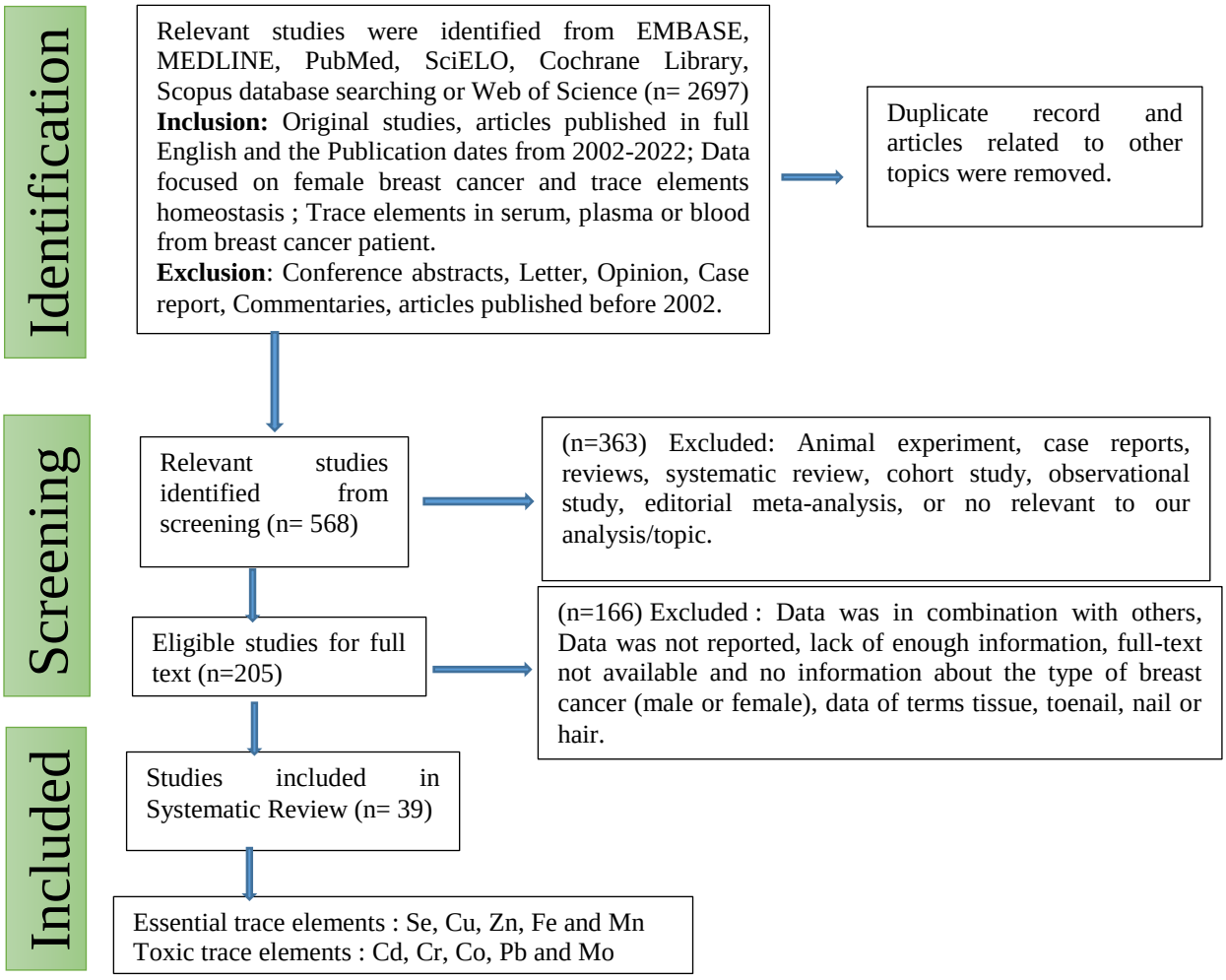

Figure 1. Flow chart of study selection in the systematic review (PRISMA), inclusion and exclusion[24]

Study Design and Selection

The study investigated the circulating trace elements (TEs) homeostasis in biological samples including blood, serum and plasma whose levels showed significant changes among cases and healthy groups (HG) in studies. The studies which used the terms tissue, hair, nail or toenail from breast cancer were excluded during screening. The studies from different countries or geographic regions were eligible for the investigation. The criteria for exclusion of the study were as follows: Comments, minireviews, reviews, editorials, opinions, reports, systematic reviews, meta-analyses, guidelines, letters, abstracts of conference and others in detail presented in Figure 1. The criteria for inclusion were based on year (from 2002 up to 2022), type of journal publication, original studies and only the articles published in full English were considered. The study characteristics including title, authors, location, journal, and analytical methods, publication date or year as well as study design details including study sample size, patients' baseline demographics and disease characteristics were screened. The studies were also considered if the publication year was in 2002 or later. The titles (step 1), abstracts (step 2) and full texts (step 3) of different articles were screened and then were reviewed by three (3) reviewers [WH, JGM, RHB] independently for each paper and when there was disagreement, other reviewers [NMS, DPH, CJH, KBB, BV] were required for clarification and the final list was chosen after consensus among the reviewers.

Data Extraction and Quality Assessment

The data extraction was conducted by four (4) reviewers [WH, JGM, RHB, NMS] for each paper and any disagreements were discussed and resolved with other reviewers [LA, KBB, DPH] independently. The final list was chosen by consensus. To assess the quality of the study, the Newcastle-Ottawa Scale (NOS) was used. The Cochrane RoB 2 tool was used to assess the Risk of bias.[25] The risk of bias was independently assessed by each author and consensus was reached after discussion.

Data Analysis

The research group discussed the homogeneity of different studies regarding their study populations and methods used as well as the presentation of all data with respect to the treatment comparisons made.

RESULTS

Selection of studies included

Following the strategy adopted for the present study, 2697 articles were identified and after removing the irrelevant articles, 568 references were assessed in step 1. Thus, after reading the titles and abstracts, 205 relevant articles were considered in full-text in step 2. In step 3, 168 articles were excluded and finally 39 references were included in this systematic review. Figure 1 shows the details of the selection of different references. Different steps of the process, including identification, exclusion and inclusion of studies are also summarized in Table 1.

Characteristics of studies

The literature search was conducted from November 2021 up to April 2022. The articles considered were published from 2002 to 2022. The articles were in the majority published during the last five years (58.97%, n=23), while the medium dated articles were published between 2010 and 2016 (28.94%, n= 11) and old references were between 2002 and 2015 (13.16%, n=5) across different continents (Table 1). The majority of studies were conducted in Asia (79.49%, n=31) followed by Africa (7.69%, n=3), Europe (5.26%, n=2) and transcontinental countries (Europe, Asia) (5.26%, n=2) (Table 1).

Women in the pre- and postmenopausal status with different clinical stages of BC were included. The number of women tested in the studies was 5173 (2891 in the case groups and 2282 in the health groups) aged from 19 - 88 and from 10-88 years in BC and health groups, respectively (Table 1). The majority of biological samples were 32 serum studies (Table 1), three plasma studies[26,27,28] and two whole blood studies[29,30]. Of all the studies, five were adjusted for confounding factors. The circulating TEs measurement was conducted by eight methods (Table 1), but the majority of studies were evaluated by AAS (65.80%, n= 25) followed by ICP-MS (13.16%, n= 5).

The risk of bias was assessed using Newcastle-Ottawa Scale (NOS) which indicated that most studies had a very low risk of bias. Thirty (30) studies had received the maximum score of 4, 2, 1 for a total score of seven suggesting low risk of bias. Additionally, five (5) other studies received a total score of six.[26, 27,31,36,37] The overall mean quality of the studies included was 7 stars except for five studies[26,27,31,36,37]. Thus, the risk of bias for the present review was not significant.

Main results of the study

The results summarized in Table 1 showed the upregulation and downregulation of essential and toxic TEs concentrations in biological samples including whole blood, plasma and serum used in different studies. For essential TEs, Se concentrations were downregulated in 88% (n=15) of the studies in patients with BC compared to HG, while 11% (n=2) of the studies revealed upregulated Se concentrations.[31,32]

Table 1. Study characteristics of the Systematic Review of trace elements levels in breast cancer (BC)

Authors (References)	Year	Country	Breast cancer		Health controls		Biological Samples	Stages/ types of BC	Analytical methods used	Significant levels increase in BC compared to healthy	Significant levels increase in BC compared to healthy
			Age	N	Age	N					
Sahan (30)	2022	Iraq	30-60	60	30-60	40	Serum	NS	AAS	Cu, Pb	Zn
Skalny et al. (71)	2022	Russia	20-80	310	20-80	100	Serum	II	ICP-MS	Cu, Cr	Zn, Mn
Cao et al. (41)	2021	China	20-80	146	20-80	95	Serum	I-IV	ICP-MS	Cu	Zn, Fe
Pavithra et al. (76)	2014	India	47 ± 8	54	46 ± 8	54	Serum	NS	AAS	Cu, Fe	Zn
Dolapo et al. (50)	2014	Nigeria	29-70	50	30-68	50	Serum	NS	AAS	/	Zn, Se, Mn
Hassan et al. (51)	2017	India	40-45	100	40-45	100	Serum	NS	AAS	Cu	Zn, Se
Ismail et al. (32)	2017	Iraq	/	40	/	40	Serum	NS	AAS	Cd, Co, Cr, Fe, Se	Mn
Mardanshali et al. (28)	2017	Iran	50-70	100	50-70	100	Plasma	NS	AAS	Pb	Zn
El-Deeb et al. (38)	2016	Egypt	50 ± 10	45	47 ± 10	20	Serum	I-III	AAS	Cu, Zn, Cd	/
Hashemi et al. (52)	2017	Iran	19-88	142	10-88	158	Serum	I-IV	AAS	/	Zn, Se
Sarkar and Vamne (67)	2017	India	/	100	/	100	Serum	I-IV	Auto-Bioch anal	Fe, Cu	Zn
Afrin et al. (36)	2018	Bangladesh	49 ± 9	23	49 ± 8	22	Serum	III-IV	AAS	/	Zn, Cu
Cabré et al. (27)	2018	Span	50-60	49	43-60	49	Plasma	NS	ICP-MS	/	Zn, Cu
Naidu et al. (44)	2019	India	55 ± 7	40	49 ± 5	40	Serum	NS	SRXRF	Fe, Cu, Pb	Zn, Mn, Se, Co, Cr, Br
Toker et al. (45)	2019	Turkey	/	40	/	40	Serum	NS	ICP-OES	/	Se, Mn, Cr
Gupta (71)	2019	India	30-40 >	25	30-40 >	25	Serum	NS	Auto-analyzer	Cu	Zn
Naidu et al. (93)	2020	India	55 ± 7	40	49 ± 7	40	Serum	NS	PIXE	Fe, Cu, Cr	Zn, Se, Mn, Co,Br
Laklan et al. (80)	2021	Pakistan	26 ± 19	150	24 ± 16	50	Serum	NS	AAS	Cu, Fe	Zn
Chanihoon et al. (83)	2021	Pakistan	22-35	96	22-35	115	Serum	I-IV	AAS	Cd	Zn
Ding et al. (42)	2015	China	26-62	88	26-62	84	Serum	I	SVD-PAES	Cu, Cd, Co, Cr	Mn, Fe
Siddiqui et al. (37)	2006	India	30-67	50	30-67	25	Serum	I-IV	AAS	Zn, Fe	/
Xue et al. (55)	2021	China	52 ± 14	45	46 ± 12	96	Serum	NS	ICP-MS	/	Se
Khalaf et al. (74)	2021	Iraq	30-70	60	20-60	25	Serum/ Blood	NS	ICP-MS	Cu, Zn, Cr, Cd, Pb	/
Arinola and Charles-Davies (75)	2008	Nigeria	47 ± 2	29	46 ± 2	30	Serum	NS	AAS	Cu	Mn
Wu et al. (48)	2006	Taiwan	/	68	/	26	Serum	I-III	ICP-AES	Cu, Cr, Cd	Zn, Se, Mn
Lopez-Saez et al. (47)	2003	Spain	32-82	200	32-82	100	Serum	I-IV	AAS	/	Se
Kuo et al. (46)	2002	Taiwan	/	68	/	25	Serum	I-IV	ICP-AES/AAS	Cu	Zn, Se
Al-Dahlan et al. (39)	2020	Iraq	28-80	100	28-80	60	Serum	IV	AAS	Cu, Fe, Zn	Se
Jasim et al. (54)	2020	Iraq	/	50	/	50	Serum	NS	AAS	/	Se
Alta'ee et al. (93)	2016	Iraq	46 ± 5	40	31 ± 9	50	Serum	NS	AAS	/	Co
Zohair et al. (35)	2015	Iraq	19-60	30	20-43	8	Serum	I-II	AAS	Zn, Mn, Cr	Cu
Mohamood et al. (49)	2012	Iraq	40-60	25	40-60	25	Serum	NS	AAS	Cu	Zn
Pasha et al. (26)	2014	Pakistan	30-65	59	30-62	60	Plasma	NS	AAS	Zn, Cu, Mn, Cr, Cd, Pb, Mo	/
Najim (31)	2016	Iraq	26-62	75	26-62	75	Serum	NS	AAS	Cr, Cd, Se, Fe, Cu, Co, Zn, Mn	/
Adedapo et al. (31)	2014	Nigeria	52 ± 1	63	54 ± 1	63	Serum	NS	AAS	Pb, Cd	Zn, Se, Fe, Cu
Arooj et al. (33)	2012	Pakistan	22-77	23	22-77	12	Serum	III	AAS	/	Zn, Cu, Cd, Co
Sarita et al. (43)	2012	India	30-75	21	25-62	30	Serum	NS	PIXE	Fe, Cu	Zn, Se, Cr, Mn
Memon et al. (29)	2007	Pakistan	30-60	50	30-60	50	Blood	NS	AAS	/	Zn
Choi et al. (40)	2019	Korea	≥ 18	137	≥ 18	150	Serum	I-IV	ICP-AES	Cu, Mn, Mo	Se

BC : Breast cancer ; N : number ; Not specified ; AAS : Atomic absorption spectrophotometry ; ICP-MS : inductively coupled plasma mass spectrometry ; SRXRF : Synchrotron radiation based X-ray fluorescence; ICP-OES : Inductively coupled plasma omission emission spectrometry ; PIXE : Particle induced X-ray emission ; ICP-AES : Inductively coupled plasma atomic emission spectrometry ;; Auto-Bioch anal : Auto-Biochemistry analyzer, SVD-PAES : Spectraspan V direct current plasma atomic emission spectrometer

Cu concentrations downregulated in 81% (n=22) studies in comparison with health groups (HG) while, 18% (n=5) of the studies revealed the decline of Cu concentrations[27,33-36] comparable to the HG. The concentrations of Zn (77%, n=23) declined in BC patients in comparison with HG while 23% (n=7) of the studies showed an upregulated concentration of Zn.[26,30,31,35,37-39] The contents of Mn were downregulated in 71%, n=10) studies in BC patients compared to HG, while 26% (n=4) of the studies showed an increase.[26,31,35,40] However, Fe content was upregulated in 77% (n=10) of the studies in patients with BC compared to HG and only 23% (n=3) of the studies showed the opposite results.[34,41,42] Regarding the toxic TEs, Cd and Pb concentrations were increased in 100% (n=7, n=7, respectively) of the studies in BC patients compared to HG. Also, 75% (n=9) of the studies showed an increase in Cr concentration compared to HG and 25% (n=3) of the studies[43-45] showed a decrease in BC patients. The concentration of Co and Mo in different studies varied also significantly among the samples (Table 1).

DISCUSSION

In the present systematic review (SR), the changes in the concentrations of circulating TEs in different biological samples including serum, plasma and blood were investigated for circulating biomarkers in BC patients in comparison with health groups (HG). The results revealed that serum was more widely used than the levels of TEs in whole blood and plasma samples. This may be due to the fact that serum is still considered the gold standard and remains the required sample for assays and plays a critical role in patient care, especially for clinical research. Similarly, in order to prevent modifications of some analyses due to the coagulation process and related interferences, serum is preferable in clinical test than whole blood and plasma. The conventional method, AAS was mostly used to determine circulating TEs which could be due to the availability of equipment (instruments), low cost, ease-of-use and suitability for assessing medium and long-term accumulation of these elements, which can be used to explore the long-term trends of changes in the TEs in breast tumor patients. The results showed significantly lower levels of Se in BC patients[39,44-52,54,55] comparable to control groups except for only two studies[31,32] which showed a significant increase in Se in group cases.

These results can be explained by the conditions of analyses such as the quality samples in BC patients which were not reported during the studies including their age and clinical stages of BC among other parameters. The concentrations of Se in BC patients may vary with the clinical stages of the cancerous tumor. Hashemi *et al.*[52] reported that Se concentration increased at early and advanced stages of BC compared to metastatic stages at which the levels of Se decreased significantly. Besides, Choi *et al.*[40] found Se concentrations were significantly lower in patients with stage IV BC compared to those without stage IV BC.

The BC patients' status may also affect Se concentration as observed by Smith *et al.*[56] who found the premenopausal women showed higher Se concentration than those with a menopausal status. This alteration of TEs concentration suggested that cancer cells may use Se for antioxidant properties in order to regenerate cells, hence depleting these circulating antioxidants. This result may confirm that Se has high anticancer and chemopreventive properties.[5] It seems that the decrease in Se in BC patients may be the consequence of malignant cancer rather than the determinant of cancerous tumor. However, the majority of studies (89%) showed decreased Se concentrations in BC patients which may serve as a potential tool to be used as a new tumor biomarker for early diagnosis of BC in individuals.

Cu is one of the essential TEs for cell growth and a cofactor by many enzymes.[44] The increased levels of Cu in BC patients compared to health groups (HG) may be due to the mechanisms involved for combating BC progression.[58] Similarly, it was reported that during tumor cancer progression, emerging necrosis in cancer tissues can, in turn, increase the concentration of serum Cu by releasing Cu into the circulation.[46,59] Additionally, oxidative stress occurring in BC patients may increase Cu during reactive oxygen species formation by Cu ions cupric (Cu (II)) and cuprous (Cu (I)) or Fenton-oxidation.[60,61] The significant decrease in Cu in BC patients in 19% (N=5) of the studies in comparison to healthy subjects may result from differences in studies including genetic factors, sample types, diets, lifestyles, clinical stages of cancerous tumor and menopausal status which significantly affect the homeostasis of the whole blood, plasma or serum Cu concentrations.[62,63] The results are consistent with those obtained by Choi *et al.*[40] who reported that Cu concentrations were significantly higher in patients with stage IV BC than in patients without stage IV BC.

Zn is another essential TEs which acts as an antioxidant in the human body and helps in the formation of glutathione peroxidase, which protects humans from oxidative and free radical impairment, as well as the activation of DNA repair enzymes; thus, it protects against carcinogenesis.[29,64-66,69] Therefore, these different roles of Zn in the human body may explain the significant reduction of Zn in BC patients' serum, plasma or blood.[68] The decrease in Zn in BC

patients was in agreement with the study by Cao *et al.*[41] who reported that Zn is consumed in high quantities because malignant tumor cell growth and metabolism are vigorous and tumor growth and cell division rates are also higher at this phase. This result is in line with the study by Skrajnowska and Bobrowska-Korczak[69], who reported that Zn is an anti-tumor TE, and, thus, can be used as a tumor biomarker. Besides, an increased concentration of Cu in malignant breast patients causes a compensatory decrease in the concentration of Zn[41], and thus the decrease in Zn in BC patients was considerable. Additionally, it was reported by Gupta[70] that the decrease in Zn and Cu in BC patients plays a role in the pathogenesis of BC patients.

It is conjectured that the decrease in antioxidant defense capacity and the decline in immunological competence caused by decreased concentrations of Zn and Se may have influenced the carcinogenic process.[71,72] The contradictory results found in 23% (n=7) of the studies[26,30,31,35,37,38], may be associated with sample types, diet, and menopausal status which affect the homeostasis of blood Cu concentrationss[7,62,63], as well as geographical location as reported by Ding *et al.*[73] who stated that different regions have their own distinct patterns of TEs. High concentrations of Cu in serum might have also led to tumor progression through angiogenesis.[43] Furthermore, it was reported that Zn concentrations varied with the clinical stages of BC[52,74], while the present results indicate that it can serve potentially as a promising tumor biomarker for prevention and treatment of BC patients.[41]

Mn is among essential TEs which has antioxidative and immunoprotective potential in the human body. The reduction of Mn in 74% of the studies of BC patients may indicate the use of Mn in breast tumor. It was reported that tumor development may increase the consumption of Mn for tumor cell growth and enzymatic activity leading to the decreased Mn concentration in the blood in BC patients.[31,75] However, among different studies, four[26,35,40] of them showed the opposite results. The increased Mn concentrations in the blood of BC patients may be the result of the stages of BC, which is in agreement with the study by Jouybari *et al.*[7] who stated that the controversies of circulating TEs in BC patients may be due to clinical stages of BC. This may be also due to lifestyles, dietary intake, smoking, geographical location, other diseases such as diabetes, obesity as well as measurement methods of TEs. In this line, Shen *et al.*[53] reported in their meta-analysis that Mn concentrations had been influenced by geographical location.

Fe plays an essential role in the transfer of oxygen from lungs to other body parts and it is a component of several enzymes involved in the synthesis of DNA and immune function.[76,77] A significant increase in Fe concentrations in 77% of the studies on BC patients with respect to HG indicates that Fe is the generator of reactive oxygen species which, in turn, is associated with the progression of carcinogenesis.[78] The results suggest that BC patients had higher Fe concentrations to meet the needs of increased cell proliferation and DNA synthesis.[41,79,80] For instance, the highest concentrations of Fe might have possibly led to the inception and development of BC in patients by causing oxidative DNA damage through the generation of free radicals.[43,81] Marques *et al.*[82] reported the correlation of BC progression with high Fe concentrations. Thus, an increase in Fe might be due to its catalytic activity on mutagenic radicals and a suppression action on the host immune function.[83] However, the decreased concentrations of Fe[34,41,42] in BC patients may be attributed to genetic factors, stages of breast tumor, menopausal status and sample types used in the studies as well. A significant increase in Cd[26,30,31,34,48,83] and Pb[26,30,34,52, 49, 34, 38, 85] concentrations in 100% of the studies in BC patients may indicate the proliferation lesions and tumor progression in cancerous tumor since these TEs are toxics.

Ding *et al.*[74] reported a significant lower concentration of Cd in patients with BC compared to HG. The Cd alters the expression of several ERα-responsive genes and increases the malignancy of BC cells.[86] This role of Cd in BC progression was found in the study conducted by Jablonska *et al.*[87] The TEs, Cd may induce the proliferation of estrogen-dependent BC cells and increase the transcription and expression of estrogen-regulated genes such as the progesterone receptor.[88-91] Thus, these toxic TEs can serve as a vital biomarker for early diagnosis of breast malignancy and monitoring the progression of BC. The increased concentrations of Cr in different studies may be due to the induction of oxidative stress, DNA damage and cell cycle alterations during BC progression.[92] However, the results could provide an insight into Cr to be used as a potential marker in circulating biological samples in BC patients.

However, the concentrations of Co increased in three studies[31,32,42], and decreased in four studies.[33,44,93] These studies were in small size and the measurement methods were different, which may explain the inconsistent results. Mo levels decreased in two studies[26,40], but they were evaluated in small scale studies and the measurement methods of these TEs were different; therefore, the result may not be conclusive and other studies must be conducted routinely in order to confirm its variations in BC patients.

Limitations

This is the first SR to report the essential and toxic circulating TEs changes in serum, plasma or whole blood for use as new potential biomarkers for BC compared to healthy groups. However, there are some limitations that should be considered in this SR. The included studies widely vary in demographic variables, including age, ethnicity, education and menopausal state, and in the extent to which these were taken into account. Some authors did not provide sufficient information to decide whether a measure to reduce bias was taken. Some information regarding dietary intake in different studies was not reported or partially reported.

High heterogeneity was found among the included studies. Although, only the studies on serum and plasma or whole blood were included to eliminate the differences in the sample types, or differences in study population characteristics, other confounding factors that may influence serum/plasma TEs levels could be considered, including geographic region, dietary, lifestyle, age, oral supplement, estrogen exposure and genetics factors that might have affected the results of this review; the limited number of studies that assessed alteration of TEs in BC patients must be also considered as a limitation. However, quantative alterations in biological samples markers may be useful as biomarkers. The future study will consider these factors in order to clarify the clinical significance of these TEs dyshomeostasis in BC patients as new potential biomarkers.

CONCLUSION

The present systematic review investigated the feasibility of using the dyshomeostasis (changes) of circulating trace elements in biological samples as new emerging biomarkers for early diagnosis and prognosis of female breast cancer patients. The study indicates that some circulating TEs can be used as potential circulating biomarkers of BC for diagnosis. The significant decrease in essential TEs Se followed by Cu and Zn, respectively and an increased level of Fe and an increase in toxic TEs Cd, Pb and Cr can serve as new potential candidate biomarkers for BC diagnosis. However, further clinical studies focusing on these circulating biomarkers will be needed to specifically determine their roles in tumorigenesis of BC and distinguish a list of prognostic and diagnostic BC biomarkers that have high potential of specificity and sensitivity. These circulating TEs can serve as a new emerging biomarker for early diagnosis and chemotherapy of breast malignancy for appropriate prediction and treatment. We further study their clinical applications to validate them as clinical biomarkers in BC.

ABBREVIATIONS

ASCO: American Society of Clinical Oncology, AUA: American Urological Association, BC: Breast Cancer, Cd: Cadmium, Co: Cobalt, Cr: Chromium, Cu: Copper, ER: Estrogen receptor, ESMO: European Society of Medical Oncology, Fe: Iron, HER2: Human Epidermal growth factor Receptor 2, HG: Healthy Groups, Mn: Manganese, Mo: Molybdenum, NOS: Newcastle-Ottawa Scale, Pb: Lead, PR: Progesterone Receptors, PRISMA : Preferred Reporting Items for Systematic Review and Meta-Analyses, Se: Selenium, SOD: Superoxide Dismutase, TEs: Trace Elements, Zn: Zinc

ETHICAL CONSIDERATIONS

Not applicable.

FUNDING

Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are openly available in PubMed, MEDLINE, EMBASE, and the Cochrane databases.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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