



A meta-analysis of zinc levels in breast cancer

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ABSTRACT

Background: Breast cancer is the most commonly occurring neoplasm in females, comprising 16% of all female cancers worldwide. Various studies indicate some discrepancies regarding zinc (Zn) levels in various samples of breast cancer patients.

Objective: The present study evaluated by meta-analysed the published data for Zn levels analyzed in breast tissue, plasma, serum, and hair samples and its relationship with breast cancer.

Methods: The present meta-analysis included 36 studies, all of which were published in the years between 1984 to 2017 and selected by searching the databases MEDLINE, EMBASE, Cochrane Library, PubMed, Scopus, and the ISI Web of Knowledge. The articles were analyzed, and I² statistics were used to examine heterogeneity. The objective analysis was performed on data from the 36 studies, with total 1699 study subjects and 2009 controls.

Results: Significant statistical differences overall were observed, based on a random effects model (SMD (95 % CI), $-0.78[-1.40, -0.16]$, $P = 0.014$). Data from 19 of these studies indicated significant statistical differences between cancerous patients and controls with regard to serum and plasma Zn concentration (SMD [(95 % CI): $-1.61(-2.43, -0.79)$]. There was a significant statistical difference between the breast tissue and hair as regards Zn status (SMD (95%CI): $2.32(1.42, 3.21)$) and (SMD (95%CI): $-1.80(-3.41, -0.20)$, respectively). Zn concentration levels typically decreased in blood and hair samples of patients with breast cancer, whereas it was elevated in tumor tissues.

Conclusions: There is a significant relationship between lowered serum Zn concentrations and risk of breast cancer onset or recurrences in women, but because of high heterogeneity, we recommend other primary studies.

1. Introduction

Breast cancer (BC) is the most commonly occurring neoplastic disorder in women worldwide. Its incidence is steadily increasing in developing countries due to many factors, including those related to dietary habits and lifestyle [1–4]. Several concurrent factors may occur at the onset and progression of breast cancer, including xenobiotic

biochemical compounds or metals, the intake of which would likely be due to diet. Deficiency or accretion of essential trace elements, such as Zn may contribute to breast cancer. Evidence suggests a very finely regulated homeostasis of such elements in humans [5–7].

Recent data reported that a quartile of the total recent cancer and 14% of all cancer deaths are linked to the incidence of BC worldwide in women [8–11]. This neoplasia is also the most common malignancy

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Table 1
Quality assessment of the meta-analysis of zinc levels in breast cancer.

Researchers	Selection				Comparability		Exposure		
	1	2	3	4	A	B	1	2	3
Kuo et al. 2002 [21]	*	*		*	*		*	*	
Ionescu et al. 2006 [81]	*	*		*	*		*	*	
Cavallo et al. 1991 [82]	*	*	*	*	*		*	*	
Cui et al. 2007 [40]	*	*		*	*		*	*	
Feng et al. 2012 [83]	*	*		*	*		*	*	
Al-Ebraheem et al. 2009 [33]	*	*		*	*		*	*	*
Magalhães et al. 2008 [15]	*	*		*	*		*	*	*
Rizk and Sky-Peck 1984 [97]	*	*		*	*		*	*	*
Singh et al. 1998 [85]	*	*		*	*		*	*	
Piccinini et al. 1996 [86]	*	*		*	*		*	*	
Yucel et al. 1996 [87]	*	*		*	*		*	*	
Silva et al. 2012 [99]	*	*		*	*		*	*	
Drake et al. 1989 [96]	*	*	*	*	*		*	*	
Geraki et al. 2002 [98]	*	*		*	*		*	*	
Pasha et al. 2010 [91]	*	*		*	*		*	*	
Magálová et al. 1999 [88]	*	*		*	*		*	*	
Zowczak et al. 2001 [89]	*	*		*	*		*	*	
Arinola et al. 2008 [90]	*	*		*	*		*	*	
Saleh et al. 2011 [75]	*	*	*	*	*		*	*	
Sarita et al. 2012 [92]	*	*		*	*		*	*	
Wang et al. 2009 [79]	*	*		*	*		*	*	
Joo et al. 2009 [101]	*	*	*	*	*		*	*	
Yoo et al. 2010 [102]	*	*	*	*	*		*	*	
Cihan et al. 2011 [103]	*	*		*	*		*	*	
Gholizadeh et al. 2013 [100]	*	*	*	*	*		*	*	
Borges de Araújo et al. 2015 [93]	*	*	*	*	*		*	*	
Karki et al. 2015 [94]	*	*		*	*		*	*	
Pavithra et al. 2015 [44]	*	*		*	*		*	*	
Rehman et al. 2014 [24]	*	*		*	*		*	*	
Wadhwa et al. 2015 [104]	*	*		*	*		*	*	

among women in both America and Western Europe [12,13]. Worldwide, approximately 500,000 women are diagnosed with BC each year. More than one-fourth of these cases occur in the United States [14,15]. Despite the promotion in the screening and treatment of breast cancer, the exact etiology of the disease has not yet been fully understood [16]. Advancing age, early menarche, postponed menopause, late age for the first birth and family history of BC are among the most prominent risk factors causing this malignancy. However, these factors do not fully explain the incidence or geographic variations related to the disease,

which may be related to nutrition, metabolism, and amount of adipose tissue [17,18].

Recently, multiple trace elements that could play a role in carcinogenesis of breast tissues have been explored [19–23]. Essential trace elements deficiencies can exhibit effects on the evolvement of a number of disorders, but the increase in the concentration of some elements, particularly their disruption in the regulation of tissue content and distribution, also appear to have genotoxic and carcinogenetic effects [24]. Hence, many trace elements, acting as catalytic or structural components for macromolecules, show specific biological functions and can be essential and indispensable reagents for hormonal function and enzymatic activities. This, in turn, can lead to the activation of defined signaling pathways in tumor growth [25]. Zinc may have a significance in breast cancer progression, as it plays an important role in the development of and/or immunity against breast cancer [11,26–29], participating in the activity of Zn-finger proteins as a co-factor and the copper (Cu)/Zn dismutase SOD1 [30–32].

Zinc is an essential nutritional element that may prevent tumor development through its participation in cell immunity of T-lymphocytes, which is known to play a fundamental role in maintaining anti-tumor immunity [33,34]. In particular, Zn may interfere with Cu, for example in the anti-oxidant response Cu, due to its ability to change its oxidation states, may well catalyze the production of hydroxyl radical, while Zn participates as a cofactor in some detoxifying enzymes. Their role as antioxidants has recently been reviewed [35–37]. In this perspective, the role of Zn is fundamental in much other pathology besides cancer [38]. However, a role in neoplastic growth and malignancy has recently been associated with Zn levels, particularly the involvement of Zn finger proteins [39,40].

Several studies have reported the percentage of trace elements, including Zn in serum and tissues in breast cancer patients [40–42]. However, further investigation has been considered necessary to provide clearer hypothesis about the role of Zn in breast cancer. Moreover, some studies have reported changed blood plasma Zn levels as an indicator or biomarker on breast cancer growth [11,43–45]. But the findings of various studies indicate some discrepancies. Some researchers have demonstrated that blood and hair levels of Zn decrease in breast cancer patients compared to controls, while others have found the opposite, suggesting that Zn exerts a modulatory effect that is still poorly understood [46–48]. The present study addresses the significance of Zn levels in breast cancer by a meta-analysis approach.

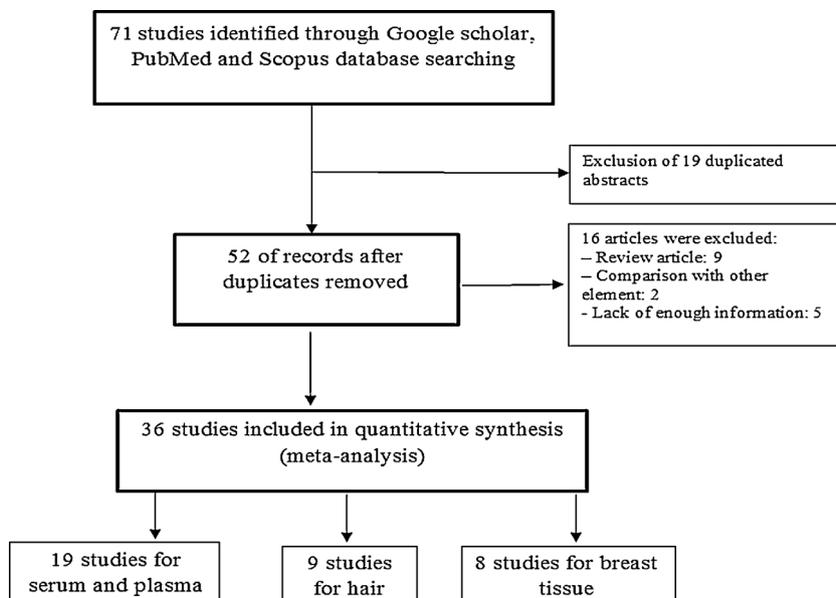


Fig. 1. Flow diagram of studies identified in the systematic review and meta-analysis.

Table 2
Study characteristics of the meta-analysis of zinc levels in breast cancer.

Research group [references]	Year	Country	Breast cancer patients			Healthy controls			Type of Cancer	Type of study	Type of Zinc measurement
			Age (mean)	N	Zn (mean ± SD)	Age (mean)	N	Zn (mean ± SD)			
Serum and plasma zinc levels											
Kuo et al. [21]	2002	China	-	43	884.86 ± 55.46	-	26	976.734 ± 92.25	Cross-sectional	ICP-AES*	
Kuo et al. [21]	2002	China	-	25	753.77 ± 86.35	-	26	976.734 ± 92.25	Cross-sectional	ICP-AES	
Ionescu et al. [81]	2006	Germany	-	20	17.075 ± 9.2	-	8	3.741 ± 2.3	Case-control	AAS-ICP-MS	
Cavallo et al. [82]	1991	Italy	49.6	214	101.8 ± 15.8	47.12	215	87.9 ± 14.6	Case-control	AAS**	
Cavallo et al. [82]	1991	France	53.1	47	90.8 ± 10.3	53.1	46	85.4 ± 10.2	Case-control	AAS	
Feng et al. [83]	2012	China	47.6	32	990.5 ± 116.5	47.2	20	1060.9 ± 86.8	Case-control	M6 AAS	
Feng et al. [83]	2012	China	48.7	56	939.1 ± 103.3	47.2	20	1060.9 ± 86.8	Case control	M6 AAS	
Gupta et al. [84]	1991	India	-	35	88.6 ± 11.7	-	30	115.1 ± 23.5	Case control	EDXRF****	
Singh et al. [85]	1998	India	35-60	10	26.3 ± 5.3	30-40	10	17 ± 7.3	Case-control	AAS	
Piccinini et al. [86]	996	Italy	58.6	38	86.43 ± 23.46	56.8	22	74.03 ± 24.22	Case-control	AAS	
Yucel et al. [87]	1994	Turkey	-	31	0.479 ± 0.130	-	35	1.355 ± 0.289	Case-control	AAS	
Magalova et al. [88]	1999	Slovakia	55.6	73	14.54 ± 2.11	51.7	87	14.99 ± 1.89	Case-control	AAS	
Zowczak et al. [89]	2001	Poland	-	8	13 ± 3.3	-	21	13.8 ± 2	Case-control	AAS	
Arimola et al. [90]	2008	Nigeria	47.17	29	143.27 ± 6.62	46.07	30	143.38 ± 7.54	Case control	Case-control	
Saleh et al. [75]	2011	Kuwait	47.2	50	0.99 ± 0.39	46.9	150	3.6 ± 1.1	Case-control	Case-control	
Sarita et al. [92]	2012	India	-	21	13 ± 2	-	30	38.5 ± 3.9	Case-control	Case-control	
Borges de Araújo et al. [93]	2015	Brazil	20-50	34	37.51 ± 8.26	20-50	32	35.97 ± 5.57	Case-control	Case-control	
Karki et al. [94]	2015	India	-	70	130.697 ± 2.839	-	70	170.153 ± 2.999	Case-control	Case-control	
Karki et al. [94]	2015	India	-	70	158.361 ± 3.718	-	70	170.153 ± 2.999	Case-control	Case-control	
Pavithra et al. [44]	2015	India	47.2	54	52.26 ± 32.58	46.8	54	79.47 ± 16.44	Case-control	Case-control	
Breast tissue zinc levels											
Cui et al. [40]	2007	USA	-	251	0.91 ± 0.24	-	249	0.81 ± 0.21	Paired sample	TXRF****	
Ebrahim et al. [95]	2007	Sudan	-	40	35.509 ± 9.75	-	40	26.88 ± 3.82	Paired sample	INAA***	
Drake et al. [96]	1989	USA	-	26	-	-	26	25.6 ± 12.1	Paired sample	INAA	
Rizk and Sky-Peck 1984 [97]	1984	USA	-	25	68.1 ± 26.9	-	25	-	Paired sample	AAS	
Geraki et al. [98]	2002	UK	-	20	7.38 ± 5.16	-	20	1.69 ± 0.91	Paired sample	TXRF	
Magalhães et al. [15]	2008	Portugal, Germany	-	15	37.3 ± 7.3	-	15	5.8 ± 2.9	Paired sample	TXRF	
Silva et al. [99]	2012	Brazil	-	34	7.1 ± 2.9	-	38	2.1 ± 1.3	Paired sample	TXRF	
Hair zinc levels											
Piccinini et al. [86]	1996	Italy	58.6	38	86.43 ± 23.46	56.8	22	74.03 ± 24.22	Case-control	AAS	
Wang et al. [79]	2006	China	54.2	50	247.6 ± 121.7	52.2	50	195.9 ± 50.2	Case-control	Case-control	
Gholizadeh et al. [100]	2013	Iran	36-50	21	12.3 ± 5.3	47.8	10	24 ± 6	Case-control	Case-control	
Joo et al. [101]	2009	Korea	47.1	40	145 ± 7.23	47.8	144	163.54 ± 4.93	Cross-sectional	Cross-sectional	
Yoo et al. [102]	2010	Korea	47.08	37	14.33 ± 0.72	47.75	144	16.35 ± 0.49	Cross-sectional	Cross-sectional	
Ghan et al. [103]	2011	Turkey	50.3	52	29.374 ± 20.367	47.4	52	63.7 ± 6.187	Case-control	Case-control	
Wadhwa et al. [104]	2015	Pakistan	-	47	114 ± 14	-	94	247 ± 17.4	Case-control	Case-control	
Pasha et al. [91]	2010	Pakistan	30.2	33	391 ± 203	30.3	35	206 ± 192.86	Case-control	Case-control	
Pasha et al. [91]	2010	Pakistan	27.8	36	457 ± 150	30.3	35	206 ± 192.86	Case-control	Case-control	

*Inductively coupled plasma-atomic emission spectrometry (ICP-AES). **Atomic absorption spectrophotometry (AAS). ***Instrumental neutron activation analysis (INAA). ****X-ray fluorescence spectrometry (TXRF). *****Energy dispersive X-ray fluorescence (EDXRF).

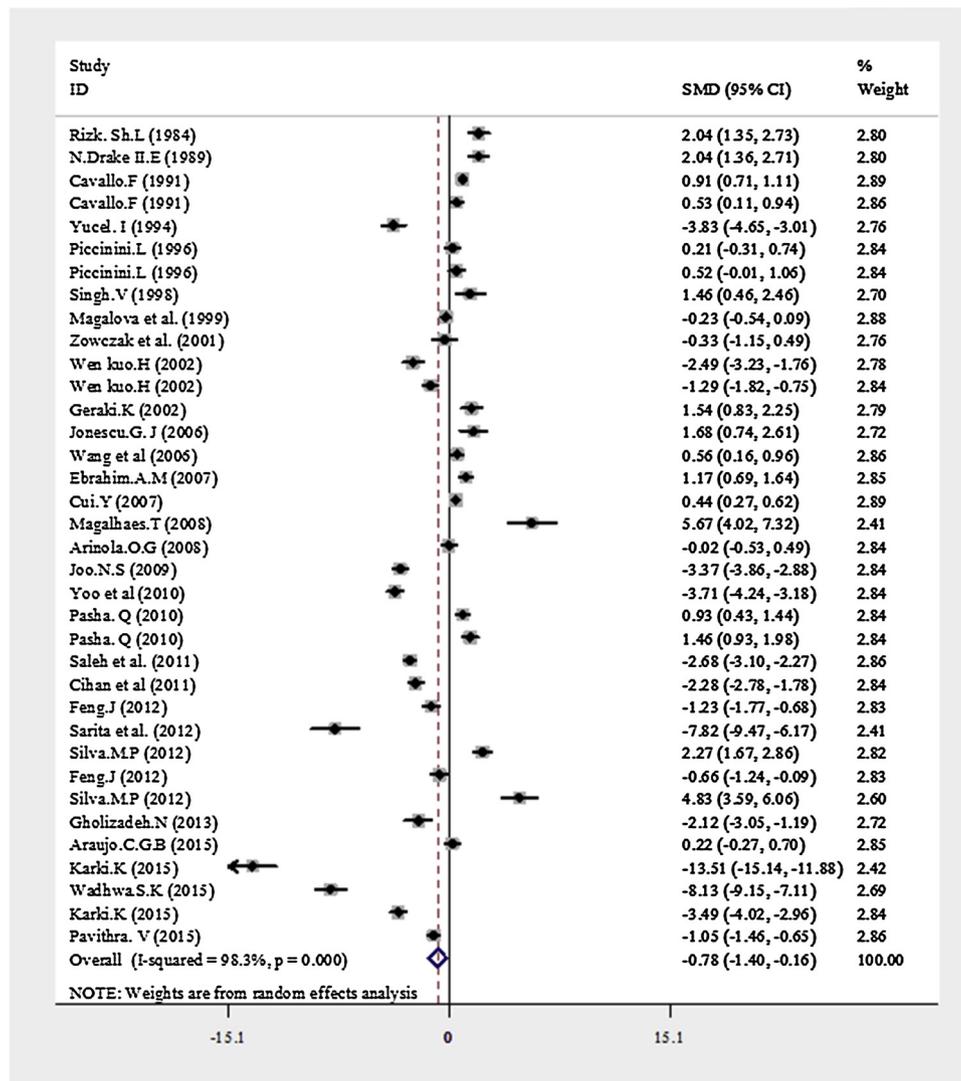


Fig. 2. Meta-analysis of the association of Zinc with breast cancer risk. Square represents an effect estimate of individual studies with more than 95 % confidence intervals with the size of squares proportional to the weight assigned to the study in the meta-analysis. In this chart, studies are stored in order of the year of publication and author's names, based on a random effects model.

2. Materials and methods

2.1. Data sources and search strategy

Aiming at finding the most relevant articles for this review, a thorough comprehensive web search was conducted from MEDLINE, EMBASE, Cochrane Library, PubMed, Scopus, and the ISI Web of Knowledge databases between 1984 to December 2017, using the key words: breast cancer, trace elements, Zn, plasma concentration, breast tissues concentration, and their combination without any limitation as to study languages, with Boolean algorithms.

To narrow down and widen, the search results, Boolean operators ('AND,' 'OR,' 'NOT') were therefore used. The titles from the search results were evaluated closely and determined to be acceptable for potential inclusion criteria. Also, references from the selected articles were examined as further search tools. Relevant studies noted in the reference lists of each selected article were also evaluated for inclusion.

2.2. Study selection

Selection of research reports has been conducted to earn a significant bulk of eligible studies, all written in English, published in

impacted journals of the scientific community of experts and presenting data about the analysis of Zn levels in diagnosed cases of breast cancer. In each paper, Zn levels could be assayed indifferently in blood/serum, breast tissue, and hair; any of these reports were included in this study. Studies with an epidemiological survey showing data about Zn levels in these districts were considered for the meta-analysis. Studies relative to duplications, poor sample size, poor study design, missed confounders and variables, and review articles, were excluded from the research.

2.3. Data extraction and quality assessment

A standard extraction of data was applied, and the following variables were extracted from each paper: sample characteristics, Zn concentration, mean difference, Zn screening method, and sample specimens. Abstracts and full articles were reviewed independently by two of the authors, and if the results were different, papers were checked jointly until the differences were resolved. To assess the quality of the study, the Newcastle-Ottawa Scale (NOS) was applied [49]. The NOS ranged from zero to 9 asterisks. Selected papers were ranked in three groups according to NOS quality assessment: 1- Low quality (up to 3 stars), 2- Medium quality (4–6 stars) and 3- High quality (more than seven stars) (Table 1).

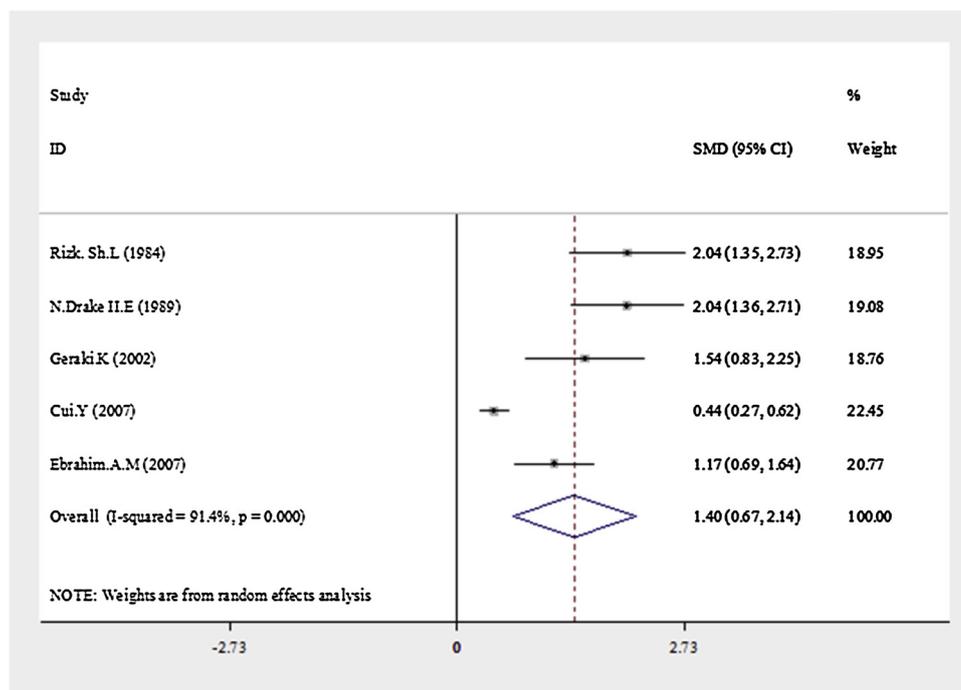


Fig. 3. A meta-analysis of the association between breast tissues and zinc concentration with breast cancer risk. Square represents an effect estimate of individual studies with more than 95 % confidence intervals with the size of squares proportional to the weight assigned to the study in the meta-analysis. In this chart, studies are stored in order of the year of publication and author's names, based on a random effects model.

2.4. Statistical analysis

Studies were combined based on mean, standard deviation, and sample size. The difference between the average variance of the normal distribution was calculated using the formula of two integrated variances. The Cochran test and the I^2 statistics were used to assess heterogeneity between studies. As heterogeneity between studies was high, random effect models were applied to calculate standardized mean differences (SMD) between concentration levels in cancer cases and controls and corresponding confidence intervals (CI). The Begg Plot method was used to examine publication bias. A two-sided p -value < 0.05 was considered statistically significant. Sensitivity analyses were pre-specified. All statistical analyses were done using Stata version 12.

3. Results

The present study was written according to the PRISMA checklist [50]. The initial search strategy identified 71 potential articles for inclusion. Of these studies, 35 articles (16 duplicated studies, nine review articles, eight lacked enough information, and two comparisons with another element) were excluded. In a study by Silva et al. [51], standard deviations (SD) were not specified, and in another one [15] SD was shown only in a bar chart. For statistical estimation and analysis determined these two studies, SD was performed once by including and then by excluding of them.

Finally, 36 studies (comprising 1699 cases and 2009 controls) were selected for inclusion in the meta-analysis (Fig. 1). Summary characteristics of the 36 included studies were tabulated in Table 2. Zinc status in five and 14 studies, was based on serum and plasma analysis, respectively. Whereas, in eight studies breast tissues were sample specimens while nine studies used scalp hair samples. Zinc concentrations were measured in three groups, including, serum and plasma, breast tissue, and scalp hair. There was a significant statistical difference between the Zn status of controls and BC patient and overall random effects model without a quality score showed Zn levels are lower among study cases (SMD ((95 %CI): - 0.78[-1.40, -0.16]; $P = 0.014$; $I^2 = 98.3\%$) (Fig. 2).

3.1. Serum and plasma zinc levels and breast cancer

Data from 19 studies were analyzed based on a random-effects model to comparing the serum and plasma Zn levels in BC patient and healthy controls. Serum and plasma Zn concentrations of cancerous patients were found to be significantly lower than controls (SMD ((95 %CI): -1.61[-2.43, -0.79]). Heterogeneity was significant ($P < 0.05$, $I^2 = 98.1\%$). Fig. 3 shows the results of the meta-analysis for each study and studies combination based on the random-effects model.

3.2. Breast tissue zinc levels and breast cancer

Eight studies were analyzed in a random-effects model to compare the breast tissue Zn in BC patient and healthy subject. There was the significant statistical difference between tissue Zn levels of controls and breast cancer patients using the Silva and Magalhaes method (SMD (95 %CI): 2.32(1.42, 3.21)) (Fig. 4). There was a significant statistical difference between breast tissue Zn levels of controls and breast cancer patient without the Silva and Magalhaes method (SMD (95 %CI): 1.40[0.67–2.14]). The p -value of heterogeneity was significant ($I^2 = 91.4\%$, $P < 0.05$). These results are presented in Fig. 3.

3.3. Hair zinc levels and breast cancer

Nine studies were analyzed in a random-effects model to compare the scalp hair samples Zn in BC patient and healthy subject. There was a significant statistical difference between hair Zn level of controls and breast cancer patients (SMD (95 %CI): -1.80 (-3.41, -0.20, $I^2 = 98.7\%$, $P < 0.05$). These results are shown in Fig. 3.

3.4. Subgroup analysis

Deficiency in Zn levels has been associated with breast cancer risk among Asian women [2]. As showed in Table 3, a similar result was not observed in studies of European women (SMD ((95 %CI): 0.81[0.23, 1.38]; $P = 0.006$; $I^2 = 91.8\%$); however, only eight studies of European women were included in the analysis. In all five studies in American women, low concentrations of Zn were associated with breast cancer risk SMD (SMD ((95 %CI): 1.81[0.95, 2.67]); $P = 0.000$; $I^2 = 94.8\%$;

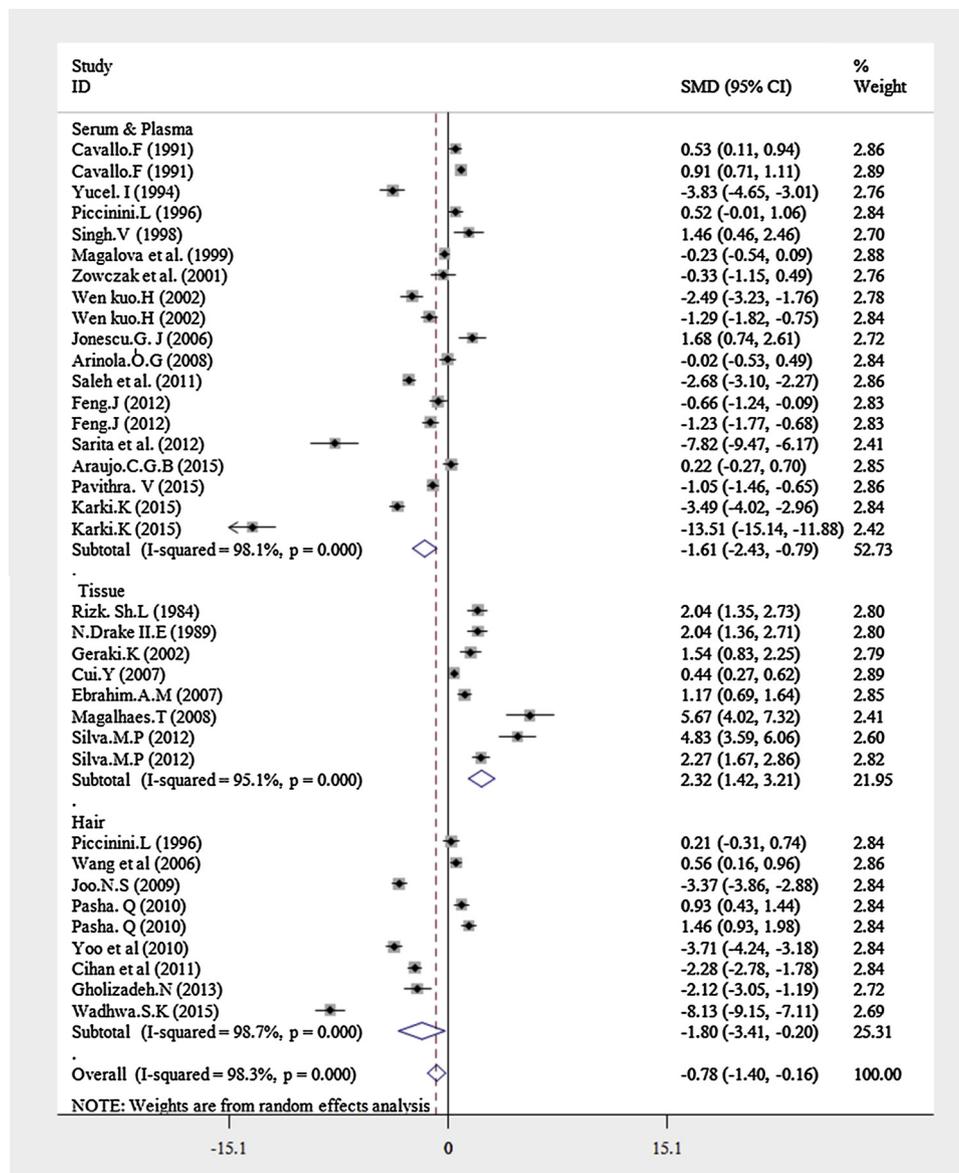


Fig. 4. A meta-analysis of the association of serum and plasma, breast tissues and scalp hair zinc concentration with breast cancer risk. Square represents an effect estimate of individual studies with more than 95 % confidence intervals with the size of squares proportional to the weight assigned to the study in the meta-analysis. In this chart, studies are stored in order of the year of publication and author’s names, based on a random effects model.

95%CI): 1.81 [0.95, 2.67]; P = 0.000; I² = 94.8%). There was no significant statistical difference between Zn statuses of controls and breast cancer patient in African women (SMD (95 %CI): 0.58 [-0.58, 1.74]; p = 0.327). However, only two studies of African women were included in the present analysis (Table 3).

The result of the present study based on breast cancer type showed that there was a significant relation with malignant tumor and risk of breast cancer in breast cancer patients (SMD (95 %CI): -1.95 [-3.65, -0.26] p = 0.024; Z = 2.260. However, this correlation was not observed when study of Silva was included in analysis (SMD (95 % CI): -1.42 [-3.00, 0.16]; p = 0.079; z = 1.76).

Regarding serum zinc, there was no correlation between benign tumor patients and controls (SMD (95 %CI): -1.58 [-3.19, 0.03]; p=0.055). Subgroup analysis based on other factors is indicated in Table 3.

Sensitivity analysis showed that the combined SMDs were all statistically significant and similar to one another, and none of the studies significantly influenced the combined SMD alone (Fig. 5).

Publication bias was studied by Begg’s funnel plot in the meta-

analysis. This plot indicated no significant bias (p = 0.15) (Fig. 6).

4. Discussion

The present meta-analysis was performed to assess if Zn may play a major role in the development and progression of breast cancer, giving insights to comprehend if this cation should exert a strategic function also in other cancers. For instance, several reports show that circulating Zn is dramatically decreased in cases of prostate cancer, which contributes to the development and progression of the malignancy [51–53]. Interestingly, a recent study indicated that prostate cancer might be treated with a Zn ionophore (Clioquinol) [54]. In a study conducted by Shetty et al. (2015), it was observed that salivary Zn levels were significantly decreased in oral pre-cancer and oral cancer patients [55]. However, there were no significant changes in Zn concentrations in hair, nail, and serum samples of patients with laryngeal cancer and controls, according to Golasik et al. (2015) [56]. Altogether, a growing body of evidence indicates that Zn plays a vital role in some bio-processes, including carcinogenesis [57]. It is, therefore, reasonable

Table 3
The results of subgroups in the meta-analysis of zinc levels in breast cancer (*).

	Subgroup	No. of studies	I ²	SMD (95% CI) ⁽¹⁾	P value	Z
Continent	Asia	19	98.3%	-2.71[-3.72, -1.69]	0.000	5.23
	Europe	8	91.8%	0.81[0.23, 1.38]	0.060	2.74
	America	7	94.8%	1.81[0.95, 2.67]	0.000	4.11
	Africa	2	90.9%	0.58[-0.58, 1.74]	0.327	0.98
Type breast cancer	Malignant	8	98.3%	-1.42(-3.00, 0.16)	0.079	1.76
	Benign	7	98.2%	-0.70(-2.44, 1.03)	0.427	0.79
Sample	Serum& plasma	19	98.1%	-1.61(-2.43, -0.79)	0.000	3.83
	Tissue	8	91.4%	2.32(1.42, 3.21)	0.000	5.07
	Hair	9	98.7%	-1.80(-3.41, -0.20)	0.028	2.20
Quality Score	Low	3	96.4%	0.69(-1.31,2.70)	0.499	0.68
	Medium	24	98.3%	-1.48(-2.28,-0.68)	0.000	3.61
	High	6	98.9%	-1.08(-2.61,0.45)	0.000	3.73
Type Study	Case control	26	98.2%	-1.26(-1.93,-0.60)	0.000	3.72
	Cross sectional	5	97.7%	-1.87(-3.58,-0.16)	0.032	2.15
	Paired sample	2	71.7%	1.56(0.71,2.42)	0.000	3.60

(*) In this Table heterogeneity is reported as I², which is the percentage of variation across studies that is due to heterogeneity rather than chance, the possibility that there is an inconsistency of studies' results is very, very low for most features reported in the Tables (p < 0.0001).

(1) SMD (95% CI) or CI₉₅. It indicates the overall confidence interval, chosen for the largest probability range. In the case of considerable heterogeneity, the 'overall prediction interval', for example, 95% PI is preferably indicated, but in our conditions, it corresponds to the SMD95%CI used in the Table.

to assume that this trace element could exert action, directly or indirectly, in the carcinogenic process of breast cancer [52–63].

As reported in multiple studies, BC tissues, in comparison to healthy tissues, contain elevated concentrations of Zn [21,57,64–67]. This is

also strongly supported by the findings in the present study. For humans, Zn is an essential element, especially in terms of proteins and nucleic acids metabolism. It is required for the catalytic activity of at least 300 enzymes [34,68], and is involved in the human immune system, in tissue repair, and in DNA syntheses [69–71]. Changes in Zn homeostasis in BC samples might be ascribed to the role of Zn for tumor growth [62]. Cui et al. (2007) reported that a relatively high level of Zn in breast tissue is associated with an increased risk of BC diagnosis [40]. It has been suggested that accumulations of relatively high concentrations of Zn in benign breast tissue predispose toward an increased risk of BC [24,72,73].

The analysis of 19 studies with discordant data regarding blood concentration of Zn suggested that there is a significantly diminished concentration of Zn in breast cancer patient's serum or plasma compared to controls. Such a decrease in Zn levels may be explained by the increased demands in cancerous tissue due to higher cellular uptake and enzymatic activity of tumors [74].

This is contradictory to the meta-analysis study performed by Wu et al., as their analysis on 16 investigations suggested that there was no difference in serum Zn level in BC patients compared to healthy subjects [22]. They also concluded that serum might not be an ideal source of Zn as a biomarker, while it seems this opinion should be reconsidered and more studies with a standard procedure and larger samples of patients are to be done to resolve the role of blood as a reliable source of Zn status determination. However, the stage of breast cancer might be relevant as regards controversies in circulating trace element concentrations. Contrarily to most of the studies indicating that Cu increases in breast cancer patients, notably Saleh et al. reported lower serum copper levels than controls in breast cancer [75].

Scalp hair samples appear to be a reliable sample type for providing information about relevant clinical parameters [76–79]. Since human scalp hair sampling is considered minimally invasive, such can serve as an alternative for other types of sampling [79]. The fact remains that using hair as a sample type is still controversial [80]. A critical issue not

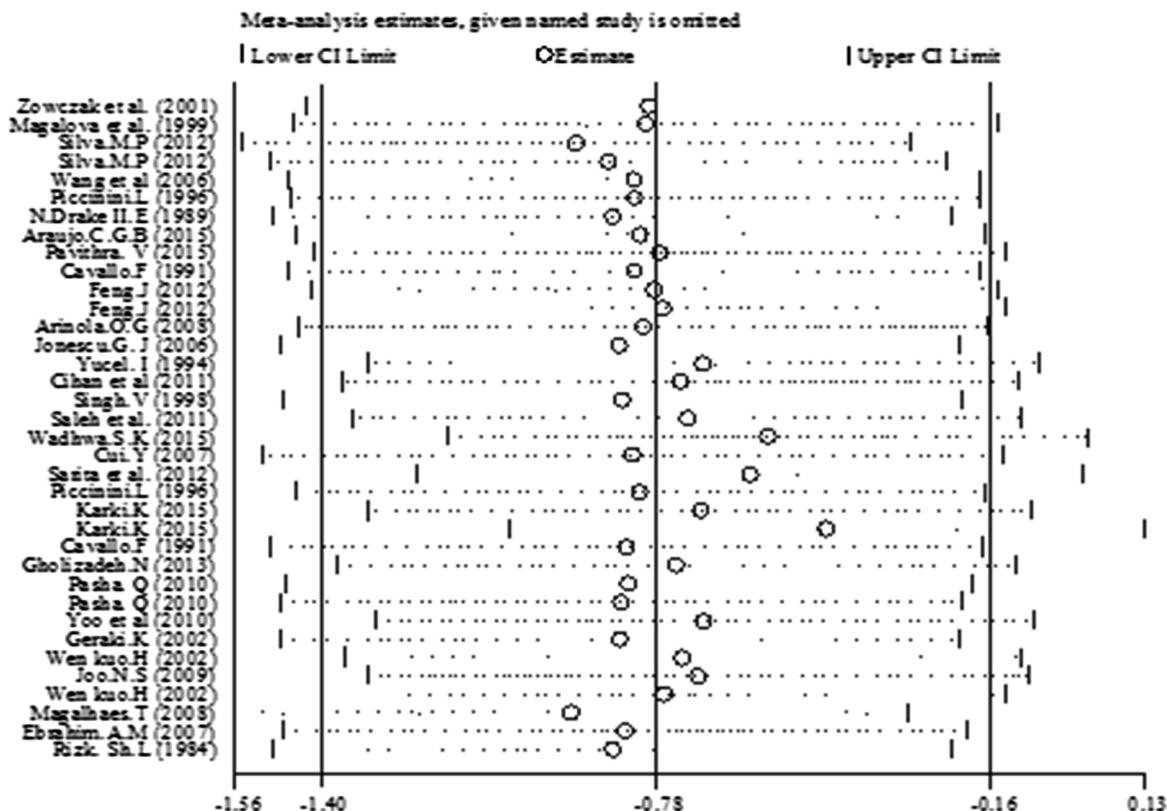


Fig. 5. Sensitivity analysis for studies in overall study zinc for breast cancer patients versus healthy controls.

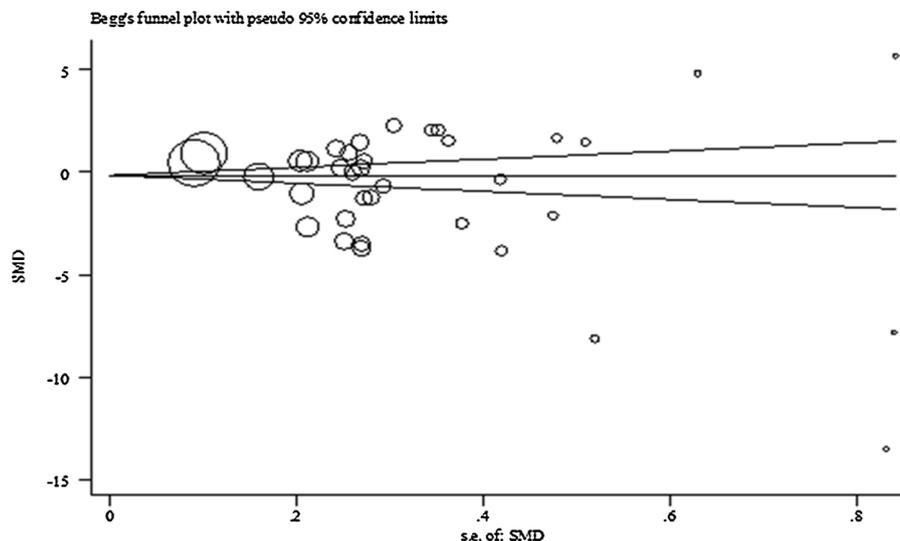


Fig. 6. Begg's funnel plot for publication bias in the risk difference (RD) analysis. The diameter of each circle represents the weight in the meta-analysis.

addressed by the relevant articles is that hair analysis is subject to many confounders, particularly external metal levels that are associated with atmospheric pollutants. In the case of Zn, many hair shampoos, particularly those with anti-dandruff properties, are enriched in Zn, which would confound results of such studies.

5. Conclusion

The present study is a comprehensive study regarding the determination of Zn levels as a biomarker for breast cancer development. The study has demonstrated that Zn concentration levels are typically decreased in blood and hair samples of patients with breast cancer. However, it has been found to be elevated in tumor tissues. The present study also demonstrates that serum and hair samples could be considered a reliable source for Zn biomarker analysis. Because of high heterogeneity, we recommend other primary studies.

Transparency document

The [Transparency document](#) associated with this article can be found in the online version.

Declaration of Competing Interest

The authors have no competing interest.

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