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The Association Between Serum Levels of Selenium, Copper, and Magnesium with Thyroid Cancer: a Meta-analysis

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Abstract There are conflicting reports on the correlation between serum levels of selenium (Se), copper (Cu), and magnesium (Mg) with thyroid cancer. The purpose of the present study is to clarify the association between Se, Cu, and Mg levels with thyroid cancer using a meta-analysis approach. We searched articles indexed in PubMed published as of January 2015 that met our predefined criteria. Eight eligible articles involving 1291 subjects were identified. Overall, pooled analysis indicated that subjects with thyroid cancer had lower serum levels of Se and Mg, but higher levels of Cu than the healthy controls [Se: standardized mean difference (SMD)= −0.485, 95% confidence interval (95%CI)=(−0.878, −0.092), p=0.016; Cu: SMD=2.372, 95%CI=(0.945, 3.799), p= 0.001; Mg: SMD=−0.795, 95%CI=(−1.092, −0.498), p<0.001]. Further subgroup analysis found lower serum levels of Se in thyroid cancer in Norway [SMD=−0.410, 95%CI=(−0.758, −0.062), p=0.021] and Austria [SMD= −0.549, 95%CI=(−0.743, −0.355), p<0.001], but not in Poland (SMD=−0.417, 95%CI=(−1.724, 0.891), p=0.532]. Further subgroup analysis also found that patients with thyroid cancer had higher serum levels of Cu in China [SMD= 1.571, 95%CI=(1.121, 2.020), p<0.001] and Turkey [SMD= 0.977, 95%CI=(0.521, 1.432), p<0.001], but not in Poland [SMD=3.471, 95%CI=(−0.056, 6.997], p=0.054]. In conclusion, this meta-analysis supports a significant association between serum levels of Se, Cu, and Mg with thyroid cancer. However, the subgroup analysis found that there was significant effect modification of Se, Cu levels by ethnic, like China and Poland. Thus, this finding needs further confirmation by a trans-regional multicenter study to obtain better understanding of causal relationship between Se, Cu, and Mg with thyroid cancer of different human races or regions.

Keywords Selenium · Copper · Magnesium · Thyroid cancer · Meta-analysis

Introduction

Trace elements are essential micronutrients for many physiological processes and are involved in many pathological changes in tissues [1]. The concentration of these elements in the thyroid gland is higher than in any other tissues [2]. More than 20 chemical elements influence the normal physiology of the thyroid gland [2, 3]. Previous meta-analysis study provides evidence on cancer-specific tissue zinc level alteration and suggests association between low zinc levels with most tumors, especially thyroid cancer [4].

Normal thyroid function depends on the presence of many trace elements for both synthesis and metabolism of thyroid hormones [5]. It is frequently assumed that trace element disturbances, such as selenium (Se), copper (Cu), and magnesium (Mg), are important risk factors for thyroid cancer [6–8]. Se incorporates into selenoproteins within cells, which is vital for the removal of damaging peroxides, reduction of oxidized proteins and membranes, regulation of intracellular reduction–oxidation signaling, and thyroid hormone

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metabolism [9]. Se concentration is higher within the thyroid than in other tissues, and Se is important for thyroid hormone metabolism [10, 11]. Cu has many important physiological functions as redox active element in maintaining thyroid activity and lipid metabolism. Cu is incorporated in the production of hemoglobin, myelin, and melanin and is essential for thyroid gland functioning [12], by stimulating production of thyroxin hormone (T4) and preventing over absorption of T4 by controlling the calcium levels. Cu can act both as antioxidant and pro-oxidant. As an antioxidant, Cu scavenges or neutralizes free radicals and may reduce or prevent some of the damage caused by them [13–15]. A high concentration of Cu can induce growth proliferation and cancer by damaging deoxyribonucleic acid (DNA) with toxic free hydroxyl radicals [16]. Experimental and clinical data have suggested that Mg deficiency might be associated with inflammation and/or increased levels of free radicals, which might lead to oxidative DNA damage and cancer formation [17, 18]. Mg is known to stabilize the structure of nucleic acids and is a vital cofactor of enzymes involved in DNA replication, repair, and gene expression; thus, any Mg deficiency may contribute to defect in these systems and appearance of DNA mutations, which may thereby lead to tumor-genesis [19, 20]. Some clinical studies show that there is a significant relationship between serum levels of Se, Cu, and Mg with thyroid cancer, indicating that patients with thyroid cancer have lower serum levels of Se and Mg and higher Cu levels than healthy control [15, 21–26]. However, other clinical studies find no association between serum level of Se and Cu with thyroid cancer [27]. Although serum Se, Cu, or Mg disturbance is plausibly linked to thyroid cancer, the inconsistency among the findings of previous studies precludes definitive recommendations at present.

Meta-analysis is an important tool for revealing trends that might not be apparent. Therefore, we performed a comprehensive and critical review of the studies, in order to draw a more clear and evidence-based conclusion on the association between serum levels of selenium, copper, and magnesium with thyroid cancer.

Methods

Search Strategy

We searched all English written articles indexed in PubMed published up to January 2015. Literature searches were performed using medical subject heading (MeSH) or free text words. The searching keywords were (“serum selenium”

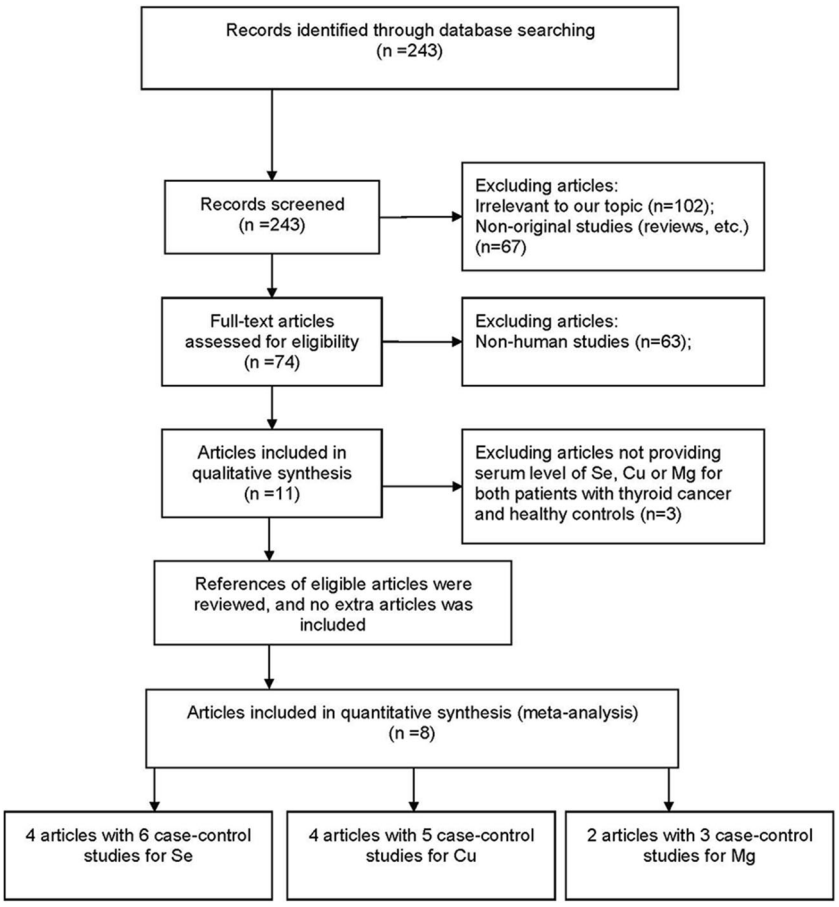


Fig. 1 Flow diagram of screened and included papers

Table 1 Characteristics of subjects in eligible studies

Studies	Country	Measurement	Age (year)	Thyroid cancer		Age (year)	Healthy controls		Weight (%)	SMD (95%CI)	Quality score
				N	Element concentration (mean±SD)		*N*	Element concentration (mean±SD)			
For selenium											
Glattre 1989	Norway	AAS	51.2	43	0.110±0.014 μg/ml	51.2	129	0.116±0.016 μg/ml	18.61	−0.410 (−0.758, −0.062)	7
Kucharzewski 2002	Poland	TRXRF	14–72	21	0.543±0.114 μg/ml	15–45	50	0.676±0.057 μg/ml	14.72	−1.707 (−2.290, −1.123)	7
Moncayo 2008 (1)	Austria	AAS	NA	42	0.076±0.021 μg/ml	41±17	554	0.090±0.021 μg/ml	19.10	−0.652 (−0.967, −0.336)	5
Moncayo 2008 (2)	Austria	AAS	NA	73	0.080±0.020 μg/ml	41±17	554	0.090±0.021 μg/ml	20.08	−0.487 (−0.732, −0.241)	5
Przybylik-Mazurek 2011 (1)	Poland	AAS	51.6±13.4	25	0.062±0.009 μg/ml	37.7±9.3	20	0.060±0.009 μg/ml	14.63	0.167 (−0.422, 0.756)	6
Przybylik-Mazurek 2011 (2)	Poland	AAS	52.5±15.3	13	0.063±0.011 μg/ml	37.7±9.3	20	0.060±0.009 μg/ml	12.85	0.312 (−0.390, 1.015)	6
For copper											
Leung 1996	China	AES	52.2	50	1.08±0.24 μg/ml	49.6	50	0.74±0.19 μg/ml	21.11	1.571 (1.121, 2.020)	6
Kucharzewski 2003	Poland	TRXRF	14–72	21	1.92±0.22 μg/ml	15–45	50	0.69±0.06 μg/ml	16.56	9.645 (7.957, 11.333)	6
Przybylik-Mazurek 2011 (1)	Poland	AAS	NA	25	1.25±0.24 μg/ml	41±17	20	1.11±0.19 μg/ml	20.76	0.675 (0.070, 1.280)	5
Przybylik-Mazurek 2011 (2)	Poland	AAS	NA	13	1.20±0.22 μg/ml	41±17	20	1.11±0.19 μg/ml	20.47	0.475 (−0.234, 1.183)	5
Kosova 2012	Turkey	AAS	41±13	47	1.32±0.34 μg/ml	42±13	37	1.06±0.11 μg/ml	21.10	0.977 (0.521, 1.432)	7
For magnesium											
Leung 1996	China	AES	52.2	50	20.67±1.77 μg/ml	49.6	50	22.34±2.67 μg/ml	53.65	−0.737 (−1.143, −0.332)	7
Al-Sayer 2004 (1)	Kuwait	AAS	33.8±5.4	22	14.61±4.18 μg/ml	18–53	23	17.60±4.00 μg/ml	22.72	−1.018 (−1.641, −0.395)	6
Al-Sayer 2004 (2)	Kuwait	AAS	31±8.2	21	15.70±3.85 μg/ml	18–53	23	17.60±4.00 μg/ml	23.63	−0.712 (−1.322, −0.101)	6

AAS atomic absorption spectrometry, *TRXRF* total reflection X-ray fluorescence, *AES* atomic emission spectrometry, *NA* not available

OR selenium OR "serum copper" OR copper OR "serum magnesium" OR magnesium) AND thyroid cancer. Reference lists of all eligible studies were screened to identify potentially eligible studies. Emails were sent to the authors of identified studies for additional information if necessary.

Selection Criteria

Three authors (Fei Shen, Jie Cao, and Bo Xu) conducted the search independently. Titles and abstracts were screened for subject relevance. Studies that could not be definitely excluded based on abstract information were also selected for full text screening. Two authors (Fei Shen and Jie Cao) independently selected eligible studies for inclusion possibility. Where there was a disagreement for study inclusion, a discussion was held (with Bo Xu) to reach a consensus. The included studies should meet the following criteria: (1) human study; (2) case–control study or cohort study; (3) studies focusing on the association between serum levels of Se, Cu, or Mg and thyroid cancer; (4) studies providing serum levels of Se, Cu, or Mg for both subjects with thyroid cancer and healthy controls; and (5) subjects with no other diseases and no drugs intake which might influence the serum levels of Se, Cu, or Mg. Exclusion criteria included the following: (1) in vitro or laboratory study; (2) animal study; (3) review or case report; (4) studies not providing serum levels of Se, Cu, or Mg for both subjects with thyroid cancer and healthy controls; (5) subjects with diseases/drugs (for Se: Keshan disease, Kashin–Beck disease, heart disease, high blood pressure, and breast cancer; for Cu: hepatocirrhosis, hepatitis, obstructive jaundice, anemia, leukemia, kidney disease, Wilson's syndrome, Addison disease, curly hair syndrome, oral zinc intake, oral Cu intake, and contraceptive medicine intake; for Mg: kidney disease, acute myocardial infarction, hypofunction of thyroid gland, hypoparathyroidism, hyperthyroidism, hyperparathyroidism, Addison's disease, multiple myeloma, acute viral hepatitis, amoebic liver abscess, liver cirrhosis, arthritis, and oral Mg intake), which might influence the serum levels of Se, Cu, or Mg; and (6) sample size <10.

Data Extraction and Quality Assessment

The following information was extracted from each included study: first author's family name; year of publication; type of study; country; demography of subjects (age and number of patients); data on serum levels of Se, Cu, or Mg; and type of trace elements measurement. Two authors (Wen-Song Cai and Jiang-Lin Li) independently extracted data using a standard form.

Two authors (Fei Shen and Zhe Feng) assessed the quality independently. The qualities of all included studies were assessed using the Newcastle–Ottawa Scale (NOS) (Supplement Material Figure S1) [28]. Using the tool, each study is judged on eight items, categorized into three groups: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to nine stars. Studies were graded as good quality if they awarded six to nine stars, fair if they awarded three to five stars, and poor if they awarded less than three stars.

Statistical Analysis

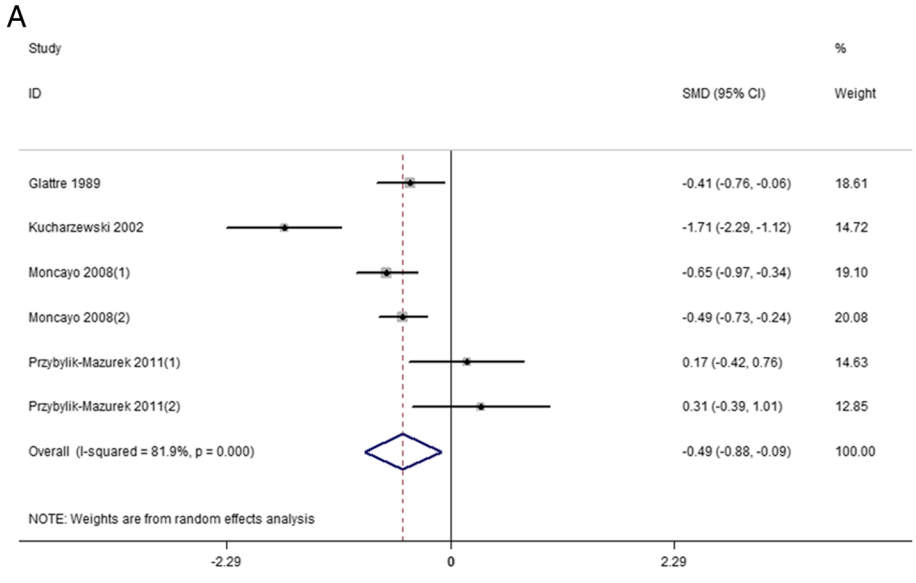
The extracted data were used to perform meta-analysis to obtain the standardized mean difference (SMD) and 95% confidence intervals (CI). The SMDs were calculated using either fixed-effects models or, in the presence of heterogeneity, random-effects models. Heterogeneity between studies was tested through the chi-square and *I*-square tests. If the I^2 value was >50%, and the $p<0.05$, the meta-analysis was considered as homogeneous. Subgroup analyses involve splitting all the participant data into subgroups, often so as to make comparisons between them, which can be done as a means of investigating heterogeneous results. Subgroup analyses stratified by the ethnicity/country and type of measurement were used to identify associations between serum levels of Se, Cu, or Mg and other relevant study characteristics as possible sources of heterogeneity. Publication bias was defined as the publication or nonpublication of studies depending on the direction and statistical significance of the results and was measured using Begg's test and visualization of funnel plot. The stability of the study was also detected by sensitivity analysis, through re-meta-analysis with one involved study excluded each time. All statistical analyses were performed with Stata version 11.0 (StataCorp, College Station, TX, USA).

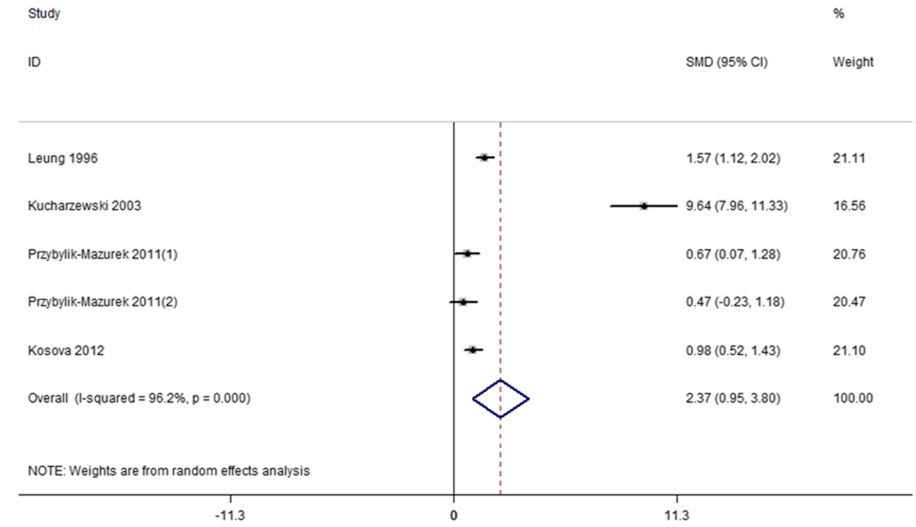
Results

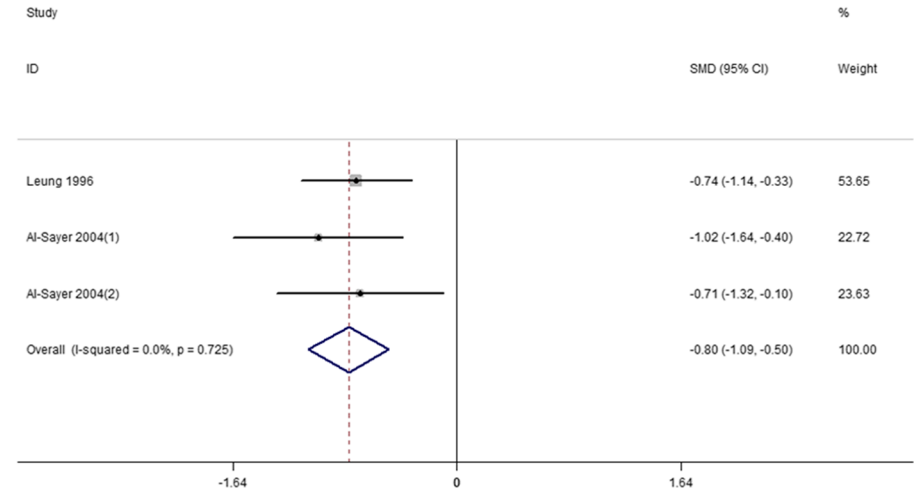
Literature Search

The literature search yielded a total of 243 primary articles. These articles were included for full-text assessment, of which 235 were excluded for one of the following reasons: (1) irrelevant to our topic ($n=102$), (2) non-original studies (reviews, etc.) ($n=67$), (3) non-human studies ($n=63$), (4) articles not providing serum level of Se, Cu, or Mg for both subjects with

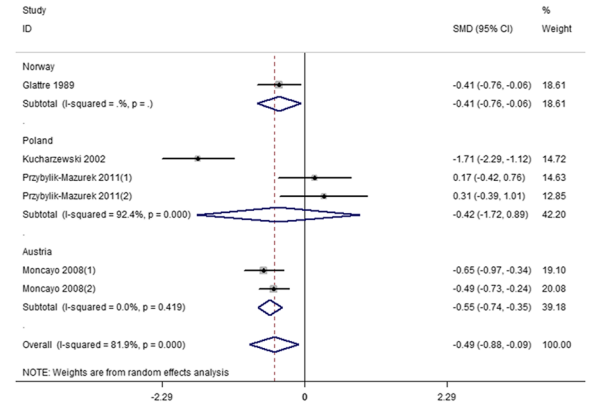
Fig. 2 Forest plots of studies in Se, Cu, and Mg levels for subjects with thyroid cancer versus healthy controls. The combined SMD and 95 % confidence intervals (CIs) were calculated using the random-effects model. **a** For serum Se, **b** for serum Cu, and **c** for serum Mg


A
Study
ID
SMD (95% CI)
%
Weight
Glattre 1989
-0.41 (-0.76, -0.06)
18.61
Kucharzewski 2002
-1.71 (-2.29, -1.12)
14.72
Moncayo 2008(1)
-0.65 (-0.97, -0.34)
19.10
Moncayo 2008(2)
-0.49 (-0.73, -0.24)
20.08
Przybylik-Mazurek 2011(1)
0.17 (-0.42, 0.76)
14.63
Przybylik-Mazurek 2011(2)
0.31 (-0.39, 1.01)
12.85
Overall (I-squared = 81.9%, p = 0.000)
-0.49 (-0.88, -0.09)
100.00
NOTE: Weights are from random effects analysis
-2.29
0
2.29

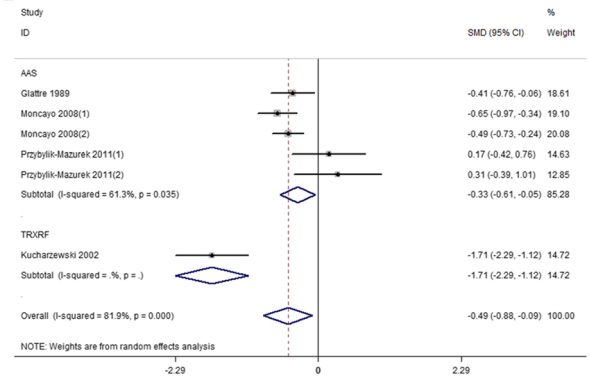

B
Study
ID
SMD (95% CI)
%
Weight
Leung 1996
1.57 (1.12, 2.02)
21.11
Kucharzewski 2003
9.64 (7.96, 11.33)
16.56
Przybylik-Mazurek 2011(1)
0.67 (0.07, 1.28)
20.76
Przybylik-Mazurek 2011(2)
0.47 (-0.23, 1.18)
20.47
Kosova 2012
0.98 (0.52, 1.43)
21.10
Overall (I-squared = 96.2%, p = 0.000)
2.37 (0.95, 3.80)
100.00
NOTE: Weights are from random effects analysis
-11.3
0
11.3


C
Study
ID
SMD (95% CI)
%
Weight
Leung 1996
-0.74 (-1.14, -0.33)
53.65
Al-Sayer 2004(1)
-1.02 (-1.64, -0.40)
22.72
Al-Sayer 2004(2)
-0.71 (-1.32, -0.10)
23.63
Overall (I-squared = 0.0%, p = 0.725)
-0.80 (-1.09, -0.50)
100.00
-1.64
0
1.64

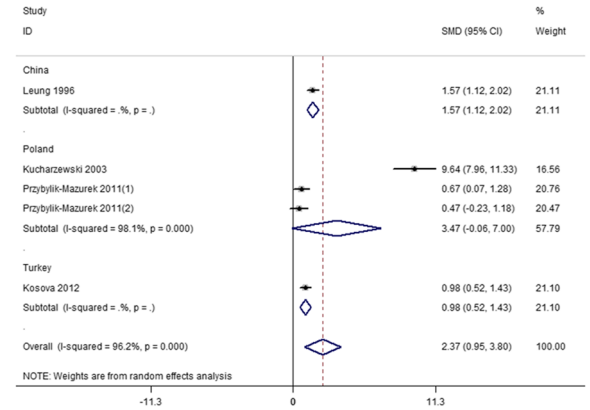
A


Study
ID
SMD (95% CI)
%
Weight
Norway
Glattre 1989 -0.41 (-0.76, -0.06) 18.61
Subtotal (I-squared = .%, p = .) -0.41 (-0.76, -0.06) 18.61
Poland
Kucharzewski 2002 -1.71 (-2.29, -1.12) 14.72
Przybylik-Mazurek 2011(1) 0.17 (-0.42, 0.76) 14.63
Przybylik-Mazurek 2011(2) 0.31 (-0.39, 1.01) 12.85
Subtotal (I-squared = 92.4%, p = 0.000) -0.42 (-1.72, 0.89) 42.20
Austria
Moncayo 2008(1) -0.65 (-0.97, -0.34) 19.10
Moncayo 2008(2) -0.49 (-0.73, -0.24) 20.08
Subtotal (I-squared = 0.0%, p = 0.419) -0.55 (-0.74, -0.35) 39.18
Overall (I-squared = 81.9%, p = 0.000) -0.49 (-0.88, -0.09) 100.00
NOTE: Weights are from random effects analysis
-2.29
0
2.29

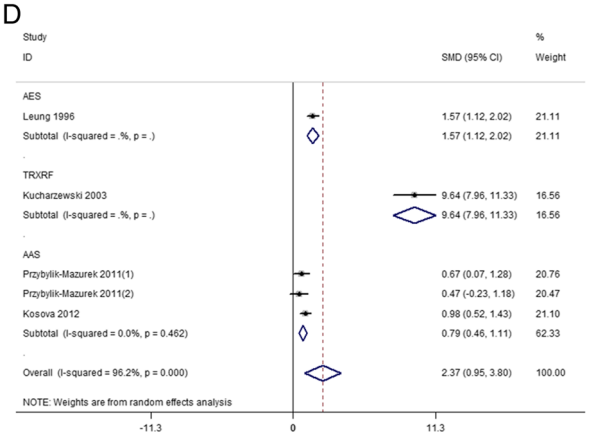
B


Study
ID
SMD (95% CI)
%
Weight
AAS
Glattre 1989 -0.41 (-0.76, -0.06) 18.61
Moncayo 2008(1) -0.65 (-0.97, -0.34) 19.10
Moncayo 2008(2) -0.49 (-0.73, -0.24) 20.08
Przybylik-Mazurek 2011(1) 0.17 (-0.42, 0.76) 14.63
Przybylik-Mazurek 2011(2) 0.31 (-0.39, 1.01) 12.85
Subtotal (I-squared = 61.3%, p = 0.035) -0.33 (-0.61, -0.05) 85.28
TRXRF
Kucharzewski 2002 -1.71 (-2.29, -1.12) 14.72
Subtotal (I-squared = .%, p = .) -1.71 (-2.29, -1.12) 14.72
Overall (I-squared = 81.9%, p = 0.000) -0.49 (-0.88, -0.09) 100.00
NOTE: Weights are from random effects analysis
-2.29
0
2.29

C


Study
ID
SMD (95% CI)
%
Weight
China
Leung 1996 1.57 (1.12, 2.02) 21.11
Subtotal (I-squared = .%, p = .) 1.57 (1.12, 2.02) 21.11
Poland
Kucharzewski 2003 9.64 (7.96, 11.33) 16.56
Przybylik-Mazurek 2011(1) 0.67 (0.07, 1.28) 20.76
Przybylik-Mazurek 2011(2) 0.47 (-0.23, 1.18) 20.47
Subtotal (I-squared = 98.1%, p = 0.000) 3.47 (-0.06, 7.00) 57.79
Turkey
Kosova 2012 0.98 (0.52, 1.43) 21.10
Subtotal (I-squared = .%, p = .) 0.98 (0.52, 1.43) 21.10
Overall (I-squared = 96.2%, p = 0.000) 2.37 (0.95, 3.80) 100.00
NOTE: Weights are from random effects analysis
-11.3
0
11.3

D


Study
ID
SMD (95% CI)
%
Weight
AES
Leung 1996 1.57 (1.12, 2.02) 21.11
Subtotal (I-squared = .%, p = .) 1.57 (1.12, 2.02) 21.11
TRXRF
Kucharzewski 2003 9.64 (7.96, 11.33) 16.56
Subtotal (I-squared = .%, p = .) 9.64 (7.96, 11.33) 16.56
AAS
Przybylik-Mazurek 2011(1) 0.67 (0.07, 1.28) 20.76
Przybylik-Mazurek 2011(2) 0.47 (-0.23, 1.18) 20.47
Kosova 2012 0.98 (0.52, 1.43) 21.10
Subtotal (I-squared = 0.0%, p = 0.462) 0.79 (0.46, 1.11) 62.33
Overall (I-squared = 96.2%, p = 0.000) 2.37 (0.95, 3.80) 100.00
NOTE: Weights are from random effects analysis
-11.3
0
11.3

thyroid cancer and healthy controls (n=3). Overall, 8 eligible articles with 1291 subjects met the inclusion criteria for meta-analysis: 4 articles with 6 case–control studies for Se, 4 articles with 5 case–control studies for Cu, and 2 articles with 3 case–control studies for Mg [15, 21–27]. Of note, two articles involved more than one trace element and were included in more than one group. A flow diagram of the study selection process is presented in Fig. 1.

Study Characteristics and Quality Assessment

The characteristics of the included studies and the results of the quality assessment are listed in Table 1. The earliest study was published in 1989, and the latest in 2012. By geographic location, 8 articles with 14 case–control studies were conducted in 6 different countries (Norway, Poland, Austria, Turkey, China, and Kuwait). The number of subjects in each study ranged from 33 to 627. Five articles with ten case–control studies measured Se, Cu, or Mg concentration by atomic absorption spectrometry (AAS); two articles with two case–control studies measured Se or Cu concentration by total reflection X-ray fluorescence (TRXRF); while one article with two case–control studies measured Cu or Mg concentration by atomic emission spectrometry (AES). The overall study quality averaged six stars on a scale of 0–9.

Serum Se and Thyroid Cancer

The random-effects meta-analysis results indicated that patients with thyroid cancer had lower serum levels of Se than the healthy controls [SMD=−0.485, 95%CI=(−0.878, −0.092), p=0.016]. The six sets of results showed a statistically significant amount of heterogeneity (I^2=98.3%, p<0.001) (Fig. 2a).

The subgroup analysis showed that geographical location and type of Se measurement had an influence on the serum levels of Se in thyroid cancer and healthy controls. Further subgroup analysis stratified by geographical location indicated that subjects with thyroid cancer had higher serum Se levels than healthy controls in Norway [SMD=−0.410, 95%CI=(−0.758, −0.062), p=0.021] and Austria [SMD=−0.549, 95%CI=(−0.743, −0.355), p<0.001], but not in Poland [SMD=−0.417, 95%CI=(−1.724, 0.891), p=0.532] (Fig. 3a). The difference of serum Se levels between thyroid cancer and healthy controls measured by TRXRF [SMD=−1.707, 95%CI=(−2.290, −1.123), p<0.001] was higher than that by AAS [SMD=−0.331, 95%CI=(−0.612, −0.050), p=0.021] (Fig. 3b). The further subgroup analysis stratified by type of measurement can successfully reduce the heterogeneity of studies (Table 2).

◀ **Fig. 3** Subgroup analyses of studies in Se and Cu levels for subjects with thyroid cancer versus healthy controls. **a** Serum Se stratified by country. **b** Serum Se stratified by type of measurement. **c** Serum Cu stratified by country. **d** Serum Cu stratified by type of measurement

Serum Cu and Thyroid Cancer

The random-effects meta-analysis results indicated that patients with thyroid cancer had higher serum levels of Cu than the healthy controls [SMD=2.372, 95%CI=(0.945, 3.799), p=0.001]. The five sets of results showed a statistically significant amount of heterogeneity (I^2=96.2%, p<0.001) (Fig. 2b).

The subgroup analysis showed that geographical location and type of Cu measurement had an influence on the serum levels of Cu in thyroid cancer and healthy controls. Further subgroup analysis stratified by geographical location indicated that subjects with thyroid cancer had higher serum Cu levels than healthy controls in China [SMD=1.571, 95%CI=(1.121, 2.020), p<0.001] and Turkey [SMD=0.977, 95%CI=(0.521, 1.432), p<0.001], but not in Poland [SMD=3.471, 95%CI=(−0.056, 6.997), p=0.054] (Fig. 3c). The

Table 2 Differences between studies by subgroup analysis

Subgroups	No. of case–control studies	SMD (95%CI)	I^2 (%)	p value
For selenium				
Geographical location				
Norway	1	−0.410 (−0.758, −0.062)	0	0.021
Poland	3	−0.417 (−1.724, 0.891)	92.4	0.532
Austria	2	−0.549 (−0.743, −0.355)	0	0.016
Type of measurement				
AAS	5	−0.331 (−0.612, −0.050)	61.3	0.021
TRXRF	1	−1.707 (−2.290, −1.123)	0	<0.001
For copper				
Geographical location				
China	1	1.571 (1.121, 2.020)	0	<0.001
Poland	3	3.471 (−0.056, 6.997)	98.1	0.054
Turkey	1	0.977 (0.521, 1.432)	0	<0.001
Type of measurement				
AAS	3	0.785 (0.461, 1.109)	0	<0.001
TRXRF	1	9.645 (7.957, 11.333)	0	<0.001
AES	1	1.571 (1.121, 2.020)	0	<0.001

difference of serum Cu levels between thyroid cancer and healthy controls measured by TRXRF [SMD=9.645, 95%CI=(7.957, 11.333), $p<0.001$] was higher than that by AAS [SMD=0.785, 95%CI=(0.461, 1.109), $p<0.001$] and AES [SMD=1.571, 95%CI=(1.121, 2.020), $p<0.001$] (Fig. 3d). The further subgroup analysis stratified by type of

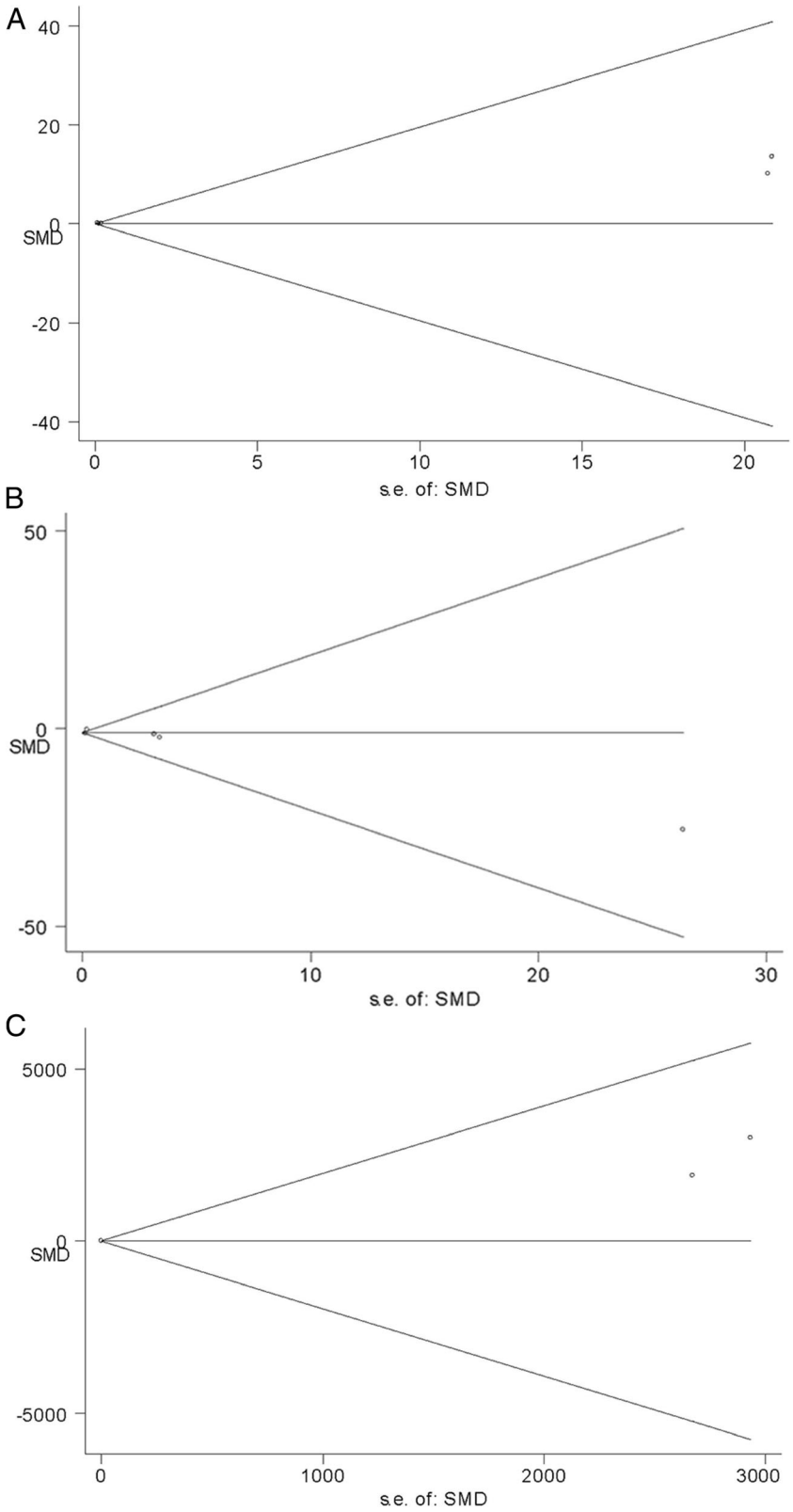


Fig. 4 Funnel plots of studies in Se, Cu, and Mg levels for subjects with thyroid cancer versus healthy controls. **a** For serum Se. **b** For serum Cu. **c** For serum Mg

measurement can successfully eliminate the heterogeneity of studies (Table 2).

Serum Mg and Thyroid Cancer

The fixed-effects meta-analysis results indicated that patients with thyroid cancer had lower serum levels of Mg than healthy controls [SMD=−0.795, 95%CI=(−1.092, −0.498), $p<0.001$]. The three sets of results showed no significant amount of heterogeneity ($I^2=0$, $p=0.725$) (Fig. 2c).

Publication Bias and Sensitivity Analysis

Publication bias was measured using Begg's tests and visualization of funnel plots. There was no evidence of publication bias for Se (Begg's test, $p=0.604$), Cu (Begg's test, $p=0.806$), and Mg (Begg's test, $p=0.296$) (Fig. 4). Sensitivity analysis showed that excluding the studies performed by Kucharzewski in 2002 and in 2003 can reduce the heterogeneity of studies for serum Se and Cu, respectively (Table 3).

Table 3 The heterogeneity of the included studies through sensitivity analysis

Excluded study arm	SMD (95%CI)	I^2 (%)	p value
For selenium			
Before excluding	−0.485 (−0.878, −0.092)	81.9	0.016
Glattre 1989	−0.496 (−0.998, 0.005)	85.3	0.052
Kucharzewski 2002	−0.331 (−0.612, −0.050)	61.3	0.021
Moncayo 2008 (1)	−0.441 (−0.952, 0.069)	85.0	0.090
Moncayo 2008 (2)	−0.476 (−1.026, 0.074)	85.5	0.090
Przybylik-Mazurek 2011 (1)	−0.597 (−1.005, −0.189)	81.9	0.004
Przybylik-Mazurek 2011 (2)	−0.601 (−0.998, −0.204)	81.9	0.003
For copper			
Before excluding	2.372 (0.945, 3.799)	96.2	0.001
Leung 1996	2.712 (0.669, 4.755)	97.1	0.009
Kucharzewski 2003	0.970 (0.494, 1.446)	67.6	<0.001
Przybylik-Mazurek 2011 (1)	2.892 (1.055, 4.730)	97.1	0.002
Przybylik-Mazurek 2011 (2)	2.914 (1.161, 4.666)	97.0	0.001
Kosova 2012	2.867 (0.825, 4.908)	97.1	0.006
For magnesium			
Before excluding	−0.795 (−1.092, −0.498)	0	<0.001
Leung 1996	−0.862 (−1.298, −0.426)	0	<0.001
Al-Sayer 2004 (1)	−0.729 (−1.067, −0.392)	0	<0.001
Al-Sayer 2004 (2)	−0.821 (−1.161, −0.481)	0	<0.001

Discussion

The result of random-effects meta-analysis indicated that the low serum levels of Se was associated with thyroid cancer. This may reflect the increased risk of thyroid cancer in patients with low serum Se levels and confirm the results of other studies. In a review of an article conducted by Rayman, the relationship between selenium and cancer was examined. This review showed that selenium has anticancer activities [29]. Many studies have shown that there is an association between selenium diet and cancer risk [6, 10, 23, 30–32]. Selenium nutritional supplements may reduce incidence of cancer [33]. Jonklaas et al. [9] has shown that serum selenium concentrations were inversely correlated with thyroid cancer stage. Although the specific selenium anticarcinogenic mechanisms are not yet fully known, multiple mechanisms have been proposed to explain these selenium characteristics. Actually, antioxidant properties of selenoenzymes are relevant in carcinogenesis and tumor progression [34]. Selenium is present in glutathione peroxidase, which protects the DNA and main cellular components from the damage of the free radicals by decreasing ROS generation; in this way, levels of dietary antioxidant vitamins and carotenoids that affect antioxidant selenoproteins modify the effect of selenium on cancer risk [35–37]. In addition, selenium enhances tumor-suppressor protein p53 activates that inhibits proliferation, increases DNA repair, and promotes apoptosis [38, 39].

The outcome of this meta-analysis also suggested that patients with thyroid cancer had higher serum levels of Cu than the healthy controls. Cu is believed to be the switch that turns on the angiogenesis process in tumor cells. Cu is cofactor of superoxide dismutase 1, which prevents the onset and progression of tumors through mechanisms of cell protection against free radicals production [40]. A high concentration of Cu can induce growth proliferation and cancer by damaging DNA with toxic free hydroxyl radicals [16]. Abnormally high serum Cu levels are found in the patients with many types of progressive tumors, making Cu an obligatory cofactor in angiogenesis process [41]. In a review by Blazewicz et al. [42], the concentration of Cu was significantly higher in the healthy thyroid in comparison with the group of benign thyroid disease. Another study found that the postoperative serum Cu levels were significantly decreased compared to those of preoperative in the benign thyroid disease [25].

The present study still found that low serum level of Mg was associated with thyroid cancer. It has been found that magnesium could impact carcinogenesis by two mechanisms [20]. Mg deficiency might be associated with inflammation and/or increased levels of free radicals. Mg-deficient animals show an increased susceptibility to in vivo oxidative stress, and their tissues are more susceptible to in vitro peroxidation [18]. There is convincing evidence from other animal studies that Mg could exert a protective effect in the early stages of carcinogenesis [17]. Mg inhibits lead- and nickel-induced carcinogenesis in the rat kidney and 3-methylcholantrene-

induced fibro-sarcomas in rats [43, 44]. It has been reported that Mg supplementation reduces the incidence of experimentally induced colon cancer in animals, which might be related to a decrease in colonic epithelial cell proliferation [45, 46]. Some studies found that a diet poor in magnesium increases the incidences of thymic tumors and leukemias [47, 48].

To the best of our knowledge, this is the first meta-analysis to estimate the association between serum levels of Se, Cu, and Mg with thyroid cancer. However, the possible limitations of our study must be considered. First, our results showed strong heterogeneity among the studies for Cu and Se. Heterogeneity indicates differences in results across the studies. In present study, the further subgroup analysis indicated that the type of Cu and Se measurement was the source of heterogeneity. We found that the further subgroup analysis stratified by type of measurement can successfully eliminate the heterogeneity of studies for Cu, and reduce the heterogeneity of studies for Se. Second, only 1291 subjects from 8 articles and no randomized clinical trial included in the meta-analysis might weaken the quality of the results. Despite these limitations, our findings point out new directions for future research, like what is the compound effect of multiple risk factors on thyroid cancer. For instance, what is the risk of thyroid cancer with both Se and Cu disturbances? To answer this question, several well designed studies with adequate control for confounding factors should be considered. In addition, our results showed the ethnic/geographical paradox; therefore, a trans-regional multicenter study is needed for the investigation of the interrelationship between Se, Cu, and Mg with thyroid cancer of different human races or regions.

In conclusion, this meta-analysis supports a significant association between serum levels of Se, Cu, and Mg with thyroid cancer.

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Conflict of Interest The authors report no conflict of interest.

References

1. Margalioth EJ, Schenker JG, Chevion M (1983) Copper and zinc levels in normal and malignant tissues. Cancer 52:868–872
2. Zaichick V, Tsyb AF, Vtyurin BM (1995) Trace elements and thyroid cancer. Analyst 120:817–821
3. Cayir A, Doneray H, Kurt N, Orbak Z, Kaya A et al (2014) Thyroid functions and trace elements in pediatric patients with exogenous obesity. Biol Trace Elem Res 157:95–100
4. Gumulec J, Masarik M, Adam V, Eckschlager T, Provaznik I et al (2014) Serum and tissue zinc in epithelial malignancies: a meta-analysis. PLoS One 9:e99790
5. Arthur JR, Beckett GJ (1999) Thyroid function. Br Med Bull 55: 658–668
6. Duntas LH (2006) The role of selenium in thyroid autoimmunity and cancer. Thyroid 16:455–460
7. Blaszczyk U, Duda-Chodak A (2013) Magnesium: its role in nutrition and carcinogenesis. Rocz Panstw Zakl Hig 64:165–171
8. Dragutinovic VV, Tatic SB, Nikolic-Mandic SD, Tripkovic TM, Dunderovic DM et al (2014) Copper as ancillary diagnostic tool in preoperative evaluation of possible papillary thyroid carcinoma in patients with benign thyroid disease. Biol Trace Elem Res 160: 311–315
9. Jonklaas J, Danielsen M, Wang H (2013) A pilot study of serum selenium, vitamin D, and thyrotropin concentrations in patients with thyroid cancer. Thyroid 23:1079–1086
10. Li X, Ding J, Li X, Ba C, Duan A et al (2006) Clinical value of determination of trace elements in serum in breast cancer. Inner Mongolia Med J 38:799–800
11. Kohrle J (2005) Selenium and the control of thyroid hormone metabolism. Thyroid 15:841–853
12. Harris ED (2001) Copper homeostasis: the role of cellular transporters. Nutr Rev 59:281–285
13. Araya M, Pizarro F, Olivares M, Arredondo M, Gonzalez M et al (2006) Understanding copper homeostasis in humans and copper effects on health. Biol Res 39:183–187
14. Bonham M, O'Connor JM, Hannigan BM, Strain JJ (2002) The immune system as a physiological indicator of marginal copper status? Br J Nutr 87:393–403
15. Kucharzewski M, Braziewicz J, Majewska U, Gozdz S (2002) Concentration of selenium in the whole blood and the thyroid tissue of patients with various thyroid diseases. Biol Trace Elem Res 88: 25–30
16. Theophanides T, Anastassopoulou J (2002) Copper and carcinogenesis. Crit Rev Oncol Hematol 42:57–64
17. Castiglioni S, Maier JA (2011) Magnesium and cancer: a dangerous liason. Magnes Res 24:S92–S100
18. Rayssiguier Y, Durlach J, Gueux E, Rock E, Mazur A (1993) Magnesium and ageing. I. Experimental data: importance of oxidative damage. Magnes Res 6:369–378
19. Anastassopoulou J, Theophanides T (2002) Magnesium–DNA interactions and the possible relation of magnesium to carcinogenesis. irradiation and free radicals. Crit Rev Oncol Hematol 42:79–91
20. Wolf FI, Maier JA, Nasulewicz A, Feillet-Coudray C, Simonacci M et al (2007) Magnesium and neoplasia: from carcinogenesis to tumor growth and progression or treatment. Arch Biochem Biophys 458:24–32
21. Moncayo R, Kroiss A, Oberwinkler M, Karakolcu F, Starzinger M et al (2008) The role of selenium, vitamin C, and zinc in benign thyroid diseases and of selenium in malignant thyroid diseases: low selenium levels are found in subacute and silent thyroiditis and in papillary and follicular carcinoma. BMC Endocr Disord 8:2
22. Glattre E, Thomassen Y, Thoresen SO, Haldorsen T, Lund-Larsen PG et al (1989) Prediagnostic serum selenium in a case–control study of thyroid cancer. Int J Epidemiol 18:45–49
23. Leung PL, Li XL (1996) Multielement analysis in serum of thyroid cancer patients before and after a surgical operation. Biol Trace Elem Res 51:259–266
24. Kucharzewski M, Braziewicz J, Majewska U, Gozdz S (2003) Copper, zinc, and selenium in whole blood and thyroid tissue of people with various thyroid diseases. Biol Trace Elem Res 93:9–18
25. Kosova F, Cetin B, Akinci M, Aslan S, Seki A et al (2012) Serum copper levels in benign and malignant thyroid diseases. Bratisl Lek Listy 113:718–720
26. Al-Sayer H, Mathew TC, Asfar S, Khourshed M, Al-Bader A et al (2004) Serum changes in trace elements during thyroid cancers. Mol Cell Biochem 260:1–5
27. Przybylik-Mazurek E, Zagrodzki P, Kuzniarz-Rymarz S, Hubalewska-Dydejczyk A (2011) Thyroid disorders-assessments

of trace elements, clinical, and laboratory parameters. Biol Trace Elem Res 141:65–75
28. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, et al. (2003) Evaluating non-randomised intervention studies. Health Technol Assess 7: iii–x, 1–173
29. Rayman MP (2005) Selenium in cancer prevention: a review of the evidence and mechanism of action. Proc Nutr Soc 64:527–542
30. Combs GF Jr (2005) Current evidence and research needs to support a health claim for selenium and cancer prevention. J Nutr 135: 343–347
31. Al-Saleh I, Billedo G (2006) Determination of selenium concentration in serum and toenail as an indicator of selenium status. Bull Environ Contam Toxicol 77:155–163
32. Xia Y, Hill KE, Byrne DW, Xu J, Burk RF (2005) Effectiveness of selenium supplements in a low-selenium area of China. Am J Clin Nutr 81:829–834
33. Hunter DJ, Morris JS, Stampfer MJ, Colditz GA, Speizer FE et al (1990) A prospective study of selenium status and breast cancer risk. JAMA 264:1128–1131
34. Lopez-Saez JB, Senra-Varela A, Pousa-Estevez L (2003) Selenium in breast cancer. Oncology 64:227–231
35. Harris HR, Bergkvist L, Wolk A (2012) Selenium intake and breast cancer mortality in a cohort of Swedish women. Breast Cancer Res Treat 134:1269–1277
36. Moradi M, Hassan Eftekhari M, Talei A, Rajaei Fard A (2009) A comparative study of selenium concentration and glutathione peroxidase activity in normal and breast cancer patients. Public Health Nutr 12:59–63
37. Rejali L, Jaafar MH, Ismail NH (2007) Serum selenium level and other risk factors for breast cancer among patients in a Malaysian hospital. Environ Health Prev Med 12:105–110
38. Aichler M, Algul H, Behne D, Holzlwimmer G, Michalke B et al (2007) Selenium status alters tumour differentiation but not incidence or latency of pancreatic adenocarcinomas in Ela-TGF-alpha p53+/ mice. Carcinogenesis 28:2002–2007
39. Fischer JL, Mihelc EM, Pollok KE, Smith ML (2007) Chemotherapeutic selectivity conferred by selenium: a role for p53-dependent DNA repair. Mol Cancer Ther 6:355–361
40. Wang D, Feng JF, Zeng P, Yang YH, Luo J et al (2011) Total oxidant/antioxidant status in sera of patients with thyroid cancers. Endocr Relat Cancer 18:773–782
41. Brem S (1999) Angiogenesis and cancer control: from concept to therapeutic trial. Cancer Control 6:436–458
42. Blazewicz A, Dolliver W, Sivsammye S, Deol A, Randhawa R et al (2010) Determination of cadmium, cobalt, copper, iron, manganese, and zinc in thyroid glands of patients with diagnosed nodular goitre using ion chromatography. J Chromatogr B Analyt Technol Biomed Life Sci 878:34–38
43. Kasprzak KS, Diwan BA, Rice JM (1994) Iron accelerates while magnesium inhibits nickel-induced carcinogenesis in the rat kidney. Toxicology 90:129–140
44. Patiroglu T, Sahin G, Kontas O, Uzum K, Saraymen R (1997) Protective effect of magnesium supplementation on experimental 3-methyl cholanthrene-induced fibrosarcoma and changes in tissue magnesium distribution during carcinogenesis in rats. Biol Trace Elem Res 56:179–185
45. Tanaka T, Shinoda T, Yoshimi N, Niwa K, Iwata H et al (1989) Inhibitory effect of magnesium hydroxide on methylazoxymethanol acetate-induced large bowel carcinogenesis in male F344 rats. Carcinogenesis 10:613–616
46. Wang A, Yoshimi N, Tanaka T, Mori H (1993) Inhibitory effects of magnesium hydroxide on c-myc expression and cell proliferation induced by methylazoxymethanol acetate in rat colon. Cancer Lett 75:73–78
47. Bois P, Sandborn EB, Messier PE (1969) A study of thymic lymphosarcoma developing in magnesium-deficient rats. Cancer Res 29:763–775
48. Hartwig A (2001) Role of magnesium in genomic stability. Mutat Res 475:113–121