Meta-Analysis

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Association between serum copper levels and lung cancer risk: A meta-analysis

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Abstract

Objective: To evaluate the association between serum copper levels and lung cancer risk.

Methods: We searched the electronic PubMed, WanFang, CNKI, and SinoMed databases to identify studies including information on serum copper levels and lung cancer. Standard mean differences and corresponding 95% confidence intervals were calculated using Stata 12.0 software. We performed a meta-analysis on the identified studies overall and according to geographic location. We also evaluated heterogeneity among the studies and the occurrence of publication bias.

Results: Thirty-three articles including 3026 cases and 9439 controls were included in our study. The combined results showed that serum copper levels were higher in patients with lung cancer compared with controls without lung cancer, though the results showed high heterogeneity. In a subgroup analysis according to geographic location, significant associations between copper levels and lung cancer were found for both Asian and European populations. No publication bias was detected in this meta-analysis.

Conclusions: High serum copper levels could increase the risk of lung cancer, suggesting that environmental copper exposure may be a risk factor for the development of lung cancer.

Keywords

Serum, copper level, lung cancer, meta-analysis, cancer risk, copper exposure

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Introduction

Lung cancer results from the uncontrolled growth of lung tissue cells, which may also cause metastasis.[1] Lung cancer is the leading cause of cancer-related death, both in China and worldwide, with 1- and 5-year survival rates of only 42% and 15%, respectively.[2] Lung cancer is reportedly the most common cancer among men and women, representing huge social and economic burdens in both developed and developing countries.[3] Although antioxidant vitamins and photochemicals have shown protective trends, the roles of trace metals in lung cancer risk remain poorly studied.[4,5]

Copper is an essential trace metal that plays a key role in maintaining DNA integrity through avoiding oxidative DNA damage or affecting gene mutations.[6,7] However, although some studies have reported higher serum copper levels in patients with lung cancer compared with controls,[8–10] others found no significant association[11,12] or indeed a converse association.[13] The effect of serum copper levels on lung cancer risk thus remains controversial. We conducted a meta-analysis to determine the relationship between serum copper levels and lung cancer, and evaluated potential heterogeneities among previous studies.

Methods

Study selection

We performed a comprehensive search of the literature for studies examining serum copper levels and lung cancer up to April 1st, 2018. The PubMed, WanFang, CNKI, and SinoMed databases were searched using the terms "copper concentration" or "copper levels" or "copper" or "Cu" or "trace element" in combination with "lung cancer" or "lung tumor". Furthermore, references in the relevant articles were also searched to identify other eligible articles.

Inclusion and exclusion criteria

Two investigators (XPZ and QY) independently searched and reviewed articles for eligibility using the following inclusion criteria: 1) studies focusing on patients with lung cancer; 2) observational studies; 3) numbers, mean and standard deviation of serum copper levels for cases and controls available; 4) studies on humans; and 5) studies published in English or Chinese.

Data extraction

Two of the authors (XPZ and QY) independently extracted the following data from the included studies and recorded it in a spreadsheet: 1) first author's name; 2) publication year; 3) study design; 4) country; 5) number of cases and controls; 6) sex of cases; 7) age; 8) mean and standard deviation of serum copper levels in cases and control; and 9) serum determination method. Other relevant data were also extracted from individual studies.

Statistical analysis

The meta-analysis was carried out using Stata 12.0 software (StataCorp, College Station, TX, USA). Continuous outcomes between serum copper levels and lung cancer were evaluated by calculating the standard mean deviation (SMD) and 95% confidence interval (CI).[14] We performed meta-analyses on the identified studies overall and also carried out a subanalysis according to geographic location. The copper concentration in the serum was converted into μmol/L for all studies. Statistical heterogeneity was assessed based on Q and I^2 tests.[15] The results were combined using a random-effects model. The high between-study heterogeneity was explored by meta-regression analysis.[16] Publication bias was

evaluated by visual investigation of Begg's filled funnel plots[17] and Egger's regression asymmetry test.[18]

Results

Search results and characteristics

The initial screening identified 87, 20, 87, and 79 articles from the PubMed, WanFang, CNKI, and SinoMed databases, respectively. Two additional records were identified through other sources. Figure 1 shows a flow diagram of the study. A total of 33 articles[8–13,19–45] involving 3026 lung cancer patients and 9439 controls was finally considered suitable for this study. The characteristics of each study are shown in Table 1.

Serum copper levels and risk of lung cancer

In the overall analysis, lung cancer patients had significantly higher serum copper levels than controls (summary SMD=1.103, 95% CI=1.040–1.165, Z=34.55, *P* for Z test <0.001), with significant between-study heterogeneity (I^2=96.4%, *P*<0.001) (Figure 2).

Thirty-two of the included 33 articles were case-control studies, and the result for these was consistent with the overall result (summary SMD=1.099, 95% CI=1.036–1.162, Z=34.30, *P* for Z test <0.001). In a stratified analysis according to geographic location, the associations between serum copper levels and lung cancer were significant for both Asian (summary SMD=1.078, 95%CI=1.013–1.142, Z=32.88, *P* for Z test <0.001] and European populations (summary

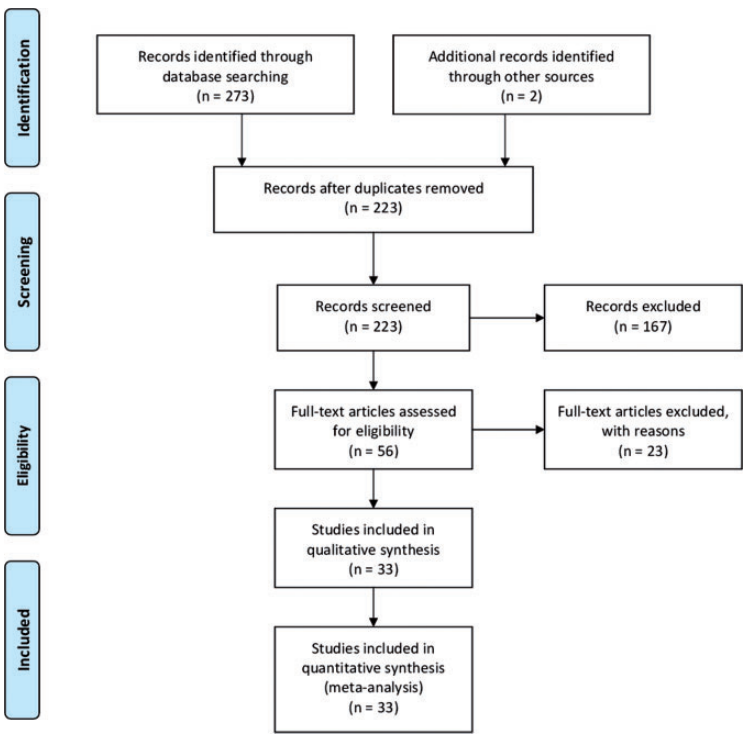

Figure 1. Study selection process for this meta-analysis

Table 1. Characteristics of all included studies

Study, year [ref]	Country	Age (year) (range or mean ± SD)	Study type	Lung cancer cases			Controls		Method of copper measurement
				n	Female (%)	Copper: mean ± SD	n	Copper: mean ± SD	
Sun et al. 1991 [8]	China	30–75	Case-control	91	0.00	1.267 ± 0.278 (μg/mL)	138	0.921 ± 0.198 (μg/mL)	AAS (IL-951, USA)
Sun et al. 1991 [8]	China	30–75	Case-control	13	100.00	1.468 ± 0.416 (μg/mL)	114	1.111 ± 0.324 (μg/mL)	AAS (IL-951, USA)
Cobanoglu et al. 2010 [13]	Turkey	54 ± 8.29	Case-control	30	33.33	0.977 ± 0.316 (μg/dL)	20	1.748 ± 0.198 (μg/dL)	UNICAM-929 spectro-photometer (Unicam Ltd., Cambridge, UK)
Diez et al. 1989 [19]	Spain	60 ± 7	Case-control	64	7.81	1.4 ± 0.316 (μg/mL)	100	1 ± 0.182 (μg/mL)	AAS (Perkin-Elmer 5.000)
Huhti et al. 1980 [20]	Finland	37–80	Case-control	149	5.37	1.42 ± 0.3 (mg/L)	19	1.03 ± 0.26 (mg/L)	AAS (Perkin-Elmer Model 303)
Jin et al. 2011 [9]	China	34.9 ± 21.3	Case-control	154	10.39	1.624 ± 0.818 (μg/mL)	154	1.285 ± 0.524 (μg/mL)	AAS (Wako Pure Chemical Industries, Osaka, Japan)
Oyama et al. 1994 [21]	Japan	26–83	Case-control	109	34.86	122.9 ± 3.77 (μg/dL)	53	109.5 ± 5.39 (μg/dL)	AAS (Wako Pure Chemical Industries, Osaka, Japan)
Zowczak et al. 2001 [22]	Poland	42–87	Case-control	14	14.29	22.9 ± 6.2 (μmol/L)	18	15 ± 1.5 (μmol/L)	Flame AAS (Perkin Elmer)
Feng et al. 2006 [23]	China	18–82	Observation trials	13	NA	19 ± 2.36 (μmol/L)	36	14.92 ± 2.71 (μmol/L)	Flame AAS
Zhang et al. 1997 [24]	China	25–80	Case-control	64	40.63	1.512 ± 0.374 (mg/L)	31	1.061 ± 0.157 (mg/L)	AAS
Jin et al. 2001 [25]	China	45–70	Case-control	40	7.50	21.7 ± 6.55 (μmol/L)	46	17.2 ± 2.48 (μmol/L)	AAS
Zhang et al. 1994 [26]	China	59 ± 9	Case-control	40	10.00	29.67 ± 5.34 (μmol/L)	24	18.84 ± 2.98 (μmol/L)	AAS
Xu et al. 1993 [11]	China	56 ± 7.5	Case-control	42	9.52	19.14 ± 4.29 (μmol/L)	40	19.61 ± 1.88 (μmol/L)	AAS
Zhou et al. 1995 [27]	China	39–69	Case-control	186	31.18	1.481 ± 0.163 (μg/mL)	150	1.035 ± 0.094 (μg/mL)	AAS
Chen et al. 1994 [28]	China	37–72	Case-control	58	25.86	20.1 ± 5.6 (mol/L)	100	18.5 ± 5.1 (mol/L)	AAS (MFX-ID)
Luo et al. 1996 [29]	China	40–70	Case-control	35	NA	17.94 ± 4.09 (μmol/L)	22	9.76 ± 1.89 (μmol/L)	AAS
Mo et al. 1995 [30]	China	58.5	Case-control	57	21.05	153.44 ± 33.38 (μg/dL)	46	93.77 ± 12.86 (μg/dL)	AAS
He et al. 1995 [31]	China	34–72	Case-control	143	39.16	24.194 ± 9.135 (μmol/L)	50	17.402 ± 5.264 (μmol/L)	AAS
Wei et al. 2002 [32]	China	22–76	Case-control	79	41.77	1.093 ± 0.073 (μg/mL)	32	0.867 ± 0.039 (μg/mL)	AAS (p-100, PE Co., USA)

(continued)

Table 1. Continued

Study, year [ref]	Country	Age (year) (range or mean ± SD)	Study type	Lung cancer cases			Controls		Method of copper measurement
				n	Female (%)	Copper: mean ± SD	n	Copper: mean ± SD	
Huang et al. 1999 [33]	China	40–72	Case-control	27	14.81	1.341 ± 0.304 (μg/mL)	45	1.084 ± 0.182 (μg/mL)	AAS
Zhao et al. 1993 [34]	China	43–62	Case-control	46	13.04	21.36 ± 4.6 (μmol/L)	50	15.76 ± 4.2 (μmol/L)	AAS (BJKP-36, Beijing, China)
He et al. 2011 [10]	China	38–69	Case-control	104	29.81	23.15 ± 3.16 (μmol/L)	122	14.52 ± 1.75 (μmol/L)	AAS
Chen et al. 1998 [35]	China	47–72	Case-control	43	32.56	19.08 ± 3.41 (μmol/L)	180	13.85 ± 2.36 (μmol/L)	AAS (A670, Shimadzu, Japan)
Liang et al. 1992 [36]	China	61	Case-control	57	21.05	28.75 ± 9.7 (μmol/L)	80	19.76 ± 3.56 (μmol/L)	AAS (WFX-ID, China)
Huang et al. 1998 [12]	China	25–65	Case-control	136	19.12	21.453 ± 5.783 (μmol/L)	7101	20.713 ± 5.508 (μmol/L)	AAS (AA670/ C2H2, Shimadzu)
Wang et al. 2003 [37]	China	28–69	Case-control	50	40.00	1.04 ± 0.2 (μg/L)	60	0.77 ± 0.22 (μg/L)	AAS
Cheng et al. 2011 [38]	China	37–68	Case-control	197	32.99	1.19 ± 0.13 (μmol/L)	93	0.87 ± 0.35 (μmol/L)	AAS
Xie et al. 2000 [39]	China	35–68	Case-control	64	45.31	25.3 ± 6.3 (μmol/L)	100	22.1 ± 1.7 (μmol/L)	AAS
Du et al. 1996 [40]	China	22–73	Case-control	73	31.51	21.3 ± 4.3 (μmol/L)	63	15.3 ± 3.4 (μmol/L)	AAS
Zhu et al. 1997 [41]	China	NA	Case-control	56	NA	21.05 ± 3.56 (μmol/L)	118	16.01 ± 2.13 (μmol/L)	AAS (3030, Perkin Elmer Zeeman, USA)
Zhang et al. 2000 [42]	China	25–77	Case-control	310	17.74	1.151 ± 0.264 (μg/mL)	48	1.068 ± 0.233 (μg/mL)	AAS (180-80, Shimadzu, Japan)
Hu et al. 2000 [43]	China	36–77	Case-control	56	17.86	1.508 ± 0.379 (μg/mL)	60	1.403 ± 0.148 (μg/mL)	AAS
Guo et al. 1994 [44]	China	55.1	Case-control	26	26.92	2.81 ± 1.54 (μg/mL)	26	0.82 ± 0.21 (μg/mL)	AAS (AA-40p, Varian, USA)
Han et al. 1999 [45]	China	NA	Case-control	400	NA	1.12 ± 0.43 (μg/mL)	100	0.87 ± 0.26 (μg/mL)	AAS (3030, PE Co., USA)

AAS, atomic absorption spectrophotometry; SD, standard deviation; NA, not available

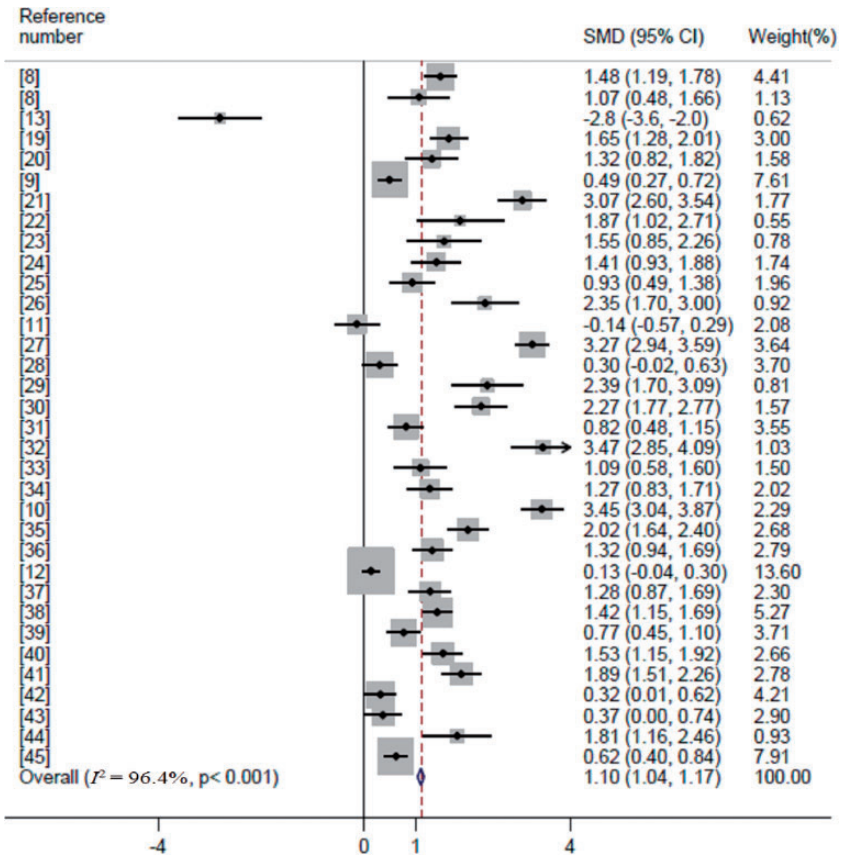

Figure 2. Forest plot of the association between serum copper levels and lung cancer risk. SMD, standard mean error; CI, confidence interval

SMD=1.568, 95%CI=1.292–1.845, Z= 11.13, *P* for Z test <0.001). Detailed results are shown in Table 2.

Between-study heterogeneity

Significant evidence of between-study heterogeneity was detected when we pooled the overall results. We therefore performed univariate meta-regression analysis to explore the source of the high heterogeneity. No specific covariate (publication year, geographic location, case number) accounted for this high heterogeneity.

Publication bias and sensitivity analysis

Egger's regression asymmetry test (*P*=0.103) and Begg's filled funnel plots (Figure 3) detected no publication bias.

Sensitivity analysis showed no apparent effect on the overall merged SMD after deleting any individual study, indicating that no single study influenced the overall effect (Figure 4).

Discussion

Previous analyses have shown inconsistent results regarding the relationship between serum copper levels and lung cancer, probably due to limited sample sizes. We therefore

Table 2. Overall and subgroup analyses of relationship between serum copper levels and lung cancer risk

Study	No. of studies	SMD (95% CI)	Z test		Heterogeneity test	
			Z	*P*-value	I^2 (%)	*P*-value
All	33	1.103 (1.040–1.165)	34.55	<0.001	96.4	<0.001
Geographic location						
Europe	3	1.568 (1.292–1.845)	11.13	<0.001	0.0	0.444
Asia	30	1.078 (1.013–1.142)	32.88	<0.001	96.6	<0.001
Study type						
Case-control	32	1.099 (1.036–1.162)	34.30	<0.001	96.5	<0.001
Observation trials	1	–	–	–	–	–

SMD, standard mean deviation; CI, confidence interval

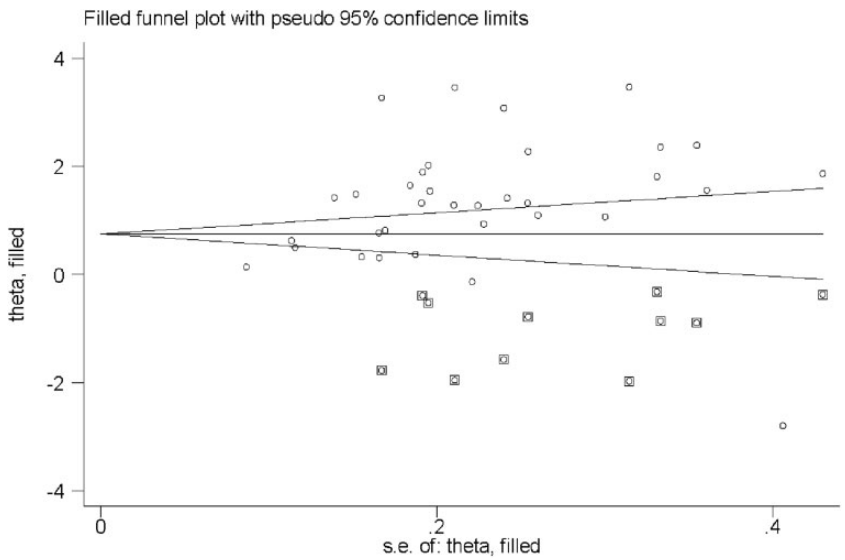

Figure 3. Filled funnel plots of the association between serum copper levels and lung cancer risk. Open circles represent studies included in this meta-analysis, circles in squares represent missing studies. s.e., standard error

conducted a meta-analysis of pooled data to obtain a comprehensive result and showed that elevated serum copper levels may increase the risk of lung cancer. Furthermore, serum copper levels were higher in lung cancer patients than in controls in both European and Asian populations.

A previous meta-analysis suggested that patients with thyroid cancer had higher copper levels than healthy controls.[46] Another meta-analysis showed that serum copper levels were markedly higher in patients with bladder cancer compared with individuals without bladder cancer.[47] Furthermore, a recent study found higher serum copper levels in patients with cervical cancer than in controls.[48] The current results are consistent with the above studies. The reason why serum copper levels may be elevated in patients with lung cancer may be

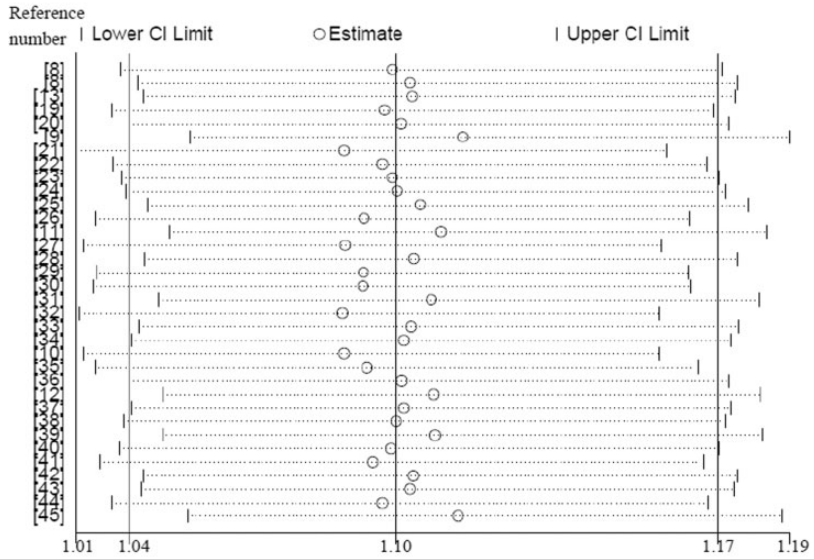

Figure 4. Sensitivity analysis of the association between serum copper levels and lung cancer risk. CI, confidence interval. Meta-analysis results with the indicated study omitted

related to copper metabolism. Serum copper levels in healthy people are associated with ceruloplasmin,[49] which is normally catabolized in the liver following cleavage of its terminal sialic acid chains by neuraminidase.[50] It has been suggested[51] that ceruloplasmin may be resialylated at the tumor cell surface or in the peripheral blood in patients with neoplasms, thus inhibiting its catabolism and potentially explaining the increase in serum copper levels in patients with malignant tumors.

This meta-analysis had several important strengths. First, the study included a large numbers of cases and participants, yielding a comprehensive result. Second, removing each individual study from the analysis had no apparent effect on the overall merged SMD, indicating that the results were stable. Third, no small study effect was detected by Egger's regression asymmetry test or Begg's filled funnel plots.

However, several limitations also need to be considered when interpreting the results. First, most of the included studies involved Asian populations and only three studies were from Europe. Although subgroup analysis identified significant associations between serum copper and lung cancer in both these subgroups, future studies in European and other populations are warranted to clarify the relationship between serum copper levels and lung cancer risk. Second, lung cancer is a complex disease with a variety of etiologic factors, including environmental and genetic factors. It is therefore possible that other factors may have influenced the results. Third, although most of the included studies measured copper levels using atomic absorption spectrophotometry, the use of instruments produced by different companies could have led to inconsistent measurements. Finally, significant heterogeneity between studies was observed in this meta-analysis. However, the heterogeneity was mainly related to the strength of the association rather than the direction of the risk estimate, suggesting that the findings in relation to the investigated outcome were

promising. Furthermore, an investigation of potential covariates by meta-regression analysis found no significant contribution of publication year, geographic location, sex, or case number to the high between-study heterogeneity. No single study accounted for the significant between-study heterogeneity or influenced the overall result according to sensitivity analysis.

Conclusions

This meta-analysis concluded that serum copper levels tend to be higher in patients with lung cancer than in controls without lung cancer. Environmental copper exposure may thus increase the risk of lung cancer.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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