Association between serum zinc levels and lung cancer: a meta-analysis of observational studies

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Abstract

Background: Inconsistent results according to numerous studies that had investigated the association between serum zinc levels and lung cancer risk were reported. The aim of this study was to explore whether serum zinc levels were lower in lung cancer patients than that in controls.

Methods: We systematically retrieved the databases of PubMed, Wanfang, Cochrane, ScienceDirect website, CNKI, and SinoMed databases for comprehensive relevant studies published before December 2018 and conducted a meta-analysis. Standard mean differences (SMD) were pooled using a random effects model.

Results: Thirty-two articles were eligible to investigate the correlation between serum zinc levels and lung cancer risk, involving 2894 cases and 9419 controls. The pooled results showed sufficient evidence approving the association between serum zinc levels and lung cancer risk. And the serum zinc levels in lung cancer were significantly lower than that in controls (summary SMD = −0.88, 95% confidence interval (CI) = −0.94, −0.82). Meanwhile, consistent results were obtained both in European populations and Asian populations. No publication bias was detected in our analysis.

Conclusions: The present meta-analysis suggested that serum zinc levels were significantly lower in lung cancer patients than that in controls.

Keywords: Serum zinc or serum zinc level, Lung cancer, Meta-analysis

Introduction

Cancer is a crucial health problem on a global scale that has become one of the primary causes of death. The increasing trend in cancer globally could be slowed and reversed if preventive measures could provide the feasible approach [1]. As we all know, smoking had been as the well-known role in the development of lung cancer [2]. Previous studies had confirmed that some external environment exposure [3, 4], dietary factors [5, 6], and physical activities [7] could affect the risk of lung cancer. However, some trace element concentrations, such as zinc, copper, and so on, could also influence the development of lung cancer. A recent meta-analysis had been performed to explore the relationship about serum copper levels in lung cancer [8]. Copper and zinc are closely related trace elements. Zinc is used for the growth of cells and is also useful in maintaining the integrity of the cell membrane. Therefore, cancer cells may consume zinc in the circulation to maintain cancer growth and maintain its membrane integrity [9]. However, there has not been an article attempting to summarize the results for serum zinc levels on the risk of lung cancer. So far, numerous researchers have examined potential effects of serum zinc levels on lung cancer risk, but existing epidemiological data are inconsistent. Hence, we aimed to evaluate results from previous studies systematically and carefully by constructing a meta-analysis of observational studies to find whether serum zinc levels were lower in lung cancer patients than that in controls.

Methods

This meta-analysis was designed and performed according to the guidelines of the preferred reporting items for...
systematic reviews and meta-analyses (PRISMA compliant) statement [10].

**Data sources and searches**
A comprehensive, computerized literature search regarding the association between serum zinc levels and lung cancer risk was conducted in six databases (PubMed, Wanfang, Cochrane, ScienceDirect website, CNKI, and SinoMed databases), from their inception to December 2018. Combinations of the following keywords were used for the search: “zinc levels” OR “zinc concentration” OR “zinc” OR “trace element” in combination with “lung cancer” OR “lung tumor”. Moreover, we also scrutinized the references of retrieved publications to identify any studies that were potentially missed.

**Study selection criteria**
To be eligible for our analysis, the studies had to meet the following criteria: (1) epidemiological studies; (2) the aim was to evaluate the associations between serum zinc levels and lung cancer risk; (3) the numbers, mean, and standard deviation (SD) of serum zinc levels for cases and control are available. It is noted that duplicated results may be published in more than one paper, so we selected the most recent or most informative paper in our analysis.

**Data extraction and quality assessment**
Two of the authors extracted all data independently, complying with the selection criteria above. A standardized data collection protocol was as follows: the last name of the first author, publication year, study design, the location of the study conducted in, subject in cases and control, gender, range or mean age of cases, method of measurement for serum zinc, and mean and SD of serum zinc levels for cases and control.

**Statistical analysis**
The strength of the association between serum zinc levels and lung cancer risk was measured by standard mean differences (SMD) and 95% confident interval (CI) by adopting random effects models that taking into account both within-study and between-study variations [11]. The analysis evaluated heterogeneity among researches via the Cochran’s Q test and I² (inconsistency index) statistic [12]. Subgroup analysis based on study design and geographic location was conducted in this meta-analysis to explore possible heterogeneity and to analyze whether there was a correlation in some subgroups. The meta-regression analysis was also performed to examine the possible heterogeneity [13]. Furthermore, sensitivity analysis was done to estimate the stability of the results by removing each study from the analysis, one at a time, which can evaluate the influence of a single comparison on the overall risk estimate. We also adopted Begg’s funnel plots [14] and Egger’s linear regression test [15] to evaluate whether publication bias existed. All the statistical analyses involved were performed with STATA software. P values were two-sided and less than 0.05 was considered statistically significant.

**Results**

**Literature search and study characteristics**
The specific step of searching and selecting relevant articles was summarized in Fig. 1. To sum up, we retrieved 204 articles from PubMed, 231 articles from Wanfang databases, 198 articles from Cochrane, 221 articles from ScienceDirect website, 265 articles from CNKI, and 248 articles from SinoMed databases. Fifty-nine articles were reviewed in full text. By evaluating the full text, 27 articles were further excluded owing to listed reasons below: review articles (n = 13), not reported mean or SD (n = 7), reported dietary factors (n = 5), and letter to the editor (n = 2). Ultimately, 32 articles [16–47] met the inclusion criteria. Three studies came from Europe and the
| Study, year       | Country    | Study type   | Age       | Lung cancer cases | Controls | Methods of measured zinc                                      |
|------------------|------------|--------------|-----------|-------------------|----------|--------------------------------------------------------------|
| Sun et al., 1991 | China      | Case-control | 30–75     | 104               | 252      | Atomic absorption spectrophotometer measurements (IL-951, USA) |
| Cobanoglu et al, 2010 | Turkey    | Case-control | 54 ± 8.29 | 30                | 20       | UNICAM-929 spectrophotometer (Unicam Ltd, York Street, Cambridge, UK) |
| Diez et al, 1989 | Spain      | Case-control | 60 ± 7    | 64                | 100      | Perkin-Elmer 5.000 atomic absorption spectrophotometer      |
| Jin et al, 2011  | China      | Case-control | 349 ± 213 | 154               | 154      | Atomic absorption spectrophotometer (Wako Pure Chemical Industries, Osaka, Japan) |
| Oyama et al, 1994 | Japan      | Case-control | 26–83     | 109               | 53       | Atomic absorption spectrophotometry                          |
| Zablocka-Slowinska et al, 2018 | Poland    | Case-control | 50–70     | 44                | 44       | Atomic absorption spectrometry                              |
| Zowczak et al, 2001 | Poland    | Case-control | 42–87     | 14                | 18       | Flame atomic absorption spectrometry using Perkin Elmer spectrometer |
| Feng et al, 2006 | China      | Observation study | 18–82   | 13                | 36       | Flame atomic absorption spectrometry                        |
| Zhang et al, 1997 | China      | Case-control | 25–80     | 64                | 31       | Atomic absorption spectrophotometer measurements            |
| Jin et al, 2001  | China      | Case-control | 45–70     | 40                | 46       | Atomic absorption spectrophotometer measurements            |
| Zhang et al, 1994 | China      | Case-control | 59 ± 9    | 40                | 24       | Atomic absorption spectrophotometer measurements            |
| Xu et al, 1993   | China      | Case-control | 56 ± 7.5  | 42                | 40       | Atomic absorption spectrophotometer measurements            |
| Zhou et al, 1995 | China      | Case-control | 39–69     | 186               | 150      | Atomic absorption spectrophotometer measurements            |
| Chen et al, 1994 | China      | Case-control | 37–72     | 58                | 100      | Atomic absorption spectrophotometer measurements (MFX-ID)    |
| Luo et al, 1996  | China      | Case-control | 40–70     | 35                | 22       | Atomic Absorption Spectrophotometer measurements            |
| Mo et al, 1995   | China      | Case-control | 585       | 57                | 46       | Atomic absorption spectrophotometer measurements            |
| He et al, 1995   | China      | Case-control | 34–72     | 143               | 50       | Atomic absorption spectrophotometer measurements            |
| Wei L et al, 2002 | China      | Case-control | 22–76     | 79                | 32       | Atomic absorption spectrophotometer measurements (American p-100) |
| Zhao et al, 1993 | China      | Case-control | 43–62     | 46                | 50       | Atomic absorption spectrophotometer measurements (BJKP-36)   |
| He et al, 2011   | China      | Case-control | 38–69     | 104               | 122      | Atomic absorption spectrophotometer measurements            |
Table 1 Characteristics of studies between serum zinc levels and lung cancer risk (Continued)

| Study, year | Country | Study type | Age | Lung cancer cases | Controls | Methods of measured zinc |
|-------------|---------|------------|-----|-------------------|----------|--------------------------|
| Chen et al., 1998 | China | Case-control | 47–72 | 43 | 11.74 ± 2.74 (μmol/L) | 180 | 13 ± 1.83 (μmol/L) | Atomic absorption spectrophotometer measurements (Japan Shimadzu-A670) |
| Liang et al., 1992 | China | Case-control | 61 | 57 | 13.86 ± 5.56 (μmol/L) | 80 | 21.81 ± 3.38 (μmol/L) | Atomic absorption spectrophotometer measurements (Chinese WFX-ID) |
| Huang et al., 1998 | China | Case-control | 25–65 | 136 | 11.933 ± 2.68 (μmol/L) | 7101 | 19.808 ± 6.43(μmol/L) | Atomic absorption spectrophotometer measurements (Japan Shimadzu-AA670/C2H2) |
| Wang et al., 2003 | China | Case-control | 28–69 | 50 | 0.74 ± 0.18 (μg/L) | 60 | 1.83 ± 1.44 (μg/L) | Atomic absorption spectrophotometer measurements |
| Cheng et al., 2011 | China | Case-control | 37–68 | 197 | 0.9 ± 0.3 (μmol/L) | 93 | 1.12 ± 0.56 (μmol/L) | Atomic absorption spectrophotometer measurements |
| Xie et al., 2000 | China | Case-control | 35–68 | 64 | 70.28 ± 106 (μmol/L) | 100 | 80.3 ± 20.7 (μmol/L) | Atomic absorption spectrophotometer measurements |
| Du et al., 1996 | China | Case-control | 22–73 | 73 | 13.1 ± 4 (μmol/L) | 63 | 15.2 ± 3.5 (μmol/L) | Atomic absorption spectrophotometer measurements |
| Zhu et al., 1997 | China | Case-control | NA | 56 | 13.16 ± 1.71 (μmol/L) | 118 | 15.46 ± 2.13 (μmol/L) | Atomic absorption spectrophotometer measurements (Perkin Elmer Zeeman/3030, USA) |
| Zhang et al., 2000 | China | Case-control | 25–77 | 310 | 0.812 ± 0.16 (μg/mL) | 48 | 1.039 ± 0.154 (μg/mL) | Atomic absorption spectrophotometer measurements (Japan Shimadzu-180-80) |
| Hu et al., 2000 | China | Case-control | 36–77 | 56 | 0.797 ± 0.176 (μg/mL) | 60 | 0.908 ± 0.022 (μg/mL) | Atomic Absorption Spectrophotometer measurements |
| Guo et al., 1994 | China | Case-control | 55.1 | 26 | 1.28 ± 0.94 (μg/mL) | 26 | 0.8 ± 0.25 (μg/mL) | Atomic absorption spectrophotometer measurements (Varian Spectr AA-40p, USA) |
| Han et al., 1999 | China | Case-control | 4–77 | 400 | 0.93 ± 0.38 (μg/mL) | 100 | 1.1 ± 0.36 (μg/mL) | Atomic absorption spectrophotometer measurements (American PE3030) |

SD standard deviation, NA not available, F female, M male
remaining 29 studies were from Asia. The characteristics of the included studies are shown in Table 1.

Serum zinc levels and lung cancer risk
In each study included in our analysis, 27 studies suggested that serum zinc levels were lower in lung cancer patients than that in controls, while four studies found a non-significant association between serum zinc levels and lung cancer. However, two studies obtained a positive association between serum zinc levels and lung cancer. Figure 2 has demonstrated the investigation results of the association between serum zinc levels and lung cancer in all the articles, as serum zinc levels in lung cancer were significantly lower than controls (summary SMD = -0.88, 95% CI = -0.94, -0.82, Z value = 28.32, P for Z test < 0.001). Extreme heterogeneity was present among the pooled results (P < 0.001, I² = 96.5%). Based on Egger’s test (P = 0.548) and the Begg’s funnel plot (Fig. 3), there existed no publication bias.

Stratified analysis
Subgroup analyses by study design and geographic location were conducted to further examine serum zinc levels and lung cancer risk. We found lower serum zinc levels in lung cancer patients than that in controls both in European populations (summary SMD = -0.65, 95% CI = -0.89, -0.41, Z value = 5.25, P for Z test < 0.001, I² = 0%) and Asian populations (summary SMD = -0.90, 95% CI = -0.96, -0.83, Z value = 27.90, P for Z test < 0.001, I² = 96.8%). Thirty-one of the 32 studies were case-control

| Author         | Year | SMD (95% CI) | Weight(%) |
|----------------|------|-------------|-----------|
| Sun ZP1        | 1991 | 0.00 (-0.26, 0.26) | 5.31     |
| Sun ZP2        | 1991 | -0.55 (-1.13, 0.03) | 1.11     |
| Cobanoglu U    | 2010 | -5.90 (-7.21, -4.59) | 0.22     |
| Diez M         | 1989 | -0.66 (-0.99, -0.34) | 3.59     |
| Jin YT         | 2011 | -1.31 (-1.55, -1.06) | 6.14     |
| Oyama T        | 1994 | -0.07 (-0.40, 0.26) | 3.45     |
| Zablocka-Slowinska K | 2018 | -0.54 (-0.97, -0.12) | 2.05     |
| Zowczak M      | 2001 | -0.90 (-1.63, -0.17) | 0.69     |
| Feng JF        | 2006 | 0.06 (-0.58, 0.69) | 0.92     |
| Zhang Y        | 1997 | -0.48 (-0.91, -0.04) | 1.97     |
| Jin ZJ         | 2001 | -0.73 (-1.17, -0.30) | 1.94     |
| Zhang TQ       | 1994 | -1.21 (-1.76, -0.66) | 1.24     |
| Xu ZF          | 1993 | -1.11 (-1.58, -0.64) | 1.71     |
| Zhou QH        | 1995 | -1.81 (-2.06, -1.55) | 5.72     |
| Chen ZH        | 1994 | 3.08 (2.61, 3.55) | 1.68     |
| Luo XR         | 1996 | -0.91 (-1.47, -0.35) | 1.19     |
| Mo LN          | 1995 | -1.57 (-2.01, -1.12) | 1.88     |
| He WD          | 1995 | -0.44 (-0.76, -0.11) | 3.52     |
| Wei L          | 2002 | -4.46 (-5.18, -3.74) | 0.72     |
| Zhao YM        | 1993 | -1.20 (-1.63, -0.76) | 1.96     |
| He ZJ          | 2011 | -4.66 (-5.16, -4.15) | 1.46     |
| Chen WY        | 1998 | -0.62 (-0.96, -0.28) | 3.26     |
| Liang GM       | 1992 | -1.80 (-2.20, -1.40) | 2.30     |
| Huang ZY       | 1998 | -1.23 (-1.41, -1.06) | 12.74    |
| Wang ZL        | 2003 | -1.02 (-1.42, -0.62) | 2.34     |
| Cheng Z        | 2011 | -0.55 (-0.80, -0.30) | 5.92     |
| Xie SY         | 2000 | -0.57 (-0.89, -0.25) | 3.64     |
| Du FL          | 1996 | -0.56 (-0.90, -0.21) | 3.15     |
| Zhu JJ         | 1997 | -1.15 (-1.49, -0.81) | 3.21     |
| Zhang Y        | 2000 | -1.43 (-1.75, -1.10) | 3.60     |
| Hu ZH          | 2000 | -0.90 (-1.28, -0.52) | 2.54     |
| Guo XH         | 1994 | 0.70 (0.14, 1.26) | 1.18     |
| Han CZ         | 1999 | -0.45 (-0.67, -0.23) | 7.62     |
| Overall (I-squared = 96.5%, p = 0.000) |          | -0.88 (-0.94, -0.82) | 100.00   |

**Fig. 2** Forest plot of standard mean difference (SMD) with corresponding 95% confidence interval (CI) of studies about serum zinc levels and lung cancer risk
studies, and the result was consistent with the overall result (summary SMD = −0.89, 95%CI = −0.95, −0.83, Z value = 28.47, P for Z test < 0.001, I² = 96.6%).

Meta-regression analysis
Meta-regression analysis was evaluated in this article, indicating that no source of heterogeneity was observed in the association between serum zinc levels and lung cancer risk.

Sensitivity analysis
Sensitivity analysis indicated that no evidence of overall result changing was observed when removed each study from the analysis, one at a time.

Discussion
The meta-analysis was conducted to investigate the association between serum zinc levels and lung cancer. Findings from our report suggested that serum zinc levels in lung cancer cases were significantly lower than that in controls. Consistent results were found both in European populations and Asian populations.

Some previous studies had been published to explore serum element levels and lung cancer risk. Chen et al. performed a meta-analysis with 13 publications to assess the association between serum iron levels and lung cancer risk [48]. The authors concluded that serum iron levels had no effect on the risk of lung cancer. Song et al. found no significant association between serum magnesium levels and lung cancer risk when pooled 11 suitable papers [49]. However, Zhang et al. performed a meta-analysis using 33 articles to explore the association between serum copper levels and the risk of lung cancer [8]. Results from their study suggested that serum copper levels were higher in lung cancer than that in controls. Copper and zinc are closely related trace elements involved in cell proliferation, growth, gene expression, apoptosis, and other processes. These two trace elements are all necessary for the proper activity of superoxide dismutase due to their integral role as cofactors or ions stabilizing the molecular structure [50]. Zinc deficiency may have adverse events, especially on immune function [51]. Gómez et al. had studied the association of zinc and its role in lung cancer [52]. In general, zinc microenvironment may play a key role in oxidative stress, apoptosis, and/or cell signaling alterations which influence the behavior of malignant cancer cells [52], and this may play a role in preventing lung cancer.

Previous studies had significantly revealed that serum zinc had a protective effect on some cancers. Xie et al. conducted a meta-analysis about serum zinc levels and cervical cancer, indicating that serum zinc levels were lower in cervical cancer patients than controls [53]. In addition, Mao et al. found that bladder cancer patients had lower serum zinc levels compared with controls [54]. Moreover, a meta-analysis published by Zhao et al. suggested that serum zinc concentrations in prostate cancer patients were significantly lower than those in normal controls [55]. Our results were consistent with the abovementioned studies.

However, there are some limitations and potential bias that must be acknowledged in our meta-analysis. First, we only included papers published in English or Chinese, which may omit some other language paper. Furthermore, we only searched published articles, which may omit some unpublished articles or some meeting articles. These factors may yield between-study heterogeneity and publications bias in the overall pooled results. Second, although most method of measurement for serum zinc was using atomic absorption spectrophotometer, different methods of measurement as well as a different instrument could also cause between-study heterogeneity. Third, evidence of high heterogeneity was found, both in overall and subgroup analysis, in our analysis. However, we could not find the source of heterogeneity due to stratified analysis and meta-regression analysis concerning the relationship between serum zinc levels and lung cancer risk. Fourth, our meta-analysis included three articles from Europe and 29 articles from Asia, thus, further epidemiological studies are warranted in the future to assess the association between serum zinc levels and lung cancer risk.

Conclusions
In summary, our meta-analysis, which included a large number of subjects of 32 articles, manifested that serum zinc levels were significantly lower in lung cancer patients than that in controls.

Abbreviations
SMD: Standard mean differences; CI: Confidence interval; SD: Standard deviation

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None
Availability of data and materials
The tables and figures supporting the conclusions of this article are included within the article.

Authors’ contributions
YW and YSZ conceived and designed the study. YW, ZYS, and APL participated in data collecting. YW analyzed the data. YW and YSZ commented on drafts of the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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