Serum magnesium levels and lung cancer risk: a meta-analysis

Xinghui Song¹, Xiaoning Zhong¹*, Kaijiang Tang², Gang Wu³ and Yin Jiang²

Abstract

Background: Whether serum magnesium levels were lower in patients with lung cancer than that in healthy controls is controversial. The aim of this study was to identify and synthesize all citations evaluating the relationship between serum magnesium levels and lung cancer.

Methods: We searched PubMed, WanFang, China National Knowledge Internet (CNKI), and SinoMed databases for relevant studies before December 31, 2017. Two authors independently selected studies, extracted data, and assessed risk of bias.

Results: Eleven citations comprising 707 cases with lung cancer and 7595 healthy controls were included in our study. Serum magnesium levels were not significantly lower in patients with lung cancer [summary SMD = 0.193, 95%CI = −1.504 to 1.890] when compared to health controls, with significant heterogeneity (I² = 99.6%, P < 0.001) found. Negative associations were found among Asian populations [summary SMD = 0.229, 95%CI = −1.637 to 2.094] and European populations [summary SMD = −0.168, 95%CI = −0.482 to 0.147]. No publication bias was found using the test of Egger and funnel plot.

Conclusions: Our study suggested that serum magnesium levels had no significant association on lung cancer risk.

Keywords: Magnesium level, Lung cancer, Meta-analysis, Healthy controls

Background

Lung cancer is the leading cause of death from cancer, resulting 1.38 million people deaths each year [1]. Its 5-year survival rate is still as low as 15%, and it is poor while compared with those in high incidence of other cancer [2]. Previous studies pointed out that lung cancer is the most common cancer among men and women, and both developed and developing countries bear a huge social and economic burden [3]. Previous publications proved that both genetic and environment factors were related to lung cancer risk [4–7]. Furthermore, trace-heavy elements also played a significant role on human health and disease [8, 9], as well as lung cancer [10].

Magnesium is one of the trace elements in our bodies, and to date, some papers had been published to investigate the association between serum magnesium levels and lung cancer risks. Two papers [11, 12] reported a higher of serum magnesium level in cases with lung cancer, while six papers [13–18] found a lack of significant association. Conversely, three papers [19–21] suggested that it is lower in lung cancer cases when compared to the healthy controls. Therefore, the aim of this study was to identify and synthesize all citations evaluating the relationship between serum magnesium levels and lung cancer risk.

Methods

Study selection

A comprehensive literature search was conducted in platforms of PubMed, WanFang, China National Knowledge Internet (CNKI), and SinoMed databases up to December 31, 2017. Free words adopted were as follows: “magnesium” or “Mg” combined with “lung cancer” or “lung carcinoma” without restrictions. Reference lists of the studies retrieved were also examined to find any additional study potentially unidentified. The course of study selection was completed by two investigators independently. Any resulting discrepancies were resolved by a third reviewer.

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from different databases. Three hundred and forty two of
other sources. There are 372 articles that were reviewed
searching and 1 additional record identified through
Knowledge Internet (CNKI), and SinoMed databases
through databases of PubMed, WanFang, China National
language or Chinese language. If more than one article
referred to the same populations, only the study that
included the most lung cancer cases or the latest publica-
tion was included.

Data extraction and quality assessment of studies
Two investigators independently extracted the following
data: (1) first author’s last name; (2) publication year; (3)
study design; (4) country; (5) number of lung cancer cases
and participants; (6) sex of cases; (7) age range or mean
age of the cases; (8) mean and SD of magnesium levels
both in lung cancer patients and healthy controls; and (9)
method used for detection of magnesium. Any resulting
discrepancies were resolved by a third reviewer.

The methodological quality of studies was evaluated
independently by two researchers using the Newcastle-
Ottawa Quality Assessment Scale [22]. The three compo-
nents were as follows: (1) patient selection (4 points); (2)
comparability (2 points); and (3) outcome (3 points) for a
total score of 9 points.

Statistical analysis
Standardized mean difference (SMD) and their 95%
confidence interval (CI) were calculated for relationship
between serum magnesium levels and lung cancer risk.
A random effect model was used in our meta-analysis
[23]. The heterogeneity among studies was evaluated
with $I^2$ and Q tests. [24]. $P < 0.05$ in Q test and $I^2 > 50$
indicated statistically significant heterogeneity [25]. Meta-
regression was adopted to assess the between-study
heterogeneity. Egger’s regression asymmetry test [26]
and funnel plot [27] were used to visually examine publi-
cation bias on study outcome. Statistical analyses were
performed using STATA version 12.0 (Stata Corporation,
College Station, TX, USA). A two-sided $P < 0.05$ was
defined as statistical significance.

Results
Study characteristics
As shown in Fig. 1, the initial 486 articles screened
through databases of PubMed, WanFang, China National
Knowledge Internet (CNKI), and SinoMed databases
searching and 1 additional record identified through
other sources. There are 372 articles that were reviewed
in the title and abstract while excluding the duplications
from different databases. Three hundred and forty two of
372 articles were excepted when screened on the basis of
title and abstract; 30 articles were examining full texts.
Nineteen studies were further excluded (reviews, not
report mean or SD, animal studies, letter to the editors).
Finally, 11 articles [11–21] were eligible to be included in
the analysis comprising 707 patients with lung cancer and
7595 healthy controls. All the included studies were
case-control studies. Nine studies were carried out from
China, 1 from Spain, and 1 from Turkey. Ten of the in-
cluded studies used the methods of atomic absorption
spectrophotometer measurements for detection of magne-
sium. In the study quality assessment, all the included
studies were with a score greater or equal to 6. The basic
features of all citations are shown in Table 1.

Serum magnesium levels and lung cancer risk
Pooled results suggested that magnesium levels in patients
with lung cancer was not significantly lower than healthy
controls [summary SMD = 0.193, 95%CI = −1.504 to
1.890, $I^2 = 99.6\%$, $P_{\text{for heterogeneity}} < 0.001$] (Fig. 2).
When we performed the subgroup analysis by geographic
location, the association was not significant either in Asian
populations [summary SMD = 0.229, 95%CI = −1.637 to
2.094] or in European populations [summary SMD =
−0.168, 95%CI = −0.482 to 0.147].

Sources of heterogeneity and meta-regression
Meanwhile, $I^2$ was 99.6% ($p < 0.001$) for the pooled sen-
tivity, suggesting high heterogeneity in the sample of
studies. Univariate meta-regression was then carried out
to determine the reason of heterogeneity. However, there
were no significant contributions about publication year,
case number, geographic location, sex, and different
methods on this high between-study heterogeneity.

Sensitivity analysis and publication bias
Sensitivity analysis conducted while removing one study
at the time revealed that no single study had essential effect
on the whole result. Figure 3 showed that no publication
was considered by the funnel plot method on the basis of
data, as well as the Egger’s test ($P = 0.586$).

Discussion
In this study, we assessed the association between serum
magnesium levels and risk of lung cancer. We did not
find a positive association between serum magnesium
levels and lung cancer risk. Through our subgroup ana-
lysis, we further found no significant association among
Asian and European populations. Significant heterogeneity
between studies observed in this meta-analysis should
be considered as a major limitation of these findings;
however, heterogeneity was mainly related to strength
of the association rather than the direction of risk estimate,
suggesting overall promising findings on the outcome investigated in the present study.

Two previous prospective cohort studies concluded that higher category of dietary magnesium intake had no significant association on lung cancer risk among German population and China population [28, 29]. However, a report [30] had been resulting that higher magnesium levels in drinking water could reduce the risk of lung cancer deaths in women. To our knowledge, no comprehensive analysis had been published to assess the serum magnesium levels on lung cancer risk. In our study, we did not find significant association of lower serum magnesium levels in patient with lung cancer. However, level of magnesium in other disease may be in the normal range, and that magnesium can have an effect on this disease [31].

The existence of heterogeneity among the studies, which is common in meta-analyses [32], may affect the pooled results. Meta-regression was performed to find the potential covariates (publication year, case number, geographic location, sex, and different methods to detect magnesium levels) which may cause this high heterogeneity. However, no covariate was found to significantly contribute to heterogeneity. In our study, most of the included studies obtained nonsignificant association between serum magnesium levels and lung cancer risk. Only one study [12] reported that serum magnesium level in patient with lung cancer is extremely higher than that in healthy controls. We reviewed the article again and confirmed the data exacted from the study; no error was made. Sensitivity analysis was performed, and no study had essential effect to the significant between-study heterogeneity and the whole result. On the other hand, we used a random effect model to combine the results. As we all know, random effect model had wider range about 95%CI than fix effect model and could obtain more accurate results. Furthermore, only three studies [12, 13, 17] reported the types and staging of lung cancer, which may also be a factor on the between-study heterogeneity. Therefore, studies with detailed information of types and staging of lung cancer are wanted to further explore this association.
| Study, year     | Country | Age (range or Mean ± SD) | Study type | Lung cancer cases | Controls | Methods of measured magnesium |
|----------------|---------|--------------------------|------------|-------------------|----------|--------------------------------|
| Cobanoglu U et al., 2010 | Turkey | 54 ± 8.29 | Case-control | 30 | 156.21 ± 22.21 μg/L | 20 | 185.8 ± 4.05 μg/L | Atomic Absorption Spectrophotometer measurements (UNICAM-929 spectrophotometer) |
| Diez M et al., 1989 | Spain | 60 ± 7 | Case-control | 64 | 20.6 ± 3.2 μg/L | 100 | 21.7 ± 8 μg/L | Perkin-Elmer 5000 atomic absorption spectrophotometer |
| Jin ZJ et al., 2001 | China | 45–70 | Case-control | 40 | 1300 ± 390 μmol/L | 46 | 1320 ± 310 μmol/L | Atomic Absorption Spectrophotometer measurements |
| Xu ZF et al., 1993 | China | 56 ± 75 | Case-control | 42 | 804.63 ± 71.29 μmol/L | 40 | 936.83 ± 93.31 μmol/L | Atomic Absorption Spectrophotometer measurements |
| He WD et al., 1995 | China | 34–72 | Case-control | 143 | 940.88 ± 11695 μmol/L | 50 | 871.24 ± 96.88 μmol/L | Atomic Absorption Spectrophotometer measurements |
| Huang ZY et al., 1998 | China | 25–65 | Case-control | 136 | 1.8275 ± 0.375 μmol/L | 7101 | 0.8254 ± 0.1778 μmol/L | Atomic Absorption Spectrophotometer measurements (Japan Shimadzu-AA670/C2H2) |
| Wang ZL et al., 2003 | China | 28–69 | Case-control | 50 | 68.29 ± 35.26 μg/L | 60 | 114.1 ± 52.12 μg/L | Atomic Absorption Spectrophotometer measurements and 721 spectrophotometer |
| Du FL et al., 1996 | China | 22–73 | Case-control | 73 | 1100 ± 300 μmol/L | 63 | 1100 ± 100 μmol/L | Atomic Absorption Spectrophotometer measurements |
| Guo XH et al., 1994 | China | 55.1 | Case-control | 26 | 20.88 ± 6.72 μg/mL | 26 | 18.84 ± 5.86 μg/mL | Atomic Absorption Spectrophotometer measurements (Varian Spectr AA-40p, USA) |
| Wang FJ et al., 2014 | China | 17–77 | Case-control | 68 | 880 ± 60 μmol/L | 60 | 860 ± 90 μmol/L | Xylene blue method |
| Fang JQ et al., 1998 | China | 55–65 | Case-control | 35 | 1.34 ± 0.35 μmol/L | 29 | 1.36 ± 0.29 μmol/L | Atomic Absorption Spectrophotometer measurements |
| Song et al. | World Journal of Surgical Oncology (2018) 16:137 | | | | | | |
Some advantages existed in our study. Firstly, a comprehensive literature search was performed to investigate the relationship between serum magnesium levels and lung cancer risk. Secondly, most of the included studies involved large numbers of patients and healthy controls, and this may strengthen the power of the pooled results. Thirdly, there was no significant publication when tested by Egger and funnel plot, which indicates that our results are stable.

The present study has some limitations. Firstly, the individual studies may have failed to control for potential confounders, which may introduce bias in an unpredictable direction. Secondly, ten of 11 studies were from Asia, and 9 were from China, and thus, more related researches from other countries are wanted to verify the association between geographic location and lung cancer risk.

**Conclusions**

Based on the obtained results, we concluded that serum magnesium levels may have no significant association in patients with lung cancer. As we experienced some limitations in our study, such as more studies were from Asia, further studies are wanted to confirm this finding.
Abbreviations
CI: Confidence intervals; SD: Standard deviation; SMD: Standard mean differences

Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors’ contributions
XNZ was the guarantor of integrity of the entire study and was responsible for the definition of intellectual content and manuscript editing. XHS contributed to the study concepts, study design, and data analysis and was responsible for the manuscript preparation. KJT and GW were responsible for the literature research. GW carried out the experimental studies. KJT and YJ were responsible for the data acquisition. All authors read and approved the final manuscript.

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

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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