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Meta-Analysis

A meta-analysis of association between serum iron levels and lung cancer risk

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Abstract: Many studies conducted on the relationship between serum iron levels and lung cancer risk had produced inconsistent results. We therefore conducted a meta-analysis to determine whether serum iron levels were lower in lung cancer patients compared to those in controls.A literature survey was conducted by searching the PubMed, WanFang, CNKI, and SinoMed databases for articles published as of Mar 1, 2018. Standard mean differences (SMD) with the corresponding 95% confidence intervals (CI) were executed by Stata 12.0 software. A total of 13 publications involving 1118 lung cancer patients and 832 controls were included in our study. The combined results showed that serum iron levels in lung cancer cases had no significantly lower when compared to those in controls [summary SMD = -0.125, 95%CI= -0.439, 0.189, Z = 0.78, p for Z test= 0.435], with high heterogeneity (I^2= 89.9%, P< 0.001) found. In the stratified analysis by geographic locations, consistent results were found for serum iron levels between lung cancer patients and controls both in Asian populations [summary SMD = -0.113, 95%CI= -0.471, 0.245] and European populations [summary SMD = -0.215, 95%CI= -0.835, 0.404]. Publication bias was not found when evaluated by Begg's funnel plot and Egger's regression asymmetry test.In summary, the current study showed that serum iron levels had no significant association on lung cancer risk.

Key words: Serum; Iron levels; Lung cancer; Meta-analysis.

Introduction

There are more than 10 million new cancer cases each year in the world and cancer accounts for about 12% of all deaths (1). The most common cause of death from cancer in Europe was lung cancer (2). In additional, it is also one of the leading causes of death in the USA (3). The overall 5-year survival rate of patients with lung cancer is less than 14%, which is much lower than that for patients with cancers in other organs (4). Therefore, it is a very important social issue to prevent lung cancer. Iron is an important element in human life. Despite this, excess iron is toxic and iron metabolism is a very well regulatory process. Until recent years, the focus on public health about iron intake has been related to iron deficiency. In fact, it is still the most common nutritional deficiency in the world (5). Many papers focusing on serum iron levels for lung cancer patients had produced inconsistent results. Five studies suggested that serum iron levels was significantly lower in lung cancer patients when compared to those in controls (6-10), while five studies did not find any significant associations between them (11-15). However, there were three studies indicated that serum iron levels were higher in lung cancer cases than controls (16-18). Until now, there was no meta-analysis systematically elucidating the serum iron levels between lung cancer patients and controls, and considering the limitations associated with specimen sizes or study methodology of single study. Consequently, we performed this study to explore whether lung cancer patients had lower serum iron levels compared to controls by gathering all related published data.

Materials and Methods

Study selection

A comprehensive search of major electronic databases including PubMed, WanFang, CNKI and SinoMed databases was conducted for literature about serum iron levels and lung cancer from beginning to Mar 1, 2018. The search utilized the terms "iron concentration" OR "iron levels" OR "iron" OR "Fe" OR "trace element" in combination with "lung cancer" OR "lung tumor". Furthermore, references of relevant articles were also researched to avoid missing articles eligible.

Inclusion and exclusion criteria

Two investigators independently searched and reviewed articles for eligibility via the following inclusion criteria: (a) studies focusing on patients with lung cancer; (b) case-control, cohort, cross-sectional design or randomized controlled trials (RCTs) or data on the studies conformed to the requirements of observational design; (c) the numbers, mean and standard deviation (SD) of serum iron levels for cases and control are available; (d) reporting the studies on humans and (e) studies published in English or Chinese language.

Studies were excluded based on the following criteria: (a) contained insufficient data for statistical analysis; (b) duplicate publication of articles; (c) obscurely reported outcomes, or lacking control groups; and (d) animal studies, case reports, basic researches, meeting summary and general overviews.

Data extraction

Data were abstracted from each identified study by using a standardized extraction form. The following information was collected: 1) first author's family name; 2) year of publication; 3) study design; 4) country; 5) number of cases and controls; 6) sex of cases; 7) age range or mean age of the study population; 8) mean and standard deviation (SD) of serum iron levels both for cases and control; 9) serum iron determination methods; and 10) covariates used in adjustments. This process was independently performed by two authors and discrepancies were discussed and resolved by consensus.

Statistical analysis

Meta-analysis was performed by STATA version 12.0 (StataCorp, College Station, TX), while association between serum iron levels and lung cancer was evaluated by standard mean deviation (SMD) and 95% confidence intervals (CI) (19). Besides, heterogeneity was assessed by Q test and I^2 test (20). The random-effects model was used to combine the results. Meta-regression analysis was used to explore the high between-study heterogeneity (21). A sensitivity analysis by exclusion of one study at the time was performed to assess the stability of results and potential sources of heterogeneity. Publication bias was evaluated by using a visual investigation of Begg's filled funnel plots (22) and Egger's regression asymmetry test (23).

Results

Characteristics of the included studies

Figure 1 showed the flow diagram of this report. In total, there were 527 records identified through our databases searching. One additional record included through other sources. Forty articles were reviewed with full text, after excluded the duplicated publications from different databases and unrelated articles while reviewed the title and abstract. Twenty-seven articles were further excluded due to the articles were reviews, not report mean or SD, animal studies, letter to the editors. Hence, 13 articles(6-18)involving 1118 lung cancer patients and 832 controls were suitable for this study. All the included studies were case-control design except one study were observation trials study. Eleven studies came from China, 1 from Spain and 1 from Turkey. The characteristics of all included studies are shown in Table 1.

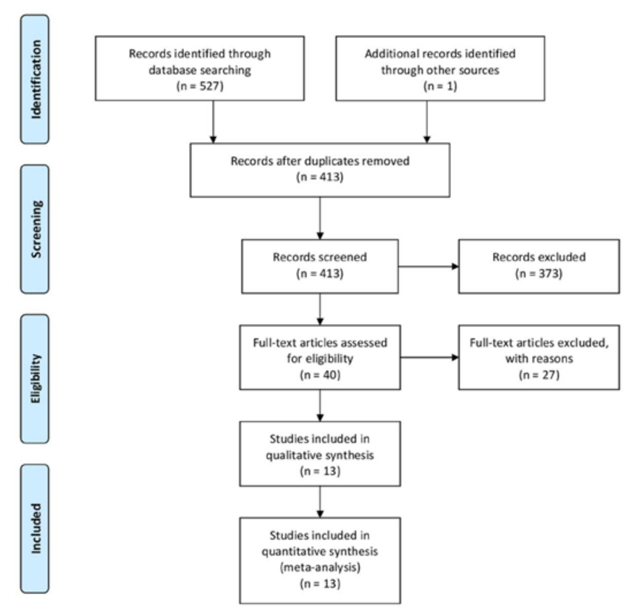

Figure 1. Study selection process for this meta-analysis.

Serum iron levels and risk of lung cancer

In the overall analysis, our study obtained that lung cancer patients had no significantly lower serum iron levels than controls [summary SMD = -0.125, 95%CI= -0.439, 0.189, Z = 0.78, p for Z test= 0.435], with significant evidence of between-study heterogeneity found (I^2= 89.9%, P< 0.001) (Figure 2).

Twelve of the included 13 articles were case-control studies, and the association was consistent with the overall result [summary SMD = -0.064, 95%CI= -0.384, 0.256, Z =0.39, p for Z test= 0.695]. In the stratified analysis by geographic locations, significant association was found for serum iron levels between lung cancer patients and controls neither in Asian populations [summary SMD = -0.113, 95%CI= -0.471, 0.245, Z =0.62, p for Z test= 0.535] nor in European populations [summary SMD = -0.215, 95%CI= -0.835, 0.404, Z =0.68, p for Z test= 0.496]. Detailed results are shown in Table 2.

Between-study heterogeneity

Significant evidence of between-study heterogeneity was appeared when we pooled the overall result. Therefore, univariate meta-regression with the covariates of publication year, geographic locations, sex and cases numbers was to explore the reason of high heterogeneity. No above covariate had contributed to this high heterogeneity (Publication year: P= 0.143; Geographic locations: P= 0.517; Sex: P= 0.352; Case number: P= 0.116).

Publication bias and sensitivity analysis

Egger's regression asymmetry test (P= 0.983) and Begg's filled funnel plots (Figure 3) indicated that no si-

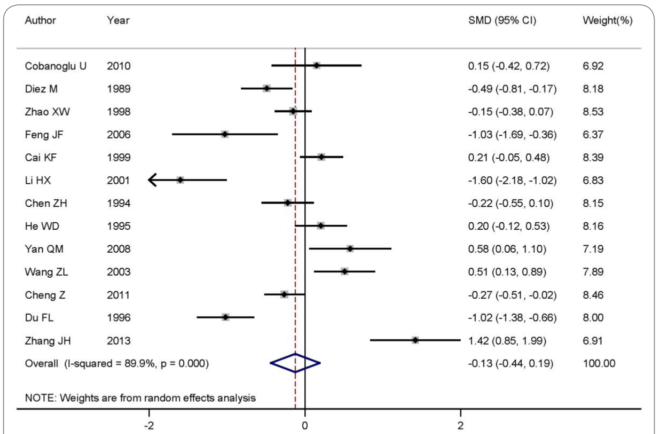

Figure 2. Forest plot of the association between serum iron levels and lung cancer risk.

Table 1. Characteristics of the studies about serum iron levels and lung cancer risk.

Study, year	Country	Age (range or Mean ± SD)	Study type	Lung cancer cases			Controls		Methods of measured serum iron
				n	Female(%)	Iron: Mean ± SD	n	Iron: Mean ± SD	
Cobanoglu U et al. 2010	Turkey	54±8.29	Case-control	30	33.33	2.178±1.934(μg/dL)	20	1.949±0.53(μg/dL)	UNICAM-929 spectrophotometer (Unicam Ltd, York Street, Cambridge, UK)
Diez M et al. 1989	Spain	60±7	Case-control	64	7.81	0.92±0.89(μg/mL)	100	1.24±0.44(μg/mL)	Perkin-Elmer 5.000 atomic absorption spectrophotometer
Zhao XW et al. 1998	China	25-72	Case-control	300	15.67	1.41±0.71(μg/mL)	100	1.51±0.46(μg/mL)	Atomic Absorption Spectrophotometer measurements (PE330)
Feng JF et al. 2006	China	18-82	Observation trials	13	46.15	13.05±2.34(μmol/L)	36	15.53±2.44(μmol/L)	Flame atomic absorption spectrometry
Cai KF et al. 1999	China	43-70	Case-control	100	34.00	1.8094±1.2092(mg/L)	120	1.5658±1.098(mg/L)	Plasma spectrometer (Japan Shimadzu ICPQ-100)
Li HX et al. 2001	China	60-81	Case-control	30	30.00	7.36±2.29(μmol/L)	30	16.01±7.3(μmol/L)	Nitro-3-phosphate adenosine-5-phosphate sulfate colorimetry
Chen ZH et al. 1994	China	37-72	Case-control	58	25.86	19.7±5.9(mol/L)	100	21±5.8(mol/L)	Atomic Absorption Spectrophotometer measurements (MFX-ID)
He WD et al. 1995	China	34-72	Case-control	143	39.16	28.083±11.689(μmol/L)	50	25.846±8.723(μmol/L)	Atomic Absorption Spectrophotometer measurements
Yan QM et al. 2008	China	38-67	Case-control	30	30.00	9.6377±3.5261(mg/mL)	30	7.8726±2.4628(mg/mL)	Atomic Absorption Spectrophotometer measurements
Wang ZL et al. 2003	China	28-69	Case-control	50	40.00	5.54±2.59(μg/L)	60	4±3.35(μg/L)	Atomic Absorption Spectrophotometer measurements
Cheng Z et al. 2011	China	37-68	Case-control	197	32.99	1.36±0.65(μmol/L)	93	1.51±0.32(μmol/L)	Atomic Absorption Spectrophotometer measurements
Du FL et al. 1996	China	22-73	Case-control	73	31.51	11.8±2.6(μmol/L)	63	14.8±3.3(μmol/L)	Atomic Absorption Spectrophotometer measurements
Zhang JH et al. 2013	China	53-86	Case-control	30	40.00	135.96±31.25(μg/dL)	30	98.05±21.32(μg/dL)	Atomic Absorption Spectrophotometer measurements (PEAA800, USA)

Table 2. the whole and subgroup analyses between serum iron levels and lung cancer risk.

Studies	No. of studies	SMD (95% CI)	Z test		Heterogeneity test	
			Z	P-value	I^2 (%)	P-value
All included	13	-0.125 (-0.439, 0.189)	0.78	0.435	89.9	< 0.001
Geographic locations						
European	2	-0.215 (-0.835, 0.404)	0.68	0.496	73.1	0.054
Asian	11	-0.113 (-0.471, 0.245)	0.62	0.535	91.1	< 0.001
Study type						
Case-control	12	-0.064 (-0.384, 0.256)	0.39	0.695	90.2	< 0.001
Observation trials	1	--	--	--	--	--

Abbreviations: SMD, standard mean deviation; CI, confidence interval.

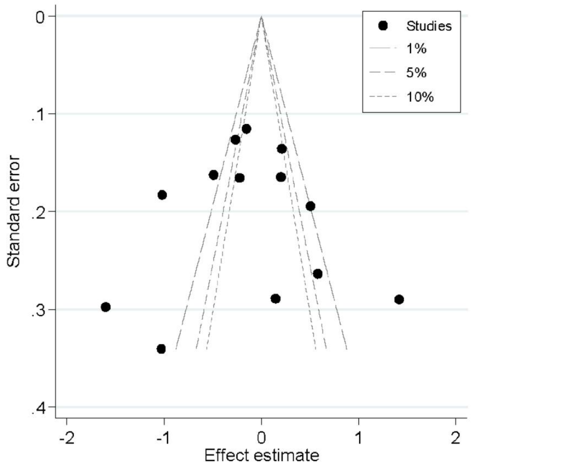

Figure 3. Filled funnel plots of the association between serum iron levels and lung cancer risk.

gnificant publication bias was found in overall analysis.

Sensitivity analysis showed that no apparent effect was found on overall merged SMD after deleting any study indicating that single studies were insensitive to overall effects.

Discussion

In this study we looked for the relationship between serum iron levels and lung cancer risk. Findings from this study suggested that serum iron levels in patients with lung cancer were lower but not significant than those in controls. Through our subgroup analysis, we further found no significant association among Asian and European populations.

A previous meta-analysis (5) on iron and cancer risk suggested that an increase of 1 mg/day of heme iron intake could increase the risk of colorectal cancer and colon cancer, but had no significant association on breast cancer and lung cancer. This meta-analysis also explored the relationship about dietary iron intake and lung cancer risk. As a result, only one case-control study (24) included in that meta-analysis indicated that highest category of dietary iron intake could increase lung cancer risk. Another meta-analysis (25) was performed to assess the association between iron intake, serum iron indices and risk of colorectal adenomas, resulted that serum iron levels had no significant association on colorectal cancer risk. These results were all consistent with our results.

Some advantages existed in our study. Firstly, to our knowledge, this is the first meta-analysis which conducted to assess the association between serum iron levels and lung cancer risk. Secondly, there were 13 studies with large numbers of patients with lung cancer and controls included in our analysis; this may strengthen the possibility of reaching accurate comparisons between serum iron levels and lung cancer risk. Thirdly, no significant publication bias by Egger's regression asymmetry test and funnel plot was found, which indicates that our results are stable across included studies.

However, some limitations in our study should be taken attention. Firstly, 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. Furthermore, meta-regression was used to explore potential covariates that caused this high between-study heterogeneity and the covariates of publication year, geographic locations, sex and cases numbers to detect serum iron levels were not found to significantly contribute to heterogeneity. No single study had essential effect to the significant between-study heterogeneity and the whole result by sensitivity analysis. Secondly, eleven of the 13 studies were form Asia and only two studies were from Europe. Therefore, the results are more applicable for Asian populations, but not for other populations. More relevant studies which conducted in other countries are wanted in the future.

In summary, our study suggested that serum iron levels were lower but not significant in patients with lung cancer than those in controls. As we experienced some limitations in our study, further investigations are required to confirm these results.

Acknowledgements

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