Correlation Between Serum Estradiol and Lung Cancer in Chinese Population

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Abstract. To analyze the correlation between the serum estradiol and lung cancer in Chinese population, PubMed, the Cochrane database and the China National Knowledge Internet database as well as VIP, WANGFANG MED, Sino Med were comprehensively searched for related studies strictly according to the selection criteria. Statistical analysis was performed using Review Manager 5.3 software. 16 studies were included for analysis, of which there were 736 subjects in the lung cancer group, 544 ones in the healthy control group. The results of Meta-analysis showed that the serum estradiol levels were higher in the lung cancer group than in the control one (SMD=0.81, 95%CI 0.31-1.30, Z=3.20, P<0.01). Meanwhile, from the subgroup analysis, the level of serum estradiol was higher in male lung cancer group (SMD=0.62, 95%CI 0.03-1.21, Z=2.06, P<0.05), but not in the female lung cancer group (SMD=0.02, 95%CI -0.51-0.55, Z=0.06, P>0.05) compared to the healthy control groups. Therefore, the serum estradiol level in the patients with lung cancer is higher than that in the healthy control population, suggesting serum estradiol level may be associated with the pathogenesis of lung cancer and expected to become a marker for the diagnosis of lung cancer, especially in Chinese population.

Introduction

Lung cancer is the most common malignancy in the world, of which the morbidity and mortality keep on the front position in all cancer types. The cancer statistical data published by Chinese National Cancer Center in 2015 showed that the morbidity and mortality of lung cancer had become the first in China [1]. It has been confirmed that smoking is the main risk factor affecting the incidence of lung cancer. However, studies found that in the same case of smoking, the risk of suffering from lung cancer in women was higher than that in men, which also appeared among the non-smokers [2]. James Gasperino proposed that gender is a risk factor for lung cancer, and there might have other important factors that affect the incidence of lung cancer except for smoking [3]. An increasing number of evidence indicated that estrogen play a role in the prognosis of lung cancer. Both basic research and clinical studies support that estradiol and cigarette smoking are co-factors in lung carcinogenesis in women. Meanwhile, the results of in vitro studies showed the estrogen could promote the proliferation and growth of lung cancer cells [4,5]. However, the correlation between serum estrogen and lung cancer has
still remained uncertain, and existing reports are inconsistent about whether the detection of serum estrogen can provide a basis for the diagnosis of lung cancer [6]. Based on the above, we are intending to analyze the correlation between the most active estrogen-serum estradiol and lung cancer using a meta-analysis.

**Methods**

**Literature Search**

PubMed, the Cochrane database and the China National Knowledge Internet database as well as VIP,WANFANG MED,SinoMed were searched for studies pertaining to the serum estrogen and lung cancer without publication or time restrictions (up to 21st July 2017), the main search terms were “(estradiol) and (lung cancer or lung carcinoma or lung neoplasms) and (case-control studies)”.

**Selection Criteria**

Eligible studies were included if they met the following criteria: (1) Domestic and foreign literature published on the serum estradiol and lung cancer, the reference languages are limited to English and Chinese; (2) patients must be clearly diagnosed with lung cancer; (3) the studies must be about the correlation of serum estradiol between patients with lung cancer and healthy population in control groups, and the cases, the levels of serum estradiol and standard deviations could be clearly pointed out in the data among the groups above.

Studies were excluded if they met any of the following criteria: (1) review articles, the qualities of literature were poor or the studies were repeatedly based on the same database or patients; (2) non-case-control studies; (3) the serum estradiol of patients was detected after the surgery or chemoradiotherapy; (4) the cases in every group, the levels of serum estradiol and standard deviations were not mentioned.

**Data Extraction and Assessment of Study Quality**

Two independent reviewers evaluated each study and extracted data independently, and any disagreements were resolved via discussion or the agreement with the third one. The selected subjects, the comparability between those two groups and the exposure were evaluated according to the NOS (a total of nine points).

**Statistical Analysis**

Statistical analysis was performed using Review Manager 5.3 software, all statistical values were combined with a 95% CI, and the P-value threshold was set at 0.05. Firstly, heterogeneity was calculated using a Q test, and the I² value represented the degree of heterogeneity. The fixed-effects model could be used if the homogeneity was of good quality (P>0.1, I² <50%), otherwise, the random-effects model should be used (P<0.1, I² ≥50%). Combined standardized mean differences (SMD) were calculated due to the different detected methods and measurement units of serum estradiol among the subjects in the selected literature. Then, publication bias was tested using a funnel plot, and by Egger’s and Begg’s tests. Sensitivity analyses were performed by excluding one study one by one to evaluate the influence of single studies on summary effect values.
Results

Characteristics of the Included Studies

Ultimately, 16 studies were selected for analysis according to the search strategy and strict selection criteria [6-21]. These comprised 736 subjects in the lung cancer groups, 544 healthy subjects in the control groups, of which there were only male subjects in 6 studies as well as only female ones in one study. The included studies were all of high quality (5≤NOS score ≤8).

The Meta-analysis of all Included Studies

All the included literature were not homogeneous according to the results of Q test (Chi²=234.86, I²=94%, P<0.01). So the random-effects model was used to analyse the total effect, whose results showed that the level of serum estradiol was higher in the lung cancer group than in healthy control population (SMD=0.81, 95%CI 0.31-1.30, Z=3.20, P<0.01). The statistically significant differences indicated the correlation between the serum estradiol and lung cancer (Figure 1).

Figure 1. Meta-analysis of serum estradiol levels in lung cancer groups and control groups. Subgroup analysis.

There were 396 subjects in male lung cancer group and 309 subjects in male healthy control group. The random-effects model was used according to the results of Q test (Chi²=115.18, I²=92%, P<0.01), whose results showed that the level of serum estradiol was higher in male lung cancer group than in male healthy control group (SMD=0.62, 95%CI 0.03-1.21, Z=2.06, P<0.05), of which the difference was statistically significant (Figure 2).
Meanwhile, there were 77 subjects in female lung cancer group and 85 subjects in female healthy control group. The random-effects model was used according to the results of Q test ($\chi^2=10.10, I^2=60\%, P<0.05$), whose results were not statistically significant ($\text{SMD}=0.02, 95\% \text{CI} -0.51-0.55, Z=0.06, P>0.05$) (Figure 3).

Discussion

In this study, 16 studies were selected for analysis, of which there were 736 subjects in the lung cancer groups, 544 ones in the healthy control groups. The results of meta analysis showed that the serum estradiol levels were higher in the lung cancer groups than in the control ones ($\text{SMD}=0.81, 95\% \text{CI} 0.31-1.30, Z=3.20, P<0.01$). Meanwhile, the level of serum estradiol was higher in male lung cancer group than in male healthy control group ($\text{SMD}=0.62, 95\% \text{CI} 0.03-1.21, Z=2.06, P<0.05$), of which the difference was statistically significant. While, there was no statistically significant difference between female lung cancer group and female control group ($\text{SMD}=0.02, 95\% \text{CI} -0.51-0.55, Z=0.06, P>0.05$).

Estrogen is an important steroid hormone, which may play some important biological effects in some kinds of cancer, but the results are inconsistent [22-24]. In a study of Zhang et al indicated that female esophageal squamous cell carcinoma (ESCC) patients with higher serum estradiol level have a favorable survival than those with lower serum estradiol levels, indicating the protective effect of serum estradiol on ESCC [22]. While, antiestrogen use in 6655 breast cancer patients in the Geneva Cancer Registry had significantly lower subsequent lung cancer mortality [25].
Estrogen has been postulated as a contributor in the development and progression of lung cancer [24]. The existing studies are inconsistent about whether there are correlations between the serum estradiol and lung cancer. It was postulated that the detection of serum estradiol levels could contribute to the clinical early diagnosis and treatment of lung cancer. In this article, the correlation was explored using a meta-analysis for determination whether serum estradiol could be used as an indicator for diagnosis of lung cancer. In subgroup analysis, the serum estradiol levels were higher in male lung cancer groups than in male healthy control ones, which was statistically significant, while there was no significant difference between female lung cancer groups and control ones, indicating the impact of female menopausal status on serum estradiol as well as the further impact on lung cancer [26]. It has been reported in the literature that high level of circulating estrogen can increase the risk of postmenopausal breast cancer, especially estrogen receptor positive (ER”) tumors [27]. One study showed that serum estrogen was significantly associated with poorer lung cancer survival, and specific genotypes affecting serum estrogen and tumor ER-α expression were associated with prognosis, also suggesting that detection of serum estrogen levels in patients with lung cancer have a positive effect in improving the diagnosis and treatment of lung cancer [28]. Increasing circulating estrogen levels may activate the estrogen receptor, promoting the development of lung cancer, while more experiments in vivo and vitro are needed to explore and prove it. In short, estrogen and estrogen receptor have the potential to be prognosticator in lung cancer [24].

Meanwhile, there are some shortcomings in this study: (1) the result in this study might be suitable only for Chinese population because no related foreign literature were retrieved. (2) We found that there may be publication bias according to the Begg’s test and Egger’s test using Stata 12.0 software, suggesting that more research is needed to demonstrate the results of our analysis. (3) Sample size of the study on the correlation between female serum estradiol and lung cancer was not enough, more related studies are needed to demonstrate the results.

Conclusion

Serum estradiol levels may be associated with the pathogenesis of lung cancer and expected to become a marker for the diagnosis of lung cancer, especially for the Chinese male population. More basic experimental studies are needed to explore the definite correlation between serum estrogen and lung cancer in the future.

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References


