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Original Contribution

Blood lipids profile and lung cancer risk in a meta-analysis of prospective cohort studies

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BACKGROUND: Emerging evidence has connected lipid metabolism disturbance with lung diseases, but the relationship between blood lipid profile and lung cancer risk is controversial and inconclusive.

OBJECTIVE: We conducted a meta-analysis of prospective cohort studies to evaluate the relationship between blood lipids profile and lung cancer incidence.

METHODS: Relevant studies were identified by searching PubMed, Cochrane Library, Web of Science, EBSCO, Ovid, CNKI, VIP, and WANGFANG MED through August 2016. Nine prospective cohort studies were included in the meta-analysis, and fixed or random effects model was used to calculate pooled relative risk (RRs). The RR was calculated using either highest vs lowest categories, or upper quantile vs lowest quantile. The thresholds were determined by the authors of each original publication, based on either predefined cut-offs or the distributions within their study population.

RESULTS: Analysis of 18,111 lung cancer cases among 1,832,880 participants showed that serum total cholesterol levels were inverse associated with lung cancer risk (RR = 0.93, 95% confidence interval [CI]: 0.85–1.03). Further analysis considered the lag time and excluded the effects of preclinical cancer, with totally 1,239,948 participants and 14,052 lung cancer cases, found a significantly inverse association between total cholesterol and lung cancer risk (RR = 0.89, 95% CI: 0.83–0.94). Analysis of 3067 lung cancer cases among 59,242 participants found that the high-density lipoprotein cholesterol levels (RR = 0.76, 95% CI: 0.59–0.97) was negatively associated with lung cancer risk and 4673 lung cancer cases among 685,852 participants showed that the total triglyceride (RR = 1.68, 95% CI: 1.44–1.96) was positively associated with lung cancer risk.

CONCLUSION: Cholesterol and fatty acid metabolism might present different and specific mechanism on lung cancer etiology and needs further elucidation.

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Introduction

Lung cancer is the most common malignant tumor in the world, it accounts for the largest part of the global new cancer diagnoses and death from cancer.[1] The 2012 world cancer report (GLOBOCAN) shows that the world's new cases of lung cancer has reached 1.8 million, 1.59 million of deaths, ranking first in the malignant tumor. Epidemiologic studies have confirmed that smoking is a major risk factor for lung cancer,[2] but an increase in lung cancer incidence in non-smokers indicates that there are other lung cancer risk factors.

It is necessary and important to test blood lipid profiles, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total triglycerides (TG) in medical diagnosis. Blood lipids are closely related to systematic lipid metabolism disturbance and cardiovascular disease. Meanwhile, studies have found there is a strong link between serum lipids and cancer morbidity and mortality, such as gastric cancer, gastrointestinal malignancies, and prostate cancer et cetera.[3–8] But the association between blood lipids profile and the incidence of lung cancer remains unclear. Dessi et al[9] observed that the TC in lung tumor tissues was more than 2 times higher than that in normal lung tissues and the level of HDL-C in patients with lung cancer was significantly lower than that in control group. Umeki[10] also discovered that the levels of TC and HDL-C in patients with lung cancer were significantly lower than those in the healthy control. Chi et al[11] found the levels of blood HDL-C, LDL-C, and TC in patients with non–small cell lung cancer were significantly lower than those in healthy controls, and the levels of TG were significantly increased. All these studies are case–control designed, inevitably introducing selection, and recall bias to the interpretation. To improve the quality and strength of evidence, the objective of this meta-analysis was to analyze the correlation between blood lipids profile and lung cancer risk in the prospective cohort studies.

When an inverse relationship was observed between serum lipid level and lung cancer incidence, it is unclear whether the observed association is causal or due to an effect of preclinical (prediagnosed) cancer on serum levels (ie, increased utilization of cholesterol during early carcinogenesis). Lag time is the time lag between serum lipid profile determination and lung cancer cases diagnosis and enrollment. To rule out the influence of preclinical cancer on the serum cholesterol level, lung cancer cases diagnosed within the lag time were not included in some prospective cohort studies, we further analyzed the TC-lung cancer risk association among these studies specifically.

Materials and methods

Literature search

Comprehensively searched articles published on PubMed, Cochrane Library, Web of Science, EBSCO, Ovid, CNKI, VIP, and WANGFANG MED through August 2016. We used the following keywords for exposure: "lipids," "cholesterol," "triglyceride," "lung neoplasms," "lung cancer," "risk," "prevalence," "incidence," and "prospective cohort studies." Moreover, we reviewed reference lists from retrieved articles to identify any potentially relevant studies.

Inclusion and exclusion criteria

The inclusion criteria for selection of published studies for this meta-analysis were as follows: (1) exposure factors were levels of lipids in blood serum or plasma, language is limited to English and Chinese; (2) studies designed as a prospective cohort study; (3) the outcome of interest was lung cancer; (4) relative risk (RR), odds risk, or hazard ratio estimates with 95% confidence intervals (CIs).

Data extraction

Two investigators independently extracted data from the selected studies, based on the predetermined selection criteria, and any disagreements were resolved by discussion and reexamination. The following information was extracted: first author, publication date, country, sample size, sex of subjects, categories of blood lipids level, lag time between first blood draw and lung cancer diagnosis, other lung cancer risk factors adjusted, and effect estimates with corresponding 95% CIs for the highest vs the lowest categories of blood lipids levels.

Quality assessment

We chose to use the 9-star Newcastle-Ottawa Scale to assess the studies' quality, and the Newcastle-Ottawa Scale consists of 3 parts of quality: selection, comparability, and outcome. The study with 7 points or more can be considered to be high quality.

Statistical analysis

Because the lung cancer incidence was low, we used both hazard ratios and odds risks to approximate RRs. The RR was calculated using either highest vs lowest categories, or upper quantile vs lowest quantile. The thresholds were determined by the authors of each original publication, based on either predefined cut-offs or the distributions within their study population. Those articles that provided data for men and women respectively were treated as 2 separate studies. Stata version 12.0 was used for statistical analysis. Cochran's Q-statistic was used to evaluate the heterogeneity across the enrolled studies, $P < .1$ referring to statistical significance. I^2 test was used to provide further evidence of heterogeneity. If heterogeneity was detected, random effects model was used for meta-analysis; otherwise fixed effects model was adopted. Then the Egger's test and Begg's test were used to analyze the publication bias. Begg's test assesses whether there is a significant correlation between the magnitude of the effect