Relationship between Serum Bilirubin Level and the Prevalence of Lung Cancer in Smokers

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Abstract

Background

The correlation between serum bilirubin level and multiple respiratory system diseases including lung cancer has been reported. We aimed to explore the relationship between serum bilirubin level and the prevalence of lung cancer among smokers in China.

Methods

We designed a retrospective case-control study and enrolled 266 lung cancer patients and 266 matched controls from The Third Xiangya Hospital of Central South University from February 2011 to May 2017. Data including diagnosis, serum bilirubin levels and smoking history were collected, which consistently showed significant differential in cases and controls.

Results

Lower total and indirect bilirubin level is correlated with smoking but they can be recuperating after cessation. The average bilirubin level in lung cancer patients was lower than matched controls. Low indirect bilirubin level within normal range is the risk factor of lung cancer in smokers (OR = 2.710). Of note, smokers whose serum bilirubin lower than 7.88 μmol / L has a higher risk of lung cancer in Chinese adults.

Conclusions

Serum indirect bilirubin level would be a screening predictor to identify higher risk smokers of lung cancer.

1. Introduction

Lung cancer is one of the malignant tumors with the highest incidence and mortality in the world. In 2017, there were 2.2 million incident cases of Tracheal, bronchus, and lung (TBL) cancer and 1.9 million (95% UI, 1.8–1.9 million) deaths. It is the second most common cancer and the leading cause of cancer death among men worldwide (1). In China, lung cancer has the incidence and is the leading cause of death in malignant tumors. According to the latest statistics of the National Cancer Center, about 787,000 patients were diagnosed lung cancer and 631,000 patients died of lung cancer in 2015. Most of the patients were in advanced stage when they were diagnosed where their five-year survival rate was only 5%. But for stage I lung cancer patients whose 5-year survival rate can be as high as 70% after surgery. Therefore, early diagnosis of lung cancer is particularly important to improve the prognosis of these patients (2). For decades, there are lots of biomarkers found including protein, microRNAs, epigenetic changes and also molecules in exhaled breath for screening and early diagnosis of lung cancer, but they

are limited in clinical application due to lower specificity and higher expenses (3, 4). Thus, it is of great significance to find a simple and efficient predictor to screening the high-risk lung cancer populations for an early detection and treatment (5, 6).

Bilirubin is one of the endogenous antioxidant and anti-inflammatory molecule, whose level is reported to negatively correlated with the incidence of cardiovascular diseases (CVD), stroke, metabolic syndrome and a variety of cancers, such as rectal cancer and breast cancer (7–13). A few cohort studies around the world and one of them in Korea showed an inverse association between bilirubin and lung cancer (14). Hence, in this work, we hypothesized this correlation is also exist in China.

Smoking is a major epidemiological cause of lung cancer, however, it's not sufficient enough to identify the highest risk individuals when using it alone (15, 16). Therefore, novel biomarkers for lung cancer incidence and mortality are urgently needed for clinical guidance of screening high-risk groups of lung cancer, particularly among smokers. Numerous studies have found that smokers have lower bilirubin levels than nonsmokers. To figure out whether bilirubin level can be a predictor for lung cancer among smokers in China, we designed this study to compare the difference of serum bilirubin level between patients with lung cancer and those without lung cancer, and analyze the influence of smoking on bilirubin level.

2. Methods

2.1 Study Subjects

From February 2011 to May 2017, 532 patients were enrolled in this study. Cases are diagnosed, histologically confirmed lung cancer patients and the exclusion criteria is as follows: serious cardiopulmonary insufficiency; chronic digestive system disease or acute and chronic liver disease; hematological system disease; serious diabetes mellitus and other diseases that significantly affect the metabolism of serum bilirubin; anticoagulant drugs taken recently. There was no restriction of age, sex, or ethnicity when recruitment. For participates in control group, they are selected randomly matching on age and gender as well as the same exclusion criteria.

2.2 Data Collection

After matching the age and gender, the subjects were divided into six groups according to the smoking history and whether they were diagnosed lung cancer: smoking + lung cancer group; nonsmoking + lung cancer group; smoking cessation + lung cancer group (quit smoking for no less than one year); smoking + non-lung cancer group; nonsmoking + non-lung cancer group; smoking cessation + non-lung cancer group. In addition, the subjects were divided into two groups according to whether they had lung cancer or not and they were also divided into three groups according to smoking condition. Demographic characteristics are recorded, including age, gender, past history, smoking history and other exposure data. We also collected the data about serum bilirubin level on their first visit (controls) or diagnosed (cases).

2.3 Statistical Analysis

GraphPad Prism 7.0 software (GraphPad Software, San Diego, CA) was used to process raw data, Two-way ANOVA, Student's t test, McNemar's Test, Kappa Test and Chi-square test were used to analyze the data. Values are presented as means ± SD. 95% confidence interval is used for calibrate the reference value range. We considered the value $p < 0.05$ to be significant. All P values were assessed two-sided.

3. Results

532 subjects were enrolled in this study, including 266 lung cancer patients and 266 non-lung cancer controls matching on age and gender. More male patients were enrolled than, especially in smoking and cessation group regardless of whether they have lung cancer or not. We also observed the average age of smoking cessation patients is much older than smoking and nonsmoking patients (Table 1).

Since bilirubin is a routine blood test in health examination, we collected the patients' bilirubin level on their first visit (controls) or diagnosed (cases). In Table 2, the results showed that for the indirect bilirubin level, "smoking + lung cancer" group was lower than "nonsmoking + lung cancer" group ($P < 0.001$) while "smoking + non-lung cancer" group was also lower than "nonsmoking + non-lung cancer" group ($P < 0.001$). The levels of total, direct and indirect bilirubin in "nonsmoking + non-lung cancer" group were significantly higher than those in lung cancer groups ($P < 0.05$). Total ($P < 0.05$) and indirect bilirubin ($P < 0.0001$) levels in the smoking group were significantly lower than those in the nonsmoking group. Comparing with non-lung cancer group, total and indirect bilirubin levels in lung cancer group were lower but the direct bilirubin level was higher ($P < 0.0001$). Additionally, there was no significant difference of total direct and indirect bilirubin levels between nonsmoking and smoking cessation group. This means, smoking can reduce total and indirect bilirubin levels, but quitting smoking can recuperate them to the level of nonsmokers.

In "smoking + lung cancer" group, we concluded their average level of indirect bilirubin was 7.47 ± 2.262 (95% CI = 7.07 ~ 7.88) μmol / L. Taking lower indirect bilirubin level within normal range as an exposure factor, the results of χ2 indicated that it has a negative effect on the risk of lung cancer in smokers ($\chi^2 = 14.15, P = 0.0002$) (Table 3) while OR value (2.710) also confirmed the same conclusion. In other words, smokers whose serum bilirubin level lower than 7.88 μmol / L have a higher risk of lung cancer.

Table 1
The basic features of patients with or without lung cancer

Group	Number of Patients (Total / Male / Female)	Average Age (Years)	the Range of Age (Years)
Smoking + Lung Cancer	121/120/1	60.50 ± 11.78	24 ~ 85
Nonsmoking + Lung Cancer	121/43/78	60.40 ± 11.50	26 ~ 88
Smoking cessation + Lung Cancer	24/24/0	65.20 ± 9.49	45 ~ 85
Smoking + non-Lung Cancer	121/120/1	60.22 ± 10.36	23 ~ 80
Nonsmoking + non-Lung Cancer	121/43/78	60.43 ± 11.80	26 ~ 84
Smoking cessation + non-Lung Cancer	24/24/0	61.96 ± 10.45	46 ~ 84

Table 2
The levels of total, direct and indirect bilirubin in different groups

Group	Total Bilirubin (μmol / L)	Direct Bilirubin (μmol / L)	Indirect Bilirubin (μmol / L)
Smoking + Lung Cancer	10.89 ± 3.03$^{\wedge\wedge\wedge\wedge}$	3.42 ± 1.28$^{\wedge\ \wedge}$	7.47 ± 2.26$^{++/\wedge\wedge\wedge\wedge}$
Nonsmoking + Lung Cancer	11.74 ± 3.82$^{\wedge\wedge\wedge\wedge}$	3.26 ± 1.46$^{\wedge\wedge\wedge}$	8.48 ± 2.91$^{\wedge\wedge\wedge\wedge}$
Smoking cessation + Lung Cancer	10.66 ± 2.46$^{\wedge\wedge\wedge}$	3.00 ± 1.31$^{\wedge}$	7.66 ± 2.17$^{\wedge\wedge\wedge}$
Smoking + non-Lung Cancer	13.42 ± 4.37^{++++}	4.28 ± 1.73^{++++}	9.14 ± 3.07$^{\wedge\ \wedge}$
Nonsmoking + non-Lung Cancer	14.35 ± 3.89	4.09 ± 1.87	10.26 ± 2.60
Smoking cessation + non-Lung Cancer	14.28 ± 3.73^{++}	4.63 ± 1.60^{++}	9.65 ± 2.61
Lung Cancer	11.26 ± 3.39 ****	4.23 ± 1.37****	7.95 ± 2.61****
Non-Lung Cancer	13.92 ± 4.12	3.31 ± 1.79	9.70 ± 2.87
Smoking	12.15 ± 3.96$^{\#}$	3.85 ± 1.58	8.31 ± 2.82$^{\#\square\square\square}$
Nonsmoking	13.05 ± 4.06	3.68 ± 1.73	9.37 ± 2.89
Smoking cessation	12.47 ± 3.63	3.82 ± 1.67	8.65 ± 2.58

$^{++}$P□0.01, $^{++++}$P□0.0001, comparing with nonsmoking + lung cancer group,; $^{\wedge}$P□0.05, $^{\wedge\wedge}$P□0.01, $^{\wedge\wedge\wedge}$P□0.001, $^{\wedge\wedge\wedge\wedge}$P□0.0001, compared with nonsmoking + non-lung cancer group; ****P□0.0001, comparing with non-lung cancer group; $^{\#}$P□0.05, $^{\square\square\square\square}$P□0.0001, comparing with nonsmoking group.

Table 3
The effect of low indirect bilirubin level on the risk of lung cancer in smokers

Lung Cancer	Indirect Bilirubin Level		Sum
	- lower (< 7.88 μmol/ L)	+ Higher (≥ 7.88 μmol / L)	
+	83	38	121
-	54	67	121
Sum	137	105	242

4. Discussion

The purpose of this study is to identify whether bilirubin can be the potential biomarker for high-risk smokers of lung cancer development in China. From the characteristics results, male take the majority of smoking and lung cancer, suggesting that smoking is correlated with lung cancer in male, which is consistent with the main causes of lung cancer and the characteristics of the susceptible population. It is shown that people who smoke or suffer from lung cancer have lower bilirubin levels than matched controls but cessation can recuperate them to the level of nonsmokers. This probably because the oxidant stress generated by smoking consumes the indirect and thus total bilirubin while quitting smoking can restore the body's own antioxidant capacity, thus decreasing the consumption of bilirubin. We also found high indirect bilirubin level (≥ 7.88 μmol / L) within the normal range is a protective factor for smokers on risk of lung cancer through Chi-square test and OR value calculation. Therefore, the serum indirect bilirubin level would be a potential predictor to identify higher risk smokers for lung cancer in China.

High bilirubin level is strongly associated with longer overall, disease-free and distant metastasis-free survival where it is regarded as an independent significant prognostic factor, among non-small cell lung cancer (NSCLC) patients who had received curative resection in China (17). It is also reported low serum bilirubin level in the normal range have a higher risk of lung cancer (18). And some even give us the specific measurement as for every 0.1 mg/dl increase in bilirubin, the incidence of lung cancer in men and women could be reduced by 8% and 11% respectively (19). Meanwhile, active smoking is associated with low serum bilirubin level within normal range, but the level of serum bilirubin can recuperate after cessation (20, 21). A large cohort study in conjunction with global metabolomics profiling showed in Caucasians, male smokers had lower serum bilirubin level compared with non-smokers, and lower bilirubin group had higher lung cancer prevalence and mortality compared with high one (22). These phenomena also exist in our study when all the participants are Chinese adults.

The correlation of lung cancer and low serum bilirubin levels in smokers helps increasing the accuracy in predicting lung cancer at an individual level with reasonable coast and establishes the necessity of prevention behaviors for specific smokers, thus providing stronger incentives to end unhealthy lifestyle. But this experiment also has some limitations, which need to be further improved. Most of participants in this study come from Hunan Province, so the results only represent this area. And there were fewer women in the study, especially the female smokers who suffering from lung cancer, so the data were not analyzed by different gender group. Therefore, whether the conclusion that low bilirubin level is a risk factor of lung cancer in smokers can also concluded in female needs further study with larger sample size. In data analysis, due to uncorrected pathological stage, alcohol usage, education level, occupation and other factors, the final result may be biased to some extent, which needs to be improved in data collection and processing.

Declarations

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

This is an observational study. The Third Xiangya Hospital of Central South University Research Ethics Committee has confirmed that no ethical approval is required.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no conflict of interest.

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Author Contributions

Literature search: WLL, MHL. Data collection: TF, LW. Study design: WLL, MHL. Analysis of data: WLL, MHL. Manuscript preparation: WLL, MHL, TF, LW. Review of manuscript: CL, WLL, MHL, TF, LW.

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