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Serum levels of retinol-binding protein 4 and the risk of non-small cell lung cancer

A case-control study

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Abstract

Retinol binding protein 4 (RBP4), as an adipokine, has been identified to be associated with several types of cancer. However, no studies have assessed its effect on non-small cell lung cancer (NSCLC) risk. The objective of this study was to assess the association between serum RBP4 levels and the risk of NSCLC.

A case-control study design was used to recruit 256 confirmed NSCLC cases and 256 age- and gender-matched healthy controls by frequency between August 2017 and January 2019. Serum RBP4 was measured using enzyme-linked immune absorbent assay before treatment. Unconditional logistic regression analysis was applied to estimate the odds ratio and 95% confidence interval (CI).

Serum RBP4 level was significantly higher in NSCLC patients than those in the healthy control group (36.05 ± 8.28 vs 29.54 ± 7.71 μg/mL, $P < .05$). Higher serum RBP4 level was associated with increased risk of NSCLC (P trend = .001). Compare with those in the lowest tertile, the adjusted odds ratios were 1.85 (95% CIs 1.07–3.2) ($P = .029$) for the second tertile and 2.18 (95% CIs 1.37–3.45) ($P = .001$) for the highest tertile after adjusting for confounding variables. No interactions were observed after stratified analyses by body mass index and smoking status (P for interaction: .584 and .357).

Our study indicated that serum RBP4 level was positively related to the risk of NSCLC. Additional studies with prospective design are required to confirm this finding.

Abbreviations: BMI = body mass index, CI = confidence interval, FBG = fasting glucose, NSCLC = non-small cell lung cancer, RBP4 = retinol binding protein 4, T2DM = treatment of type 2 diabetes mellitus, TC = total cholesterol, TG = total triglycerides.

Keywords: case-control study, non-small cell lung cancer, obesity, retinol binding protein 4

1. Introduction

Lung cancer is the leading cause of cancer death in China and across the globe. Statistics show that there are about 18.1 million malignant tumors in 2018 and 9.6 million deaths of malignant tumors worldwide.[1] Lung cancer is the most commonly diagnosed cancer (2.1 million new cases, 11.6% of the total cancer cases) and the leading cause of cancer death (1.8 million deaths, 18.4% of the total cancer deaths).[1] The incidence and death rates will continue to rise, mainly as a result of an increase in global tobacco use, particularly in Asia.[2] Non-small cell lung cancer (NSCLC) accounts for approximately 80% to 85% of lung cancer cases. NSCLC is not diagnosed until advanced-stage disease is present, resulting in delays that may adversely affect survival.[2] Despite advances in the treatment of NSCLC in recent years, the prognosis for NSCLC patients is still poor compared with the other types of cancer (eg, breast cancer and colorectal cancer), especially in China, with the 5-year survival rate < 20%.[1] Therefore, it is of great significance to identify the biomarkers of NSCLC in order to identify individuals at high risk.

Retinol-binding protein 4 (RBP4) is a secretory molecule in the RBP family synthesized in the liver. It is secreted mainly by adipocytes and hepatocytes and has an important effect in assisting retinol to play its normal physiological function.[3] It has been shown that circulating RBP4 has been implicated as a mediator in the development of insulin resistance and the metabolic disease. Animal study in mice suggested that elevated RBP4 levels may play an important role in the development of insulin resistance.[2] RBP4 involves in the occurrence of insulin resistance and obesity, which can lead to disorders of glycolipid metabolism, and plays an important role in fatty liver, diabetes and cardiovascular diseases.[4–6]

In addition as a transport protein, RBP4 might also serve as a signaling molecule binding to the membrane receptor stimulated by retinoic acid 6 and triggering downstream activation of pro-oncogenic pathways, and thus RBP4 may be associated with

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cancer risk.[2] Epidemiological studies showed that RBP4 was related to the occurrence and development of various malignant tumors, and it was highly expressed in liver cancer, pancreatic cancer, acute leukemia and other tumors.[7–10] For example, comparing with those in the lowest quartile, participants in the highest quartile of serum RBP4 levels was associated with 2.07 (95% confidence interval [CI]: 1.07–4.00) times increased risk of breast cancer.[3] However, there is no report on the relationship between RBP4 and NSCLC.

Thus, this study aimed to assess association between the level of serum RBP4 and the risk factors of NSCLC through a case-control study among a Chinese population. In addition, we also investigated whether the association between serum RBP4 levels and NSCLC risk was influence by body mass index (BMI) and smoking status.

2. Methods

2.1. Study population

This was a case-control study conducted between June 2018 and June 2019. The NSCLC cases recruited from Central Hospital of Xiaogan. Inclusion criteria for NSCLC cases:

(1) new cases (no more than 3 months prior to the diagnosis) of NSCLC without treatment, the first diagnosis time was between August 2017 and January 2019;
(2) confirmed by histological examination from the physician and medical records of hospitals at or above the county level; and
(3) signed informed consent, voluntary participation in research and good compliance. Participants were excluded if they simultaneously suffered a history of any other types of cancer.

Frequency matching method was used to select healthy residents who were similar to the case group in sex (5-year interval) and age, and who lived in the same area for more than 5 years as the control group. Except for a diagnosis, the same selection criteria for the cases were applied for controls. In total, 256 pair cases and controls were successfully recruited and had blood samples.

A written informed consent form was signed by all study participants. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and was approved by the Ethical Committee of Xiaogan Central Hospital.

2.2. Data collection

Investigators used a unified questionnaire to investigate the general situation (e.g., gender, age, height, nationality, education level, and occupation), family history of NSCLC and behavioral factors (eg, smoking status). Individuals were grouped as current smokers if a person who has smoked daily or occasionally in the last 30 days for at least 6 months, or as former smokers if a person who has a history of smoking for at least 6 months and currently stopped. Height and weight were measured and BMI was calculated by dividing weight (kg) by height (m^2).

The subjects were all in the morning state of fasting, 5 mL of peripheral venous blood was collected in a vacuum tube containing ethylenediaminetetraacetic acid and centrifuged at room temperature for 3 000 r/min for 10 minute. The upper serum was taken for measurement within 4 hours. Serum lipids, such as total cholesterol (TC), high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, and total triglycerides (TG), as well as fasting glucose (FBG) were measured with a Hitachi 7600–010 automatic analyzer.

The serum RBP4 level was determined by enzyme-linked immune absorbent assay. The kit was purchased from Kanto Chemical Company of Japan. Inter- and intra-assay coefficients of variation (Epercentages) were 5.9% and 3.0%.

2.3. Statistical analysis

The survey data was carried out using SPSS 21.0 software. Means and standard deviation was used for continuous variables, and independent t-test was used for comparison between the 2 groups. Categorical variables were expressed by presented as number and percentage and the difference was assessed using Pearson Chi square test. Serum RBP4 was categorized into tertiles (T1–T3) based on the distribution among controls for men and women separately.

We used unconditional logistic regression models to assess the odds ratios (ORs) and 95% CIs for the associations between serum RBP4 and NSCLC risk, using the lowest tertile as the reference group. Potential confounders were selected into multivariable adjusted models. In model 1, we only adjusted age and gender. In model 2, we further adjusted BMI, smoking status, education, household income, family history of cancer, TC, TG, HDL, LDL, and FBG. Tests for trend were calculated by including the categorical variables as continuous variables.

Stratified analysis by BMI ($<25\,kg/m^2$ vs $\geq 25\,kg/m^2$) and smoking status (current, ever or never) were also conducted. The interaction was assessed using the likelihood ratio test with a multiplicative interaction term.

Statistical analyses were conducted using the SPSS 13.0 software (Chicago, IL). Significance was set at 0.05 (2-sided).

3. Results

The characteristics for all patients are displayed in Table 1. NSCLC cases were more likely to report higher proportions of current smoking and family history of NSCLC than those in control group (all $P < .05$). The serum levels of TC, TG, LDL and RBP4 in the case group were higher than those in the control group (all $P < .05$), and HDL was lower than those in the control group ($P < .05$). There were no significant differences in sex, age, height, nationality, BMI, BMI grade, education level, occupation and FBG between the 2 groups (all $P > .05$). The mean serum RBP4 level was (36.05 ± 8.28) ug/mL for cases and (29.54 ± 7.71) ug/mL for controls, and the difference was significant ($P < .001$).

After adjusting age and sex (Table 2), participants with higher serum RBP4 level had increased risk of NSCLC (P trend $< .001$). The associations were attenuated but remained significant after further adjustments (P trend $= .001$) (Table 2). Comparing participants in the highest tertile, the odds ratio (95% CI) for those in lowest tertile were 1.85 (95% CIs 1.07–3.2) ($P = .029$) for the second tertile and 2.18 (95% CIs 1.37–3.45) ($P = .001$) for the highest tertile, respectively.

Multivariate linear regression analysis was conducted with RBP4 as strain and metabolic indices and basic clinical characteristics as independent variables (Table 3). The level of RBP4 in serum of NSCLC patients and controls were both positively correlated with BMI ($P = .003$ and .048) and the level of RBP4 in control group was also positively correlated with TG ($P = .041$).

Table 1

Clinical characteristics of included cases and controls.

Clinical characteristics	Cases (n = 256)	Control (n = 256)	*P*
Age, yr			.658
<60	117 (45.7)	122 (47.66)	
≥60	139 (54.3)	134 (52.34)	
Gender			.174
Men	203 (79.30)	190 (74.22)	
Women	53 (20.70)	66 (25.78)	
BMI, kg/m^2	24.81 ± 9.24	25.36 ± 8.91	.493
Smoking status			.032
Current smoking	105 (41.02)	90 (35.16)	
Ever smoking	72 (28.13)	100 (39.06)	
Never smoking	79 (30.86)	66 (25.78)	
Education level, n *(%)*			.226
Primary school below	48 (18.75)	62 (24.22)	
Primary school	69 (26.95)	66 (25.78)	
Secondary school	51 (19.92)	45 (17.58)	
High school	45 (17.58)	46 (17.97)	
High school above	43 (16.8)	37 (14.45)	
Household income, Yuan/month/person, n *(%)*			.281
≤1000	72 (28.13)	60 (23.44)	
1001∼3000	101 (39.45)	99 (38.67)	
3000∼5000	43 (16.8)	41 (16.02)	
>5000	40 (15.63)	56 (21.88)	
Family history of cancer			<.001
Yes	51 (19.92)	19 (7.42)	
No	205 (80.08)	237 (92.58)	
TC, mmol/L	5.15 ± 1.04	4.48 ± 0.96	<.001
TG, mmol/L	1.73 ± 0.34	1.29 ± 0.26	<.001
HDL, mmol/L	1.40 ± 0.52	1.98 ± 0.27	<.001
LDL, mmol/L	2.82 ± 0.37	2.42 ± 0.21	<.001
FBG, mmol/L	5.33 ± 0.69	5.24 ± 0.75	.158
RBP4, ug/ml	36.05 ± 8.28	29.54 ± 7.71	<.001

Continuous variables were described by means ± standard deviation; categorical variables were described by *n* (%).

BMI = body mass index, FBG = fasting glucose, HDL-C = high density lipoprotein-cholesterol, LDL-C = low density lipoprotein-cholesterol, RBP4 = retinol binding protein 4, TC = total cholesterol.

Stratified analysis by BMI showed that serum RBP4 level was positively associated with NSCLC risk among those with BMI < 25 kg/m^2 and ≥25 kg/m^2, whereas no significant association was found (*P* trends: .002 and .012; *P* interaction = .584) (Table 4). Similarly, after stratification by smoking status, higher serum RBP4 level was associated with increased NSCLC risk irrespective of smoking status, and the *P* trends were .015, .024, and .020 (*P* interaction = .357).

4. Discussion

In this case–control study, a significant positive association was found between serum RBP4 level and the risk of NSCLC.

Table 3

Correlation between serum retinol-binding protein 4 and metabolic index.

	Cases		Controls	
Index	*β*	*P*	*β*	*P*
BMI	0.281	.003	0.151	.048
HDL	0.042	.205	-0.102	.205
LDL	0.035	.712	0.024	.904
TC	0.069	.458	-0.008	.968
TG	0.081	.306	0.157	.041
FBG	0.002	.987	0.014	.935

BMI = body mass index, FBG = fasting glucose, HDL-C = high density lipoprotein-cholesterol, LDL-C = low density lipoprotein-cholesterol, TC = total cholesterol, TG = total triglycerides.

Stratified analysis by BMI and smoking status showed that the positive association of RBP4 level with NSCLC risk was found for all strata.

NSCLC is a serious threat to the health of every individual around the globe. The etiology of NSCLC is not completely clear up to now. A lot of data shows that there is a very close relationship between long-term smoking and the occurrence of NSCLC. Proven by previous studies, the probability of NSCLC in long-term heavy smokers is 10–20 times higher than that in non-smokers, and the younger the age at which smokers begin to smoke, the higher the risk of NSCLC.[11,12] Furthermore, smoking not only directly affects personal health, but also has a negative impact on the health of the surrounding population, leading to a significant increase in the incidence of NSCLC among passive smokers.[13,14] The incidence of NSCLC in urban residents is higher than that in rural areas, which may be related to urban air pollution and the carcinogens contained in smoke and dust.[15] Therefore, non-smoking should be advocated and urban environmental sanitation should be strengthened. Likewise, ionizing radiation, gene and other lung diseases such as pulmonary tuberculosis and bronchiectasis increase the risk of NSCLC.[16–18] This study shows that family history and smoking history of NSCLC can increase the incidence of NSCLC, which is consistent with many studies.[19]And the serum lipids TC, TG, LDL, RBP4 in NSCLC patients are higher than those in normal people, and HDL is lower than that of normal people. It shows that hyperlipidemia is related to the incidence of NSCLC.

Early diagnosis of NSCLC is of great significance because only by early diagnosis and treatment of NSCLC can we obtain better curative effect. There is no typical symptom in the early stage of NSCLC, chest X-ray screening should be carried out regularly for people over 40 years old, and patients with primary or metastatic symptoms of NSCLC should be examined by chest X-ray or chest CT in time.[20] When lung mass shadow is found, the diagnosis of NSCLC should be considered first, and further examination

Table 2

Odds ratio (95% CIs) of non-small cell lung cancer for tertiles of serum retinol-binding protein 4.

RBP4, ug/mL	Cases (*n* = 256)	Controls (*n* = 256)	*OR*[*]	*P*	*OR*[†]	*P*
<23.5	49 (19.14)	87 (33.98)	1.00		1.00	
23.5∼32.7	60 (23.44)	53 (20.7)	1.89 (1.11–3.21)	.019	1.85 (1.07–3.2)	.029
≥32.7	147 (57.42)	116 (45.32)	2.21 (1.42–3.44)	<.001	2.18 (1.37–3.45)	.001

BMI = body mass index, FBG = fasting glucose, HDL-C = high density lipoprotein-cholesterol, LDL-C = low density lipoprotein-cholesterol, OR = odds ratio, TC = total cholesterol.

[*] Covariates adjusted for age and gender.

[†] Covariates adjusted for age, gender, BMI, smoking status, education, household income, family history of cancer, TC, TG, HDL, LDL, and FBG.

Table 4

Stratification analyses for association between tertiles of serum retinol-binding protein 4 and non-small cell lung cancer*.

	RBP4, ug/mL	Cases (n=256)	Controls (n=256)	OR (95%CIs)	P
BMI, kg/m^2					
<25	<23.5	30 (20.41)	60 (36.81)	1	
	23.5–32.7	40 (27.21)	29 (17.79)	2.759 (1.442–5.276)	0.002
	≥32.7	77 (52.38)	74 (45.4)	2.081 (1.210–3.579)	0.008
≥25	<23.5	19 (17.43)	27 (29.03)	1	
	23.5–32.7	20 (18.35)	24 (25.81)	1.184 (0.514–2.728)	0.691
	≥32.7	70 (64.22)	42 (45.16)	2.36 (1.175–4.772)	0.016
Smoking status					
Current smoking	<23.5	15 (14.29)	27 (30)	1	
	23.5–32.7	32 (30.48)	22 (24.44)	2.618 (1.139–6.019)	0.022
	≥32.7	58 (55.24)	41 (45.56)	2.546 (1.206–5.376)	0.013
Ever smoking	<23.5	16 (22.22)	36 (36)	1	
	23.5–32.7	8 (11.11)	13 (13)	1.385 (0.480–3.994)	0.546
	≥32.7	48 (66.67)	51 (51)	2.118 (1.043–4.301)	0.036
Never smoking	<23.5	18 (22.78)	24 (36.36)	1	
	23.5–32.7	20 (25.32)	18 (27.27)	1.481 (0.613–3.581)	0.382
	≥32.7	41 (51.9)	24 (36.36)	2.278 (1.032–5.029)	0.040

BMI = body mass index, FBG = fasting glucose, HDL-C = high density lipoprotein-cholesterol, LDL-C = low density lipoprotein-cholesterol, RBP4 = retinol binding protein 4, TC = total cholesterol, TG = total triglycerides.

* Covariates adjusted for age, gender, BMI, smoking status, education, household income, family history of cancer, TC, TG, HDL, LDL, and FBG.

should be made to make a definite diagnosis through histopathological examination. At present, there is no good serum markers for diagnosis and differential diagnosis of NSCLC, so it is very important to find serum markers for diagnosis of NSCLC.

RBP4 is a kind of protein responsible for binding and transporting active metabolites of vitamin A retinol in vivo, which plays an important role in assisting vitamin A to play its physiological role.[21] RBP4 can specifically bind all-trans retinol to vitamins and it is mainly synthesized by hepatocytes, followed by adipocytes.[22] After RBP4 was released into blood, it binds to retinol and thyroxine carrier proteins and forms a retinol-RBP4-TTR ternary complex in the form of 1:1:1, which transports retinol to target tissues for specific physiological functions.[23] Early studies found that RBP4 was associated with fatty liver, glycolipid metabolic diseases such as diabetes mellitus and cardiovascular diseases.[4,24] It was deemed that RBP4 was a fat-derived factor in the blood and was considered as an important target for the treatment of type 2 diabetes mellitus (T2DM), insulin resistance, non-alcoholic fatty liver and visceral obesity. Yamaaki et al[25] indicated that the level of RBP4 in serum was independently and positively correlated with remnant-like particles triglyceride in subjects with T2DM, which suggested that RBP4 was involved in regulating the pathway of glucose metabolism in patients with T2DM. It has been reported that a region near the RBP4 gene on human chromosome 10q is closely related to the high risk of T2DM. Saucedo et al[26] used data from100 pregnant women and 100 normal women, the results showed that the 2 variant genotypes of RBP4 (rs3758539 and rs34571439) were closely related to insulin level and insulin resistance in gestational diabetic women. Healthy non-diabetic high-risk population, Bose et al[27] showed that high levels of serum RBP4 was positively correlated with serum insulin and blood sugar, which could be used as a predictor of diabetes. In recent years, studies have shown that RBP4 is related to the occurrence and development of tumors. RBP4 is highly expressed in many malignant tumors, such as breast cancer,[10] pancreatic cancer,[7] colon cancer[28] and is related to the invasion and metastasis of tumors. Studies have shown that the higher the expression level of RBP in ovarian cancer, the higher its metastasis and invasion ability.[29]

The results showed that the level of RBP4 was correlated with the risk of NSCLC, and the risk of NSCLC rose with the increase of RBP4 level. It is suggested that RBP4 level is an independent risk factor, and early detection of RBP4 may have a good predictive value for the detection of high-risk population of NSCLC. Smoking and BMI are important confounding factors in the analysis of the association between RBP4 and NSCLC. In order to reduce the residual confounding interference of smoking and BMI, this study made a detailed stratified analysis of the relationship between RBP4 and NSCLC adjusted the possible confounding factors. Our results show that the serum RBP4 level of NSCLC patients is higher than that of the control group regardless of whether they smoke or quit smoking. The increase of serum RBP4 level in patients with NSCLC also increases the risk of NSCLC, indicating that serum RBP4 level is positively correlated with the occurrence of NSCLC and is a risk factor for NSCLC. It is also worth noting, we found that after adjusting for age, sex, smoking and family history, serum RBP4 levels in NSCLC patients were positively correlated with BMI, suggesting that serum RBP4 levels in NSCLC patients were also related to metabolic factors such as obesity, which was consistent with relevant reports.[30]

As a case-control study, this study inevitably has some limitations. First, selection bias, such as admission bias, is difficult to rule out in a case-control study. The NSCLC cases were recruited from only 1 hospital. Second, we collected the serum samples after the cases diagnosed, thus the associations do not necessarily indicate causality. To minimize this bias, we included only newly diagnosed cases and interviewed them as we collected samples before treatment. Third, although some known confounders that might be strongly associated with the risk of NSCLC (eg, gender and smoking status) were adjusted, there was still the possibility of residual confounding from additional

factors. Fourth, random measurement error for serum RBP4 is also of concern in the estimation of usual level, since this misclassification bias is likely to lead the OR to the null, and thus our results may tend to be conservative.

To sum up, our study indicated that serum RBP4 level was positively related to the risk of NSCLC. However, the use of serum RBP4 as an indicator for NSCLC needs to be confirmed by further large-scale and prospective studies.

Author contributions

Conceived and designed the research: Shaomin Wang.
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Data analysis and interpretation: Xiaoping Hu.
Drafting of the manuscript: Xiaoping Hu.

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