

# Meta-analysis of lung cancer in Chinese population in genetic predisposition

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**Abstract.** The prevention and diagnosis of lung cancer in the Chinese population has received extensive attention in past few years. Many studies have suggested that genetic predisposition may be a risk factor for lung cancer and an important means for early diagnosis of carcinoma of the lung . At present, the research on the molecular mechanism of lung cancer has been carried out on the whole genome, and a large number of SNPs have also been found in the Chinese population, these results suggest that the genetic predisposing factors of lung cancer in Chinese population are different from those in foreign population.

## 1. Introduction

Lung cancer is the second most common malignant tumor in the world with the highest mortality [1] . By 2020, lung cancer will be ranked as the world's largest cancer. Today, lung cancer is still the world's leading cause of death. In 2020, there were about 9958,133 cancer deaths and 1796,144 cases of lung cancer worldwide, accounting for 18.0% [2] of total lung cancer mortality. In recent years, research at the genetic predisposition has focused on early detection and treatment of lung cancer. Therefore, the study based on genetic susceptibility provides new insights into the pathogenesis and effective screening and treatment of lung cancer. Single-nucleotide polymorphism is a DNA variation produced at the genome level by the transposition or transposition of a single nucleotide, and is the most common type of heritable variation in the human. Numerous studies have confirmed that the incidence of lung cancer may be significantly affected by genetic factors. A study by Wang [3] suggests that the rs17079281 locus C>T on the *DCBLD1* promoter of 6q22.2 may reduce the risk of lung adenocarcinoma by creating a YY1 binding site that inhibits the expression of *DCBLD1*. Khadhraoui [4] found that people with a heterozygous rs1982809-AG genotype for the B and T lymphocyte attenuator (*BTLA*) had a higher risk of lung cancer. In addition, we found that the same type of SNP mutation in different ethnic groups in different regions has different effects on the risk of lung cancer. Long-term environmental interactions produce genetic mutations that lead to genetic evolution, while nicotine dependence and smoking are sick factors for lung

cancer. Although nicotine itself can not cause cancer, many researchers have demonstrated that nicotine has many characteristics of promoting tumor development through in vivo and in vitro experiments[5-11]. Genetic association studies have shown that variations in the *CHRNA3* gene cluster on chromosome 15q24-25.1 are associated with nicotine dependence, smoking and lung cancer risk in populations of European descent. In addition, the *CHRNA3* SNP ( rs16969968 ) was also associated with nicotine dependence in European American [12] , but not in African Americans. However, Niu [13] and others have found that the allele frequency of Asian population is lower than that of white population by exploring the same SNP ( rs16969968 ) of *CHRNA3* gene in Chinese Han population. We think that Asian population has lower nicotine dependence than white population, which may reduce the risk of lung cancer in Asian population. We believe that the Asian population is less nicotine dependent than the white population. This may reduce the risk of lung cancer in people in Asia, which reflects differences in genetic mutations across regions and ethnic groups that have different effects on lung cancer. A controlled research on the basis of the Chinese Han population found that the GT genotype at rs3743073 was significantly associated with an increased risk of lung cancer. The type of G mutation at rs3743073 was associated with significantly reduced survival in non-small cell carcinoma (NSCLC) . Therefore, the mutation types of the same SNP locus have different effects on the patients with lung cancer in different nationalities. In a mouse study [14] , a dominant mutation at the rs2279744 (T/G) site significantly increased the risk of lung cancer in mice, as demonstrated in Bangladeshis, who found that

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carrying the TG or GG allele at rs2279744 was a high penetration risk factor for carcinoma of the lungs (OR = 2.13). However, in China, the TG and GG genotypes were considered as a low-permeability risk factor for lung cancer (OR = 1.21)[15]. Overall, the incidence, mortality, and cure rates of lung cancer are influenced by genetic predisposition.

Based on the above literature, we found that SNP mutations affect the prevalence of lung cancer. Therefore, SNP mutation can be used as an early diagnostic marker of lung cancer, so as to achieve the effect of early prevention. Research suggests [16] that *MMP-9* and *MMP-13* Single-nucleotide polymorphism are found in the metalloproteinase of South China, the CC genotype of *MMP9-1562* CT and GG genotype of *MMP13-77* G/A were associated with increased NSCLC risk. *MMP-13* and *MMP-9* may be the key oncogenes in the NSCLC. Therefore, the combined detection of SNP and enzyme activity between *MMP-9* and *MMP-13* may be a potential diagnostic method for NSCLC. SNP mutations can be used not only for early diagnosis, but also for late treatment. To evaluate the association between genetic variants in T cell cancer immune response genes and clinical outcomes in NSCLC patients, Wang [17] explored 2,450 SNPs of T-cell cancer immune response-related genes. rs1964986 (*TRB*) is an important variant associated with the risk of recurrence, while rs10108662 (*IDO1*) is an important SNP associated with the risk of death from lung cancer. The study found that lung adenocarcinoma is a highly heterogeneous illness, with patients often exhibiting different histopathology, genetic changes, and genomic aberrations, making it difficult to predict and diagnose the disease. It's also interfering the patient's recovery. For prognostic survival, Zhang [18] explored the association between rs7214723 of the Ca<sup>2+</sup>/calmodulin-dependent protein kinase 1(*CAMKK1*) gene and prognosis in patients with lung cancer, recessive genotype CC significantly increased the overall survival rate, inhibited the proliferation and migration of cancer cells, and promoted cell apoptosis. In addition, the CC genotype of rs7214723 (*CAMKK1*) significantly reduces the risk of death in men, those with a history of smoking, or those with stage III + IV cancer. These studies provide numerous genetic markers for molecular diagnosis of lung cancer and indicates that genetic mutation as a molecular diagnosis of lung cancer will play a greater role in the medical field. Compared with traditional disease diagnosis, molecular diagnosis has the advantages of more accurate, reliable and early diagnosis, which is helpful for doctors to carry out early prevention, early diagnosis and early treatment of genetic disorder.

Previously, we have shown that genetic mutations can be used as an indicator for the early diagnosis and prevention of lung cancer, and for patients who already have lung cancer during drug therapy, a number of studies have also confirmed that some SNP mutations may cause more severe adverse reactions during treatment. Regarding the efficacy hematologic toxicity of functional SNP *CDA 435* C > T in Chinese NSCLC patients treated with Gissi, Hu [19] recruited 63 patients with stage IB or IIIA lung cancer and 100 patients with advanced NSCLC, which were treated with the Gissi-platinum regimen. The

results showed that patients with *CDA 435* C/T or T/T genotype had better efficacy. Similar effects can be seen in docetaxel. Docetaxel is a cytotoxic drug widely used in the treatment of various cancers, SNP mutations in the ATP-binding cassette (ABC) transporter/multidrug resistance protein (MRP) *ABCC10/MRP7* gene involved in the transport of statins are associated with drug resistance and metabolism. The study of Kazuki [20] and others on the variation of blood samples from NSCLC patients indicated that the T/C polymorphism of *ABCC10* ( rs2125739 ) was significantly associated with the cytotoxicity of docetaxel, patients without the T/C genotype, on the other hand, have febrile neutrophil. In conclusion, SNP plays a part in the diagnosis, treatment and prognosis of lung cancer.

Here, we systematically reviewed the literature on SNP in lung cancer in Pub-Med nearly three years and meta-analyzed the SNP sites that were qualified for quality evaluation. The final study included nine articles and compared SNP mutations involved in lung cancer studies to date, through a systematic review of meta-analysis, we see more protective and risky genetic mutations for lung cancer in the Chinese, which can be used as a marker for molecular diagnosis in the Chinese population, for the Chinese population for the prevention and treatment of lung cancer to create a new program. Our systematic review provides a reference for the study of genetic predisposing factors of lung cancer in China, and provides a basis for the prediction and treatment of lung cancer in later stage.

## 2. Method

### 2.1 Document retrieval and exclusion

In this paper, we used the keyword "lung cancer, SNP" to search Pub Med database, and selected the literatures related to the genetic predisposing factors of lung cancer in recent three years, we used the publication date from 2019 to February 2022 as the time screening criteria for inclusion in the literature. After that, the meta-analysis literature was selected according to the strict inclusion and discharge criteria. The main results were as follows: (1) the topic of the article was related to the SNP of lung cancer; (2) the meta-analysis articles were excluded; (3) the data were complete. Such as: with OR value and SNP specific distribution of mutation; (4) Case-control study; (5) NOS rating scale up to standard.

### 2.2 Data extraction

Extract relevant raw information from all eligible studies. Data extraction is done by a team, the following data were collected from each study: First Author's name, year of publication, country, population's race, genotyping method, sex, smoking status, stage of lung cancer, the main studies were the observed OR, P values and genotype frequencies in both cases and controls.

## 2.3 Quality assessment

The quality of observation studies was assessed using Newcastle-ottawa scale (NOS), which were conducted by at least two or more team members. NOS mainly includes 8 items, divided into three aspects: study group selection, comparability and benefit exposure. The quality score for the study was as follows: for selection and exposure, each item scored a maximum of 1, and for comparability, a maximum of 2. Studies with a score of more than 5 (up to a maximum of 9) are considered "high quality", while studies with a score of less than 5 are considered "low quality".

## 2.4 Statistical analysis

Software was used to analyze the data, and the results were expressed by the value of the two-category variable relative risk coefficient, OR, RR, and 95% CI. Statistical heterogeneity of literature was evaluated by  $\chi^2$  test. If there was no significant difference ( $P > 0.05$ ), random effect model was used to analyze the sensitivity and

subgroup, because there are many factors affecting lung cancer susceptibility, the author selected the regional factors from the literature and analyzed them, observed the differences of lung cancer susceptibility between different regions, and explored the overall heterogeneity of the source.

## 3. Result

### 3.1 Results of literature search and inclusion

204 articles published between 2019 and February 2022 were selected by searching the Pub-Med electronic database using terms such as "lung cancer". Using strict inclusion and exclusion criteria, we first excluded 99 articles by searching for SNP unrelated to lung cancer, and then conducted a meta-analysis of 9 articles, thirty-one articles with incomplete data and 34 articles without control were deleted. Finally, 9 articles were selected (Fig. 1) by using the paper quality evaluation table, (Table 1, Table 2) meta analysis was performed on 10,083 controls and 9,946 patients. (Table 3)

Table 1 NOS

#### NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

##### Selection

- 1) Is the case definition adequate?
  - a) yes, with independent validation \*
  - b) yes, eg record linkage or based on self reports
  - c) no description
- 2) Representativeness of the cases
  - a) consecutive or obviously representative series of cases \*
  - b) potential for selection biases or not stated
- 3) Selection of Controls
  - a) community controls \*
  - b) hospital controls
  - c) no description
- 4) Definition of Controls
  - a) no history of disease (endpoint) \*
  - b) no description of source

##### Comparability

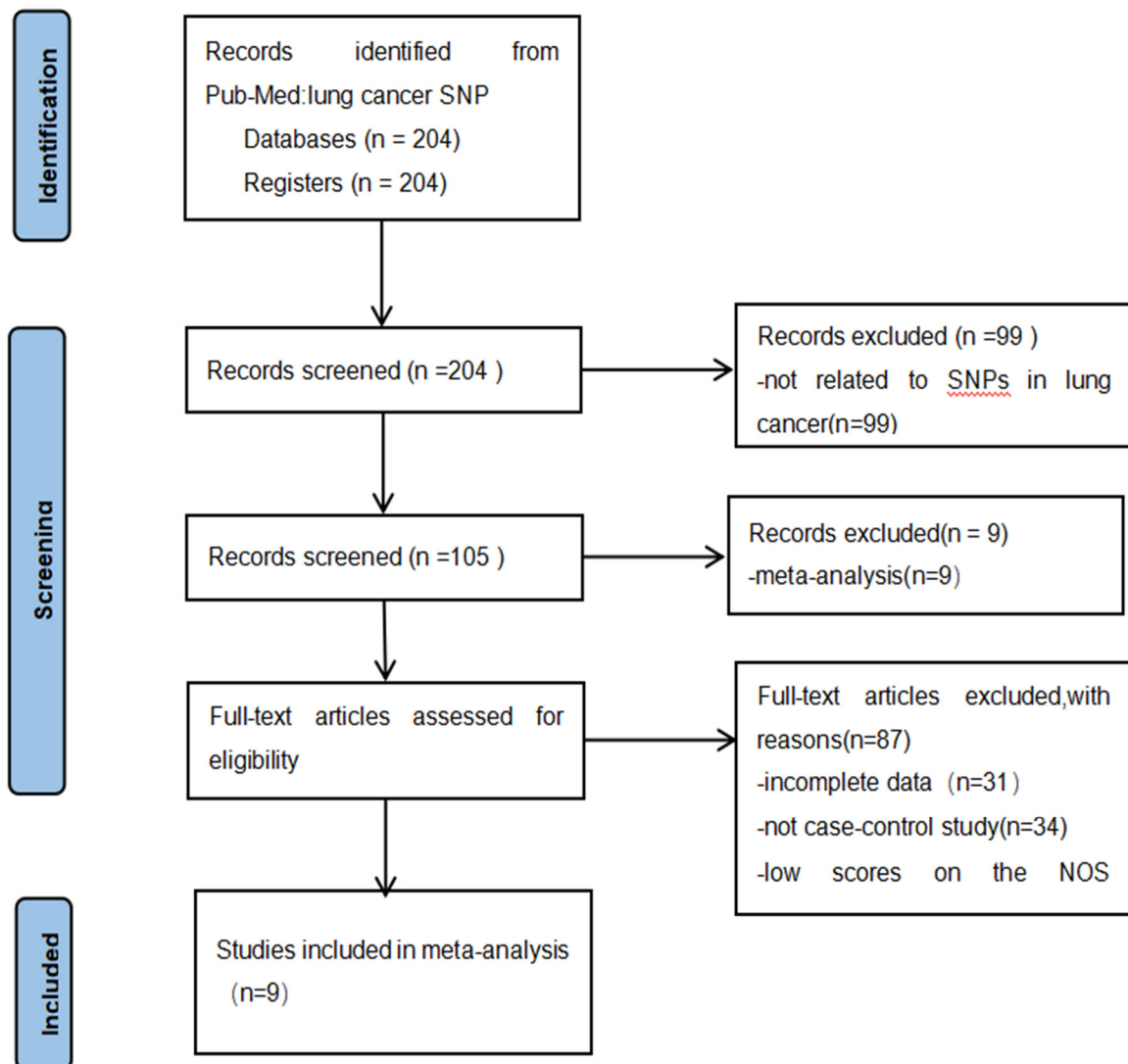
- 1) Comparability of cases and controls on the basis of the design or analysis
  - a) study controls for \_\_\_\_\_ (Select the most important factor.) \*
  - b) study controls for any additional factor \* (This criteria could be modified to indicate specific control for a second important factor.)

##### Exposure

- 1) Ascertainment of exposure
  - a) secure record (eg surgical records) \*
  - b) structured interview where blind to case/control status \*
  - c) interview not blinded to case/control status
  - d) written self report or medical record only
  - e) no description
- 2) Same method of ascertainment for cases and controls
  - a) yes \*
  - b) no
- 3) Non-Response rate
  - a) same rate for both groups \*
  - b) non respondents described
  - c) rate different and no designation

**Table 2** Article evaluation results

question/article	1.Qian Y	2.Liu D	3.Hu W	4.Yu WL	5.Li W	6.Long J	7.Wang WP	8.Wang R	9.Yang S
case definition adequate	★	★	★	★	★	★	★	★	★
representation of medical records	★	★	★	★	★	★	★	★	★
choice of controls	★	★	★	★	★	★	★	★	★
definition of controls	★	★	★	★	★	★	★	★	★
comparability of cases and controls	★	★	★	★	★	★	★	★	★
ascertainment of exposure	★	★	★★	★	★	★★	★	★	★
ethod of ascertainment for cases and controls	★	★	★	★	★	★	★	★	★
non-response rate	★	★	★	★	★	★	★	★	★
score	7	6	6	6	6	7	6	6	7



**Figure.1** Article filtering flow chart

**Table 3** Basic information of the article

Literature	Genotype	Demographic	Number		Total (n)	Method
			Case	Control		
Wei-Ling Yu,2021	PRNCR1,RS1456315,CC	Han population in southern China	30	30	60	TapMan
Wei-Ling Yu,2021	PRNCR1,RS1456315,TT	Han population in southern China	231	210	441	TapMan
Wei-Ling Yu,2021	PRNCR1,RS1456315,TC	Han population in southern China	175	185	360	TapMan
Wei-Ling Yu,2021	PRNCR1,RS1456315,C	Han population in southern China	235	305	540	TapMan
Wei-Ling Yu,2021	CCAT2,RS6983267,TG	Han population in southern China	219	219	438	TapMan
Wei-Ling Yu,2021	CCAT2,RS6983267,GG	Han population in southern China	110	90	200	TapMan
Wei-Ling Yu,2021	CCAT2,RS6983267,G	Han population in southern China	439	401	840	TapMan
Dan Liu,2021	BRCA1,RS799917,C/T	Han Chinese people in Liaoning Province	278	319	579	TaqMan quantitative PCR
Dan Liu,2021	BRCA1,RS799917,T/T	Han Chinese people in Liaoning Province	81	99	180	TaqMan quantitative PCR
Wen Li,2019	MMP13,RS2252070,AA	People in southern China	108	140	248	PCR-RFLP
Wen Li,2019	MMP-13, RS2252070,A	People in southern China	310	367	677	PCR-RFLP
Wen Li,2019	MMP-9, RS3918242,CT	People in southern China	44	85	129	PCR-RFLP
Wen Li,2019	MMP-9 ,RS3918242,C	People in southern China	446	431	877	PCR-RFLP
Wan-ping Wang,2021	ERBB4,RS1836724,C	Chinese Han people	228	150	378	TapMan-MGB
Wan-ping Wang,2021	ERBB4,RS1836724,CC	Chinese Han people	64	28	92	TapMan-MGB
Jieyi Long,2021	OCRs,RS13064999,AA	Chinese	245	197	442	Sequenom MassArray;TapMan
Weiwei Hu,2019	Ang-2 RS12674822,GT	Chinese Han people	352	407	759	TapMan
Ying Qian,2021	SHBG,RS12233719,TT	Shenyang never smoked women	8	10	18	TapMan
Ying Qian,2021	SHBG,RS12233719,TG	Shenyang never smoked women	128	78	206	TapMan
Ying Qian,2021	SHBG,RS12233719,TT	Tianjin never smoked women	8	1	9	TapMan
Ying Qian,2021	SHBG,RS12233719,TG	Tianjin never smoked women	78	63	141	TapMan

### 3.2 Partial results of Meta analysis

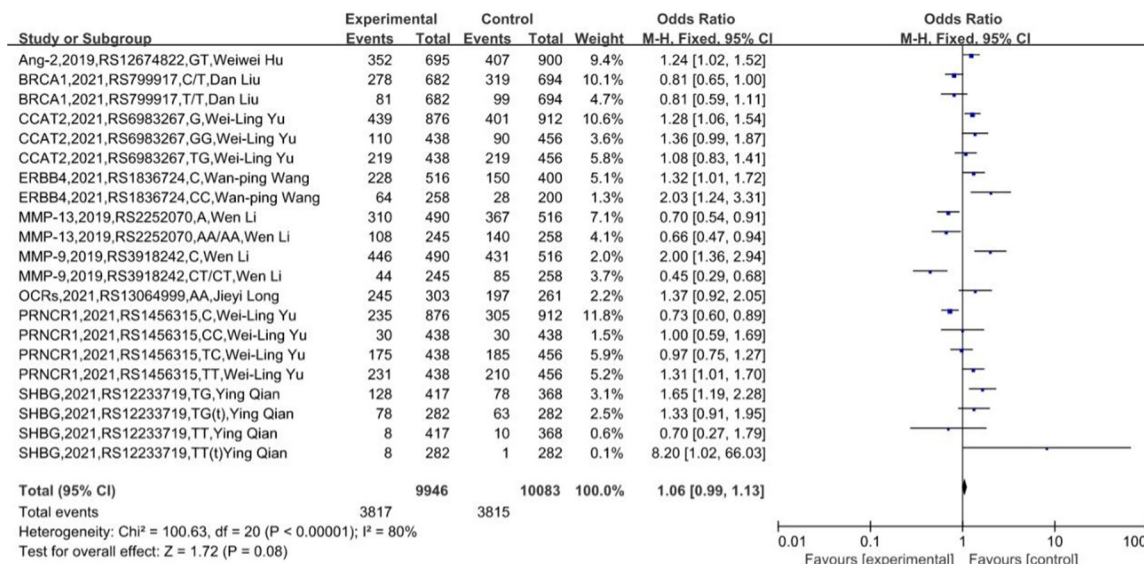
In this study, we studied rs1456315 (*PRNCR1*, CC, TT, TC, C), rs6983267 (*CCAT2*, TG, GG, G), rs799917 (*BRCA1*, C/T, T/T), rs2252070 (*MMP-13*, AA, A), rs3918242 (*MMP-9*, CT, C), rs1836724 (*ERBB4*, C, CC), rs13064999 (*OCRs*, AA), rs12674822 (*Ang-2*, GT), rs12233719 (*SHBG*, TT, TG) reintegrates the genetic predisposing factors of lung cancer. In addition, for SNP rs1456315 (*PRNCR1*), rs6983267 (*CCAT2*) and rs799917 (*BRCA1*), subgroup analysis was performed by

region. Firstly, five genes were identified as protective factors for lung cancer, including rs1456315 (*PRNCR1*, CC, TC, C), rs799917 (*BRCA1*, C/T, T/T), rs2252070 (*MMP-13*, AA, A), rs3918242 (*MMP-9*, CT), rs12233719 (*SHBG*, TT). In addition, 13 loci of 7 genes were risk factors for lung cancer, including: rs12674822 (*Ang-2*, GT), rs6983267 (*CCAT2*, G, GG, TG), rs1836724 (*ERBB4*, C, CC), rs3918242 (*MMP-9*, C), rs13064999 (*OCRs*, AA), rs1456315 (*PRNCR1*, TT), rs1223719 (*SHBG*, TG). In our forest map, we found that the C mutation of *ERBB4* was a risk factor for lung cancer, and as the probability of C mutation increased, the risk of lung cancer was significantly increased in the Chinese



population (OR = 2.03, fig2) . In addition, we found that the a gene of *MMP-13* was a protective factor for lung cancer, and the OR value increased with the increase of a frequency (OR = 0.66) . We also found that the T mutation of rs12674822 of Ang-2 gene was a risk factor for lung cancer (OR = 1.24) , and the AA genotype of rs13064999

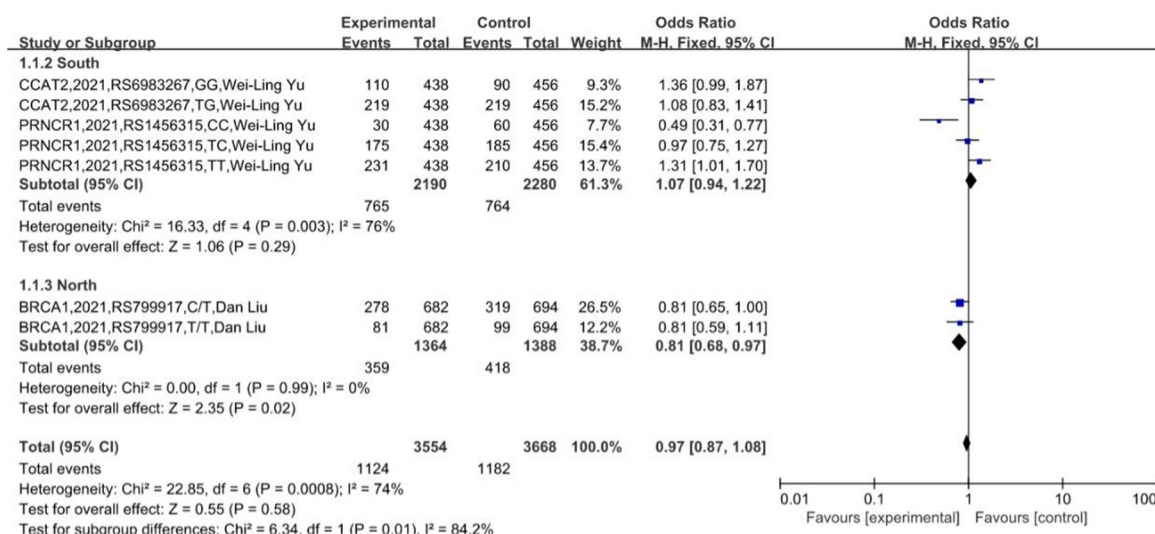
of OCRs was also a risk factor for lung cancer (OR = 1.37) . *SHBG*'s rs12233719 TT genotype was a protective factor (OR = 0.70) for lung cancer in Liaoning province, China, but a risk factor (OR = 8.20) for lung cancer in Tianjin, China. *SHBG*'s rs12233719 TG genotype is a risk factor for both Liaoning and Tianjin populations in China.



**Figure.2** Forest map of all genotypes

To further explore the effect of genetic differences between regions on lung cancer in Chinese populations, we looked at genetic predisposition differences between Chinese Han populations from north to south. By subgroup analysis, we found that CC, CT genotype of the SNP rs1456315 of *PRCA1* gene were protective factors of lung cancer, TT was risk factor of lung cancer (OR = 1.31, Fig3) , however, no relevant studies in the northern Han population suggest that the locus of this gene is a risk factor for lung cancer. In the Han population of southern

China, we found that the rs1456315 SNP of *PRCA1* was associated with a lower risk of lung cancer (OR = 0.49) as the genotype with C mutation increased. So C gene is the protective gene of lung cancer in Han population in South China. In addition, GG and TG genotypes at SNP rs6983267 locus of *CCAT2* were risk factors for lung cancer. Finally, we found that both T/T and C/T of SNP rs79917 locus in *BRCA1* were protective factors for lung cancer in the Han population of northern China, which has not been reported in the Han population of southern China.



**Figure.3** North and south sub-group forest map

## 4. Discussion

In order to study the Single-nucleotide polymorphism of lung cancer susceptibility in Chinese, we used forest plot in meta-analysis and subgroup analysis of population. First, we found that the TG genotype of rs12233719(*SHBG*) was a risk factor for lung cancer in women who had never smoked in Liaoning and Tianjin, China, while TT genotype was a risk factor for women who had never smoked in Tianjin and a protective factor for women who had never smoked in Liaoning. Secondly, as the gene frequency increases, the corresponding OR value will also change. Finally, regional factors also influence the genetic predisposition of lung cancer. In the process of data collection and processing, we found that the NOS scale evaluation of the article in the process also appeared some problems. The question of "does the article describe the non-response rate" in the questionnaire is the most common one in the screening of articles. On closer inspection, we found that none of the 9 papers included described the non-response rate problem. The non-response rate refers to the proportion of cases and controls who are unwilling to participate in the study, which has the role of scientific judgment on whether the data source of the literature is objective and reasonable. Secondly, few of the 9 literatures used community control, most of them used hospital control, and individual studies did not describe the source of control, which made the reliability and accuracy of the literature data source doubtful. This study therefore suggests that additional research into this issue is needed to increase the credibility of the study in the genetic predisposition.

In our literature review, we found that researchers were more interested in exploring targeted drugs for lung cancer treatment than in the genetic predisposition. In the past three years, the number of genome wide Genetic predisposition for lung cancer has dropped dramatically, slowing the search for genetic predisposing factors in modern Chinese Han populations. Although the results of some European researchers suggest candidate sites, such as Zawadzka [21], to assess the relationship between ABCB1 gene SNP3435 and lung cancer gene expression in Poles by PCR. The results showed that the distribution of genotype incidence was similar to that of Caucasians, German Caucasians, French and even Chinese, but unlike Africans, Africans dominated the CC genotype [22-26]. However, such candidate sites are not representative of the genetic susceptibility mechanism of lung cancer in Chinese and even Asian populations due to population evolution and population drift. There is a large genetic gap in the prevalence of carcinoma of the lungs. Truong [27] identified rs16969968(15q25) as a risk factor for lung cancer in Europeans by genotyping of Europeans and Asians, none of the 15q25 variants was linked to lung cancer in Asians. Tantai [28] used meta-analysis to analyze the SNP in 6p21(rs4324798, rs3117582 and rs9295740) for lung cancer genetic predisposition, rs9295740 is associated with an increased risk of lung cancer in Caucasians, and there is no evidence in any model for a significant association of this SNP in the East

Asian population. Yao [29] studied the NSCLC susceptibility of *ERAP1* SNPs (rs26653G > C, rs26618T > C, rs30187C > T and rs27044C > G) in Chinese and Polish subjects, but not among Poles. These discoveries increase by racial differences in the genetics of lung cancer susceptibility. Therefore, we should attach importance to the exploration of risk sites of lung cancer in China and strengthen the research in this area. It is suggested that a larger Han study sample should be included to explore the susceptibility of the whole genome.

Finally, this article has many limitations, such as the small sample size, the insufficient persuasiveness of the result analysis and the short time-span of data collection, more studies and data on the Chinese population are needed to support our conclusions.

## 5. Conclusion

Our meta-analysis combined 13 loci that had been studied as risk factors and 8 as protective factors for lung cancer in the population of China. These loci possess different genotype frequencies and risk in populations from different regions of China. In the end, we found a relatively small sample size of lung cancer related genetic predisposition in the Chinese population, which is expected to expand later. Our study provides guidance and reference significance for the later study of population of China.

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