ABO blood classification and the risk of lung cancer: A meta-analysis and trial sequential analysis

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Abstract. Patients with certain ABO classifications are at increased risk of certain types of malignancies. In the present study, a meta-analysis was performed to explore the association between the ABO blood group and the risk of lung cancer from an evidence-based medical perspective. The PubMed, Embase, Web of Science, Medline, China National Knowledge Infrastructure, Google Scholar, Science Direct and Wanfang databases were searched for relevant papers. Review Manger 5.4 was used to analyze the association between the ABO blood group and the risk of lung cancer. Trial Sequential Analysis (TSA) was used to determine whether the sample size of the meta-analysis was sufficient. A total of 29 studies were included in this paper. The results of the case-controlled studies showed that the proportion of patients with blood type A in patients with lung cancer was significantly higher than that in healthy individuals [odds ratio (OR), 1.10; 95% confidence interval (CI), 1.02-1.19]. Based on the subgroup analysis, type A blood showed heterogeneity in ethnicity and source of control (social or hospital). Additionally, type O blood was determined to be a protective factor for lung cancer in Caucasians (OR, 0.92; 95% CI, 0.85-0.99). TSA results suggested that there were sufficient participants in the case-controlled studies. Overall, the results of the cohort studies showed that the risk of lung cancer and blood type were weakly associated, and that the difference was not statistically significant. The case-controlled studies suggested that blood type A was associated with a higher risk of lung cancer. In addition, the analysis confirmed that Caucasians with type O blood had a lower risk of lung cancer. However, prospective cohort studies have not been able to draw this conclusion. Different experimental designs may have had a notable influence on the results obtained.

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Introduction

Lung cancer is one of the leading causes of cancer morbidity and mortality in the world. According to GLOBOCAN estimates for 2020, lung cancer is the most common type of cancer in men and the third most common type of cancer in women (1). Furthermore, lung cancer has the highest cancer-associated death rate in men and the second highest cancer-associated death rate in women (1). The World Health Organization predicts that by 2025, the number of individuals with lung cancer in China will reach 1 million (2). Thus, lung cancer is a considerable public health concern.

The development of lung cancer is affected by several factors, such as environmental and genetic factors (3). Environmental factors include smoking, drinking, infection and exposure to ionizing radiation, amongst others (4). As environmental factors play such a strong role in lung cancer, less attention is paid to genetic factors. The ABO blood types are a very stable genetic trait. Reports have linked it to cancer risk (5-7); however, the molecular mechanisms involved are less clear. Blood group antigens may influence systemic inflammatory responses associated with malignancy (8-11). In addition, blood group antigens are expressed in several tissues, including certain malignant cells. However, there are some differences between ABO antigens expressed on the surface of malignant cells and those on normal tissues (12,13). This may influence the behaviors of the tumor cells, thereby promoting or inhibiting the proliferation of tumor cells (14).

The association between gastric cancer and blood type A was first noted by Aird *et al* (5) in 1953. Since this, a study by Hems (6) reported a correlation between breast cancer and type A blood, and a study by Vioque and Walker (7) also reported that type A blood was associated with an increased risk of pancreatic cancer in 1991. There have been several reports on the association between lung cancer and blood type. However, consistent conclusions have not been drawn. Urun *et al* (15) showed that non-O blood types were associated with an increased risk of lung cancer. However, Peng *et al* (16) reported that the occurrence of lung cancer was independent of blood type. Association studies with small sample sizes lack statistical power and may result in contradictory results. Based on the aforementioned points, a

meta-analysis was conducted on the association between the ABO blood classification types and the occurrence of lung cancer.

Materials and methods

Search strategy. A comprehensive search of PubMed (pubmed.ncbi.nlm.nih.gov/), Embase (embase.com/landing?status=grey), Web of Science (webofscience.com), Medline (https://www.nlm.nih.gov/medline/index.html), China National Knowledge Infrastructure (CNKI, https://www.cnki.net/), Google Scholar (scholar.google.com), Science Direct (https://www.sciencedirect.com) and Wanfang databases (https://www. wanfangdata.com.cn/) was performed for studies published before February 1, 2022. The following English search strategy was used: ('lung carcinoma' OR 'lung cancer') AND 'ABO'. A manual search was performed by reviewing a list of references in the retrieved studies. The studies were included if they were in English or Chinese only.

Eligibility criteria. The literature inclusion criteria were: i) Clear pathological diagnosis and ABO blood group typing; ii) case-controlled study or a cohort study; iii) the source and the raw data for the cases and controls were present; and iv) data on ethnicity, geographical distribution and publication year of the study were available.

The exclusion criteria were: i) Review articles and meta-analyses; ii) irrelevant or repetitive literature; iii) studies without a control group; and iv) studies with no useful data.

Data extraction. Information was extracted from all eligible studies by two reviewers independently. The information was then cross-checked to ensure no required data were missing. The following variables were extracted from each study: The year of publication, the name of the first author, the country of origin, the source of the control group (social means that the control group used routine patients attending health checkups or healthy blood donors from the area. Hospital means that the control group used non-cancer patients or patients attending health checkups from the same hospital as the experimental group), the study design, and the number of cases and controls with different ABO blood group types. If there was a disagreement in the extraction of information, it was discussed and reviewed with a third author. All the data presented in the study were agreed upon.

Study quality assessment. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included articles. Articles with a NOS score of ≥6 were considered high quality (17). The evaluation of case-controlled studies included selection (4 points), comparability (2 points) and exposure (3 points). The evaluation content of the cohort study included selection (4 points), comparability (2 points) and outcome (3 points).

Trial sequential analysis (TSA). TSA was performed using TSA v0.9.5.10 Beta software developed by The Clinical Trial Center in Copenhagen, Denmark (18). In a case-controlled study, the OR was set to be reduced to 20% with a probability of type I error of A=0.05 and b=0.2 to estimate the required information size (RIS). If the cumulative Z value exceeded the RIS threshold, the result was considered statistically significant and the sample size was sufficient. If it did not exceed the RIS, the sample size was considered insufficient, suggesting that additional data were needed to draw the conclusion.

Statistical analysis. Case-controlled studies and cohort studies used odds ratios (ORs) and relative risks (RRs) with 95% confidence intervals (CIs) to assess the association between different blood types and lung cancer risk, respectively. Heterogeneity was assessed using I^2 statistics and a χ^2 test. I^2>50% or P<0.10 was considered statistically significant heterogeneity. In cases where significant heterogeneity was detected, the random-effects model was used. Otherwise, the fixed-effect model was used. In this paper, funnel plots were used to identify publication bias. Each article was sequentially removed for sensitivity analysis to determine the impact and stability of merging OR or RR from individual studies. In addition, subgroup analysis was conducted for publication year, ethnicity, study type and source of control. P<0.05 was considered to indicate a statistically significant difference. All analyses were performed using Software Review Manager 5.4 (RevMan 5.4; Cochrane).

Results

Study selection and characteristics. According to the search strategy, 372 articles were identified from the PubMed, Embase, Web of Science, Medline, CNKI, Google Scholar, Science Direct and Wanfang databases. A total of 6 articles were identified through citation searching. After removal of duplications, the search returned 232 records. Finally, after further screening using the aforementioned inclusion and exclusion criteria, 29 studies (15,16,19-45) were eligible for evaluation of ABO blood types and lung cancer risk (Fig. 1). There were 26 case-controlled studies involving 12,598 patients with lung cancer and 3,299,927 healthy controls. The characteristics of the included studies are shown in Table I. Of these, 22 experiments were based on individuals of Chinese descent and 4 were based on individuals of Caucasian descent. In terms of selection of the control group, 20 studies were from the general populace and 6 studies were from healthy individuals in hospitals. Blood types were recorded for both the case and control groups in all studies. There were 3 cohort studies with 363,805 participants, and ultimately, 2,198 patients with lung cancer. The characteristics of the included studies are shown in Table II.

Study quality. The quality of the included literature was evaluated according to the NOS. Finally, 29 high-quality studies were included. The 26 case-controlled studies included were of high quality (Table III). The 3 cohort studies were all of high quality as well (Table IV).

Meta-analyses of the case-controlled studies

Meta-analysis regarding blood type A. Based on the results of 26 case-controlled studies, the OR (CI; P-value) of type A blood and the risk of lung cancer was 1.10 (1.02-1.19; P=0.02). This showed that there was a difference in the distribution of

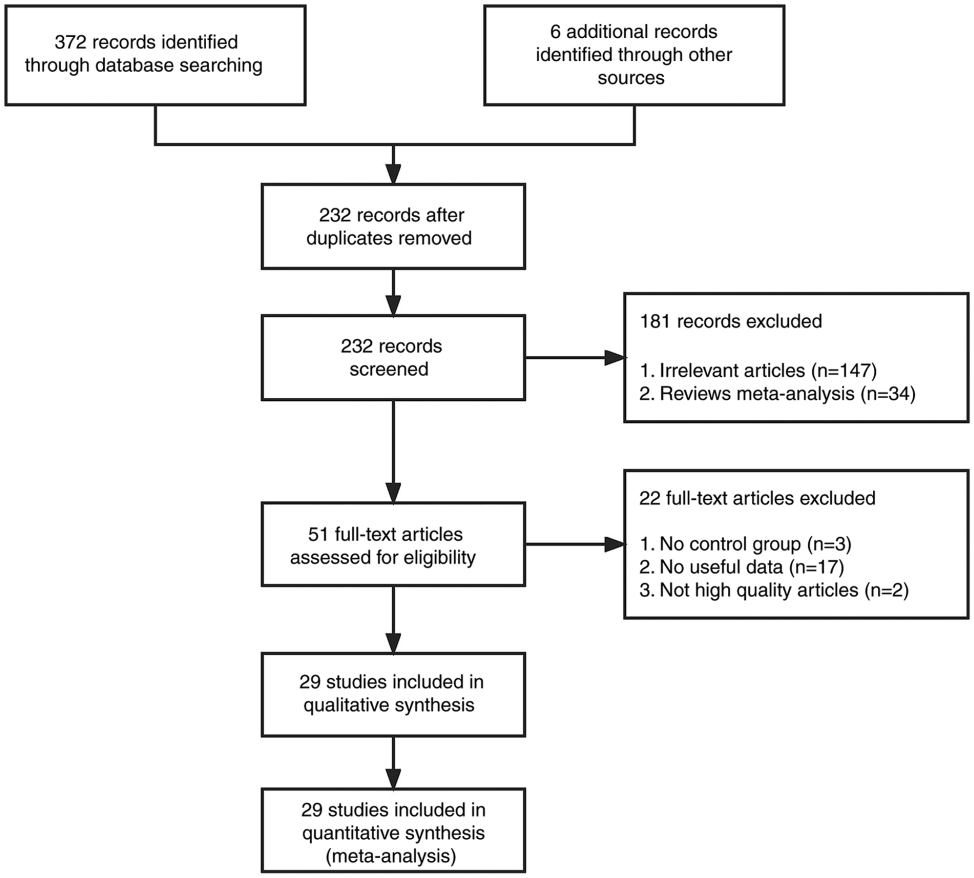

Figure 1. Flowchart showing the search strategy for studies reporting on the ABO blood group and lung cancer susceptibility.

type A blood between healthy individuals and patients with lung cancer (Fig. 2). The heterogeneity in the study was statistically significant (I^2=67%; P<0.00001), and the random-effects model was used.

Meta-analyses regarding blood type B. Based on the results of 26 case-controlled studies, the OR of type B blood and the risk of lung cancer was 0.96 (0.89-1.04; P=0.30). This showed that there was no significant difference in the proportion of type B blood between healthy individuals and patients with lung cancer (Fig. 3). The heterogeneity in the study was statistically significant (I^2=58%; P=0.0001), and the random-effects model was used.

Meta-analyses regarding blood type AB. Based on the results of 26 case-controlled studies, the OR of type AB blood and the risk of lung cancer was 0.96 (0.82-1.12; P=0.57). This showed that there was no significant difference in the proportion of type AB blood between healthy individuals and patients with lung cancer (Fig. 4). The heterogeneity in the study was statistically significant (I^2=72%; P<0.00001), and the random-effects model was used.

Meta-analyses regarding blood type O. Based on the results of 26 case-controlled studies, the OR of type O blood and the risk of lung cancer was 0.94 (0.86-1.02; P=0.14). This shows that there was no significant difference in the proportion of type AB blood between healthy individuals and patients with lung cancer (Fig. 5). The heterogeneity in the study was statistically significant (I^2=72%; P<0.00001), and the random-effects model was used.

Sensitivity analyses. Sensitivity analysis was performed by removing each individual study in turn. The results showed that the combined results were not significantly affected by any specific individual, indicating that the combined results of the meta-analysis were reliable (Table V).

Publication bias regarding blood type. Publication bias was assessed using funnel plots. The funnel diagram of the association between the ABO blood group and the risk of lung cancer is shown in Fig. 6. Funnel plots were mostly symmetric, and the corresponding points of the majority of data were within the 95% CI, indicating that publication bias had been adequately controlled.

Subgroup analysis. To assess the effect of each parameter on outcomes, subgroup analyses were performed based on ethnicity and the source of the control group (Table VI). In the subgroup analysis of ethnicity, blood type A was associated with the risk of lung cancer in patients from China (P=0.03), but was not associated with lung cancer risk in Caucasians (P=0.18). Blood type O was not associated with lung cancer risk in patients from China (P=0.14), but was associated with lung cancer risk in Caucasian patients (P=0.03). The other blood types did not show heterogeneity regarding ethnicity. In the subgroup analyses of the control source, type A blood was associated with the risk of lung cancer in the control groups that were from the general populace (P=0.04). In the control groups from healthy individuals in the hospital, there was no

Table I. Main characteristics of case-control studies included in the present meta-analysis.

First author/s	Publication year	Area	Source of control[a]	Lung cancer group, n				Control group, n				(Refs.)
				A	B	AB	O	A	B	AB	O	
Xu *et al*	2006	China	Social	10	14	3	17	1952	1211	434	1822	(19)
Oguz *et al*	2013	Turkey	Social	97	30	20	74	7756	2819	1316	5423	(20)
Li *et al*	2014	China	Hospital	357	279	83	373	648	492	168	670	(21)
Sun and Zheng	2001	China	Social	76	24	29	53	92	66	31	115	(22)
Yang *et al*	2000	China	Social	47	56	45	41	984	1060	344	909	(23)
Li *et al*	1995	China	Social	35	49	23	44	5979	7184	2189	5899	(24)
Wang and Liang	2000	China	Social	30	24	9	55	238	281	79	265	(25)
Gao *et al*	1998	China	Social	128	114	42	98	312	252	96	340	(26)
Xiao *et al*	2021	China	Hospital	297	276	74	256	342	259	81	379	(27)
Feng and Ying	2013	China	Social	164	122	37	140	9274	7986	2717	10542	(29)
Chen *et al*	2004	China	Social	230	270	50	346	11958	13979	2634	14848	(30)
Tang *et al*	2001	China	Social	29	58	11	45	23	36	13	49	(32)
McConnell *et al*	1954	UK	Social	312	55	31	379	406	81	32	481	(33)
Peng *et al*	2014	China	Hospital	306	265	69	367	4101	3308	975	4819	(16)
Zhao *et al*	1993	China	Social	45	51	11	69	1664	1712	406	2714	(34)
Rennie and Haber	1961	Australia	Social	90	18	3	107	11520	2910	900	14670	(35)
Jiang and Wang	1989	China	Social	92	62	22	112	6262	4672	1463	6781	(36)
Pan *et al*	2006	China	Social	382	268	93	399	771	727	251	714	(37)
Liu *et al*	2017	China	Hospital	41	30	15	29	24	33	7	34	(39)
Zhang	1990	China	Social	139	81	8	113	6382	4491	1581	7207	(40)
Jin *et al*	2000	China	Hospital	43	45	19	51	331	402	123	403	(41)
Urun *et al*	2013	Turkey	Social	896	354	167	627	1276032	493769	229554	1023528	(15)
Liu *et al*	2006	China	Social	97	46	9	67	3576	1870	824	3820	(43)
Guo	2001	China	Social	99	43	13	66	9270	6060	2463	10055	(42)
Cai *et al*	2006	China	Hospital	187	152	41	228	998	1087	297	1312	(44)
Wang	1993	China	Social	178	163	26	119	1484	1922	650	1597	(45)

[a]Social means that the control group used routine patients attending health checkups or healthy blood donors from the area. Hospital means that the control group used non-cancer patients or patients attending health checkups from the same hospital as the experimental group.

Table II. Main characteristics of cohort studies included in this meta-analysis.

First author	Publication year	Area	All participants, n				Lung cancer group, n				(Refs.)
			A	B	AB	O	A	B	AB	O	
Huang *et al*	2017	China	5586	4891	1890	5702	302	256	104	302	(28)
Hsiao *et al*	2015	China	1716	1388	335	2865	54	35	13	67	(31)
Sun *et al*	2015	China	90972	82631	20279	145550	294	281	61	429	(38)

association with the risk of lung cancer (P=0.34). The other blood types did not show heterogeneity regarding the source of the control group.

TSA. TSA was used to reduce the risk of type 1 error, and the RIS was evaluated by maintaining a 5% risk of type 1 error and a 20% relative risk reduction (80% power). As

Table III. Newcastle-Ottawa Scale scores for case-control studies.

	Selection					Exposure				
First author, year	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability cases/controls	Ascertainment of exposure	Same method of ascertainment	Non-response rate	Total scores	(Refs.)
Li *et al*, 2014	0	1	0	1	2	1	1	1	7	(21)
Urun *et al*, 2013	1	1	1	1	1	1	1	1	8	(15)
Liu *et al*, 2017	1	1	0	1	2	1	1	1	8	(39)
Oguz *et al*, 2013	1	1	1	1	1	1	1	1	8	(20)
Rennie and Haber, 1961	0	1	1	1	1	1	1	1	7	(35)
McConnell *et al*, 1954	1	1	1	1	1	1	1	1	8	(33)
Xiao *et al*, 2021	1	1	0	1	2	1	1	1	8	(27)
Peng *et al*, 2014	1	1	0	1	1	1	1	1	7	(16)
Cai *et al*, 2006	1	1	0	1	1	1	1	1	7	(44)
Xu *et al*, 2006	1	1	1	1	1	1	1	1	8	(19)
Feng and Ying, 2013	0	1	1	1	1	1	1	1	7	(29)
Liu *et al*, 2006	1	1	1	1	1	1	1	1	8	(43)
Pan *et al*, 2006	0	1	1	1	1	1	1	1	7	(37)
Guo, 2001	1	1	1	1	1	1	1	1	8	(42)
Tang *et al*, 2001	1	1	1	1	2	1	1	1	9	(32)
Sun and Zheng, 2001	1	1	1	1	1	1	1	1	8	(22)
Chen *et al*, 2004	0	1	1	1	1	1	1	1	7	(30)
Gao *et al*, 1998	1	1	1	1	1	1	1	1	8	(26)
Yang *et al*, 2000	1	1	1	1	1	1	1	1	8	(23)
Jin *et al*, 2000	0	1	0	1	1	1	1	1	6	(41)
Wang and Liang, 2000	1	1	1	1	1	1	1	1	8	(25)
Jiang and Wang, 1989	1	1	1	1	1	1	1	1	8	(36)
Zhang, 1990	1	1	1	1	2	1	1	1	9	(40)
Zhao *et al*, 1993	1	1	1	1	1	1	1	1	8	(34)
Wang, 1993	0	1	1	1	1	1	1	1	7	(45)
Li *et al*, 1995	1	1	1	1	1	1	1	1	8	(24)

Table IV. Newcastle-Ottawa Scale scores for cohort studies.

	Selection				Comparability of cohorts on the basis of the design or analysis	Outcome			
First author, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposed	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total scores (Refs.)
Huang *et al*, 2017	1	1	1	1	2	1	1	1	9 (28)
Hsiao *et al*, 2015	1	1	1	1	1	1	1	1	8 (31)
Sun *et al*, 2015	1	1	1	1	2	1	1	1	9 (38)

shown in Fig. 7, when studying the effects of blood type A on the occurrence of lung cancer, the sample size of study 21 (Jun Feng, 2013) crossed the TSA boundary and reached a positive conclusion in advance. This is consistent with previous meta-analysis results, suggesting that blood type A increases the risk of lung cancer. In the study of the influence of blood types B, O, and AB blood on the occurrence of lung cancer, the Z-curve did not cross the TSA boundary, but crossed the RIS line (Figs. 8-10). The results showed that blood types B, AB, and O had no effect on the occurrence of lung cancer. Moreover, the sample size was sufficient and no more case-controlled trials are required.

Meta-analyses of cohort studies

Forest plot for meta-analysis. Based on the results of 3 cohort studies, the RR of blood type A and lung cancer was 1.05 (0.96-1.15; P=0.32), the RR of blood type B and lung cancer was 1.04 (0.94-1.14; P=0.47) the RR of blood type AB and lung cancer was 1.03 (0.88-1.20; P=0.71), and the RR of blood type O and lung cancer was 0.92 (0.85-1.01; P=0.08). This indicated that there was no statistically significant difference in blood type regarding the risk of lung cancer (Fig. 11). Heterogeneity was not statistically significant in the study, and a fixed-effect model was adopted.

Publication bias regarding the cohort studies. Due to the small number of included cohort studies, funnel plots were not used to assess publication bias.

Discussion

Lung cancer seriously affects the quality of life of patients. Thus, identifying similarities in the occurrence and development of lung cancer is key to identifying methods to reduce the incidence and mortality of affected patients. Since the discovery of the ABO blood group system by Landsteiner (46,47), >20 independent systems have been developed for human erythrocyte surface antigens. Due to its stable heritability, an increasing number of medical researchers are paying attention to its role in the occurrence and development of diseases (5-7). Multiple researchers have performed studies on the ABO blood group and the risk of lung cancer (15,16).

The present study comprehensively analyzed the influence of the ABO blood classification on the risk of lung cancer. By reviewing all eligible case-controlled studies, it was determined that blood type A was associated with the occurrence of lung cancer, and that this blood type may be a risk factor for lung cancer. The other blood types were not associated with the overall risk of lung cancer. In addition, to further explore the impact of ethnicity and source of control, subgroup analyses were performed. The results showed that type A blood was heterogeneous regarding ethnicity and source of control. These results were obtained when the study ethnicity was Chinese or the control group was from the social population. In addition, type O blood was determined to be a protective factor for lung cancer in Caucasian individuals. In Chinese individuals, type O blood had no effect on the prevalence of lung cancer. TSA results suggested that the sample size of the case-controlled

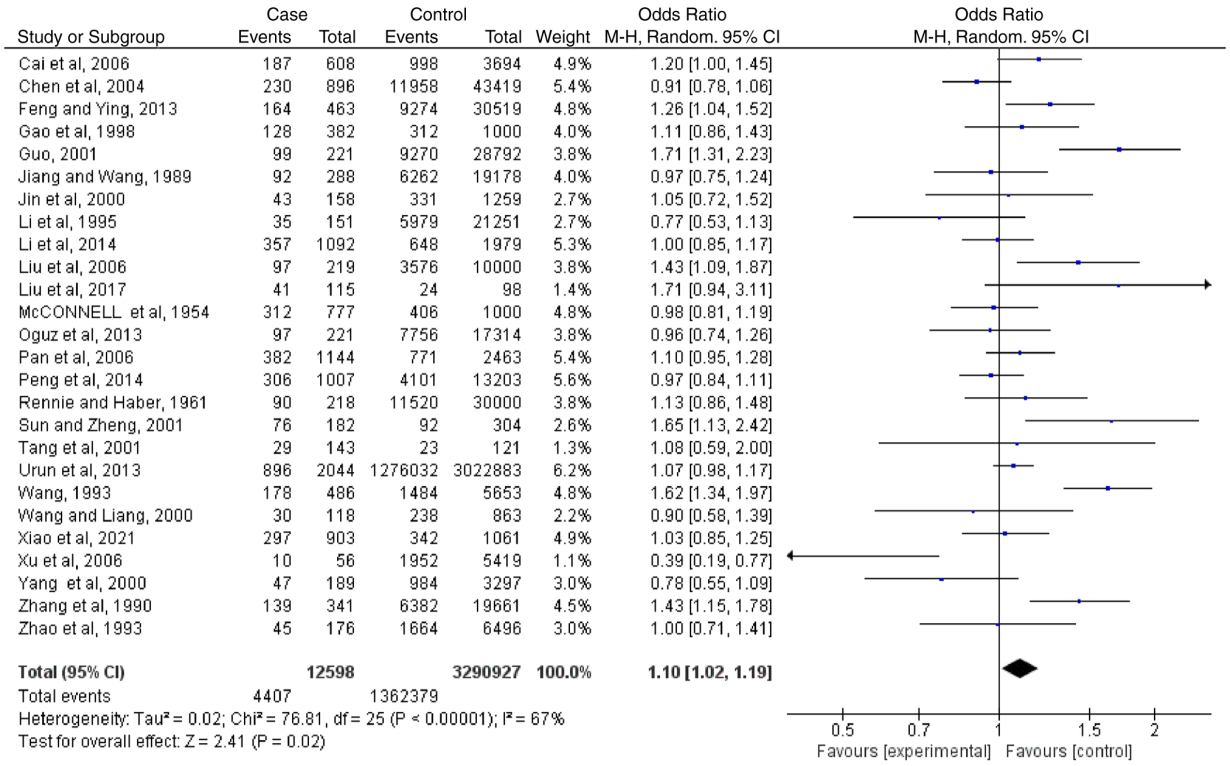

Figure 2. Forest plot for meta-analysis of blood type A and lung cancer risk in the case-controlled studies. CI, confidence interval.

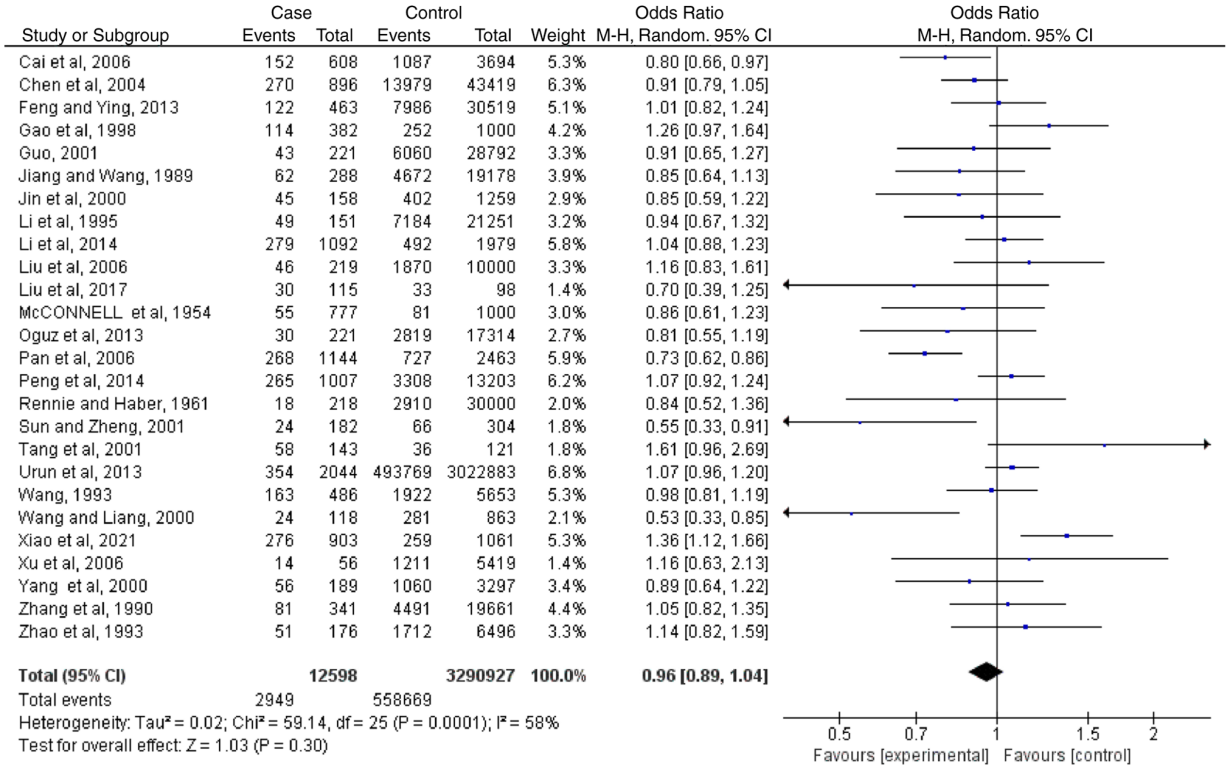

Figure 3. Forest plot for meta-analysis of blood type B and lung cancer risk in the case-controlled studies. CI, confidence interval.

study was sufficient; thus, additional case-controlled studies are not needed. Furthermore, the results from the cohort studies suggested that blood type was not associated with the risk of lung cancer.

The ABO blood group system consists of A and B antibodies and their corresponding antigens. The ABO blood type of can be determined by simply testing for the presence of antigens A or B in the blood. Individuals with type

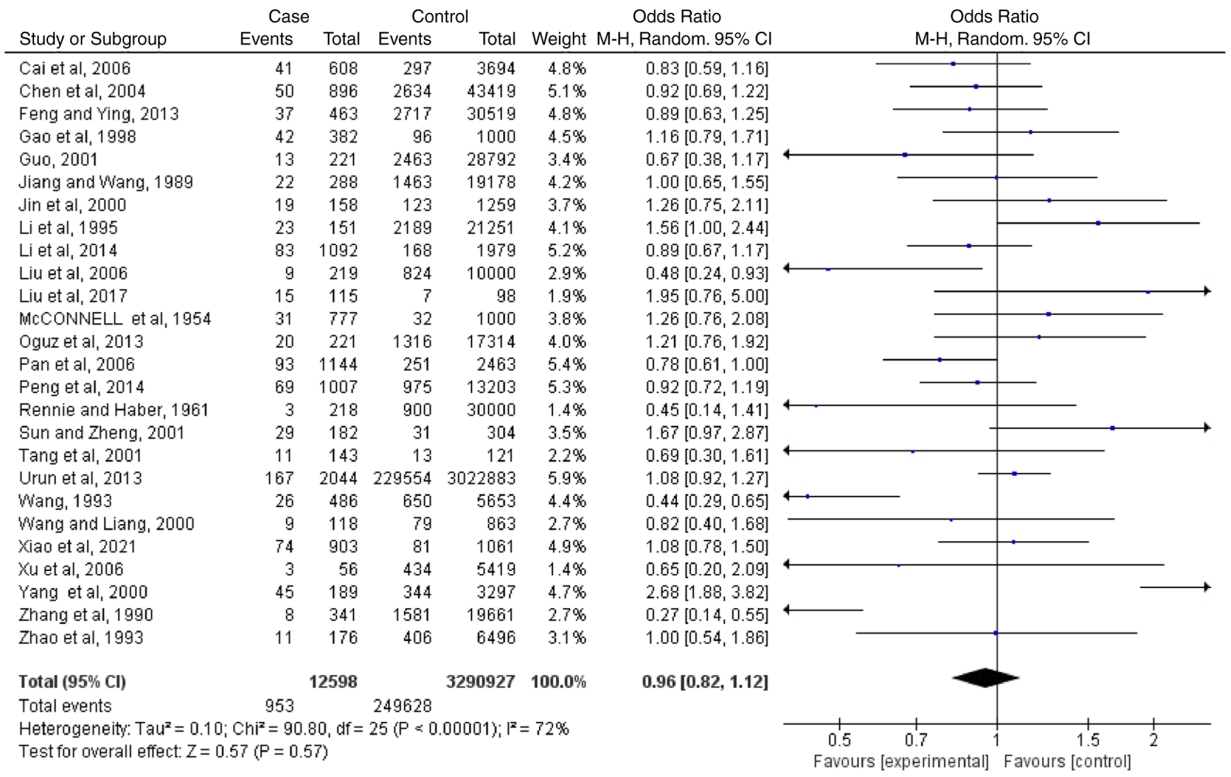

Figure 4. Forest plot for meta-analysis of blood type AB and lung cancer risk in the case-controlled studies. CI, confidence interval.

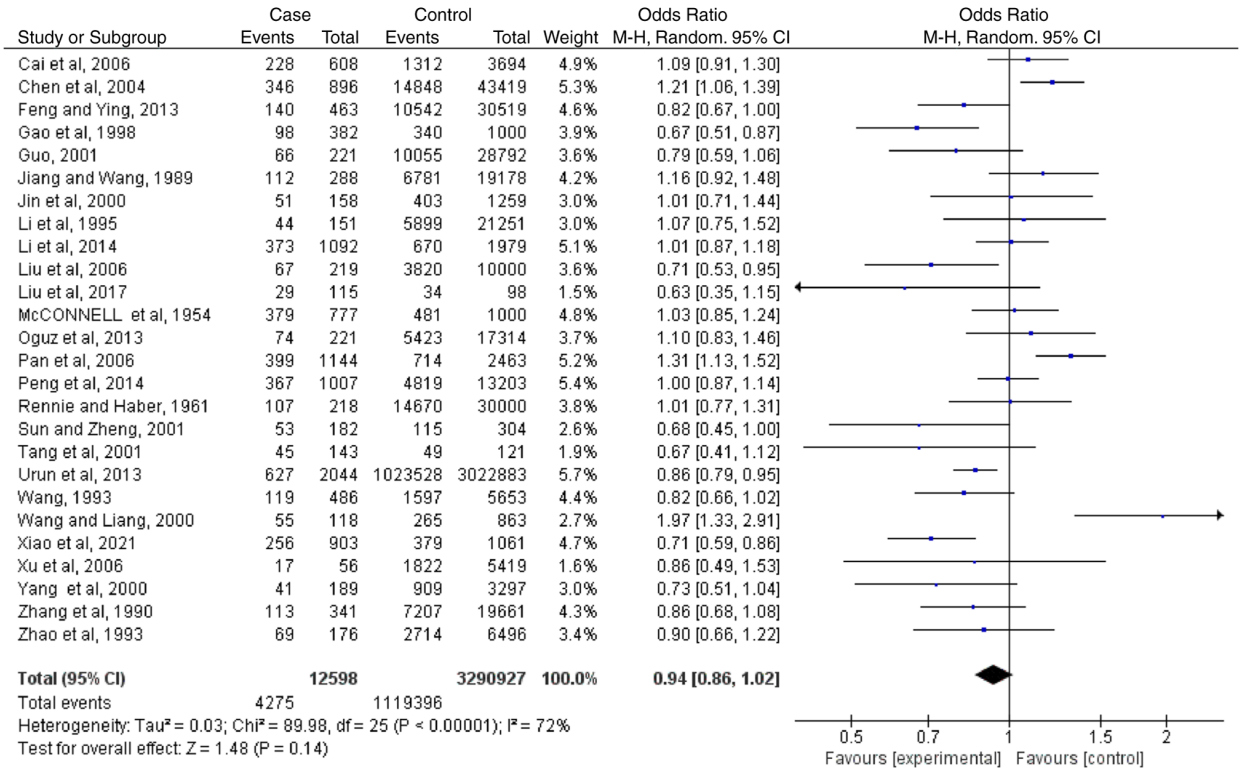

Figure 5. Forest plot for meta-analysis of blood type O and lung cancer risk in the case-controlled studies. CI, confidence interval.

A blood have only A antigens on their red blood cells, and individuals with type B blood have only B antigens on their red blood cells. Individuals with type O blood have neither A nor B antigens in their red blood cells. Conversely, individuals with type AB have both A and B antigens. These antigens are present on the surface of red blood cells and also in several other tissues in the human body. The genes that determine ABO blood groups are located in the

Table V. Sensitivity analysis of the association between blood type A and lung cancer risk in the case-controlled studies.

First author	Publication year	OR	(95%CI)	P-value	I^2 %	(Refs.)
Cai *et al*	2006	1.10	1.01-1.19	0.030	68	(44)
Chen *et al*	2004	1.11	1.03-1.21	0.008	66	(30)
Feng and Ying	2013	1.10	1.01-1.19	0.030	68	(29)
Gao *et al*	1998	1.10	1.02-1.20	0.020	69	(26)
Guo	2001	1.08	1.00-1.17	0.040	63	(42)
Jiang and Wang	1989	1.11	1.02-1.20	0.010	68	(36)
Jin *et al*	2000	1.10	1.02-1.20	0.020	69	(41)
Li *et al*	2014	1.11	1.02-1.20	0.020	68	(21)
Li *et al*	1995	1.11	1.03-1.21	0.008	67	(24)
Liu *et al*	2017	1.10	1.01-1.19	0.020	68	(39)
Liu *et al*	2006	1.09	1.01-1.18	0.030	67	(43)
McConnell *et al*	1954	1.11	1.02-1.20	0.010	68	(33)
Oguz *et al*	2013	1.11	1.02-1.20	0.010	68	(20)
Pan *et al*	2006	1.10	1.01-1.20	0.020	69	(37)
Peng *et al*	2014	1.11	1.02-1.21	0.010	67	(16)
Rennie and Haber	1961	1.10	1.01-1.20	0.020	69	(35)
Sun and Zheng	2001	1.09	1.01-1.18	0.030	67	(22)
Tang *et al*	2001	1.10	1.02-1.19	0.020	69	(32)
Urun *et al*	2013	1.10	1.01-1.21	0.030	69	(15)
Wang	1993	1.08	1.00-1.16	0.040	60	(45)
Wang and Liang	2000	1.11	1.02-1.20	0.010	68	(25)
Xiao *et al*	2021	1.11	1.02-1.20	0.020	69	(27)
Xu et al	2006	1.12	1.03-1.20	0.005	65	(19)
Yang *et al*	2000	1.11	1.03-1.21	0.007	67	(23)
Zhang	1990	1.09	1.01-1.18	0.030	66	(40)
Zhao *et al*	1993	1.11	1.02-1.20	0.020	69	(34)

long arm of chromosome 9, region 3 and band 4 (9q34) (48). It was found that 9q34 contains the human DNA repair gene XPA, and proto-oncogene C-abl. If these genes are mutated or defective, they may cause tumor cell proliferation (49). Additionally, blood group antigen-associated glycosyltransferases encoded by the 9q34 gene can regulate intercellular adhesion and signal transduction (50). This may play an important role in immune monitoring of tumor cells and their sensitivity to apoptosis (51). On the other hand, the underlying mechanism associated with the ABO blood group and tumorigenesis also includes the inflammatory state of the body. Studies have identified an association between the ABO blood group and the circulating levels of TNF-α, soluble ICAM-1, e-selectin and p-selectin. The association was precisely found to be associated with the genotype of the A allele (8-10). This suggests that blood type A may influence inflammation throughout the body, leading to the development of cancer. Experimental study has also found that antigen A may improve immune escape capacity and prevent apoptosis (52). The aforementioned conclusions may underlie the increased incidence of patients with lung cancer with type A blood. The effect of ethnicity on the results may be due to the fact that lung cancer is caused by several factors. The incidence of lung cancer differs in different regions due to the different lifestyles of individuals. Furthermore, the ABO blood group affects several diseases. Therefore, the proportion of blood types in the control group from the hospital may differ from that of the total population, resulting in different results in the control groups from the different sources in this study.

The present study covered a wide range of subjects over a relatively large span of time. ABO blood group is a very stable genetic factor, which has not changed over decades. Therefore, the data from early studies are still valuable and can be included in this study. This meta-analysis provides a more accurate assessment of the association of the ABO blood type with lung cancer risk than previous studies. Additionally, the cohort study was added based on the inclusion of case-controlled studies. However, this analysis also has

Table VI. Subgroup analysis of the association between ABO blood group and lung cancer risk in case-control studies.

Variable	n	Blood type	OR (95% CI)	P-value	Test for heterogeneity		Analysis model
					I^2, %	P-value	
Ethnicity							
Chinese	22	A	1.12 (1.01-1.23)	0.03	72	<0.0001	R
	22	B	0.96 (0.88-1.05)	0.40	62	<0.0001	R
	22	AB	0.93 (0.78-1.12)	0.47	75	<0.0001	R
	22	O	0.93 (0.83-1.03)	0.14	75	<0.0001	R
Caucasian	4	A	1.05 (0.98-1.13)	0.18	0	0.7300	F
	4	B	1.02 (0.92-1.13)	0.73	17	0.31	F
	4	AB	1.08 (0.94-1.25)	0.27	0	0.42	F
	4	O	0.92 (0.85-0.99)	0.03	41	0.17	F
Source of control							
Social	20	A	1.11 (1.00-1.23)	0.04	72	<0.0001	R
	20	B	0.94 (0.86-1.03)	0.21	52	0.0030	R
	20	AB	0.92 (0.75-1.13)	0.45	78	<0.0001	R
	20	O	0.94 (0.84-1.04)	0.24	75	<0.0001	R
Hospital	6	A	1.04 (0.96-1.12)	0.34	19	0.29	F
	6	B	1.00 (0.84-1.18)	0.97	71	0.004	R
	6	AB	0.96 (0.83-1.10)	0.53	0	0.43	F
	6	O	0.94 (0.81-1.08)	0.36	64	0.02	R

F, fixed-effect model; R, random-effect model; OR, odds ratio; CI, confidence interval.

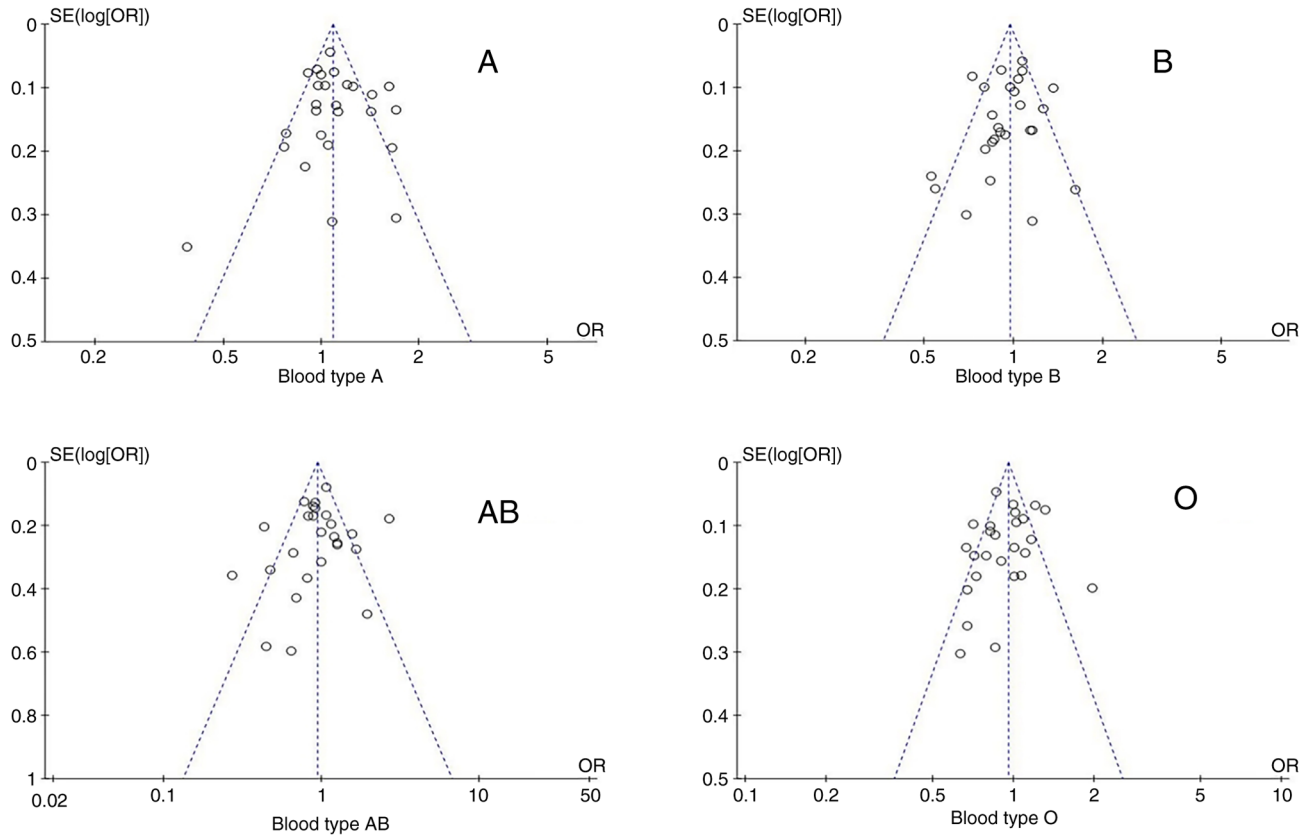

Figure 6. Funnel plot analysis of blood type. Funnel plot analysis of (A) blood type A, (B) blood type B, (C) blood type AB and (D) blood type O and lung cancer risk in the case-controlled studies. OR, odds ratio; SE, standard error.

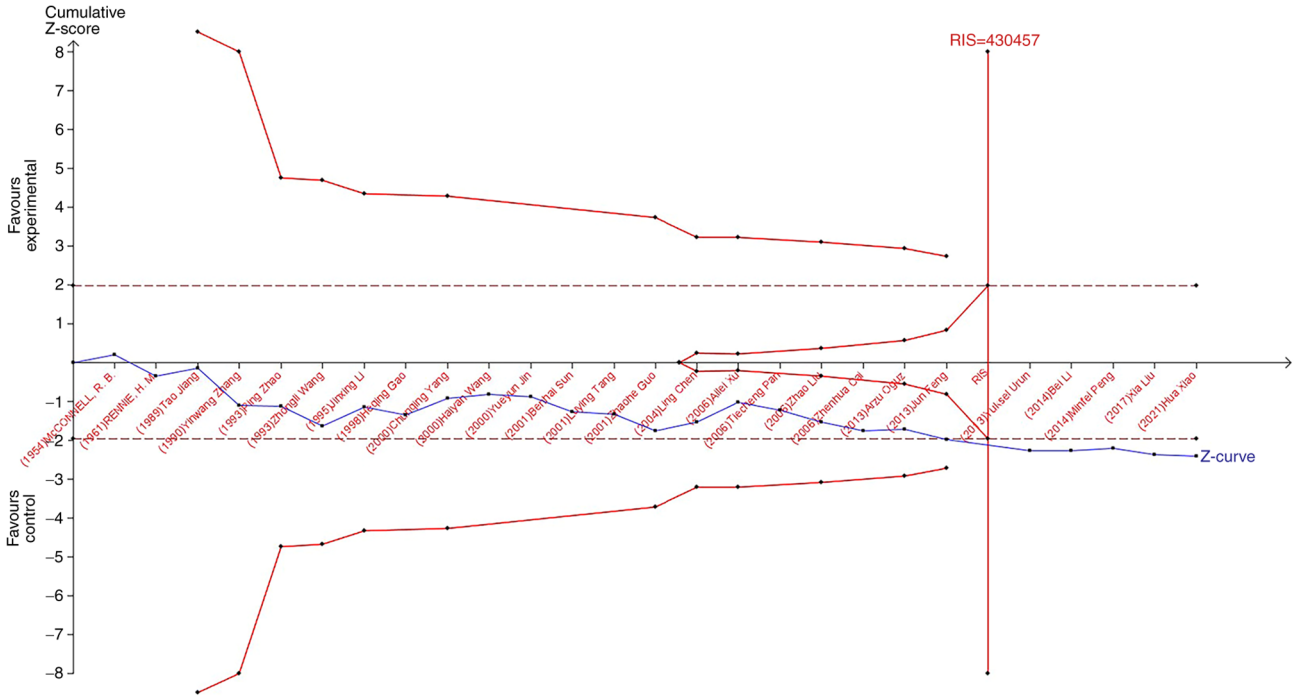

Figure 7. Trial Sequential Analysis of the association between blood type A and the risk of lung cancer. The required information size was calculated based on a two-sided α=5% and β=15% (power 80%), and a relative risk reduction of 20%. RIS, required information size.

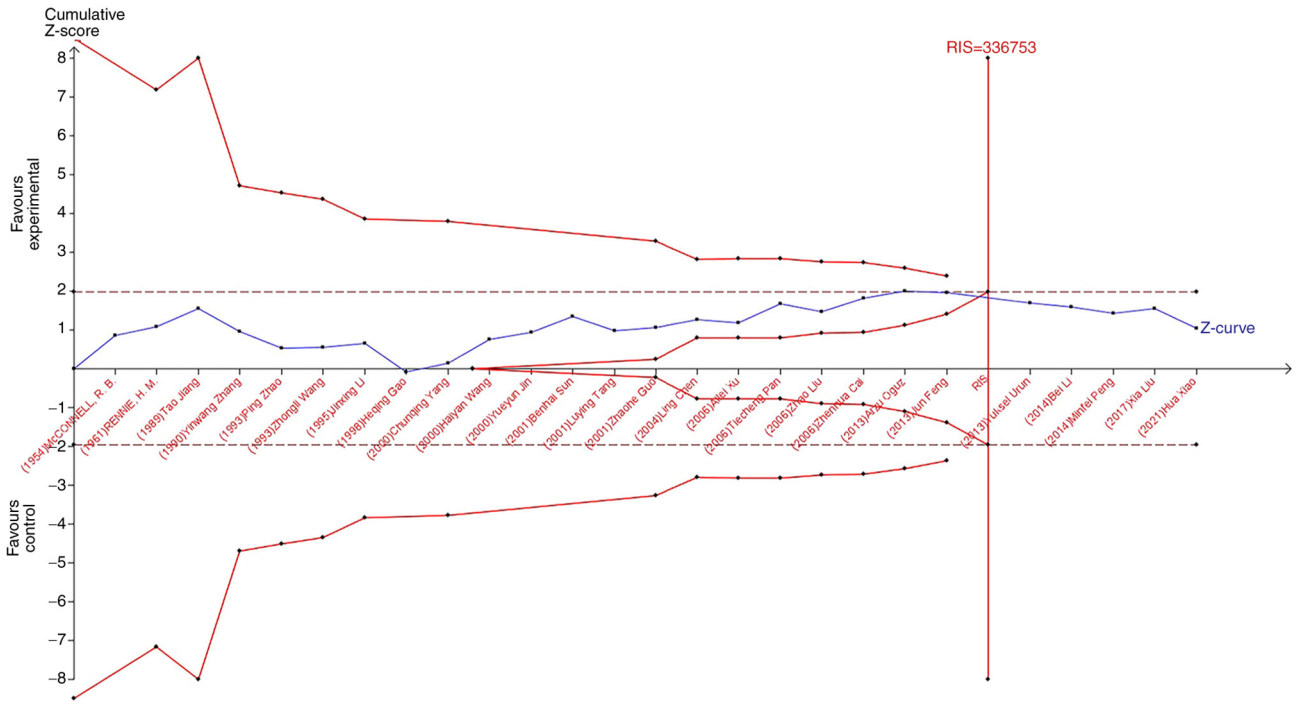

Figure 8. Trial Sequential Analysis of the association between blood type B and the risk of lung cancer. The required information size was calculated based on a two-sided α=5% and β=15% (power 80%), and a relative risk reduction of 20%. RIS, required information size.

some limitations, as follows: i) Most of the studies included in the paper included patients of Chinese descent, thus there is a notable selection bias; ii) lung cancer has several different types of pathology, and different pathological types have different paths of pathogenesis (53); therefore, the study results may change when studying a specific pathological type of lung cancer; iii) case-controlled studies are observational studies that may have a selection bias due to incomplete randomization; iv) only a portion of the case-controlled studies retrieved in this paper corrected for traditional risk factors; therefore, the confounding effect of other risk factors cannot be completely controlled; and v) only the Chinese and English literature were included in this study, and the results may be affected by the inclusion of incomplete data.

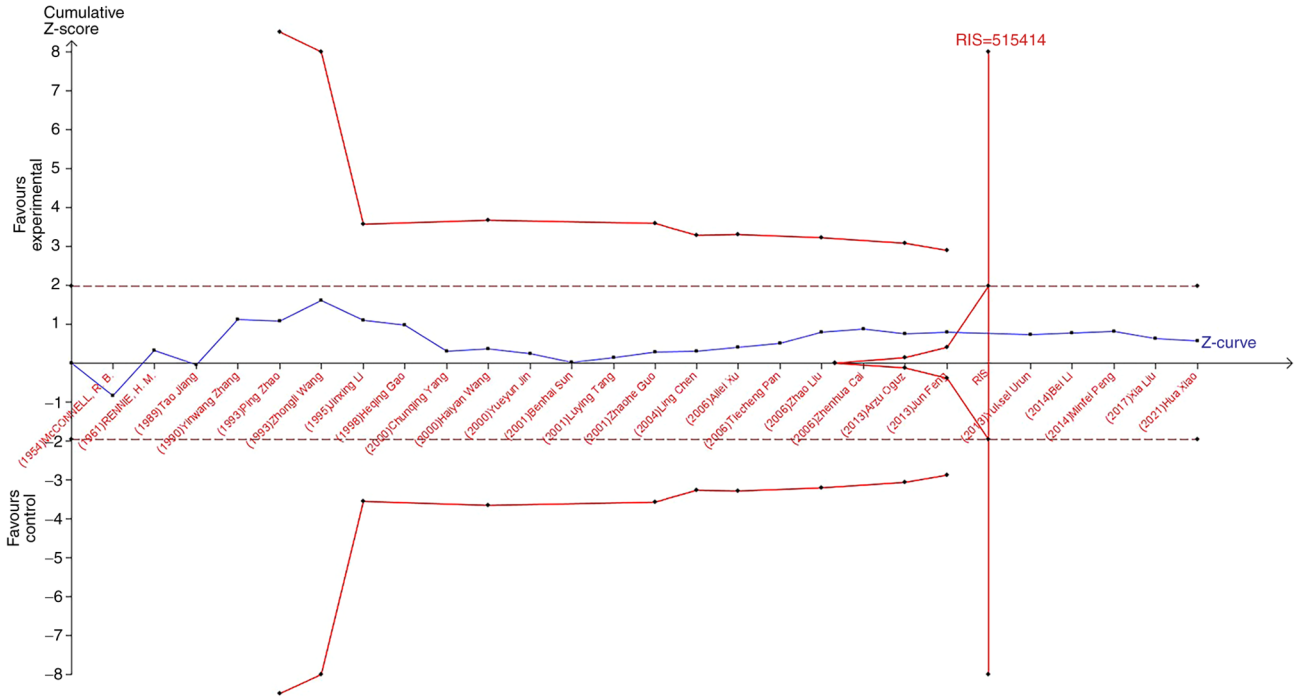

Figure 9. Trial Sequential Analysis of the association between blood type AB and the risk of lung cancer. The required information size was calculated based on a two-sided α=5% and β=15% (power 80%), and a relative risk reduction of 20%. RIS, required information size.

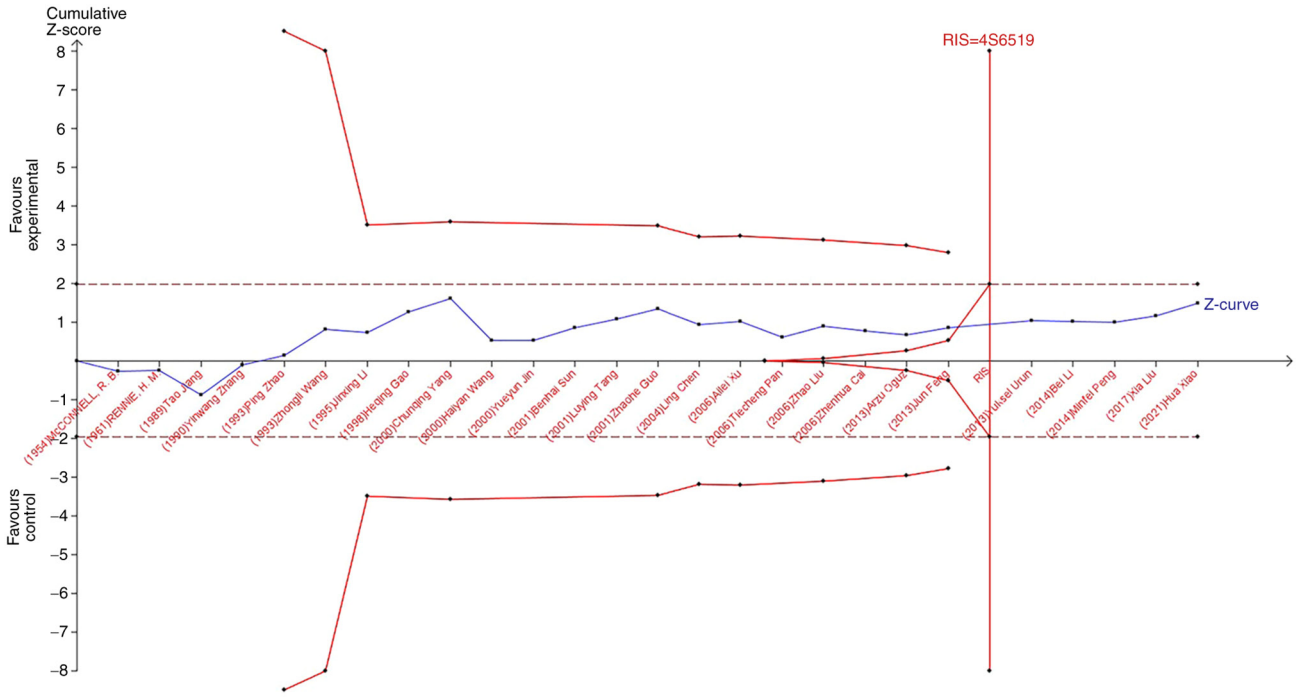

Figure 10. Trial Sequential Analysis of the association between blood type O and the risk of lung cancer. The required information size was calculated based on a two-sided α=5% and β=15% (power 80%), and a relative risk reduction of 20%. RIS, required information size.

In conclusion, the meta-analysis of the case-controlled studies analyzed in the present study suggest that patients with blood type A are at a higher risk of lung cancer. However, this result does not apply to Caucasians. In addition, this study also confirmed that Caucasians with type O blood have a lower risk of lung cancer. No association was found between other blood types and the prevalence of lung cancer. Differing study designs have a considerable impact on the research outcomes. The results of only three cohort studies showed that blood type was not associated with the risk of lung cancer. Larger and higher quality prospective studies recruiting patients from several international hospitals are required to better explore a more precise association between ABO blood group and the risk of lung cancer.

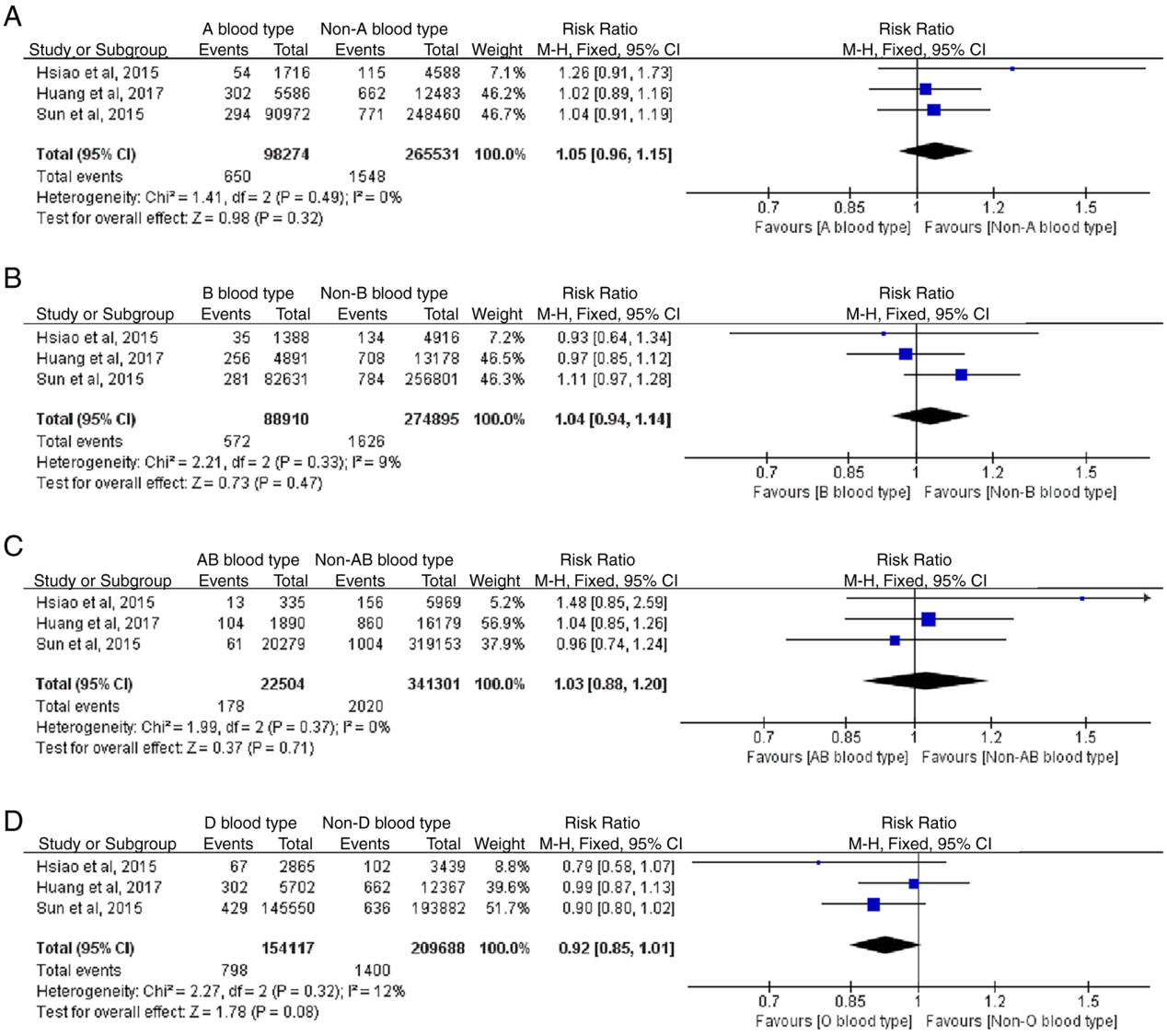

Figure 11. Forest plot for the meta-analysis of blood type and lung cancer risk. Forest plot for the meta-analysis of (A) blood type A, (B) blood type B, (C) blood type AB and (D) blood type O with lung cancer risk in the cohort study. CI, confidence interval.

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Availability of data and materials

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

Authors' contributions

PH, HY and ZT contributed to the conception and design of the study. HY, ZT, YZ and JS prepared the materials, collected the data and performed the analysis. HY drafted the manuscript. HY and ZT confirm the authenticity of all the raw data. All authors revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.

2. Wu X, Zhao H, Suk R and Christiani DC: Genetic susceptibility to tobacco-related cancer. Oncogene 23: 6500-6523, 2004.
3. Vachani A, Sequist LV and Spira A: AJRCCM: 100-Year anniversary. The shifting landscape for lung cancer: Past, present, and future. Am J Respir Crit Care Med 195: 1150-1160, 2017.
4. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B and Aggarwal BB: Cancer is a preventable disease that requires major lifestyle changes. Pharm Res 25: 2097-2116, 2008.
5. Aird I, Bentall HH and Roberts JA: A relationship between cancer of stomach and the ABO blood groups. Br Med J 1: 799-801, 1953.
6. Hems G: Epidemiological characteristics of breast cancer in middle and late age. Br J Cancer 24: 226-234, 1970.
7. Vioque J and Walker AM: Pancreatic cancer and ABO blood types: A study of cases and controls. Med Clin (Barc) 96: 761-764, 1991 (In Spanish).
8. Melzer D, Perry JR, Hernandez D, Corsi AM, Stevens K, Rafferty I, Lauretani F, Murray A, Gibbs JR, Paolisso G, *et al*: A genome-wide association study identifies protein quantitative trait loci (pQTLs). PLoS Genet 4: e1000072, 2008.
9. Barbalic M, Dupuis J, Dehghan A, Bis JC, Hoogeveen RC, Schnabel RB, Nambi V, Bretler M, Smith NL, Peters A, *et al*: Large-scale genomic studies reveal central role of ABO in sP-selectin and sICAM-1 levels. Hum Mol Genet 19: 1863-1872, 2010.
10. Paterson AD, Lopes-Virella MF, Waggott D, Boright AP, Hosseini SM, Carter RE, Shen E, Mirea L, Bharaj B, Sun L, *et al*: Genome-wide association identifies the ABO blood group as a major locus associated with serum levels of soluble E-selectin. Arterioscler Thromb Vasc Biol 29: 1958-1967, 2009.
11. Qi L, Cornelis MC, Kraft P, Jensen M, van Dam RM, Sun Q, Girman CJ, Laurie CC, Mirel DB, Hunter DJ, *et al*: Genetic variants in ABO blood group region, plasma soluble E-selectin levels and risk of type 2 diabetes. Hum Mol Genet 19: 1856-1862, 2010.
12. Vowden P, Lowe AD, Lennox ES and Bleehen NM: The expression of ABH and Y blood group antigens in benign and malignant breast tissue: The preservation of the H and Y antigens in malignant epithelium. Br J Cancer 53: 313-319, 1986.
13. Strauchen JA, Bergman SM and Hanson TA: Expression of A and B tissue isoantigens in benign and malignant lesions of the breast. Cancer 45: 2149-2155, 1980.
14. Le Pendu J, Marionneau S, Cailleau-Thomas A, Rocher J, Le Moullac-Vaidye B and Clément M: ABH and Lewis histo-blood group antigens in cancer. APMIS 109: 9-31, 2001.
15. Urun Y, Utkan G, Cangir AK, Oksuzoglu OB, Ozdemir N, Oztuna DG, Kocaman G, Coşkun HŞ, Kaplan MA, Yuksel C, *et al*: Association of ABO blood group and risk of lung cancer in a multicenter study in Turkey. Asian Pac J Cancer Prev 14: 2801-2803, 2013.
16. Peng M, Yu S, Wang J and Wang D: Relationship between ABO blood group and risk of 8 kinds of malignant tumors. Chin J Health Inspection 24: 811-813+823, 2014 (In Chinese).
17. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P: The Newcastle-Ottawa scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Appl Eng Agric 18: 727-734, 2014. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed March 2, 2022.
18. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G and Gluud C: User Manual for Trial Sequential Analysis (TSA) 2nd edition. Copenhagen: Copenhagen Trial Unit, pp 1-119, 2017.
19. Xu A, He X, Wang W, Tang Y and Ping W: Relationship between ABO blood group and gastric cancer, liver cancer and lung cancer. J Clin Mil Med: 722-723, 2006 (In Chinese).
20. Oguz A, Unal D, Tasdemir A, Karahan S, Aykas F, Mutlu H, Cihan YB and Kanbay M: Lack of any association between blood groups and lung cancer, independent of histology. Asian Pac J Cancer Prev 14: 453-456, 2013.
21. Li B, Tan B, Chen C, Zhao L and Qin L: Association between the ABO blood group and risk of common cancers. J Evid Based Med 7: 79-83, 2014.
22. Sun B and Zheng Y: ABO blood group typing in lung cancer patients. J Clin Pulmonology 2: 30, 2001 (In Chinese).
23. Yang C, Zhang R, Zhou S and Wang Q: Discussion on the relationship between ABO blood group and lung cancer, liver cancer and gastric cancer. Clin Transfus Lab 1: 11-12, 2000 (In Chinese).
24. Li J, Hu J and Wang M: The correlation between esophageal cancer, lung cancer and ABO blood group. Chin J Blood Transfus 1: 45-46, 1995 (In Chinese).
25. Wang H and Liang X: Relationship between ABO blood group and 10 kinds of malignant tumors of Han nationality in Guangxi. Med Lit 5: 643-644, 2000 (In Chinese).
26. Gao H, Zhao L, Wu S, Wang D, Li Y and Heyun S: Relationship between malignant tumor and ABO blood group. Chin J Prim Med 4: 41-42, 1998 (In Chinese).
27. Xiao H, Xiang S, Shan Z and Bin X: Relationship between ABO blood group and different pathological types of lung cancer in southern Sichuan. Chin J Mod Med 31: 98-102, 2021 (In Chinese).
28. Huang JY, Wang R, Gao YT and Yuan JM: ABO blood type and the risk of cancer-findings from the Shanghai cohort study. PLoS One 12: e0184295, 2017.
29. Feng J and Ying X: Correlation analysis between ABO blood group and lung cancer in Zhejiang Han people. Harbin Med 33: 96-97, 2013 (In Chinese).
30. Chen L, Heng C, Shen W and Xiao X: Correlation analysis between ABO blood group and malignant tumor. Chin J Oncol 3: 131-133, 2004 (In Chinese).
31. Hsiao LT, Liu NJ, You SL and Hwang LC: ABO blood group and the risk of cancer among middle-aged people in Taiwan. Asia Pac J Clin Oncol 11: e31-e36, 2015.
32. Tang L, Ren Z, Zhou X, Su Z and Zhuang Z: ABO blood group and its interaction with smoking and lung cancer susceptibility. Chronic Dis Prev Control China 2: 70-71, 2001 (In Chinese).
33. McConnell RB, Clarke CA and Downton F: Blood groups in carcinoma of the lung. Br Med J 2: 323-325, 1954.
34. Zhao P, Wu Q and Wang S: Lung cancer and ABO blood group relationship. Chin J Eugenics Genet: 59-60, 1993 (In Chinese).
35. Rennie HM and Haber RW: Blood groups and carcinoma of the lung. Med J Aust 48: 61-62, 1961.
36. Jiang T and Wang Z: ABO blood group distribution in 288 patients with lung cancer. J Chongqing Med Univ: 220-221, 1989 (In Chinese).
37. Pan T, Zheng Z, Li J, Chen T, Wei X, Hu M and Liu L: ABO blood group and lung cancer in Hubei province and literature review. Sixth National Thoracic and Cardiovascular Surgery Conference: Beijing, China. pp 2, 2006. (In Chinese).
38. Sun W, Wen CP, Lin J, Wen C, Pu X, Huang M, Tsai MK, Tsao CK, Wu X and Chow WH: ABO blood types and cancer risk-a cohort study of 339,432 subjects in Taiwan. Cancer Epidemiol 39: 150-156, 2015.
39. Liu X, Chen X, Yang J and Guo R: Association of ABO blood groups with von Willebrand factor, factor VIII and ADAMTS-13 in patients with lung cancer. Oncol Lett 14: 3787-3794, 2017.
40. Zhang YW: Preliminary analysis of ABO blood group distribution in cancer patients. J Hubei Med Coll: 369-371, 1990 (In Chinese).
41. Jin YY, Wang ZY and Cheng CH: Relationship between ABO blood group and 3 common cancers. J Luoyang Med Coll 3: 248, 2000 (In Chinese).
42. Guo ZH: Lung cancer and ABO blood group. Chin J Mod Med 1: 61-63, 2001 (In Chinese).
43. Liu Z, Qiao Z and Huang P: Association between ABO blood group and lung cancer. Mod Med Health 14: 2134-2135, 2006 (In Chinese).
44. Cai Z, Fang W, Qin J, Chen S and Lai K: Correlation between ABO blood group and malignant tumors in Guangzhou area. J Appl Med Technol 21: 3727-3729, 2006 (In Chinese).
45. Wang Z: ABO blood group distribution analysis of lung cancer patients. Shaanxi Med Lab: 242-243, 1993 (In Chinese).
46. Landsteiner K: ZTo know the antifermentative, lytic and agglutinative effects of blood serum and lymph. Centr Bakt Orig 27: 357-362, 1900 (In German).
47. Landsteiner K: About agglutination symptoms of normal human blood. Wien Klin Wochschr 14: 1132-1134, 1901 (In German).
48. Wagner FF, Flegel WA, Bittner R and Döscher A: Molecular typing for blood group antigens within 40 min by direct polymerase chain reaction from plasma or serum. Br J Haematol 176: 814-821, 2017.
49. Tang Z: Introduction to modern oncology. Med Res Lett: 24, 2001.
50. Hakomori S: Antigen structure and genetic basis of histo-blood groups A, B and O: Their changes associated with human cancer. Biochim Biophys Acta 1473: 247-266, 1999.
51. Zhang S, Zhang HS, Cordon-Cardo C, Reuter VE, Singhal AK, Lloyd KO and Livingston PO: Selection of tumor antigens as targets for immune attack using immunohistochemistry: II. Blood group-related antigens. Int J Cancer 73: 50-56, 1997.
52. Marionneau S, Le Moullac-Vaidye B and Le Pendu J: Expression of histo-blood group A antigen increases resistance to apoptosis and facilitates escape from immune control of rat colon carcinoma cells. Glycobiology 12: 851-856, 2002.
53. Sequist LV and Lynch TJ: EGFR tyrosine kinase inhibitors in lung cancer: An evolving story. Annu Rev Med 59: 429-442, 2008.