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ABO blood groups and liver cancer: prospective results from an HBsAg cohort study

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ABSTRACT

Objective The association between ABO blood group and risk of liver cancer is unclear, although few studies have reported positive results. This study examined the relationship between ABO blood group and liver cancer in hepatitis B surface antigen (HBsAg)-positive individuals.

Design A high-risk population-based cohort study.

Setting The study was started in 2007 and closed in 2019; the number of observed person-years as obtained by ABO blood group.

Participants The study included 3663 individuals with positive HBsAg, including men aged 30–70 and women aged 40–70.

Outcome measures The frequencies of ABO group in the cohort population and patients with liver cancer were calculated, respectively. χ^2 test was used to compare differences, and the relative risk (95% CI) for development of liver cancer was evaluated.

Results The frequency distribution of blood types A, B, O and AB was 1118 (30.52%), 1073 (29.29%), 1104 (30.14%) and 368 (10.05%), respectively, among 3663 cohort individuals. In the cohort, patients with liver cancer (n=336) were of the following frequencies: type A: 104 (30.95%); type B: 97 (28.87%); type O: 95 (28.27%); and type AB: 40 (11.90%). No significant difference was found between patients with liver cancer and other individuals. The annual incidence rate of liver cancer was 906.34 per 100 000 person-years, and for blood type A, B, O and AB the rates were 917.76, 893.78, 846.02 and 1093.43 per 100 000 person-years, respectively. The relative risk (95% CI) was 0.97 (0.74 to 1.29), 0.92 (0.70 to 1.22) and 1.19 (0.82 to 1.72) for blood types B, O and AB, respectively, compared with blood type A.

Conclusion There were no significant differences in the frequency distribution of ABO blood groups in patients with liver cancer within this high-risk cohort, which demonstrates lack of positive association between ABO blood group and risk of liver cancer.

Strengths and limitations of this study

- ► This is an at-risk population-based cohort study in an endemic area in China designed to examine whether ABO blood groups are associated with development of liver cancer.
- ► A prospective follow-up study can be the best approach to overcome the limitations inherent in most case–control studies or clinical observations.
- ► The Rh blood group system was not tested since almost 99% of the local Han people are Rh-positive.
- ► No possible confounders, such as body mass index, smoking, alcohol intake or hepatitis C virus, were adjusted since no association was found in our previous observations.
- ► No further laboratory data were examined on the genotypes of the ABO blood groups.

INTRODUCTION

At present, there are dozens of known blood classifications, which are based on whether there are genetic antigens on the surface of red blood cells. However, only two, namely the ABO blood group classification system and the Rh blood group classification system, are widely used in medical practice.[1–3] Because the vast majority of the general population are Rh-positive (eg, the positive rate in the Chinese population is 98.98%[4]), the relationship between the Rh blood system and diseases lacks universality. In recent years, more and more attention has been paid to the relationship between ABO blood groups and many human diseases, and there has been evidence suggesting that ABO blood groups may be related to infection, cardiovascular disease and occurrence of malignant tumours.[4–6]

Due to the inherited antigenic substance characteristics of blood groups, people from different ethnic groups or geographical regions have different characteristics or distinctions in the distribution of ABO blood types.[1–3 7] The first link between blood groups and diseases was found at the start of the last century; the association between blood group and cancer (gastric cancer) was found in the early 1950s, and in 2009 a significant association between a single nucleotide polymorphism located within the ABO glycosyltransferase gene and an increased risk of pancreatic cancer was described through a genome-wide association study.[6] Chinese

scholars have also noticed the relationship between the ABO blood group system and cancer for a long time.[8 9] However, most of these studies are based on the distribution of ABO blood groups from clinical cases, which may be affected substantively by the distribution of ABO blood groups in the population. Hence, the causal link between ABO blood type and disease aetiology cannot be fundamentally clarified. A study[10] reported that the most common ABO blood group in Chinese residents was type A, followed by types O, B and AB. However, there are great disparities in the distribution of ABO blood groups among 56 ethnic populations in China. For example, the frequency distribution of A, B, O and AB blood groups in the Han population was 28.39%, 29.33%, 33.20% and 9.08%, while that of the Yao population was 20.63%, 21.01%, 55.11% and 3.26%,[7] respectively. Hence, if each of two sets of cases came from these two different ethnic groups, the difference in the frequency of blood group distribution between these sets would not be of aetiological significance.

In fact, the frequency distribution of ABO blood groups in clinical cases must be affected by the inherent distribution characteristics of the population. Therefore, to study the relationship between the ABO blood group and diseases, the first step is to determine the frequency distribution of the ABO system in the population from where the cases are derived. However, the source of clinical cases is often complex and the distribution characteristics of their 'representative' populations are usually 'unknown', so the real frequency distribution of ABO blood groups in clinical cases based on collection from outpatients or hospitalised cases certainly has great contingency and uncertainty. Because of the widespread prevalence of liver cancer worldwide,[11 12] the relationship between ABO blood type and risk of liver cancer has drawn attention.[13–15] Recently, a Shanghai cohort study has reported a relationship between ABO blood type and risk of cancer (including liver cancer), where blood type AB was associated with significantly increased risk of liver cancer.[16] However, there are no other prospective research data sets to confirm this relationship, with one report showing a different finding.[17] To study the distribution of ABO blood groups and the hypothesised link between ABO blood type and risk of liver cancer, we analysed the results from a prospective cohort of hepatitis B surface antigen (HBsAg) carriers that had been established in 2007 in a liver cancer epidemic area.

MATERIALS AND METHODS

Cohort population and case confirmation

A screening programme of a high-risk population for liver cancer was conducted in 2007 in Qidong City, Jiangsu Province, China. A total of 38 016 people including men aged 30–70 and women aged 40–70 were screened; 3703 individuals were found to be HBsAg-positive, with a rate of 9.74%. These HBsAg-positive people entered the cohort and were thereafter screened twice a year through 2019 for early detection of liver cancer.[18] In this study, 3663 participants were assessed for ABO blood type and were included in the analysis; 40 individuals without ABO blood type results were excluded. Patients with liver cancer found during the cohort screening and in the follow-up intervals were confirmed to have cancer if they met the clinical diagnosis criteria for liver cancer[19] and were identified by the Qidong Cancer Registry, which is a member unit of the International Association of Cancer Registries.[20]

Laboratory test for HBsAg

HBsAg serological testing was performed at participants' initial screening using an ELISA diagnostic kit provided by Shanghai Kehua Bio-Engineering. The results were determined by reading the optical density (OD) value at 450 nm of each well after calibrating the blank well to zero. If the ratio of the OD value of sample / average OD value of negative control was ≥2.1, the sample was judged as positive for HBsAg; otherwise it was negative.

ABO blood grouping

The ABO blood typing (A, B, O and AB) was conducted using the standard forward antigen typing method. ABO blood groups were determined by anti-A and anti-B blood grouping agents monoclonal antibody, which was produced by Shanghai Blood Biological Medicine. The interpretation of test results was based on the instruction manual. Briefly, the blood groups are divided into A, B, O and AB according to the presence or absence of A and/or B antigens on the red blood cells: that is, anti-A(+)/anti-B(−): A blood group; anti-A(−)/anti-B(+): B blood group; anti-A(−)/anti-B(−): O blood group; anti-A(+) / anti-B(+): AB blood group.

Follow-up and statistical methods

The endpoint date (close date) of follow-up for all cohort individuals was 31 December 2019, from which the number of observed person-years (PY) was calculated. The formula used to calculate PY was: PY=(close date−start date)/365.25. For cases of liver cancer, the close date of follow-up was the date of diagnosis, and the close date of other deaths (except for liver cancer) was the date of death. The ABO blood group distributions (frequency, %) in the cohort population and patients with liver cancer were calculated by gender and age. χ^2 test was used to compare the differences in frequency of ABO blood distribution. The incidence rate of liver cancer in each ABO group was calculated relative to PY (per 100 000). The relative risk (RR) of development of liver cancer was the ratio of the incidence rate in each of the B, O and AB blood groups (I_B, I_O, I_{AB}) with respect to the rate of the A blood group (I_A, as the reference 1). For instance, the RR for the B group was $RR_B=I_B/I_A$. The 95% CI of RR_B was Exp $[ln\, RR_B \pm 1.96\sqrt{var(lnRR_B)}]$. The significance of the difference between frequencies and between incidence rates (RR, 95% CI) of liver cancer was tested at a p value less than 0.05.

Table 1 Distribution and comparison of ABO blood groups in the whole cohort population and liver cancer cases

	Male		Female		Total		
	n	%	n	%	n	%	Male vs female
Whole cohort population							
A	536	29.04	582	32.03	1118	30.52	χ^2=7.0189, df=3, p>0.05
B	564	30.55	509	28.01	1073	29.29	
O	547	29.63	557	30.65	1104	30.14	
AB	199	10.78	169	9.30	368	10.05	
All combined	1846	100.00	1817	100.00	3663	100.00	
Patients with liver cancer							
A	70	29.54	34	34.34	104	30.95	χ^2=1.5024,df=3, p>0.05
B	67	28.27	30	30.30	97	28.87	
O	71	29.96	24	24.24	95	28.27	
AB	29	12.24	11	11.11	40	11.90	
All combined	237	100.00	99	100.00	336	100.00	
Patients with liver cancer vs other individuals in the cohort	χ^2=1.0317, df=3, p>0.05		χ^2=2.1441, df=3, p>0.05		χ^2=1.7440, df=3, p>0.05		

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

RESULTS

Frequency distribution of ABO blood group

Among the 3663 individuals whose ABO blood group was confirmed, 1118 (30.52%) were of A blood group, 1073 (29.29%) B blood group, 1104 (30.14%) O blood group and 368 (10.05%) AB blood group. There were 1846 men and 1817 women in the cohort, and the frequency distribution of ABO blood groups did not differ by gender. Three hundred and thirty-six cases of liver cancer were identified in the cohort during the entire follow-up period, including 104 (30.95%) with type A, 97 (28.87%) with type B, 95 (28.27%) with type O and 40 (11.90%) with type AB. No significant differences were found among the frequency distributions of the ABO blood groups in men or women. In terms of comparison between patients with liver cancer and other individuals in the cohort, there was also no significant difference in the frequency distribution of ABO blood groups (table 1).

Observed PY and incidence of liver cancer

The total observed PYs in the cohort population from 2007 to 2019 were 37 072.10, including 18 016.85 PYs in men and 19 055.25 PYs in women (table 2). For people with blood types A, B, O and AB, 11 331.96, 10 852.83, 11 229.11 and 3658.20 PYs were observed, respectively (table 2). The number of patients with liver cancer was 104, 97, 95 and 40, with an annual incidence rate of 917.76, 893.78, 846.02 and 1093.43 per 100 000 PYs, respectively. The combined incidence rate of liver cancer in all individuals was 906.34 per 100 000 PYs (table 3).

In men, the highest incidence of liver cancer was in the 50–59 years age group (1599.92 per 100 000) and in women in the over 60 years age group (743.98 per 100 000). The peak incident age of individuals with blood types A and AB could be seen in the 50–59 years age group, at 1272.75 and 1431.86 per 100 000, respectively. The peak age for people with blood type B was at over 60 years of age, at a rate of 1266.95 per 100 000, and for blood type O the highest incident rate was at the age of 40–49, at a rate of 919.10 per 100 000 (table 3).

RR of liver cancer by blood type

Assuming that the incidence of liver cancer in people with blood type A is 1 (reference group), the RR (95% CI) was 0.97 (0.74 to 1.29), 0.92 (0.70 to 1.22) and 1.19 (0.82 to 1.72) in blood types B, O and AB, respectively; namely the risk of developing liver cancer from the highest to the lowest was AB > A > B > O, but with no statistical significance in ranking. For men, it was AB > A > O > B, and for women it was AB > B > A > O, again with no significant differences observed (table 4).

DISCUSSION

Many studies have used a case–control design to study the frequency distribution of ABO blood groups and to estimate the OR. Li *et al*[15] compared the ABO blood groups and the risk of liver cancer in Chinese patients with chronic hepatitis B using a hospital case–control study design and indicated that type A patients with chronic hepatitis B were at increased risk of liver cancer and that this association was gender-related. In a clinical case–control study reported by Iavarone *et al*,[21] non-O blood group was associated with higher risk of liver cancer compared with cirrhosis without liver cancer and healthy subjects. Shim *et al*[14] compared the ABO genotypes and

Table 2 Person-years of HBsAg cohort by sex, age and ABO blood type

Sex	Age	ABO blood group A	B	O	AB	Total
Male	30–39	867.59	1004.35	868.06	323.99	3063.99
	40–49	1835.97	1908.87	1836.06	723.91	6304.81
	50–59	1566.56	1796.71	1818.38	481.29	5662.94
	60–	924.60	796.67	864.00	399.84	2985.11
	Total	5194.72	5506.60	5386.50	1929.03	18016.85
Female	30–39	–	–	–	–	–
	40–49	2807.71	2365.52	2407.24	810.54	8391.01
	50–59	2597.65	2277.72	2663.47	705.98	8244.82
	60–	731.88	702.99	771.90	212.65	2419.42
	Total	6137.24	5346.23	5842.61	1729.17	19055.25
Total	30–39	867.59	1004.35	868.06	323.99	3063.99
	40–49	4643.68	4274.39	4243.30	1534.45	14695.82
	50–59	4164.21	4074.43	4481.85	1187.27	13907.76
	60–	1656.48	1499.66	1635.90	612.49	5404.53
	Total	11331.96	10852.83	11229.11	3658.20	37072.10

HBsAg, hepatitis B surface antigen.

the risk of liver cancer of hospital cases with controls from the general population in Korea. The adjusted OR (aOR) and 95% CI were calculated using logistic regression models, adjusting for gender, age, smoking, alcohol drinking, and hepatitis B and C status. The results showed that the risk of liver cancer in genotype AA was significantly higher than genotype OO (aOR=1.77, 95% CI 1.16 to 2.71), and the risk in blood group A was higher than in blood group O (aOR=1.45, 95% CI 1.01 to 1.90). No significant differences were found among genotypes AA, BO, BB and AB, or blood groups B and AB. Liu *et al*[13] used meta-analysis to explore the relationship between ABO blood groups and risk of liver cancer. Combined results from seven case–control studies showed that the proportion of type O in patients with liver cancer was lower than that of healthy subjects (OR=0.76, 95% CI 0.66 to 0.87), but no significant differences between patients with liver cancer and patients with hepatitis or cirrhosis

Table 3 Liver cancer incidence by sex, age and ABO blood type, per 100 000 person-years

Sex	Age	ABO blood group A	B	O	AB	Total
Male	30–39	230.52	398.27	230.40	308.65	293.73
	40–49	1143.81	1414.45	1797.33	1657.66	1475.06
	50–59	2042.69	1280.12	1539.83	2285.52	1659.92
	60–	1622.32	1631.79	925.93	1250.50	1373.48
	Total	1347.52	1216.72	1318.11	1503.35	1315.44
Female	30–39	–	–	–	–	–
	40–49	320.55	422.74	249.25	370.12	333.69
	50–59	808.42	614.65	450.54	849.88	642.83
	60–	546.54	853.50	777.30	940.51	743.98
	Total	553.99	561.14	410.78	636.14	519.54
Total	30–39	230.52	398.27	230.40	308.65	293.73
	40–49	646.04	865.62	919.10	977.55	823.36
	50–59	1272.75	908.10	892.49	1431.86	1056.96
	60–	1147.01	1266.95	855.80	1142.88	1091.68
	Total	917.76	893.78	846.02	1093.43	906.34

Table 4 Relative risk and 95% CI of ABO blood types in the cohort by sex

Sex	Blood group	Person-years	Liver cancer (n)	Incidence ($1/10^5$)	Relative risk	95% CI
Male	A	5194.72	70	1347.52	1.00	
	B	5506.60	67	1216.72	0.90	0.65 to 1.27
	O	5386.50	71	1318.11	0.98	0.70 to 1.36
	AB	1929.03	29	1503.35	1.11	0.72 to 1.72
Female	A	6137.24	34	553.99	1.00	
	B	5346.23	30	561.14	1.01	0.62 to 1.66
	O	5842.61	24	410.78	0.74	0.44 to 1.25
	AB	1729.17	11	636.14	1.15	0.58 to 2.27
Total	A	11331.96	104	917.76	1.00	
	B	10852.83	97	893.78	0.97	0.74 to 1.29
	O	11229.11	95	846.02	0.92	0.70 to 1.22
	AB	3658.20	40	1093.43	1.19	0.82 to 1.72

were observed. Also in studies of ABO blood groups focused on other cancers, such as oesophageal cancer,[22] a hospital-based case–control study design was used to examine the association between ABO blood group and risk of cancer.

One of the limitations of clinical case–control studies is that the selective bias of case (or control) is often difficult to overcome. For example, in some clinical studies, blood donors are used as controls for blood group distribution, although the blood group distribution of these donors may not be representative of the general population. For example, due to the characteristics of blood supply (selective screening) of the O blood group, the frequency distribution of the ABO blood system may have a large bias in any clinical blood bank. It has been reported[10] that the blood group distribution among blood donors in Chengdu, China was O > A > B > AB, at a proportion of 35.51%, 31.88%, 24.41% and 8.20%, with blood group O being of relatively high frequency.

Prospective follow-up studies can be the best approach to overcome these limitations. However so far there have been few studies that evaluated the RR of liver cancer in ABO blood groups using a prospective design. A 25-year prospective study[16] was conducted in a cohort population of 18244 men in Shanghai to explore the relationship between ABO blood type and risk of cancer. The results showed that compared with A blood group, the HR of the AB blood group was 1.45 (95% CI 1.04 to 2.04), with significant difference, while the HR of the B and O blood groups was 0.98 (95% CI 0.73 to 1.30) and 1.10 (95% CI 0.84 to 1.43), with no significant difference. In a Taiwanese follow-up study,[17] it was found that the HR of liver cancer for the AB blood group in men was 1.78 (95% CI 0.90 to 3.52), but the difference was not significant, while the HR of the A blood group liver cancer in women was 1.88 (95% CI 1.03 to 3.43), but the difference was significant. In another prospective study in Taiwan,[23] 339432 people were observed for an average of 8.75 years and no association was observed between ABO blood types and risk of liver cancer.

In this study, 3663 HBsAg-positive patients were followed up for an average of more than 10 years, with an annual incidence of 906.34 per 100000 for liver cancer, indicating that these cohort individuals were at high risk of liver cancer. We analysed the relationship (risk) between blood group and development of liver cancer from two perspectives. In view of the ABO blood group distribution in patients and other individuals in the cohort, it can be seen that the frequency distribution of A (30.95%), B (28.27%), O (28.87%) and AB (11.90%) blood groups in liver cancer cases has no significant distinction to other people in the cohort. In fact, the blood group distribution (A: 30.52%, O: 30.14%, B: 29.29%, AB: 10.05%) in all the cohort individuals in this paper is almost the same as that of the Chinese population (A: 30.5%, O: 30.4%, B: 29.4%, AB: 9.7%),[3] that is, A > O > B > AB. Another important indicator of the outcome of the different at-risk exposures in cohort studies is the PY incidence rate of disease. In this study, the average annual incidence rates of liver cancer were 917.76, 893.78, 846.02 and 1093.43 per 100000 PYs in A, B, O and AB blood groups. Compared with the A blood group (RR=1), the risk of liver cancer in the B, O and AB blood groups was 0.97 (95% CI 0.74 to 1.29), 0.92 (95% CI 0.70 to 1.22) and 1.19 (95% CI 0.82 to 1.72), respectively. While it seems that the RR of liver cancer in AB blood group was slightly higher, and in the O blood group was lower, the differences were not significant. However, the peak incident ages of liver cancer were different: O blood group at the age of 40–49 years, A and AB blood groups at 50–59 years, and B blood group over 60. The reasons for these disparities may not be clear, but random variations could not be ruled out.

Based on the results of this cohort study, the relationship between ABO blood group and risk of liver cancer could not be established. The possible reasons are as follows: First, ABO blood groups may not be related to the risk of

liver cancer.[13 23] The proportion (or risk) of a blood group (such as type A) in the few literature reports for patients with liver cancer may be affected by the proportion of the blood group in the population represented by cases (especially in hospital case–control studies). Second, the association between the ABO blood group system and risk of liver cancer may not be excluded, but can be regarded only as 'weak association' (eg, compared with other factors such as hepatitis B virus (HBV) infection). The possible risk of type AB or type A shown in the literature was relatively higher,[14–17] while that of type B or type O was lower,[13 14] which may need to be confirmed. Third, the possible link between the ABO blood group system and the risk of liver cancer may be due to confounding factors. For example, is it possible that HBV infection is related to the ABO blood group system? According to the literature,[4] compared with the AB blood group, the OR of the O blood group infected with HBV (HBsAg-positive) was 1.22 (95% CI 1.20 to 1.25). For instance, a report showed that the ABO blood group was related to hepatitis B and that people with B blood group infected with HBV were less likely to develop hepatitis B.[9] A recent meta-analysis that summarised 38 reports[24] indicated that ABO blood groups may be related to HBV infection. Compared with the non-B blood group, the risk of HBV infection in the B blood group was reduced by 8% (RR=0.92, 95% CI 0.86 to 0.98).

Perhaps in relatively high-incidence areas in Qidong, there are even stronger aetiological factors for the development of liver cancer, such as HBV infection and aflatoxin contamination,[25–27] concealing the relationship between ABO blood type and liver cancer. However, our findings, at the very least, showed that ABO blood type does not appear to be a very important driver in the aetiology of liver cancer.

Our study is limited in that the Rh blood system was not determined. However, since the vast majority of the local Han people are Rh-positive,[4] it is likely that the Rh system could not influence liver cancer at the population level. The other limitation is that we did not adjust for other possible confounding factors such as body mass index, cigarette smoking status, alcohol intake, hepatitis C virus or diabetes. However, based on our previous observations in the Qidong area of no associations with these factors, we do not expect that it would overturn our conclusion. A third limitation is that we did not differentiate among genotypes within the ABO blood system; however, from our main results, we can conclude that this distinction seems to be no longer of importance. We also did not compare our cohort individuals with HBsAg-negative individuals based on the knowledge that HBsAg-positive individuals were a high-risk group for developing liver cancer, while HBsAg-negative individuals were a low-risk group, as shown by our previous reports.[26 27] Lastly, potential confounders such as age, sex, race and occupation should be noted or adjusted, although almost over 99% of participants in our cohort are of Han nationality and majority were farmers and the impact of these factors should be small.

In summary, case studies or case–control studies, as well as results from very few cohort studies, have reported positive or negative relationship between the ABO blood system and risk of liver cancer. Our prospective study did not demonstrate a positive association, but supports a negative association between ABO blood type and development of liver cancer.

Contributors Conceptualisation and study design: J-GC. Guarantor of the article: J-GC, L-LL, Y-HZ. Data collection: L-LL, Y-HZ, M-HY, J-HL, Y-SC, JX, JZ, H-ZC. Laboratory test: L-LL, J-HL, M-HY, JX. Data analysis: L-LL, Y-HZ, H-ZC, J-GC. Resources: Y-HZ, JZ, J-GC. Project administration: Y-HZ, J-HL, Y-SC, J-GC. Draft writing: L-LL, Y-HZ, J-GC. Funding acquisition and supervision: J-GC. All authors approved the final version of the manuscript.

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Data availability statement Data are available upon reasonable request. Individual participant data will be available (including data dictionaries). Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures and appendices), will be shared. Other documents will not be available. Data will be available beginning 6 months and ending 36 months following article publication to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Data will be for individual participant data meta-analysis. Proposals should be directed to chenjg@ntu.edu.cn. To gain access, data requestors will need to sign a data access agreement.

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