ABO blood group and the risk of cancer among middle-aged people in Taiwan

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Abstract

Aim: The relationship between ABO blood group and cancer was observed in many epidemiological researches. Our aim is to study the relationship between ABO blood group and the risk of cancer in the Taiwanese population.

Methods: We followed 3180 men and 3124 women with baseline ages ranging from 20 to 65 years for 27 years. Blood group information was obtained from registration on Identity Card. Cancer incidence information was confirmed by reviewing National Cancer Registry. Hazard ratios (HRs) for cancers according to ABO blood group were calculated using Cox proportional hazards models with multivariate adjustment.

Results: During an average of 27 years of follow-up, the adjusted HR of total cancer was 1.66 (95% CI, 1.20–2.30) for blood group AB in men and 1.28 (95% CI, 1.03–1.59) for blood group A in women, compared to blood group O of their respective gender. A significant excess risk was found among subjects with presence of A antigen. This positive association was mainly observed in cancers from lung cancer (HR: 1.88 [95% CI: 1.29–2.75]) and gastrointestinal cancer (HR: 1.25 [95% CI: 1.00–1.61]) in men, as well as liver cancer (HR: 1.69 [95% CI: 1.02–2.79]) and gastrointestinal cancer (HR: 1.49 [95% CI: 1.10–2.04]) in women.

Conclusion: These data suggest that ABO blood group is significantly associated with cancer risk. Men with blood group AB, women with blood group A, and subjects with presence of A antigen were more likely to develop cancers.

Key words: ABO blood group, cancer, Taiwan.

INTRODUCTION

Cancer is a leading cause of death worldwide and has become a major health issue. In Taiwan, the number of deaths due to cancer accounted for 28% of all deaths.1

The occurrence of cancer is the result of the interaction between genetic factors and environment factors. Most of cancers are attributed to environmental factors, including cigarette smoking, diet and obesity, radiation, and infections.2 Genetic mutations accounts for 5–10% of all cancer cases.3 Although hereditary cancers are rare, some inherited characteristics, for example, blood groups, have been reported associated with the risk of cancers.

The ABO blood group system was found by Austrian scientist Karl Landsteiner at the University of Vienna in 1901.4 The ABO locus is located on chromosome 9, and the ABO gene is autosomal. Distribution of the four different blood groups varies between countries. Generally, blood group O has the highest prevalence, while blood group AB has the lowest. In Taiwan, the proportion of ABO blood groups is 26% for A, 24% for B, 44% for O and about 6% for AB.5
Previous studies have observed an association between ABO blood group and risk of certain malignancies. Aird et al. reported that the frequency of gastric cancer is higher in blood group A, and less in group O. A higher frequency of blood group A was also seen in gastric cancer patients in a Taiwanese study.

In recent studies, the ABO blood groups were reported associated with pancreatic cancer risks. However, no prospective studies of the association between ABO blood group and cancer risk are available in Taiwan. Our aim is to study the relationship between ABO blood group and the risk of total cancer in middle-aged Taiwanese population.

METHODS

Study subjects

This study is based on the Six-Community Hypertension Intervention Project (SCHIP) that was designed to be a nationwide population-based survey. The SCHIP study is a prospective epidemiological investigation on hypertension and cardiovascular risk factors which started in 1982. The baseline data were collected between October 1982 and September 1983 by trained nurses during home visits. Participants with a history of cancer at baseline or who were older than 65 years were excluded. Participants who developed cancer within the first 3 years were also excluded for avoiding previously undetected cancer. This study received approval from the Institutional Review Board of Mackay Memorial Hospital.

Data collection

Sociodemographic data, including gender, age, smoking status, alcohol consumption and physician-diagnosed diseases (e.g. cancer, hypertension and diabetes), were documented using a structured questionnaire. The blood group data of the participants were initially self-reported and later confirmed by the registration on their Identity Card. In Taiwan, personal blood group information was registered on the Identity Card from 1965 to 1986.

On the first visit in 1982, sitting blood pressure and anthropometric data were measured. Smoking was categorized as current (two groups: less than a pack of cigarettes a day and more than a pack of cigarettes a day), past or never during the previous 3 months. Alcohol drinking status was categorized as frequent (more than once a week), less frequent or never. According to the body mass index (BMI) cutoff values suggested for the Taiwanese population, subjects were classified into obesity if BMI ≥ 27 kg/m². Hypertension was defined by physician-diagnosed hypertension, or measured systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Diabetes was defined by physician-diagnosed diabetes or plasma fasting glucose ≥ 140 mg/dL, according to the American Diabetes Association diagnostic criteria in 1983. The method of data collection has been described in a previous research.

Identification of cancer cases

Cancer incidence through December 31, 2009 was ascertained by review of Cancer Registry files from the Department of Health in Taiwan. If the subjects have second cancer, we account two periods of follow-up time length terminated from the data of an incident cancer.

Statistical analyses

Comparisons of characteristic data among the four ABO blood groups were carried out using analysis of variance (ANOVA) tests. The study subjects were followed up to the date of cancer diagnosis, death from another cause, or the end of our investigation (December 2009). Esophageal cancer, gastric cancer and colon cancer were treated as a group “gastrointestinal cancer” to gain sufficient numbers for analysis. Cox’s proportional hazards models were used to evaluate the association between blood group and risk of cancer by adjusting for age, smoking status, alcohol drinking, hypertension, diabetes and BMI. Study subjects with blood group O served as controls. All statistical analyses were performed using the SAS 9.2 statistical package (SAS Institute, Cary, NC, USA), and all P-values were derived from two-sided tests.

RESULTS

The number of subjects with adequate data for inclusion in this statistical analysis was 6,304 (3,180 male and 3,124 female). Ages of the subjects ranged from 20 to 65 years at the time of initial examination in 1982, with an average of 48.6 ± 10.1 years. Differences in characteristics of the study’s population are shown in Table 1. The distribution of O (45%), A (27%), B (22%) and AB (5%) blood groups was similar to that reported for the Taiwanese population. Baseline characteristics of participants including age, smoking status, alcohol...
drinking, hypertension, diabetes, blood pressure and BMI in this study were highly similar across the four ABO blood groups (Table 1).

During 27 years of follow-up, there were 1,067 confirmed cases of cancer with a cumulative incidence of 18.9% in men and 15.0% in women. The cancer-specific incidence rates were shown in Table 2. A large proportion of cancers were liver cancer, lung cancer and colon cancer. Our results showed that ABO blood group was associated with total cancer incidence. The cumulative incidence of total cancer was significantly lower for the groups without presence of A antigen (blood groups O and B) as compared to those groups with presence of A antigen (blood groups A and AB). The incidence rates for total cancer per 1,000 person-years for participants with blood group O were 7.83 in men and 5.95 in women, for those with blood group A were 9.05 in men and 7.54 in women, for those with blood group B were 8.58 in men and 5.79 in women, and for those with blood group AB were 11.74 in men and 7.28 in women.

The relationship between ABO blood group with total cancer and specific cancer incidences, including lung cancer, liver cancer and gastrointestinal cancer, is presented in Table 3. The cancer incidence of the blood group O was used as a reference. A significant excess risk was found among men with blood type AB (HR 1.66, 95% CI: 1.20–2.30). Total cancer incidence was higher in the blood group A (HR: 1.28 [95% CI: 1.03–1.59]) in women. The association was statistically significant in the lung cancer with blood group A (HR: 1.88 [95% CI: 1.03–3.43]) in men. The positive association was also found in liver cancer with blood group A (HR: 1.88 [95% CI: 1.03–3.43]) in women. The relationship between blood group with gastrointestinal cancer dominated in men with blood group AB (HR: 1.86 [95% CI: 1.16–2.97]) and women with blood group A (HR: 1.58 [95% CI: 1.12–2.23]).

In analyses of presence versus absence of A antigen, total cancer incidence was higher in the group with presence of A antigen (A and AB groups) as compared to the group without presence of A antigen (O and B groups) (HR: 1.20 [95% CI: 1.01–1.42] for men, 1.29 [95% CI: 1.07–1.56] for women). This positive association was mainly observed in cancers from lung cancer (HR: 1.88 [95% CI: 1.29–2.75]) and gastrointestinal cancer (HR: 1.25 [95% CI: 1.00–1.61]) in men, as well as liver cancer (HR: 1.69 [95% CI: 1.02–2.79]) and gastrointestinal cancer (HR: 1.49 [95% CI: 1.10–2.04]) in women. The number of prostate cancer,
Table 2  Major cancer incidences during follow-up according to ABO blood group categories

|                  | Men                     | Women                    |
|------------------|-------------------------|--------------------------|
|                  | ABO blood group categories |                          |
|                  | A | B | AB | O | A | B | AB | O |
|                  | n=849 | n=697 | n=176 | n=1548 | n=867 | n=691 | n=159 | n=1407 |
| Number of cancer incidence | 169 | 131 | 44 | 256 | 152 | 93 | 26 | 196 |
| Follow-up time (person-years) | 18681.1 | 15273.4 | 3746.6 | 32688.6 | 20172.3 | 16056.1 | 3571.1 | 32963.0 |
| All-cancer incidence rates (/1,000 person-years) | 9.05 | 8.58 | 11.74 | 7.83 | 7.54 | 5.79 | 7.28 | 5.95 |
| Major cancers incidence rates n (/1,000 person-years) | | | | | | | | |
| Lung cancer | 41 (2.19) | 19 (1.24) | 10 (2.67) | 39 (1.19) | 13 (0.64) | 16 (0.10) | 3 (0.84) | 28 (0.85) |
| Liver cancer | 37 (1.98) | 21 (1.37) | 10 (2.67) | 53 (1.62) | 24 (1.19) | 14 (0.87) | 5 (1.40) | 20 (0.61) |
| Pancreatic cancer | 5 (0.27) | 3 (0.20) | 0 | 1 (0.03) | 2 (0.10) | 1 (0.06) | 0 | 2 (0.06) |
| Gastrointestinal cancer | 44 (2.36) | 44 (2.88) | 14 (3.74) | 59 (1.80) | 41 (2.03) | 17 (1.06) | 1 (0.28) | 49 (1.49) |
| Esophageal cancer | 4 (0.21) | 5 (0.33) | 0 | 5 (0.15) | 0 | 0 | 0 | 3 (0.09) |
| Gastric cancer | 15 (0.80) | 12 (0.79) | 6 (1.60) | 17 (0.52) | 13 (0.64) | 8 (0.50) | 1 (0.28) | 12 (0.36) |
| Colon cancer | 23 (1.23) | 26 (1.70) | 8 (2.14) | 37 (1.13) | 27 (1.34) | 9 (0.56) | 0 | 34 (1.03) |
| Prostatic cancer | 11 (0.59) | 14 (0.92) | 3 (0.80) | 33 (1.00) | – | – | – | – |
| Breast cancer | – | – | – | – | – | – | – | – |
| Cervical cancer | – | – | – | – | – | – | 14 (0.69) | 12 (0.75) |

Table 3  Relationship of categories of ABO blood group to all-cancer and major cancer incidences

|                  | Men                     | Women                    |
|------------------|-------------------------|--------------------------|
|                  |                          |                          |
|                  | All cancers | Lung cancer | Liver cancer | Gastrointestinal cancer | All cancers | Lung cancer | Liver cancer | Gastrointestinal cancer |
|                  | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| ABO blood group categories | O | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
|                  | A | 1.18 (0.97–1.44) | 1.80 (1.16–2.80) | 1.17 (0.76–1.80) | 1.29 (0.96–1.72) | 1.28 (1.03–1.59) | 0.76 (0.39–1.48) | 1.88 (1.03–3.43) | 1.58 (1.12–2.23) |
|                  | B | 1.17 (0.94–1.45) | 1.06 (0.61–1.87) | 0.85 (0.51–1.43) | 1.31 (0.96–1.80) | 0.97 (0.76–1.25) | 1.13 (0.64–2.09) | 1.48 (0.75–2.92) | 0.95 (0.62–1.46) |
|                  | AB | 1.66 (1.20–2.30) | 2.64 (1.31–5.33) | 1.78 (0.90–3.52) | 1.86 (1.16–2.97) | 1.27 (0.84–1.92) | 1.06 (0.32–3.51) | 2.34 (0.87–6.25) | 0.85 (0.37–1.96) |
| A antigen† | Absent (O/B) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
|                  | Present (A/AB) | 1.20 (1.01–1.42) | 1.88 (1.29–2.75) | 1.33 (0.92–1.93) | 1.25 (1.00–1.61) | 1.29 (1.07–1.56) | 0.77 (0.44–1.37) | 1.69 (1.02–2.79) | 1.49 (1.10–2.04) |

†A antigen absent groups are blood groups O and B; A antigen present groups are blood groups A and AB; Cox proportional hazards models adjusted for age, smoking status, alcohol consumption, hypertension, diabetes, body weight index and obesity. CI, confidence interval; HR, hazard ratio.
breast cancer and cervical cancer was insufficient for analysis.

**DISCUSSION**

The results showed an elevated risk for total cancer among men with blood group AB and women with blood group A. Moreover, we found significantly higher risk for lung cancer in men with blood groups A and AB, for liver cancer in women with blood group A, as well as for gastrointestinal cancer in men with blood AB and in women with blood group A. We observed a statistically significant positive association with presence versus absence of the A antigen for developing cancers. The association dominated in lung and gastrointestinal cancer of men, as well as liver and gastrointestinal cancer of women.

The relationship between ABO blood group and the risk of cancer had been reported since the mid-1900s. Subjects carrying blood group A tended to contract different types of tumors.\(^1\)\(^\text{11}\) Consistent evidence was noted that gastric cancer risk in the blood A group was higher than that in the non-A groups in case-control studies.\(^2\)\(^\text{12,13}\) cohort studies\(^3\)\(^\text{14}\) and meta-analysis,\(^4\)\(^\text{15}\) with estimates of the relative risk ranging from 1.11 to 1.59. Several retrospective studies have reported that subjects with blood group A increased pancreatic cancer risk.\(^5\)\(^\text{15–19}\) One meta-analysis study in 2010 observed that the association between ABO blood group and cancer was limited to pancreas malignancy.\(^6\)\(^\text{20}\) Although specific risks for gastric and pancreatic cancers were not included in our study due to insufficient numbers of cases, our results showed a positive association between presenting A antigen and risk of gastrointestinal malignancies in both genders. These findings in our study were consistent with many other research data.

A case–control study in China observed increased risk of hepatocellular carcinoma with blood group A in men with chronic hepatitis B.\(^7\)\(^\text{21}\) In a multicenter retrospective study, non-O blood group increased the risk of lung cancer.\(^8\)\(^\text{22}\) In our study, higher risks for hepatocellular carcinoma and lung cancer also occurred in the presence of A antigen.

ABO blood groups are inherited through genes on chromosome 9q34, which encodes glycotransferases that catalyze the transfer of nucleotide donor sugars to the H antigen to form the ABO blood group antigens. The A allele encodes a glycosyltransferase that bonds α-N-acetylgalactosamine to the D-galactose end of the H antigen, producing the A antigen.\(^9\)\(^\text{23}\) The mechanism for the relationship between blood group and cancer risk is unknown, but several possible explanations exist. Blood group antigens may alter the systemic inflammatory response. Paré et al.\(^\text{10}\) found that ABO (9q34.2) locus is highly correlated with soluble intercellular adhesion molecule 1 (sICAM-1) concentrations,\(^\text{24}\) but have not been identified as oncogenes. Glycosylation could also affect the clearance rate of sP-selectin, sE-selectin and sICAM-1 from blood.\(^\text{25,26}\) The ABO locus may have regulatory role of histo-blood group antigens in inflammatory adhesion processes.

Some research has shown that the structure of certain tumor antigens is similar to the structure of antigens of ABO blood group system. Smith and Prieto\(^\text{27}\) presented the Forssmann antigen that, predominantly in stomach and colon tumors, is almost structurally identical to the A antigen determinant. One study found neoexpression of ABH blood group antigens in hepatocellular carcinoma tissues.\(^\text{28}\) Therefore, the blood group A carrier may have diminished tumor immune response due to reduced ability to recognize and attack tumor cells that express the antigen structurally similar to the ABO antigen.\(^\text{29}\)

To our knowledge, this is the first large prospective study done on the Taiwanese population. Previous studies about relationship between ABO blood group and cancers were mostly of retrospective design. The community-based population, long follow-up period and large sample size are all strengths of this study. However, our study has several possible limitations. First, blood group in this study was self-reported, making it susceptible to measurement error due to inaccurate reporting. We excluded teenagers younger than 20 years to minimize potential bias. Nevertheless, we confirmed the consistency of blood group data with the information registered on the Identity Card. Second, liver cancer could be attributed to chronic hepatitis B or C, but the data are insufficient for our statistical analysis. Third, a lot of previous studies showed that non-O blood group, especially blood group A, increased the risk of pancreatic cancer. The number of pancreatic cancers in our study is insufficient for analysis. Fourth, the blood group did not change, but changes in risk factors assessed in the cohort during follow-up were not considered, because little change from baseline occurred across the four ABO blood groups.

The results of our study suggest that ABO blood group status may represent an inherited susceptibility for cancer. Further studies are necessary to confirm these findings and to determine the potential mechanisms by which ABO antigens may influence total cancer risk.
ACKNOWLEDGMENT

We would like to thank all the investigators of the Six-Community Hypertension Intervention Project for their contribution to the compilation and validation of the data.

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