

RESEARCH ARTICLE

ABO Blood Groups and Risk of Cancer: a Systematic Review and Meta-analysis

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Abstract

Background: For decades, studies have been performed to evaluate the association between ABO blood groups and risk of cancer. However, whether ABO blood groups are associated with overall cancer risk remains unclear. We therefore conducted a meta-analysis of observational studies to assess this association. **Materials and Methods:** A search of Pubmed, Embase, ScienceDirect, Wiley, and Web of Knowledge databases (to May 2013) was supplemented by manual searches of bibliographies of key retrieved articles and relevant reviews. We included case-control studies and cohort studies with more than 100 cancer cases. **Results:** The search yielded 89 eligible studies that reported 100,554 cases at 30 cancer sites. For overall cancer risk, the pooled OR was 1.12 (95% CI: 1.09-1.16) for A vs. non-A groups, and 0.84 (95% CI: 0.80-0.88) for O vs. non-O groups. For individual cancer sites, blood group A was found to confer increased risk of gastric cancer (OR=1.18; 95% CI: 1.13-1.24), pancreatic cancer (OR=1.23; 95% CI: 1.15-1.32), breast cancer (OR=1.12; 95% CI: 1.01-1.24), ovarian cancer (OR=1.16; 95% CI: 1.04-1.27), and nasopharyngeal cancer (OR=1.17; 95% CI: 1.00-1.33). Blood group O was found to be linked to decreased risk of gastric cancer (OR=0.84; 95% CI: 0.80-0.88), pancreatic cancer (OR=0.75; 95% CI: 0.70-0.80), breast cancer (OR=0.90; 95% CI: 0.85-0.95), colorectal cancer (OR=0.89; 95% CI: 0.81-0.96), ovarian cancer (OR=0.76; 95% CI: 0.53-1.00), esophagus cancer (OR=0.94; 95% CI: 0.89-1.00), and nasopharyngeal cancer (OR=0.81; 95% CI: 0.70-0.91). **Conclusions:** Blood group A is associated with increased risk of cancer, and blood group O is associated with decreased risk of cancer.

Keywords: Blood group - cancer - systematic review - meta-analysis

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Introduction

ABO blood group system, identified in 1900, classifies human blood based on the presence or absence of the antigens A and B carried on the surface of erythrocytes. As an easily accessible factor in an individual's genetic makeup, ABO blood groups have been statistically associated with many diseases (Levitan et al., 1959; Lewis et al., 1961; Strang, 1965; Maurer et al., 1969; Erikssen et al., 1980). During the past several decades, numerous studies have shed light on the relationship between ABO blood groups and risk of cancer at different sites, but the results were inconsistent. Recent Genome-wide Association Studies (GWASs) have identified single nucleotide polymorphisms (SNPs) mapped to the ABO blood group gene as the top hit for cancer susceptibility out of millions of SNPs (Amundadottir et al., 2009; Tanikawa et al., 2012), rekindling the old fire. Several meta-analyses have been performed and reported significant association between ABO blood groups and cancer at specific sites, including gastric cancer (Wang et al., 2012), pancreatic cancer, and breast cancer. However, the relationship

between ABO blood groups and overall cancer risk still remains unclear. Therefore, we conducted a systematic review and meta-analysis to evaluate the association between ABO blood groups and overall cancer risk, as well as the risk of individual cancer sites.

Materials and Methods

Search strategy

We performed a systematic literature search (up to May 2013) of Pubmed, Embase, ScienceDirect, Wiley, and Web of Knowledge for studies reporting the association between ABO blood groups (self-reported or lab tested) and cancer risk. In addition, we searched the reference lists of relevant articles and reviews. Only articles published in English were considered. Two search themes were combined using the Boolean operator 'and'. The first theme, cancer, combined exploded versions of the Medical Subject Headings (MeSH) cancer, tumor, carcinoma, neoplasm or malignancy. The second theme, blood group, combined exploded versions of MeSH terms blood group, or blood type.

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Selection criteria

Eligibility of the literature was assessed independently by two investigators (N. H. and Y. H.), and disagreements were resolved by another investigator (F. S.). Articles were included in the meta-analysis if: (1) the authors presented original, peer-reviewed study (i.e., not meeting report or review articles); (2) the study was a case-control study or cohort study; (3) no less than 100 cancer cases were included in the study; (4) the authors provided odds ratio (OR) estimates, relative risk (RR) estimates and confidence intervals (CIs) for A vs non-A, B vs non-B, O vs non-O, and AB vs non-AB, or reported enough data to calculate them. If data were published as duplicate in more than one study, we included only the most recent study.

Data extraction

The following information was extracted from the selected studies: study characteristics (study name, authors, publication year, and journal), characteristics of the study population (country, race, case number and control number, and cancer site), and key indicators of study quality (study design, sample size, and sampling methods). The quality of the studies was evaluated using the Newcastle-Ottawa Scale (NOS). Each study was assessed based on three broad characteristics: selection, comparability, and exposure (outcome for cohort study) with a score ranging from 0 to 9. A score of 7 or greater indicates a high quality study.

Data synthesis

For the case-control studies included, ORs (A vs non-A, B vs non-B, O vs non-O, and AB vs non-AB) were calculated based on the number of cases and controls in each blood group. For cohort studies included, corresponding relative risks (RRs) were calculated based on the number of cases and participants. As the majority of the studies included were case-control studies, the ORs were used as the common measure of association across studies, and the RRs were considered equivalent to ORs. Forest plots were produced to visually assess the ORs and corresponding 95% confidence intervals (CIs) across studies. Heterogeneity of ORs across studies was evaluated by the Cochrane Q statistic ($p < 0.10$ was considered indicative of statistically significant heterogeneity) and the I^2 statistic (values of 25%, 50%, and 75% were considered to represent low, medium, and

high heterogeneity, respectively) (Higgins et al., 2002; Higgins et al., 2003). The ORs were pooled using the fixed-effect model if low heterogeneity was detected, or the DerSimonian and Laird random-effects model otherwise (Takkouche et al., 1999). The possibility of publication bias was evaluated using the Begg test and visual inspection of a funnel plot (Begg et al., 1994; Egger et al., 1997). Moreover, stratified analyses and sensitivity analyses were performed to evaluate the influences of selected study and participant characteristics on study results. The analyses were performed with Stata statistical software version 11.0 (StataCorp, College Station, Texas). Two sided P values of 0.05 were considered significant.

Results

Literature search

Using the search strategy, we retrieved 14 240 citations. After the first round of screening based on titles and abstracts, 13 974 citations were excluded, and 266 articles remained for further full-text review. After 2 rounds of screening, 167 were excluded for reasons listed in Figure 1. In total, 89 studies met the inclusion criteria and were included in the meta-analysis.

Study characteristics

Characteristics of the 89 selected studies (82 case-control studies, 7 cohort studies) are shown in Supplementary Table 1 (for case-control studies) and Supplementary Table 2 (for cohort studies). These studies were conducted in 30 countries, published between 1953 and 2013, including 30 cancer sites, and involving 100 554 cancer cases. Some studies included multiple cancer sites, and we analyzed these data separately by site, and the total number of studies by site is 123. Among these studies, we identified 36 studies reported results on gastric cancer (AIRD et al., 1953; AIRD et al., 1954; BILLINGTON, 1956; SEGI et al., 1957; BUCKWALTER et al., 1958; EISENBERG et al., 1958; MACMAHON et al., 1958; BIRNBAUM et al., 1959; BEASLEY et al., 1960; DOLL et al., 1960; BECKMAN et al., 1961; COTTER et al., 1961; NEWMAN et al., 1961; Hartmann et al., 1964; LISKER et al., 1964; Hoskins et al., 1965; Macafee et al., 1967; Glober et al., 1971; van Wayjen et al., 1973; Newell et al., 1974; Akumabor et al., 1986; Kurtenkov et al., 1995; Klaamas et al., 1999; Su et al., 2001; Kamlesh et al., 2005; El et al., 2007; Edgren et al., 2010; Akhtar et al., 2010; Nakao et al., 2011; Qiu et al., 2011; Urun et al., 2012; Wang et al., 2012; Gong et al., 2012; Rizzato et al., 2013; Song et al., 2013), 13 studies on pancreatic cancer (AIRD et al., 1960; Newell et al., 1974; Annese et al., 1990; Wolpin et al., 2009; Greer et al., 2010; Wolpin et al., 2010; Ben et al., 2011; Nakao et al., 2011; Engin et al., 2012; Gong et al., 2012; Wang et al., 2012; Woo et al., 2013; Rizzato et al., 2013), 11 studies on breast cancer (AIRD et al., 1954; BUCKWALTER et al., 1958; MITRA et al., 1962; Hartmann et al., 1964; Newell et al., 1974; Anderson et al., 1984; Costantini et al., 1990; Ronco et al., 2009; Dede et al., 2010; Gates et al., 2012; Urun et al., 2012), 8 studies on cervical cancer (SEGI et al., 1957; MITRA et al., 1962; ROTKIN et al., 1965;

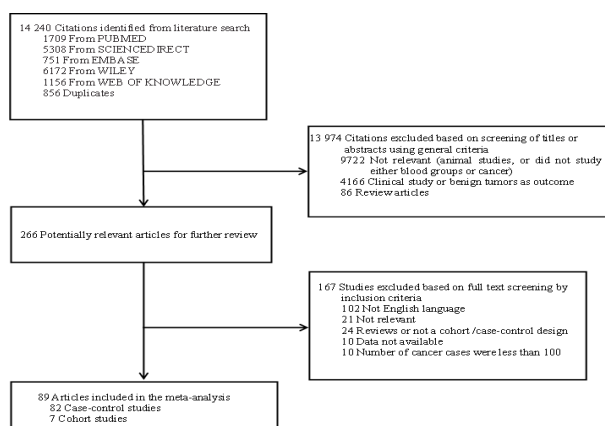


Figure 1. Literature Search for the Meta-Analysis

Table 1. Analyses of Odds Ratio (OR) of Overall Cancer, and Cancer by Site According to ABO Blood Groups

Cancer site (number of studies and cancer cases)	A vs non-A		B vs non-B		O vs non-O		AB vs non-AB	
	OR (95% CI)	Weight, %	OR (95% CI)	Weight, %	OR (95% CI)	Weight, %	OR (95% CI)	Weight, %
Overall (123, 100 554)	1.12 (1.09, 1.16)	100	1.01 (0.97, 1.05)	100	0.84 (0.80, 0.88)	100	0.98 (0.94, 1.03)	100
Common cancer (77, 66 671)	1.12 (1.09, 1.16)	63.91	0.97(0.93, 1.02)	64.07	0.87 (0.82, 0.91)	62.02	1.00(0.94, 1.06)	61.18
Rare cancer (46, 33 883)	1.14 (1.08, 1.21)	36.09	1.07(1.00, 1.14)	35.93	0.79 (0.73, 0.86)	37.98	0.95(0.88, 1.03)	38.82
Gastric (36, 31 783)	1.18 (1.13, 1.24)	29.17	0.95 (0.89, 1.01)	30.25	0.84 (0.80, 0.88)	29.48	0.98 (0.90, 1.07)	28.93
Pancreatic (13, 8068)	1.23 (1.15, 1.32)	9.49	1.03 (0.91, 1.14)	10.03	0.75 (0.70, 0.80)	10.68	0.98 (0.81, 1.17)	10.55
Breast (11, 11 460)	1.12 (1.01, 1.24)	10.02	0.94 (0.79, 1.09)	10.54	0.90 (0.85, 0.95)	9.53	0.97 (0.81, 1.13)	11.16
Cervical (8, 4031)	1.06 (0.89, 1.24)	5.7	0.98 (0.85, 1.12)	6.36	0.89 (0.66, 1.11)	5.7	1.00 (0.70, 1.31)	5.97
Colorectal (8, 6931)	1.05 (0.98, 1.13)	7.4	1.12 (0.94, 1.29)	6.16	0.89 (0.81, 0.96)	6.45	1.07 (0.88, 1.26)	5.99
Ovarian (7, 9956)	1.16 (1.04, 1.27)	6.59	1.05 (0.90, 1.20)	6.76	0.76 (0.53, 1.00)	6.48	0.97 (0.81, 1.13)	8.13
Esophagus (6, 8975)	0.92 (0.82, 1.02)	5.87	1.18 (1.04, 1.32)	4.09	0.94 (0.89, 1.00)	4.76	1.03 (0.85, 1.21)	4.24
Lung (4, 1561)	1.12 (0.73, 1.52)	2.91	0.81 (0.66, 0.95)	3.2	0.87 (0.20, 1.55)	3.11	1.18 (0.88, 1.48)	1.93
Nasopharyngeal (3, 1872)	1.17 (1.00, 1.33)	1.8	1.06 (0.90, 1.21)	2.21	0.81 (0.70, 0.91)	2.17	1.17 (0.85, 1.48)	1.49
Liver (2, 1319)	1.24 (1.08, 1.40)	1.55	0.95 (0.83, 1.06)	2.12	0.85 (0.74, 0.96)	1.67	1.02 (0.83, 1.22)	2.12
Oral cavity (2, 795)	1.91 (1.03, 2.80)	0.78	0.98 (0.70, 1.26)	1.78	0.62 (0.51, 0.73)	1.73	0.66 (0.45, 0.87)	2.01
Endometrial (2, 1509)	1.26 (0.94, 1.57)	1.65	0.94 (0.80, 1.09)	2.14	0.85 (0.63, 1.08)	1.74	0.96 (0.75, 1.17)	2.43
Leukemia (2, 1531)	1.29 (0.65, 1.93)	1.41	0.90 (0.20, 1.60)	1.75	0.82 (0.72, 0.93)	1.56	1.11 (0.18, 2.05)	0.99
Melanoma (2, 1130)	0.93 (0.82, 1.04)	2.13	0.98 (0.80, 1.15)	1.81	1.01 (0.97, 1.22)	1.67	0.92 (0.69, 1.16)	2.01
Bronchogenic (2, 1261)	1.01 (0.82, 1.20)	1.91	1.62 (0.94, 2.31)	1.11	0.80 (0.68, 0.92)	1.79	1.27 (0.86, 1.67)	1.04
Tongue (1, 160)	1.29 (0.94, 1.76)	0.49	1.10 (0.65, 1.88)	0.31	0.82 (0.59, 1.14)	0.67	0.33 (0.08, 1.32)	0.45
Biliary (1, 826)	0.65 (0.49, 0.86)	1	1.66 (1.27, 2.17)	0.49	0.92 (0.70, 1.21)	0.7	0.91 (0.58, 1.43)	0.8
Lip (1, 569)	1.28 (1.08, 1.51)	0.91	0.74 (0.53, 1.04)	0.92	0.83 (0.70, 0.99)	0.9	1.09 (0.71, 1.66)	0.68
Burkitt's Tumour (1, 100)	1.11 (0.69, 1.76)	0.33	0.87 (0.54, 1.42)	0.51	1.06 (0.72, 1.57)	0.44	0.76 (0.24, 2.41)	0.17
Glioma (1, 674)	0.77 (0.60, 0.98)	0.98	1.21 (0.95, 1.56)	0.78	0.99 (0.78, 1.26)	0.73	1.21 (0.84, 1.76)	0.72
Brain (1, 2254)	1.12 (1.02, 1.23)	1.23	0.99 (0.83, 1.16)	1.2	0.91 (0.83, 1.00)	0.99	0.89 (0.67, 1.18)	1.42
Central nervous (1, 112)	1.99 (1.32, 3.01)	0.16	1.89 (1.29, 2.76)	0.23	0.16 (0.07, 0.34)	0.92	0.52 (0.24, 1.13)	0.75
Salivary gland (1, 250)	1.36 (1.05, 1.75)	0.59	1.02 (0.70, 1.47)	0.6	0.74 (0.57, 0.96)	0.81	0.93 (0.51, 1.68)	0.5
Thyroid (1, 798)	0.70 (0.54, 0.89)	1.03	1.30 (1.02, 1.66)	0.74	1.07 (0.84, 1.35)	0.7	1.07 (0.73, 1.57)	0.81
Bladder (1, 511)	1.11 (0.93, 1.33)	0.96	0.84 (0.60, 1.16)	0.85	0.94 (0.79, 1.12)	0.87	1.08 (0.70, 1.66)	0.67
Kidney (1, 251)	1.30 (1.01, 1.67)	0.63	1.07 (0.75, 1.53)	0.59	0.74 (0.57, 0.96)	0.81	1.01 (0.64, 1.60)	0.67
Bone (1, 189)	1.25 (0.88, 1.79)	0.42	1.83 (1.36, 2.47)	0.36	0.42 (0.28, 0.63)	0.85	0.62 (0.36, 1.09)	0.97
Other gynaecological (1, 300)	0.71 (0.52, 0.99)	0.86	1.28 (0.84, 1.95)	0.36	1.31 (0.94, 1.83)	0.42	0.81 (0.44, 1.50)	0.58
Mesothelioma (1, 252)	0.96 (0.75, 1.24)	0.83	1.11 (0.81, 1.54)	0.64	0.94 (0.72, 1.23)	0.7	1.11 (0.71, 1.73)	0.61
Multiple unspecified (1, 1126)	0.96 (0.85, 1.08)	1.2	1.03 (0.85, 1.25)	1.09	1.04 (0.92, 1.17)	0.94	0.98 (0.72, 1.32)	1.22

*Common cancer: Top ten cancer by incidence worldwide according to Global Cancer Statistics, including breast cancer, colorectal cancer, lung cancer, prostate cancer, gastric cancer, liver cancer, cervical cancer, esophagus cancer, bladder cancer, and non-Hodgkin lymphoma (CA CANCER J CLIN 2011;61:69–90). Rare cancer: Cancer sites not included as common cancer

Adelusi et al., 1977; Kaur et al., 1992; Xu et al., 2011; Akhtar et al., 2011; Yuzhalin et al., 2012), 8 studies on colorectal cancer (AIRD et al., 1954; Macafee et al., 1967; Newell et al., 1974; Mousseron-Canet et al., 1984; Henry et al., 1993; Khalili et al., 2011; Urun et al., 2011; Urun et al., 2012), 7 studies on ovarian cancer (OSBORNE et al., 1963; Bjorkholm et al., 1984; Henderson et al., 1993; Gates et al., 2011; Akhtar et al., 2011; Poole et al., 2012; Yuzhalin et al., 2012), 6 studies on the esophagus cancer (AIRD et al., 1960; BEASLEY et al., 1964; Hartmann et al., 1964; Su et al., 2001; Gong et al., 2012; Yuzhalin et al., 2012), 4 studies on lung cancer (BUCKWALTER et al., 1958; Oguz et al., 1961; Gong et al., 2012; RENNIE et al., 2013), and 3 studies on nasopharyngeal (SEOW et al., 1964; Hawkins et al., 1974; Sheng et al., 2013). We also found 2 studies provided data on liver cancer, oral cavity cancer (Akhtar et al., 2011; Jaleel et al., 2012), endometrial cancer (Xu et al., 2011; Yuzhalin et al., 2012), bronchogenic cancer (AIRD et al., 1954; Roots et al., 1988), melanoma (Xie et al., 2010; de Giorgi et al., 2011), and leukemia (MACMAHON et al., 1958; Newell et al., 1974). Moreover, 1 study was found for each of the following cancer sites: biliary (Gong et al., 2012), other gynaecological (KROKFORS et al., 1954), tongue (Hartmann et al., 1964), lip (Hartmann et al., 1964), Burkitt's tumour (Williams et al., 1966), glioma (Gong et al., 2012), brain (Pearce et al., 1965), central nervous

(Akhtar et al., 2011), salivary gland (OSBORNE et al., 1962), thyroid (Gong et al., 2012), bladder (Llopis et al., 1990), kidney (Joh et al., 2012), bone (Akhtar et al., 2011), mesothelioma (Utkan et al., 2013), and multiple cancer unspecified (Holley et al., 1966). The blood groups were detected using routine clinical tests in most of the studies, and only seven studies acquired the information from blood bank records or questionnaires. Cancer was evaluated or detected/document in medical records. We extracted OR and 95%CI for each blood group directly from one article, and extracted data on the number of cancer cases and controls that corresponds to each blood type from 88 articles. ORs, RRs, and 95%CIs were calculated based on the data extracted.

Blood groups and risk of cancer

The results on the association between ABO blood groups and risk of cancer are presented in Table 1. For overall cancer, our results suggested that people with blood group A have a significantly higher risk compared with non-A groups (OR=1.12; 95%CI: 1.09-1.16), and those with blood group O showed a significantly decreased risk of overall cancer, compared with non-O groups (OR=0.84; 95%CI: 0.80-0.88). Blood group B and AB were not significantly associated with overall cancer risk. Similar results were found between common cancer and rare cancer (Table 1). There was evidence of heterogeneity

among studies (A vs non-A, $I^2=77.3\%$, $p<0.001$; B vs non-B, $I^2=65.1\%$, $p<0.001$; O vs non-O, $I^2=89.2\%$, $p<0.001$; AB vs non-AB, $I^2=40.6\%$, $p<0.001$). Influence analyzes omitting one study or one cancer site in each turn showed that no study or cancer site had substantial influence on the results.

Gastric cancer

A total of 36 studies (including 31 783 cancer cases) investigated the association between gastric cancer and ABO blood groups, including 35 case-control studies and 1 cohort study. Seven studies were performed in Asia and 29 were performed in Europe. Most of the studies reported positive association between gastric cancer and blood group A and inverse association for O vs non-O groups, 5 studies reported a contrary result, but not statistically significant. The pooled ORs from random-effects model showed that there was a significantly increased risk of gastric cancer for A vs non-A groups (OR=1.18; 95%CI: 1.13-1.24). For O vs non-O groups, we found a protective effect on gastric cancer, the pooled OR was 0.84 (95%CI: 0.80-0.88) (Table 1). The heterogeneity among studies was found (A vs non-A, $I^2=64.9\%$, $p<0.001$; B vs non-B, $I^2=57.3\%$, $p<0.001$; O vs non-O, $I^2=59.7\%$, $p<0.001$; AB vs non-AB, $I^2=38.7\%$, $p=0.011$). The influence analysis omitting one study in each turn showed that none of the studies influence the results substantially.

Pancreatic cancer

A total of 13 studies (12 case-control studies and 1 cohort study) provided data on pancreatic cancer comprising 8068 cases. Only one study reported an inverse association for A vs non-A groups, but not statistically significant. The pooled OR showed an increased risk for blood group A on pancreatic cancer (OR=1.23; 95%CI: 1.15-1.32) and a protected effect for blood group O on pancreatic cancer (OR=0.75; 95%CI: 0.70-0.80) (Table 1). A median heterogeneity was detected (A vs non-A, $I^2=30.7\%$, $p=0.13$; B vs non-B, $I^2=47.8\%$, $p=0.02$; O vs non-O, $I^2=29.1\%$, $p=0.15$; AB vs non-AB, $I^2=54.0\%$, $p=0.008$).

Breast cancer

The 11 studies on breast cancer (10 case-control studies and one cohort study) were all conducted in Europe, including 11 460 cases. The pooled OR for A vs non-A groups was 1.12 (95%CI: 1.01-1.24), and was 0.90 (95%CI: 0.85-0.95) for O vs non-O groups, suggesting an increased risk of breast cancer for blood group A and a decreased risk for blood group O (Table 1). We found a high heterogeneity across studies (A vs non-A, $I^2=80.3\%$, $p<0.001$; B vs non-B, $I^2=83.9\%$, $p<0.001$; O vs non-O, $I^2=33.0\%$, $p=0.14$; AB vs non-AB, $I^2=62.1\%$, $p=0.003$).

Colorectal cancer

A total of eight studies reported the association between colorectal cancer and blood groups with 6931 cancer cases, among them 7 were case-control studies and 1 was cohort study. We observed a decreased risk of colorectal cancer for people with blood group O (OR=0.89; 95%CI: 0.81-0.96) (Table 1). A high heterogeneity was found across studies (A vs non-A, $I^2=37.5\%$, $p=0.14$; B vs non-B, $I^2=70.3\%$, $p=0.003$; O vs non-O, $I^2=59.0\%$, $p=0.02$; AB vs non-AB, $I^2=45.1\%$, $p=0.09$).

Ovarian cancer

There were 7 studies reported data on ovarian cancer involving 9956 cases. All studies reported positive associations on A vs non-A groups except for one study (OR<1.00), which was not statistically significant. The pooled OR showed that blood group A was associated with increased risk of ovarian cancer (OR=1.16; 95%CI: 1.04-1.27), and blood group O was associated with decreased risk (OR=0.76; 95%CI: 0.53-1.00) (Table 1). There was evidence of high heterogeneity across studies (A vs non-A, $I^2=71.9\%$, $p=0.002$; B vs non-B, $I^2=72.0\%$, $p=0.002$; O vs non-O, $I^2=97.2\%$, $p<0.001$; AB vs non-AB, $I^2=50.8\%$, $p=0.06$).

Esophagus cancer

There were six studies about esophagus cancer and blood groups, all the studies indicated that type B blood was a risk factor of esophagus cancer but only one study

Table 2. Stratified Analysis of Odds Ratio (OR) of Cancer According to ABO Blood Groups

Subgroups (number of studies)	A vs non-A		B vs non-B		O vs non-O		AB vs non-AB	
	OR (95% CI)	Weight,%	OR (95%CI)	Weight,%	OR (95%CI)	Weight,%	OR (95%CI)	Weight,%
Publication year								
Before 2000 (69)	1.10 (1.06, 1.13)	58.23	1.02 (0.97, 1.07)	51.89	0.87 (0.85, 0.90)	54.98	0.98 (0.91, 1.04)	47.1
After 2000 (54)	1.17 (1.11, 1.25)	41.77	1.00 (0.94, 1.05)	48.11	0.78 (0.71, 0.86)	45.02	0.99 (0.92, 1.05)	52.9
Case number								
<1000 (93)	1.13 (1.08, 1.19)	66.74	1.01 (0.95, 1.06)	65.29	0.83 (0.78, 0.89)	71.74	0.95 (0.89, 1.02)	58.2
≥1000 (30)	1.13 (1.09, 1.17)	33.26	1.02 (0.97, 1.08)	34.71	0.87 (0.84, 0.90)	28.26	1.02 (0.96, 1.08)	41.8
Number of studies on each cancer site								
≥3 (96)	1.13 (1.09, 1.17)	78.95	0.99 (0.95, 1.03)	79.6	0.84 (0.80, 0.88)	78.36	0.99 (0.94, 1.05)	78.39
<3 (27)	1.10 (1.01, 1.20)	21.05	1.08 (0.98, 1.17)	20.4	0.84 (0.75, 0.92)	21.64	0.93 (0.84, 1.01)	21.61
Study quality								
High (30)	1.26 (1.17, 1.35)	22.68	0.98 (0.91, 1.05)	28.15	0.73 (0.62, 0.83)	26.45	1.01 (0.91, 1.10)	32.24
Low (93)	1.09 (1.05, 1.13)	77.32	1.02 (0.97, 1.06)	71.85	0.87 (0.85, 0.89)	73.55	0.97 (0.92, 1.02)	67.76
Race								
White (87)	1.13 (1.09, 1.17)	75.12	1.02 (0.97, 1.07)	72.04	0.82 (0.77, 0.87)	76.55	0.98 (0.92, 1.04)	70.38
Yellow (27)	1.10 (1.02, 1.18)	24.88	1.00 (0.94, 1.06)	27.96	0.87 (0.82, 0.91)	23.45	1.00 (0.93, 1.06)	29.62
Study type								
Case-control study (116)	1.13 (1.09, 1.17)	93.09	1.01 (0.97, 1.05)	93.85	0.84 (0.80, 0.88)	93.83	0.97 (0.92, 1.02)	92.4
Cohort study (7)	1.03 (0.95, 1.11)	6.91	1.05 (0.93, 1.17)	6.15	0.89 (0.80, 0.97)	6.17	1.06 (0.96, 1.16)	7.6

was statistically significant. The pooled analysis found that the risk of esophagus cancer for blood group B was significantly higher than non-B groups (OR=1.18; 95%CI: 1.04-1.32), the risk for blood group O was significantly lower than non-O groups (OR=0.94; 95%CI: 0.89-1.00) (Table 1). Low heterogeneity was found across studies (A vs non-A, $I^2=49.9%$, $p=0.08$; B vs non-B, $I^2=24.9%$, $p=0.25$; O vs non-O, $I^2=0.0%$, $p=0.51$; AB vs non-AB, $I^2=13.1%$, $p=0.33$).

Lung cancer

Four studies with 1561 cancer cases investigated the relationship between lung cancer and blood groups. All the studies showed a protective effect of lung cancer for B vs non-B groups, but not statistically significant. The pooled OR from random-effects model was 0.81 (95%CI: 0.66-0.95) for B vs non-B groups (Table 1). Statistically significant heterogeneity was observed among studies (A vs non-A, $I^2=88.6%$, $p<0.001$; B vs non-B, $I^2=0.0%$, $p=0.88$; O vs non-O, $I^2=98.0%$, $p<0.001$; AB vs non-AB, $I^2=0.0%$, $p=0.99$).

Nasopharyngeal cancer

Three studies provided data on nasopharyngeal cancer, including 1872 cases, all performed in Asia. The results showed that the risk of nasopharyngeal cancer for blood group A was significantly higher than non-A groups (OR=1.17; 95%CI: 1.00-1.33), and for blood group O, the risk was significantly lower than non-O groups (OR=0.81; 95%CI: 0.70-0.91) (Table 1). There was no evidence of heterogeneity across studies (A vs non-A, $I^2=0.0%$, $p=0.62$; B vs non-B, $I^2=0.0%$, $p=0.91$; O vs non-O, $I^2=0.0%$, $p=0.88$; AB vs non-AB, $I^2=0.0%$, $p=0.81$).

Subgroup and sensitivity analyses

To further explore the origin of heterogeneity among studies of blood groups and cancer, we conducted subgroups and sensitivity analysis. We stratified the analysis to subgroups by publication year (before or

after 2000), case number ($n<1000$ or $n\geq 1000$), number of studies on each cancer site ($n<3$ or $n\geq 3$), study quality (high or low), race (white or Asian) and study type (case-control study or cohort study). The subgroup analysis based on all these variables was not observed to markedly influence the results (Table 2).

Analysis of publication bias

For overall cancer, Publication bias was found for AB vs non- AB as indicated by funnel plots (Figure 2), the Begg's test was significant ($z=2.21$, $p=0.03$). We didn't observe publication bias for A vs non-A, B vs non- B and O vs non-O ($z=0.13$, $p=0.90$; $z=0.05$, $p=0.96$ and $z=1.11$, $p=0.27$, respectively).

Discussion

In this, to the best of our knowledge, the largest systematic meta-analysis on ABO blood groups and cancer, we found blood group A associated with a 12% increased risk of overall cancer, and cancer of the gastric (18%), pancreatic (23%), breast (12%), ovarian (16%), and nasopharyngeal (17%). Blood group O was found to be associated with a 16% decreased risk of overall cancer, and cancer of the gastric (16%), pancreatic (25%), breast (10%), colorectal (11%), ovarian (24%), esophagus (6%), and nasopharyngeal (19%).

Strength of our meta-analysis is the use of exhaustive search strategy to have included studies from 30 countries published over the last 60 years at 30 cancer sites, with 100 554 cases. Our results were generally consistent with the three previous meta-analysis on gastric cancer, breast cancer, and pancreatic cancer. However, our comprehensive search strategy identified more eligible studies than previous ones. For example, we included 36 studies with 31 783 gastric cancer cases in this meta-analysis, while the previous one published in 2012 included 24 studies with 15 843 gastric cancer cases (Wang et al., 2012). Our analysis has more statistical power, as we found significant association between blood group A and increased risk of breast cancer, and blood group O with decreased risk of breast cancer, rather than the borderline association reported in the previous meta-analysis (Miao et al., 2013). Moreover, we set criteria of no less than 100 cancer cases in each study to avoid inclusion of missing data in any group in our analysis, and this will enhance the credibility of our results. In contrast, the previous meta-analysis on pancreatic cancer (Risch et al., 2013) even included the study with 12 cancer cases.

Certain limitations of this meta-analysis should be addressed. First, the number of studies on different cancer sites included in this meta-analysis varied largely. The results for overall cancer may be driven by the cancer sites with more studies included. However, in our influence analyses excluding one cancer site each time, significant association remained in every analysis. Moreover, in our subgroup analysis according to the number of studies on each cancer site, we found similar results for the two subgroups. Nonetheless, certain common cancers, i.e., prostate cancer and lymphoma were not included, and for several cancer sites, only one or two studies were

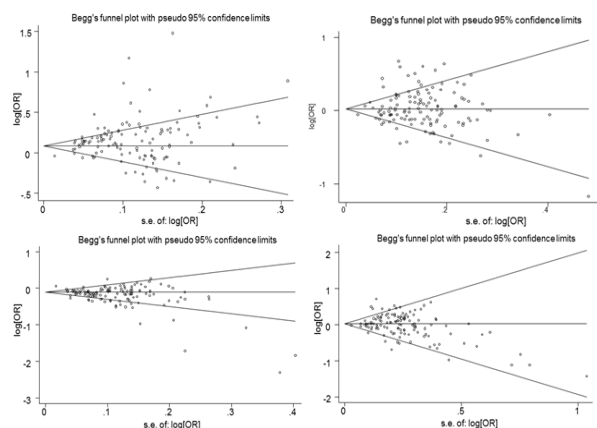


Figure 2. Funnel Plots for Blood group A vs non-A groups and Risk of Cancer (upper left), Blood group B vs non-B groups (upper right), Blood group O vs non-O groups (lower left) and Blood groups AB vs non-AB groups (lower right). The SE of log (OR) is showed on horizontal axis and the log of OR is showed on vertical axis. The funnel plots are drawn with 95% confidence limits. OR: odds ratio; SE: standard error

included, their associations with ABO blood groups can only be confirmed in future studies. Second, significant heterogeneity was found across studies, which may be caused by sample sizes, participants' characteristics, study design, and confounding factors. Although heterogeneities still remained in subgroup analysis, the pooled ORs showed consistent associations in most subgroups. Confounding factors were not included in our meta-analysis as the case in most of the studies included. Several studies performed multivariate analysis, while the results changed little compared with univariate analysis (Xie et al., 2010; Joh et al., 2012).

Direct mechanisms of the impact of ABO blood group system on cancer development are elusive. However, several lines of biological evidence might explain the associations observed. The ABO gene encodes a glycosyltransferase with three main variant alleles (A, B and O) with different substrate specificities (Reid et al., 2004). The A, B and O glycosyltransferases transfer N-acetylgalactosamine, D-galactose or no sugar residue, respectively, to a protein backbone known as the H antigen (Yazer et al., 2005). Blood group antigens are expressed on the surface of red blood cells and numerous other tissues throughout the body. For a variety of tumor types, the blood group antigens expressed on the surface of malignant cells was found to be different from the antigens expressed on normal cells (Hakomori et al., 1999). Modified expression of blood group antigens on the surface of cancer cells may alter cell motility, sensitivity to apoptosis and immune escape, and thus influence the initiation and spread of cancer (Le Pendu et al., 2001). In addition, recent studies have reported associations between ABO blood groups and circulating levels of tumor necrosis factor- α and soluble ICAM-1, E-selectin and P-selectin (Melzer et al., 2008; Paterson et al., 2009; Barbalic et al., 2010; Qi et al., 2010), suggesting that blood group antigens may influence the systemic inflammatory response. Chronic inflammation has been extensively linked with cancer development (Grivennikov et al., 2010), and provides a further potential mechanism by which ABO antigens may influence cancer risk. Finally, some researchers have shown that structure of certain tumor antigens is similar to the structure of antigens of ABO system. For example, Forssmann antigen is synthesized predominantly in stomach and colon tumors, and structurally it is almost identical to the A antigen determinant. Therefore, carriers of blood group A may have diminished tumor immune response due to reduced ability to recognize and attack tumor cells that express Forssmann antigen. Although these mechanisms are biologically plausible to explain the association between ABO blood groups and risk of cancer, the underlying mechanism for the discrepancy among different cancer sites still remains a challenge.

In conclusion, our meta-analysis provides strong evidence for the association between ABO blood groups and risk of cancer. The public health importance of this study is considerable. Our findings will facilitate the identification of high-risk population of cancer, which will potentially benefit from cancer screening programs. Further studies are warranted to explore the underlying mechanism for this association.

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