Published OnlineFirst March 17, 2011; DOI: 10.1158/1055-9965.EPI-10-1250

Research Article

Cancer Epidemiology, Biomarkers & Prevention

ABO Blood Group and Risk of Colorectal Cancer

Hamed Khalili[1], Brian M. Wolpin[2,4], Edward S. Huang[1], Edward L. Giovannucci[3,5], Peter Kraft[5], Charles S. Fuchs[2,3,4], and Andrew T. Chan[1,3]

Abstract

Background: Recent studies have shown an association between non-O blood group and risk of pancreatic cancer. It is unclear whether this association is observed with other gastrointestinal malignancies, including colorectal cancers.

Methods: We examined the relationship between ABO blood group and the risk of incident colorectal cancer in two large prospective cohorts. We calculated HR using Cox proportional hazard modeling while adjusting for known risk factors of colorectal cancer.

Results: During 996,779 person-years of follow-up, we documented 1,025 incident cases of colorectal cancers. Compared to individuals with blood group O, the multivariate-adjusted HR were 1.08 (95% CI, 0.94–1.24) for blood group A, 1.20 (95% CI, 1.00–1.45) for blood group B, and 1.08 (95% CI, 0.85–1.36) for blood group AB.

Conclusion: In two large prospective cohorts, we did not observe a statistically significant association between ABO blood group and risk of colorectal cancer.

Impact: These results do not support an association between ABO blood group and risk of colorectal cancer.

Cancer Epidemiol Biomarkers Prev; 20(5); 1017–20. ©2011 AACR.

Introduction

Studies have suggested a link between inherited human blood group antigens and the risk of various cancers (1, 2). Recently, we have shown an association between non-O blood group serotype and risk of pancreatic cancer that has been confirmed in other studies (3–7). Whether this association is also observed with other gastrointestinal malignancies, including colorectal cancer, is unclear. We therefore sought to examine the relationship between ABO blood group and colorectal cancer risk in two large prospective cohort studies.

Materials and Methods

Our methods have been previously described in detail (3). Briefly, we examined male and female health professionals enrolled in the Nurses' Health Study (NHS) and Health Professional Follow Up Study (HPFS) who returned the 1996 biennial questionnaire in which they were specifically queried about their blood group (A, B, AB, O, or unknown). In a subsample of 98 participants, this self-reported blood group was 91% concordant with the results of serological testing in the medical record (3). Among 187 participants, self-reported blood group was 92% concordant with the results of genotype-derived blood typing (4). As previously reported, the distributions of ABO blood groups in these cohorts are similar to those for other US white populations.[3] We excluded participants with ulcerative colitis or history of cancer (except nonmelanoma skin). In both cohorts, when a participant (or next-of-kin for decedents) reported a diagnosis of colorectal cancer we obtained their hospital records and pathology reports. We identified deaths through the National Death Index and next-of-kin. A study physician reviewed records to confirm cancer diagnoses.

Follow-up time was calculated from the date of return of the 1996 questionnaire to the date of colorectal cancer diagnosis, death, or June 30, 2006, whichever came first. We used Cox proportional hazards models to calculate adjusted HR and 95% CIs. We evaluated effect modification by diabetes mellitus, based on prior report suggesting potential interactions between diabetes and blood group type using cross-classified categories (8); significance of the interaction was assessed using the log–likelihood ratio test. Based on the number of cases of colorectal cancer and prevalence of each blood group, our study had greater than 80% power at a significance level of 0.05 to detect a HR of 1.2 when comparing non-O blood groups with blood group O.

Authors' Affiliations: [1]Division of Gastroenterology, Massachusetts General Hospital; [2]Department of Medicine; and [3]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School; [4]Department of Adult Oncology, Dana-Farber Cancer Institute; and [5]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

Corresponding Author: Andrew T. Chan, Gastrointestinal Unit, Massachusetts General Hospital, 55 Fruit Street, GRJ-728A, Boston, MA 02114. Phone: 617-724-0283; Fax: 617-726-3673; E-mail: achan@partners.org

doi: 10.1158/1055-9965.EPI-10-1250

Published OnlineFirst March 17, 2011; DOI: 10.1158/1055-9965.EPI-10-1250

Table 1. Baseline characteristics of study participants according to ABO blood group type[a]

Characteristic	Blood group type			
	O	A	AB	B
No. of participants (%)				
NHS	32,820 (42.9)	27,184 (35.6)	6,075 (8.0)	10,329 (13.5)
HPFS	12,253 (43.0)	10,551 (37.1)	2,164 (7.6)	3,509 (12.3)
Total	45,073 (43.0)	37,735 (36.0)	8,239 (7.8)	13,838 (13.2)
Age-median (years)	61.9	61.6	63.4	61.6
Female (%)	72.8	72.1	73.7	74.6
White (%)	96.9	97.8	95.8	95.7
BMI (kg/m^2), %				
<21	11.7	11.8	12.7	11.0
21–22.9	13.3	13.2	14.0	13.3
23–24.9	18.8	19.2	19.0	19.2
25–29.9	36.3	36.5	35.5	36.9
>30	19.9	19.3	18.8	19.6
Smoking, %				
Never	43.5	44.6	43.0	43.5
Past	46.0	45.1	45.6	45.8
Current	8.3	8.0	9.1	8.6
Unknown	2.1	2.2	2.2	2.1
Family Hx, %[b]	14.2	14.1	14.2	14.5
History of Polyps, %	15.3	14.4	14.6	13.9
Regular aspirin use, %[c]	46.8	48.3	48.4	48.0

[a]NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; BMI, body mass index.
[b]History of colorectal cancer in a participant's mother, father, or sibling.
[c]Regular aspirin use defined as two ore more standard aspirin tablets per week in NHS and two or more times per week in HPFS.

Results

Among 104,885 participants (76,408 females and 28,477 males), we documented 1,025 colorectal cancer cases after a mean follow up of 9.8 years. Baseline characteristics of the participants were similar with regards to regular aspirin use, family history of colorectal cancer, and history of polyps (Table 1). The risk of developing colorectal cancer did not significantly differ by ABO blood group (Table 2). Compared with blood group O, we did observe a modest association of blood group B with colon cancer, but not rectal cancer that was statistically significant only in the multivariate analysis. However, there did not appear to be statistically significant risk associated with blood group AB.

Among subgroups defined by the presence or absence of diabetes mellitus, there was no statistically significant association between any blood group and colorectal cancer ($P_{\text{interaction}} = 0.91$).

Discussion

Several lines of evidence had suggested a potential association between ABO blood group and risk of colorectal cancer (1, 2). Human blood group antigens are expressed on the surface of red blood cells and other tissues, including cells of the gastrointestinal tract. These glycoconjugates may participate in modifying intercellular adhesion, membrane signaling, and immune surveillance, which could in turn influence tumorigenesis (9). In addition, recent genome-wide association studies (GWAS) have linked single nucleotide polymorphisms (SNPs) at the ABO blood locus with serum levels of circulating TNF-α and diabetes mellitus (8, 10). TNF-α

Published OnlineFirst March 17, 2011; DOI: 10.1158/1055-9965.EPI-10-1250

Table 2. Risk of colorectal cancer, colon cancer, and rectal cancer according to ABO blood group type[a]

	Blood group type				
	O	A	AB	B	Non-O[b]
Colorectal cancer[c]					
No. of cases/No. of person-years	418/428666	369/358785	86/77737	152/131590	607/568113
Age-adjusted HR (95% CI)	1.00	1.07 (0.93–1.24)	1.06 (0.84–1.34)	1.19 (0.98–1.43)	1.10 (0.97–1.24)
Multivariable-adjusted HR (95% CI)[d]	1.00	1.08 (0.94–1.24)	1.08 (0.85–1.36)	1.20 (1.00–1.45)	1.11 (0.97–1.25)
Colon cancer					
No. of cases/No. of person-years	299/428666	278/358785	64/77737	113/131590	455/568113
Age-adjusted HR (95% CI)	1.00	1.13 (0.96–1.33)	1.10 (0.84–1.44)	1.24 (1.00–1.54)	1.15 (0.99–1.33)
Multivariable-adjusted HR (95% CI)[d]	1.00	1.14 (0.96–1.34)	1.11 (0.84–1.45)	1.26 (1.01–1.56)	1.16 (1.00–1.34)
Rectal cancer					
No. of cases/No. of person-years	98/428666	70/358785	19/77737	33/131590	122/568113
Age-adjusted HR (95% CI)	1.00	0.89 (0.65–1.21)	1.02 (0.62–1.67)	1.09 (0.73–1.62)	0.96 (0.73–1.25)
Multivariable-adjusted HR (95% CI)[d]	1.00	0.88 (0.65–1.20)	1.05 (0.64–1.73)	1.07 (0.72–1.59)	0.95 (0.73–1.24)

[a] Represent total number of cases form NHS I (Nurses Health Study) and HPFS (Health Professional Follow up Study).

[b] Non-O category included individuals with blood groups A, B, and AB. HR are compared to blood group O.

[c] In 51 cases, exact anatomic location could not be confirmed.

[d] Adjusted for age (years), body mass index (kg/m^2), history of diabetes (yes, no), level of physical activity (METs/wk), smoking status (current, past, never, or unknown), history of polyps (yes, no, unknown), history of screening (yes, no, unknown), folate intake (quantiles), regular aspirin use (yes $\geq$ 2/wk, no < 2/wk, unknown), red meat intake (< 2/wk, 2–4/wk, 5–6/wk, $\geq$ 1/day) and family history (sibling, mother, or father) of colon cancer (yes, no, unknown), race (white, non-white), and gender.

is an inflammatory marker that has been associated with colorectal neoplasia (11). Diabetes and colorectal cancer share risk factors and potentially have common pathogenic mechanisms (e.g., insulin-related pathways; ref. 12).

Despite this rationale, in two large prospective cohorts, we did not find a consistent association between blood group serotypes and overall risk of colorectal cancer. We did observe a borderline significant association between blood group B and overall risk of colon cancer. However, there is no clear biological mechanism that would explain the differential association of group B compared with group A antigen with cancer. Taken together with the lack of similar associations observed with blood group AB and overall risk of colon cancer, these findings for blood group B are likely due to chance. Finally, we did not observe a differential effect between blood group and risk of colorectal cancer according to presence or absence of diabetes.

These findings contrast with our previous analysis of ABO blood group and risk of pancreatic cancer using these same population cohorts in which, compared with blood group O, the multivariate adjusted HRs were 1.32 (95% CI, 1.02–1.72) for blood group A, 1.51 (95% CI, 1.02–2.23) for blood group AB, and 1.72 (95% CI, 1.25–2.38) for blood group B (3). These results have been subsequently supported by findings from other pancreatic cancer cohorts (5, 6). The lack of similar associations of blood group type with colorectal cancer suggest that ABO blood group-related mechanisms of tumorigenesis may uniquely influence specific types of cancers including pancreatic cancer (7). Nonetheless, further research into a potential, more modest effect of ABO blood group type on colorectal cancer, is needed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

Funded by R01 CA137178, P01 CA55075, P01 CA87969. Dr. Chan is a Damon Runyon Cancer Research Foundation Clinical Investigator. Dr. Khalili is supported by a career development award from the IBD Working Group.

Received December 1, 2010; revised February 24, 2011; accepted March 1, 2011; published OnlineFirst March 17, 2011.

References

1. Halvorsen TB. ABO blood groups, rhesus types, and colorectal adenocarcinoma. A retrospective study of 747 cases. Scand J Gastroenterol 1986;21:979–83.

2. Slater G, Itzkowitz S, Azar S, Aufses AH Jr. Clinicopathologic correlations of ABO and Rhesus blood type in colorectal cancer. Dis Colon Rectum 1993;36:5–7.

Published OnlineFirst March 17, 2011; DOI: 10.1158/1055-9965.EPI-10-1250

3. Wolpin BM, Chan AT, Hartge P, Chanock SJ, Kraft P, Hunter DJ, et al. ABO blood group and the risk of pancreatic cancer. J Natl Cancer Inst 2009;101:424–31.
4. Wolpin BM, Kraft P, Gross M, Helzlsouer K, Bueno-de-Mesquita HB, Steplowski E, et al. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium. Cancer Res 2010;70:1015–23.
5. Ben Q, Wang K, Yuan Y, Li Z. Pancreatic cancer incidence and outcome in relation to ABO blood groups among Han Chinese patients: a case-control study. Int J Cancer 2011;128:1179–86.
6. Risch HA, Yu H, Lu L, Kidd MS. ABO blood group, *Helicobacter pylori* seropositivity, and risk of pancreatic cancer: a case-control study. J Natl Cancer Inst 2010;102:502–5.
7. Iodice S, Maisonneuve P, Botteri E, Sandri MT, Lowenfels AB. ABO blood group and cancer. Eur J Cancer 2010;46:3345–50.
8. Qi L, Cornelis MC, Kraft P, Jensen M, van Dam RM, Sun Q, et al. Genetic variants in ABO blood group region, plasma soluble E-selectin levels and risk of type 2 diabetes. Hum Mol Genet 2010;19:1856–62.
9. Hakomori S. Antigen structure and genetic basis of histo-blood groups A, B and O: their changes associated with human cancer. Biochim Biophys Acta 1999;1473:247–66.
10. Melzer D, Perry JR, Hernandez D, Corsi AM, Stevens K, Rafferty I, et al. A genome-wide association study identifies protein quantitative trait loci (pQTLs). PLoS Genet 2008;4:e1000072.
11. Kim S, Keku TO, Martin C, Galanko J, Woosley JT, Schroeder JC, et al. Circulating levels of inflammatory cytokines and risk of colorectal adenomas. Cancer Res 2008;68:323–8.
12. Giovannucci E. Insulin and colon cancer. Cancer Causes Control 1995;6:164–79.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

ABO Blood Group and Risk of Colorectal Cancer

Hamed Khalili, Brian M. Wolpin, Edward S. Huang, et al.

Cancer Epidemiol Biomarkers Prev 2011;20:1017-1020. Published OnlineFirst March 17, 2011.