RISK OF GASTRIC CANCER AND PEPTIC ULCERS IN RELATION TO ABO BLOOD TYPE: A COHORT STUDY

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ABSTRACT
Blood group A was found to be associated with gastric cancer in the 1950s. Strikingly, for peptic ulcers an increased risk has been shown for blood group O. However, previous investigations have generally been poorly conducted and have failed to take a unifying approach to these observations. Using the Scandinavian donations and transfusions (SCANDAT) database, we established a cohort of Swedish and Danish blood donors with known blood type and followed these for the occurrence of gastric cancer and peptic ulcers. Cases were ascertained using nationwide cancer and hospital registers. Altogether, 1,089,022 donors were followed for up to 35 years, during which 688 gastric cancer cases and 5667 peptic ulcer cases accrued. Poisson regression analyses confirmed an increased risk of gastric cancer among individuals with blood group A (incidence rate ratio, 1.20; 95% confidence interval: 1.02, 1.42) and conversely that peptic ulcer risk was instead highest among those with blood group O. In this large, population-based cohort study we have confirmed the association between blood group A and gastric cancer. In addition, we give further support to the notion that individuals with blood group O have a higher risk of peptic ulcers than those with other blood groups.
INTRODUCTION

In 1953 Aird et al reported a relationship between blood group A and cancer of the stomach (1). Subsequently, this association has been demonstrated in several studies (2-8). However, an elevated risk among those with blood group B has also been reported (9). Despite somewhat contradictory results and an unexplained biological mechanism, blood group A is widely considered an established risk factor for gastric cancer (10). Recently, similar observations have also been made demonstrating a lower risk of pancreas cancer among individuals with blood group O (11, 12).

Intriguingly, numerous studies have demonstrated an association in the opposite direction for the risk of peptic ulcers, where those with blood group O have the highest risk of both gastric and duodenal ulcers (2, 13-16).

Under the premise that detailed knowledge about risk factors, especially genetic ones, may help in the understanding of disease etiology, we wanted to investigate and better quantify the relationship between ABO blood group and risk of gastric cancer as well as between ABO blood type and risk of hospitalization for gastric and duodenal ulcers. Thus, we conducted a cohort study among Swedish and Danish blood donors included in the Scandinavian Donations and Transfusions (SCANDAT) database (17).
METHODS
All available computerized donation and transfusion registers from Swedish and Danish blood banks and transfusion medicine clinics were collected and entered it into a common database. These records, dating back as far as 1968 and 1981, in Sweden and Denmark, respectively, include detailed donation data on 1,134,290 blood donors. Using unique national registration numbers that are assigned to all residents of both countries, record linkages with nationwide death, population, cancer and inpatient care registers provided demographic data, dates of diagnoses and anatomical sites of all recorded malignancies as well as records of discharge diagnoses, performed surgical procedures and dates of entry and discharge for all hospital care. The assembly of the SCANDAT database has been described in greater detail previously (17).

From this database, we extracted, for all blood donors with a valid identification number, their sex, ABO blood type as well as dates of birth, emigration, death and first electronically recorded blood donation. We did not consider autologous donations. Where available, we also extracted the date of diagnosis of the first primary gastric cancer (coded as 151 according to the 7th revision of the international classification of diseases [ICD]). In addition, we extracted the date of the first recorded hospital admission for gastric (ICD-8/9 code 530 or ICD-10 code K25) or duodenal ulcers (ICD-8/9 code 531 or ICD-10 code K26) from the respective inpatient registers. Both main and contributory discharge diagnoses were included. For the Danish study participants we also acquired data on country of birth, where applicable.

All individuals for whom we could not determine a blood group or who had a history of malignant disease prior to blood donation were excluded from the analyses. For
the cancer analyses, we followed donors in the cohort from the first recorded blood
donation to date of death, emigration, first cancer diagnosis or end of follow-up (31st of
December 2002), whichever came first. Individuals for whom the first recorded cancer
diagnosis came before the start of follow-up were therefore not included in the cancer
analyses. We did not exclude patients with a history of a peptic ulcer diagnosis from the
cancer analyses.

Follow-up was defined somewhat differently for the analysis of peptic ulcers.
Since the Swedish register of inpatient care was not in nationwide operation until 1987,
we began follow-up of Swedish subjects on January 1st 1987 unless the first recorded
blood donation was after this date. Subjects were followed until the date of death,
emigration, first hospitalization for either gastric or duodenal ulcers or 31st of December,
2002, whichever came first. As with the cancer analysis, individuals with a
hospitalization for gastric or duodenal ulcers prior to entry into the cohort were excluded
from the analyses. In a sensitivity analysis, the analyses of ulcer incidence were restricted
to patients who presented with either a hemorrhaging or perforated ulcer. Finally, we
repeated the analyses of gastric cancer risk in relation to ABO blood type among patients
with a gastric ulcer diagnosis. In these analyses, follow-up was started at first
hospitalization for gastric ulcer disease and was extended until first cancer diagnosis. Due
to small numbers, only unadjusted analyses were performed.

The ratios of cancer or ulcer incidence among blood donors with blood group A, B
or AB, respectively, relative to the incidence among blood donors with blood group O,
i.e. the incidence rate ratios, were estimated using a multivariate log-linear Poisson
regression model. These risk estimates were adjusted for sex, country (i.e. Sweden or
Denmark), attained age (in 5-year intervals) and calendar period (in 5-year intervals). 95% confidence intervals were calculated using likelihood ratio tests. All considered factors were analyzed as categorical variables; attained age and calendar period were treated as time-dependent allowing individuals to move between categories with time. As an indirect test of whether recent changes in the ethnic composition of the Swedish and Danish populations, which up until the late 1980’s were ethnically rather homogenous, predominantly Caucasian (18, 19), we also tested for interactions between blood group and calendar time. This was done both with calendar time as a linear variable and split in two strata, before or after 1990. For the Danish portion of the data, where we had access to information on country of birth, we also performed analyses restricted to the Danish sub-cohort to assess whether the effect estimates changed noticeably when donors of non-Caucasian origin were excluded.

All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC). All P-values were two sided. P-values less than 0.05 were considered statistically significant. The creation of SCANDAT and the conduct of this study were approved by all regional ethics committees in Sweden, the Danish Scientific Ethics Committee and the Danish Data Protection Agency.
RESULTS
From the database we identified a total of 1,110,329 individuals with a valid identification number who had performed at least one whole-blood, plasma or platelet donation. From this previously established donor cohort (20), we established two sub-cohorts, one cancer and one ulcer cohort. After exclusion of 2847 donors with a record of a previous diagnosis of malignant cancer and 18,460 donors with unknown ABO blood type, a total of 1,089,022 blood donors remained for analysis in the cancer cohort.
Similarly, in the gastric and duodenal ulcer analyses, we excluded 11,606 donors who died or emigrated before the start of follow-up, which for the ulcer analyses was delayed until 1987, and 3832 donors with a prior hospitalization for gastric or duodenal ulcer disease, whereby a total of 1,073,584 donors remained for analysis in the ulcer cohort.

The mean age at entry into the cancer cohort was 33.4 years (37.2 and 31.9 years in Denmark and Sweden respectively). The age at entry was only marginally higher in the ulcer cohort, 35.4 years. In both cohorts, a majority of the study participants were male (56% in both the cancer and ulcer cohorts). The median length of follow-up was 10.0 and 9.9 years in the cancer and ulcer cohorts, respectively. In the Danish sub-cohort, where we had access to information on country of birth, no fewer than 97.7% of donors were born in Denmark and 98.6% were of Caucasian origin (i.e. were born in Western Europe and had Western European parents). The proportion of donors of non-Caucasian origin increased from 0.75% among donors who had their first donation recorded in 1981 to 3.1% among donors who donated first in 2002. Major characteristics of the two cohorts are presented in Table 1.
In the cancer analyses, we observed 688 cases of gastric cancer during a total of 12,611,021 years of follow-up. Table 2 presents crude and adjusted incidence rate ratios [IRR] for gastric cancer according to ABO blood type. All variables considered in the multivariate model were significantly associated with gastric cancer risk. The adjusted IRR of gastric cancer among blood donors with blood group A compared to those with blood group O was 1.20 (95% confidence interval [CI]: 1.02, 1.42). There was also an elevated risk, albeit not statistically significant, among those with blood group AB (IRR, 1.26; 95% CI: 0.91, 1.71). We observed a lower risk in donors with blood group B, but again this was not statistically significant (IRR, 0.92; 95% CI: 0.69, 1.20). In sub-analyses conducted in the Danish portion of the data only, the effect estimates did not change noticeably when donors of non-Caucasian origin were excluded (data not shown). There was no interaction between blood group and calendar period of first donation, neither when considered as a linear (P=0.83), nor categorical term (P=0.81).

The ulcer cohort was followed for a total of 10,425,134 person years during which 2938 and 2729 donors were hospitalized for gastric or duodenal ulcers, respectively (Table 3). The risk profiles for gastric and duodenal ulcers were similar. For both conditions, blood donors with blood group A, B or AB all had significantly lower risk than those with blood group O. The relative risk estimates for gastric ulcers ranged from 0.77 (95% CI: 0.64, 0.91) for those with blood group AB and 0.83 (95% CI: 0.73, 0.94) for blood group B, to 0.91 (95% CI: 0.85, 0.99) for blood group A. For duodenal ulcers, the estimated relative risks were 0.85 (95% CI: 0.71, 1.00) for blood group AB, 0.75 (95% CI: 0.65, 0.85) for blood group B, and 0.81 (95% CI: 0.74, 0.87) for blood group A. Results from the analyses considering only cases who presented with a
haemorrhaging or perforated ulcer followed essentially the same pattern as the overall analyses (data not shown), but the point estimates were consistently somewhat lower than in the overall analyses. As in the cancer analyses, there was no interaction between blood group and calendar period neither in linear (P=0.09), nor categorical analyses (P=0.13). As for the cancer analyses, exclusion of non-Caucasian donors from sub-analyses conducted in the Danish cohort did not modify the association between blood group and risk of peptic ulcers to any noticeable extent (data not shown).

Only 44 cases of gastric cancer occurred among patients with a prior diagnosis of gastric ulcer. In neither blood group did the cancer risk depart significantly from that of the reference category (data not shown).
DISCUSSION
In this prospective study carried out within a well-defined cohort of Swedish and Danish blood donors, we have confirmed that blood group A is indeed associated with a higher risk of gastric cancer. In addition, we have granted further support to the notion that individuals with blood group O have a higher risk of peptic ulcers than those with other blood groups.

The strengths of this study include the population-based study design and unbiased ascertainment of the study participants’ blood groups. Since the blood group data was collected from computerized blood donation registers with high data quality – ensured by transfusion safety, medico-legal and administrative requirements – any exposure misclassification should be minimal. Furthermore, the use of nationwide and essentially complete cancer and inpatient registers ensures that misclassification of the cancer outcome is minimal. Nonetheless, some caution is warranted when using data on gastric and duodenal ulcers from hospital registers, since both under-reporting and misclassification is likely to have been present. However, any such misclassification should be non-differential with regards to the blood group and should consequentially only bias our risk estimates towards a null result.

Meanwhile, even though blood donors can be expected to have knowledge about their ABO blood type and despite obscure diet systems such as the blood group diet (21), where followers are recommended to follow a particular diet system based on their ABO blood type, it is unlikely that this knowledge will have any direct impact on behavior. As such, there should be only minor differences in the prevalence of other important risk factors for gastric cancer and peptic ulcers such as smoking, alcohol consumption and use
of non-steroidal anti-inflammatory drugs between the different blood groups, and consequently, such possible confounders should not have an important effect on our results. Meanwhile, it is still quite possible that the effects of ABO blood type are on gastric cancer and peptic ulcer risks are modified by traditional risk factors for these diseases.

A number of further caveats need to be considered when interpreting these results. Firstly, the external validity of this study should be viewed in the light of the fact that blood donors represent a very select population with low risk of cancer (20, 22), who thus could be expected to have a low prevalence of other confirmed risk factors for both gastric cancer and peptic ulcers. Thus, if the excess risk conferred by the ABO blood type somehow interacts with life-style risk factors, the magnitude of our risk estimates may not be entirely applicable to other populations. Although blood donors can be expected to be aware of their blood type, it is unlikely that this knowledge – nor the blood group itself – will have any influence on behavior. Thus the prevalence of other important risk factors for gastric cancer and peptic ulcers such as smoking, alcohol consumption and use of non-steroidal anti-inflammatory drugs should be similar in the different blood groups, and consequently should not have an important confounding effect on our results. Notably, despite a presumed healthy lifestyle (20), it has been shown previously that the Helicobacter pylori seroprevalence in a sample of Swedish blood donors in age groups below 50 years was equal to, or even higher than that of the background population (23).

It is possible that having a rare blood group may have a positive influence on the decision to become and remain a blood donor, these donors may not appear as healthy as those with common blood groups. However, we observed an increased risk of cancer in
both a common and rare blood group (A and AB, respectively) and a low risk of ulcers in all non-O groups relative to group O, suggesting that differences in health behavior of those with common and rare blood groups is not likely to have influenced our results to any great extent. Since the distribution of blood groups in this sample closely resembles that of the background population, this is not likely to have influenced our results to any great extent. Also, the possibility of confounding by ethnicity cannot be ruled out, given the different distributions of the ABO blood type in different ethnic groups and the association between ethnicity and risk of both gastric cancer and peptic ulcers (24, 25). However, both Sweden and Denmark have been ethnically quite homogenous until recently, and we found no evidence of the effect of ABO blood type being modified by calendar period in either of our analyses. Also, with a mere 1.3% of the Danish donors being born outside of Denmark, the opportunity for an important confounding effect of ethnicity seems quite unlikely. Finally, since most patients with peptic ulcer disease never require hospitalization for their condition, or are treated exclusively on an outpatient basis, the patients analyzed in this study should represent only a small and more severely ill subset of all patients with peptic disease. Thus, if the severity of symptoms or possibly the inclination to seek medical treatment somehow differs between blood groups, the association between ABO blood type and peptic ulcer disease may have been exaggerated or concealed, depending on the direction of this association. However, since ABO blood type remained associated with hospitalization for peptic ulcers even when the outcome was restricted to the most severe cases, this does not seem to be the case.

The association between ABO blood group and gastric cancer as well as with peptic ulcers has been consistently demonstrated previously (1-8, 13-16), but we provide
here precise estimates of the extent of these associations. In addition to confirming that individuals with blood group A are at a slightly increased risk of stomach cancer, we have, quite strikingly, also shown that individuals with blood group O have a clearly elevated risk of hospitalization for gastric and duodenal ulcers compared to the other blood groups. Although no definitive conclusions can be drawn from this strictly observational investigation, with no access to data about H pylori infection, a possible explanation is that these observations may result from different susceptibility and immunological response to such infection (8, 15, 26-35).
ACKNOWLEDGEMENTS
We are greatly indebted to the personnel at all blood banks and transfusion medicine clinics in Sweden and Denmark who contributed data to the SCANDAT database.
REFERENCES


### Tables

**Table 1. Characteristics of the Study Population**

<table>
<thead>
<tr>
<th></th>
<th>Cancer cohort</th>
<th>Ulcer cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>1,089,022</td>
<td>1,073,584</td>
</tr>
<tr>
<td><strong>Sex, N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>480,164 (44.1)</td>
<td>476,757 (44.4)</td>
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<tr>
<td>Male</td>
<td>608,858 (55.9)</td>
<td>596,827 (55.6)</td>
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<tr>
<td><strong>Nationality, N (%)</strong></td>
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</tr>
<tr>
<td>Danish</td>
<td>321,291 (29.5)</td>
<td>319,601 (29.8)</td>
</tr>
<tr>
<td>Swedish</td>
<td>767,731 (70.5)</td>
<td>753,983 (70.2)</td>
</tr>
<tr>
<td><strong>Age at entry into cohort, N (%)</strong></td>
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<td></td>
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<tr>
<td>&lt; 30 years</td>
<td>503,714 (46.3)</td>
<td>417,770 (38.9)</td>
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<tr>
<td>30-44 years</td>
<td>387,691 (35.6)</td>
<td>423,833 (39.5)</td>
</tr>
<tr>
<td>45-59 years</td>
<td>184,914 (17.0)</td>
<td>203,843 (19.0)</td>
</tr>
<tr>
<td>≥60 years</td>
<td>12,703 (1.17)</td>
<td>28,138 (2.62)</td>
</tr>
<tr>
<td><strong>Mean age at entry into cohort, yrs. (SD)</strong></td>
<td>33.4 (11.2)</td>
<td>35.4 (11.6)</td>
</tr>
<tr>
<td><strong>AB0 blood type, N (%)</strong></td>
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<td></td>
</tr>
<tr>
<td>A</td>
<td>478,964 (44.0)</td>
<td>472,247 (44.0)</td>
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<tr>
<td>AB</td>
<td>57,949 (5.32)</td>
<td>56,958 (5.31)</td>
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<tr>
<td>B</td>
<td>122,885 (11.3)</td>
<td>121,146 (11.3)</td>
</tr>
<tr>
<td>O</td>
<td>429,224 (39.4)</td>
<td>423,233 (39.4)</td>
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<tr>
<td><strong>Length of follow-up, N (%)</strong></td>
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<tr>
<td>0-4 years</td>
<td>282,994 (26.0)</td>
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<td>5-9 years</td>
<td>261,712 (24.0)</td>
<td>423,833 (39.5)</td>
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<td>10-19 years</td>
<td>365,823 (33.6)</td>
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<td>≥20 years</td>
<td>178,493 (16.4)</td>
<td>28,138 (2.62)</td>
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<td><strong>Median length of follow-up, yrs. (range)</strong></td>
<td>10.0 (0-35)</td>
<td>9.9 (0-22)</td>
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<tr>
<td><strong>Total length of follow-up, yrs.</strong></td>
<td>12,611,021</td>
<td>10,425,134</td>
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</table>
Table 2. Crude and Adjusted Incidence Rate Ratios of Gastric Cancer among Blood Donors According to ABO Blood Group

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>Person-yrs at risk</th>
<th>No. of cases</th>
<th>Crude Rate Ratio (95% CI)</th>
<th>Adjusted Rate Ratio (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5,575,468</td>
<td>331</td>
<td>1.19 (1.01-1.40)</td>
<td>1.20 (1.02-1.42)</td>
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<td>AB</td>
<td>690,052</td>
<td>45</td>
<td>1.30 (0.94-1.77)</td>
<td>1.26 (0.91-1.71)</td>
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<td>B</td>
<td>1,429,675</td>
<td>66</td>
<td>0.92 (0.70-1.20)</td>
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<td>O</td>
<td>4,915,827</td>
<td>246</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
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</table>

CI denotes confidence interval

<sup>a</sup>The analyses were adjusted for sex, country, attained age and calendar period of observation
Table 3. Crude and Adjusted Incidence Rate Ratios of Gastric and Duodenal Ulcers among Blood Donors According to ABO Blood Group

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>Person-yrs at risk</th>
<th>No. of cases</th>
<th>Crude Rate Ratio (95% CI)</th>
<th>Adjusted Rate Ratio (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
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<tr>
<td><strong>Gastric ulcers</strong></td>
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<td></td>
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<tr>
<td>A</td>
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<td>1,241</td>
<td>0.88 (0.81-0.95)</td>
<td>0.91 (0.85-0.99)</td>
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<td>AB</td>
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<td>135</td>
<td>0.77 (0.64-0.92)</td>
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<td>B</td>
<td>1,184,398</td>
<td>305</td>
<td>0.84 (0.74-0.95)</td>
<td>0.83 (0.73-0.94)</td>
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<tr>
<td>O</td>
<td>4,077,069</td>
<td>1,257</td>
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<td>1.00 (ref)</td>
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<tr>
<td><strong>Duodenal ulcers</strong></td>
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<td></td>
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</tr>
<tr>
<td>A</td>
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<td>AB</td>
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<td>0.84 (0.71-1.00)</td>
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<td>B</td>
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<td>267</td>
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<td>4,077,069</td>
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<td>1.00 (ref)</td>
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</table>

CI denotes confidence interval

<sup>a</sup>The analyses were adjusted for sex, country, attained age and calendar period of observation