Original article

Is ABO blood group a risk or prognostic factor for patients with endometrioid endometrial cancer? A retrospective analysis in Germany

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Background - A relationship is known to exist between gastric and pancreatic cancers and ABO antigens, caused by various immune modulations related to the ABO blood group of the patient. A similar relationship with regard to gynaecological cancers remains controversial.

Materials and methods - Patients who underwent surgery for endometrioid endometrial cancer in International Federation of Gynaecology and Obstetrics (FIGO) stage I, II, III or IV from 2006 to 2018 were identified. The research explored the existence of a relationship between the patients' blood group or Rhesus factor and the incidence of endometrial cancer, grade (G1, G2, G3), FIGO stage, nodal status, recurrence, menopausal status, parity, and body mass index. Statistical methods such as the chi-square test, analysis of variance and the Scheffé post-hoc test were used.

Results - Two hundred and two patients with endometrioid endometrial cancer were included: 96 had blood group A, 19 blood group B, 75 blood group 0, and 12 had blood group AB. This distribution corresponds to the general blood group distribution in Germany. The vast majority of the dependent variables, such as grade, FIGO stage, nodal status or recurrence were not significantly associated with ABO blood group or Rhesus factor status. The relative frequencies of G1 and G3 endometrial cancers with respect to blood group were similar. Menopausal status, parity, and body mass index were not related to more advanced FIGO stages at initial diagnosis or to ABO blood group.

Discussion - Blood group screening would probably not be helpful in the diagnosis of endometrioid endometrial carcinomas in early stages compared to the current gold standard. Furthermore, a specific blood group does not increase either the risk of recurrence or the risk of a dedifferentiated type of endometrial carcinoma.

Keywords: *ABO blood group, endometrial cancer, risk factor, outcome, prognosis.*

INTRODUCTION

The ABO system is recognised as the most important of the 38 different blood type classification systems and is an essential factor in blood transfusion[1]. Landsteiner identified the ABO antigens as surface components of the erythrocyte[2]. Blood antigens ABO consist of an oligosaccharide chain linked to proteins or lipids and are transferred from various carbohydrates, which do not affect their phenotype[3].

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Since the first association between gastric cancer and blood type A was published in 1953[4], many reports concerning other cancer types have been published. These include the pancreas[5,6], gall bladder[7], kidney[8], and breast[9]. Furthermore, a few studies have analysed the correlation between gynaecological cancers and the ABO blood group system. Some hypotheses mention high levels of oestradiol in association with the presence of A-B transferase proteins in human endometrial cells[10,11]. However, the data published so far have been inconsistent. Some studies indicate a positive correlation between ABO blood group and the risk of endometrial cancer[12] or other types of cancer[13,14].

Endometrial carcinoma is the most common cancer of the female reproductive tract in developed countries, estimated to account for about 4.8% of all cancers in women[15]. The main factor in the pathogenesis of this type of tumour, which has a fairly good prognosis, is prolonged hyperoestrogenism[16], which may be caused by early menarche, late menopause, nulliparity, obesity, or hormone therapy[17].

ABO blood group types were found to influence pathogenic mechanisms of the body and affect the progress of disease in general. The absence of blood group antigens (O) protects the body from infection with *Plasmodium falciparum* malaria[18]. Furthermore, people with blood group A are more sensitive to infection by *Pseudomonas aeruginosa* than are those with other blood groups[19]. Individuals with blood group A, B, or AB antigens are known to be more resistant to cholera compared to those with blood group O[20].

Apart from infectious diseases, correlations have been observed between blood group and other diseases such as venous thromboembolism. In 2007, a higher prevalence of venous thromboembolism was reported in people with blood group A or B antigens than in those with blood group O[21]. This might be due to higher levels of coagulation factor VIII and von Willebrand factor in the presence of blood group A or B antigens compared to the levels in people with blood group O. However, cases of gastric infection by *Helicobacter pylori* –and consequently gastritis, gastric ulcer, and gastric adenocarcinoma– are less frequent in subjects with blood groups A and B than in those with blood group O[22].

Currently, there is a limited body of published data concerning the molecular mechanisms underlying the association between ABO antigens and malignant disease. The aim of our study was to determine whether the risk of developing endometrial cancer is higher in people with a specific blood group of the ABO system. This information is expected to enhance our understanding of carcinogenesis, prevention, and early diagnosis, which are the key aspects of the successful treatment of endometrial carcinomas. Furthermore, we examined possible interactions between the blood group ABO and the outcome of patients after 2 years (following initial surgery) in order to evaluate the usefulness of the ABO blood group as a prognostic marker.

MATERIALS AND METHODS

This retrospective study was carried out at the Department of Obstetrics and Gynaecology, University of Luebeck, from 2006 to 2018. We used the hospital electronic information system of the University of Luebeck to identify women who had undergone surgery for endometrioid endometrial cancer. Medical history, histology, and post-operative data of the patients were thoroughly anonymised and recorded. Microsoft Excel was used to register the information and process it.

The International Federation of Gynaecology and Obstetrics (FIGO) system was used to categorise the disease. The pathologists referred to the FIGO classification in their reports. The initial diagnosis of endometrial cancer had been established by curettage. The patients then received appropriate surgery consisting of hysterectomy, adnexectomy, and further operative staging such as lymphadenectomy, if necessary.

We compared the frequency of ABO blood groups in the general German population with that in the study population. We also looked for a correlation between blood group, tumour grade (G1, G2, G3), FIGO stage, and recurrence (follow-up period 2 years). A subgroup analysis was performed with regard to menopausal status (pre-menopausal and post-menopausal), parity, and body mass index (BMI).

SPSS 19.0 software (SPSS Statistics for Windows 2010, IBM Corporation, Armonk, NY, USA) was used for the statistical analysis. Odds ratios with 95% confidence intervals (95% CI) were generated. p-values equal to or less than 0.05 were considered to be statistically significant. The chi-square test and analysis of variance (ANOVA) were used to compare the groups. These statistical analyses were

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appropriate for the categorical variables in the present analysis. The chi-square test is an undirected statistical method. In other words, it enables the investigator to determine differences between two groups, regardless of the direction of the difference.

ANOVA is a multivariate statistical analysis to detect interactions between variables that influence the target variable. ANOVA compares variance among group means. A *post hoc* test (Scheffé) was performed to determine those variables or combination of variables responsible for the variation of the target variable.

The study is in compliance with the Helsinki declaration, and was approved by the Medical Ethics Committee of the University of Luebeck.

RESULTS

Out of 202 patients included in this study, 96 had blood group A, 19 blood group B, 75 blood group O, and 12 blood group AB. Additionally, 77.6% of the patients were Rhesus positive, while 22.4% of the patients were Rhesus negative. In more detail, 36.6%, 6.9%, 28.7% and 5.4% had blood group A, B, O or AB and were Rhesus positive, whereas the corresponding figures for Rhesus negative patients were 11.0%, 2.5%, 8.4% and 0.5%, respectively. This distribution resembles the general blood group distribution in Germany (p=0.243). Data from the German blood donor service was used for comparison[23]. Of all patients, 165 had FIGO stage I and 37 had FIGO stage II, III, or IV. Most of the patients had a highly differentiated tumour (123 patients) (G1). In 49 cases the tumour was classified as moderately differentiated (G2), and in 30 cases the tumour was poorly differentiated (G3).

The mean age of the patients at the initial diagnosis was 64.5±12.3 years (95% CI: 62.9-66.1 years). With regard to BMI as a risk factor for endometrial carcinoma, none of the four sets of patients divided according to blood group had a significantly higher BMI than any other set (p=0.97). The relative number of women who gave birth to three or more children and then developed endometrial carcinoma was comparable among all sets (overall 21.8%) (**Table I**).

Our results differ from those of other studies which suggest a significant correlation between the patient's blood group and endometrial carcinoma. We did not find any significant evidence of a higher relative frequency of G3 endometrial carcinomas compared to G1 with respect to ABO group (p=0.967, 95% CI: 1.34-2.12). Blood group did not influence tumour grade (p=0.287) and was also not related to FIGO stage at initial diagnosis (p=0.203). Multivariate analysis revealed a significant association between FIGO stage and grade (p=0.007).

The majority of patients (80%) were post-menopausal. The analysis suggests that menopausal status did not affect the severity of endometrial carcinoma because there was a non-significant difference between patients grouped by FIGO stage at initial diagnosis, depending on the ABO blood group (p=0.203).

BMI and FIGO stage were significantly correlated (p=0.021). A high BMI is a well-known risk factor for endometrial carcinoma. However, in the subgroup analysis there was no evidence of higher FIGO stages at initial diagnosis in patients with a BMI higher than 30 kg/m^2 (p=0.206).

In patients treated at the University Hospital of Luebeck between 2006 and 2014, just a few tumours (83 endometrial cancers) were tested for oestrogen and progesterone receptors. No significant correlation was noted between blood group and type I endometrial carcinomas (p=0.067). Blood group did not influence FIGO stage at initial

Table I - *Clinical characteristics of the tested population*

Clinical characteristics	BG A (n = 96)	BG B (n = 19)	BG O (n = 75)	BG AB (n = 12)	p-value
Median age (years)	63.1	64.7	65.0	65.0	0.72
Mean BMI (kg/m^2)	31.7	31.4	30.7	30.7	0.97
Mean ECOG score	0.6	0.6	0.5	0.5	0.75
Average parity	79.6%	75%	81.3%	80%	0.98
Proportion of postmenopausal patients	1.4	1.2	1.9	1.9	0.34

BG: blood group; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group performance status.

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diagnosis or nodal status (p=0.203). Twenty-three of 202 patients experienced a recurrent endometrial cancer after an average disease-free survival of 22.3 months. Recurrence rates were in not related to blood group types (p=0.494, 95% CI: 0.46-0.14).

DISCUSSION

A small number of studies have addressed associations between blood group and endometrial cancer, and reported diverse results. The current study revealed no correlation between either ABO group or Rhesus factor and grade or stage of endometrial cancer. The results of the present study are in line with data reported by Yuzhalin *et al.*[24] on 440 patients with endometrial cancer. The authors did not detect any correlation between ABO group and clinical parameters.

However, the results of the present study do not concur with others indicating that blood group A or B is related to a lower or higher risk of endometrial cancer compared to blood group O. Most of these studies identified blood type A or O as an independent risk factor. The fact that these blood groups are the most common blood group types may induce statistical bias. In a retrospective cohort study comprising 203 patients, Mandato *et al.* reported that patients with blood group A are at lower risk of developing G3 endometrial cancer type I compared to patients with other blood groups[25]. They suggested the use of blood groups as an economical biomarker. Moreover, they found an association between blood group A and the risk of endometrial cancer, independently of menopausal status, BMI, family history of cancer, or oral contraceptive use.

In contrast, a retrospective analysis by Marinaccion *et al.* comprising 968 Italian women indicated that endometrial cancer occurred more frequently in women with blood group A than in those with other blood groups[26]. However, Nakashidze *et al.* concluded that blood group O is associated with a higher risk of endometrial cancer compared to other blood groups[27] and, following an analysis of 548 Armenian women with endometrial cancer, Adamian *et al.* reported that women with blood group AB have a significantly higher risk of developing endometrial cancer compared to patients with blood group O[28].

Many mechanisms, such as inflammation, intercellular adhesion, cell-cell interactions and immune surveillance might be influenced by blood group[29]. Consequently, altered levels of tumour necrosis, membrane signalling, and immune surveillance for malignant cells have been reported. These mechanisms could theoretically be responsible for an association between ABO group and endometrial cancer[6,30,31].

It has been shown that ABO glycosyltransferases may influence circulating plasma levels of von Willebrand factor and consequently increase the risk of thrombosis[32]. Furthermore, it has been reported that von Willebrand factor modulates angiogenesis and apoptosis[33], which are associated with carcinogenesis. We still lack clear evidence of any specific blood group being associated with a higher risk of developing endometrial cancer. Many authors mention that A and B glycosyltransferases induce carcinogenesis[34]. Other studies have indicated that the risk of endometrial carcinoma is higher in women with blood group O than in women with other blood groups. However, aberrant glycosylation patterns are important factors in carcinogenesis and might be useful to clarify the mechanism of metastasis[35].

In order to identify any correlations between gynaecological cancers and blood groups, Gates *et al.* analysed data from 49,153 women of a mixed US population[36]. A statistically significant increase in the frequency of epithelial ovarian cancer was noted in carriers of B blood group antigen (AB and B) compared to that in women with blood group O or A. In contrast, in a retrospective investigation of 1,261 English women with ovarian cancer, Herderson *et al.* found blood group A significantly more often than other blood groups[37]. Herderson *et al.* also reported that the above-mentioned association was more notable in married women than in single women, probably reflecting differences associated with parity[37].

Other authors aimed to correlate parity and other parameters such as menopausal status with blood group antigen[24]. The current analysis suggests that menopausal status does not affect the malignancy of endometrial carcinoma; no significant difference was registered between FIGO stage at initial diagnosis and ABO blood group (p=0.203). Notably, the present study revealed an association between FIGO stage and grade of endometrial carcinoma. A high-grade tumour is obviously associated with a higher FIGO stage at initial diagnosis.

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One of the advantages of the present study is that follow-up data were well-documented electronically. Thus, the authors were able to test for more interactions than in other published studies (ABO antigen, FIGO stage, lymph node status, and recurrence) and evaluate the role of various potential characteristics such as parity, BMI, and menopausal status. All blood group categories had equivalent demographic characteristics and included patients with all tumour stages. The retrospective nature of the study might be considered a disadvantage. However, a prospective study would not have provided better documentation than a retrospective analysis. To our knowledge, this is the first study in which ABO antigens were analysed as prognostic and diagnostic markers (follow-up period 2 years). Nevertheless, the relatively small number of cases in our cohort does not permit conclusive statements about the possible interactions between ABO blood group and the risk of developing endometrial cancer. Moreover, the small sample size did not permit an extended subgroup analysis for various factors such as the site of recurrence. Further large studies are needed.

CONCLUSIONS

The present study revealed no dependence of clinical parameters of endometrioid endometrial carcinoma on ABO blood group. We conclude that blood group screening is probably not useful as an early biomarker of endometrioid endometrial carcinomas. The few but very heterogeneous study results reported in the published literature suggest that ABO type may not be a key mechanism in endometrial carcinogenesis. More extensive research in larger populations of patients is called for in order to achieve early diagnosis of endometrial cancer, which is the key aspect for successful treatment.

DECLARATIONS

Ethics approval and consent to participate

Approval was obtained from the Ethics Committee of the Medical Faculty of the University of Luebeck (ethics committee approval number 19-381). Consent was obtained from the patients. The report has drawn up in accordance with the *Declaration of Helsinki*.

Consent for publication

Patients' consent was obtained.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

AUTHORSHIP CONTRIBUTIONS

GG, PL, BS: protocol/project development; GG, PL, AI, TD, KC: data collection or management; GG, PL, RA: data analysis; GG, PL, AI: manuscript writing/editing.
All Authors read and approved the final manuscript.

The Authors declare that they have no conflicts of interests.

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