The ABO Blood Groups in Neoplastic Disease of the Ovary

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STUDIES OF THE RELATIVE FREQUENCY of the ABO blood groups in various diseases have demonstrated statistical associations between this blood group system and a number of different disease entities (Clarke, 1959; Matsunaga, 1959; Roberts, 1957, 1959), but have failed to provide satisfactory explanations as to the biological basis for the associations observed (Osborne and De George, 1962, Roberts, 1959). In an earlier study, tumors of the parotid and submaxillary glands were selected for the investigation of this critical problem (Osborne and De George, 1962). It was found that blood group associations occurred with benign as well as with malignant tumors of these two glands, but only with tumors of certain histological appearances. The study of the ABO blood groups in neoplastic disease of the ovary which is reported here is a sequel of the salivary gland study.

Diseases of the ovaries were selected for the present investigation because: (a) the ovaries, like the salivary glands, are subject to a great variety of both benign and malignant neoplasms; (b) pseudomucinous cysts of the ovary contain the ABO (H) group specific substances in women who secrete these substances in their saliva; (c) carcinoma of the ovary has been reported to associate with the ABO blood group system, (Helmbold, 1961).

The purposes of the present study are to determine: (1) whether benign as well as malignant disease of the ovary associates with the ABO blood groups as in the salivary gland tumors; (2) whether the blood group frequencies differ in the various histological types of ovarian disease; (3) whether any such differences when interpreted in the light of the salivary gland experience will further elucidate the basis of blood group disease associations.

MATERIAL AND METHODS

Utilizing the 1951-1961 records of Memorial Hospital in New York City, New York, 713 cases of ovarian disease were obtained in which blood group and type of ovarian disease could be established. The number of benign and malignant cases and their classifications are given in table 1. A simple classification of ovarian neoplasms is difficult because of their varied histology and

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the frequency of transitional or mixed types (Willis, 1960). This has necessitated a hierarchical order of classification for the purposes of this study. Each case is classified by the following order of histological description: pseudomucinous, mucinous, serous, papillary, anaplastic, cystadenocarcinoma, adenocarcinoma, dermoid, teratoma, thecoma, and granulosa cell. In some instances the left and right ovaries were affected by different types of disease. For example, at surgery or autopsy a patient with papillary cystadenocarcinoma might be found to have a small dermoid cyst or focus of endometriosis on the opposite ovary. Such a case is listed as a papillary cystadenocarcinoma. In any instance where an obvious choice as to classification could not be made, the case is listed under miscellaneous. No patient is listed in more than one classification.

Blood group control values were obtained for volunteer blood donors at Memorial Hospital and are the same as used in the salivary gland study (Osborne and De George, 1962). To establish blood transfusion credit, volunteer donors are solicited by the patients and their families. Members of the patients' families constitute approximately 15 per cent of all donors, and the remainder come from their friends and work associates. Paid donors have been excluded from the control. Since all patients with ovarian disease are females, the volunteer donors are listed by sex, and as there is no difference in the blood group frequencies of male and female, the sexes are combined for the calculation of control values (table 2). In this way the arithmetic contribution of the control in the present study is the same as in the salivary gland study.

TABLE 1. CLASSIFICATION AND NUMBER OF OVARIAN NEOPLASMS

Benign		Malignant	
Classification	n	Classification	n
Pseudomucinous cyst	28	Pseudomucinous cystadenocarcinoma	17
Mucinous cyst & cystadenoma	6	Mucinous adeno-	
Simple cyst	11	& cystadenocarcinoma	15
Serous cyst	32	Cystadenocarcinoma	9
Endometrial cyst	13	Serous cystadenocarcinoma	14
Endometriosis	57	Anaplastic adenocarcinoma	20
Dermoids	47	Adenocarcinoma	103
Teratomas	9	Papillary adenocarcinoma	234
Fibroma & adenofibroma	29	Secondary carcinoma	14
Thecoma & granulosa cell	8	Granulosa cell	12
Miscellaneous*	20	Miscellaneous	15
Total	260	Total	453

*Represents different histological types with only 1-5 patients in any single classification and in those in which no classification other than benign or malignant was given.

TABLE 2. ABO BLOOD GROUP DISTRIBUTION IN THE CONTROL

			O	A	B	AB	Total
Volunteer donors	♂	n	1,728	1,561	535	201	4,025
		%	42.93	38.78	13.29	4.99	
	♀	n	301	267	101	44	713
		%	42.22	37.45	14.16	6.17	
Total		n	2,029	1,828	636	245	4,738
		%	42.82	38.58	13.42	5.17	

In the statistical analysis of the data the method proposed by Woolf (1955) is followed. By this method, the blood group associations are given as a ratio, which is the incidence of the disease in persons of one blood group relative to the incidence in persons of another blood group or groups. Chi-square with one degree of freedom is used to obtain the probability levels of these ratios.

RESULTS

In the volunteer donor control the frequency of blood group O is 42.82 per cent and that of blood group A is 38.58 per cent (table 2). In patients with ovarian disease the percentage of group O is 39.97 and that of group A is 44.04 (table 3). The frequency of ovarian disease in group A is 1.22 relative to one in group O, which is statistically significant, $P = .025$ (table 4). When benign and malignant disease are examined separately the ratios in group A are 1.29 and 1.19, respectively; neither ratio is statistically significant.

The blood group distributions in different classifications of benign and malignant neoplasms are given in tables 5 and 6. The blood group distributions differ markedly from one classification to the next. In benign disease the magnitude of the differences in the frequency of blood groups A and O are consistently greater than in comparable malignant classifications. The consistency of this pattern is reflected in the larger ratio observed for benign as compared to malignant ovarian disease, (1.29 and 1.19) (table 4).

In the benign disease classification the excess of blood group A is contributed

TABLE 3. BLOOD GROUP DISTRIBUTION IN OVARIAN NEOPLASMS

		O	A	B	AB	Total
Benign	n	98	114	35	13	260
	%	37.69	43.85	13.46	5.00	
Malignant	n	187	200	47	19	453
	%	41.28	44.15	10.38	4.19	
Totals	n	285	314	82	32	713
	%	39.97	44.04	11.50	4.49	

TABLE 4. OVARIAN NEOPLASMS: RELATIVE FREQUENCY IN PERSONS OF GROUP A COMPARED WITH FREQUENCY OF ONE IN PERSONS OF GROUP O

Comparisons	Blood Group A	Blood Group O	Relative Frequency in Group A	χ^2	P
Benign	114	98	1.29	3.24	.07
Control	1,828	2,029			
Malignant	200	187	1.19	2.66	.10
Control	1,828	2,029			
Total	314	285	1.22	5.13	.025
Control	1,828	2,029			

by only four of the ten categories: pseudomucinous cysts, simple cysts, endometriosis, and dermoid cysts (table 7). There were only eleven simple cysts in these data and these are therefore excluded for the purpose of statistical comparisons. While impressive ratios occur in all three categories given, only in dermoids is the ratio (2.40) statistically significant, P = .013.

In the nine categories of malignant disease the excess of blood group A is contributed only by two: papillary adenocarcinoma and secondary carcinoma (table 8). The ratio of 1.44 for papillary adenocarcinoma is statistically significant, P = .015, as is the ratio of 6.10 for secondary carcinoma, P = .017.

With the exceptions of papillary adenocarcinoma and adenocarcinoma the number of cases in a given category are inadequate for statistical comparisons. The relative frequency of papillary adenocarcinoma compared with adenocarcinoma is 1.80 in persons of group A to one in persons of group O, P = .022. It would appear that the ABO blood groups may relate in some way to the presence of papillary features in an ovarian adenocarcinoma.

DISCUSSION

Since demonstration by Aird, Bentall and Roberts (1953) of the association between stomach cancer and blood group A, most subsequent blood group-cancer studies have been designed to test the proposition that blood group A is correlated with carcinogenesis by virtue of the fact that an established malignancy has been the customary basis for selection of patient or disease populations. Such a study design precludes the possibility of detecting a blood group

TABLE 5. BLOOD GROUP DISTRIBUTION IN DIFFERENT CLASSIFICATIONS OF BENIGN OVARIAN NEOPLASMS

Classification		O	A	B	AB	Total
Pseudomucinous	n	7	15	4	2	28
	%	25.00	53.57	14.29	7.14	
Mucinous	n	5	1	—	—	6
	%	83.33	16.67	—	—	
Simple cyst	n	4	5	2	—	11
	%	36.36	45.45	18.18	—	
Serous cyst	n	14	13	4	1	32
	%	43.75	40.63	12.50	3.13	
Endometrial cyst	n	6	5	2	—	13
	%	46.15	38.46	15.38	—	
Endometriosis	n	20	29	6	2	57
	%	35.09	50.88	10.53	3.51	
Dermoid	n	12	26	8	1	47
	%	25.53	55.32	17.02	2.13	
Teratoma	n	6	2	—	1	9
	%	66.67	22.22	—	11.11	
Fibroma	n	13	9	3	4	29
	%	44.83	31.03	10.34	13.79	
Thecoma & granulosa cell	n	11	5	4	—	20
	%	55.00	25.00	20.00	—	

TABLE 6. BLOOD GROUP DISTRIBUTION IN DIFFERENT CLASSIFICATIONS OF MALIGNANT OVARIAN NEOPLASMS

Classification		O	A	B	AB	Total
Pseudomucinous	n	8	8	—	1	17
	%	47.06	47.06	—	5.88	
Mucinous	n	7	4	4	—	15
	%	46.67	26.67	26.67	—	
Cystadenocarcinoma	n	5	2	—	2	9
	%	55.56	22.22	—	22.22	
Serous cystadenocarcinoma	n	6	6	2	—	14
	%	42.86	42.86	14.29	—	
Anaplastic adenocarcinoma	n	9	8	3	—	20
	%	45.00	40.00	15.00	—	
Adenocarcinoma	n	54	39	8	2	103
	%	52.43	37.86	7.77	1.94	
Papillary adenocarcinoma	n	84	109	28	13	234
	%	35.90	46.58	11.97	5.56	
Secondary carcinoma	n	2	11	1	—	14
	%	14.29	78.57	7.14	—	
Granulosa cell	n	7	4	1	—	12
	%	58.33	33.33	8.33	—	

TABLE 7. BENIGN OVARIAN NEOPLASMS: RELATIVE FREQUENCY IN PERSONS OF GROUP A COMPARED WITH FREQUENCY OF ONE IN PERSONS OF GROUP O

	Blood Group A	Blood Group O	Relative Frequency in Group A	χ^2	P
Pseudomucinous	15	7	2.38	3.57	.06
Control	1,828	2,029			
Endometriosis	29	20	1.61	2.65	.09
Control	1,828	2,029			
Dermoid cyst	26	12	2.40	6.24	.013
Control	1,828	2,029			

TABLE 8. MALIGNANT OVARIAN TUMORS: RELATIVE FREQUENCY IN PERSONS OF GROUP A COMPARED WITH FREQUENCY OF ONE IN PERSONS OF GROUP O

	Blood Group A	Blood Group O	Relative Frequency in Group A	χ^2	P
Papillary Adenocarcinoma	109	84	1.44	6.02	.015
Control	1,828	2,029			
Secondary Carcinoma	11	2	6.10	5.52	.017
Control	1,828	2,029			

association with a pre-malignant condition or other biological process which may be responsible for the increased cancer susceptibility observed for persons of blood group A. In the present study, as in the study of salivary gland tumors (Osborne and De George, 1962), benign as well as malignant disease has been included for the express purpose of determining whether some process other than carcinogenesis may be responsible for an observed blood group-cancer association.

In the 713 cases of ovarian disease analyzed in the present study there are 453 cases of malignant and 260 cases of benign disease. In women with blood group A, the frequency of ovarian carcinoma is 1.19 relative to one in women with blood group O, $P = .10$. While not statistically significant, these data are consistent with the German data reported by Helmbold (1961). In a series of 1,300 cases of ovarian carcinoma obtained from fourteen different patient populations, Helmbold found a frequency of ovarian carcinoma of 1.165 in women with blood group A relative to one in women of blood group O. In these larger data, $P = .018$.

The benign ovarian diseases in the present study have a frequency of 1.29 in women of blood group A relative to one in women of blood group O, $P = .07$. Though neither benign nor malignant disease associates significantly with blood group A when taken separately, both contribute to the significant ratio of 1.22, $P = .025$, obtained for the total series of 713 cases. It would appear that in the ovary, as in the salivary glands (Cameron, 1958; Osborne and De George, 1962), the blood group A association relates to benign as well as malignant neoplastic disease. It can therefore be concluded that the associations which have been demonstrated between blood group A and cancer at other anatomical sites, may also relate to some pre-malignant condition or other biological process rather than to carcinogenesis per se.

To extend the interpretation of these data nineteen different classifications of ovarian disease were made, and analyzed separately. It is found that only six classifications (four benign and two malignant) contribute to the increased frequency of ovarian disease in women of blood group A. These are: pseudomucinous cysts, endometriosis, dermoid cysts, simple cysts, papillary adenocarcinoma and secondary carcinoma. Some of the characteristics common to these ovarian diseases are of interest. Pseudomucinous cysts, in addition to their specific content in secretor women, are lined by a high columnar epithelium resembling the epithelium of the uterine cervix or large intestine (Anderson, 1948; Willis, 1960). The extra-ovarian and cystic characteristics of endometriosis and of dermoids are implicit. Papillary adenocarcinoma is distinguished from adenocarcinoma by the presence of papillary development or over-growth atypical of the adult ovarian epithelium by which the ovarian adenocarcinoma is defined. The possible significance of these papillary features to the blood group A association is strongly implied by a significant difference between these two varieties of carcinoma in the frequency of blood group A relative to that of blood group O, (ratio = 1.80, $P = .022$). Secondary carcinoma, which has a sixfold increase in the frequency of blood group A, is classified on the basis of the fact that the cell type of the malignant ovarian tissue is of another anatomical site,

principally gastrointestinal, mammary and cervical. In these secondary carcinomas, no other ovarian disease was described. Some secondary cases also occurred in which there was additional ovarian disease; these were classified as miscellaneous. When all such cases are reclassified as secondary carcinoma there are seventeen blood group A and four blood group O, giving a ratio of 4.72, $P = .005$.

Certain generalizations are possible from these data. The ovarian neoplasms which associate with blood group A are of a glandular type of epithelium, are of either a cystic or papillary structure, and include development of some atypical or extra-ovarian type of epithelium. In contrast, the ovarian diseases which do not appear to associate with blood group A are solid rather than cystic (Corscaden, 1956), and, if of an epithelial origin, they are entirely of an ovarian type.

The findings of this study are similar in all major respects to those of the parotid and submaxillary gland study. At both sites it was found that individuals of blood group A have a greater likelihood than do individuals of blood group O of developing benign as well as malignant disease, but only of limited histological types. These types are also similar at the two sites. In both the ovary and the parotid gland, tumors with papillary features associate with blood group A (papillary adenocarcinoma, adenolymphoma or papillary cystadenoma) while adenocarcinoma without papillary features is not associated with blood group A. As in the ovary, all types of salivary gland tumors with an increased frequency in individuals of blood group A (mixed tumors, mucoepidermoid tumors, squamous tumors, and adenolymphomas) possess some form of atypical or metaplastic epithelium (Evans, 1956; Frazell, 1954; Stewart, Foote and Beaker, 1945; Willis, 1960). In the salivary gland study, the potential importance of this characteristic to the blood group A association is most apparent in the mucinous tumors of the parotid gland, which arise by metaplasia (Willis, 1958). It was this observation which importantly lead to the suggestion that "the blood groups are associated with neoplastic processes which involve the mucous secreting elements of the glandular epithelium" (Osborne and De George, 1962). From the blood group A association with dermoid cysts of the ovary, it would appear that while the neoplastic processes which associate with the blood group A genotype may predominantly involve columnar mucous-secreting epithelium, it is the characteristic of atypical cell regeneration or metaplasia which is critical to this association rather than mucus secretion itself.

The reparative and regenerative capabilities of different tissues and organs vary greatly, and in all probability differ also between individuals. The epithelium in general, and quite markedly that of the salivary glands and ovary, is capable of extensive regeneration. While proliferating adult cells are most typically unipotential and accurately reproduce cells of a fixed type, certain environmental conditions such as inflammation or nutritional deficiencies may incline some proliferating cells to differentiate along a different or atypical pathway (Ham and Leeson, 1961). The salivary gland and ovarian epithelium is known to possess dormant potential for widely aberrant differentiation in regenerative or other proliferative lesions (Willis, 1958, and many others). Both the salivary

gland and ovarian disease data suggest that under conditions which may stimulate or demand epithelial regeneration at these two sites, different potentials for atypical cell differentiation or metaplasia may be associated with different ABO blood group genotypes. Such a thesis is equally compatible with the present evidence concerning the blood group associations with gastrointestinal disease; an investigation of this is now in progress.

The ovarian disease data, like those of the salivary gland study, unquestionably indicate that the increased cancer risk of individuals of blood group A is a consequence of a blood group A association with some pre-malignant process. The fact that a specific pre-malignant process may be involved is implied by the limitation of the blood group A association with only certain histological types of ovarian disease. The similarity in histological characteristics of the ovarian diseases and salivary gland tumors which associate with blood group A indicate the presence of some common denominator; this suggests that there may well be some common basis for all blood group disease associations.

SUMMARY

Neoplastic diseases of the ovary were investigated with respect to the ABO blood groups as a sequel to a study of salivary gland tumors in which it was found that blood group associations occurred with benign as well as with malignant tumors, but only with tumors of certain histological appearances. The findings for the blood group associations with ovarian disease are compatible with those of the salivary gland study in all major respects.

The ovarian disease data, like those of the salivary gland study, unquestionably indicate that the increased cancer risk of individuals of blood group A is a consequence of a blood group A association with some pre-malignant process. On the basis of the types of neoplastic diseases of the ovary and of the salivary gland which associate with blood group A, it is probable that different potentials for atypical cell differentiation may be associated with the different ABO blood group genotypes.

An unexpected finding which will require verification from further investigation, but one with great potential importance to the cancer problem, is the four to sixfold excess of secondary carcinomas of the ovary in women of blood group A relative to that in women of blood group O.

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