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Positive Correlation between Breast Cancer Incidence and HLA Antigens

Claire Bouillenne and Jean-Marie Deneufbourg

Laboratoires de transfusion sanguine et des groupes sanguins (Head: Prof. André), Université de Liège, and Service de Radiothérapie (Head: Prof. Closon), Hôpital universitaire de Bavière, Liège

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Abstract. HLA determinations were made at the time of diagnosis among a lot of 141 patients with breast cancer. Values of relative risk as well as frequencies of antigens at the first and the second locus were confronted to data found in a control population. Subdivisions of the neoplastic population according to hormonal status and parity led to the emergence of significant differences: frequency of A28 in menopausal nulliparous women with breast cancer is 26 vs. 7 % in controls (p corrected = 0.038) with relative risk = 6.63 (p 0.001).

Introduction

The relationships of the major histocompatibility system and cancer incidence are being studied extensively. Some reports already indicate significant associations betwen definite HLA antigens and several neoplastic diseases [*Murphy et al.,* 1977; *Rosner et al.,* 1977].

To our knowledge no clear-cut correlation has been demonstrated up to now concerning breast cancer frequency. The present work deals with our preliminary results among such a patients population.

Patients and Methods

Our patients group consists of 141 women who were studied as they presented for the first time to treatment at the Radiotherapy Department of the University of Liège. All had histologically proven breast cancer on biopsy material. Clinical data were recorded about hormonal status and parity for each case.

Our control group is a healthy population of 198 female blood donors matched for age distribution by decades and comparable for race and habitat. The histocompatibility testing was carried out by the Blood Transfusion Department of the University of Liège.

The HLA specificities are determined by microlymphocytotoxicity test according to Kissmeyer-Nielsen's technique [*Kissmeyer-Nielsen and Thorby,* 1970]. The patient group as well as the control group were investigated for the following antigens: HLA A1, A2, A3, A9, A10, A11, A28, W19; HLA B5, B7, B8, B12, B13, B14, B27, BW15, BW17, BW35, BW40. All cases have been tested with the same antisera. The NIH of Bethesda provided us with specific antisera and we also used sera from local origin whose specificity has been well confirmed by other laboratories. Antigen frequencies in the whole patients population and in subdivisions of the patients population according to hormonal status and parity were compared to antigen frequencies in the control population. Statistical interpretations were corrected in order to take into account the 19 HLA specificities investigated and the two-sidedness of the test [*Svejgaard et al.,* 1974]. Values of p corrected (pc = p × 19 × 2) inferior to 0.05 were considered to be significant.

The results were also expressed by calculation of the relative risk (x) indicating how many times more frequent breast cancer is in individuals carrying a given antigen as compared to individuals lacking this antigen [*Woolf,* 1955]. Statistical interpretation of x values divergent from 1 were made according to Haldane formulas [*Haldane,* 1955].

Results

Antigen frequencies in percent and values of relative risk for each HLA specificity are presented in tables I and II respectively for first and second locus. As compared to controls, the antigen A28 is nearly fourfold increased in patients who are at one and the same time menopausal and nulliparous (26 vs. 7%; p corrected = 0.038). Highly significant values for x correspond to that increased frequency: x = 4.87 at A28 for nullipa-

Table I. Antigen frequency at first locus (%, upper line) and relative risk (x, lower line)

	n	HLA							
		A1	A2	A3	A9	A10	A11	A28	W19
Controls		29	46	23	28	7	9	7	5
	198								
All cases		26 (%)	50	28	20	11	11	9	4
	141	0,82 (x)	1.15	1.35	0.64	1.56	1.19	1.75	0.52
Meno+		19	45	28	25	13	11	11	5
	87	0.58	1	1.3	0.88	1.9	1.3	2.44	0.69
Meno–		35	57	30	11	7	9	4	2
	54	1.31	1.58	1.43	0.33**	1.05	1.02	0.72	0.27
Par+		26	43	28	17	11	13	5	5
	98	0.87	0.88	1.29	0.54	1.66	1.52	1	0.60
Par–		24	38	29	32	9	6	21	3
	34	0.74	0.72	1.40	1.24	1.27	0.62	4.87***	0.43
Meno+Par+		21	49	30	23	12	14	7	7
	57	0.64	1.14	1.44	0.77	1.84	1.63	1.41	1.07
Meno+Par–		17	30	17	39	13	9	26[1]	0
	23	0.50	0.51	0.72	1.67	1.97	0.95	6.63****	0.29
Meno–Par+		34	61	24	10	10	12	2	0
	41	1.25	1.83	1.1	0.28*	1	0.28	0.47	0.17
Meno–Par–		36	36	45	18	0	0	9	9
	11	1.38	0.67	4.08*	0.47	0.55	0.42	1.88	1.42

Signification of x: * <0.05; ** <0.02; *** <0.01; **** <0.001.

[1] pc = 0.038 (pc = p × 19 × 2).

Table II. Ag frequency at second locus (%, upper line) and relative risk (x, lower line)

	n	HLA										
		B5	B7	B8	B12	B13	B14	BW17	B27	BW35	BW40	BW15
Controls		21	23	18	28	6	12	9	5	17	11	12
	198											
All cases		13 (%)	28	9	28	5	7	8	5	31	12	18
	141	0.60 (x)	1.3	0.47*	0.99	0.80	0.55	0.90	0.98	2.19***	1	1.56
Meno+		16	22	8	26	7	6	8	7	31	11	17
	87	0.73	0.95	0.40*	0.93	1.15	0.44	0.93	1.39	2.17***	1.04	1.51
Meno–		9	37	11	30	2	9	7	2	31	13	19
	54	0.39	2*	0.58	1.09	0.29	0.74	0.85	0.35	2.21*	1.19	1.5
Par+		18	29	7	29	5	5	8	4	28	12	21
	98	0.86	1.42	0.35	1	0.83	0.38	0.94	0.80	1.92*	1.10	1.97
Par–		9	23	12	26	3	12	3	9	41	12	12
	34	0.37	0.40	0.62	0.90	0.46	0.96	0.32	1.80	3.37***	1.06	0.96
Meno+Par+		23	26	9	26	9	2	9	7	28	11	19
	57	1.13	1.21	0.44	0.93	1.49	0.13*	1.02	1.42	1.88	0.94	1.73
Meno+Par–		13	13	4	30	4	13	0	9	39	13	17
	23	0.51	0.51	0.21	1.14	0.70	1.08	0.22	1.79	3.1***	1.2	1.53
Meno–Par+		12	34	5	34	0	10	7	0	29	15	24
	41	0.53	1.76	0.24	1.35	0.18	0.78	0.84	0.22	2	1.37	2.33*
Meno–Par–		0	45	27	18	0	9	9	9	45	9	0
	11	0.16	2.8	1.74	0.58	0.65	0.73	1.06	1.88	4*	0.80	0.31

Legends for signification of x: see table I.

rous women and x = 6.63 at A28 for menopausal and nulliparous population. A high relative risk for breast cancer is also linked to BW35 with very significant values whichever cohort is considered: for general population x = 2.19 and subdivisions according to hormonal status and parity leads to comparable values; relative risk for nonmenopausal nulliparous women is as high as 4.

On the other part, significant low relative risks are found at several HLA specificities: x = 0.47 at B8 for general population; x = 0.33 at A9 for nonmenopausal women; x = 0.13 at B14 for menopausal women with parity.

Discussion

Possible correlations between breast cancer and major histocompatibility system have already been investigated but with rather negative results. *Patel et al.* [1972] have found an excess of HLA 7 in 52 breast cancer as compared to 123 healthy blood donors. However, the statistical interpretation of their data did not take into account the first-order error possible when comparing the frequencies of many antigens with one disease [*Svejgaard et al.*, 1974]. When corrected for this overestimation the difference between patients and controls is no longer significant. *Martz and Benacerraf* [1973] studied 48 patients with carcinoma of the breast and concluded to a lack of correlation with HLA antigens. The absence of association was confirmed by the work of *Cordon and James* [1973] among a lot of 97 patients. *De-Jong-Bakker et al.* [1974] as well as *Oh and MacLean* [1977] also failed to show any correlation between HLA antigens and breast cancer when using appropriate statistical methods.

A recent Breast Cancer Task Force report by *Lynch et al.* [1977] reported no single HLA antigen or haplotype common to breast cancer prone-kindreds or cancer family syndrome kindreds.

The present work deals with our preliminary results among a lot of 141 patients with breast carcinoma. HLA typing was always carried out at time of tumour diagnosis in order to avoid cases preselection due to success or failure of the cancer treatment. As a matter of fact, the bias of cases preselection occurs if one considers at one and the same time newly diagnosed cancers and patients cured for many years.

The control population and the patients group are of the same sex, their distribution according to age by decades are superposable, racial origin and habitat areas are comparable. Our work illustrates rather well the advantage of subdividing populations under study into defined classes: most of significant values only appear among particular groups and rarely in the cancerous population considered as a whole. Subdivision criteria firstly took into account that breast cancer differs on clinical course and prognosis according to hormonal status of the host at onset and, on the other part, that nulliparity seems to constitute one of the most clear-cut factors of high incidence [*Juret,* 1976].

The study is still going on to confirm the fourfold increase of A28 in menopausal nulliparous women with breast cancer. Larger groups are also required before drawing definite conclusions as regard to high and low relative risks associated with several HLA specificities. We hope that, in the next future, when breast cancer families will come under investigation, the discovery of HLA markers will help to point out high-risk populations and therefore to settle accurate early diagnosis and prevention.

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Dr. J.M. Deneufbourg, Service de Radiothérapie, Hôpital universitaire de Bavière, Boulevard de la Constitution, B-4000 Liège (Belgium)