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## HLA ANTIGENS AND BRONCHOGENIC CARCINOMA IN THE GREEK POPULATION

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### Abstract

The distribution of HLA antigens was studied in 85 Greek patients with bronchogenic carcinoma. Fifty-seven specific HLA antisera were used to determine 27 HLA-A and B antigens, with the two-stage standard NIH microlymphocytotoxicity assay. The results were compared with those in a control group, consisting of 400 healthy individuals. In the whole group of patients there was a significantly higher frequency of HLA-AW19 and HLA-A29 ( $p < 0.003$  and  $p < 0.006$  respectively) and a lower frequency of HLA-A2 and HLA-A3 ( $p < 0.014$  and  $p < 0.006$  respectively) than in the control population. In patients with squamous cell carcinoma there was a significantly higher frequency of HLA-AW19 and lower frequency of HLA-A2 ( $p < 0.02$  and  $p < 0.05$  respectively). In small cell carcinoma patients there was a significantly lower frequency of HLA-A3 ( $p < 0.04$ ) than among the controls. In patients with adenocarcinoma no significant change of HLA antigen frequencies was observed when compared to the controls.

*Key words:* HLA-antigens, bronchogenic carcinoma.

In recent years, several investigators have reported associations between various HLA antigens and bronchogenic carcinoma (1–12). As in other reports of relationships between HLA antigens and malignancy, the statistical associations have been rare, weak and, occasionally, contradictory.

It is interesting to note that the number of patients with lung cancer studied worldwide is not large. Furthermore, in some studies histological relationships were not considered at all. It has been suggested that weak associations may be strengthened by subdivisions of cancer into smaller and more specific groups and also by increasing the number of patients (13). Moreover, studies of 'pure' ethnic groups have been proven to be of special interest considering associations between HLA antigens and disease (14–15).

In the present study we have attempted to survey the association of HLA-A and B in a group of Greek patients with bronchogenic carcinoma and to analyse the findings according to the histology of the disease.

### Material and Methods

The distribution frequency of HLA antigens was studied in 85 Greek patients with a recent diagnosis of bronchogenic carcinoma. Seventy-seven of them were men aged 41 to 75 years (mean 62 years). The remaining eight were women aged 52 to 75 years (mean 60 years). The diagnosis was based on bronchial biopsies. Forty of them had squamous cell carcinoma, twenty-four had small cell carcinoma, thirteen adenocarcinoma, three large cell carcinoma and five unclassified bronchogenic carcinoma. Sampling for HLA typing was performed prior to any specific treatment regimen.

The results were compared to those in a control group consisting of 400 healthy, randomly selected Greek individuals (blood donors), 222 males and 178 females with a mean age of 51 years.

Histocompatibility antigens in both groups were typed by 57 antisera testing for 27 HLA-A and B specificities (12 and 15 respectively). The two-stage standard NIH microlymphocytotoxicity assay was applied (16). For the statistical evaluation, Fisher's exact test was applied and the  $p$ -values were corrected for the comparisons made. Relative risks (RR) were also calculated (17–18).

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### Results

The frequency of the HLA antigens in controls and patients with all histological types of bronchogenic cancer are shown in Table 1. Among the patients there was a significantly increased frequency of the antigens HLA-AW19 and HLA-AW29 ( $p < 0.003$ /RR 5.79 and  $p < 0.006$ /RR 3.81 respectively) and a decreased frequency of the antigens HLA-A2 and HLA-A3 ( $p < 0.014$  RR 0.43 and  $p < 0.006$  RR 0.27 respectively) compared to the controls.

By dividing the patients into subgroups according to histology the results were modified as follows: In the squamous cell carcinoma group ( $n = 40$ ) there was a significant increase in frequency of HLA-AW19 and a decrease in frequency of HLA-A2 ( $p < 0.02$ , RR 7.47 and  $p < 0.05$  RR 0.44 respectively). In the small cell carcinoma group ( $n = 24$ ) there was a significant decrease in frequency of HLA-A3 ( $p < 0.04$  RR 0.06) (Table 2). In the adenocarcinoma group ( $n = 13$ ) no significant difference was found concerning the HLA antigen frequency compared to the controls.

**Table 1**

*HLA antigen frequencies in patients with bronchogenic carcinoma and healthy controls*

HLA antigens	Controls		Patients	
	n = 400	%	n = 85	%
HLA-A1	103	25.8	29	34.1
A2	207	51.8	28	32.9 (a)
A28	40	10.0	15	17.6
A3	99	24.8	7	8.2 (b)
A9	130	32.5	16	18.8
A10	55	13.8	8	9.4
A11	34	8.5	8	9.4
AW19	9/326	2.8	12	14.1 (c)
A29	12/290	4.2	12	14.1 (d)
A23	2/46	4.4	6	7.0
A25	5/65	7.7	0	0.0
A26	2/65	3.3	0	0.0
HLA-B5	122	30.5	25	29.4
BW35	69	17.3	8	9.4
B7	57	14.3	16	18.8
B8	55	13.8	16	18.8
B12	74	18.5	13	15.2
B13	40	10.0	12	14.1
B14	37	9.3	8	9.4
B15	30	7.5	3	3.5
B16	15/267	5.6	11	12.9
B17	39	9.8	10	11.7
B18	87/366	23.8	12	14.1
BW22	16/318	8.0	6	7.0
B27	27	6.8	9	10.6
B37	4/78	8.0	1	1.1
B40	21/313	6.7	5	5.9

(a)  $p < 0.014$ ; RR = 0.43, (b)  $p < 0.006$ ; RR = 0.27,

(c)  $p < 0.003$ ; RR = 5.79, (d)  $p < 0.006$ ; RR = 3.81

Large cell and unclassified carcinoma cases were not analysed separately, due to their small number.

### Discussion

In the last 15 years, several HLA antigens have been found to be associated with the risk of developing lung cancer. Increased frequency has been reported for HLA-B40 (7), HLA-B12 (8) and HLA-B18 (11) in lung cancer patients considered as a whole group and for HLA-A1, HLA-B13 and HLA-B17 (12) in patients with squamous cell carcinoma and for HLA-B5 (7) and HLA-BW44 (9) in patients with small cell carcinoma. Decreased frequency has been found for HLA-A2 (5) and HLA-A40 (12) in lung cancer patients and for HLA-B12 (7) and HLA-B15 (2) in patients with lung adenocarcinoma. Corrected for the number of antigens analysed, all these associations became statistically non-significant, except those between HLA-B18, HLA-A40 and lung cancer considered as a whole group (11-12) and HLA-BW44 (B12) and small cell carcinoma (9).

In the present study we have found a definite increase of HLA-AW19 and HLA-A29 ( $p < 0.003$  and  $p < 0.006$  respectively) and a decrease of HLA-A2 and HLA-A3 ( $p < 0.02$  and  $p < 0.006$  respectively) in the whole group of our patients.

The presence of the antigen HLA-AW19 in higher frequency among the patients may indicate that this antigen acts as a predisposing factor for the disease. It has been suggested by survival studies that HLA-AW19 gives increased resistance to progression of bronchogenic carcinoma (3, 4, 6). These two observations are not necessarily contradictory. HLA-AW19 is a 'long' antigen including HLA-A29, HLA-AW30, HLA-AW31, HLA-AW32 and HLA-AW33. Some of these antigens may be predisposing factors and others may confer resistance to disease progression.

Although HLA-A2 is the commonest HLA antigen in all healthy populations studied, in our study it was found in decreased frequency in lung cancer patients. This is in agreement with the finding of Sengar et al. (5).

An interesting finding of the present study is the absence of HLA-A3 in small cell carcinoma patients. Although a decreased expression of HLA antigens has been found in the malignant cells of this histological type (19), the absence of HLA-A3 may represent a factor predisposing to this histological type of lung cancer.

Finally we could not demonstrate any association between HLA antigens and adenocarcinoma which may be due to the small number of cases examined. However, it is worthy to mention that Lam et al. (10) also failed to find any significant association between HLA antigens and 33 Chinese females with lung adenocarcinoma.

Our results suggest that further investigations are needed on the possible role of the HLA system in the pathogenesis

**Table 2**

*HLA antigen frequencies in patients with different histological types of bronchogenic carcinoma and healthy controls*

HLA antigens	Controls %	Patients		
		SqCLC (n = 40) %	SmCLC (n = 24) %	Adeno (n = 13) %
HLA-A1	25.8	30.0	41.6	23.1
A2	51.8	32.5 a	33.3	30.8
A28	10.0	15.0	20.0	23.1
A3	24.8	15.0	0.0 c	15.4
A9	32.5	20.0	16.6	23.1
A10	13.8	5.0	16.6	0.0
A11	8.5	12.5	4.0	15.4
AW19	2.8	17.5 b	12.5	7.7
A29	4.2	12.5	12.5	23.1
A23	4.4	2.5	8.0	23.1
A25	7.7	0.0	0.0	0.0
A26	3.3	0.0	0.0	0.0
HLA-B5	30.5	22.5	29.0	30.8
BW35	17.3	7.5	4.0	15.4
B7	14.3	25.0	16.6	7.7
B8	13.8	25.0	4.0	23.1
B12	18.5	12.5	19.2	0.0
B13	10.0	10.0	16.6	30.8
B14	9.3	12.5	16.6	7.5
B15	7.5	0.0	4.1	15.4
B16	5.6	10.0	12.5	7.7
B17	9.8	10.0	20.0	15.4
B18	23.8	12.5	4.0	0.0
BW22	8.0	15.0	0.0	7.0
B27	6.8	17.5	4.0	7.7
B37	8.0	0.0	4.0	0.0
B40	6.7	2.5	8.0	15.4

a)  $p < 0.05$ ; RR = 0.44, b)  $p < 0.02$ ; RR = 7.47, c)  $p < 0.04$ ; RR = 0.06

of bronchogenic carcinoma. Research on this subject in homogeneous populations should be encouraged. Studies on the possible role of HLA-D/DR types are also needed.

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