**HL-A Antigens in Solid Tumors**

Mitsuo Takasugi, Paul I. Terasaki, Brian Henderson, Max R. Mickey, Herman Menck, and Ronald W. Thompson

**SUMMARY**

The possible association of 23 HL-A specificities with susceptibility to cancer was investigated in a total of 1996 patients and 906 controls. Cancer patients whose cancers were subdivided into the broad location categories of bladder, breast, cervix, colon, endometrium, lung, lymphoma, melanoma, ovary, prostate, rectum, sarcoma, and stomach showed significant departure in some HL-A antigen frequencies from that of controls. In a series of 321 Hodgkin’s disease patients, HL-A5 and W18 antigens were increased. Application of the most conservative statistical correction of p values, however, caused all differences to fall short of statistical significance.

**INTRODUCTION**

Interest derived from observations in animal systems showing linkage of immune responsiveness (5) and host range of oncogenic viruses to histocompatibility (7, 8, 10), has focused considerable attention recently on the association of various diseases with the HL-A specificities (1). Hodgkin’s disease has been the most frequently studied, although many of the reports were inconclusive and contained fewer than 50 patients. Certain antigen frequencies were often noted as being elevated in different Hodgkin’s disease studies. Some antigens of the 4c-HL-A5 complex (6) and HL-A1 (4) were reported to be increased.

In the present study, we have attempted to survey the association of HL-A in a large series of cancer patients. Difficulties in the ethnic and racial stratification of patients and controls were also examined.

**MATERIALS AND METHODS**

A total of 1996 cancer patients and 906 normal individuals, who were tissue typed from May 1971 to August 1972, was included in the study. Because of ethnic and racial differences in the frequencies of HL-A specificities, only typing results for Caucasians were considered, excluding those with Jewish and Mexican surnames. The frequencies of HL-A antigens for normal persons with Jewish and Mexican surnames are shown with controls to illustrate how these frequencies may be influenced by ethnic origin.

HL-A antigens were identified with the use of a panel of 115 highly select antisera defining 23 specificities in the lymphocyte microcytotoxicity test. Comparisons were made by χ² calculations at the University of California Los Angeles Health Sciences Computer Center.

**RESULTS**

The basic data were reduced to frequencies of the 23 HL-A specificities tested (Table 1). Control normals were subdivided into populations by ascertainment methods, care being exercised to eliminate family members, duplicate typings, and those tests on persons with Mexican and Jewish surnames. As can be seen, with increased numbers of individuals in each group, some degree of stability and uniformity in frequencies is obtained. Some obvious deviations attributable to sampling errors from small numbers among normal laboratory personnel can be noted. Even with populations of 100 to 300, 2-fold differences in frequencies are sometimes noted, e.g., in W28, W30, W22, and W13. The higher frequencies of HL-A9, W28, and W30 among parous women and the observation that these antigen frequencies were highest among normal individuals with Mexican surnames may suggest an admixture of Indian genes in this population. If Mexican surnames are used to exclude Indian genes, the exclusion should be more complete among males than among married females.

Further influence of ethnic origins on HL-A antigen frequencies was noted when controls with Jewish surnames were separately tallied. Obviously, the mixture of Caucasoid genes in the United States would preclude separation into areas of origin in Europe. Fortunately, within Europe the differences are not grossly disparate, as shown by a comparison of the frequencies obtained in this study with those obtained in Denmark (4) or France (2).

Among cancer patients, separation into the broad categories of tumor origin has revealed certain significant deviations from control frequencies. However, none of these differences remained statistically significant if the p values were multiplied by the number of specificities tested. If trends are to be sought, this method of correcting p values may be too stringent. The comparisons that yielded p 0.002 to 0.05 are designated by Footnote a in Table 1. In Hodgkin’s disease HL-A5 and W18 were elevated as previously noted (4, 6). W5, on the other hand, was not altered in frequency.

In cervical carcinoma HL-A1 and HL-A12 were increased...
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*a Frequencies with 0.002 < p < 0.05.
relative admixtures of the European HL-A genes. With large
Caucasians in different areas of Europe are now available.

Collaborative study, the frequencies of the various antigens in
Caucasians can be made (11). From a recent international
study, Takasugi et al.
HL-A1 and HL-A12 and higher frequencies of HL-A9. In a
large series of 383 breast cancer patients, the frequency of
HL-A1 was high (32%) in comparison to controls (27%).

The antigen that showed the greatest extremes in deviation
was W5, which was low in bladder, lung, and colon and high in
lymphoma. Some caution must be exercised in interpreting
this result, since W5 is an antigen which has been difficult to
define accurately. Antigens, such as HL-A2, which can be
identified with precision were remarkably stable in frequency
among the different populations. Generally, if one considers
the sources of sampling and potential serological errors, it is
surprising how similar the antigen frequencies are to control
levels. For all cancer patients, only W18 was higher (12%) than
controls (9%) \( p = 0.02 \), uncorrected). Lymphosarcomas show
the highest and lowest extremes in 8 specificities, but this
group also contains the fewest number of patients.

DISCUSSION

One conclusion that can be drawn from this study is that an
outstandingly significant association between HL-A antigens
and susceptibility to the common types of cancer as studied
here does not appear to exist. Since HL-A antigens segregate
precisely as a single locus in families whereas the genetics of
cancer susceptibility is not attributable to simple segregation, a
high association should not be anticipated. In genetic diseases,
such as psoriasis, a strong association together with family
linkage to HL-A has been shown (11). In Hodgkin’s disease the
degree of genetic penetrance does not approach that of
psoriasis, where the risk for 1st-degree relatives is about 4
times as high as in the random population (3).

Similarly, newer approaches are suggested by the recent
discovery in 2 independent studies that the highest HL-A
association with disease occurs in celiac disease, in which 78
and 88% of patients had HL-A1 and HL-A8 in comparison to
33% and 29% in controls (9). If HL-A is linked to
susceptibility to disease, the association can be extremely high.
In the study by Stokes et al., 4 patients had cancers in
addition to celiac disease (3 lymphomas and 1 carcinoma). All
had HL-A1 and HL-A8. The experience with celiac disease shows
that penetrance could be extremely low, for not all
persons with HL-A1 and HL-A8 (about 20% in Caucasians)
have the disease. Obviously, narrower subdivisions of patients
within each tumor classification is one of the next steps. As we
found in psoriasis, some patients may have an inherited disease
or a nongenetic disease that exhibits the same manifestations.

Breakdown of the ethnic background of “Caucasians” has
shown another complicating factor which must be dealt with
in studies such as this. Although previous studies have assumed
that Caucasians are a single group, a clear distinction of Jewish
Caucasians can be made (11). From a recent international
collaborative study, the frequencies of the various antigens in
Caucasians in different areas of Europe are now available.
Studies done in the United States will be influenced by the
relative admixtures of the European HL-A genes. With large
numbers, some stability in the frequencies can, however, be
achieved as shown here.

The increase in frequency of W18 and HL-A5 in Hodgkin’s
patients appears to be genuine. Higher levels of significance
should be reached by elimination of those histological
categories which may not be associated with disturbance of
HL-A frequency (6).

The results obtained are suggestive but need to be
implemented with greater numbers for significance so that
stronger interpretations can be made. Weak associations may
also be strengthened by finer subdivisions of cancer into
smaller more specific categories and other considerations such
as the age of onset and resistance to the disease once it is
contracted. However, smaller and finer subdivisions of cancer
and studies of association with less common HL-A antigens
mean that a much larger total number must be tested before
significant results can be obtained in each category.

ACKNOWLEDGMENTS

We would like to acknowledge the help of Mr. Phillip Arroyo, Mr.
Roger Smith, and Miss Judy Walker for their excellent technical
assistance.

ADDENDUM

A disease with the highest degree of association with HL-A was
recently found in ankylosing spondylitis. Whereas 8% of the controls
had W27, 88% of the patients possessed this antigen (L. Schlosstein, P.
I. Terasaki, R. Bluestone, and C. M. Pearson. High Association of an
in press).

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