HLA Antigens in Cancer of the Gallbladder

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Department of Hygiene and Preventive Medicine, *Department of Internal Medicine I, †Department of Surgery I, Niigata University School of Medicine, Niigata 951, and ‡Prefectural Cancer Center, Niigata Hospital Niigata 951

YAMAMOTO, M., HAGA, M., TAKAGI, S., ENDOH, K., ITO, S., YOSHIDA, K., KATO, K. and AKAI, S. HLA Antigens in Cancer of the Gallbladder. Tohoku J. Exp. Med., 1990, 161(1), 67-71 — Thirty one patients with gallbladder cancer (GBC) and 32 healthy controls were typed using antisera against 12 HLA-A, 31 HLA-B, 7 HLA-C and 13 HLA-DR antigens. The DR4 frequency of 61.3% (19/31) in GBC was significantly different from that of 28.1% (9/32) in the control (p=0.00794 by Fisher’s exact test). The relative risk and the etiologic fraction were 4.0 and 0.46, respectively. —— gallbladder cancer; HLA

The mortality rate for biliary tract cancer (BTC) in Niigata Prefecture is the highest in Japan (Yamamoto et al. 1988). It is shown that the higher incidence of gallbladder cancer (GBC) rather than extrahepatic bile duct cancer may account for the higher mortality for BTC in Niigata (Kato and Akai 1990). In order to explain the geographical clustering of deaths from GBC, extensive studies have been conducted from various aspects in our laboratory (Yamamoto et al. 1986; Magara et al. 1989; Takagi 1990). As a part of our investigations, a preliminary study of HLA typing of the patients is undertaken to search for the presence of genetic difference in susceptibility to the occurrence of GBC. It is of particularly interest to examine the association, since very few associations have been noted in the case of cancer (Anderson 1985) and to our knowledge, an HLA typing in itself has not been undertaken before.

Thirty one patients were extracted from those who were surgically operated in four main hospitals in Niigata Prefecture from 1987 to 1989. The control subjects were selected from our colleagues in the laboratory and employees in a steel-manufacturing company located in Niigata City. The mean ages were 65.6 ± 10.81 (mean ± s.d.) and 43.5 ± 9.90 years old in the GBC and the control groups, respectively. The mean age of the control group was younger than than that in the GBC group. The difference in the age may give a bias, since a control individual has a risk of developing GBC in the future. Nevertheless, in this case, this bias may play a role on minimizing the strength of association, if there is a positive relationship between HLA and GBC.

The HLA antigens were examined by the Terasaki-NIH standard method (Terasaki and McClelland 1964; Terasaki et al. 1978). The HLA specificities were determined using

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antisera as follows: A Locus: A1, A2, A3, A9, A10, A11, A23(9), A24(9), A25(10), A26(10), A31(w19), Aw38(w19), B Locus: B5, B7, B8, B12, B13, B14, B15, B16, B17, B18, Bw22, B27, B35, B38(16), B39(16), B40, B44(12), B45(12), Bw46, Bw48, B51(5), Bw52(5), Bw53(5), Bw54(w22), Bw55(w22), Bw56(w22), Bw59, Bw60(40), Bw61(40), Bw62(15), Bw67, Bw70, C Locus: Cw1, Cw2, Cw3, Cw4, Cw5, Cw6, Cw7, DR Locus: DR1, DR2, DR3, DR4, DR5, DR6, DR7, DR8, DR9, DRw11(5), DRw12(5), DRw13(w6), DRw14(w6).

Statistical analysis of difference in frequencies of phenotypes between the cases and the controls was undertaken by Fisher's exact test of probability. The corrected p value, which is referred to as the value obtained by multiplying Fisher's probability by numbers of antigens examined in each locus, was computed. An estimate of the strength of association between HLA and GBC was made by calculating the values of relative risk and etiologic fraction introduced by Miettinen(1976).

Concerning the HLA-A, B, C antigens, none of them was associated with GBC (the data not shown). The positive association was found only in the DR locus as shown in Table 1. The DR4 frequency of 61.3% (19/31) in GBC was statistically higher than that of 28.1% (9/32) in the control at the probability level of 0.00794 by Fisher's exact test. The corrected p value of 0.0715 did not reach the statistically significant level. The relative risk and its 95% confidence limits were 4.0 and 1.4 to 11.4, respectively. The value of etiologic fraction was 0.46, that is, the HLA-DR4 attributed 46% to the occurrence of GBC in terms of the genetic susceptibility.

Although the values of relative risk and etiologic fraction are high, the present result may indicate a borderline association since the corrected p value does not reach the statistically significant level of 0.05. It is therefore urged to conduct a supplementary investigation by adding more cases of GBC to confirm the present finding and, if a consistent finding is still obtained, inference should be made from the probable mechanism of immune response as an etiological role on occurrence of GBC.

**References**

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