Prevalence of Antibodies to Hepatitis C Virus among Japanese Workers with a History of Blood Transfusion

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We conducted an epidemiological study on prevalence of antibodies to hepatitis C virus (anti-HCV) among Japanese workers with a history of blood transfusion and on risks of blood transfusion for anti-HCV positivity. Of 3,693 workers, 241 (76 males and 165 females) had a history of blood transfusion. For each of these 241 cases, a control, matched for area of residence, sex and age, was selected from those workers who never had blood transfusion. Data on these 482 workers were analyzed. Prevalence of anti-HCV was 12.4% among subjects with a history of blood transfusion and 3.7% among those without (p<0.001). Among subjects with a history of blood transfusion, prevalence of anti-HCV rose with age and was higher in males (19.7%) than in females (9.1%) (p<0.05). Before 1970, most transfused blood was supplied by commercial donors, and prevalence of anti-HCV was much higher among subjects who received blood transfusion before 1970 than among those who received blood transfusion after 1970. A logistic regression analysis was conducted. Adjusted relative risks for anti-HCV positivity were 3.70 (95% confidence interval : 1.71-8.00) for blood transfusion (p<0.001), 1.98 (1.01-3.87) for age (age ≥50 vs age 20-49) (p<0.05), and 1.51 (0.75-3.01) for sex. J Epidemiol, 1995; 5 : 75-80.

Liver cancer is a major health problem in Japan. In 1991, the crude death rate for liver cancer was 31.1 (per 100,000 population) for males and 11.2 for females. In males especially, liver cancer mortality has been gradually increasing year by year; the age adjusted death rate rose from 17.7 in 1970 to 29.5 in 1990(1).

Japan is one of the countries in which hepatitis C virus (HCV) is prevalent. It has been reported that HCV plays the most important role in the development of hepatocellular carcinoma (HCC) and liver cirrhosis in Japan(2-4). Nishioka et al.(2) reported that 76.2% of HCC patients were positive for antibodies to HCV (anti-HCV).

It is recognized that blood transfusion has been the most important route of HCV transmission(5-9). Hayashi et al.(3) reported that 119 anti-HCV positive patients, who were suffering from liver diseases including chronic hepatitis, liver cirrhosis and HCC, 48.7% had a history of blood transfusion.

There have been many papers on the prevalence of anti-HCV among patients with post-transfusion hepatitis(6-9), but few papers on the risk of blood transfusion for anti-HCV positivity among ordinary workers or in the general population.

We compared the prevalence of anti-HCV among workers with a history of blood transfusion to that among workers without. The relative risk of blood transfusion for anti-HCV positivity was estimated with a logistic regression analysis.

SUBJECTS AND METHODS

Subjects of our study were 3,693 workers (1,459 males and 2,234 females) in a supermarket chain who had annual health checkups in 1991. Of the 3,693 workers, 241 (76 males and 165 females) had a history of blood transfusion. For each of these 241 cases, a control, matched for area of residence, sex and age (within 5 years), was selected from those workers who never had blood transfusion.

We took fasting blood samples at the annual health checkups in 1991. In the 482 subjects, anti-HCV was examined by the Ortho-HCV ELISA test (Anti-C100-3). Serum alanine aminotransferase (ALT) was determined.

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Table 1. Proportions of workers with a history of blood transfusion by sex and age.

| Age   | Male     | Female    | Total    |
|-------|----------|-----------|----------|
| 20-29 | 1/ 69 (1.4%) | 1/ 130 (0.8%) | 2/ 199 (1.0%) |
| 30-39 | 12/340 (3.5%) | 8/ 211 (3.8%) | 20/ 551 (3.6%) |
| 40-49 | 39/797 (4.9%) | 90/1,288 (7.0%) | 129/2,085 (6.2%) |
| 50-59 | 15/178 (8.4%) | 53/ 531 (10.0%) | 68/ 709 (9.6%) |
| 60-69 | 9/ 75 (12.0%) | 13/ 74 (17.6%) | 22/ 149 (14.8%) |
| Total | 76/1,459 (5.2%) | 165/2,234 (7.4%) | 241/3,693 (6.5%) |

Table 2. Comparison of prevalence of anti-HCV between subjects with and without a history of blood transfusion.

| HCV antibody | Positive | Negative | Total |
|--------------|----------|----------|-------|
| Blood transfusion (+) | 30 (12.4%) | 211 (87.6%) | 241 (100%) |
| Blood transfusion (−) | 9 (3.7%) | 232 (96.3%) | 241 (100%) |

Note: Statistical significance was observed between subjects with a history of blood transfusion and those without (p<0.001).

RESULTS

1. Percentage of workers with a history of blood transfusion

   As shown in Table 1, of 3,693 workers, 241 (6.5%) had a history of blood transfusion. The percentage of workers with a history of blood transfusion rose with age; from 1.0% in the 20-29 age-group to 14.8% in the 60-69 age-group. The overall percentage was higher in females (7.4%) than in males (5.2%).

2. Prevalence of anti-HCV among subjects with and without a history of blood transfusion

   Table 2 shows a comparison of prevalence of anti-HCV between subjects with a history of blood transfusion and those without. Prevalence of anti-HCV was significantly higher among subjects with a history of blood transfusion (12.4%) than among those without (3.7%) (p<0.001).

   As shown in Table 3, 264 subjects were examined by both the first generation assay and the second generation assay.

Table 3. Comparison of prevalence of anti-HCV obtained using first generation and second generation assays.

| Blood transfusion | First generation | Second generation |
|-------------------|-----------------|------------------|
| (+)               | 12/122 (9.8%)   | 13/122 (10.7%)   |
| (−)               | 6/142 (4.2%)    | 4/142 (2.8%)     |

Note: 264 subjects were examined by both the first generation assay and the second generation assay.

Table 4. Prevalence of anti-HCV among subjects with a history of blood transfusion by sex and age.

| Age   | Male     | Female    | Total    |
|-------|----------|-----------|----------|
| 20-29 | 0/ 1 (0.0%) | 0/ 1 (0.0%) | 0/ 2 (0.0%) |
| 30-39 | 1/12 (8.3%) | 0/ 8 (0.0%) | 1/ 20 (5.0%) |
| 40-49 | 4/39 (10.3%) | 8/ 90 (8.9%) | 12/129 (9.3%) |
| 50-59 | 5/15 (33.3%) | 6/ 53 (11.3%) | 11/ 68 (16.2%) |
| 60-69 | 5/ 9 (55.6%) | 1/ 13 (7.7%) | 6/ 22 (27.3%) |
| Total | 15/76 (19.7%) | 15/165 (9.1%) | 30/241 (12.4%) |

Note: The difference in overall prevalence between males and females was statistically significant (p<0.05).

with an autoanalyser (Hitachi 7350); the upper normal limit for serum ALT was 50 IU/liter.

Of the 482 subjects, 264 had annual health checkups again in 1994, and were examined for anti-HCV using a second generation assay (Ortho HCV Ab Immunoradiometric Assay Test II for anti-C22-3 and anti-C200, Ortho Diagnostic Systems Inc.). None of the 264 had blood transfusion or interferon therapy after previous health checkups in 1991.

We obtained information on blood transfusion, including frequency of blood transfusion, the calendar year in which each blood transfusion was received, the volume transfused, and incidence of post-transfusion hepatitis, at the annual health checkups in 1991. Of the 241 subjects with a history of blood transfusion, 19 had blood transfusions at least twice. In our study, we used information relating to their first blood transfusion.

Adjusted relative risk (RR) of blood transfusion for anti-HCV positivity was estimated by modeling the data through unconditional logistic regression, using the SAS statistical package. Statistical significance was assessed with the chi-square test and Mantel-Haenszel test.
assay, and prevalence of anti-HCV was compared between these two assays. Among those who had a history of blood transfusion, the second generation assay showed a slightly higher prevalence of anti-HCV than the first generation assay (10.7% as against 9.8%); among those with no history of blood transfusion, the prevalence was slightly lower on the second generation assay than on the first generation assay (2.8% as against 4.2%).

3. Prevalence of anti-HCV among subjects with a history of blood transfusion by sex and age

Table 4 shows how the prevalence of anti-HCV among subjects with a history of blood transfusion varied with sex and age. The overall prevalence of anti-HCV was significantly higher in males (19.7%) than in females (9.1%) (p<0.05), and the difference remained statistically significant when adjusted for age. The prevalence of anti-HCV in males rose with age; from 0% in the 20-29 age-group to 55.6% in the 60-69 age-group. However, the prevalence of anti-HCV in females showed no such clear trend; 8.9% in the 40-49 age-group, 11.3% in the 50-59 age-group and 7.7% in the 60-69 age-group, and null in the 20-29 and 30-39 age-groups.

4. Prevalence of anti-HCV by calendar year in which blood transfusion was received

Table 5 shows prevalence of anti-HCV according to the calendar year in which blood transfusion was received. It shows that the prevalence of anti-HCV decreased after 1970. In particular, the prevalence of anti-HCV in males fell from 34.4% before 1970 to 7.7% after 1970. The collection of blood from commercial donors was discontinued in 1969, because post-transfusion hepatitis attributable to blood from commercial donors became a social issue in Japan. Since 1970, all blood for transfusion has been supplied by volunteer donors.

Table 6. Prevalence of anti-HCV among subjects with and without a history of post-transfusion hepatitis.

Note: PTH = Post-transfusion hepatitis
Prevalence of anti-HCV was significantly higher among subjects with a history of post-transfusion hepatitis than among those without (p<0.001).

Table 7. Serum ALT value among subjects with and without a history of blood transfusion.

Note: Parentheses under number of subjects show number of anti-HCV positives.
Overall prevalence of elevated serum ALT (≥ 50 IU/liter) was significantly higher among subjects with a history of blood transfusion than among those without (p<0.001).
5. Prevalence of anti-HCV among subjects with and without a history of post-transfusion hepatitis

Table 6 shows the prevalence of anti-HCV among subjects with and without a history of post-transfusion hepatitis. Prevalence of anti-HCV was significantly higher among subjects with a history of post-transfusion hepatitis (47.1%) than among those without (9.8%) (p<0.001). Prevalence of anti-HCV among subjects with a history of post-transfusion hepatitis was higher in males (62.5%) than in females (33.3%), but this difference was not statistically significant.

6. Serum ALT value and anti-HCV among subjects with and without a history of blood transfusion

As shown in Table 7, the overall prevalence of elevated serum ALT was significantly higher among subjects with a history of blood transfusion (9.5%) than among those without (2.1%) (p<0.001). Among subjects with a history of blood transfusion, prevalence of elevated serum ALT was higher in males (17.1%) than in females (6.1%) (p<0.01). Of the 30 anti-HCV positive subjects with a history of blood transfusion, 7 males (46.7%) and 4 females (26.7%) had elevated serum ALT. In particular, of 6 males with a serum ALT value of more than 100 IU/liter, 5 (83.3%) were anti-HCV positive.

Table 8 shows the prevalence of anti-HCV among subjects with and without a history of post-transfusion hepatitis. Prevalence of anti-HCV was significantly higher among subjects with a history of post-transfusion hepatitis (47.1%) than among those without (9.8%) (p<0.001). Prevalence of anti-HCV among subjects with a history of post-transfusion hepatitis was higher in males (62.5%) than in females (33.3%), but this difference was not statistically significant.

7. Serum ALT value among subjects with and without anti-HCV

As shown in Table 9, prevalence of elevated serum ALT was significantly higher among subjects with anti-HCV (28.2%) than among those without (3.6%) (p<0.001). Non-drinkers were more among subjects with anti-HCV (64.1%) than among those without (51.7%).

8. Adjusted relative risk of blood transfusion for anti-HCV positivity

A logistic regression analysis was conducted to clarify the RR of blood transfusion for anti-HCV positivity. As shown in Table 10, adjusted RRs were 1.51 (95% confidence interval: 0.75-3.01) for sex, 1.98 (1.01-3.87) for age (age ≥50 vs age 20-49) (p<0.05), and 3.70 (1.71-8.00) for blood transfusion (p<0.001).

DISCUSSION

Both hepatitis B virus (HBV) and HCV are prevalent in Japan. It has been noted that in Japan HCV plays a more important role in the development of chronic hepatitis, liver cirrhosis and HCC than HBV. Hayashi et al. reported that the prevalence of HBs antigen and anti-HCV was 30.2% and 36.9% in patients with chronic hepatitis, 24.0% and 49.0% in those with liver cirrhosis, 12.8% and 67.0% in those with HCC. In recent years, liver cancer mortality has been rising sharply in Japan. The recent increase in mortality from liver cancer can be attributed to an increase in HCC with HCV infection.

HCV is parenterally transmitted with blood transfusion, intravenous drug use and so on and has accounted for most post-transfusion hepatitis since the screening test for HBV was introduced. Takano et al. reported that HCV was detected in 62% of cases with post-transfusion hepatitis one year after blood transfusion. Blood transfusion is recognized as a main route of HCV transmission in...
Prevalence of anti-HCV was significantly higher among subjects with a history of blood transfusion (12.4%) than among those without (3.7%). The prevalence of anti-HCV (anti C100-3) was 2.1% among volunteer blood donors in the area where our study was conducted. There was some variation between the sexes, but the overall prevalence of anti-HCV among subjects without a history of blood transfusion did not differ much from that for the volunteer blood donors.

The prevalence of anti-HCV among subjects with a history of blood transfusion increased with age. In particular, high prevalence of anti-HCV was observed in the 50-59 and 60-69 age-groups for males. Of 10 males aged 50-69 with anti-HCV, 9 had received blood transfusion before 1970. As mentioned before, the collection of blood from commercial donors was discontinued in 1969, and since 1970, all blood for transfusion has been supplied by volunteer donors. This may explain why prevalence of anti-HCV was lower among the subjects who received blood transfusion after 1970. Katayama reported that incidence of post-transfusion hepatitis had fallen sharply after exclusion of commercial donors; from 50.9% in 1963-1964 to 14.3% in 1973-1985. Commercial plasma donors were found to have much higher prevalence of anti-HCV than volunteer donors in the US (10.08% vs 0.38%)12). Blood transfusion from commercial donors before 1970 probably contributed to the high prevalence of anti-HCV in males aged 50-59 and 60-69, and the recent increasing male mortality from liver cancer in Japan.

Incidence of post-transfusion hepatitis varies from country to country and over the years. Incidence of post-transfusion hepatitis is known to be higher in Japan than in European countries and the US. Investigating 2,996 blood recipients from 1982 to 1987, Takano et al.7) reported that 22.7% of them developed post-transfusion hepatitis (10.3% definite post-transfusion hepatitis and 12.4% probable). In our study, incidence of post-transfusion hepatitis was low; but this figure may be an underestimate, because our information on post-transfusion hepatitis came only from self-report.

Prevalence of anti-HCV was significantly higher in males than in females among subjects with a history of blood transfusion, while it was lower in males than in females among those without. Therefore, the risks of blood transfusion for anti-HCV positivity were higher in males than in females. Among subjects with a history of post-transfusion hepatitis, prevalence of anti-HCV was also higher in males than in females, though this difference was not statistically significant. Investigating incidence of hepatitis C in acute post-transfusion hepatitis among 1,476 patients with open-heart surgery, Peter et al.6) reported that all cases of acute hepatitis C were found in men. However, Takano et al.7) reported that the incidence of post-transfusion hepatitis is independent of both the age and the sex of the recipient, and instead is dependent primarily on the volume transfused. Volume transfused might explain the difference between males and females in the risk of blood transfusion for anti-HCV positivity. Unfortunately, however, we could not adequately estimate the relationship between the volume transfused and anti-HCV, because information on the volume transfused was available for only a few subjects. Thus the cause of the difference in the risk between males and females remains unclear.

Although subjects with a history of blood transfusion had higher prevalence of elevated serum ALT than those without, the two groups showed little difference in drinking habits. In our previous paper,14) we reported that HCV infection was one of the predominant factors in elevated serum ALT among Japanese workers, while alcohol drinking was a minor factor. Of anti-HCV positive subjects with a history of blood transfusion, 46.7% of males, but only 26.7% of females, had an elevated serum ALT value (more than 50 IU/liter). In particular, of 6 males with a serum ALT value of more than 100 IU/liter, 5 were anti-HCV positive. They might be regarded as having chronic hepatitis. Among cases with anti-HCV, males seem more likely to develop chronic hepatitis than females. These findings are consistent with previous reports.15) Males more often have histories of drinking, and drinking is possibly associated with chronicity in males.16) In addition, there may be some unknown factors which encourage the chronicity more in males than in females.

Since second generation assays were generally unavailable at the 1991 annual health checkups, we used a first generation assay to detect anti-HCV. First generation assays are less sensitive and specific than second generation assays.18) We reexamined anti HCV for 264 subjects who had annual health checkups again in 1994, using a second generation assay. We compared the results obtained with the two assays; the prevalence of anti-HCV found using the second generation assay was slightly higher among subjects with a history of blood transfusion, and slightly lower among those without, than those found using the first generation assay. Therefore, if the second generation assay had been used for all the 482 subjects in our study, the estimated RR of blood transfusion for anti-HCV positivity would presumably have been slightly higher than the 3.70 found with the first generation assay. Investigating 731 patients with chronic hepatitis or liver cirrhosis, Yabuuchi et al.20) reported that adjusted RR for anti-HCV positivity was estimated to be 2.97 for patients with a history of blood transfusion.
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