Epidemiologic study of the relationship between schistosomiasis due to Schistosoma japonicum and liver cancer/cirrhosis

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Abstract. In Yamanashi Prefecture, one of the former areas in Japan endemic for Schistosoma japonicum, there have been no cases of schistosomiasis since 1976. We attempted to find out in this study whether there was still a chronic effect of schistosomiasis, e.g., liver cancer or liver cirrhosis present in this region. The subjects studied were the population in Yamanashi Prefecture from 1973 through 1992. We divided the population into residents in an area endemic for schistosomiasis and those in a nonendemic area. We calculated the standardized mortality ratios (SMRs) for liver cancer and liver cirrhosis in both areas. The schistosome egg-positive rate of liver cancer and liver cirrhosis specimens from the patients in these two endemic areas was also calculated. Male SMRs for liver cancer in the endemic area were 188.5% in 1985 and 188.0% in 1990. Even today, many years after the last case of schistosomiasis, schistosome eggs can be found in the livers of deceased liver cancer and cirrhosis patients. The chronic effect of S. japonicum could contribute to the current high mortality rate for liver cancer in the endemic area, although we need to consider the other etiologic factors of liver cancer, e.g., hepatitis B virus, hepatitis C virus, and alcohol intake.

In the past, there has been a high incidence of Schistosoma japonicum infection, (schistosomiasis japonica) in three areas of Japan: the Chikugo and the Hiroshima-Okayama areas in the western part of Japan, and the Yamanashi area in the eastern part of Japan. Among the three areas, Yamanashi had the largest region (18,000 hectares) in which schistosomiasis japonica was present. However, the incidence of schistosomiasis japonica in these three areas has become much lower because of national and prefectural projects for schistosomiasis prevention and control, including snail control, reduction of water contact and contamination, and improving living standards. In the Chikugo area, no snails that are the intermediate host of S. japonicum have been observed since 1983, and no patients with schistosomiasis have been reported since 1976. Cementing over or enclosing irrigation ditches has led to eliminating schistosomiasis in the Hiroshima-Okayama area. In Yamanashi Prefecture, there have been no patients with schistosomiasis since 1978. In March 1996, the Yamanashi prefectural authority declared that the area was free of schistosomiasis (no longer an endemic area).

The chronic effect of schistosomiasis has been investigated by many researchers. Many believe that liver cirrhosis is the major chronic effect of schistosomiasis japonica. Some researchers suspect that some kinds of cancers, including liver cancer, colorectal cancer, gastric cancer, and esophageal cancer might be the outcome of schistosomiasis japonica. Several studies indicated that hepatitis B virus infection and alcohol ingestion, in addition to schistosomiasis, are also important risk factors for liver cancer.

For these reasons, we should continue to observe schistosomiasis japonica because of its possible chronic effect, even though its acute effect has almost been eliminated. The purpose of this study was to examine the chronic effect of schistosomiasis japonica, i.e., liver cancer and liver cirrhosis, in Yamanashi Prefecture, and to show the possible ongoing problems resulting from this disease.

Materials and Methods

Study populations. The subjects in this study were the population in Yamanashi Prefecture from 1973 through 1992. All activities were conducted in accordance with human subject review policy at the Juntendo University School of Medicine and with the approval of the Ethics Committee at this university. Informed consent was not necessary because the study was retrospective and there was no identification of the persons involved in the study. Yamanashi Prefecture is an inland area located in the mountains on the island of Honshu, Japan. The average temperature is approximately 12°C. Eighty-three percent of the area is covered by forest. The population density of this prefecture was approximately 180 persons/km² in the 1980s, and emigration and immigration rates in this prefecture were among the lowest of the 47 prefectures in Japan. The chief industries in this prefecture were tertiary (service- or commerce-related) ones in the 1970s, but they changed to secondary (manufacturing) ones in the 1990s. More than 20% of the residents of this prefecture were involved in agriculture in 1970s, but only 10% were involved in the 1990s.

The population in this prefecture was divided into two groups, the people in the schistosomiasis-endemic area and those in the schistosomiasis-nonendemic area. The endemic area was defined as the area where there was at least one patient with schistosomiasis japonica from 1960 through 1970, and the nonendemic area was defined as the area where there were no patients with schistosomiasis during the period. The population in the endemic area was approximately 180,000 in 1970s, which was nearly the same as that in the nonendemic area. There was no significant difference in socioeconomic status between the endemic and nonendemic areas of this prefecture (χ² = 0.15, P = 0.93).

Measures. We used the standardized mortality ratio (SMR) to compare the mortality rates for liver cancer and liver cirrhosis in the schistosomiasis-endemic area with those in the nonendemic area. The SMR was also calculated to compare the mortality rate for each disease in 1975 with that in 1990. We obtained the observed number of deaths from liver cancer and from liver cirrhosis in the endemic and nonendemic areas in 1975, 1980, 1985, and 1990 from the Annual Health Statistical Report in Yamanashi Prefecture. The observed number of deaths is the five-year average number of observed deaths. To obtain the expected number of deaths from liver cancer and from liver cirrhosis, age-specific mor-
tality rates for each disease in the standard population and the age-specific population of the endemic and non-endemic areas in each calendar year were obtained. We used the 1960 national population data in Japan as the standard population. The age-specific population in each area in each calendar year was obtained from the Vital Statistics of Japan in each calendar year.

All data from pathologic autopsy cases in Yamanashi Prefecture between 1973 and 1992 were obtained from the Annual of the Pathological Autopsy Cases in Japan from 1972 through 1992. The patient’s address in the Annual is the patient’s final address. The schistosome egg-positive rates of liver cancer/cirrhosis specimens were defined as follows. The schistosome egg-positive rate of liver cancer specimens was the number of egg-positive liver cancer specimens divided by the total number of liver cancer patients. The schistosome egg-positive rate of liver cirrhosis specimens was the number of egg-positive liver cirrhosis specimens divided by the total number of liver cirrhosis patients.

We compared the schistosome egg-positive rates of liver cancer/cirrhosis specimens from the patients in the schistosomiasis-endemic area with those in the schistosomiasis-nonendemic area between 1973 and 1992. We also compared the schistosome egg-positive rate of the liver cancer/cirrhosis patients between 1973 and 1982 with that between 1983 and 1992.

Statistical analysis. The z approximation test was used to compare the observed death rate for liver cancer/cirrhosis with the expected death rate for these diseases (SMR) with 100%. The z approximation test was also used to compare the SMR for liver cancer/cirrhosis in the schistosomiasis-endemic area with that in the schistosomiasis-nonendemic area, or to compare the SMR for each disease in 1975 with that in 1990.

The chi-square test was used to compare the schistosome egg-positive rates of liver cancer/cirrhosis specimens from the patients in the schistosomiasis-endemic area with the rates in the schistosomiasis-nonendemic area, or to compare the schistosome egg-positive rate of liver cancer/cirrhosis patients between 1973 and 1982 with that between 1983 and 1992. However, Fisher’s exact test was used if a calculated expected frequency was less than 2. All data were stored and analyzed using the SAS (SAS Institute, Cary, NC) software version 6 on an IBM (Yorktown Heights, NY) computer.

RESULTS

The SMR for male liver cancer in the schistosomiasis-endemic area was higher than that in the nonendemic area in 1985 and 1990 (Table 1). There was no significant difference between the SMR for female liver cancer in the endemic area and that in the nonendemic area except in 1990 when the SMR in the nonendemic area was significantly smaller (Table 1). The low number of observed cancer deaths in females in 1990 in the nonendemic area was the reason for this significant finding. When we observed the chronologic change of the SMR, we found that the SMR for male liver cancer in the endemic area in 1990 was higher than that in 1975 (127.3% versus 188.6%; z = 2.10, P < 0.05).

The SMR for liver cirrhosis in the schistosomiasis-endemic area was higher than that in the nonendemic area in 1975 and 1990 (males) and in 1980 (females) (Table 2). The difference between the SMR for male liver cirrhosis in 1990 and female liver cirrhosis in 1980 in the endemic area versus the nonendemic area could be due to the low SMR in the nonendemic area rather than the high SMR in the endemic area (Table 2). The SMR for liver cirrhosis in 1990 was smaller than that in 1975 both in the endemic area (males = 198.7% versus 112.4%; z = 3.15, P < 0.005; females = 165.5% versus 95.4%; z = 2.25, P < 0.05) and the nonendemic area (males = 115.1% versus 74.5%; z = 74.5, P < 0.05), but the difference between the SMR for female liver cirrhosis in the endemic area in 1975 and that in 1990 was not significant (100.8% versus 61.7%; z = 1.71).

Table 3 shows that the proportion of liver cancer autopsy cases with S. japonicum eggs was higher in the endemic area than in the nonendemic area. However, the proportion male patients in 1983–1992 in the endemic area was significantly higher compared with the nonendemic area (Table 3). There was no significant difference between the schistosome egg-
positive rate of liver cancer specimens from the patients between 1973 and 1982 and that between 1983 and 1992. Table 4 shows that the proportion of liver cirrhosis autopsy cases with *S. japonicum* eggs was also higher in the endemic area compared with the nonendemic area. The difference was statistically significant in the male patients (Table 4). As in the case of liver cancer specimens, there was, however, no significant difference between the schistosome egg-positive rate of liver cirrhosis specimens from the patients between 1973 and 1982 and that between 1983 and 1992.

**DISCUSSION**

The comparison of two SMRs is a controversial issue because each SMR has different standards. Rothman criticizes the SMR as an appropriate measure for comparison. He states that comparing SMRs amounts to comparing measures with different standards and is invalid, even if the same set of unexposed rates is used in the comparison of the SMRs. However, other researchers have indicated that comparing SMRs is valid. Fukutomi and Hashimoto emphasized that indices have, in addition to mathematical properties, important statistical properties, and that the SMR is numerically close to the comparative mortality rate (CMR) index derived from direct methods, and that this equality is statistically robust. Breslow and Day have indicated that the SMR and the CMR usually provide numerical results that are remarkably similar in practice. We decided to use the SMR for comparison of two mortality rates, accepting the latter point of view because we believe it was practical.

We found that the SMRs for male liver cancer and male liver cirrhosis in the schistosomiasis-endemic area were statistically higher compared with those in the nonendemic area. The study of Inaba and others also showed the same result and they concluded that the higher mortality of liver cirrhosis in Yamanashi Prefecture might have been caused by schistosomiasis, and that of liver cancer might have been caused not only by schistosomiasis, but by other unknown etiologic factors. They also reported that three factors, the presence of hepatitis B surface antigen, a history of schistosomiasis, and daily intake of alcoholic beverages, had been significant in the development of liver cancer and liver cirrhosis. There is no disagreement on this point that schistosomiasis might be associated with these liver diseases.

This study reveals that only males had a high SMR for liver cancer and liver cirrhosis in the schistosomiasis-endemic area. The reason for this could be that boys spend more recreation time in cercariae-infected water than girls. Male adolescents and male adults have more potential exposure to the cercariae during vocational activities, e.g., agricultural work.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Standardized mortality ratio (SMR) for liver cirrhosis in the schistosomiasis endemic area and nonendemic area between 1975 and 1990</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calendar year</strong></td>
<td><strong>Endemic area</strong></td>
</tr>
<tr>
<td></td>
<td>Observed†</td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>1975</td>
<td>63.0</td>
</tr>
<tr>
<td>1980</td>
<td>56.0</td>
</tr>
<tr>
<td>1985</td>
<td>51.0</td>
</tr>
<tr>
<td>1990</td>
<td>56.2</td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>1975</td>
<td>33.6</td>
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<tr>
<td>1980</td>
<td>28.4</td>
</tr>
<tr>
<td>1985</td>
<td>31.6</td>
</tr>
<tr>
<td>1990</td>
<td>31.4</td>
</tr>
</tbody>
</table>

* This observed number of deaths is the five-year averaged observed number of deaths.
† We used the 1960 national population data in Japan as the standard population.
‡ z1 is the z of the z approximation test to compare the observed number of deaths and the expected number of deaths or SMR, with 1.
§ z2 is the z of the z approximation test to compare the SMR in the endemic area with the SMR in the nonendemic area.
¶ P < 0.005.
# P < 0.05.

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<table>
<thead>
<tr>
<th>Table 3</th>
<th>Schistosome egg-positive rate of liver cancer specimens from the patients in the schistosomiasis-endemic area and nonendemic area between 1973 and 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Periods</strong></td>
<td><strong>Endemic area</strong></td>
</tr>
<tr>
<td></td>
<td>Total liver cancer</td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>1973–1982</td>
<td>50</td>
</tr>
<tr>
<td>1983–1992</td>
<td>101</td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>1973–1982</td>
<td>8</td>
</tr>
<tr>
<td>1983–1992</td>
<td>31</td>
</tr>
</tbody>
</table>

* *Schistosoma* (*S.*) egg (+) rate = (*S. egg (+)* liver cancer/total liver cancer) × 100.
† The chi-square test was used to compare the *S. egg (+)* rate of patients in the schistosomiasis-endemic area with that of patients in the nonendemic area.
‡ NS = not significant.
§ The Fisher’s exact test was performed instead of the chi-square test if a calculated expected frequency was less than 2.
activities and construction activities in the water. In fact, the vital statistics of Japan from 1950 to 1980 indicate that the mortality rate for schistosomiasis japonica in Japan has been high in the male population compared with that in females.\textsuperscript{23} A pathologic study showed that there was a higher incidence of liver cirrhosis and liver cancer in male patients with schistosomiasis japonica than in female patients in Yamanashi Prefecture.\textsuperscript{20} Iuchi and Isawa discussed the possibility that the high incidence of liver cirrhosis might be linked to high alcohol intake and malnutrition in males, and the high incidence of liver cancer might be a result of the high incidence of liver cirrhosis. The other reason could be that the acute effects of schistosomiasis might be more lethal in females, and they might not live long enough for cancer or cirrhosis to appear. Many physicians who have treated residents in the endemic area of Yamanashi Prefecture have impression that new residents, such as new wives from other areas who were joining the husband’s family in the endemic area, were more susceptible to schistosomiasis japonica than long-time residents, such as the husbands. This might be the reason that new wives or new residents in the endemic area lack immunity to \emph{S. japonicum} because they had never had been exposed to this parasite. Unfortunately, the data of male and female fatality rates of schistosomiasis in the Yamanashi area are not available.

The SMR for male liver cancer in the schistosomiasis-endemic area in 1990 was higher than that in 1975. The national vital data also showed an increased mortality rate for male liver cancer in Japan over the past 20 years (national population: 121/1,000,000 in 1975, 172 in 1980, 236 in 1985, and 299 in 1990; Yamanashi residents: 207/1,000,000 in 1975, 306 in 1980, 343 in 1985, and 410 in 1990).\textsuperscript{23} This increase could contribute to the increase in the SMR for male liver cancer in the endemic area. However, if we consider the higher SMRs in the endemic area and the high schistosome egg-positive rate in males with liver cancer in this area between 1983 and 1992, it is suspected that the chronic effect of schistosomiasis infection is the additional risk factor for male liver cancer in the endemic area, in addition to the other factors that increase the national mortality rate for male liver cancer, e.g., hepatitis infection or intake of alcoholic beverages. It is also proposed that the higher SMR for liver cirrhosis in 1975 could contribute to this increase in the SMR for male liver cancer in 1990 because liver cirrhosis of any type predisposes one to the development of liver cell carcinoma.\textsuperscript{30}

The present study shows that the SMR for liver cirrhosis in 1990 decreased when compared with that in 1975. The national vital data also indicate no significant increase in the mortality rate for liver cirrhosis in Japan for the past 15 years (national population: 135/1,000,000 in 1975, 141 in 1980, 142 in 1985, and 136 in 1990; Yamanashi residents: 212/1,000,000 in 1975, 169 in 1980, 164 in 1985, and 148 in 1990).\textsuperscript{23}

This study demonstrated the high schistosome egg-positive rate of male liver cancer and cirrhosis in the schistosomiasis-endemic area between 1983 and 1992, although there have been no patients with schistosomiasis japonica in this area since 1978 and no infected snails, the intermediate host of \emph{S. japonicum}, have been found since 1976.\textsuperscript{4} Contrary to our expectations, we cannot statistically confirm the decrease in the schistosome egg-positive rate of liver cancer and liver cirrhosis from 1973–1982 to 1982–1992 in Yamanashi Prefecture. However, there are a few limitations related to the changes in the egg-positive rate. The first limitation is the small size of the sample. A second is possible bias in selecting the autopsy cases. Autopsies are usually done in Japan after the permission of the patient’s family is obtained. Thus, the autopsy rate in Japan varies between 10% and 70–80%. Some characteristics of the pathologic autopsy cases include 1) large-scale medical facilities, e.g., medical school hospitals, perform more autopsies than small hospitals; 2) patients with cancer undergo autopsies more frequently; 3) patients with intractable diseases undergo autopsies more frequently; 4) older patients undergo autopsies less frequently; and 5) male patients undergo autopsies more frequently. Therefore, there was a selection bias for autopsies included in this study.

The current high schistosome egg-positive rate in the schistosomiasis-endemic area could contribute to the high SMR for male liver cancer in the area in 1990. As previously mentioned, several epidemiologic studies by Japanese researchers showed a positive relationship between liver cancer and schistosomiasis japonica, and these findings could explain this contribution.\textsuperscript{5, 9} Several studies have also suggested that the egg or worm itself may affect a liver cell directly and cause the cancer. Amano and Oshima published findings to the effect that hepatoma was formed in mice by

<table>
<thead>
<tr>
<th>Periods</th>
<th>Total</th>
<th>S. egg (+)</th>
<th>S. egg (+) rate (÷100)</th>
<th>Total</th>
<th>S. egg (+)</th>
<th>S. egg (+) rate (÷100)</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1973–1982</td>
<td>70</td>
<td>27</td>
<td>38.6</td>
<td>21</td>
<td>3</td>
<td>14.3</td>
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<tr>
<td>1983–1992</td>
<td>114</td>
<td>36</td>
<td>31.6</td>
<td>57</td>
<td>2</td>
<td>3.5</td>
<td>17.32</td>
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<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1973–1982</td>
<td>14</td>
<td>6</td>
<td>42.9</td>
<td>16</td>
<td>3</td>
<td>18.8</td>
<td>2.07</td>
<td>NS</td>
</tr>
<tr>
<td>1983–1992</td>
<td>52</td>
<td>13</td>
<td>25.0</td>
<td>8</td>
<td>0</td>
<td>0.0</td>
<td>−§</td>
<td>NS</td>
</tr>
</tbody>
</table>

\textsuperscript{* S. japonicum egg (+) rate = (S. japonicum egg positive liver cirrhosis/total liver cirrhosis) × 100.}

\textsuperscript{‡ The chi-square test was used to compare the S. japonicum egg (+) rate of patients in the schistosomiasis-endemic area with that of patients in the nonendemic area.}

\textsuperscript{§ The Fisher’s exact test was performed instead of the chi-square test if a calculated expected frequency was less than 2.}
schistosomes. The promoting effect of schistosomiasis japonica on liver cancer was reported in animal experiments. However, other studies maintain that no correlation had been found between schistosomiasis japonica and liver cancer.

We also need to consider other contemporary factors that could increase the SMR for male liver cancer in the endemic area. As previously mentioned, Inaba and others reported that hepatitis B and daily intake of alcoholic beverages may have contributed to liver cancer. The International Agency for Research of Cancer the World Health Organization has stated that hepatitis B viral infection might confound the association between S. japonicum infection and liver cancer in hospital patients. However, other studies show no significant difference between the hepatitis B surface antigen positive rate of schistosomiasis-infected patients with hepatocellular carcinoma diagnosed histologically and that of patients with hepatocellular carcinoma but not infected with schistosomiasis. One of these studies also showed no significant difference between the volume and duration of the alcohol intake of patients with histologically diagnosed liver disorders with schistosomiasis compared with those without schistosomiasis. Studies have not yet been conducted to find how hepatitis C viral infection affects liver cancer in Yamanashi Prefecture in conjunction with or in addition to schistosomiasis, hepatitis B, and intake of alcoholic beverages. It is possible that the patients with schistosomiasis patients acquired hepatitis C virus when they received chemotherapy involving the intravenous injection of sodium antimonials tartrate (Stibnal); Banyu Pharmaceutical Co., Tokyo, Japan). This drug is an anti-schistosomiasis agent and has not been reported to have hepatotoxicity. The Yamanashi prefectural authority stopped this chemotheraphy in the 1960s because of its strong adverse effects and the long duration of the therapy duration; however, patients infected with hepatitis C virus can have liver cancer due to this virus even after more than 30 years. Further research is needed to determine the relationship between liver cancer and hepatitis C virus in this area.

The actual cause of the current high SMR for liver cancer in the schistosomiasis-endemic area is not known. We believe that the Yamanashi prefectural authority should continue to observe people with a history of schistosomiasis japonica even after the complete eradication of schistosomiasis in the area. The authority continues to measure serum antibody levels for schistosomiasis japonica in 1,000 students in the endemic area and to check for the presence of the snail (intermediate) host of S. japonicum in the area, even though the authority declared the area free of schistosomiasis in 1996.

There are several epidemiological studies by Japanese investigators that showed a positive relationship between liver cancer and schistosomiasis due to S. japonicum. However, present study has some advantages over these studies. One advantage is that the mortality rate (SMR) data for liver cancer/cirrhosis in a schistosomiasis-endemic area was obtained over a much longer period. A second advantage is that the data in the present study are recent. Extended follow-up has shown that the positive relationship between liver cancer and schistosomiasis might continue even more than 10 years after the last patient with schistosomiasis was reported in Yamanashi Prefecture. This long follow-up also makes it possible to assess chronologic changes in the SMRs for liver cancer and cirrhosis in the endemic and nonendemic areas. A third advantage is that this study used the data from pathologic autopsy cases in Yamanashi Prefecture, which provided more direct evidence in support of a positive relationship between schistosomiasis, liver cancer, and cirrhosis.

An estimated 500–600 million people in 75 countries are now exposed to schistosomiasis infection and about 200 million are believed to be infected. Further studies are needed to document the chronic effects of schistosomiasis to relieve these people from the possible terminal illness these effects may cause.

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