Liver Cancer Risk in Japanese Male Dentists: A Long-Term Retrospective Cohort Study

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Abstract: Liver Cancer Risk in Japanese Male Dentists: A Long-Term Retrospective Cohort Study: Hideo Tanaka, et al. Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases—It has been speculated that dentists are at high risk for occupational exposure to bloodborne viruses such as hepatitis B and hepatitis C viruses. To assess the risk of the development of liver cancer among Japanese male dentists, we conducted a retrospective cohort study on 3,314 dentists of the Osaka Dental Association who were members between 1964 and 1985, the year before HBV immunization became available. By linking to the Osaka Cancer Registry, we found that during the period of 1964–1997, 36 of the dentists were diagnosed with liver cancer over a mean follow-up of 23.6 yr. The observed number of liver cancer cases was compared with the expected number, which was calculated by multiplying the number of person-years at risk by the corresponding age- and calendar time-specific incidence rate from the Osaka Cancer Registry data. The male dentists had a significantly lower risk of developing liver cancer than the general population of Osaka (O/E=0.71, 95% CI=0.50–0.98). On subcategorical analysis by birth year or duration of follow-up, there was no significantly increased risk of developing liver cancer among the dentists. Contrary to our expectation, our findings indicate that Japanese dentists were not at increased risk of developing liver cancer compared with the general population.

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Key words: Dentist, Liver cancer, Cancer registry, Incidence, Retrospective cohort study

Japan has one of the highest incidence rates of liver cancer in the world1). Chronic hepatitis B virus (HBV)2) and hepatitis C virus (HCV)3) infections are both risk factors for the development of hepatocellular carcinoma, the dominant histological type of liver cancer. HBV and HCV exist in the saliva of individuals infected with the respective virus4, 5); therefore, before universal precautions for protecting against bloodborne viral transmission were established and HBV immunization became available, dentists may have been at high risk of occupational exposure to such viruses. It has been reported that the prevalence of HBV surface antibody (HBsAb) before the early 1980s and the prevalence of the antibody to HCV among Japanese dentists were higher than those in the general population6–8). We suspected that Japanese dentists were at increased risk of liver cancer.

There has been no well-designed cohort study for assessment of the risk of liver cancer among dentists in Japan. There have only been two assessments on the risk of liver cancer among dentists by using the standardized mortality ratio (SMR) in cross-sectional studies9, 10). These studies reported that the SMR of liver cancer among male dentists was 0.519) and 0.6210), respectively. Niwa10) proposed that one factor that contributes to the lower mortality rate among male dentists is the healthy worker effect, which reduces the mortality risk among occupational populations compared with the general population11). We performed this retrospective cohort study to assess whether the incidence of liver cancer was higher among dentists than among the general population, due to occupational exposure to bloodborne hepatitis viruses. Studies that use the incidence rate may be less influenced by the healthy worker effect than studies that use the mortality rate.

Universal guidelines for protecting dentists against occupational exposure to bloodborne viruses were established in Japan in the late 1980s. A long-term retrospective cohort study is needed to assess the risk of liver cancer among dentists by the year of birth and by
the duration of observation. The Osaka Dental Association is one of the largest professional groups of dentists in Japan, and their membership information is considered to be appropriate to assess the risk of liver cancer among Japanese male dentists in a retrospective study. We therefore chose the subjects in this study from members of the Osaka Dental Association.

**Subjects and Methods**

The cohort comprised members of the Osaka Dental Association who were identified from membership files that were available since January 1, 1960. Each record contains the following information: name, sex, address, birthdate, date of joining the Osaka Dental Association, and date of leaving the Osaka Dental Association. Membership in the Osaka Dental Association expires in the following cases: the dentist moved outside of Osaka Prefecture; the dentist no longer performs dental work for some reason; or the dentist died. We excluded the following individuals from our study: (1) 103 dentists who left the Osaka Dental Association before 1964; (2) 1,814 dentists who joined the Osaka Dental Association after 1985, when HBV immunization became available in Japan; (3) 806 dentists aged 50 yr or older on January 1, 1964, when the data of the Osaka Cancer Registry became available; (4) the 256 female dentists; (5) 357 dentists who resided outside of Osaka Prefecture; and (6) 18 dentists whose date of leaving the Osaka Dental Association was unavailable. Those who were 50 yr old or older on January 1, 1964 were excluded because they would become very old in this long-term follow up period and it might increase the chance of misclassification in diagnosis of cancer. The remaining 3,314 members were eligible for this study. The subjects comprised 1,033 dentists who were alive on January 1, 1964, the date that the data of the Osaka Cancer Registry became available and who had joined as a member of the Osaka Dental Association prior to that date, and 2,281 dentists who had joined the Osaka Dental Association between January 1, 1964 and December 31, 1985. The date of entry into the study of the former group was January 1, 1964, and that of the latter group was the date of joining the Osaka Dental Association.

The subjects were followed up by using the records at the Osaka Cancer Registry, which covers all of Osaka Prefecture, having 8.8 million residents in 1995. It registers cancer cases by using reports from hospitals and clinics, and death certificates collected from the Osaka Prefectural Government. Parameters used in the record linkage were sex, date of birth, name and address (city, ward, town and village). The end of follow-up was the date of leaving the Osaka Dental Association including the date of death, date of diagnosis of liver cancer, or December 31, 1997, whichever occurred first. This study protocol was approved by the Ethical Committee of the Osaka Cancer Registry.

We calculated person-years at risk from the date of entry into the study to the end of follow-up by each individual and accumulated them by five-year age and five-year calendar time. We compared the observed number of liver cancer cases with the expected number. The expected number was obtained by multiplying the number of person-years at risk, stratified by five-year age and five-year calendar time, with the incidence rate of liver cancer among Osaka residents in each corresponding stratum, which were prepared by the Osaka Cancer Registry. Statistical tests of the ratio of observed to expected numbers (O/E ratio) were based on the assumption that the observed number followed a Poisson distribution. If the 95% confidence interval (CI) did not include 1.00, the O/E ratio was considered to be statistically significant (p<0.05). Data analyses were performed with the SAS/PC statistical package (SAS Institute, Cary, NC).

**Results**

The birth year of the 3,314 subjects ranged from 1914 to 1959, and their mean age at the beginning of follow-up was 32 yr (Table 1). During the follow-up period (mean, 23.6 yr), 12 percent (392/3314) of the subjects died and 36 subjects were diagnosed with liver cancer. The total risk of developing liver cancer among the subjects was significantly lower than that among the general population (O/E=0.71, 95% CI=0.50–0.98). When the subjects were divided into 4 groups according to the birth year (1914–24, 1925–34, 1935–44, 1945–59), there were no significantly increased risks of developing liver cancer in the groups compared with the respective group in the general population, although the risk of developing liver cancer among the subjects born in 1945–59 was relatively high (O/E=1.81, O=4, 95% CI=0.49–4.63, Table 1). The subjects born in 1925–34 had a significantly lower risk of developing liver cancer (O/E=0.57, O=14, 95% CI=0.31–0.95). When the subjects were categorized according to the duration of follow-up, there was no significantly increased risk of developing liver cancer in each group compared with the general population (Table 2). Those subjects who were observed for 20 yr or longer had a significantly lower risk of developing liver cancer than the general population (O/E=0.63, 95% CI=0.40–0.95).

**Discussion**

We did not observe an increased risk of liver cancer among the Japanese dentists, as we had suspected before the study. On the contrary, the liver cancer risk was significantly lower among male members of the Osaka Dental Association than among the general population in Osaka (O/E=0.71, 95% CI=0.50–0.98). There was also no significantly increased risk of developing liver cancer.
in each subgroup categorized by birth year or duration of follow-up. There have been a few cohort studies on the morbidity of liver cancer among dentists. In previous studies conducted in Finland\textsuperscript{14} and Sweden\textsuperscript{15}, dentists did not have an increased risk of liver cancer.

As to the causes of liver cancer among males in Osaka prefecture, it has been reported that 15\% of the cases were caused by chronic HBV infection and 75\% were caused by chronic HCV infection\textsuperscript{3}. The prevalence of HBsAb among Japanese dentists was higher than that among the general population, and the difference in the prevalence appeared to be larger in older age groups\textsuperscript{6}. This finding indicates that horizontal HBV transmission from patients continued to occur in Japanese dentists.

The incidence of HBV infection caused by a needle stick injury with exposure to HBV-positive blood without adequate protection was reported to be more than 30\%\textsuperscript{16} in Japan. Nevertheless, the lower probability of chronicity through adult horizontal transmission of HBV genotype C\textsuperscript{17}, which is the dominant genotype (85\%) of HBV in Japan\textsuperscript{18}, may have resulted in the absence of increased risk of HBV-related liver cancer among the study subjects, even though the dentists had a potential risk of HBV infection through occupational exposure.

In the natural history of chronic HCV infection, the interval from HCV transmission to the development of hepatocellular carcinoma is 20 to 40 yr\textsuperscript{19}. Our results, however, did not show increased incidence of liver cancer among dentists who were observed for 20 yr or longer. Toyota\textsuperscript{20} reported that there was no case of seroconversion of antibody to HCV among eight dental workers who had suffered stab accidents on HCV positive patients. Our results together with this previous report on stab accidents in dentistry\textsuperscript{20} support the notion that the probability of HCV transmission into a dentist’s fingertip from the patient’s saliva was low even before universal precautions were established in Japan.

Unfortunately, we could not obtain information on the

### Table 1. Observed number (O), expected number (E) and risk ratio (O/E) of liver cancer among members of the ODA* who were categorized according to birth year

<table>
<thead>
<tr>
<th>Birth year</th>
<th>n</th>
<th>Mean age at the beginning of follow-up (S.D.) (yr)</th>
<th>Mean length of follow-up (S.D.) (yr)</th>
<th>O</th>
<th>E</th>
<th>O/E (S.D.)</th>
<th>Mean age at the time of diagnosis of liver cancer (S.D.) (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1914–24</td>
<td>395</td>
<td>43.4 (3.3)</td>
<td>28.7 (6.6)</td>
<td>13</td>
<td>15.42</td>
<td>0.84 (1.44)</td>
<td>67.9 (7.0)</td>
</tr>
<tr>
<td>1925–34</td>
<td>719</td>
<td>34.4 (3.3)</td>
<td>30.8 (6.4)</td>
<td>14</td>
<td>24.66</td>
<td>0.57 (0.95)</td>
<td>55.3 (7.4)</td>
</tr>
<tr>
<td>1935–44</td>
<td>770</td>
<td>29.6 (4.0)</td>
<td>26.8 (6.1)</td>
<td>5</td>
<td>8.35</td>
<td>0.60 (1.41)</td>
<td>53.2 (3.4)</td>
</tr>
<tr>
<td>1945–59</td>
<td>1,430</td>
<td>28.5 (2.4)</td>
<td>16.8 (4.7)</td>
<td>4</td>
<td>2.21</td>
<td>0.81 (4.63)</td>
<td>45.0 (2.6)</td>
</tr>
<tr>
<td>Total</td>
<td>3,314</td>
<td>31.8 (5.8)</td>
<td>23.6 (8.4)</td>
<td>36</td>
<td>50.64</td>
<td>0.71 (0.98)</td>
<td>58.4 (10.0)</td>
</tr>
</tbody>
</table>

S.D., standard deviation; 95\%CI, 95\% confidence interval; O/E, ratio of observed number to expected number

*Osaka Dental Association

### Table 2. Observed (O) and expected (E) numbers of liver cancer among members of the ODA according to the number of years since the beginning of follow-up

<table>
<thead>
<tr>
<th>Duration of follow-up (yr)</th>
<th>O</th>
<th>E</th>
<th>O/E</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–</td>
<td>0</td>
<td>0.10</td>
<td>0.00</td>
<td>0.00 – 35.38</td>
</tr>
<tr>
<td>1–4</td>
<td>0</td>
<td>0.63</td>
<td>0.00</td>
<td>0.00 – 5.81</td>
</tr>
<tr>
<td>5–9</td>
<td>2</td>
<td>1.72</td>
<td>1.17</td>
<td>0.13 – 4.21</td>
</tr>
<tr>
<td>10–14</td>
<td>4</td>
<td>4.01</td>
<td>1.00</td>
<td>0.27 – 2.55</td>
</tr>
<tr>
<td>15–19</td>
<td>7</td>
<td>7.90</td>
<td>0.89</td>
<td>0.35 – 1.83</td>
</tr>
<tr>
<td>20–</td>
<td>23</td>
<td>36.36</td>
<td>0.63</td>
<td>0.40 – 0.95</td>
</tr>
</tbody>
</table>

C, with the dominant genotype (85\%) of HBV in Japan\textsuperscript{18}, may have resulted in the absence of increased risk of HBV-related liver cancer among the study subjects, even though the dentists had a potential risk of HBV infection through occupational exposure. In the natural history of chronic HCV infection, the interval from HCV transmission to the development of hepatocellular carcinoma is 20 to 40 yr\textsuperscript{19}. Our results, however, did not show increased incidence of liver cancer among dentists who were observed for 20 yr or longer. Toyota\textsuperscript{20} reported that there was no case of seroconversion of antibody to HCV among eight dental workers who had suffered stab accidents on HCV positive patients. Our results together with this previous report on stab accidents in dentistry\textsuperscript{20} support the notion that the probability of HCV transmission into a dentist’s fingertip from the patient’s saliva was low even before universal precautions were established in Japan.

Unfortunately, we could not obtain information on the
history of heavy alcohol drinking in the subjects, which is an independent risk factor for liver cancer.\textsuperscript{21–23} Nevertheless, it is realistic to consider that the prevalence of heavy alcohol drinking among Japanese dentists may be lower than that in the general population because of their professionalism. The lower prevalence of heavy alcohol drinking in the study subjects possibly led to underestimation of the impact of liver cancer risk by occupational factors in the current analysis, although the attributable risk of heavy alcohol drinking on liver cancer is smaller than that of chronic HBV or HCV infection in Japan.\textsuperscript{24} The incidence rate of liver cancer in Osaka is considerably high in Japan,\textsuperscript{25} which is mainly due to the higher prevalence of HCV infection among Osaka residents.\textsuperscript{24} This background might also lead to underestimation of the impact of liver cancer risk by occupational factors in the study.

From the results of this long-term cohort study, we consider that Japanese dentists did not have a higher risk of developing liver cancer than the general population. Our findings also indicate that dentists were not at increased risk of developing chronic HBV or HCV infection even before universal guidelines for protecting against bloodborne viral transmission were established and HBV immunization became available in our country.

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