Autopsy Cases of Lung Cancer and Liver Cancer among Japanese Dentists—A Review of the Annual of the Pathological Autopsy Cases in Japan

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Abstract: Dentists are exposed to carcinogenic metals during their work. It has been speculated that dentists are also at high risk for occupational exposure to bloodborne viruses such as hepatitis B and hepatitis C. We suspected that Japanese dentists were at increased risk for lung and liver cancer. To assess this question, we compared the number of pathological diagnoses of lung cancer and liver cancer among autopsy cases of male dentists (n=225) with that among autopsy cases of male medical doctors (n=1,296), based on data from the Annual of the Pathological Autopsy Cases in Japan from 1992 to 1999. We calculated the mortality odds ratio of lung cancer and liver cancer, using stomach cancer as the control. No difference between the dentist group and the medical doctor group was observed in the pathological diagnoses of lung cancer among all autopsy cases ($p=0.703$, Odds Ratio: 0.846, 95% confidence interval: 0.461–1.554). Liver cancer was observed less often among dentists than among medical doctors ($p=0.047$, Odds Ratio: 0.474, 95% confidence interval: 0.239–0.941). Based on the results of this study, we suggest that Japanese male dentists do not have a higher risk of developing lung cancer than male medical doctors, and have a lower risk of developing liver cancer.

Key words: Dentist, Medical doctor, Lung cancer, Liver cancer, Pathological diagnosis

Introduction

Respiratory dusts are generated at dental clinics during treatment and dental laboratory work^{1–4}. Dental techniques including grinding dental material are included in the role of dentists^{5, 6}. Sakuraba reported large amounts of respiratory dusts and scattered around the operator during treatment². Brune and Fukuzawa reported that respiratory dust, chrome, cobalt and nickel

were generated in the dental laboratory room, and measured the volume^{3, 4, 7–10}. It is assumed that dentists have also been exposed to beryllium during their work as dental technicians^{11, 12}. Beryllium, chromium (VI) compounds and nickel compounds are classified as group 1 (Carcinogenic), and cobalt is classified as group 2B (Possibly Carcinogenic) by IARC^{13–15}. Dentists have inhaled and will inhale the dust of these agents during their work. It has been reported that the dust generated through grinding metallic dental materials caused lung disorders in dentists, dental students and dental technicians^{16–21}. A pathological report of a dental techni-

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cian's lung cancer found metal deposit in his lung²²).

Hepatitis B virus (HBV) and hepatitis C virus (HCV) exist in the saliva of infected individuals^{23, 24}). Dentists may also be at high risk for occupational exposure to such viruses through the saliva. Infection with HCV, as indicated by the presence of antibodies to HCV in serum, appeared to be associated with an increased risk for hepatocellular carcinoma²⁵). Japan Dental Association (JDA) advises their member to be aware of hepatitis virus infection among patients in their dental practices²⁶).

We suspected that Japanese dentists were at increased risk for lung and liver cancer. Previously, we reported from a retrospective cohort study that the risk of lung cancer among male members of the Osaka Dental Association (ODA) was equivalent to that among the general population of Osaka Prefecture, and that the risk of liver cancer was lower than that among the general population of Osaka Prefecture; the number of ODA member was assumed to be 7% of all Japanese dentists during that time period^{27, 28}). In our previous study, we counted numbers of lung and liver cancer cases among ODA members, using the Osaka cancer registration, which is largely based on a clinical diagnosis²⁹). Also in our previous study, we compared ODA members and the general male population in Osaka prefecture, and may thus have underestimated socioeconomic confounding factors^{27, 28}).

To control for socioeconomic factors as a confounding factor in the present study, we counted and compared the number of dentists and medical doctors who had lung cancer or liver cancer by pathological diagnosis from a review of the Annual of the Pathological Autopsy Cases in Japan (hereafter referred to as APAC) from 1992 to 1999. It was assumed that dentists and medical doctors had similar social environments.

In Japan, there were several medical investigations based on APAC^{30–36}). Cases in APAC were recorded from pathological diagnoses by board-certificated pathologists. As is often done in clinical diagnosis, cases identifying metastatic cancer as the primary cancer were excluded. Even if they were not a main cause of death, malignant tumors are recorded as the principal pathological diagnosis on APAC, according to regulation. Tsuda presented the possibility of estimating incidence ratio of cases and controls collected from APAC, through a case control study-like design using a mortality odds ratio (MOR)³⁷). In the present study, we counted the number of lung cancer or liver cancer pathological diagnoses among dentists and medical doctors, based on APAC. Subsequently, we calculated the MOR of lung cancer and liver cancer, using stomach cancer as the control. The MOR method has been used

in several previous studies and is similar to a classical case-control study^{38–42}). We investigated the risk for lung cancer and liver cancer among Japanese dentists using a more precise pathological diagnosis than clinical diagnosis, and controlled for the socioeconomic factor by comparison with medical doctors.

Material and Methods

We reviewed APAC data from 1992 to 1999 in order to count the number of dentists who had lung cancer or liver cancer. There were 147,332 male autopsy cases in this period, and the proportion of cases among all male deaths that underwent autopsies was 3.7%.

From APAC data during these 8 yr, we extracted all male cases whose current or past jobs were dentist (225 cases) or medical doctor (1,297 cases). There was one medical doctor case with no description of age at the time of death, and this case was therefore excluded from our analysis.

Except for metastatic cancer, we counted the number of dentists and medical doctors who had lung cancer (C34), liver cancer (C22) and stomach cancer (C16) in pathological diagnosis based on the 10th International Diagnostic Related Groups (ICD-10). In the present study, we excluded cholangiocarcinoma and intrahepatic cholangiocarcinoma (C22.1) from liver cancer. We compared the proportion of all lung cancer and liver cancer autopsy cases, between the dentist group and the medical doctor group. Subsequently, we calculated the MOR and 95% confidence interval (CI) for cases with lung cancer or liver cancer among male dentists compared with male medical doctors. In a case control study that uses the dying cases as control, the cause of their death that relates to the exposure being researched should be excluded⁴³). In our study, we used stomach cancer as control for calculating MOR.

To control for age as a confounding factor, data were analyzed using the Mantel-Haenszel test. Validity of the ordinary χ^2 test of association for two categorical variables is usually said to require expected values of at least 4 or 5 for each cell⁴⁴). To avoid that limitation, we divided the subjects into 2 stratum in liver cancer and 3 stratum in lung cancer by age for the Mantel-Haenszel test; 2 stratum, below 69 yr of age, and 70 or more years of age; 3 stratum, below 69 yr of age, 70–79 yr of age, 80 or more years of age. We divided the subjects into 4 stratum or less in stomach cancer by age for the Mantel-Haenszel test; 4 stratum, below 59 yr of age, 60–69 yr of age, 70–79 yr of age, 80 or more years of age. Data analyses were performed with the SPSS 15.0J statistical package (SPSS Institute, Tokyo, Japan).

Results

The average age of the dentist group was 68.0 yr and that of the medical doctor group was 69.6 yr. The age distribution of the dentist group had the highest percentages in the 60 to 69 yr age range (27.1%) and the medical doctor group had the highest percentages in the 70 to 79 yr age range (36.0%) (Table 1). There was a significant difference in age distribution between the dentist group and the medical doctor group according to the χ^2 test ($p=0.000$), which was calculated by 7 stratum; 20 to 39 yr age range was recalculated as

the youngest stratum. We compared the proportion of autopsy cases with lung cancer or liver cancer pathological diagnosis (ICD10 Chapter) between the dentist group and the medical doctor group. In both groups, the principal pathological diagnosis, in descending order, was Neoplasms (Chapter 2), Diseases of the Circulatory System (Chapter 9), Diseases of the Respiratory System (Chapter 10) and Diseases of the Digestive System (Chapter 11) (Table 2).

There were 27 dentists (12%) and 141 medical doctors (10.9%) who had lung cancer by pathological diagnosis. No difference was observed between the dentist

Table 1. Age distribution of male dentists and male medical doctors

Age group	20–29 yr	30–39 yr	40–49 yr	50–59 yr	60–69 yr	70–79 yr	80–89 yr	≥90 yr	total
Dentists (%)	1 (0.4)	6 (2.6)	24 (10.7)	22 (9.8)	61 (27.1)	54 (24.0)	50 (22.2)	7 (3.1)	225
Medical doctors (%)	6 (0.5)	29 (2.2)	56 (4.3)	116 (9.0)	379 (29.2)	466 (36.0)	196 (14.8)	48 (3.7)	1,296

*Difference was observed between the age distribution among dentist group and the medical doctor group by χ^2 test ($p=0.000$); Calculating with 7 stratum; 20 to 39 yr age range as the youngest.

Table 2. Number of principal pathological diagnosis by ICD10

Chapter	Blocks	Title	Dentists		Medical doctors	
			number	%	number	%
I	A00-B99	Certain infectious and parasitic diseases	13	5.78	47	3.63
II	C00-D48	Neoplasms	139	61.78	860	66.36
III	D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	5	2.22	7	0.54
IV	E00-E90	Endocrine, nutritional and metabolic diseases	13	5.78	44	3.40
V	F00-F99	Mental and behavioural disorders	1	0.44	0	
VI	G00-G99	Diseases of the nervous system	5	2.22	23	1.77
VII	H00-H59	Diseases of the eye and adnexa	0		0	
VIII	H60-H95	Diseases of the ear and mastoid process	0		0	
IX	I00-I99	Diseases of the circulatory system	61	27.11	369	28.47
X	J00-J99	Diseases of the respiratory system	52	23.11	297	22.92
XI	K00-K93	Diseases of the digestive system	37	16.44	221	17.05
XII	L00-L99	Diseases of the skin and subcutaneous tissue	1	0.44	0	
XIII	M00-M99	Diseases of the musculoskeletal system and connective tissue	5	2.22	16	1.23
XIV	N00-N99	Diseases of the genitourinary system	11	4.89	32	2.47
XV	O00-O99	Pregnancy, childbirth and the puerperium	0		0	
XVI	P00-P96	Certain conditions originating in the perinatal period	0		0	
XVII	Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities	1	0.44	1	
XVIII	R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	0		7	0.54
XIX	S00-T98	Injury, poisoning and certain other consequences of external causes	2	0.89	8	0.62
XX	V01-Y98	External causes of morbidity and mortality	0		2	0.15
XXI	Z00-Z99	Factors influencing health status and contact with health services	0		0	
XXII	U00-U99	Codes for special purposes	0		3	0.23
Number of pathological diagnosis			346	1.54 per person	1,937	1.49 per person
Number of people			225		1,296	

group and the medical doctor group in the proportion of pathological diagnosis of lung cancer among all autopsy cases (Mantel-Haenszel analysis by age class, $p=0.614$, Odds Ratio (OR): 1.151, 95%CI: 0.739–1.794). There were 15 dentists (6.7%) and 148 medical doctors (11.4%) who had liver cancer by pathological diagnosis. Liver cancer was observed less often among dentists than among medical doctors (Mantel-Haenszel test, $p=0.033$; OR: 0.536, 95%CI: 0.309–0.931). There were 28 dentists (12.4%) and 130 medical doctors (10.0%) who had stomach cancer by pathological diagnosis. No difference was observed between the dentist group and the

medical doctors (Mantel-Haenszel test, $p=0.547$, OR: 1.173, 95%CI: 0.759–1.815). (Table 3) There was no lung cancer, liver cancer or stomach cancer cases among the 20–29 yr age group.

We calculated the MOR of lung cancer and liver cancer, using stomach cancer as the control. No difference between the dentist group and the medical doctor group was observed in the lung cancer diagnoses among autopsy cases ($p=0.649$, OR: 0.833, 95%CI: 0.462–1.502) (Table 4a). Liver cancer was observed less often among dentists than among medical doctors ($p=0.043$, OR: 0.470, 95%CI: 0.237–0.930) (Table 5a).

Table 3. Age distribution of lung cancer, stomach cancer and liver cancer among male dentists and male medical doctors

Age group		30–39 yr	40–49 yr	50–59 yr	60–69 yr	70–79 yr	80–89 yr	≥90 yr	total	
Lung cancer	Dentists (%)	0	2 (8.3)	0	6 (9.8)	9 (16.7)	10 (20.0)	0	27 (12.0)	*]
	Medical doctors (%)	1 (3.4)	4 (7.1)	7 (6.0)	36 (9.5)	61 (13.1)	24 (12.2)	8 (16.7)	141 (10.9)	
Liver cancer	Dentists (%)	0	2 (8.3)	3 (13.6)	4 (6.6)	6 (11.1)	0	0	15 (6.7)	†]
	Medical doctors (%)	1 (3.4)	2 (3.6)	18 (15.5)	65 (17.2)	50 (10.7)	11 (5.6)	1 (2.1)	148 (11.4)	
Stomach cancer	Dentists (%)	0	1 (4.2)	4 (18.2)	6 (9.8)	9 (16.7)	8 (16.0)	0	28 (12.4)	‡]
	Medical doctors (%)	3 (10.3)	6 (10.7)	11 (9.5)	33 (8.7)	58 (12.4)	15 (7.7)	4 (8.3)	130 (10.0)	

*No difference was observed between the dentist group and the medical doctor group in the proportion of pathological diagnosis of lung cancer using the Mantel-Haenszel test categorized into 3 groups, 69 yr of age and younger, 70–79 yr, 80 yr old and older ($p=0.614$).

(Odds ratio : 1.151, 95% confidence interval: 0.739–1.794)

†Liver cancer was observed less often among dentists than among medical doctors using the Mantel-Haenszel test categorized into 2 groups, 69 yr of age and younger, 70 yr old and older. ($p=0.033$).

(Odds ratio : 0.536, 95% confidence interval: 0.309–0.931)

‡No difference was observed between the dentist group and the medical doctor group in the proportion of pathological diagnosis of stomach cancer using the Mantel-Haenszel test categorized into 4 groups, 59 yr of age and younger, 60–69 yr, 70–79 yr, 80 yr old and older.

($p=0.547$). (Odds ratio : 1.173, 95% confidence interval: 0.759–1.815)

(%) Proportion of the cancer among subjects in that age group.

There is no lung cancer, liver cancer or stomach cancer among the 20–29 yr age group.

Table 4. Age distribution of Lung cancer and Stomach cancer among male dentists and male medical doctors for MOR (4a).

4b shows the same distribution excluding subjects who had both lung cancer and stomach cancer.

4a*						4b†					
Age group		≤69 yr	70–79 yr	≥80 yr	total	Age group		≤69 yr	70–79 yr	≥80 yr	total
Lung cancer	Dentists	8	9	10	27	Lung cancer	Dentists	8	9	8	25
	Medical doctors	48	61	32	141		Medical doctors	47	56	31	134
Stomach cancer	Dentists	11	9	8	28	Stomach cancer	Dentists	11	9	6	26
	Medical doctors	53	58	19	130		Medical doctors	52	53	18	123

*No difference between the dentist group and the medical doctor group was observed in the lung cancer diagnoses among autopsy cases using the Mantel-Haenszel test categorized into 3 groups, below 69 yr, 70–79 yr, 80 yr old and older. ($p=0.649$)

(Odds ratio : 0.833, 95% confidence interval: 0.462–1.502)

†No difference between the dentist group and the medical doctor group was observed in the lung cancer diagnoses among autopsy cases using the Mantel-Haenszel test categorized into 3 groups, below 69 yr, 70–79 yr, 80 yr old and older. ($p=0.703$)

(Odds ratio : 0.846, 95% confidence interval: 0.461–1.554)

Table 5. Age distribution of Liver cancer and Stomach cancer among male dentists and male medical doctors for MOR (5a). 5b shows the same distribution excluding subjects who had both liver cancer and stomach cancer

5a*					5b†				
	Age group	≤69 yr	≥70 yr	total		Age group	≤69 yr	≥70 yr	total
Liver cancer	Dentists	9	6	15	Liver cancer	Dentists	9	6	15
	Medical doctors	86	62	148		Medical doctors	85	55	141
Stomach cancer	Dentists	11	17	28	Stomach cancer	Dentists	11	17	28
	Medical doctors	53	77	130		Medical doctors	52	70	122

*Liver cancer was observed less often among dentists than among medical doctors using the Mantel-Haenszel test categorized into 2 groups, below 69 yr, 70 yr old and older. ($p=0.043$)

(Odds ratio : 0.470, 95% confidence interval: 0.237–0.930)

†Liver cancer was observed less often among dentists than among medical doctors using the Mantel-Haenszel test categorized into 2 groups, below 69 yr, 70 yr old and older. ($p=0.047$)

(Odds ratio : 0.474, 95% confidence interval: 0.239–0.941).

Two dentists had both primary lung cancer and primary stomach cancer. No dentist had both primary liver cancer and primary stomach cancer. Seven medical doctors had both primary lung cancer and primary stomach cancer. Eight medical doctors had both primary lung cancer and primary stomach cancer. Excluding those case, we also calculated the MOR of lung cancer and liver cancer, using stomach cancer as the control. Again, no difference between the dentist group and the medical doctor group was observed in the lung cancer diagnoses among autopsy cases ($p=0.703$, OR: 0.846, 95%CI: 0.461–1.554) (Table 4b). Liver cancer was observed less often among dentists than among medical doctors ($p=0.047$, OR: 0.474, 95%CI: 0.239–0.941) (Table 5b).

No case had multiple primary lung cancers or multiple primary liver cancers. One medical doctor had double primary stomach cancer; for calculating the MOR, we counted this as one stomach cancer case.

Discussion

In the present study, we compared the proportion of the disease and calculated MOR based on pathological diagnosis, which should provide a more reliable estimate than based on clinical diagnosis. Pathological diagnosis is considered to be more exact and reliable than a clinical diagnosis^{33, 45}, and can often detect occult cancers that are missed when diagnosis is based on clinical symptoms^{30, 46}.

In Japan, there were several medical investigations based on APAC. However, with the use of APAC, there are some limitations in our study. Yamamoto assumed that cases in APAC were not extracted through random sampling, but instead were extracted from a population with death caused by several disease, each with its own individual extracting rate³³. Cases on APAC are almost always reported from hospitals at which a board

certified pathologist belonging to the Japan Association of Pathology is working. Therefore, selection bias can occur because the cases in APAC are presented under the informed consent by relatives of deceased for pathological autopsy by the medical doctor. It is assumed that cases with lung cancer and liver cancers selectively undergo pathological autopsy more often cases with other disease⁴⁵.

Since 2000, in APAC, occupation status of the cases has been transcribed by categories, and it has been impossible to distinguish the case of dentists from those of medical doctors. Until 1999, APAC had depended on the pathological report description of the past occupation of the dentists or medical doctors; for example retired dentists, retired medical doctor or unemployed. It is assumed that neither medical doctors in the past nor dentists in the past were transcribed as unemployed as their pathological reports were far less likely to describe their occupations as unemployed compared to the reports of other people's past occupations. In our study, we compared the dentists with medical doctors, both of which were extracted from APAC by the same method; therefore, it was assumed that the healthy worker effect, if it occurred, was not large⁴⁷.

Both in dentists and medical doctors, the most frequent principal pathological diagnosis was Neoplasms (Chapter 2; 61.8%, 66.4%). In this study, we did not investigate the pathological diagnosis of whole male autopsy cases from APAC. Tomioka counted pathological diagnosis of 1,806 male autopsy cases extracted from APAC, and found malignant neoplasm in 63% (1,151/1,806). The frequency of pathological diagnosis among whole male cases might be similar to the male dentist cases or male medical doctors.

In this study, we compared cases with lung cancer and liver cancer in dentists and medical doctors by a case control study-like method using MOR. In the case control study, overlap among the case group and

the control group was not allowed. For calculating the MOR, we excluded cases that had both lung cancer and stomach cancer, or liver cancer and stomach cancer; there was no clear difference regardless of whether cases were excluded or not excluded (Tables 4a, 4b, 5a, 5b).

It was assumed that dentists and medical doctors had similar social environments. Until 2005, only dentists and medical doctors were required to study 6 yr of school coursework to get a license in Japan. In Japan, the occupational prestige score of dentists and medical doctors are same^{48, 49}. We assumed that there was no difference in socioeconomic factors among dentists and medical doctors.

Based on the results of this study, Japanese dentists do not have a higher risk of developing lung cancer than medical doctors. This result is compatible with our past findings²⁷. Ikuta studied the insurance bill data on the Tokyo Dental Association (TDA) members and showed that the Standardized Mortality Ratio (SMR) of lung cancer was 0.96; the study was compared with the Tokyo male population, the Japanese male working population and the Japanese male population⁵⁰. Niwa examined similar insurance bill data on the JDA members, and showed that the SMR of lung cancer was 0.71; the study was compared with the Japanese male population⁵¹. In previous studies conducted in Finland⁵² and Sweden⁵³, dentists did not have an elevated risk for lung cancer; the Finnish study was compared with the general working population and the Swedish study was compared with general population. Our results agree with the findings of these studies. Tomioka, using APAC data from 1980 to 1984, reported that there have been less pathological diagnoses of trachea, bronchus and lung cancer in medical doctors compared with the general population³¹.

The present study showed that the proportion of liver cancer among male dentists was significantly lower than that among medical doctors, based on APAC data. Ikuta studied the data of the TDA members by insurance bills and showed that the SMR of liver cancer was 0.51⁵⁰. Niwa examined similar data of the JDA members by insurance bills and showed that the SMR of liver cancer was 0.62⁵¹. Again, our results agree with the findings of these studies. In previous studies conducted in Finland⁵² and Sweden⁵³, dentists did not have an elevated risk for liver cancer. Few reports are known about mortality or incidence among Japanese dentists. Tomioka, using APAC data from 1980 to 1984, reported that there might have been more pathological diagnoses of liver disease in medical doctors compared with the general population, but no significant difference was seen in the rate of liver cancer³¹.

Regarding 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 infection⁵⁴. It has been said that both medical doctors and dentists have higher infection rates of HBV and HCV than the general population, but large-scale investigations have not been reported^{55, 56}. Toyota reported that there was no case of seroconversion of HCV antibody among eight dental workers who had suffered stab accidents while working on HCV positive patients⁵⁷. Our results, together with this previous report on stab accidents in dentistry, 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. On the contrary, there were no reports on how often transmission of HCV virus has occurred in dentists whose clinical practice included treatment of patients with HCV.

Based on the results of this study, we suggest that Japanese male dentists have a lower risk of developing liver cancer than medical doctors. The reason for this lower incidence of liver cancer among dentists is unknown. There is a difference in the prevalence of liver cancer between eastern and western Japan, but differences in distribution of the areas of residence between dentists and medical doctors whom we investigated were not seen⁵⁴.

The smoking prevalence of male members of Hyogo Dental Association in 1997 (38.5%) was lower than that of the general population, and it was assumed that the smoking prevalence of male medical doctors in 2000 (27.1%) was also lower than that of general population^{58, 59}. Kaetsu reported that the smoking prevalence of male physicians in Fukuoka was 43.4% in 1983⁶⁰. There are few medical reports that suggested the smoking prevalence of dentists or medical doctors in 1970s and 1980s might have affected the autopsy cases of lung cancer such as those that were observed in the present study.

It has also been reported that both medical doctors and dentists drink less than the male general population^{61, 62}. Takei reported that the proportion of frequent drinkers among dental students (16.1%), who drink every other day or more, was more than that among other college students (9.7%)⁶³. However, there are few medical reports that suggest the drinking habits of dentists or medical doctors in the 1970s and 1980s might have affected the autopsy cases of liver cancer such as those that were observed here.

In the present study, we excluded cholangiocarcinoma and intrahepatic cholangiocarcinoma (C22.1) from liver cancer. It has been reported that HCV related cirrho-

sis is a risk factor for primary cholangiocellular carcinoma of the liver (PCC-L) in Japanese patients^{64, 65}. However, it is assumed that the risk factors for PCC-L have not been fully investigated. In the present study, no dentist or medical doctor had hepatic hemangiosarcoma (C22.3).

Conclusion

Based on data from the APAC from 1992 to 1999, it is suggested that Japanese male dentists do not have a higher risk of developing lung cancer than male medical doctors, and have a lower risk of developing liver cancer than male medical doctors.

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