

## Tooth brushing, tooth loss, and risk of upper aerodigestive tract cancer: a cohort study of Japanese dentists

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### ABSTRACT

Previous studies have focused on the association between poor oral health and upper aerodigestive tract (UADT) cancer. However, whether toothbrushing and tooth loss are associated with UADT cancer risk is still unclear. Therefore, we investigated the association between toothbrushing or tooth loss and UADT cancer in the Longitudinal Evaluation of Multi-phasic, Odontological, and Nutritional Associations in Dentists (LEMONADE) cohort study. From 2001 to 2006, we recruited 20,445 dentists (mean age  $\pm$  standard deviation, 51.8  $\pm$  12.0 years; 1,607 women [7.9%]) and followed for incidence or mortality of UADT cancer through March 2014. Information on lifestyle and oral health was collected by the baseline questionnaire. The Cox proportional hazards model was used to estimate hazard ratios (HRs) for UADT cancer and corresponding 95% confidence intervals (CI) for brushing frequency and tooth loss with adjustment for covariates. During the mean follow-up of 9.5 years, we confirmed 62 incident or fatal cases of UADT cancer. Infrequent toothbrushing (< 2 times/day) was significantly associated with increased risk of UADT cancer (multivariate HR = 2.13, 95% CI: 1.04–4.37). On the contrary, tooth loss was not significantly correlated with UADT cancer risk; multivariate HR was 1.03 (95% CI: 0.41–2.61) for loss of 15–27 teeth and 1.37 (0.50–3.75) for that of 28 teeth compared to tooth loss of 0–14 teeth. In conclusion, infrequent toothbrushing was significantly associated with the risk of UADT cancer.

Keywords: toothbrushing, tooth loss, oral health, head and neck cancer, cohort study

#### Abbreviations:

UADT: upper aerodigestive tract

JDA: Japan Dental Association

HR: hazard ratio

CI: confidence interval

SD: standard deviation

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Received: October 6, 2020; accepted: November 16, 2020

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## INTRODUCTION

Upper aerodigestive tract (UADT) cancer (including cancers of the lip, oral cavity, oropharynx, hypopharynx, larynx, and esophagus) is the sixth most prevalent cancer worldwide.<sup>1</sup> The incidence rates of UADT depend on ethnicity and region,<sup>2-5</sup> but its incidence and mortality have been increasing in both developed and developing countries.<sup>3</sup> In Japan, more than 40,000 new cases and 19,000 deaths owing to UADT cancer (International Classification of Diseases and Related Health Problems, 10th revision [ICD-10] code C00-15) are reported each year, and the incidence rates have increased by five times between 1979 and 2014.<sup>6</sup> Using 2012 as a baseline, the projected burden of lip and oral cavity cancer (ICD-10 C00-08) by 2030 is estimated to increase among men and women by 59.5% and 62.3%, respectively, in developing countries, compared with an estimated increase by 21.6% and 22.1%, respectively, in developed countries.<sup>3</sup> Esophageal cancer has followed a similar increasing trend.<sup>7,8</sup>

In recent years, the prevention of UADT cancer has been a World Health Organization priority for action. UADT cancer may cause burdens to individuals and communities, such as pain and suffering, functional impairment, and a reduced quality of life. The current incidence of UADT cancer is particularly high among older people, as well as disadvantaged and poor populations, and has a significant negative impact on their quality of life.<sup>9,10</sup>

Identifying modifiable risk factors is an important task in preventing UADT cancer. Tobacco and alcohol consumption are well established as major risk factors for UADT cancer.<sup>3</sup> Previous studies have suggested that genetic factors,<sup>2,11,12</sup> periodontal disease,<sup>4,11,13-15</sup> human papillomavirus infection,<sup>16,17</sup> tooth loss,<sup>5,11,18-21</sup> and poor oral hygiene<sup>4,5,16,19-23</sup> increase the risk of UADT cancer.

Dental plaque causes periodontal disease and tooth loss, and removing dental plaque by tooth brushing is effective in improving oral hygiene and preventing dental disease.<sup>24,25</sup> The evidence regarding periodontal disease has led to the hypothesis that tooth brushing plays a role in the prevention of UADT cancer. Several studies have investigated the association between tooth brushing and the risk of UADT cancer.<sup>4,5,19-21,23,26-28</sup> However, most studies have been conducted using a case-control design and the findings are inconsistent. In Japan, only one case-control study<sup>29</sup> reported that a decreased risk for UADT cancer was significantly associated with the frequency of brushing twice a day.

In this cohort study, we primarily aimed to investigate the effects of tooth brushing on the incidence of UADT cancer. We also examined the associations between tooth loss and the risk of UADT cancer.

## PARTICIPANTS AND METHODS

### *Study population and data collection*

This study is part of the Longitudinal Evaluation of Multi-phasic, Odontological, and Nutritional Associations in Dentists (LEMONADE) cohort study.<sup>30-33</sup> Members of the Japan Dental Association (JDA) were invited to participate in this study, and 21,272 of 58,792 members in 46 prefectures who received a questionnaire returned valid responses (response rate, 36.2%). The baseline survey was conducted between February 2001 and July 2006. The questionnaire included questions about medical history (such as a history of physician-diagnosed stroke or diabetes), oral health, and lifestyle factors (such as diet and smoking and drinking habits). Questions related to oral health included brushing frequency and the number of teeth lost (excluding third molars). The brushing frequency was determined by the question, "How often do you brush your teeth a day?" and responses were categorized into four groups: "none or once a day", "twice a day",

“three times a day”, or “four or more times a day”. The number of teeth lost, except for the loss of third molars, was classified in two ways—0–14, 15–27, or 28 teeth and 0–9, 10–19, or 20–28 teeth—to examine the effect of categorization. The interdental cleaning frequency was assessed using the question, “How often do you use an interdental cleaning instrument?” and responses were categorized into four groups: “less than once a week”, “1–2 times/week”, “3–4 times/week”, or “5 times/week or more”. The scaling frequency was elucidated using the question, “How often do you have dental tartar removed?” and responses were classified into four groups: “less than once a year”, “1–2 times/year”, “3–5 times/year”, or “6 times/year or more”. Smoking habits were determined with the question, “Have you ever smoked almost daily for at least 1 year?” and responses were categorized into five groups: “never smokers”, “former smokers”, “0–19 cigarettes/day”, “20–39 cigarettes/day”, and “≥ 40 cigarettes/day”. Similarly, alcohol consumption was evaluated with the question, “Have you ever consumed alcohol at least once a month for at least 1 year?”. Ethanol intake was estimated based on the reported frequencies and amounts consumed for six types of alcoholic beverages. The respondents were categorized into five groups: “never drinkers”, “former drinkers”, “0–199 g/week”, “200–399 g/week”, or “≥ 400 g/week”.

We followed up annually with study participants until the end of March 2014, except for those in two prefectures with an earlier finish date (December 2010 or March 2012) and those in three prefectures with a later finish date (March 2015). The mortality and morbidity data were accumulated based on information from the fraternal insurance program of the JDA and prefectural dental associations.<sup>33</sup> Morbidity data were not available in 2 of the 46 prefectures. Of the 21,272 respondents, we excluded 15 with missing information on brushing frequency or tooth loss, 14 with inconsistent follow-up information, and 798 with a history of cancer, leaving 20,445 dentists included in the present study.

In this study, UADT cancer was defined as cancer of the lip (ICD-10 code C00), base of tongue (C01, C02), gum (C03), floor of mouth (C04), palate (C05), other and unspecified parts of mouth (C06), oropharynx (C10), hypopharynx (C13), and esophagus (C15). Malignant neoplasms of salivary glands (C07 and C08), tonsil (C09), pyriform sinus (C12), and nasopharynx (C11 and C14) were excluded, in accordance with previous studies.<sup>4,5,18,20-22,26-28,29,34-36</sup> UADT cancer cases recorded on death certificates were included in the analysis, if no data on the incidence were available for the cases.

Written informed consent for participation was obtained from all eligible respondents. The ethics committees of the Nagoya University Graduate School of Medicine and the Aichi Cancer Center (a former affiliation of the principal investigator) approved the protocol of the LEMONADE Study.

### *Statistical Analysis*

We calculated the follow-up period for each participant from baseline to the date of UADT cancer diagnosis, death from any cause, loss to follow-up, or the end of follow-up (March 2014), whichever came first. Among participants included in the present analysis, 553 (2.7%) were lost to follow-up. As a sensitivity analysis, we performed analyses excluding those without a 1-year follow-up. The first year of follow-up was left out of the risk period.

To compare the characteristics at baseline among the groups according to tooth brushing frequency, the chi-squared test was used for categorical variables and the Kruskal–Wallis test was applied for continuous variables. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for UADT cancer according to brushing frequency and the number of teeth lost. In accordance with previous studies, those who brushed twice a day was set as a reference group.<sup>18,20,21,23,35,37,38</sup> Age (years) and sex were

considered predefined confounders (Model 1). Other factors included in the models were smoking history and alcohol consumption (Model 2) and tooth brushing frequency or the number of teeth lost (Model 3). Further adjustment for frequencies of interdental cleaning and scaling was made for statistically significant findings. We also estimated the HRs and corresponding 95% CIs for esophageal cancer (the most common UADT cancer) according to brushing frequency and the number of teeth lost. The *P* values for trend were computed by including ordinal variables in the Cox proportional hazards models; 0, 1, 2, and 3 for the four groups of brushing frequency and 0, 1, and 2 for the three categories of number of teeth lost.

We also examined the association of smoking and drinking habits with the risk of UADT using a proportional hazards model with adjustment for sex, age, and smoking and drinking habits. *P* for trend was calculated by assigning 0, 1, 2, 3, and 4 to a variable for five categories of smoking or drinking, and including the variable in the hazard model for smoking or alcohol drinking. Two-sided *P* values < 0.05 were considered statistically significant. Analyses were performed using the Stata 13.1 statistical software package (StataCorp, College Station, TX, USA).

## RESULTS

For the 20,445 participants included in our analysis, the mean age was 51.8 years (standard deviation [SD], 12.0 years; range, 26–98 years). The percentage of respondents aged < 40, 40–49, 50–59, 60–69, and ≥ 70 years was 13.3%, 35.3%, 29.3%, 12.1%, and 10.0%, respectively. There was a total of 1,607 (7.9%) female dentists, and the proportion was nearly the same as that for all JDA members at the time of the baseline survey (8.0% in 2009).

Table 1 shows the baseline characteristics of study participants according to brushing frequency category. Those who brushed teeth once a day or less were likely to be older and have fewer teeth than those who did so more than twice a day. Additionally, those who brushed teeth once a day or less were more likely to be a former or current smoker. The proportion of current drinkers was somewhat lower among respondents who reported brushing their teeth once a day or less.

During the mean follow-up period of 9.5 years, we confirmed 62 incident or fatal cases of UADT cancer (11 oral cancers, 10 pharyngeal cancers, and 41 esophageal cancers) in 193,489 person-years. For 3 of the 62 cases, data on the incidence were unavailable; these cases were registered based on information from death certificates. Participants who brushed their teeth once a day or less at baseline demonstrated a significantly increased risk of UADT cancer compared with those who brushed twice a day (multivariate HR in model 3 = 2.13 [95% CI: 1.04–4.37], *P* trend = 0.22) (Table 2). The risk of UADT cancer was significantly increased even after adjustment for frequencies of interdental cleaning and scaling (HR = 2.42 [95% CI: 1.17–5.01] for brushing less than twice a day, *P* trend = 0.12). When excluding those without a 1-year follow-up from the baseline survey, the HR of brushing teeth less than twice a day was 1.86 (95% CI: 0.89–3.88, *P* trend = 0.36). The HR for esophageal cancer in all respondents showed a similar association, although it was not statistically significant (HR = 1.92 [95% CI: 0.80–4.61] for less than twice a day, *P* trend = 0.35) (Table 3).

We did not find a statistically significant association of tooth loss with the risk of UADT cancer. The multivariate HR in model 3 was 1.03 (95% CI: 0.41–2.61) for the loss of 15–27 teeth and 1.37 (95% CI: 0.50–3.75) for the loss of 28 teeth, relative to the loss of 0–14 teeth (Table 4). Comparing the loss of 10–19 and ≥ 20 teeth with the loss of 0–9 teeth produced HRs of 1.14 (95% CI: 0.45–2.87) and 1.10 (95% CI: 0.46–2.62), respectively. Excluding those without a 1-year follow-up did not essentially alter the findings of no significant association between tooth loss and UADT cancer risk.

## Tooth brushing and risk of UADT cancer

**Table 1** Characteristics of participants according to brushing frequency category

	Brushing frequency (times/day)								<i>P</i>
	≤ 1 (n = 2804)		2 (n = 6078)		3 (n = 8483)		≥ 4 (n = 2864)		
Age (years ± SD)	55.5 ± 13.9		51.2 ± 11.5		50.2 ± 11.2		53.0 ± 11.1		< 0.001
Sex, n (%)									
Men	2694	(96.1)	5740	(94.4)	7652	(90.2)	2555	(89.2)	< 0.001
Women	110	(3.9)	338	(5.6)	831	(9.8)	309	(10.8)	
Smoking, n (%)									
Never	788	(28.4)	1914	(31.7)	3504	(41.7)	1135	(40.0)	< 0.001
Former	1033	(37.2)	2038	(33.8)	2855	(34.0)	961	(33.9)	
Current	959	(34.5)	2080	(34.5)	2051	(24.4)	741	(26.1)	
< 20 cigarettes/day	270	(9.7)	598	(9.9)	729	(8.7)	240	(8.5)	< 0.001
20–39 cigarettes/day	555	(20.0)	1283	(21.3)	1146	(13.6)	432	(15.3)	
≥ 40 cigarettes/day	131	(4.7)	190	(3.2)	172	(2.1)	65	(2.3)	
Drinking, n (%)									
Never	663	(24.0)	1194	(19.7)	1663	(19.7)	575	(20.2)	< 0.001
Former	121	(4.4)	189	(3.1)	236	(2.8)	103	(3.6)	
Current	1,983	(71.7)	4663	(77.1)	6530	(77.5)	2163	(76.1)	
< 200 g/week	981	(35.5)	2466	(40.8)	3697	(43.9)	1171	(41.2)	< 0.001
200–399 g/week	476	(17.2)	1051	(17.4)	1439	(17.1)	522	(18.4)	
≥ 400 g/week	418	(15.1)	867	(14.3)	1074	(12.7)	347	(12.2)	
Consumption unknown	108	(3.9)	279	(4.6)	320	(3.8)	123	(4.3)	
Number of teeth lost, n (%)									
0–14	2330	(83.6)	5742	(94.9)	8063	(95.5)	2698	(94.7)	< 0.001
15–27	173	(6.2)	239	(4.0)	282	(3.3)	125	(4.4)	
28	284	(10.2)	69	(1.1)	102	(1.2)	27	(0.9)	
0–9	2256	(80.9)	5597	(92.5)	7885	(93.3)	2627	(92.2)	< 0.001
10–19	127	(4.6)	245	(4.0)	280	(3.3)	128	(4.5)	
20–28	404	(14.5)	208	(3.4)	282	(3.3)	95	(3.3)	

**Table 2** Hazard ratios for upper aerodigestive tract cancer according to brushing frequency

n	Person-years	No. of UADT cases	Model 1 <sup>a</sup>		Model 2 <sup>b</sup>		Model 3 <sup>c</sup>		
			HR	95% CI	HR	95% CI	HR	95% CI	
Brushing frequency (times/day)									
≤ 1	2,804	25,945	19	2.27	1.13–4.57	2.24	1.11–4.50	2.13	1.04–4.37
2	6,078	57,738	14	1	(reference)	1	(reference)	1	(reference)
3	8,483	80,776	21	1.15	0.58–2.27	1.25	0.63–2.46	1.24	0.63–2.45
≥ 4	2,864	27,187	8	1.12	0.47–2.68	1.21	0.51–2.89	1.21	0.51–2.90
				<i>P</i> trend = 0.086		<i>P</i> trend = 0.16		<i>P</i> trend = 0.22	
Brushing frequency (times/day): excluding those without 1-year follow-up									
≤ 1	2,788	25,938	17	2.05	1.00–4.21	2.01	0.98–4.11	1.86	0.89–3.88
2	6,051	57,725	14	1	(reference)	1	(reference)	1	(reference)
3	8,459	80,762	20	1.10	0.56–2.19	1.18	0.59–2.34	1.17	0.59–2.32
≥ 4	2,857	27,183	8	1.14	0.48–2.71	1.20	0.50–2.88	1.21	0.51–2.90
				<i>P</i> trend = 0.15		<i>P</i> trend = 0.25		<i>P</i> trend = 0.36	

<sup>a</sup> Adjusted for sex and age (continuous variable).

<sup>b</sup> Adjusted for sex, age (continuous variable), alcohol consumption (never, former, current [0–199, 200–399, ≥ 400 g/week]), and smoking (never, former, current [0–19, 20–39, ≥ 40 cigarettes/day]).

<sup>c</sup> Adjusted for sex, age (continuous variable), alcohol consumption (never, former, current [0–199, 200–399, ≥ 400 g/week]), smoking (never, former, current [0–19, 20–39, ≥ 40 cigarettes/day]), and number of teeth lost (0–14, 15–27, 28). UADT: upper aerodigestive tract cancer

HR: hazard ratio

CI: confidence interval

**Table 3** Hazard ratios for esophageal cancer according to brushing frequency

n	Person-years	No. of cancer cases	Model 1 <sup>a</sup>		Model 2 <sup>b</sup>		Model 3 <sup>c</sup>		
			HR	95% CI	HR	95% CI	HR	95% CI	
Brushing frequency (times/day)									
≤ 1	2,804	25,964	11	1.87	0.78–4.45	1.85	0.78–4.40	1.92	0.80–4.61
2	6,078	57,742	10	1	(reference)	1	(reference)	1	(reference)
3	8,483	80,796	16	1.26	0.57–2.77	1.38	0.63–3.06	1.39	0.63–3.07
≥ 4	2,864	27,203	4	0.81	0.26–2.60	0.90	0.28–2.89	0.90	0.28–2.89
				<i>P</i> trend = 0.23		<i>P</i> trend = 0.37		<i>P</i> trend = 0.35	
Brushing frequency (times/day): excluding those without 1-year follow-up									
≤ 1	2,789	25,957	10	1.72	0.71–4.18	1.69	0.70–4.11	1.73	0.70–4.26
2	6,051	57,729	10	1	(reference)	1	(reference)	1	(reference)
3	8,459	80,781	15	1.17	0.53–2.62	1.28	0.57–2.87	1.28	0.57–2.87
≥ 4	2,857	27,199	4	0.81	0.26–2.60	0.90	0.28–2.87	0.90	0.28–2.87
				<i>P</i> trend = 0.28		<i>P</i> trend = 0.42		<i>P</i> trend = 0.41	

<sup>a</sup> Adjusted for sex and age (continuous variable).

<sup>b</sup> Adjusted for sex, age (continuous variable), alcohol consumption (never, former, current [0–199, 200–399, ≥ 400 g/week]), and smoking (never, former, current [0–19, 20–39, ≥ 40 cigarettes/day]).

<sup>c</sup> Adjusted for sex, age (continuous variable), alcohol consumption (never, former, current [0–199, 200–399, ≥ 400 g/week]), smoking (never, former, current [0–19, 20–39, ≥ 40 cigarettes/day]), and number of teeth lost (0–14, 15–27, 28).

HR: hazard ratio

CI: confidence interval

**Table 4** Hazard ratios for upper aerodigestive tract cancer according to number of teeth lost

n	Person-years	No. of UADT cases	Model 1 <sup>a</sup>		Model 2 <sup>b</sup>		Model 3 <sup>c</sup>		
			HR	95% CI	HR	95% CI	HR	95% CI	
Number of teeth lost									
0–14	18,935	181,059	50	1	(reference)	1	(reference)	1	(reference)
15–27	830	6,925	6	1.08	0.43–2.77	1.05	0.42–2.66	1.03	0.41–2.61
28	585	4,620	6	1.38	0.52–3.64	1.48	0.56–3.92	1.37	0.50–3.75
				<i>P</i> trend = 0.54		<i>P</i> trend = 0.47		<i>P</i> trend = 0.58	
0–9	18,456	176,802	47	1	(reference)	1	(reference)	1	(reference)
10–19	794	6,937	6	1.27	0.50–3.19	1.11	0.44–2.79	1.14	0.45–2.87
20–28	1,100	8,865	9	1.15	0.49–2.72	1.17	0.50–2.76	1.10	0.46–2.62
				<i>P</i> trend = 0.71		<i>P</i> trend = 0.70		<i>P</i> trend = 0.81	
Number of teeth lost: excluding those without 1-year follow-up									
0–14	18,876	181,028	47	1	(reference)	1	(reference)	1	(reference)
15–27	820	6,920	6	1.29	0.50–3.32	1.26	0.49–3.23	1.24	0.48–3.18
28	575	4,613	6	1.68	0.63–4.49	1.82	0.67–4.89	1.77	0.63–4.92
				<i>P</i> trend = 0.29		<i>P</i> trend = 0.24		<i>P</i> trend = 0.28	
0–9	18,400	176,773	45	1	(reference)	1	(reference)	1	(reference)
10–19	788	6,933	5	1.18	0.44–3.21	1.06	0.39–2.85	1.08	0.40–2.91
20–28	1,083	8,855	9	1.32	0.55–3.16	1.36	0.57–3.24	1.31	0.54–3.16
				<i>P</i> trend = 0.52		<i>P</i> trend = 0.51		<i>P</i> trend = 0.56	

<sup>a</sup> Adjusted for sex and age (continuous variable).

<sup>b</sup> Adjusted for sex, age (continuous variable), alcohol consumption (never, former, current [0–199, 200–399, ≥ 400 g/week]), and smoking (never, former, current [0–19, 20–39, ≥ 40 cigarettes/day]).

<sup>c</sup> Adjusted for sex, age (continuous variable), alcohol consumption (never, former, current [0–199, 200–399, ≥ 400 g/week]), smoking (never, former, current [0–19, 20–39, ≥ 40 cigarettes/day]), and brushing frequency (≤ 1, 2, 3, ≥ 4 times a day).

UADT: upper aerodigestive tract cancer

HR: hazard ratio

CI: confidence interval

Regarding smoking habits, the HR for UADT cancer was 1.15 (95% CI: 0.56–2.35) for former smokers, and 1.43 (95% CI: 0.54–3.82), 1.84 (95% CI: 0.83–4.06), and 3.38 (95% CI: 1.16–9.81) for current smokers who smoked 0–19, 20–39, and  $\geq 40$  cigarettes/day, respectively, compared with never smokers after adjustment for sex, age (continuous variable), and alcohol consumption (never, former, current [0–199, 200–399,  $\geq 400$  g/week]) ( $P$  trend = 0.019). For drinking habits, the HR was 5.60 (95% CI: 1.11–28.34) for former drinkers, and 3.44 (95% CI: 0.98–12.07), 8.16 (95% CI: 2.28–29.21) and 17.65 (95% CI: 5.05–61.62) for current drinkers who consumed 0–199, 200–399, and  $\geq 400$  g/week, respectively, compared with never drinkers after adjustment for sex, age (continuous variable), and smoking (never, former, current [0–19, 20–39,  $\geq 40$  cigarettes/day]) ( $P$  trend < 0.001).

## DISCUSSION

In this cohort study, infrequent brushing of once a day or less was significantly associated with an increased risk of UADT cancer. Tooth loss was not found to be significantly associated with this risk.

Infection with pathogens causes inflammation, which is an important component of carcinogenesis, including progression. Inflammation also damages normal cell growth control.<sup>39,40</sup> In the oral cavity, dental plaque is a community of oral microorganisms present on the surface of the teeth and causes local or general inflammation. Moreover, oral microorganisms produce nitrosamine, which may be involved in carcinogenesis.<sup>39,41</sup> Some studies have reported that poor oral health is associated with an increased risk of UADT cancer.<sup>4,5,16,18,20–22,40,42</sup> However, the relationship between oral hygiene and UADT cancer has been inconsistent. Tooth brushing is the most effective and convenient method to remove dental plaque and nitrosamine.<sup>25,43–45</sup> Moreover, human papillomavirus, alcohol residue, nicotine, tar, and many other toxic substances contained in tobacco, which are established as major etiologic factors in UADT cancer, can be removed or decreased by tooth brushing.<sup>16,34</sup>

Currently, tooth brushing is the most important way to improve oral hygiene worldwide, but 14.7%–43.0% of people still do not brush their teeth twice a day.<sup>46–48</sup> On the basis of the findings of the present and previous studies, the UADT cancer risk may be higher in the general population with a lower brushing frequency. Several previous studies have reported that tooth brushing once a day or less increases UADT cancer risk.<sup>20,21,34,35</sup> Thus, more frequent and effective brushing may decrease the risk of UADT cancer in those who do not brush their teeth twice a day or more.

Dental plaque biofilms initiate gingival inflammation, which leads to the progressive destruction of the tooth-supporting apparatus and causes periodontal disease and tooth loss.<sup>22</sup> Periodontal disease is a common inflammatory disease in the oral cavity and a major cause of tooth loss. Additionally, because periodontal disease has been related to UADT cancer,<sup>4,11,13–15</sup> it may play a direct role in cancer development. Therefore, tooth loss may be an indicator of the risk of UADT cancer.

Nevertheless, our results did not show any significant association between tooth loss and the risk of UADT cancer. In previous cohort studies, a significant association was reported between tooth loss and the risk of esophageal cancer,<sup>49</sup> although three studies showed no association.<sup>50–52</sup> Our findings agree with those three reports but are inconsistent with those of numerous case-control studies.<sup>5,11,18–21,29,35,53–55</sup> Tooth loss is the final outcome of oral care that begins in childhood. Tooth loss may be related to various factors, such as self-care attitudes, trauma, orthodontic treatment, health insurance status, access to dental care, and quality of dental care received.<sup>50</sup> It is

noteworthy that all respondents in this study were dentists and have greater oral care knowledge and skills than the general population<sup>56</sup>; thus, our findings might differ from those of many previous studies. However, because the number of UADT cancer cases in the current study was small among study participants who had lost many teeth, further investigation is warranted to determine whether tooth loss can serve as an indicator of risk for UADT cancer.

Our study has several key strengths. First, its prospective cohort design ensured the temporality of association; the tooth brushing frequency and number of teeth lost were reported before the development of UADT cancer. Second, to our knowledge, this is the first cohort study to consider the relationship between tooth brushing and the risk of UADT cancer. Third, this cohort study involved a relatively homogeneous group of dentists in terms of socioeconomic status and accessibility to dental care.

Our study also has several limitations. First, we did not specify the cause of tooth loss. Second, the number of teeth lost was self-reported. However, the acceptable validity of self-reported number of teeth has been demonstrated in a general population,<sup>57,58</sup> and we anticipate higher validity in dentists. Third, all variables were based on the baseline questionnaire, and we did not consider temporal changes in the covariates. Fourth, our study included only dentists who belonged to a dental association; the results may not apply to the general population. Nevertheless, the potential underlying mechanisms, including inflammation, production of nitrosamine, and other etiological factors, should be common to both dentists and the general population. Fifth, over 92% of study participants were men. Dental health might contribute differently to cancer risk in men and women. Finally, although our results showed a statistically significant association between tooth brushing and the risk of UADT cancer, the number of UADT cancer cases ( $n = 62$ ) was relatively small. Therefore, a larger cohort study is needed to confirm the association between tooth brushing and the risk of UADT cancer.

In conclusion, infrequent tooth brushing was associated with the risk of UADT cancer whereas no significant association was detected between tooth loss and UADT cancer risk.

## ACKNOWLEDGEMENTS

We thank the prefectural Dental Associations of Japan for their cooperation in establishing and following the cohort. We thank Dr. Takeshi Sakai (former director of the JDA) for greatly contributing to the initiation of this cohort study. We also thank Ms. Yuko Watanabe, Ms. Etsuko Kimura, and Ms. Yukari Sawano for technical assistance. We thank Nicole Okoh, PhD, from Edanz Group (<https://en-author-services.edanzgroup.com/ac>) for editing a draft of this manuscript.

## FUNDING

This study was funded by Grants-in-Aid from the 8020 (20 teeth until 80 years old) Promotion Foundation and the Ministry of Health, Labour and Welfare of Japan (H19-Iryo-Ippan-008). This study was also supported by MEXT/JSPS KAKENHI (grant numbers 14770166, 16390189, 2059642, 2359788, and 26463161) of the Japanese Ministry of Education, Culture, Sports, Science and Technology.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.



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