

Time to First Cigarette and Upper Aerodigestive Tract Cancer Risk in Japan

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Abstract

Background: Cigarette smoking is the major cause for upper aerodigestive tract (UADT) cancers. The time to first cigarette (TTFC) of the day is a distinct indicator of nicotine dependence, but scanty information is available on its possible relation with UADT cancers (oral, oropharyngeal, hypopharyngeal, laryngeal, nasopharyngeal, and esophageal cancers).

Methods: This case-control study includes a total of 1,009 incident UADT cancer cases and 3,027 age- and sex-matched noncancer controls admitted to the Aichi Cancer Center (Nagoya, Japan) between 2001 and 2005. We estimated OR and 95% confidence intervals (CI) for TTFC using logistic regression models after adjustment for several potential confounders.

Results: TTFC was inversely related to the risk of UADT cancer, and this association was consistent across subtypes of head and neck cancer and esophageal cancer. For all UADT cancers considered among ever smokers and after accurate allowance for smoking quantity and duration, besides other relevant covariates, compared with TTFC more than 60 minutes, the adjusted ORs were 1.40 (95% CI: 0.93–2.11) for 31 to 60 minutes, 1.76 (95% CI: 1.20–2.58) for 6 to 30 minutes, and 2.43 (95% CI: 1.64–3.61) for within 5 minutes. No significant heterogeneity was found in strata of sex, age, alcohol consumption, fruit and vegetable intake, and occupation for overall and site-specific analysis.

Conclusion: Nicotine dependence, as indicated by the TTFC, is associated with increased risk of UADT cancers and is therefore an independent marker of exposure to smoking.

Impact: Our result indicates more detailed risk evaluation of UADT cancers that is enabled by the TTFC. *Cancer Epidemiol Biomarkers Prev*; 21(11); 1986–92. ©2012 AACR.

Introduction

Cigarette smoking is a major cause of upper aerodigestive tract (UADT) cancers. The risk of UADT cancers is strongly related to younger age at starting smoking, greater numbers of cigarettes per day, larger duration of

cigarette smoking, and decreases with increasing years since quitting smoking (1–4). However, the quantification of such association may be affected by misclassification of smoking exposure because of self-reported information.

The time to first cigarette (TTFC) after waking is a distinct indicator of nicotine dependence, being one of the 6 items of the Fagerstrom Test for Nicotine Dependence (5, 6), and one of the 2 items of the Heavy Smoking Index (HSI; ref. 5), which has been shown to provide a good measure of high nicotine dependence (7). However, scanty information is available on the possible relation between TTFC and smoking-related cancers. Recently, a case-control study from the New York metropolitan area including 1,055 oral and pharyngeal cancers and 795 controls, and 570 laryngeal cancer cases and 343 controls, who were ever cigarette smokers, reported significant inverse associations between TTFC after waking and the risk of UADT cancers (8, 9). Using data from the same database on 4,775 lung cancer cases and 2,835 controls, a similar association was reported for lung cancer (10). The

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inverse associations with TTFC were independent from other established indicators of tobacco consumption, including pack-years, duration of smoking, and number of cigarettes per day. Thus, TTFC might reflect not only nicotine dependence (5, 11–15) but also intensity of smoking, not satisfactorily measured by conventional measures of smoking exposure.

Here, we investigate the association between TTFC and UADT cancer in a Japanese population, using data from large case–control study.

Materials and Methods

Study population

The case participants were 1,009 patients with no prior history of cancer who were histologically diagnosed with UADT cancer (257 with oral cavity cancer, 72 oropharyngeal, 80 hypopharyngeal, 92 laryngeal, 51 nasopharyngeal cancer, 23 with cancer of the oral cavity–oropharynx–hypopharynx not otherwise specified, and 434 esophageal cancers) between January 2001 and December 2005 at Aichi Cancer Center Hospital in Nagoya, Japan. Esophageal cancer cases are mixture of squamous cell carcinoma (more than 90%) and other histologic subtype. All participants were recruited within the framework of the hospital-based Epidemiologic Research Program at Aichi Cancer Center (Nagoya, Japan) with written informed consent (16–18). UADT cancers were defined according to the following codes of the International Classification of Diseases and Related Health Problems (ICD-10): oral cavity (C00.3–C00.9, C02.0–C02.3, C03, C04, C05.0, and C06), oropharynx (C01, C02.4, C05.1–C05.2, C09, and C10), hypopharynx (C12, C13), oral cavity–oropharynx–hypopharynx not otherwise specified (C02.8, C02.9, C05.8, C05.9, and C14), larynx (C32), nasopharynx (C11), and esophagus (C15).

The controls were 3,027 first-visit outpatients during the same period who were confirmed to have no cancer and no history of neoplasms. Noncancer status was confirmed by medical examinations, including radiographic examinations, with participants suspected of having UADT cancer first examined by physical or endoscopic inspection, and subsequently radiographically, if indicated. Controls were selected randomly and individually matched by age (± 4 years), sex (male, female), and cancer subsite, with a case–control ratio of 1:3. A total of 4,036 participants (1,009 cases and 3,027 controls) were included in the study. Response rate was more than 95% for both cases and controls. The study was approved by the Institutional Ethical Committee of Aichi Cancer Center.

Information on time to the first cigarette of the day

Information on TTFC was collected from first-visit outpatients ages 20 to 79 years using a self-administered questionnaire. Each participant was asked at the time of first visit to our hospital about lifestyle factors concerning environmental exposures before the current symptoms developed that made them visit our hospital. We asked

TTFC with following 4 options: 5 minutes or less, 6 to 30, 31 to 60, and more than 60 minutes. Responses were checked by trained interviewers.

Evaluation of other lifestyle factors

Information on smoking status was obtained in the 3 categories of nonsmoker, former smoker, and current smoker, with former smokers defined as those who had quit smoking at least 1 year before the study enrolment. Cigarette consumption was categorized into less than 15, 15 to 24, and 25 or more cigarettes per day. For the present analyses, lifetime alcohol consumption of various common beverages (Japanese sake, beer, shochu, whiskey, and wine) was determined in terms of the average number of drinks per day, which was then converted into a Japanese sake (rice wine) equivalent (180 mL), which contains 23 g of ethanol. Drinking status was classified into the 3 categories of never drinker, light-moderate drinker (< 5 days per week or ≥ 5 days per week, < 2 go per day), and heavy drinker (≥ 5 days per week, ≥ 2 go per day). Consumption of fruits and vegetables was determined using a food frequency questionnaire (FFQ), including 43 single food items with 8 frequency categories (19). The FFQ was validated using a 3-day weighed dietary record as standard, which showed that reproducibility and validity were satisfactory (20, 21). Participants were divided into 3 groups based on the distribution of fruit and vegetable consumption among controls (tertiles). Participants were also asked about their occupation as a measure of socioeconomic status (SES), and were categorized into 3 groups, that is, white collar, blue collar, or others, including workers at part time job, housewives, students, unemployed, retired, and inactive.

Data analyses

To assess the association between TTFC and the risk of UADT cancer, we estimated the OR and the corresponding 95% confidence intervals (CI) using multiple logistic regression models. First, we evaluated impacts of TTFC among current and former smokers separately relative to never smokers by using all the subjects. For this analysis, conditional logistic regression models included terms for alcohol consumption, fruit and vegetable intake, and occupation. Furthermore, to allow for possible differences in smoking intensity and duration across levels of TTFC, we evaluated TTFC excluding never smokers. For this analysis, we used unconditional logistic regression models adjusted for the same covariates of the overall analysis after further allowance for smoking status (ex- and current smoker), number of cigarettes per day (< 15 , 15–24, and ≥ 25), and duration of smoking (< 20 , 20–29, 30–39, and ≥ 40 years). Missing values for covariates were treated as dummy variables in the models. Consistency across subtypes of head and neck cancer and esophageal cancer and across strata of confounders was assessed by likelihood ratio tests between models with and without interaction term for corresponding confounding. All analyses were conducted using STATA SE version 11.2 (STATA Corp).

Table 1. Participants characteristics

	Cases N (%)	Controls N (%)
Overall	1,009	3,027
Sex		
Male	813 (80.6)	2,439 (80.6)
Female	196 (19.4)	588 (19.4)
Age		
<40	56 (5.6)	172 (5.7)
40–49	91 (9)	277 (9.2)
50–59	307 (30.4)	917 (30.3)
60–69	365 (36.2)	1,149 (38)
>70	214 (21.2)	584 (19.3)
Smoking status		
Never	195 (19.3)	1,104 (36.5)
Former	251 (24.9)	943 (31.2)
Current	561 (55.6)	976 (32.2)
Unknown	2 (0.2)	4 (0.1)
Smoking duration (only among ever smokers: 812 cases and 2,099 controls)		
<20 years	104 (12.8)	449 (23.3)
20–29 years	119 (14.6)	378 (19.7)
30–39 years	280 (34.4)	570 (29.6)
40 or more years	309 (38)	522 (27.1)
Unknown	2 (0.2)	4 (0.2)
Cigarette per day (only among ever smokers: 812 cases and 2,099 controls)		
<15 pieces	106 (13)	397 (20.7)
15–24 pieces	366 (45)	837 (43.6)
25 or more pieces	331 (40.7)	663 (34.5)
Unknown	9 (1.1)	22 (1.1)
TTFC (only among ever smoker: 812 cases and 2,099 controls)		
>60 minutes	46 (5.7)	280 (14.6)
31–60 minutes	97 (11.9)	358 (18.7)
6–30 minutes	282 (34.6)	672 (35)
5 or less minutes	374 (45.9)	542 (28.2)
Unknown	13 (1.6)	67 (3.5)
Alcohol consumption		
Never	201 (19.9)	1026 (33.9)
Light	177 (17.5)	855 (28.2)
Frequently moderate	230 (22.8)	712 (23.5)
Frequently heavy	401 (39.7)	467 (15.4)
Unknown	24 (2.4)	39 (1.3)
Fruits and vegetable intake		
Lowest tertile (<110.5 g/day)	456 (45.2)	988 (32.6)
Middle tertile (<200.5 g/day)	313 (31)	994 (32.8)
Highest tertile (>= 200.5 g/day)	202 (20)	987 (32.6)
Unknown	37 (3.7)	58 (1.9)
Occupation		
White collar	214 (21.2)	903 (29.8)
Blue collar	369 (36.6)	821 (27.1)
Other	413 (40.9)	1,253 (41.4)
Unknown	13 (1.3)	49 (1.6)

*(Continued on the following column)***Table 1.** Participants characteristics (Cont'd)

	Cases N (%)	Controls N (%)
Cancer site ^a		
Head and neck cancer	575 (57)	1725 (57)
Oral cavity cancer	257 (25.5)	771 (25.5)
Oropharyngeal cancer	72 (7.1)	216 (7.1)
Hypopharyngeal cancer	80 (7.9)	240 (7.9)
Laryngeal cancer	92 (9.1)	276 (9.1)
Nasopharyngeal cancer	51 (5.1)	153 (5.1)
Oral cavity–oropharyngeal–hypopharyngeal cancers NOS	23 (2.3)	69 (2.3)
Esophageal cancer	434 (43)	1,302 (43)

^aControls were matched to cases individually, therefore, number of controls according to cancer sites represent number of matched controls.

Results

Demographic characteristics and selected lifestyle habits of participants are shown in Table 1. Age and sex were appropriately matched. The proportion of smokers and drinkers was higher in cases than in controls. Cases smoked more cigarettes per day and for longer time, with significant trends in risk. Compared with controls, cases ate less vegetables and fruits and were more frequently blue collar workers.

Table 2 presents the association between FTTC in former and current smokers and UADT cancer, overall and according to specific cancer subsite. In analysis of UADT cancer overall, compared with never smokers, ORs for more than 60, 31 to 60, 6 to 30, 5 or less minutes were 1.03 (95% CI: 0.64–1.64), 1.38 (95% CI: 0.92–2.07), 2.01 (95% CI: 1.44–2.81), and 2.37 (95% CI: 1.66–3.39) for former smokers and 1.30 (95% CI: 0.72–2.36), 2.11 (95% CI: 1.42–3.13), 2.80 (95% CI: 2.11–3.73), and 4.47 (95% CI: 3.38–5.91) for current smokers, respectively. Although ORs for current smokers were larger than those for former smokers, ORs for shorter FTTC were consistently associated with increased UADT cancer risk. Although the point estimates fluctuate, the inverse association with FTTC was consistently observed across separate subsites, that is, oral cavity cancer, oropharyngeal cancer, hypopharyngeal cancer, laryngeal cancer, nasopharyngeal cancer, and esophageal cancer. Supplementary Table S1 shows only age-adjusted ORs in the similar pattern as Table 2 and indicating FTTC confounded with factors adjusted in the multivariate model.

When the analysis was restricted to ever smokers (Table 3) and accurate allowance was made for smoking status plus quantity and duration of smoking, compared with FTTC more than 60 minutes after waking, the ORs for all UADT cancers were 1.40 (95% CI: 0.93–2.11) for 31 to 60 minutes, 1.76 (95% CI: 1.20–2.58) for 6 to 30 minutes, and 2.43 (95% CI: 1.64–3.61) for within 5 minutes. With

Table 2. Associations between TTFC combined with smoking status and UADT cancer risks stratified by subsite.

Combined categories of smoking dependence and smoking status	Site																							
	UADT Cancer			Head and neck cancer			Laryngeal			Nasopharyngeal			Esophageal cancer											
	Case	Control	OR (95%CI)	Case	Control	OR (95%CI)	Case	Control	OR (95%CI)	Case	Control	OR (95%CI)	Case	Control	OR (95%CI)									
Never smokers	195	1104	Reference	145	664	Reference	101	353	Reference	9	74	Reference	9	67	Reference	15	61	Reference	50	440	Reference			
Former smokers																								
> 60 minutes	28	196	1.03 (0.64-1.64)	20	109	1.06 (0.61-1.83)	8	45	0.67 (0.29-1.54)	6	17	4.57 (1.11-18.7)	2	25	0.46 (0.05-3.92)	3	14	3.76 (0.71-20.0)	0	7	NE	8	87	0.97 (0.39-2.40)
31-60 minutes	44	214	1.38 (0.92-2.07)	24	100	1.46 (0.86-2.46)	13	37	1.44 (0.68-3.07)	3	15	1.30 (0.23-7.16)	2	20	0.55 (0.06-4.96)	3	21	3.96 (0.78-20.1)	2	3	3.35 (0.33-33.6)	20	114	1.67 (0.85-3.29)
6-30 minutes	91	289	2.01 (1.44-2.81)	40	159	1.50 (0.96-2.35)	10	57	0.61 (0.28-1.35)	8	24	3.60 (1.00-13.0)	6	20	3.21 (0.82-16.5)	11	33	7.01 (1.95-25.2)	3	18	0.85 (0.15-4.82)	51	130	3.27 (1.86-5.78)
5 or less minutes	78	197	2.37 (1.66-3.39)	34	98	1.77 (1.09-2.89)	13	27	1.84 (0.81-4.18)	5	14	5.00 (1.16-21.5)	7	15	4.60 (0.81-26.0)	6	28	4.52 (1.10-18.6)	3	7	2.58 (0.43-15.3)	44	99	4.03 (2.25-7.22)
Current smokers																								
> 60 minutes	18	84	1.30 (0.72-2.36)	10	51	1.03 (0.48-2.20)	6	24	0.90 (0.35-2.42)	0	10	NE ^a	1	7	0.81 (0.06-11.7)	1	4	6.86 (0.52-90.6)	1	4	2.46 (0.18-33.5)	8	33	2.23 (0.81-6.14)
31-60 minutes	53	144	2.11 (1.42-3.13)	33	90	1.77 (1.08-2.89)	12	39	0.89 (0.42-1.91)	1	11	0.82 (0.08-8.33)	9	8	12.3 (2.30-65.4)	8	13	12.2 (2.88-52.1)	2	12	0.62 (0.09-4.08)	20	54	3.47 (1.69-7.11)
6-30 minutes	191	383	2.80 (2.11-3.73)	100	221	2.05 (1.44-2.93)	35	92	0.99 (0.58-1.71)	13	23	5.19 (1.62-16.6)	9	44	3.07 (0.86-10.9)	18	38	8.34 (2.48-28.0)	10	16	1.84 (0.55-6.18)	91	162	5.46 (3.26-9.14)
5 or less minutes	296	345	4.47 (3.38-5.91)	160	200	3.57 (2.52-5.06)	56	83	2.02 (1.22-3.32)	27	27	8.34 (2.62-26.5)	23	27	5.71 (1.40-23.3)	32	39	18.9 (6.52-65.0)	15	21	4.06 (1.15-14.3)	136	145	7.45 (4.52-12.3)
Unknown subjects	15	71		9	33		3	14		0	1		2	7		4	5		0	4		6	38	

NOTE: ORs were calculated by conditional logistic regression model adjusted for alcohol consumption, fruit and vegetable intake, and SES.

^aNE, not estimated

reference to specific cancer sites, the ORs for less than 5 versus more than 60 minutes were 2.04 (95% CI: 1.06-3.92) for oral/oropharyngeal cancers, 2.25 (95% CI: 0.84-5.98) for oropharyngeal/laryngeal cancers, and 3.09 (95% CI: 1.58-6.04) for esophageal cancer. When the analysis was further restricted to current smokers, compared with FTTC more than 60 minutes, the ORs for all UADT cancers were 1.65 (95% CI: 0.86-3.15) for 31 to 60 minutes, 1.95 (95% CI: 1.07-3.54) for 6 to 30 minutes, and 2.86 (95% CI: 1.56-5.25) for within 5 minutes. Corresponding values for less than 5 versus more than 60 minutes after waking were 2.40 (95% CI: 0.81-7.07) for oral/oropharyngeal cancers, 3.25 (95% CI: 0.69-18.0) for hypopharyngeal/laryngeal cancers, and 3.10 (95% CI: 1.18-8.09) for esophageal cancer. Supplementary Table S2 shows age- and sex-adjusted ORs in the similar pattern as Table 3. Larger values of point estimates compared with multivariate-adjusted ones.

To examine the consistency of the association between the FTTC and UADT cancer risk, Table 4 shows adjusted ORs for FTTC within 5 minutes relative to FTTC more than 60 minutes stratified by selected covariates. The association was consistent across strata of age, sex, drinking, fruit/vegetable intake, and SES, and was observed for UADT cancer, head and neck, and esophageal cancer in the absence of a statistically significant heterogeneity.

Discussion

In this large case-control study, the first one in an Asian population, we found that the TTFC was independently associated with risk of UADT cancers after adjustment for smoking status, quantity, and duration of smoking. A shorter TTFC is associated with increased risk and risk increased in a dose-dependent manner. This association was consistent across head and neck cancers overall, esophageal cancer, and various detailed subsites of head and neck cancer. Moreover, the associations found were consistent across strata of potential confounders, warranting robustness of results.

TTFC is a valid measure of nicotine dependence (5, 12, 22) and is also associated with other aspects of smoking dependence, including difficulty in smoking cessation (11, 12), smoking relapse (14), and tolerance (15). TTFC was appreciably shorter in this Japanese population as compared with the United States and European ones. In this study, 2 of 3 smoking controls reported TTFC less than 30 minutes, as compared with 50% in the U.S. population including about 85% whites (10), and the proportion more than 60 minutes was 15% in this Japanese population versus 29% in the U.S. population. A survey on the general Italian adult population found that more than 2 of 3 smokers of both sexes reported low or very low dependence on the basis of the 6 items Fagerstrom test (6).

Despite different values in various populations, TTFC is a marker of exposure to smoking. In fact, Muscat and colleagues reported that the levels in plasma/urine cotinine, the major nicotine metabolite, showed different

Table 3. Associations between TTFC and UADT cancers among ever- and current smokers stratified by subsite

Combined categories of smoking dependence and smoking status	Sites														
	UADT cancer			Head and neck cancer						Esophageal cancer					
	Case	Control	OR (95%CI)	Overall		Oral/Oropharyngeal		Hypopharyngeal/Laryngeal		Case	Control	OR (95%CI)			
Ever smokers															
> 60 minutes	46	280	Reference	30	160	Reference	20	96	Reference	7	50	Reference	16	120	Reference
31–60 minutes	97	358	1.40 (0.93–2.11)	57	190	1.29 (0.76–2.18)	29	102	1.11 (0.56–2.19)	22	62	2.01 (0.72–5.58)	40	168	1.53 (0.76–3.08)
6–30 minutes	282	672	1.76 (1.20–2.58)	140	380	1.32 (0.81–2.15)	66	196	1.14 (0.61–2.14)	54	135	1.78 (0.68–4.65)	142	292	2.55 (1.33–4.89)
5 or less minutes	374	542	2.43 (1.64–3.61)	194	298	2.03 (1.22–3.35)	101	151	2.04 (1.06–3.92)	68	109	2.25 (0.84–5.98)	180	244	3.09 (1.58–6.04)
			<0.001			0.001			0.013			0.143			<0.001
Current smokers															
> 60 minutes	18	84	Reference	10	51	Reference	6	34	Reference	2	11	Reference	8	33	Reference
31–60 minutes	53	144	1.65 (0.86–3.15)	33	90	1.45 (0.62–3.41)	13	50	1.09 (0.34–3.50)	17	21	4.32 (0.74–25.3)	20	54	1.69 (0.59–4.85)
6–30 minutes	191	383	1.95 (1.07–3.54)	100	221	1.55 (0.70–3.46)	48	115	1.33 (0.46–3.85)	37	82	2.07 (0.38–11.3)	91	162	2.44 (0.94–6.32)
5 or less minutes	296	345	2.86 (1.56–5.25)	160	200	2.57 (1.14–5.78)	83	110	2.40 (0.81–7.07)	55	66	3.25 (0.69–18.0)	136	145	3.10 (1.18–8.09)
			<0.001			0.001			0.011			0.439			0.01

NOTE: ORs were calculated by unconditional logistic regression model adjusted for smoking status, duration of smoking, cigarettes per day, alcohol consumption, fruit and vegetable intake, and SES.

pattern of increase with the numbers of cigarettes per day between "low-" and "high-"dependent groups defined by TTFC (23). In that study, cotinine levels increased linearly in the low-dependent group, whereas in the high-depen-

dent group, cotinine levels remained high from a small number of cigarettes per day, showing a plateau around 30 cigarettes per day (22). This might indicate that the levels of nicotine uptake differ by the levels of nicotine

Table 4. Stratified analysis for TTFC less than 5 minutes compared with TTFC greater than 60 minutes among ever smokers.

Stratified by	UADT Cancer				Head and Neck Cancer				Esophageal Cancer			
	Case	Control	OR (95%CI)	P heterogeneity	Case	Control	OR (95%CI)	P heterogeneity	Case	Control	OR (95%CI)	P heterogeneity
(UATC overall)												
Overall	374	542	2.43 (1.64–3.61)		194	298	2.03 (1.22–3.35)		80	244	3.09 (1.58–6.04)	
Sex				0.956				0.096				0.5761
Male	342	516	2.35 (1.56–3.56)		177	276	1.87 (1.11–3.15)		165	240	3.08 (1.53–6.23)	
Female	32	26	4.26 (0.95–19.2)		17	22	8.43 (0.83–85.2)		15	4	0.68 (0.001–604.5)	
Age category				1				0.345				0.334
<60	175	250	2.29 (1.24–4.24)		100	152	2.41 (1.19–4.88)		75	98	3.04 (0.67–13.9)	
60 or more	199	292	2.40 (1.41–4.06)		94	146	1.89 (0.90–3.96)		105	146	2.98 (1.37–6.50)	
Alcohol consumption				0.463				0.557				0.8231
Non	30	120	1.48 (0.52–4.18)		25	64	2.41 (0.75–7.72)		5	56	1.96 (0.13–30.4)	
Light–moderate	142	271	2.68 (1.51–4.76)		80	148	1.91 (0.93–3.91)		62	123	4.08 (1.42–11.8)	
Heavy	196	144	2.76 (1.39–5.47)		84	83	2.23 (0.87–5.73)		112	61	3.01 (1.03–8.83)	
Fruits and vegetables intake				0.854				0.6312				0.8838
Lowest tertile	192	229	3.81 (1.94–7.50)		105	125	3.54 (1.57–8.00)		87	104	4.72 (1.28–17.3)	
Middle tertile	114	180	1.91 (0.97–3.75)		58	99	1.50 (0.59–3.84)		56	81	2.13 (0.73–6.23)	
Highest tertile	59	120	2.10 (0.94–4.70)		24	66	1.63 (0.54–4.91)		35	54	3.91 (1.07–14.3)	
Occupation				1				1				1
White collar	148	204	3.25 (1.53–6.87)		73	117	2.37 (1.00–5.60)		33	62	9.26 (1.67–51.2)	
Blue collar	76	147	1.32 (0.65–2.67)		43	85	1.34 (0.36–2.21)		75	87	1.65 (0.41–6.62)	
Other	147	190	3.03 (1.59–5.77)		76	95	2.89 (1.10–7.60)		71	95	3.34 (1.35–8.27)	

NOTE: ORs were calculated by unconditional logistic regression model adjusted for age, sex, cigarette per day, duration of smoking, smoking status, alcohol consumption, fruit and vegetable intake, and occupation except for a stratifying factor.

dependence measured by TTFC. Although we do not have data on the association between nicotine levels in plasma/urine and TTFC in this study, our results confirmed the observation (8, 9) that TTFC is an independent indicator of UADT cancer risk.

It is of interest, what is the mechanism behind TTFC shows increased risk of UADT cancer risk. One possibility is that TTFC is an indicator of tobacco dependence impinging on cancer risk that is not adequately measured by other variables used in epidemiologic studies like cigarette per day or duration of smoking. Supporting this, TTFC is highly correlates with cotinine levels (23) and cotinine levels correlate with tobacco-related carcinogens and polycyclic aromatic hydrocarbons (24). In addition, genetic polymorphisms on chromosome 15, which are associated with risk of lung cancer (25) and UATC cancer in female (26), showed a significant correlation with smoking dependence (27), supporting TTFC as an phenotype reflecting cancer susceptibility. A significant association even after adjustment of usual smoking-related indicators in this study and formers may partially support this view (8–10).

Our study had several methodologic strengths. First, potential confounding by age, sex, alcohol drinking, fruit and vegetable intake, and SES was considered by individual matching and statistical adjustment in the analyses. Second, the size of the study was large, participation was almost complete for both cases and controls, and the FFQ was satisfactorily valid and reproducible (17, 18). Potential limitations of our study also warrant mention. First, measurement of FTTC might be affected by the status of cases at recruitment. To avoid this, we asked about FTTC when the participants were healthy or before the current symptoms developed. Second, the control participants were selected among noncancer patients at our hospital. Because cases and controls were selected from the same hospital and almost all patients lived in the Tokai area of central Japan, the internal validity of this case–control study is likely to be acceptable (16). In addition, to dilute any bias that might have resulted from the inclusion of a specific diagnostic group that is related to the exposure, we did not set eligibility criteria for control diseases. Third, as the lifestyle factors considered as potential confounders

were based on self-report, it is difficult to rule out some information bias. If present, however, the effect of such misclassification in relation to possible underadjustment would be limited, also considering consistency of results across stratified analysis by several potential confounders. Finally, residual confounding by unmeasured factors such as HPV infection cannot be ruled out. This, however, would have a selective impact on oropharyngeal cancer only (28), whereas we observed strong inverse association with FTTC for all the head and neck cancers considered.

In conclusion, our case–control study has shown that TTFC is a risk factor for UADT cancers, head and neck, and esophageal cancers, independent of conventional smoking exposure measurement.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Matsuo, H. Ito, M. Shinoda, C.L. Vecchia, H. Tanaka
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