Table 4. Distribution of stage of change and nicotine dependence among currently smoking dental patients

	Total	Age group (years)			*P*-value[a]
		20–39	40–59	≥60	
Males					
Stage of change	*n* = 1962	*n* = 520	*n* = 786	*n* = 656	0.022
Pre-contemplation without interest to quit	28.9	29.6	29.3	27.9	
Pre-contemplation with interest to quit or contemplation	64.2	64.8	65.3	62.5	
Preparation	6.9	5.6	5.5	9.6	
Nicotine dependence[b,c]	*n* = 1828	*n* = 499	*n* = 731	*n* = 598	0.082
≥5 points	68.1	64.1	69.6	69.6	
<5 points	31.9	35.9	30.4	30.4	
Females					
Stage of change	*n* = 896	*n* = 377	*n* = 346	*n* = 173	0.260
Pre-contemplation without interest to quit	19.0	18.0	19.1	20.8	
Pre-contemplation with interest to quit or contemplation	71.1	71.1	73.4	66.5	
Preparation	9.9	10.9	7.5	12.7	
Nicotine dependence	*n* = 796	*n* = 349	*n* = 306	*n* = 141	0.019
≥5 points	60.8	65.9	58.5	53.2	
<5 points	39.2	34.1	41.5	46.8	

[a]Chi-square test.
[b]Dependence was assessed by using the Tobacco Dependence Screener (TDS).
[c]The total number of current smokers was 2624 for nicotine dependence, due to missing values for the TDS.

Table 5. Distribution of dentists by smoking status

	Category	Smoking status		
		Current smokers % (*n*)	Former smokers % (*n*)	Nonsmokers % (*n*)
Sex	Males	27.1 (184)	32.6 (222)	40.3 (274)
	Females	3.4 (2)	8.5 (5)	88.1 (52)
Age group (years)	20–29	0.0 (0)	0.0 (0)	100.0 (2)
	30–39	34.1 (28)	18.3 (15)	47.6 (39)
	40–49	28.5 (72)	30.0 (76)	41.5 (105)
	50–59	22.4 (61)	34.2 (93)	43.4 (118)
	60–69	20.3 (24)	24.7 (41)	44.9 (53)
	≥70	8.3 (1)	16.7 (2)	75.0 (9)
Total		25.2 (186)	30.7 (227)	44.1 (326)

older were significantly more likely to be in the preparation stage as compared with younger age groups, whereas no such difference among age groups was seen in women. The prevalence of nicotine dependence (≥5 TDS points) among dental patients was 65.2% (67.1% in men and 60.7% in women). Men had a significantly higher prevalence of nicotine dependence than did women ($P < 0.001$). Among women, those aged 20 to 39 years had a higher prevalence of nicotine dependence than did older age groups, whereas no such difference among age groups was found in men.

The prevalence of current smoking among Japanese dentists was 25.2% in the present study (27.1% in men and 3.4% in women; Table 5). Approximately 90% of female dentists were nonsmokers. Among current smokers, the highest prevalence was seen in those aged 30 to 39 years (34.1%), followed by those aged 40 to 49 years (28.5%). The prevalence of former smoking among male dentists was 32.6%. The prevalence of current smoking among male dentists in 2008 (27.1%) was significantly higher than that among male physicians in 2008 (15.0%) and equivalent to that among male physicians in 2000 (27.1%).[19]

Table 6 shows the attitudes of dentists toward the effects of smoking on their patients, according to smoking status among dentists. Two-thirds of dentists answered that they were very concerned about the effects of tobacco smoke on their patients' health. More than three-fourths of dentists answered that they prohibited smoking inside their clinic. Significant differences in the responses to both questions were observed with regard to smoking status ($P < 0.001$). Current smokers were less likely to be concerned about the effects of tobacco smoke on their patients' health than were nonsmokers or former smokers. In addition, current smokers less frequently prohibited smoking in their offices than did nonsmokers or former smokers.

DISCUSSION

In the present study, we collected data on smoking from dentists and their patients. To the best of our knowledge, this nationwide survey is the first of its kind in Japan. The high response rate of 78.2% suggests that the questionnaire was neither too lengthy nor too difficult to answer and that Japanese dentists were interested in the scope of the study.

The overall smoking prevalence among dental patients was 25%, which was similar to that reported in the NHNS population. There was only a small difference in overall

Table 6. Attitudes of dentists toward the effects of smoking on their patients, by smoking status of dentists

Question and category of response	Total[a] (%)	Smoking status			*P*-value[b]
		Current smokers (%)	Former smokers (%)	Nonsmokers (%)	
1. Are you concerned about effects of tobacco smoke on patient's health?	*n* = 733	*n* = 185	*n* = 224	*n* = 324	
Very concerned	66.0	44.9	70.5	75.0	<0.001
Somewhat concerned	28.8	45.4	26.8	20.7	
Not concerned	5.2	9.7	2.7	4.3	
2. What preventive measure against passive smoking do you implement in your offices?	*n* = 738	*n* = 186	*n* = 227	*n* = 325	
Smoking is prohibited inside entire clinic	76.8	58.6	81.1	84.3	<0.001
Other measures	18.8	36.6	16.7	10.2	
No measures	4.3	4.8	2.2	5.5	

[a]Total number of 733 for question 1 and 738 for question 2, due to incomplete responses on questionnaires.
[b]Chi-square test.

smoking prevalence, despite the fact that among some sex–age groups, there was a clear difference in smoking prevalence between dental patients and the NHNS population, which was presumably due to the difference in age-distribution between the 2 groups. Continuing smokers are expected to receive more dental treatment than nonsmokers because of a higher prevalence of perceived dental needs[20]; however, it has been reported that smokers in the United States are less likely than nonsmokers to visit a dental clinic because of their low awareness of dental health.[21] Current smokers in Japan are less likely to avoid dental visits than those in the United States.[21] This inconsistency is likely due to differences in the healthcare systems of the United States and Japan, including issues such as insurance coverage and copayment.[22]

Smoking prevalence in female patients aged 20 to 29 and 30 to 39 years was significantly higher than that in the NHNS population. This might be influenced by the fact that women frequently seek dental care or that young female smokers were more concerned about the esthetic effects of smoking.[23] As compared with male smokers, female smokers had a higher level of readiness to quit smoking. In addition, younger female smokers had a higher prevalence of nicotine dependence than did older women. The proportion of female patients in their 20s and 30s who sought dental care (22.3%) was higher than that of women in the same age groups who sought normal delivery and puerperal care (5.5%).[24] Therefore, dental professionals may have the opportunity to examine many young female smokers. The development of a smoking cessation program directed at young women who visit dental clinics could reduce the prevalence of smoking in women, which has been increasing in Japan. Such interventional programs conducted in dental clinics could support young smokers who, due to restrictions based on the Brinkman index (ie, cigarettes per day × years smoked), are mostly not eligible for insurance coverage for treatment of nicotine dependence in Japan.

In both male and female patients aged 50 to 59 years, the proportion of current smokers was higher than that in the NHNS population, possibly due to the marked influence of smoking on periodontal tissue in smokers aged 40 years or older, which invariably compels them to visit dental clinics.[25] Furthermore, periodontal disease is the most frequent reason for tooth extraction in adults aged 45 years or older.[26] Smokers are more likely to experience tooth loss than are nonsmokers or former smokers.[27] In this age group, the general health benefits of quitting smoking are more obvious,[28] considering that smoking-related systemic diseases generally appear in middle-aged smokers. Smoking cessation activities by dental professionals can enhance public health efforts to reduce smoking-attributable morbidity and mortality.

Among current smokers who visited dental clinics, more than 70% were interested in quitting. This indicates that dentists have frequent opportunities to intervene with patients who smoke and are interested in quitting. However, the percentage of smokers who were ready to quit smoking within 1 month (ie, those who were in the preparation stage) was very low (8%). Therefore, motivational approaches using techniques such as the 5 R's (relevance, risks, rewards, roadblocks, and repetition)[8] and motivational interviewing[7] account for many of the smoking cessation interventions in dental practice. A brief intervention using available resources on the various oral effects of smoking (eg, tooth discoloration), which can visually depict the effects, was effective in educating dental patients who were not ready to quit.[16,29] This approach is unique to the dental setting; dental clinics are therefore a health resource for organizing interventional programs for smokers, independently of medical facilities.

More than 60% of current smokers had a TDS score of 5 points or higher for nicotine dependence. This result suggests a strong need for nicotine dependence treatment in the dental setting, using pharmacologic aids. Arranging referrals to medical specialists for smokers willing to quit can increase

their chances of quitting. Specialist referral services are available in the United States[30,31] and United Kingdom,[32,33] although the impact of specialist referral requires further evaluation.[34]

The prevalence of smoking among Japanese dentists (27.1% in men and 3.4% women) was lower than that noted in a survey conducted during the period between 2001 and 2006 (30.2% in men and 10.7% in women), although the response rate for that survey was 36%.[35] However, the prevalence of smoking was considerably higher than that in some other developed countries such as the United States (6%),[36] United Kingdom (9%),[37] Norway (7%),[38] and Australia (4%).[39] The high prevalence of smoking among Japanese men partly explains the high overall prevalence of smoking, since about 80% of Japanese dentists are men. A survey of physicians revealed that smoking prevalence among male surgeons and otorhinolaryngologists, whose medical practices have characteristics in common with that of dentists, was once significantly higher than that of other specialties.[19] Although the JDA announced a Declaration for the Nation's Dental Professionals to Combat Smoking in 2005, smoking prevalence among male dentists in 2008 was still equal to that of male physicians in 2000. Further measures to promote smoking cessation among dentists are therefore necessary.

Interestingly, despite the high prevalence of smoking among dentists, approximately 70% were very concerned about the effects of smoking on their patients' health and implemented preventive measures against passive smoking. Presumably, this was because of concern regarding the negative effects of smoking on the outcome of treatments. Another reason could be that dentists frequently see young women and children, who are generally sensitive to passive smoking. The implementation rate of smoking prohibition inside the clinic was higher than that in medical clinics (64%), according to the Survey of Medical Institutions, 2008.[40] Most dentists seemed to support anti-smoking activities in their practice. However, as compared with dentists who were nonsmokers or former smokers, those who currently smoked appeared to be less concerned about the effects of smoking on their patients. The continued promotion of nonsmoking among dentists is essential to increase the public impact of anti-smoking activities in dental clinics.

This study has several limitations. Regarding the dentist survey, the primary limitation was the representativeness of the sample, because not all dentists are JDA members. However, because 70% of dentists working in medical institutes were JDA members as of 2007, the effect of sampling bias due to participation was estimated to be small. A second limitation was that the prevalence of smoking among dentists may have been underestimated in the present study if most dentists who did not return the questionnaires were smokers. Conversely, attitudes toward the effects of smoking on patient health may have been overestimated. In fact, smoking prevalence among dentists who responded to the follow-up letters was higher than that among those who responded to the initial letters (22.5% for the initial, 34.1% for the second, and 45.5% for the third letters; data not shown), which suggests that smokers were less willing to participate in the study than were nonsmokers. A third limitation was that the exclusion rate for patient data was 20% of the collected data, which may cause selection bias. The sex and age distributions of patients were similar to those reported in a patient survey conducted by the Ministry of Health, Labour and Welfare, Japan, in October 2005.[24] Therefore, the sample of patient surveys in the present study seems to be representative of dental patients throughout Japan. Information on smoking status was available in approximately three-quarters of excluded data. The overall smoking prevalence in these data was 24.3% (data not shown), which was similar to that of the analyzed data (25.1%). Therefore, bias caused by the exclusion of data would be limited with respect to smoking.

In conclusion, many smokers who were interested in quitting smoking, particularly young women, visited dental clinics. In addition, despite their high prevalence of current smoking, most dentists were concerned about the effects of smoking on their patients. These results indicate that smoking cessation interventions undertaken in dental clinics are necessary; furthermore, dentists have positive attitudes toward such interventions for their patients. The dental clinic is more likely to have a significant public impact as a potential health resource if dentists believe that "dentists should not smoke" as well as that "patients should not smoke." Further studies are required so as to provide information that will enable dental clinics in Japan to improve their ability in implement smoking cessation strategies for their patients.

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Conflicts of interest: None declared.

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Cancer Epidemiology, Biomarkers & Prevention

Research Article

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.
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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).

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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)

[a]Controls 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

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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																						Esophageal cancer		
				Overall			Oral cavity			Oropharyngeal			Hypopharyngeal			Laryngeal			Nasopharyngeal								
	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)	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	6	81	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 (0.62–16.5)	11	33	7.01 (1.95–25.2)	3	18	0.85 (0.15–4.82)	51	130	3.27 (1.86–5.76)			
5 or less minutes	78	197	2.37 (1.66–3.39)	34	98	1.77 (1.08–2.89)	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 (0.33–2.42)	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 (5.52–65.0)	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.

[a]NE, 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

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

	Sites														
	UADT cancer			Head and neck cancer									Esophageal cancer		
				Overall			Oral/Oropharyngeal			Hypopharyngeal/Laryngeal					
Combined categories of smoking dependence and smoking status	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)
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-dependent 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.

	UADT Cancer				Head and Neck Cancer				Esophageal Cancer			
Stratified by	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 90.83–85.2)		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.

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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

Conception and design: K. Matsuo, K. Tajima, C.L. Vecchia
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Matsuo, D. Kawakita, I. Oze, S. Hosono, H. Ito, S. Hatooka, Y. Hasegawa, M. Shinoda, K. Tajima
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K. Matsuo, C.L. Vecchia
Writing, review, and/or revision of the manuscript: K. Matsuo, S. Gallus, E. Negri, I. Oze, K. Tajima, C.L. Vecchia
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Matsuo, H. Ito, M. Shinoda, C.L. Vecchia, H. Tanaka
Study supervision: H. Tanaka

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Impact of smoking status on clinical outcome in oral cavity cancer patients

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SUMMARY

The association between smoking status and survival in oral cavity squamous cell carcinoma (OSCC) patients remains unclear. Therefore, we evaluated the association between smoking status before treatment and clinical outcome in OSCC patients. We conducted a retrospective cohort study of 222 OSCC patients who were treated at Aichi Cancer Center in Japan. Of these, 82 patients (36.9%) were non-smokers, 65 (29.3%) were light smokers (pack-years smoking (PY) <30), 54 (24.3%) were moderate smokers ($30 \leqslant PY < 60$), and 21 (9.5%) were heavy smokers ($60 \leqslant PY$). The survival impact of pre-treatment smoking status was evaluated using multivariate proportional hazard models. Five-year overall survival for non-, light, moderate, and heavy smokers was 72.9% (95% confidence interval CI): (61.4–81.5), 85.5% (74.0–92.2), 59.9% (44.3–72.4) and 69.0% (42.8–85.0). Adjusted hazard ratios (HRs) for moderate and heavy smokers in comparison with light smokers were 2.44 (1.07–5.57, $P = 0.034$) and 2.66 (0.97–7.33, $P = 0.058$) and the dose–response relationship among smokers was statistically significance ($P_{trend} = 0.024$). In addition, adjusted HR for non-smokers relative to light smokers was 2.27 (0.84–6.15, $P = 0.108$). We observed a suggestive heterogeneity in the impact of smoking status by treatment method (P for heterogeneity = 0.069). Effect of smoking was evident only among the chemoradiotherapy or radiotherapy group. In this study, we found the significant positive dose–response relationship among smokers on clinical outcome in OSCC patients and that non-smokers were worse prognosis than light smokers. In addition, this effect might differ by treatment method.

Introduction

Oral cavity cancer, which typically arises from epithelial squamous cells, is a serious and growing problem worldwide. Oral cavity squamous cell carcinoma (OSCC) accounts for approximately 3% of all malignancies, and two-thirds of the estimated annual incidence of 275,000 cases occur in developing countries.[1] In Japan, mortality due to OSCC increased steadily from 1960 to 2000, reaching levels observed in western countries in the 1990s, and a total of 12,105 cases were newly diagnosed between 1993 and 2001.[2,3]

At least 80% of OSCC diagnosed in developed countries are attributable to tobacco and alcohol consumption, either alone or in combination. Although the association between smoking status and the risk of OSCC has been established,[4–7] that between smoking status and clinical outcome remains unclear. Several studies have evaluated the association between smoking status and clinical outcomes in head and neck cancer patients,[8–15] but we are aware of only one report on this association in OSCC patients.[16]

It is well known that tobacco smoking promotes tumor hypoxia associated with resistance to radiotherapy (RT), and that a mutation of the p53 gene is associated with resistance to apoptosis.[17–19] In addition, two distinct disease patterns have been recognized in young OSCC patients, who have had relatively little smoking exposure, namely an extremely aggressive course with a high mortality rate within 2 years, and a more indolent course with a lower mortality rate.[20] The clinical outcomes of non-smokers may therefore be distinct from that of smokers among OSCC patients. Moreover, we previously found an interaction between smoking status and treatment method in esophageal cancer patients.[21]

Here, we evaluated the association between smoking status and clinical outcome of OSCC patients, and the interaction between smoking status and treatment method in a retrospective cohort study in 222 patients with OSCC treated at Aichi Cancer Center (ACC).

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Materials and methods

Patients

Patients were selected from the database of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), based at ACC in Nagoya, Japan. The HERPACC frame-work has been detailed elsewhere.[22,23] Briefly, 23,408 HERPACC-enrolled, first-visit outpatients treated between January 2001 and November 2005 at Aichi Cancer Center Hospital (ACCH) were asked to provide blood samples and information on lifestyle factors. Of those who participated, 22,727 (97.1%) patients completed a self-administered questionnaire on lifestyle factors, which was checked by a trained interviewer, and approximately 60% provided blood samples. This study was approved by the Institutional Ethics Review Board of ACC, and all participants provided written informed consent.

HERPACC-enrolled patients diagnosed as having primary oral cavity cancer who met the following criteria were included: (a) no prior history of cancer, (b) the following codes of the International Classification of Diseases for Oncology (ICD-O-3)[24]: C02.0–C02.3, C03, C04, C05.0, C06, (c) histological diagnosis of squamous cell carcinoma (ICD-O-3 code: M-8070/3), and (d) performance status (PS) of 0–2 according to the Eastern Cooperative Oncology Group criteria.[25] Finally, 222 patients were eligible for this study.

Treatment and follow-up

In OSCC, surgery and chemoradiotherapy (CRT) or RT with or without induction chemotherapy (IC) are considered the definitive treatment methods. The treatment of each patient was selected by the attending physician in consideration of disease clinical stage, primary tumor site, and PS. Following the end of treatment, patients underwent a history and physical examination, complete blood cell count, and imaging examination every 3–6 months for 5 years. Vital and disease status were confirmed by checking medical records at the date of the last follow-up visit. Vital status in patients lost to follow-up was confirmed by a census registration conducted annually.

Smoking and drinking status

The HERPACC questionnaire includes items related to demographic characteristics, individual and family medical history, height and weight, exercise, smoking and drinking habits, vitamin supplement use, and consumption of selected foods and beverages in the period preceding the development of the present symptoms or reason for the visit to ACCH.

Cumulative smoking exposure was examined as pack-years of smoking (PY), the product of the number of packs consumed per day and number of years of smoking. In this study, patients were divided into four groups based upon PY, namely non-, light ($PY < 30$), moderate ($30 \leqslant PY < 60$), and heavy smokers ($60 \leqslant PY$). Since we had no a priori threshold for these categories, threshold values were defined by sensitivity analyses at 10 to 60 PY by 10-PY intervals for all OSCC patients. Based on the results, we dichotomized patients by a PY-30 threshold.

Alcohol consumption was used to divide patients into three groups, namely non-, light, and heavy drinkers. Heavy drinkers were defined as individuals who consumed alcoholic beverages in a daily amount of 46 g ethanol (equivalent to two Japanese drinks) or more for 5 days or more per week.[26] The remaining patients were categorized as non- or light drinkers using data from the HERPACC study for head and neck cancers.[26]

Statistical methods

The primary endpoint of this study was overall survival (OS), which was defined as the interval between the beginning of treatment and the date of death or last follow-up. Disease-free survival (DFS) was measured as a secondary endpoint, and was defined as the number of days from the beginning of treatment to the date of relapse, which was evaluated and recorded by each physician. The associations between smoking status and OS or DFS were evaluated by the Kaplan–Meier product-limit method and uni- and multivariate Cox proportional hazards models. The measure of association in this study was hazard ratio (HR) with a 95% confidence interval (CI).

Smoking status (non- vs light vs moderate vs heavy) was a major exposure in this study. Confounders considered in the uni- and multivariate analyses were age (continuous variable), sex (male vs female), Eastern Cooperative Oncology Group performance status (ECOG PS) (0–2), alcohol consumption (non- vs light vs heavy), Union for International Cancer Control (UICC) stage (1–4), and treatment method (surgery vs CRT/RT).

In addition, the interaction between smoking status and treatment method or primary tumor site was examined using a multivariate Cox proportional hazards model. Distribution of patient characteristics was assessed by the χ^2 test or Fisher's exact test as appropriate. All statistical analyses were performed using the software STATA ver. 10 (Stata Corp, College Station, TX, USA). All tests were two-sided, and P-values of < 0.05 were considered statistically significant.

Results

Patient characteristics and survival

Characteristics of the 222 patients evaluated in the study are summarized in Table 1. Median age was 59 years (range, 21–79) and median follow-up time was 4.9 years (range, 0.7 month–9.1 years). The proportion of smokers was higher among males and drinkers. With regard to treatment, 115 patients (51.8%) underwent surgery with or without IC (14 vs 101), and 107 patients (48.2%) were treated with CRT/RT with or without IC (7 vs 100). IC and CRT treatment schedules are detailed in supporting information Table S1. Five-year OS among all patients was 73.1% (95% CI: 66.3–78.7).

Impact of smoking status on clinical outcomes

Five-year OS stratified by smoking status was 72.9% (95% CI: 61.4–81.5) for non-smokers, 85.5% (95% CI: 74.0–92.2) for light smokers, 59.9% (95% CI: 44.3–72.4) for moderate smokers, and 69.0% (95% CI: 42.8–85.0) for heavy smokers (Fig. 1). Because we expected to observe the difference between non-smokers and smokers, we defined light smokers as the reference group in uni- and multivariate analysis. Table 2 shows the results of uni- and multivariate analyses for OS and DFS. Smoking status and several other factors were identified as statistically significant by univariate analysis. Smoking status, ECOG PS and UICC stage remained statistically significant in multivariate analysis for OS. Adjusted HRs for non-, moderate and heavy smokers in comparison with light smokers were 2.27 (95% CI: 0.84–6.15, $P = 0.108$), 2.44 (95% CI: 1.07–5.57, $P = 0.034$), and 2.66 (95% CI: 0.97–7.33, $P = 0.058$) for OS, respectively. In the multivariate analyses, the dose–response relationship among smokers was statistically significance for OS ($P_{trend} = 0.024$) and marginal statistical significance for DFS ($P_{trend} = 0.055$). Additionally, we evaluated this association according to sex. We found a similar tendency in males. In contrast,

Table 1
Characteristics of oral cavity squamous cell carcinoma patients according to smoking status and treatment method.

Characteristics	All (n = 222)				CRT or RT (n = 107)				Surgery (n = 115)			
	Light n = 65 (%)	Moderate n = 54 (%)	Heavy n = 21 (%)	Non n = 82 (%)	Light n = 30 (%)	Moderate n = 27 (%)	Heavy n = 7 (%)	Non n = 43 (%)	Light n = 35 (%)	Moderate n = 27 (%)	Heavy n = 14 (%)	Non n = 39 (%)
Median age (range)	52 (24–78)	62 (43–77)	61 (51–72)	59 (21–79)	50 (28–78)	64 (43–77)	61 (54–72))	57 (25–79	54 (24–76)	62 (51–77)	61 (51–68)	59 (21–79)
Sex												
Male	50 (77)	52 (96)	21 (100)	25 (30)	24 (80)	26 (96)	7 (100)	13 (30)	26 (74)	26 (96)	14 (100)	12 (31)
Female	15 (23)	2 (4)	0 (0)	57 (70)	6 (20)	1 (4)	0 (0)	30 (70)	9 (26)	1 (4)	0 (0)	27 (69)
ECOG PS												
0	31 (48)	18 (33)	8 (38)	31 (38)	17 (57)	7 (26)	2 (29)	13 (30)	14 (40)	11 (41)	6 (43)	18 (46)
1	32 (49)	33 (61)	12 (57)	50 (61)	11 (37)	18 (67)	4 (57)	29 (68)	21 (60)	15 (55)	8 (57)	21 (54)
2	2 (3)	3 (6)	1 (5)	1 (1)	2 (6)	2 (7)	1 (14)	1 (2)	0 (0)	1 (4)	0 (0)	0 (0)
UICC stage												
I	10 (15)	15 (28)	5 (24)	19 (23)	2 (7)	5 (19)	0 (0)	4 (9)	8 (23)	10 (37)	5 (35)	15 (38)
II	20 (31)	14 (26)	7 (33)	25 (31)	8 (27)	8 (29)	3 (43)	13 (30)	12 (34)	6 (22)	4 (29)	12 (31)
III	15 (23)	9 (17)	4 (19)	13 (15)	7 (23)	5 (19)	3 (43)	9 (21)	8 (23)	4 (15)	1 (7)	4 (10)
IV	20 (31)	16 (29)	5 (24)	25 (31)	13 (43)	9 (33)	1 (14)	17 (40)	7 (20)	7 (26)	4 (29)	8 (21)
Alcohol consumption												
Non	12 (19)	3 (6)	2 (10)	51 (62)	5 (17)	1 (4)	0 (0)	30 (70)	7 (20)	2 (7)	2 (14)	21 (54)
Light	34 (52)	25 (46)	7 (33)	22 (27)	18 (60)	14 (52)	1 (14)	8 (18)	16 (46)	11 (41)	6 (43)	14 (36)
Heavy	15 (23)	24 (44)	11 (52)	5 (6)	6 (20)	12 (44)	5 (72)	3 (7)	9 (26)	12 (45)	6 (43)	2 (5)
Unknown	4 (6)	2 (4)	1 (5)	4 (5)	1 (3)	0 (0)	1 (14)	2 (5)	3 (8)	2 (7)	0 (0)	2 (5)

Smoking status was divided as follows: Non, light (PY < 30), moderate (30 < PY < 60), and heavy (60 < PY).
Abbreviation: ECOG, eastern cooperative oncology group; UICC, union for international cancer control; PS, performance status; CRT, chemoradiotherapy; RT, radiotherapy; PY, pack-years smoking.

Figure 1 Kaplan–Meier survival curves according to smoking status. Five-year overall survival (OS) was 72.9% (95% confidence interval: 61.4–81.5) for non-, 85.5% (74.0–92.2) for light, 59.9% (44.3–72.4) for moderate, and 69.0% (42.8–85.0) for heavy smokers, respectively.

alcohol consumption showed no significant association with both OS and DFS.

Interaction between smoking status and treatment method or primary tumor site

Survival curves of patients according to treatment method are shown in Fig. 2A and B. Among patients treated with CRT/RT, 5-year OS was 60.4% (95% CI: 43.4–73.8) for non-smokers, 93.2% (95% CI: 75.5–98.3) for light smokers, 54.4% (95% CI: 32.8–71.7) for moderate smokers, and 53.6% (95% CI: 13.2–82.5) for heavy smokers (Fig. 2A). On multivariate analysis, non-smokers had significantly worse survival than light smokers (HR, 8.42: 95% CI, 1.49–47.57, P = 0.016, Table 3).

Among patients treated with surgery, 5-year OS was 86.9% (95% CI: 71.4–94.4) for non-smokers, 79.3% (95% CI: 61.4–89.6) for light smokers, 65.3% (95% CI: 41.9–81.2) for moderate smokers, and 78.6% (95% CI: 47.3–92.5) for heavy smokers (Fig. 2B). In multivariate analysis, non-smokers had improved survival (HR, 0.70: 95% CI, 0.16–3.11, P = 0.639) in comparison with light smokers albeit that the difference was not statistically significant.

Although a marginal interaction between smoking status and treatment method was observed (P for heterogeneity = 0.069), treatment method did affect survival, particularly in non-smokers. When stratified by smoking status and treatment method combined using light smokers treated with CRT/RT as the reference group, non-smokers treated with CRT/RT tended to have worse survival than those treated with surgery (adjusted HR, 7.31: 95% CI, 1.49–35.88 vs HR, 3.26: 95% CI, 0.55–19.24).

With regard to primary tumor site, 147 patients were located in tongue and 75 cases in other oral cavity which include gum, floor of mouth, hard palate and cheek mucosa. We also examined the interaction between smoking status and primary tumor site (tongue vs other oral cavity) of OSCC (Table 3). We observed no significant interaction between smoking status and primary tumor site on OS.

Relapse and second primary tumor

During follow-up, 70 OSCC patients (30.6%) had relapsed, which consisted of 36 local (16.2%), 28 regional (12.6%) and 8 distant (3.6%). The no significant association between relapse lesion and smoking status was observed in this study (P = 0.370).

Table 2
Uni- and multivariate analysis for clinical outcomes in oral cavity squamous cell carcinoma proteins.

Baseline and clinical features of all patients	Overall survival						Disease-free survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-values	HR	95% CI	*P*-values	HR	95% CI	*P*-values	HR	95% CI	*P*-values
Smoking status												
Light	Reference	–	–	Reference	–	–	Reference	–	–	Reference	–	–
Moderate	3.26	1.50–7.07	0.003	2.44	1.07–5.57	0.034	2.25	1.25–4.04	0.007	1.80	0.96–3.38	0.065
Heavy	2.68	1.04–6.96	0.042	2.66	0.97–7.33	0.058	2.02	0.96–4.29	0.066	1.90	0.85–4.24	0.118
P_{trend}	(smokers)	0.006	0.024	0.011	0.055							
Non	1.91	0.88–4.16	0.101	2.27	0.84–6.15	0.108	1.54	0.87–2.73	0.135	2.08	1.04–4.15	0.039
Alcohol consumption												
Non	Reference	–	–	Reference	–	–	Reference	–	–	Reference	–	–
Light	0.97	0.52–1.84	0.937	0.91	0.38–2.19	0.833	1.12	0.67–1.87	0.657	1.05	0.54–2.05	0.885
Heavy	1.51	0.78–2.90	0.219	1.44	0.55–3.78	0.455	1.38	0.80–2.39	0.251	1.34	0.63–2.83	0.448
Age	1.03	1.00–1.05	0.017	1.02	0.99–1.04	0.130	1.02	1.00–1.04	0.029	1.01	0.99–1.03	0.253
Sex												
Male	Reference	–	–	Reference	–	–	Reference	–	–	Reference	–	–
Female	0.80	0.46–1.38	0.417	0.76	0.27–2.17	0.608	0.75	0.48–1.18	0.216	0.69	0.34–1.40	0.301
ECOG PS												
0	Reference	–	–	Reference	–	–	Reference	–	–	Reference	–	–
1	4.59	2.17–9.70	<0.001	4.39	2.04–9.42	<0.001	2.19	1.36–3.53	0.001	2.14	1.30–3.52	0.003
2	15.26	4.56–51.09	<0.001	8.70	2.27–33.41	0.002	7.05	2.86–17.41	<0.001	4.49	1.63–12.33	0.004
UICC stage												
1	Reference	–	–	Reference	–	–	Reference	–	–	Reference	–	–
2	1.92	0.60–6.12	0.271	2.19	0.67–7.19	0.196	1.37	0.70–2.71	0.361	1.49	0.73–3.03	0.272
3	3.92	1.26–12.16	0.018	3.22	1.00–10.30	0.049	1.55	0.74–3.22	0.244	1.35	0.63–2.89	0.444
4	10.40	3.69–29.33	<0.001	10.10	3.49–29.23	<0.001	3.71	1.99–6.94	<0.001	3.34	1.73–6.44	<0.001
Treatment method												
Surgery	Reference	–	–	Reference	–	–	Reference	–	–	Reference	–	–
CRT or RT	1.80	1.07–3.00	0.025	1.14	0.65–1.98	0.648	1.49	0.99–2.24	0.057	1.15	0.74–1.79	0.540

Smoking status was divided as follows: Non, light (PY < 30), moderate (30 ⩽ PY < 60), and heavy (60 ⩽ PY).
Abbreviation: ECOG, eastern cooperative oncology group; UICC, union for international cancer control; PS, performance status; CRT, chemoradiotherapy; RT, radiotherapy; HR, hazard ratio; CI, confidence interval; PY, pack-years smoking.

In addition, second primary head and neck cancer had occurred in 13 cases (5.9%), which consisted of 7 cases located in oral cavity, 4 in oropharynx and 2 in hypopharynx. According to smoking status, there were 4 cases for non-, 1 case for light, 6 cases for moderate and 2 cases for heavy smokers. The no significant association between second primary tumor and smoking status was observed in this study ($P = 0.135$).

Discussion

In this study, we found that pre-treatment smoking status was associated with survival in OSCC patients. This effect was evident only among the CRT/RT group, suggesting that it might differ by treatment method, which would be consistent with the findings of our previous study in patients with esophageal squamous cell carcinoma.[21] To our knowledge, this is the first study to evaluated the association between smoking status and survival according to treatment method in OSCC patients.

Our results suggest that smoking might affect the response to CRT/RT. Several studies have demonstrated an association between smoking and poor survival in head and neck cancer patients treated with CRT/RT.[8–10,13] Among the potential mechanisms reported, the effect of smoking in inducing chronic hypoxia hampers the efficacy of RT, which depends on oxygenation for the production of free radicals.[19] Second, smoking-induced p53 mutations might also decrease the efficacy of RT.[27–30] Third, the carboxyhemoglobin complex, which is formed when carbon monoxide from smoking binds with hemoglobin, might increase the radiation dose required for local control.[31] Finally, smoking's contribution to hypoxia within tumor tissues may result in the upregulation of epidermal growth factor receptor (EGFR).[32] These reports might explain the poor survival in OSCC patients treated with CRT/RT.

Interestingly, we found that non-smokers had the lowest survival among OSCC patients treated with CRT/RT in this study. To our knowledge, only one study has evaluated the impact of smoking status on prognosis in OSCC patients, which found that prognosis did not significantly differ by smoking status.[16] Regarding head and neck cancer, all studies to date have demonstrated that non-smokers have better survival than smokers.[8–15] This inconsistency with head and neck cancers may come from heterogeneity in (1) primary tumor site, (2) data handling of treatment modalities, (3) method of evaluating smoking exposure, and (4) biological status, which might affect the RT resistance of non-smoking OSCC patients.[33]

With regard to the first of these possibilities, two distinct disease patterns has been recognized in young OSCC patients, who have had relatively little smoking exposure, namely an extremely aggressive course with a high mortality rate within 2 years, and a more indolent course with a lower mortality rate 20. Validation in a different large patient cohort is essential.

Our study had several methodological strengths. First, because pre-treatment smoking status remained unchanged for individual OSCC patients, the chronological relation between exposure and outcome could be clearly evaluated. Second, because the analyses took account of potential confounders, such as clinical disease stage and PS, the observed associations were theoretically independent of confounders, although we cannot completely rule out the effect of residual confounding by unevaluated factors, for example human papilloma virus (HPV) infection.

Our study also had several limitations. First, our information about smoking reflected pre-treatment smoking status only.

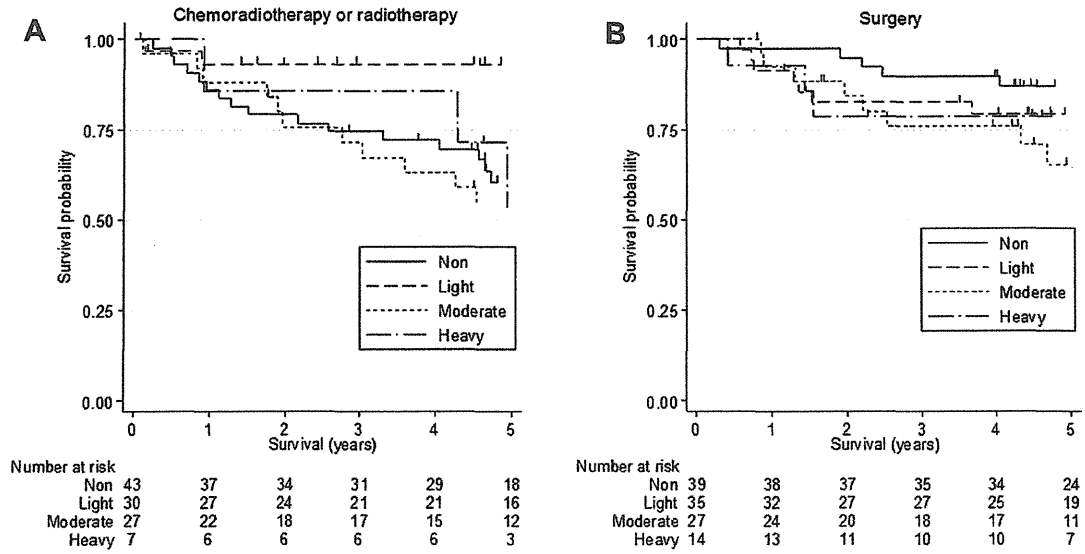

Figure 2 Kaplan–Meier survival curves for treatment methods. (A) Among the patients treated with chemoradiotherapy or radiotherapy, 5-year OS was 60.4% (95% confidence interval: 43.4–73.8) for non-, 93.2% (75.5–98.3) for light, 54.4% (32.8–71.7) for moderate and 53.6% (13.2–82.5) for heavy smokers, respectively. (B) Among patients treated with surgery, 5-year OS was 86.9% (71.4–94.4) for non-, 79.3% (61.4–89.6) for light, 65.3% (41.9–81.2) for moderate and, 78.6% (47.3–92.5) for heavy smokers, respectively.

Table 3
Interaction between smoking status and treatment method for overall survival in oral cavity squamous cell carcinoma patients.

Clinical characteristics		Smoking status	*n*	Multivariate analysis for OS				Multivariate analysis for OS		
				HR	95% CI	*P*-values	*P* for heterogeneity	HR	95% CI	*P*-values
Treatment method	CRT or RT	Light	30	Reference	–	–		Reference	–	–
		Moderate	27	5.31	1.09–25.90	0.039		6.26	1.36–28.85	0.019
		Heavy	7	5.35	0.80–35.86	0.084		8.25	1.41–48.26	0.019
		Non	43	8.42	1.49–47.57	0.016	0.069	7.31	1.49–35.88	0.014
	Surgery	Light	35	Reference	–	–		4.39	0.88–21.82	0.071
		Moderate	27	1.27	0.43–3.77	0.668		6.10	1.26–29.61	0.025
		Heavy	14	1.02	0.24–4.28	0.977		5.23	0.85–32.33	0.075
		Non	39	0.70	0.16–3.11	0.639		3.26	0.55–19.24	0.193
Primary tumor site	Tongue	Light	45	Reference	–	–				
		Moderate	35	2.42	0.85–6.93	0.100				
		Heavy	10	2.10	0.51–8.67	0.303				
		P_{trend} (smokers)				0.046				
		Non	57	1.64	0.42–6.31	0.475	0.897			
	Other oral cavity	Light	20	Reference	–	–				
		Moderate	19	3.29	0.80–13.50	0.099				
		Heavy	11	3.71	0.65–21.05	0.139				
		P_{trend} (smokers)				0.078				
		Non	25	3.71	0.45–30.44	0.221				

Note: adjusted by age, sex, performance status, clinical disease stage, alcohol consumption Smoking status was divided as follows: Non, light (PY < 30), moderate (30 < PY < 60), and heavy (60 < PY). Other oral cavity include gum, floor of mouth, hard palate and cheek mucosa.
Abbreviation: CRT, chemoradiotherapy; RT, radiotherapy; HR, hazard ratio; CI, confidence interval; PY, pack-years smoking; OS, overall survival.

Several studies have reported that smoking cessation during RT was beneficial to clinical outcome.[8,9,13,34] Second, our analysis used PY, not smoking habits. Therefore, we divided patients into three groups according to smoking habits (non vs former vs current), and identified a similar tendency among them (data not shown). Third, the study might also have been biased by the impact of competing risks, namely smoking-related comorbidities such as coronary artery disease, cerebral infarction, peripheral vascular disease, and chronic obstructive pulmonary disease. If death due to these competing risks were common in the heavy smoking group, our study would have overestimated the impact of heavy smoking on OSCC death. In fact, while the proportion of patients who died from OSCC alone was 67.2%, information on the cause of death was unavailable for 21.3%. Fourth, although we tried to estimate bias by potential confounders in the multivariate analysis, the effect of residual confounders including HPV infection cannot be completely ruled out. However, the prevalence of HPV among OSCC patients are lower than oropharyngeal cancer patients.[35] Finally, the moderate sample size, although the largest to date for an oral cancer-only cohort, may have limited the study, necessitating the duplication of this work in an independent cohort.

In conclusion, we found that pre-treatment smoking status has prognostic value in OSCC patients. In addition, we observed that treatment method might affect survival in these patients, particularly non-smokers. Further study to validate our results and evaluate the impact of tumor characteristics, genetic polymorphisms, or both, on the differing sensitivities to CRT and RT by smoking status is warranted.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.oraloncology.2011.09.012.

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Nicotine Dependence and Cost-Effectiveness of Individualized Support for Smoking Cessation: Evidence from Practice at a Worksite in Japan

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Abstract

Given the lack of economic studies evaluating the outcomes of smoking cessation programs from the viewpoint of program sponsors, we conducted a case study to provide relevant information for worksites. The present study was carried out between 2006 and 2008 at a manufacturing factory in the Toyama Prefecture of Japan and included subjects who voluntarily entered a smoking cessation program. The program included face-to-face counselling followed by weekly contact to provide encouragement over six months using e-mail or inter-office mail. Nicotine patches were available if required. All 151 participants stopped smoking immediately. Over the 24-month study period, self-report showed 49.7% abstained continuously from smoking. The rate of 24-month consecutive abstinence was higher in participants with lower Fagerström Test scores for Nicotine Dependence at baseline than in those with higher scores (63.6% for 0–2 points vs. 46.5% for 3–6 points vs. 43.8% for 7–10 points; chi-square test $p = 0.19$). A logistic regression model showed a significant linear trend for the association between the score and abstinence status after adjustment for possible confounding factors ($p = 0.03$). The crude incremental cost for one individual to successfully quit smoking due to the support program was ¥46,379 (i.e., ¥100 = $1.28, £0.83, or €1.03 at foreign exchange rates). The corresponding costs for the three categories of the Fagerström Test score for Nicotine Dependence were ¥31,953, ¥47,450 and ¥64,956, respectively. When a sensitivity analysis was conducted based on the 95% confidence interval of the success rate, the variance in the corresponding costs was ¥25,514–45,034 for 0–2 points, ¥38,344–61,824 for 3–6 points, and ¥45,698–108,260 for 7–10 points. The degree of nicotine dependence may therefore be an important determinant of the cost-effectiveness of smoking cessation programs.

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Introduction

Cigarette smoking is a crucial but avoidable cause of premature disability and death due to cardiovascular disease, cancer, and respiratory tract disease [1–3]. In Japan, where the rate of smoking in males exceeds that of males in developed Western countries [4,5], 38.6% of cancer-related deaths, 23.4% of deaths due to respiratory tract disease, and 23.0% of deaths due to cardiovascular disease among Japanese males have been attributed to a history of smoking [2]. Smoking is burdensome because of the effects on premature disability and excess mortality [2,3] and also because of the substantial costs to medical insurers in Japan [6,7]. Izumi et al [6] showed that over a follow-up period of 30 months, Japanese males with a history of smoking incurred medical costs averaging ¥3,000 per month in excess of the costs attributed to individuals who had never smoked. As a result, up to four percent of total medical expenditures in the Japanese population may be attributable to smoking [6].

A key strategy for promoting smoking cessation in people intending to quit is to provide individualized support including professional counselling and pharmacological therapy [8,9]. In addition to assistance rendered in clinics and hospitals, employers can also offer similar support given that health care providers, such as occupational health physicians and nurses, are available at worksites [10–15]. Furthermore, worksites present favorable settings for implementing smoking cessation programs for several reasons. First, worksites employ young adult and middle-aged smokers who are candidates for early smoking cessation intervention. Second, the work environment readily promotes favorable interaction between employees attempting to stop smoking and health care providers, as they are peers who all belong to the same worksite. Third, easy accessibility to both health care providers and employees in the worksite is advantageous as it allows flexible delivery of smoking cessation therapies without the need for missing work or having communications in private. Finally, all

employers are responsible for managing the health care of their employees.

Previous studies, including randomized controlled trials and case studies, have examined the effectiveness of various worksite support systems for smoking cessation in Japan [10–15] and in other countries [16–22]. However, in the majority of previous studies the follow-up periods were incomplete and the status of successful smoking cessation was assessed for only 12 months after program initiation despite evidence that some individuals may resume smoking even after abstaining for one year [23,24]. Therefore, the outcomes of individuals attempting to quit smoking may be inaccurately reflected in the current published literature. Furthermore, in spite of the practical importance of considering both the effectiveness and cost-effectiveness of smoking cessation programs, economic evidence supporting the implementation of these programs, particularly from the perspective of program sponsors, is limited throughout the world [16,25–28]. To assist with promoting smoking cessation in the worksite, we conducted a case study with the aim of providing preliminary information on the effectiveness and cost-effectiveness of an individualized support program at a worksite in Japan. First, we employed a two-year follow-up period in order to evaluate the long-term outcomes of individuals who participated voluntarily in a six-month program at a single worksite. Second, we estimated the cost-effectiveness of this program from the perspective of the employer who paid for this program. Finally, we evaluated these outcomes in the subjects stratified by nicotine dependence status. Published studies have indicated that compared to smokers who scored lower on measures of nicotine dependence, smokers who scored higher have more frequently elected to use nicotine replacement therapy [29] but have succeeded in smoking cessation less often [30]. The guideline also recommends physicians to consider nicotine replacement therapy more positively in the case of greater nicotine dependence [31]. Nicotine dependence, therefore, may influence the cost-effectiveness of smoking cessation programs.

Methods

Study setting and participants

This case study was conducted at a metal products factory in the Toyama prefecture of Japan. Approximately 4,800 male and 2,500 female workers were employed at this factory, where smoking is allowed in limited areas. At the initiation of the study in 2006, an annual health examination conducted in the same year indicated that 48.4% of male workers and 6.1% of female workers, aged 20 years or older were active smokers. During the three-year interval spanning the fiscal years 2006 and 2008, a total of 155 workers who smoked (150 men and five women) participated voluntarily in the study and signed a smoking cessation declaration form. We allocated all the participants to the intervention group without establishing a control group. The study was approved by the Institutional Review Committee of Kanazawa Medical University for Ethical Issues.

Smoking cessation program

A worksite clinic at the target factory employed an occupational health physician and six nurses with each of the nurses sharing responsibility for the participants. Using an individualized approach, the smoking cessation program consisted of the following three steps. First, in order to educate the participants on the hazards of smoking and the benefits of cessation and to strengthen self-efficacy, the occupational health physician and a nurse conducted a joint introductory face-to-face counselling session at the worksite clinic. At this time, the participants provided information on the number of cigarettes smoked each day, cessation history, nicotine dependence, alcohol drinking habits, and disease profiles through self-reported questionnaires or physical and medical records of annual health examinations. The levels of nicotine dependence were assessed using the Fagerström Test for Nicotine Dependence (FTND) [32]. The participants were next required to submit a diary on smoking cessation via e-mail or inter-office mail once a week for a period of six months. The responsible nurse inspected the diary to confirm smoking cessation status and then provided a tailor-made, encouraging comment every week. For participants who did not submit a diary, the nurse confirmed smoking cessation status every month. Lastly, nicotine replacement therapy was offered to participants who desired to use it or if the physician considered this therapy would be beneficial after reference to the FTND scores and/or the number of cigarettes smoked each day. The nicotine patches were the only aid used to simplify the study design. The physician basically followed the Manual on Smoking Cessation Support issued by relevant Japanese medical societies, which recommends that nicotine replacement therapy is more applicable to smokers with greater nicotine dependence, starting with 30 mg patches [31]. However, the study left this matter to the discretion of the physician and/or desire of the participant, as is often the case in a practice setting, a fact that this study regarded as important. Participants who elected nicotine replacement therapy paid for 30% of the treatment costs. Only nicotine patch users were required to visit the worksite clinic mainly to obtain a prescription for this medication. This support was stopped at the end of the sixth month. Incentives were also offered, with participants who abstained for six consecutive months being congratulated for completing the six-month support program, and presented with an award. Finally, smoking cessation status was assessed on the basis of self-reporting after a further 18 months of follow-up, during which time no support was provided. Individuals who refrained from smoking for 24 consecutive months after initially stopping were regarded as successful quitters.

Other smokers at the factory

We also examined the characteristics of workers who smoked and did not participate in the smoking cessation support program. In addition, we examined the smoking pattern in these non-participating smokers over a two-year follow-up period from 2006 to 2008 in order to estimate the natural quit rate in smokers at the target factory. In employees who underwent an annual health examination in 2006 (enrolment rate >90% of total employees), there were 2,216 non-participating smokers, aged 20 years or older (2,069 men and 147 women), after excluding the 155 smokers who received support to stop smoking. Data were collected from physical and medical records obtained at the annual health examinations on smoking habits, cigarettes smoked each day, alcohol drinking habits, disease profiles in 2006, and smoking habits in 2008. This procedure was conducted as part of a cohort study that consisted of workers in the factory who provided their approval to take part after considering the ethical issues. The details of the study subjects and methods have been described elsewhere [33,34].

Data analysis

First, we calculated the rate of consecutive abstinence in the 24th month after cessation of smoking had commenced. Next, using reference to a previous study [25], we assessed the cost-effectiveness of our support program from the viewpoint of the employer who was the program sponsor. In this economic evaluation, the costs were expressed in Japanese Yen, with the

program costs consisting of the following three components: 1) material costs (diaries, documents, nicotine patches, and awards), 2) opportunity costs for health care providers, and 3) opportunity costs for participants, which represented the loss in production time due to attendance at the worksite clinic for initial counselling, and prescription of nicotine patches and diary entries during work time. To calculate the opportunity costs for participants, this study assumed that the employer who was the program sponsor allowed the participants to engage in these activities during work time. No developmental costs were incurred based on the assumption that the program did not require the health care providers to have specialized skills for smoking cessation. The opportunity costs for health care providers were calculated by multiplying the time (hours) spent for each procedure by the respective average 2006 hourly salary rates (¥/hour) for physicians and workers at manufacturing companies in Japan [35]. The crude incremental cost for one individual to successfully quit smoking due to the support program was calculated as the total costs incurred in the program divided by the number of 24-month consecutive abstainers. Because success rate is an important determinant of cost-effectiveness [36], we performed a sensitivity analysis to evaluate the extent to which the cost-effectiveness changed in response to variations in success rate. The 95% confidence interval of success rate was calculated for test parameters used in the sensitivity analysis. The upper limit of the 95% confidence interval was calculated using F-distribution functions as: $\{2(y+1)\times F_{(2(y+1),\ 2(n-y);\ 0.05/2)}\}/\{2(y+1)\times F_{(2(y+1),\ 2(n-y);\ 0.05/2)}+2(n-y)\}$, where $F_{(2(y+1),\ 2(n-y);\ 0.05/2)}$ was the F-value with $2(y+1)$ and $2(n-y)$ degrees of freedom, n was the number of participants, and y was the number of successful quitters [37]. The lower limit of the 95% confidence interval was calculated as: $2y/\{2(n-y+1)\times F_{(2(n-y+1),\ 2y;\ 0.05/2)}+2y\}$, where $F_{(2(n-y+1),\ 2y;\ 0.05/2)}$ was the F-value with $2(n-y+1)$ and $2y$ degrees of freedom, and n and y were the same as described above [37]. Variance in the number of successful quitters was determined by multiplying the number of participants by the lower and upper limits of the success rate. The lower and upper limits of incremental cost for one individual to successfully quit smoking due to the support program was then calculated as the total costs incurred in the program divided by the upper and lower limits of the number of successful quitters, respectively.

It is likely that some of our study participants may have successfully stopped smoking without our support (i.e., natural quitters) [13,25]. It is therefore necessary to evaluate the net cost-effectiveness, taking into account individuals who stopped smoking unassisted. Using the results on the natural quit rate in smokers who had not received support to stop smoking, we calculated the number of abstainers in an unassisted situation as the number of participants multiplied by the natural quit rate. The net incremental cost for one individual to successfully quit smoking due to the support program was calculated as {(total costs incurred in the program) minus (no costs incurred in an unassisted situation)} divided by {(the number of 24-month consecutive abstainers in the support program) minus (the number of abstainers in an unassisted situation)} [38].

Finally, the chi-square test was used to compare the rates of 24-month consecutive abstinence in participants grouped according to the FTND score at baseline (0–2 points, 3–6 points or 7–10 points, classified as mild, moderate, or severe nicotine dependence, respectively [32]). The significance of the linear trend for the association between FTND score (continuous variable) and successful smoking cessation was tested using a logistic regression model that incorporated the following variables as covariates: age (continuous variable), sex (male or female), cigarettes smoked each day (continuous variable), cessation history (yes or no), alcohol drinking habits (drinker or non-drinker (including occasional drinker)), and history of either heart disease, stroke, cancer, chronic respiratory disease, hypertension (defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mm Hg and/or taking medication for hypertension), hypercholesterolemia (defined as a serum low-density lipoprotein cholesterol ≥3.62 mmol/l (140 mg/dl) and/or taking medication for hypercholesterolemia), or diabetes (defined as a the Japan Diabetes Society-Hb_{A1c}≥6.1 % (or the National Glycohemoglobin Standardization Program-Hb_{A1c}≥6.5 %) and/or taking medication for diabetes). Following stratification of the participants into the three levels of nicotine dependence, defined by the baseline FTND scores, we assessed the effect of varying the rates of nicotine patch use and smoking cessation success on cost-effectiveness. It has been reported that these factors may be influenced markedly by FTND score [29–31]. In addition, we performed a similar sensitivity analysis using the various FTND scores, basing the test parameters for the sensitivity analysis on the 95% confidence interval of success rate which was calculated in a similar manner.

The statistical analyses were performed using the Statistical Package for the Social Sciences Version 12.0J for Windows (SPSS Japan Inc., Tokyo, Japan). All probability values were two-tailed and the significance level was set at $p<0.05$.

Results

Characteristics of study participants

Of the 155 smokers who participated voluntarily in the study (150 men and five women), one participant retired one month after stopping smoking without relapse and further three participants had missing baseline survey data. After excluding these four participants, the remaining 151 participants (146 men and five women) were considered eligible for inclusion in the analysis.

At baseline, the mean age±standard deviation of the 151 study participants was 44.2±11.2 years (Table 1). The mean number of cigarettes smoked each day was 20.5±7.5, while the mean FTND score was 4.6±2.5 points. The FTND scores of the participants were distributed as follows: 21.9% scored 0–2 points, 57.0% scored 3–6 points, and 21.2% had 7–10 points. Of the participants, 46.4% had attempted to quit smoking previously, and 55.6% had a health problem at study entry (defined as any combination of a history of heart disease, stroke, cancer, chronic respiratory disease, hypertension, hypercholesterolemia, and/or diabetes), while 3.3% had a severe health problem (defined as any combination of heart disease, stroke, cancer, and/or chronic respiratory disease). When stratified according to the FTND score, the means of age and cigarettes smoked each day and the prevalence of having previously attempted to quit smoking and having a severe health problem were higher with increasing FTND score.

The means of age and cigarettes smoked each day and the prevalence of having a health problem were higher in smokers who participated in the smoking cessation support program than in the 2,166 non-participating smokers, after exclusion of those with missing baseline survey data (n = 50).

Success rate in the study participants

Nicotine patches were used by 61.6% (n = 93) of all the participants, with the total quantities consumed by the study population being 1,091 person-pieces for 30 mg patches, 889 person-pieces for 20 mg patches, and 560 person-pieces for 10 mg patches (Table 2). Nicotine patches were used more frequently by