はじめに

2009年８月に看護の科学社から出版された『－事例で学ぶ－禁煙治療のためのカウンセリングテクニック』は，主にこれから禁煙治療に従事する医療職を対象として，事例中心のマニュアル本として作成しました。あれから3年が経過し，読者の一部から，「カウンセリングの理論を用いた，より専門的な禁煙治療のためのカウンセリング技法について学びたい」という声が寄せられました。そこで，禁煙治療で用いるカウンセリング技術のレベルアップを図りたい医療職を想定した「エキスパート編」を同社から再び刊行することになりました。

本書の最大の特徴は，日本で禁煙治療がはじまる前に海外で理論構築されていた様々なカウンセリングに関する一般理論の中から，著者の喫煙者に対するカウンセリングの豊富な経験に基づいて，禁煙治療への適用を念頭に，諸理論を比較・整理したことにあります(第１章)。そして，その比較・整理に基づいて，禁煙カウンセリングに役立つ理論と技術を，「聴く」「分析(評価)する」「介入する」という，医療行為の基本的な思考パターンに近い3つのカテゴリーに新たに分類して再構築したことです(第2，3，4章)。これによって，これまで読者の皆さんが頭の中でモヤモヤしていたカウンセリングの一般理論と効果的な禁煙カウンセリングの実践との対応が，スッキリするのではないかと思われます。

また，前書でも好評だった，禁煙カウンセリングのプロセスレコードのうち，失敗例を中心に今回も提示しています(第６章)。何がどう失敗だったか，そしてどうすれば良かったのかを，再構築されたカウンセリング理論から学べるように工夫してあり，これを読み解くことでスキルアップの効果が期待できるものと思われます。さらに，禁煙治療中によく見られる患者さんの体重増加への指導など，身体的な問題の対処についても今回新たに追加しました(第５章)。

本書が禁煙治療における個別指導，カウンセリングの技術に行き詰まりを感じていたり，さらにレベルアップを図りたいと考えておられる方の一助となりましたら幸いです。また，本書の作成後に感じたことですが，本書が記すカウンセリングの理論構成と技術は，禁煙だけでなく，食事や運動などのその他の保健行動の変容を目指した指導，カウンセリングにも応用できる部分が多いと思われます。

最後になりましたが，本書の企画にインスピレーションとモチベーションを与えて下さった，多くの禁煙外来の患者さんに心から謝意を表します。

平成24年7月20日

編者
田中 英夫

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事例で学ぶ
禁煙治療のためのカウンセリングテクニック　エキスパート編
2012年8月31日　第１版　第１刷 ©
著　者　谷口　千枝
編　集　田中　英夫
発行者　赤塚　静子
発行所　看護の科学社
http://www.kango.co.jp
〒112-0012　東京都文京区大塚3-19-10
☎03-3943-0244　郵便振替 00100-9-43439
印刷・製本／ハラ工芸
Printed in Japan
落丁・乱丁などの不良品はお取替えいたします。　ISBN978-4-87804-067-2

J Epidemiol 2012;22(1):57-63
doi:10.2188/jea.JE20110038

Original Article

Necessity and Readiness for Smoking Cessation Intervention in Dental Clinics in Japan

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Received April 5, 2011; accepted September 14, 2011; released online December 10, 2011

ABSTRACT

Background: The necessity and readiness for smoking cessation intervention in dental clinics was assessed by investigating smoking status and stage of behavior change in patients and the attitudes of dentists toward the effects of smoking on their patients, respectively.

Methods: A self-administered questionnaire was mailed to 1022 dentists randomly selected from the Japanese Dental Association database. The questionnaire survey consisted of 1 section for dentists and 1 for patients aged 20 years or older and was scheduled to be completed at the dentists' clinics on a designated day in February 2008.

Results: The response rate to the questionnaire was 78.2% from among target dental clinics and 73.7% and 74.7% for patient and dentist questionnaires, respectively. Data from 11 370 patients and 739 dentists were analyzed. The overall smoking prevalence among the patients (25.1%) was similar to that reported by the National Health and Nutrition Examination Survey, and young female patients had a markedly higher smoking prevalence. More than 70% of patients who smoked were interested in quitting. Although the prevalence of current smoking among dentists (27.1%) was significantly higher than that reported among Japanese physicians (15.0%), approximately 70% of dentists were concerned about the effects of smoking on patient health and prohibited smoking inside their clinic.

Conclusions: Many smokers who were interested in quitting, particularly young women, visited dental clinics, and most dentists believed that smoking was harmful for their patients. These results indicate that smoking cessation intervention in dental settings is necessary and that dentists are ready to provide such interventions.

Key words: dentist; patient; health care survey; smoking; smoking cessation

INTRODUCTION

Smoking is the most important preventable cause of morbidity and mortality. The prevalence of metabolic syndrome is higher among Japanese male smokers than among their nonsmoking counterparts.[1] The estimated population-attributable fraction of all-cause mortality due to smoking among Japanese aged 40 to 79 years is 27.8% in men and 6.7% in women.[2] In Japan, the prevalence of smoking in men is the highest among industrialized countries, whereas that in women is low but has recently increased. Current smoking patterns indicate that comprehensive tobacco control programs should be implemented to reduce the public health burden of smoking-related diseases, which will persist over the next several decades if necessary measures are not taken.[3]

Health professionals have a prominent role in tobacco control.[4] They interact with smokers when tobacco users are most open to health advice and help them quit smoking through the services they provide in their daily practices. Many studies have shown that behavioral counseling and pharmacotherapy by health professionals are effective in managing nicotine dependence.[5–7] Treatment delivered by clinicians in different specialties increased abstinence rates and was more effective than interventions delivered by clinicians in a single speciality.[8] In short, a multidisciplinary approach is required to identify smokers and treat nicotine dependence.

Dental clinics are expected to have a unique role in creating strategies for smoking cessation intervention.[9] Oral screening and patient education have always been an important part of routine dental practice. Dental visits therefore provide dental professionals with frequent opportunities to educate their patients with regard to the effects of smoking.[10,11] In addition, many studies have reported the efficacy of smoking cessation

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interventions in the dental setting (ie, the effectiveness of interventions under ideal conditions). A systematic review revealed that behavioral interventions conducted by dental professionals for tobacco users also increased abstinence rates.[12] Another study reported that the smoking abstinence rate approximately tripled after 1 year of counseling by dental professionals using pharmacologic aids.[13]

Although the potential and efficacy of smoking cessation programs in dental practice are known, the necessity and readiness for such interventions remain unclear because there are few large-scale studies or healthcare data on such interventions in dental clinics. Such data could be used to evaluate how many smokers visit dental clinics, how many are interested in quitting, and how many can be referred to medical institutions for treatment of nicotine dependence. In addition, there are insufficient data on dentists' attitudes and concern toward the effects of smoking on their patients, which could affect such interventions in their practice.

The present study assessed the necessity and readiness of dental clinics to execute interventional programs for smoking cessation among patients. The study evaluated smoking status, stage of behavior change, and the level of nicotine dependence among dental patients, as well as smoking status among dentists and their attitudes toward the effects of smoking on their patients.

METHODS

Data collection

An economic study was designed and conducted to test the hypotheses that smoking-related dental diseases increase the costs of dental care and that smoking cessation interventions in dental clinics decrease those costs. This survey of dental clinics was conducted as part of that economic study. The survey was conducted at each dental clinic on a designated day during the period from 19 to 22 February 2008. Reminder letters were sent twice to nonrespondents, in May and July 2008. For the survey, 1022 dentists were randomly selected from the list of general dental practitioners registered with the Japan Dental Association (JDA; total membership 65 329) in fiscal 2007. The survey comprised 2 parts: 1 for dentists and 1 for their patients. Each dental clinic received a self-administered questionnaire requiring no name identification, a recommendation letter from the director of the JDA, and a cover letter requesting the return of the completed questionnaire by mail. Patients aged 20 years or older who visited the dental clinic on the designated day were informed of the study protocol by their dentist. Patients who gave informed consent to participate in the study completed the questionnaire while waiting for their appointment. Each dentist was asked to enclose the completed questionnaire in an envelope, seal it, and return it in a pre-addressed stamped envelope. The study protocol was approved by the Ethics Committee of Fukuoka Dental College (Ethics Approval No. 115).

Measures

The questionnaire included questions regarding the smoking status of patients, their readiness to quit smoking, and nicotine dependence. Smoking status was defined as follows: current smoker (an individual who currently smokes and has smoked more than 100 cigarettes since starting), former smoker (an individual who does not smoke currently but has previously smoked more than 100 cigarettes), and nonsmoker (an individual who has never smoked or has smoked no more than 100 cigarettes).[14]

Stage of behavior change, ie, level of readiness to quit smoking, was assessed using the following stages: (1) pre-contemplation stage with no interest to quit (ie, an individual who is not interested in quitting), (2) pre-contemplation stage with an interest to quit or contemplation stage (an individual who is interested in quitting but is not ready to do so within 1 month), and (3) preparation stage (ie, an individual who is ready to quit smoking within 1 month).[15,16] The level of nicotine dependence was estimated on the basis of the Tobacco Dependence Screener (TDS), which comprises 10 questions.[17] Smokers with a TDS score of 5 or higher were defined as being nicotine-dependent.

Dentists were questioned about their smoking status and their attitude regarding the effects of smoking on their patients. Their smoking status was defined in the same manner as that described for patients. Their attitude toward the effects of smoking on their patients was assessed by their answers to the following questions: "Are you concerned about the effects of tobacco smoke on your patients' health?" and "What preventive measures against passive smoking do you implement in your offices?".

Analyses

For the patient data set, we calculated the prevalence of current smokers and 95% CIs for each sex and each of 6 age groups (20–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years). The prevalence of current smoking among dental patients, according to sex and age group, was compared with that of the community, which was assessed during the National Health and Nutrition Examination Survey (NHNS) conducted in November 2007.[18] The distribution of stage of change and nicotine dependence among current smokers was compared among age groups within each sex. Smoking prevalence among dentists was calculated for each sex and age group. The prevalence of current smoking among male dentists in 2008 was compared with that among male physicians reported in 2000 and 2008.[19] The percentages of each answer to the questions regarding dentists' attitudes toward the effects of smoking on their patients were compared among current smokers, former smokers, and nonsmokers. Crosstab procedures were performed using statistical software (PASW Statistics 18, IBM Corporation, NY). The Z and chi-square tests were used to determine statistical significance. The significance level was set at P less than 0.05.

Table 1. Sex and age distribution of dental patients

	Category	n	%
Sex	Males	4853	42.7
	Females	6517	57.3
Age group (years)	20–29	1063	9.3
	30–39	1531	13.5
	40–49	1528	13.4
	50–59	2147	18.9
	60–69	2632	23.1
	≥70	2469	21.7
Total		11 370	100.0

Table 2. Sex and age distribution of dentists

	Category	n	%
Sex	Males	680	92.0
	Females	59	8.0
Age group (years)	20–29	2	0.3
	30–39	82	11.1
	40–49	253	34.2
	50–59	272	36.8
	60–69	118	16.0
	≥70	12	1.6
Total		739	100.0

Table 3. Comparison of the prevalence of current smoking in dental patients and the population in a national survey[a]

Sex	Age group (years)	Dental patients		Population of survey[a]	P value[b]
		n	% (95% CI)	%	
Males	20–29	186/366	50.8 (45.7–55.9)	47.5	0.226
	30–39	334/585	57.1 (53.1–61.1)	55.6	0.490
	40–49	337/628	53.7 (49.8–57.6)	49.1	0.023
	50–59	449/907	49.5 (46.2–52.8)	42.3	<0.001
	60–69	422/1211	34.8 (32.1–37.5)	32.8	0.147
	≥70	234/1156	20.2 (17.9–22.5)	18.6	0.174
	All	1962/4853	40.4 (39.0–41.8)	39.4	
Females	20–29	175/697	25.1 (21.9–28.3)	16.7	<0.001
	30–39	202/946	21.4 (18.8–24.0)	17.2	0.001
	40–49	173/900	19.2 (16.6–21.8)	17.9	0.332
	50–59	173/1240	14.0 (12.1–15.9)	9.3	<0.001
	60–69	121/1421	8.5 (7.0–10.0)	7.3	0.091
	≥70	52/1313	4.0 (2.9–5.1)	3.7	0.617
	All	896/6517	13.7 (12.9–14.5)	11.0	
Total		2858/11 370	25.1 (24.3–25.9)	24.1	

[a]National Health and Nutrition Survey, 2007.[18]
[b]Z-test for proportion.

RESULTS

Among 1022 dental clinics, 799 responded to the survey (a response rate of 78.2%): 753 (73.7%) to the patient survey, 763 (74.7%) to the dentist survey, and 717 (70.2%) to both surveys. Of the collected data for 14 187 patients obtained from 753 dentists, information from 2817 (20%) was excluded because of incomplete responses: 4% for the item on smoking status and 16% for other items. Data for the remaining 11 370 patients were then analyzed (Table 1). The mean number of patients per clinic was 15.7 (SD = 7.6). Of the 763 dentists who responded to the dentist survey, 24 were excluded because of lack of information on smoking status. The remaining data for 739 dentists were analyzed. Analysis of the sex and age distributions revealed that males were predominant (92% males and 8% females) and that very few dentists were aged 20 to 29 years or 70 years or older (Table 2).

Table 3 compares the prevalence of current smoking among dental patients and the NHNS population. The overall smoking prevalence among dental patients was 25.1% (40.4% in men and 13.7% in women), which was similar to that of the NHNS population (24.1%). The prevalences of current smoking among male patients aged 40 to 49 and 50 to 59 years were higher than that reported for the NHNS population ($P = 0.023$ and <0.001, respectively). Among female dental patients, the prevalences of current smoking in the age groups of 20 to 29, 30 to 39, and 50 to 59 years were significantly higher than that reported in the NHNS population ($P < 0.001$, 0.001, and <0.001, respectively).

Table 4 shows the distribution of stage of behavior change and nicotine dependence among patients who currently smoked. The distributions of stage of behavior change and nicotine dependence differed by sex and age group. The overall distribution was 25.8% in pre-contemplation lacking interest to quit, 66.4% in pre-contemplation with interest to quit or contemplation, and 7.8% in the preparation stage. As compared with men, women had a higher level of readiness to quit smoking ($P < 0.001$). Among men, those aged 60 years or

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 non-smokers 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.

ACKNOWLEDGMENTS

The authors thank the Japan Dental Association for recruiting participants for the study. They declare that they have no competing interests. The study was supported by a Grant-in-Aid for Comprehensive Research on Cardiovascular Diseases (19-007) and a Grant-in-Aid for Cancer Research (17-1) from the Ministry of Health, Labour and Welfare, Japan.

Conflicts of interest: None declared.

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Published OnlineFirst September 12, 2012; DOI:10.1158/1055-9965.EPI-12-0662

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. *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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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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doi: 10.1158/1055-9965.EPI-12-0662

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)

[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

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

	Site																							
	UADT Cancer			Head and neck cancer																		Esophageal cancer		
Combined categories of smoking dependence and smoking status				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)
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 (1.86–5.78)
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

Published OnlineFirst September 12, 2012; DOI:10.1158/1055-9965.EPI-12-0662

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: Overall			Head and neck cancer: Oral/Oropharyngeal			Head and neck cancer: Hypopharyngeal/Laryngeal			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)
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.

Stratified by	UADT Cancer: Case	Control	OR (95%CI)	*P* heterogeneity	Head and Neck Cancer: Case	Control	OR (95%CI)	*P* heterogeneity	Esophageal Cancer: 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.

Published OnlineFirst September 12, 2012; DOI:10.1158/1055-9965.EPI-12-0662

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

Grant Support

This study was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, Culture and Technology of Japan, for Cancer Research from the Ministry of Health, Labour and Welfare of Japan, and for the Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare of Japan. The work of S. Gallus, E. Negri, and C.L. Vecchia was supported by the Italian Association of Cancer (Grant no.: 10068). These grantors were not involved in the study design, subject enrollment, study analysis or interpretation, or submission of the manuscript for this study.

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Received June 4, 2012; revised August 20, 2012; accepted September 4, 2012; published OnlineFirst September 12, 2012.

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Published OnlineFirst September 12, 2012; DOI:10.1158/1055-9965.EPI-12-0662

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Oral Oncology 48 (2012) 186–191

Contents lists available at SciVerse ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

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

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ARTICLE INFO

Article history:
Received 26 July 2011
Received in revised form 16 September 2011
Accepted 19 September 2011
Available online 12 October 2011

Keywords:
Cohort study
Oral cavity cancer
Squamous cell carcinoma
Smoking
Survival

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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doi:10.1016/j.oraloncology.2011.09.012

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.

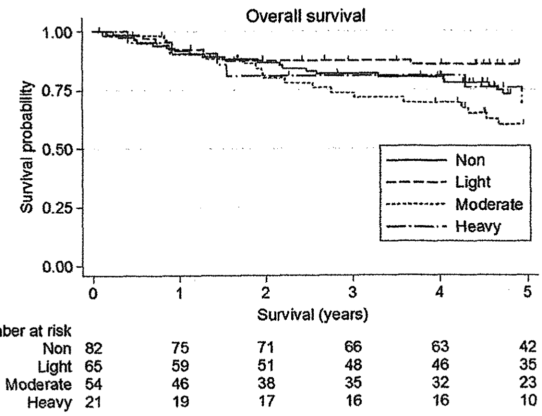

Figure 1 Kaplan–Meier survival curves according to smoking status. Five-year overall survival (OS) was 72.9% (95% confidence interval: 61.4–81.5) for non-, 85.5% (74.0–92.2) for light, 59.9% (44.3–72.4) for moderate, and 69.0% (42.8–85.0) for heavy smokers, respectively.

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.