Original Article

Nicotine Dependence Phenotype, Time to First Cigarette, and Risk of Head and Neck Cancer

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BACKGROUND: A behavioral phenotype that characterizes nicotine dependence, the time to first cigarette after waking, is hypothesized to increase the risk of head and neck cancer. **METHODS:** A case-control study of histologically confirmed head and neck cancer was conducted that included 1055 cases and 795 controls with a history of cigarette smoking. **RESULTS:** The pack-years–adjusted odds ratio was 1.42 (95% confidence interval [95% CI], 1.02-1.99) for an interval of 31 minutes to 60 minutes to first cigarette after waking and 1.59 (95% CI, 1.19-2.11) for an interval of 1 minute to 30 minutes. The risk estimates were similar when smoking was modeled as total years, smoking status (current vs former), number of cigarettes smoked per day, years since quitting, and excess odds ratio. Findings were consistent for cancers of the floor of the mouth, palate, and pharynx. **CONCLUSIONS:** Time to first cigarette is an indicator of increased nicotine dependence, smoke uptake, and risk of head and neck cancer. This high-risk group of individuals would benefit from targeted smoking interventions. ***Cancer*** **2011;117:5377–82.** © *2011 American Cancer Society.*

KEYWORDS: nicotine, addiction, dependence, head and neck cancer, smoking, cotinine, case-control.

The risk of head and neck cancer increases with the frequency and duration of cigarette smoking.[1-4] The physiological dependence on nicotine determines the degree of nicotine uptake and associated tobacco toxins. This is not readily quantifiable in population-based studies. Smoke uptake has traditionally been characterized by age of smoking onset, frequency, duration, and years since quitting. These measures have satisfactorily documented the high rates and risks of many cancers as well as cardiovascular disease from cigarette smoking despite the moderate association noted between self-reported measures of cigarette frequency and biochemical exposure markers.[5,6]

The time to first cigarette (TTFC), an item of the Fagerstrom Test for Nicotine Dependence (FTND),[7] is a objective measure of nicotine dependence[8,9] and is associated with the many behavioral traits of nicotine addiction, including smoking amount,[10] inability to quit,[11,12] smoking relapse,[13] and tolerance.[14] Nicotine dependence can also be measured biochemically by quantifying the blood levels of cotinine, the major nicotine metabolite. The levels of cotinine are associated with the number of cigarettes smoked per day and, to a lesser extent, the nicotine content of cigarettes. A shorter time elapsed between waking and the first cigarette smoked recently was found to be associated with significantly higher levels of cotinine in several hundred current smokers who smoked ≥ 5 cigarettes per day.[15] Two nicotine dependence phenotypes were found. The "low" dependent phenotype was characterized by smoking > 30 minutes after waking and smoking ≤ 20 cigarettes per day. In this group, cotinine levels were relatively low but increased linearly with cigarette consumption. The "high" dependent phenotype was characterized by smoking ≤ 30 minutes after waking but having a wide range in the number of cigarettes smoked (eg, 6-70 cigarettes smoked per day). In this group, cotinine levels were much higher but there were few differences noted in these levels by cigarette frequency. If the TTFC is an independent marker of nicotine dependence and tobacco smoke exposure, subjects with early TTFC might have an increased risk of smoking-related cancers. The current study examined whether the TTFC is a predictor of oral and pharyngeal cancer risk.

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MATERIALS AND METHODS

The methods were previously described in an analysis that demonstrated increased risks of oral cancer with smoking and alcohol consumption.[16] In brief, the study was conducted in large academic medical centers in the New York metropolitan area between 1985 and 1991. Case subjects were identified on a daily basis from surgery schedule logs. Eligibility criteria included being able to speak English and being free of any mental impairment. All newly diagnosed subjects with histologically confirmed cancer of the oral cavity, pharynx, or nasal cavity were asked to participate and sign an Institutional Review Board-approved consent form. All subjects were interviewed in person by a trained interviewer using the same structured questionnaire. Controls were consented subjects who were admitted to the same hospital for conditions unrelated to tobacco smoke exposure and frequency matched to cases by sex, age (within 5 years), race, and month of diagnosis. Controls were selected from daily admission rosters and interviewed using the same structured questionnaire. There was a wide range of control diagnoses including acute conditions; fractures and injuries; nonmalignant diagnoses such as benign prostatic hypertrophy; and cancers not known to be caused by tobacco smoking, including those of the breast and prostate. Information regarding the subsite of the lesion was obtained from the pathology report, and *International Classification of Diseases, Ninth Revision* (ICD-9) codes were abstracted. The response rate for both cases and controls, which was the rate of participation for eligible subjects who were approached and asked to participate, was $> 90\%$. Reasons for not participating included not feeling well or a lack of interest.

The current analysis included only subjects with a history of smoking at least 1 cigarette per day for ≥ 1 year. Never-smokers were excluded, leaving 1850 subjects, including 1055 cases and 795 controls. The data were analyzed using R (R Foundation for Statistical Computing, Vienna, Austria) and SAS (SAS Institute Inc, Cary, NC) statistical software packages. All tests were 2-sided. Unconditional logistic regression procedures were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI).

The subject's smoking history was obtained directly from the subject interview. A subject was considered as having ever smoked cigarettes if he or she smoked cigarettes at least once a day for ≥ 1 year. A subject was defined as a current smoker if he or she smoked within the last year and a former smoker if he or she quit at least 1 year earlier. Information regarding TTFC was also obtained directly from the structured questionnaire. It included the following categories of responses: 1 minute to 30 minutes, 31 minutes to 60 minutes, and > 1 hour (reference category). All subjects were asked about the frequency and amount of beer, wine, and hard liquor consumed. Subjects were defined as current drinkers of beer if they drank at least 1 glass within the past month. Similar questions were used to define wine and liquor drinkers.

Adjustment for cigarette smoking was performed in several ways. Models were fitted that controlled for pack-years; intensity (eg, number of cigarettes smoked per day); smoking status (current vs former); years since quitting (0 years [current smoker], 1-5 years, 6-10 years, and > 10 years); and the excess OR (EOR), in which pack-years was linear and the logarithm of number of cigarettes smoked per day and its square was exponential.[17] Because the risk of oral cancer varies by smoking intensity, the risk associated with TTFC adjusted for EOR was stratified by categories of smoking intensity. The following covariates were included in the models: age (≤ 50 years, 51-60 years, 61-70 years, and > 70 years), sex (male vs female), race (black vs white), education (≤ 12 years, 12 years, 13-15 years, and ≥ 16 years), alcohol consumption (current beer drinker vs not current beer drinker; current wine drinker vs not current wine drinker; and current hard liquor drinker vs not current hard liquor drinker), and body mass index (weight [lbs]*703/(height [in])^2). A multiplicative interaction for ever-alcohol use and pack-years was estimated using a product term of those 2 variables in the logistic regression model. ORs were calculated for specific subsites within the oral cavity or for pharyngeal cancer using the entire control series as the comparison group. Statistical significance was set at $P < .05$, and all tests were 2-sided. There were no missing values in this analysis. A goodness-of-fit test for every model was performed using the Hosmer and Lemeshow chi-square statistic.[18]

RESULTS

Table 1 shows the basic characteristics of the study subjects. After excluding never-smokers, there were a larger number of cases than controls (1055 vs 795). Head and neck cancer was more frequent in men than in women. Approximately 91% of all subjects were white and 9% were black. The crude OR associated with TTFC was 1.71 (95% CI, 1.26-2.34) for an interval of 31 minutes to 60 minutes after waking and 2.54 (95% CI, 1.98-3.25) for an interval of 1 minute to 30 minutes after waking

Table 1. Characteristics of Head and Neck Cancer Cases and Controls

Characteristic	Cases N=1055 (%)	Controls N=795 (%)
Mean age, y	58	58
Sex		
Men	754 (71.5)	616 (77.5)
Women	301 (28.5)	179 (22.5)
Race		
White	945 (89.6)	732 (92.1)
Black	103 (9.8)	62 (7.8)
Other	7 (0.6)	1 (0.1)
Smoking status[a]		
Current	759 (71.9)	342 (43.0)
Former	296 (28.1)	453 (57.0)
TTFC, min		
1-30	751 (71.2)	444 (55.8)
31-60	168 (15.9)	147 (18.5)
>60	136 (12.9)	204 (25.7)
Tumor site		
Floor of mouth	259 (24.6)	
Tongue	294 (27.9)	
Pharynx	133 (12.6)	
Palate	101 (9.6)	
Other	268 (25.4)	

Abbreviation: TTFC, time to first cigarette.
[a] A current smoker was defined as an individual who had smoked at least 1 cigarette per day for ≥1 year (ever smoked) and within the last year. A former smoker was defined as an ever-smoker who quit ≥1 year ago.

compared with waiting 1 hour after waking before smoking.

The pack-years–adjusted risk of cancer was 1.42 (95% CI, 1.02-1.99) for smoking within 31 minutes to 60 minutes after waking and 1.59 (95% CI, 1.19-2.11) for smoking within 30 minutes after waking (Table 2). The total years of smoking-adjusted OR was 1.43 (95% CI, 1.02-2.0) for 31 minutes to 60 minutes after waking and 1.69 (95% CI, 1.45-1.98) for smoking within 30 minutes after waking. The inclusion of the product term of pack-years and current alcohol consumption was found to have no effect on the ORs for TTFC. Consequently, a product term for smoking and alcohol consumption was excluded from subsequent models. The OR in a model that adjusted for number of cigarettes smoked per day was 1.63 (95% CI, 1.18-2.26) for smoking within 31 minutes to 60 minutes after waking and 2.11 (95% CI, 1.61-2.77) for smoking within 30 minutes after waking. Findings were similar when smoking was adjusted for by smoking status and years since quitting (Table 2).

Figure 1 shows the risk of cancer associated with TTFC adjusted for the EORs stratified by 7 categories of smoking intensity (number of cigarettes smoked per day). Compared with the referent group, the risks associated with smoking 31 minutes to 60 minutes after waking and 1 minute to 30 minutes after waking were elevated for

Table 2. ORs and 95% CIs for Head and Neck Cancer and TTFC in Ever-Smokers, Adjusting for Different Measures of Smoking History

TTFC, Minutes	OR Adjusted for Pack-Years of Smoking[a]	95% CI	OR Adjusted for Total Years of Smoking	95% CI	OR Adjusted for No. of Cigarettes per Day	95% CI
>60	1.0		1.0		1.0	
31-60	1.42	1.02-1.99	1.43	1.02-2.0	1.63	1.18-2.26
1-30	1.59	1.19-2.11	1.69	1.45-1.98	2.11	1.61-2.77
Chi-square test for trend	$P < .01$		$P < .01$		$P < .01$	

TTFC, Minutes	OR Adjusted for Smoking Status	95% CI	OR Adjusted for Years Since Quitting[b]	95% CI
>60	1.0		1.0	
31-60	1.50	1.07-2.09	1.47	1.05-2.06
1-30	1.77	1.34-2.32	1.69	1.28-2.23
Chi-square test for trend	$P < .01$		$P < .01$	

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; TTFC, time to first cigarette.
[a] The ORs adjusted for pack-years of smoking included a product term for pack-years and alcohol consumption.
[b] The ORs adjusted for years since quitting included current smokers.ORs we adjusted for age, sex, race, education, alcohol consumption, and body mass index.

each smoking intensity category, except for the heaviest smokers (> 30 cigarettes smoked per day).

Early TTFC was found to be associated with an increased risk of cancer for the majority of subsites (Table 3). In Table 3, findings are presented for cancers of the floor of the mouth, palate, base and anterior tongue, and pharynx, which comprised approximately 75% of all cases. The strongest association was observed between smoking within 30 minutes of waking and cancer of the pharynx (OR, 2.19; 95% CI, 0.99-4.83). Increased risks were observed for cancers of the floor of mouth and palate. The effect was smallest for cancers of the tongue.

DISCUSSION

The TTFC is a distinct nicotine dependence phenotype associated with the uptake of nicotine and tobacco smoke.

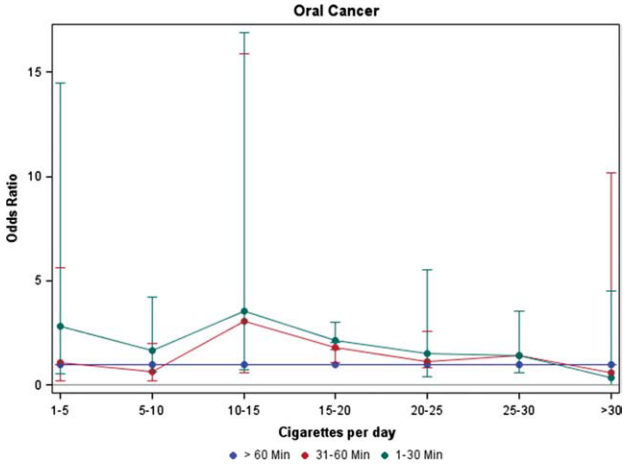

Figure 1. Time to first cigarette and head and neck cancer risk in ever-smokers adjusted for the excess odds ratio per pack-years are shown by cigarette intensity (number of cigarettes smoked per day).

The high dependent phenotype is associated with significantly higher cotinine levels than the low dependent phenotype per cigarette smoked. The TTFC is biochemically validated and can be considered a risk factor for smoking-related diseases. The results of the current study indicate that an early TTFC is significantly associated with an increased risk of head and neck cancer. The association was consistent for most cancer sites. The highest risk was found for pharyngeal cancer, which has the highest smoking-related risk of these sites.[19]

Cotinine has a 24-hour half-life and has little value as a biomarker of smoke uptake in case-control studies. The dose of smoke uptake in epidemiologic studies has traditionally been determined by proxy measures such as the frequency and duration of cigarette smoking. However, to the best of our knowledge, the effect of interindividual variability in nicotine dependence on cancer risk has not been determined. One study of 55 smoking lung cancer cases and 49 smoking controls did find a significant trend in the risk associated with the FTND score, although this association just reflected to a certain extent the association with smoking frequency, which is the single biggest contributor to the FTND index.[20] The results of the current study have demonstrated that the TTFC after waking is a strong and independent predictor of head and neck cancer risk in a large study of ever-smokers. A pack-years–adjusted risk of 1.6 was associated with smoking within 30 minutes after waking. The risk may be even higher among subjects who smoked within the first 15 minutes after waking.

Limitations of the current study include those that are known to be common in case-control studies, including bias, measurement error, and confounding. Cases and controls were hospitalized patients whose lifestyles might be different from the general population. Responses regarding smoking and alcohol consumption are subject

Table 3. ORs and 95% CIs for Head and Neck Cancer and TTFC in Ever-Smokers by Tumor Site, Adjusting for Pack-Years of Smoking[a]

TTFC, Minutes	OR for Floor of Mouth	95% CI	OR for Palate	95% CI	OR for Anterior and Base of Tongue	95% CI	OR for Pharynx	95% CI
>60	1.0		1.0		1.0		1.0	
31-60	1.19	0.63-2.27	1.43	0.68-3.02	1.01	0.67-1.54	2.07	1.02-4.18
1-30	1.76	1.0-3.0	1.87	0.82-4.23	1.21	0.75-1.94	2.19	0.99-4.83
Chi-square test for trend	$P < .05$		$P = .45$		$P = .96$		$P = .06$	

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; TTFC, time to first cigarette.
[a] ORs were adjusted for age, sex, race, education, alcohol consumption, and body mass index.

to recall biases. Although it is not possible to completely validate lifetime lifestyle habits, repeat interviews in a random sample of subjects demonstrated high internal consistency for smoking and alcohol consumption. To the best of our knowledge, little is known regarding smoking behaviors such as TTFC over the course of a lifetime. This behavior was assessed by a single question, and it is possible that this particular smoking behavior may change over time or change in relation to smoking habits. Subjects may have switched from high-yield cigarettes to low-yield cigarettes, which could potentially affect symptoms of nicotine dependence and smoking behaviors. However, the associations were similar for current and former smokers, indicating that recall bias was unlikely to have affected the findings. The association might have been confounded by smoking, although the current study did carefully control for smoking dose in several different ways and the results were fairly consistent. The large sample size suggests that the findings are generalizable to the larger population of white smokers. However, there were few black or other minority subjects in the current study and the results may not be applicable to these groups. Finally, the association might have been confounded by other factors. Human papillomavirus causes oropharyngeal carcinoma; however, it is unlikely that this was a major confounder for those cases with oropharyngeal carcinoma in the current study. The incidence of this malignancy has increased dramatically since 2000, which was after the data collection period of the current study.

A shorter time interval between waking and the first cigarette is associated with higher blood cotinine levels. Early morning smokers might have a greater craving for nicotine. The temporal effect is dose-dependent, in which prolonging smoking abstinence after waking is associated with lower cotinine levels. If the association between TTFC and cotinine is because of cravings, it likely reflects greater cravings throughout the day because intensive smoking of just the first cigarette only would not appreciably raise cotinine levels. We did not collect information concerning nicotine cravings throughout the day because this is not possible in case-control studies, especially for subjects who have quit smoking. To our knowledge, there are few data regarding the relation between TTFC and the urge to smoke or cravings. In a clinical smoking cessation trial of 207 smokers who were treated with buproprion, craving and withdrawal symptoms were reduced after smoking the first cigarette of the day. The TTFC was not found to be correlated with a 10-item questionnaire that assessed the urge to smoke.[13]

The cancer risk associated with TTFC might reflect differences in smoking topography associated with nicotine cravings. To our knowledge, there are also few data concerning this topic. The TTFC after waking was found to be unrelated to puffing intensity in a British study.[21] Variation in the TTFC could be because of genetic differences in nicotine dependence, nongenetic behavioral and socioeconomic factors, or both genetic and nongenetic factors interacting together.

To validate the current findings, prospective cohort studies with nicotine metabolite determinations are needed. Such studies would need to demonstrate the relation between TTFC and cotinine, and determine the incidence rate of cancer according to TTFC groups. In conclusion, the significance of the current study findings is that TTFC may be a behavioral phenotype that identifies smokers who are at high risk of developing head and neck cancer. The risk of head and neck cancer was found to be substantially elevated even among ever-smokers. This underscores the need to recognize nicotine dependence rather than smoking habits as the major risk factor in smoking research because it the physiological dependence on nicotine that affects the dose of exposure. The results of the current study indicate that smokers who smoke soon after waking may require special efforts to make them aware of their increased risk and the need for smoking cessation therapies.

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CONFLICT OF INTEREST DISCLOSURES

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