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ORIGINAL PAPER

The nicotine dependence phenotype, time to first cigarette, and larynx cancer risk

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Abstract
Purpose Cigarette smoking is the major cause of laryngeal cancer. The time to first cigarette after waking in the morning is a behavior associated with several dimensions of nicotine dependence including the dose of smoke uptake. We hypothesized that a short TTFC increases the risk of laryngeal cancer.
Methods The analysis was based on data from a hospital-based case–control study of laryngeal cancer. The current analysis included only subjects who were ever cigarette smokers, including 570 cases and 343 controls (832 whites and 81 blacks). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression adjusting for smoking history and other potential confounders. Incidence data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute from 1975 to 2006 were analyzed for trends in laryngeal cancer.
Results There was a dose–response relationship between TTFC and supraglottic cancer. Compared to subjects who smoked more than 60 min after waking, the adjusted odds ratio was 1.51 (95% CI, 0.63–3.61) for 30–60 min and 3.13 (95% CI, 1.56–6.30) for 0–30 min. No association was observed between TTFC and cancer of the glottis. In blacks, the TTFC was not associated with the risk of laryngeal cancer. Trends in SEER rates were similar for cancer of the glottis and supraglottis, indicating that the site-specific differences were not affected by unknown confounders.
Conclusion A nicotine dependence behavior that is associated with cigarette smoke uptake increases the risk of cancer of the supraglottis larynx, but not glottis larynx.

Keywords Nicotine · Smoking · Addiction · Larynx cancer

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Introduction

Cigarette smoking causes cancers, cardiovascular disease, and other illnesses in a dose-dependent relationship. Smoking history is usually quantified by the smokers' age at smoking initiation, the frequency and duration of smoking, and the years since quitting. The effects of smoking on health outcomes can be detected even in small studies even though a self-reported smoking behavior like cigarettes per day is only a proxy measure for the dose of smoke exposure.

The accuracy of self-reported cigarette frequency as a measure of smoke uptake can be measured by blood, urine, or saliva cotinine levels. These levels vary by as much as 20-fold in one-pack-a-day smokers [1]. This variation in cotinine highlights some potentially important limitations in cancer risk studies. It indicates that misclassification of exposure might affect the relative and absolute risk of disease due to cigarette smoking. Secondly, because smoking may be indicative of other unhealthy lifestyle factors that affect disease risk, misclassification of smoking as a confounding variable in observational studies may impact the ability to detect associations with other nonsmoking risk factors. Thirdly, despite the abundance of evidence that tobacco smoking is caused by a physiological dependence

on nicotine, smoking has been traditionally considered a "lifestyle" factor in medical research. However, smokers are addicted to nicotine, and the degree of nicotine dependence affects smoking behaviors such the frequency of smoking, ability to quit, and relapse.

There are many dimensions of nicotine dependence including psychological, physiological, and pharmacologic properties. Social factors such as shared familial environments, social support, stress, and perceptions of tobacco may also affect nicotine dependence behaviors. In addition, genetic and environmental influences may play a significant role in nicotine dependence [2]. In association studies, it is not meaningful or practical to measure nicotine dependence symptoms from biological markers or psychometric measures because of the long latency between exposure and health outcomes, and the need to conduct such measures under controlled and timed protocols.

One specific measure that is highly correlated with the variation in cotinine levels in active smokers is the time to first cigarette after waking (TTFC). Like cigarette frequency, TTFC is one of two items of the Fagerstrom Test for Nicotine Dependence (FTND) that is quantifiable, whereas other items of the FTND are subjective indicators of nicotine cravings [3]. A shorter TTFC is significantly associated with increased cotinine levels. Two nicotine dependence phenotypes have been characterized by the TTFC time interval [1]. The "low" dependent phenotype are smokers who smoke >30 min after waking and smoke ≤20 cigarettes per day. The "high" dependent phenotype are smokers who smoke ≤30 min after waking, but in contrast to the low dependent phenotype, have a wide range of daily cigarette consumption.

While the time to first cigarette is highly correlated with cotinine, it is also associated with many other dimensions of nicotine addiction including smoking amount [3, 4], inability to quit [4–6], smoking relapse [7], tolerance [8], and nighttime smoking [9]. It is unknown what accounts for these associations, but the TTFC is thought to reflect the intensity of smoking such as the depth and frequency of puffing. The time to first cigarette is considered a measure of the intensity of smoking whereas cigarettes per day is a measure of the frequency of smoking.

Laryngeal cancer is caused primarily by smoking. We hypothesized that an early TTFC was associated with the risk of laryngeal cancer and its major subsites the supraglottis and glottis.

Materials and methods

The methods for the study were previously described [10]. The study was conducted primarily in large academic medical centers in the New York Metropolitan area to study the effects of tobacco exposure and larynx cancer risk. In brief, all newly diagnosed patients with histologically confirmed laryngeal cancer were identified from admission, surgical, and oncology logs on a daily basis. Patients were eligible if they were identified within one year of diagnosis, spoke English, and were free of any mental impairment. Nearly all patients were interviewed within several days post surgery. A trained interviewer abstracted information from their medical record, including the histology report and ICD codes. Eligible patients were approached and requested to participate by a trained interviewer with the consent of the treating physician. The study did not include proxy interviews. After signing an informed consent that was approved by the ethics committee of both the hospital and the American Health Foundation, the interviewer administered a structured questionnaire that contained detailed questions on lifetime smoking history, alcohol consumption, occupation, and sociodemographics. Information on smoking included the age that a subject started smoking regularly, and for each brand smoked the frequency and duration of smoking. If a subject was no longer smoking, the years since quitting was obtained. Subjects were classified as ever having regularly smoked cigarettes if they smoked at least 100 cigarettes in their lifetime [11]. The question "Approximately how many minutes after you wake (woke) up do(did) you have your first cigarette?" was asked of all subjects. Subjects were given the following categories of responses: 1–30 min, 31–60 min, >1 h (reference category), and "do not know." None of the subjects responded as not knowing. Controls were consented patients 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 included subjects with a wide range of conditions such as acute conditions, fractures and injuries, nonmalignant diagnosis such as benign prostatic hypertrophy, and cancers not caused by tobacco including breast and prostate. The study was conducted between 1977 and 1999, and the response rates were very high. About 97% of cases and 91% of controls who were approached agreed to participate [12]. Subjects who declined to participate reported not feeling well or lack of interest.

SAS (Cary, NC) statistical software was used to analyze the data. Unconditional logistic regression procedures were used to derive odds ratios (OR) and 95% confidence intervals (CI) associated with the TTFC. We fitted models that adjusted for smoking status (current vs. former), total years of exposure, and cigarettes per day. A few subjects reported quitting less than one year prior to the interview and were classified as current smokers. The following risk factors were included in the final models: age (≤50, 51–60, 61–70, and >70), sex (male vs. female), race (blacks vs.

whites), education (≤12, 12, 13–15, and ≥16 years), body mass index (Weight[lbs] × 703/(height[in.])^2), and alcohol consumption. These factors have been previously established to affect the risk of laryngeal cancer or are associated with the incidence rates of laryngeal cancer [13, 14]. For alcohol consumption, we determined the total number of alcohol drinks consumed on a weekly basis, including 12-oz. bottle or cans of beer, glasses of wine, and shots of hard liquor. About 1/4th of subjects were nondrinkers or light drinkers (less than one drink per week). Alcohol consumption was classified as a binary variable, comparing the upper three quartiles of consumption to the lower quartile. Site-specific models were developed by comparing cases with supraglottis cancer and glottis cancer to the entire control series. For all the analyses, statistical significance was set at $p < 0.05$, and all tests were two-sided. A goodness-of-fit test for every model was performed using the Hosmer and Lemeshow chi-square statistic [15].

The current analysis included subjects who had a smoking history of at least one cigarette per day for one or more years. Excluded were never-smokers or smokers who smoked only cigars or pipes since the question "Approximately how many minutes after you wake (woke) up do(did) you have your first cigarette?" did not apply to them. There were 248 controls who were excluded, of which 61% were men. Ninety-three percent of excluded controls were white. There were a wide range of control diagnoses, and there were little differences in the types of control diagnoses that were included versus excluded. In contrast, only 88 cases never smoked cigarettes regularly and were excluded from the current study. Of these, 59% were men and 90% were white. The final dataset included 570 cases and 343 controls. Laryngeal cancer cases included 247 glottis (International Classification of Diseases (ICD-IX): 161.0), 266 cases of supraglottis (ICD-IX: 161.1), and 57 unspecified cases (ICD-IX: 161.9).

SEER*Stat version 6.5.2 software was used to analyze trends in laryngeal cancer rates in the Surveillance, Epidemiology, and End Results registry (SEER) [16]. Age-adjusted incidence rates per 100,000 persons were calculated according to the US standard population for the year 2000. The annual percent change (APC) was calculated from 1975 to 2006. Joinpoint Regression Program was used to determine inflection points in trends based on significant changes in the APC for glottis and supraglottic cancer.

Results

Table 1 shows the basic characteristics of the study subjects. Controls were more likely to be never-smokers and excluded from the current analysis of ever-smokers, resulting in a larger number of cases than controls for the current analysis. The mean age was about 59 in both cases and controls. Seventy-eight percent of both cases and controls were men, and over 90% of both cases and controls were white. Seventy-eight percent of cases and 48% of controls were current smokers. Eighty-one percent of cases and 58% of controls reported smoking their first cigarette within 30 min after waking.

In logistic regression models of laryngeal cancer, the three smoking terms, smoking status, total years of smoking, and cigarettes per day, were all statistically significant ($p < 0.01$). There was no overall association between the TTFC and risk of laryngeal cancer. The adjusted odds ratio was 0.97 (95% CI, 0.55–1.70) for 31–60 min after waking and 1.39 (95% CI, 0.89–2.15) for 1–30 min after waking (Table 2). There was no association with alcohol consumption when comparing the upper quartile with the lower 3 quartiles (OR = 1.0; 95% CI, 0.9–1.0). Interaction terms were fitted between total years of smoking and TTFC, and total years of smoking and alcohol consumption. No significant interactive effects were found.

A significant association was found between TTFC and cancer of the supraglottis. The OR was 1.51 (95% CI, 0.63–3.61) for 31–60 min and 3.13 (95% CI, 1.56–6.3) for 1–30 min. All three smoking terms were statistically significant. A significant inverse association was observed with body mass index. The OR for alcohol consumption was 1.0 (95% CI, 1.0–1.0). Interaction terms for smoking

Table 1 Characteristics of laryngeal cancer cases and controls

Characteristic	Cases, $n = 570$ (62.4%)	Controls, $n = 343$ (37.6%)
Mean age	58.7 (SD: 8.5)	58.8 (SD: 8.6)
Sex		
Men	442 (77.5%)	269 (78.4%)
Women	128 (22.5%)	74 (21.6%)
Race		
White	514 (90.2%)	318 (92.7%)
Black	56 (9.8%)	25 (7.3%)
Smoking status		
Current	445 (78.1%)	164 (47.8%)
Former	125 (21.9%)	179 (52.2%)
Alcohol consumption		
Q1–3	134 (23.5%)	85 (24.8%)
Q4	436 (76.5%)	258 (75.2%)
Time to first cigarette		
>60 min	59 (10.4%)	93 (27.1%)
31–60 min	50 (8.8%)	50 (14.6%)
1–30 min	461 (80.8%)	200 (58.3%)

Q quartile

Table 2 Odds ratios and 95% confidence intervals for laryngeal cancer and time to first cigarette in ever-smokers

	Larynx cancer		Glottis cancer		Supraglottis cancer	
	OR	95% CI	OR	95% CI	OR	95% CI
Time to first cigarette						
>60 min	1.0		1.0		1.0	
31–60 min	0.97	0.55–1.70	0.80	0.43–1.49	1.51	0.63–3.61
1–30 min	1.39	0.89–2.15	0.77	0.35–1.70	3.13	1.56–6.30
Whites						
>60 min	1.0		1.0		1.0	
31–60 min	1.11	0.62–1.99	0.73	0.38–1.39	2.07	0.80–5.33
1–30 min	1.43	0.90–2.27	0.80	0.35–1.82	3.43	1.58–7.43
Blacks						
>60 min	1.0		1.0		1.0	
31–60 min	0.18	0.02–1.67	1.4	0.01–713	0.11	0.01–3.82
1–30 min	1.04	0.21–5.11	–	–	0.55	0.04–7.14

Odds ratios adjusted for age, sex, race, education, body mass index, alcohol consumption, smoking status, years of smoking, and cigarettes per day

and TTFC, and total years of smoking and alcohol consumption were not significant.

In logistic models of glottis cancer, no significant association was found for a TTFC of either 31–60 or 1–30 min. There were no significant interactions between smoking and TTFC and alcohol. Body mass index was not significantly associated with the risk. The association between TTFC and unspecified laryngeal cancers was 0.52 (95% CI, 0.05–6.12) for 31–60 min and 3.41 (95% CI, 0.64–18.2) for 1–30 min.

In an analysis limited to white subjects, the findings for laryngeal cancer, supraglottis cancer only, and glottis cancer only, the findings were very similar to that for all subjects. The odds ratios associated with TTFC are shown in Table 2. The only differences in the analysis restricted to whites versus all subjects was that while total years of smoking and cigarettes per day were significantly associated with cancer of the glottis, cigarette status was not a significant predictor ($p = 0.22$).

In black subjects, none of the smoking terms including the TTFC were statistically significant.

SEER rates of supraglottic cancer were approximately 1.5-fold higher than that for glottis cancer since 1975 in both men and women. Table 3 shows the trends in SEER data by laryngeal cancer subsite in whites. Annual age-adjusted rates increased slightly from 1975 to the mid-1980s, with inflection points found at 1984 for supraglottic cancer and 1987 for glottis cancer. Rates declined slightly afterward. There were no significant differences in the trends in rates between glottis and supraglottic cancer.

Table 3 Trends in age-adjusted SEER incidence rates for cancer of the glottis and supraglottis, white race, 1975–2006

Year	Glottis APC (95% CI)	Supraglottis APC (95% CI)
1975–1987	0.63 (−0.3, 1.5)	
1975–1984		3.0 (1.2, 4.8)
1987–2006	−2.72 (−3.1, −2.3)	
1984–2006		−1.8 (−2.3, −1.4)

APC annual percent change

Discussion

Cigarette smoking was associated with an increased risk of laryngeal cancer in white study subjects. The association with smoking appeared to be greater for supraglottis cancer since all three smoking terms were statistically significant, whereas smoking status was not significant for glottis cancer. Most previous studies that had site-specific smoking information found higher smoking-related risks relative to never-smokers for supraglottic cancer than for glottis cancers [17–30]. It remains unknown why there is a difference in smoking risk by site. The tumor histology of both subsites is squamous cell carcinoma, but their progenitor cells differ. Supraglottic lesions arise from cylindrical and not squamous cells, and the molecular signatures of the two cancers also varies [31]. Supraglottic tumors are more clinically aggressive, with greater nodal spread and poorer survival rates. There may be differences in susceptibility to tobacco carcinogens between the two sites, although there is little data on the effects of single nucleotide polymorphisms by laryngeal tumor location. Glottis cancer is more common in the United States than cancer of the supraglottis. Because we excluded never-smokers from the current study; the ratio of glottis to supraglottis cancer was about the same in the current analysis.

There is little data on smoking-specific risks of laryngeal cancer in blacks. There were too few black subjects to detect significant associations in ever-smokers in the

current study. It is unknown whether the effects of tobacco smoke are greater for supraglottis than glottis cancer in black Americans.

One possible explanation that might help explain the differences in risk between the two sites is how cigarettes are smoked. The association between nicotine dependence and cancer risk has not been studied for several methodologic reasons as previously noted. More highly dependent smokers may have different smoking patterns that are not captured by traditional questions on smoking habits such as cigarettes per day or years of smoking. The time to first cigarette, in addition to smoking frequency, is a measure of smoking uptake. Two recent studies showed that a shorter time to first cigarette after waking nearly doubled the smoking-adjusted risk of lung and oral cancer in ever-smokers, compared to smokers who waited an hour after waking [32, 33]. The current study is consistent with these findings.

There are several potential limitations in the current study. Smoking habits may change over time or with age, and likewise a single question on TTFC might not reflect lifetime patterns. Even if TTFC does not change with time, misclassification of TTFC due to poor recall could introduce bias. The findings would not appear to be spurious, however. Since smoking is associated with glottis cancer but not as strongly as its association with supraglottic cancer, subjects with glottis cancer can be considered as positive scientific controls in that it would be expected that the TTFC is less strongly associated with glottis cancer risk. Another potential limitation is that the etiology of the tumors may differ, and the analysis failed to control for potential unknown confounders. Human papillomavirus has been detected in laryngeal carcinoma, although infection rates were relatively low during the time period of this study (1980–1990) and there is little data to indicate differential infection rates by site within the larynx [34]. We did not have extensive information on diet in these patients. A low intake of fruits and vegetables is associated with increased risk [35], but would probably not affect TTFC. There may be other unknown confounders; however, the analysis of the SEER incidence rates showed similar increasing and decreasing time trends for cancer of the glottis and supraglottis, indicating a similar etiology. Smoking is the main cause of laryngeal cancer, and the similar inflection points at about the same time in the mid-1980s for supraglottis and glottis cancer reflect the decline in adult smoking prevalence that began in the 1950s.

In considering a possible association between TTFC and laryngeal cancer risk, the possible confounding effects of alcohol need to be considered. A few studies have examined site-specific risks that indicate higher risks of supraglottic cancer [36]. The independent effect of alcohol consumption on the risk of laryngeal cancer is moderate. Alcohol consumption was not associated with a significant increased risk of glottis and supraglottis laryngeal cancer in the Central and Eastern Europe Multicenter Study in an analysis comparing heavy to light drinkers [37]. We previously reported a higher alcohol-associated risk with cancer of the supraglottis than glottis in an analysis that included nondrinkers [10]. Two other case–control studies reported higher alcohol-associated risks with supraglottic than glottis cancer [38, 39], although no pooled analyses have been conducted yet to determine whether the differences by subsite are statistically significant. Among known confounders, a complete exposure assessment was not available for alcohol consumption. Although current drinking status and frequency for different alcoholic beverages was collected, we did not have information on lifetime consumption patterns, including total years of alcohol consumption. Alcohol and smoking act multiplicatively to increase the risk of oral cancer in case–control studies [40]. Since the current data were limited to ever-smokers who by extension were more likely to have been ever-drinkers, a significant interactive effect was not detected. A more refined analysis by type of alcoholic beverage or different quantitative exposure measurements for alcohol might have yielded different findings, but it is unlikely that this would have affected the odds ratios associated with the TTFC.

Another possible limitation regarding the generalizability of the findings is the data collection period. Today's smokers smoke lower yield cigarettes than in the past, and the magnitude of the smoking association with larynx cancer might be different than that in newer studies. This might indicate that the magnitude of the TTFC association would differ as well; however, smoking-related risks using never-smokers as a referent group in this study are quite similar to the risk estimates in more recent studies [41]. It is also possible that the association with TTFC was underestimated by the use of only three categorical measures of exposure. The relationship between a shorter TTFC and increased cotinine levels in smokers is linear. The highest dose exposure category in the current study was 1–30 min after waking. If the exposure classification was based on more refined categories, it is possible that larger effects would have been detected for subjects reporting a TTFC within 5 or 15 min.

Strengths of the study included the relatively large sample size, the high response rate, and detailed tobacco assessment. The findings are likely generalizable to whites, but the external validity of the findings in blacks is less certain. This reflects the relatively small number of black subjects in the study, and that the participating treatment centers were located primarily in New York County, and not Brooklyn County or other boroughs in New York that have a large black population.

It is uncertain why a shorter TTFC is associated with increased cotinine levels, but likely reflects differences in genetic susceptibility to nicotine dependence, behavioral, and social factors. The TTFC is thought to measure the "heaviness" of smoking although the smoking behavioral patterns associated with the first cigarette may be more complex. The TTFC interval might be indicative of smoking intensity, but the intensity of smoking the first cigarette also depends on the actual hour of the day when the cigarette is actually smoked [42]. Together with behavioral factors that are potentially important, genotypic and phenotypic characterizations of nicotine dependence such as the TTFC may help with the development of tailored therapies. The current study also shows that nicotine dependence, and a specific nicotine dependence behavior, the TTFC, is a risk factor for cancer. This reconceptualizes the traditional characterization of smoking as a lifestyle risk factor for cancer, a concept that was formulated many decades ago and continues to be used currently [43, 44]. The magnitude of the risk associated with a short TTFC was similar to that of heavy versus light smokers, underscoring the importance of this measure. The current findings are also potentially useful in helping identify and inform smokers who are at increased risk due to a short TTFC. The TTFC might be useful in helping develop more effective or individually tailored smoking cessation efforts.

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Conflict of interest The authors declare no conflict of interest.

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