Original Article

Nicotine Dependence Phenotype and Lung Cancer Risk

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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 lung cancer. **METHODS:** A case-control study of histologically confirmed lung cancer was conducted. The current analysis included 4775 lung cancer cases and 2835 controls who were regular cigarette smokers. **RESULTS:** Compared with subjects who smoked their first cigarette > 60 minutes after waking, the pack-years–adjusted odds ratio was 1.31 (95% confidence interval [95% CI], 1.11-1.54) for subjects who smoked 31 minutes to 60 minutes after waking and 1.79 (95% CI, 1.56-2.07) for subjects who smoked within 30 minutes of waking. 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. The findings were consistent for all histologic types of lung cancer. **CONCLUSIONS:** The findings of the current study indicate that a specific nicotine dependence phenotype that is associated with the amount of smoke uptake per cigarette is independently associated with lung cancer risk. These findings may help to identify high-risk individuals who would benefit from targeted interventions. ***Cancer* 2011;117:5370–6.** © *2011 American Cancer Society.*

KEYWORDS: nicotine, addiction, dependence, lung cancer, smoking, cotinine, case-control.

Since the first studies of cigarette smoking and lung cancer were published in the 1950s, cigarette smoking has been considered a "lifestyle" factor that has been proven to increase the risk of many cancers as well as cardiovascular disease in a dose-dependent relation.[1-6] The conceptual approach of quantifying smoking in terms of age of initiation, cigarette frequency, and duration over the past several decades has served well to underscore both the magnitude of the risks and the benefits of smoking cessation.

The recognition of nicotine dependence as a psychological or physiological problem by the American Psychiatric Association did not occur until 1980. Although this occurred after the health risks of smoking were well established, to the best of our knowledge the nicotine dependence criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), which are based primarily on symptomology and used as the basis for pharmacologic treatment decisions, have not been examined in relation to cancer risk. The diagnostic criteria for nicotine dependence may have limited use in risk studies because many young and adult daily moderate and heavy smokers do not meet the clinical criteria for nicotine dependence.[7-10] There is only a modest concordance between the criteria and the daily frequency of smoking. Behavioral scales of nicotine dependence, such as the Fagerstrom Test for Nicotine Dependence (FTND), have also to our knowledge not been examined in relation to lung cancer risk, although cigarette frequency is the major contributor to the FTND index. The majority of other FTND items are subjective feelings regarding smoking or refraining from smoking.

Nicotine uptake can be measured biochemically by cotinine levels in saliva, blood, and urine. There is wide variation in cotinine levels among smokers, which is only partially explained by smoking frequency. This indicates that other manifestations of nicotine dependence affect nicotine and smoke uptake.

One specific behavior that explains a substantial amount of the variation in cotinine levels in active smokers is the time to first cigarette after waking (TTFC). Similar to cigarette frequency, TTFC is the other item of the FTND that is quantifiable.[11] An increasing TTFC interval is reported to be significantly associated with decreased cotinine levels.[12]

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Two nicotine dependence phenotypes are characterized by the TTFC time interval. The "low" dependent phenotype are smokers who smoke their first cigarette $>$ 30 minutes after waking and smoke $\leq$ 20 cigarettes per day. The "high" dependent phenotype are smokers who smoke their first cigarette $\leq$ 30 minutes after waking but, in contrast to the low dependent phenotype, have a wide range of daily cigarette consumption (eg, 6-70 cigarettes smoked per day).

TTFC is also associated with behavioral traits of nicotine addiction including smoking amount,[13] inability to quit,[14-16] smoking relapse,[17] and tolerance.[18] Therefore, the current study examined whether TTFC is a nicotine-dependent phenotype that predicts lung cancer risk independent of cigarette smoking frequency and duration.

MATERIALS AND METHODS

The methods used for the current study were previously described in detail.[1] The study was conducted primarily in large academic medical centers in the New York metropolitan area to study the effects of tobacco exposure and cancer risk. In brief, all newly diagnosed patients with histologically confirmed lung cancer were requested to participate in the study. Subjects were asked to provide informed consent and were interviewed by a trained interviewer using a structured questionnaire. Controls were consented patients admitted to the same hospital for conditions unrelated to tobacco smoke exposure. Controls were 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 diagnoses such as benign prostatic hypertrophy; and cancers not caused by tobacco, including those of the breast and prostate. The study dates were between 1977 and 1999 and the response rates were $>$ 90% for both cases and controls. Reasons for nonresponse included not feeling well or a lack of interest. All subjects were required to speak English and to be free of any mental impairment. In the current analysis, we restricted the database to subjects who had a smoking history of at least 1 cigarette per day for $\geq$ 1 year. The current analysis included 7610 subjects, including 4775 cases and 2835 controls. There were 6812 white subjects, 759 black subjects, and 39 subjects belonging to other racial groups.

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 derive odds ratios (ORs) and 95% confidence intervals (95% CIs).

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 to 30 minutes, 31 to 60 minutes, $>$ 1 hour (reference category), and do not know. None of the subjects responded as not knowing. In the initial models using pack-years as a measure of tobacco smoke exposure, a significant lack of fit was found. Subsequent models using a squared term for pack-years and an interaction term between pack-years and a categorical term for number of cigarettes smoked per day ($\leq$ 20 vs $>$ 20) demonstrated no evidence of lack of fit. We also fitted models that used other measures of cigarette smoking history in addition to pack-years. These included models with terms for 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 the number of cigarettes smoked per day and its square was exponential.[6] Because the risk of lung cancer varies by smoking intensity, the risk associated with TTFC adjusted for EOR was further stratified by smoking intensity. A few subjects reported quitting $<$ 1 year before the interview, and were classified as current smokers. The following covariates were included in the final models: age ($\leq$ 50 years, 51-60 years, 61-70 years, and $>$ 70 years), sex (male vs female), race (black vs white), education ($\leq$ 12 years, 12 years, 13-15 years, and $\geq$ 16 years), and body mass index (weight [lbs]*703/(height [in])^2). Histologic-specific models were developed by comparing cases with lung adenocarcinoma or squamous cell carcinoma with the entire control series. For all the analyses, statistical significance was set at $P <$ .05, and all tests were 2-sided. There were no missing data for the variables analyzed in the current report. A goodness-of-fit test for each model was performed using the Hosmer and Lemeshow chi-square statistic.[19]

RESULTS

The basic characteristics of the study subjects are shown in Table 1. Because the current analysis excluded never-smokers, there were a larger number of cases than controls (4775 vs 2835). Lung cancer was more common among men, and approximately 90% of all subjects were white.

Table 1. Characteristics of Lung Cancer Cases and Controls

Characteristic	Cases N=4775 (%)	Controls N=2835 (%)
Mean age, y	60	60
Sex		
Men	2973 (62.3)	1896 (66.9)
Women	1802 (37.7)	939 (33.1)
Race		
White	4251 (89.0)	2561 (90.3)
Black	493 (10.3)	266 (9.4)
Other	31 (0.7)	8 (0.3)
Smoking status		
Current	2843 (59.5)	1024 (36.1)
Former	1932 (40.5)	1811 (63.9)
TTFC, min		
>60	575 (12.0)	833 (29.4)
31-60	722 (15.1)	588 (20.7)
1-30	3478 (72.8)	1414 (49.9)

Abbreviation: TTFC, time to first cigarette.

Approximately 60% of cases and 36% of controls were current smokers.

In logistic regression models, the association between the dose of smoking and lung cancer risk demonstrated the expected dose-response pattern. Because the risk was calculated among ever-smokers, the ORs were substantially lower than what is typically observed in studies that include never-smokers. The OR for current versus former smoking was 2.32 (95% CI, 2.8-2.59). Compared with smoking 1 to 9 cigarettes per day, the OR was 1.40 (95% CI, 1.09-1.8) for 10 to 19 cigarettes smoked per day, 2.20 (95% CI, 1.86-2.59) for 20 to 29 smoked cigarettes per day, 2.60 (95% CI, 2.1-3.2) for 30 to 39 cigarettes smoked per day, 3.51 (95% CI, 2.9-4.3) for 40 to 49 cigarettes smoked per day, and 3.96 (95% CI, 1.1-1.5) for $\geq$ 50 cigarettes smoked per day.

Compared with smoking the first cigarette $>$ 1 hour after waking, the unadjusted OR for lung cancer was 1.78 (95% CI, 1.53-2.07) for smoking within 31 minutes to 60 minutes of waking and 3.56 (95% CI, 3.15-4.03) for smoking 1 minute to 30 minutes after waking. There was a significant association noted between TTFC and sex, age, years of education, smoking status, and pack-years ($P < .01$). No significant differences with regard to TTFC by race were found. In multivariate models controlling for sociodemographic characteristics, the pack-years–adjusted ORs were 1.31 (95% CI, 1.11-1.54) and 1.79 (95% CI, 1.56-2.07) for smoking within 31 to 60 minutes and 1 to 30 minutes, respectively (Table 2).

The results for models using alternative measures of smoking history including total years of smoking, number of cigarettes smoked per day, smoking status (current vs former), and years since quitting were similar (Table 2). The total smoking years-adjusted OR was 1.47 (95% CI, 1.25-1.72) for smoking the first cigarette 31 minutes to 60 minutes after waking and 2.34 (95% CI, 2.10-2.68) for smoking the first cigarette within 30 minutes after waking.

The OR adjusted by cigarettes smoked per day was 1.58 (95% CI, 1.35-1.84) for smoking 31 to 60 minutes after waking and 2.64 (95% CI, 2.31-3.02) for smoking within 30 minutes after waking. The smoking status-adjusted OR was 1.68 (95% CI, 1.44-1.97) for smoking the first cigarette 31 minutes to 60 minutes after waking and 3.0 (95% CI, 2.64-3.42) for smoking the first cigarette within 30 minutes after waking. When smoking was modeled by years since quitting, the OR was 1.66 (95% CI, 1.41-1.94) for smoking 31 minutes to 60 minutes after waking and 2.82 (95% CI, 2.49-3.42) for smoking within 30 minutes after waking (Table 2). In another model that adjusted for total years of smoking and number of cigarettes smoked per day, the respective ORs were 1.40 (95% CI, 1.20-1.66) and 2.12 (95% CI, 1.85-2.43).

In white subjects only, the TTFC was found to be statistically significant regardless of the method for smoking adjustment. In black subjects, smoking within 30 minutes after waking but not within 31 minutes to 60 minutes after waking was consistently associated with a significantly increased risk of lung cancer.

The adjusted ORs associated with each additional year of smoking stratified by the number of cigarettes smoked per day were all found to be statistically significant ($P < .01$). The OR was 1.04 for 1 to 10 cigarettes smoked per day, 1.04 for 11 to 20 cigarettes smoked per day, 1.06 for 21 to 30 cigarettes smoked per day, 1.06 for 31 to 40 cigarettes smoked per day, and 1.07 for $>$ 40 cigarettes smoked per day. The risk of lung cancer associated with TTFC adjusted for the EORs was 1.47 (95% CI, 1.26-1.72) for a TTFC of 31 minutes to 60 minutes and 2.23 (95% CI, 1.95-2.56) for a TTFC of 1 to 30 minutes. Figure 1 shows the association between the TTFC and lung cancer risk adjusted for the EOR, stratified by 7 categories of smoking intensity. The results were consistent with the other models. Compared with a TTFC of $\geq$ 60 minutes, the ORs were increased for a TTFC of 31 minutes to 60 minutes and even higher ORs were found for a TTFC of 1 minute to 30 minutes. The only intensity subcategory in which the risk for TTFC was not elevated was for 10 to 15 cigarettes smoked per day and $\geq$ 30

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

TTFC, Minutes	OR Adjusted for Pack-Years of Smoking	95% CI	OR Adjusted for Total Years of Smoking	95% CI	OR Adjusted for Cigarettes per Day	95% CI
>60	1.0		1.0		1.0	
31-60	1.31	1.11-1.54	1.47	1.25-1.72	1.58	1.35-1.84
1-30	1.79	1.56-2.07	2.34	2.10-2.68	2.64	2.31-3.02
Chi-square test for trend	$P < .01$		$P < .01$		$P < .01$	
Whites						
>60	1.0		1.0		1.0	
31-60	1.39	1.17-1.65	1.53	1.29-1.81	1.65	1.40-1.95
1-30	1.93	1.66-2.24	2.44	2.12-2.82	2.82	2.45-3.25
Blacks						
>60	1.0		1.0		1.0	
31-60	0.89	0.51-1.54	1.06	0.62-1.83	1.04	0.68-1.79
1-30	1.12	0.71-1.77	1.63	1.28-2.06	1.66	1.07-2.56

TTFC, Minutes	OR Adjusted for Smoking Status	95% CI	OR Adjusted for Years Since Quitting[a]	95% CI
>60	1.0		1.0	
31-60	1.68	1.44-1.97	1.66	1.41-1.94
1-30	3.0	2.64-3.42	2.82	2.49-3.22
Chi-square test for trend	$P < .01$		$P < .01$	
Whites				
>60	1.0		1.0	
31-60	1.75	1.48-2.06	1.65	1.4-1.95
1-30	3.15	2.75-3.61	2.82	2.45-3.25
Blacks				
>60	1.0		1.0	
31-60	1.21	0.71-2.05	1.04	0.61-1.79
1-30	1.79	1.17-2.75	1.66	1.07-2.56

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; TTFC, time to first cigarette.
[a] The ORs adjusted for years since quitting included current smokers. ORs were adjusted for age, sex, race, education, and body mass index.

cigarettes smoked per day for just those subjects with a TTFC of 31 minutes to 60 minutes.

The association between TTFC and risk of lung cancer was observed for all major histologic types of cancer (Table 3). The ORs were slightly higher for the lung histologies that are most strongly related to cigarette smoking, including small cell carcinoma and squamous cell carcinoma. Findings for other or mixed histologies are not shown.

DISCUSSION

The results of the current study demonstrate that a specific nicotine dependence phenotype, TTFC, is an independent predictor of lung cancer after adjustment for smoking history. The risk of lung cancer has been historically modeled based on measures of cigarette frequency, which is linearly related to cotinine concentrations up to approximately 20 cigarettes per day. The correlation between cigarette frequency and cotinine is moderate in light smokers and low in heavy smokers.[12] There is clearly interindividual variability in the way smokers regulate their nicotine intake per cigarette, with increasing frequency in a natural setting and in attempting to quit.[20] It is not feasible to measure how smokers regulate their nicotine uptake in studies of disease risk, but the TTFC is a behavior that is strongly associated with the level of cotinine per cigarette smoked. Nicotine and cotinine are not carcinogenic, but the correlation between the urinary level of cotinine and the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) from mainstream cigarette smoke is fairly high (correlation coefficient, 0.69).[21] The

TTFC is a distinct nicotine dependence phenotype and was also shown to be an independent risk factor for lung cancer in the current study.

To the best of our knowledge, there have been only a few studies published to date regarding nicotine dependence and cancer risk. One report of 55 lung cancer cases and 49 controls found a significant trend in risk associated with the FTND score, although cigarette frequency is the biggest contributor to the FTND index and TTFC was not examined separately.[22] The current study found that the risk of lung cancer was nearly doubled in smokers who smoked their first cigarette within 30 minutes after waking compared with smokers with an interval of $\geq$ 1 hour between awakening and smoking. It is possible that had this response category been defined by 15-minute intervals, an even higher risk might have been observed for smoking within the first 15 minutes after waking.

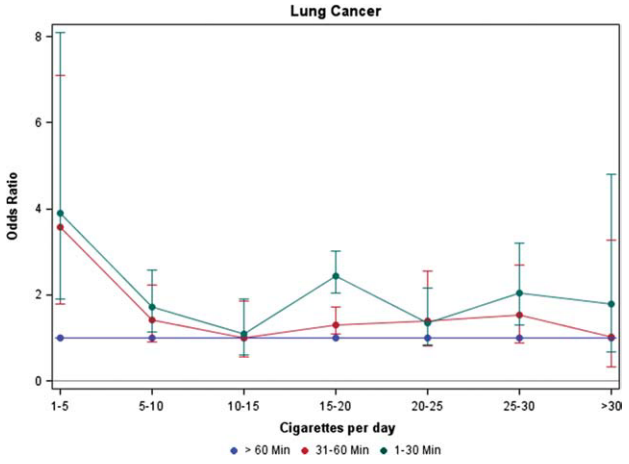

Figure 1. Time to first cigarette and lung cancer risk in ever-smokers adjusted for the excess odds ratio per pack-years are shown by cigarette intensity (number of cigarettes smoked per day).

To account for potential confounding by smoking duration, intensity, or both, lung cancer risk was modeled using several traditional methods to characterize smoking, including total years of smoking, smoking status, number of cigarettes smoked per day, and years since quitting. The ORs for TTFC were all similar after adjustment for these measures. Similarly, because the effects of total smoke exposure (pack-years) may vary for a fixed intensity, the risk associated with TTFC was adjusted for the EOR at different smoking intensities. The association between decreasing TTFC and the EOR-adjusted lung cancer risk was found to be consistent with the other methods of smoking adjustment. Compared with a TTFC of $\geq$ 60 minutes, the OR was increased for TTFC across nearly all intensity levels, with higher risks observed for a TTFC of 1 minute to 30 minutes compared with a TTFC of 30 minutes to 60 minutes. The only intensity subcategory in which the risk for TTFC was not elevated was for 10 to 15 cigarettes smoked per day and $\geq$ 30 cigarettes smoked per day for just those subjects with a TTFC of 31 minutes to 60 minutes. The reasons for this are unclear; however, the differences in ORs between strata were within the margin of error.

Recall bias is always a concern in case-control studies. Smoking habits are usually reported with a high degree of reliability. This was tested previously in a subset of subjects from the current study. In repeat interviews scheduled 6 weeks apart, the OR for lung cancer associated with smoking intensity was found to have changed very little (eg, 1-19 cigarettes smoked per day: OR, 2.4 vs 2.4; 20-29 cigarettes smoked per day: OR, 2.8 vs 3.0; and $\geq$ 30 cigarettes smoked per day: OR, 3.8 vs 3.6). Any misclassification regarding TTFC because of poor recall

Table 3. ORs and 95% CIs for Lung Cancer and TTFC in Ever-Smokers by Histologic Type, Adjusting for Pack-Years of Smoking[a]

TTFC, Minutes	OR for Lung Adenocarcinoma	95% CI	OR for Squamous Cell Carcinoma	95% CI	OR for Small Cell Carcinoma	95% CI	OR for Large Cell Carcinoma	95% CI
>60	1.0		1.0		1.0		1.0	
31-60	1.39	1.12-1.55	1.48	1.08-2.03	1.24	0.76-2.02	1.15	0.68-1.93
1-30	1.47	1.13-1.71	2.13	1.62-2.81	2.00	1.33-3.01	1.62	1.05-2.51
Chi-square test for trend	P <.01		P <.01		P <.01		P <.05	

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

would be expected to be more common at a younger age, when distant habits are less easily recalled. The similar findings in the age-stratified analysis (aged $\leq$ 50 years vs aged $>$ 50 years) would appear to suggest that recall bias concerning TTFC is not large.

The current study included a large number of individuals and had a high response rate. We believe its findings are generalizable to whites. It is less certain if the findings can be generalized to black individuals. Similar to white individuals, black subjects had increased risks for a TTFC of 1 minute to 30 minutes but, unlike whites, there was no increased risk noted for a TTFC of 31 minutes to 60 minutes. This may reflect the relatively small number of black subjects in this category. In addition, the participating institutions were located primarily in Manhattan and not Brooklyn or other boroughs that have large black populations. No inferences can be made with regard to Asian smokers.

It is uncertain what explanation there is for the relation noted between a shorter interval between waking and the first cigarette and increased cotinine levels. The reasons might reflect genetic variations in nicotine dependence, nongenetic behavioral and social factors, cigarette brand characteristics such as taste, or combinations of genetic and social factors. Early morning smokers might have a greater craving for nicotine after overnight abstinence. In a British study, the TTFC was not found to be associated with more intense puffing, although cotinine was not measured.[23] Nevertheless, the findings of the current study emphasize the importance of nicotine dependence in cancer risk. Although smoking prevalence has declined in the United States, remaining younger smokers are more highly addicted to nicotine than older smokers.[24]

Recent findings from genome-wide scans have identified variants in the 15q25 cholinergic nicotine receptor genes that are associated with both a phenotype of nicotine dependence (eg, cigarette frequency) and, as a consequence, an increased risk of lung cancer.[25] Similarly, identifying specific smoking behavior phenotypes and the role of genetic variability are emerging as new fields in the pharmacogenetics of smoking cessation.[26] These studies collectively indicate that variations in nicotine dependence caused by genetic susceptibility, behavioral factors, or both affect lung cancer risk. They also indicate that quantifying the health risks from tobacco smoke should conceptualize cigarette smoking as a physiological dependence and not a lifestyle factor. This will help to identify those smokers who are at especially high risk of cancer and help develop targeted smoking interventions to reduce this risk.

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CONFLICT OF INTEREST DISCLOSURES

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