Smoking addiction and the risk of upper-aerodigestive-tract cancer in a multicenter case-control study

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Short Title: Smoking addiction and upper-aerodigestive-tract cancer

Key Words: smoking addiction, Fagerström, upper-aerodigestive-tract cancer
Manuscript category: research article-epidemiology
Word count: 3,350
Table count: 6
Reference count: 21
Novelty and impact: This is the first study to examine the relationship between smoking addiction (beyond one component) and upper-aerodigestive-tract squamous cell carcinoma (UADT SCC) risk in the multicenter case-control study (ARCAGE) in Western Europe. We observed that smoking addiction, especially time to first cigarette after waking up was associated with UADT SCC risk among current smokers. This addiction-cancer association suggests that inclusion of smoking addiction information when accounting for smoking effect through questionnaire information is important.

Abstract

While previous studies on tobacco and alcohol and the risk of upper-aerodigestive-tract (UADT) cancers have clearly shown dose-response relations with the frequency and duration of tobacco and alcohol, studies on addiction to tobacco smoking itself as a risk factor for UADT cancer have not been published, to our knowledge. The aim of this report is to assess whether smoking addiction is an independent risk factor or a refinement to smoking variables (intensity and duration) for UADT squamous cell carcinoma (SCC) risk in the multicenter case-control study (ARCAGE) in Western Europe. The analyses included 1,586 ever smoking UADT SCC cases and 1,260 ever smoking controls. Addiction was measured by a modified Fagerström score (first cigarette after waking up, difficulty refraining from smoking in places where it is forbidden, and cigarettes per day). Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for UADT cancers with addiction variables were estimated with unconditional logistic regression. Among current smokers, the participants who smoked their first cigarette within 5 minutes of waking up were two times more likely to develop

UADT SCC than those who smoked 60 minutes after waking up. Greater tobacco smoking addiction was associated with an increased risk of UADT SCC among current smokers (OR=3.83, 95% CI 2.56-5.73 for score of 3-7 vs. 0), but not among former smokers. These results may be consistent with a residual effect of smoking that was not captured by the questionnaire responses (smoking intensity and smoking duration) alone, suggesting addiction a refinement to smoking variables.

Introduction

The Fagerström test for nicotine dependence (FTND) is a short version with six questions of Fagerström Tolerance Questionnaire (FTQ),[3] including time to first cigarette after waking up, difficulty refraining from smoking in places where it is forbidden, hate giving up the first cigarette in the morning compared to all the other cigarettes, cigarettes smoked per day, more frequent smoking during the first hour after waking up than the rest of the day, and smoking even when ill and in bed most of the day. This test has been widely used because it is convenient for clinical and research purposes as a self-administered measure.[2] To date, in the only published study on Fagerström scores and cancer risk, Deheinzelin et al. reported an association between Fagerström Tolerance Questionnaire score ≥ 7 and overall cancer risk (pack-year adjusted OR=3.45, 95% CI 1.52-7.83) in a smoking cessation group.[4] A total of 54 cases with a variety of histology and cancer sites were included in the study. Recently, Muscat et al. reported an association (pack-year adjusted OR=1.59, 95% CI 1.19-2.11 for 1-30 minutes, compared to >60 minutes) between time to first cigarette after waking (one component in Fagerström score) and oral and pharyngeal cancer risk among smokers in a case-control study.[5] Matsuo et al. also reported a similar association with adjustment by smoking quantity and duration for upper-aerodigestive-tract (UADT) cancer among ever smokers in Japan.[6]

Tobacco smoking and alcohol drinking behaviors often occur together.[7] Alcohol dependence and tobacco addiction are also correlated.[8] Tobacco smoking and alcohol drinking are well established risk factors for UADT squamous cell carcinoma (SCC).[9,10] While previous studies on tobacco and alcohol on the risk of UADT cancers have clearly shown dose-response relations with the frequency and duration of tobacco and alcohol,

no studies on addiction to tobacco itself (beyond only one component of Fagerström test) as a risk factor for UADT cancer have been published, to our knowledge. In addition to tobacco smoking, it is likely that smoking addiction is correlated with alcohol drinking, and possibly with socioeconomic status, sex, or risky sexual behaviors,[11,12,13] all of which could act as potential confounders for assessing the relationship between smoking addiction and UADT cancer risk. There is also evidence that questionnaire information on smoking captures only a part of the relationship between smoking and cancer.[14] Smoking variables including intensity and duration may play a role of a mediator in the relationship between addiction and UADT cancer. We suspect indicators of tobacco addiction may provide additional information on the smoking and UADT cancer relationship to the usual smoking questions in the surveys.

The aim of this report is to assess whether smoking addiction is a risk factor or a refinement to smoking variables (intensity and duration) for UADT SCC risk in a multicenter case-control study (ARCAGE) in Western Europe, independent of tobacco smoking. This is the first study investigating the association between smoking addiction and UADT SCC risk with stratification by tobacco smoking. Furthermore, we analyzed whether smoking, including intensity and duration (pack-years), mediates the relationship between time to first cigarette after waking up and UADT SCC.

Material and methods

Study Population

Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) is a multicenter case-control study with recruitment in 14 centers from 10 European

countries (Czech Republic, Croatia, France, Germany, Greece, Ireland, Italy, Norway, Spain and United Kingdom). The study was approved by the ethical review board of IARC, as well as the respective local boards in the participating centers. All subjects provided written informed consent for their participation in the study.

Details on the study design have been provided previously.[15] Briefly, incident cases were identified from participating hospitals and were histologically or cytologically confirmed. Eligible cases were classified under specific ICD-O codes (C00, C01, C02, C03, C04, C05, C06, C09, C10, C12, C13, C14.0, C14.8, C15.0, C15.3, C15.4, C15.5, C15.8, C15.9, and C32), 15 including cancer of the oral cavity, pharynx (excluding nasopharynx), larynx and esophagus. Recruitment was conducted from 2002 to 2005 for all centers, except for the French center, where recruitment was conducted during 1987 to 1992. Cases were identified by participating hospitals within 6 months of diagnosis. Six cases were excluded from the analysis due to missing information on age, sex or education. Among the 2,286 UADT cancer cases, 92.3% of the cases were squamous cell carcinoma (SCC). We focused our analysis on cases with SCC histology, since the etiology of UADT cancer of other histologies may differ. We also included only ever tobacco smokers, since tobacco smoking addiction was assessed only in people who smoked. The Paris center data were not included because tobacco smoking addiction information was not collected at this center. Of the 1,586 ever smoking UADT SCC cases in the remaining centers, 761 were oral cavity/oropharyngeal cancers, 623 were hypopharyngeal/laryngeal cancer cases, 127 were esophageal cancer cases and 75 were overlapping oral cavity/pharyngeal cancer cases (Table 1).

In each center, controls were frequency-matched to cases by sex, age, and referral (or residence) area. In the UK centers, population controls were randomly chosen from the same family medical practice list as the corresponding cases. In the remaining centers, hospital controls with a recently diagnosed disease were used, and admission diagnoses related to alcohol, tobacco or dietary practices were excluded. Eligible control admission diagnosis included 1) endocrine and metabolic 2) genito-urinary 3) skin, subcutaneous tissue, and musculoskeletal, 4) gastro-intestinal, 5) circulatory, 6) ear, eye and mastoid, and 7) nervous system diseases, as well as 8) plastic surgery cases, and 9) trauma patients. The proportion of controls within a specific diagnostic group did not exceed 33% of the total. In the UK centers, population controls were recruited from a randomly selected list of ten controls for every case, matched by age, sex, and same family medical practice. After excluding six controls due to missing information on age, sex or education and including ever smokers only, 1,260 ever smoking controls were included in the analysis. In the Paris center, smoking addiction information was not collected, so the data were not included in the analysis.

Cases and controls underwent identical interviews during which they completed a lifestyle questionnaire. The questionnaire included information on socio-demographic variables, as well as detailed smoking and alcohol drinking histories. The participation rates ranged from 35% to 100% for cases and from 26% to 100% for controls. The UK centers with population-based recruitment had the lowest participation rates, compared to the other centers.

Ever smokers were defined as individuals who ever smoked cigarettes, cigars, pipes or any tobacco products at least once a week for a year. Former smokers were

defined as smokers who had stopped for at least 12 months. The different types of tobacco smoking were converted to cigarette equivalents (1 cigar = 4 cigarettes and 1 pipe = 3.5 cigarettes). Heatherton et al. modified the original Fagerström test (an eight-item questionnaire) to a six-item questionnaire and suggested that with limited resources it might be most effective to score only the time to first cigarette after waking up and number of cigarettes per day.[3] In our analysis, modified Fagerström scores (range 0-7) were calculated by summing the scores from the three variables available in ARCAGE: time to first cigarette after waking up (after 60 minutes=0, within 31-60 minutes=1, within 6-30 minutes=2, within 5 minutes=3), difficulty to refrain from smoking in places where it is forbidden (no difficulties=0, difficulties=1), and intensity of smoking (<10 cigarettes/day=0, >10-20 cigarettes/day=1, >20-30 cigarettes/day=2, >30 cigarettes/day=3). Higher scores indicate more addiction while lower scores suggest less addiction.

Statistical Analysis

For the assessment of main effects of smoking addiction, all ever smoking UADT cancer cases were analyzed both together and stratified by cancer subsite. The distribution of cases and controls by age, center, sex, education, and histology was examined. Odds ratios (OR) and 95% confidence intervals (95% CI) for UADT cancers with addiction variables (time to first cigarette after waking and difficulty to refrain from smoking) were estimated with unconditional logistic regression, adjusting for center, age (categories shown in Table 1), sex, education level (categories shown in Table 1), and alcohol consumption (intensity as a continuous variable and duration as a categorical variable), tobacco smoking pack-years (continuous).

We introduced smoking-related variables (pack-years or duration of use) in the models (Figure 1) to estimate the direct effect (line A) of addiction on UADT cancer (i.e. the effect that is not mediated by pack-years or duration of use) under specific assumptions, including lack of interaction between addiction and the pack-years/duration of use in causing UADT cancer. We also followed the method suggested by Vanderweele[16] that requires testing for exposure-mediator interaction and then combining two regression models (i. with UADT cancer as the outcome and ii. with pack-years as the outcome) to estimate natural direct (line A) and indirect (line B + C) effects, as defined by Judea Pearl.[17] In brief, we considered a framework in which smoking addiction is the exposure, pack-years or duration of use are the mediators, and UADT is the outcome of interest. Then, the total effect (line A + line B + C) of smoking addiction on UADT cancer can be decomposed into two effects, a natural indirect effect which is mediated by measured smoking variables and a natural direct effect which is unmediated by measured smoking variables.

Stratified analyses by cigarettes per day of smoking and cumulative alcohol drinking were performed to evaluate whether the associations observed with time to first cigarette after waking were modified by the amount of tobacco use. Statistical analyses were conducted using the SAS 9 statistical software. All p-values were two-sided.

Results

In this analysis, we included 1,586 UADT SCC cases and 1,260 controls who ever smoked tobacco (Table 1). As expected, there was a higher proportion of the highly educated individuals among the controls (8.17%) than the cases (4.60%). In our initial assessment of the three components in the same regression model for the Fagerström test among current smokers, time to first cigarette after waking up (OR ~1.58-2.29) and number of cigarettes smoked per day (OR ~1.64-2.27) showed similar associations with UADT SCC risk, but stronger than difficulty to refrain from smoking at places where smoking is prohibited (OR ~0.74) (results not shown). Among current smokers, the mean 3-item Fagerström scores (±Standard deviation) were 3.70±1.76 for cases and 2.77±1.90 for controls; among former smokers, the mean scores were 2.93±2.03 for cases and 2.35±2.03 for controls (data not shown in table).

Among current smokers, an inverse dose-response trend was detected between time to first cigarette after waking up and UADT SCC risk ($p<0.001$) (Table 2a). No association was observed with difficulties of refraining from smoking at a place where smoking is forbidden (results not shown). The participants who smoked the first cigarette within 5 minutes were two times more likely to develop UADT SCC (OR=2.22, 95% CI 1.57-3.15) than those who smoked 60 minutes after waking up. However, a dose-response trend between time to first cigarette and UADT SCC risk was not observed among former smokers ($p=0.998$). A higher score on the modified Fagerström test, reflecting greater tobacco smoking addiction, was associated with an increased risk of UADT SCC among current smokers, but not among former smokers. We did not observe any apparent differences across the UADT subsites for relationship between smoking addiction and cancer risk among the current smokers. The relationship

between smoking addiction and UADT SCC remained similar with further adjustment by fruit and vegetable consumption (data not shown).

We did not find evidence of interaction between addiction variables and smoking variables. Table 2b shows the natural direct (Figure 1, line A) and indirect effects (Figure 1, line B + C) for UADT SCC. Consistently with results shown in Table 2a, we observed that among current smokers most, or the whole, effect was captured by natural direct effects, i.e. effects unmediated by pack-years/duration of use, while among former smoker indirect effects, i.e. effects mediated by pack-years/duration of use, were equally strong or larger than direct effects.

When stratified by sex, time to first cigarette after waking up was associated with the risk of UADT SCC among men (adjusted OR=1.69, 95% CI 1.26-2.25 for within 5 minutes), but not among women (adjusted OR=1.38, 95% CI 0.72-2.64 for within 5 minutes, p for trend=0.086) (data not shown). Among women, an association with smoking 6-30 minutes after waking up (OR=2.23, 95% CI 1.30-3.83) was detected (data not shown). Overall, dose-response trends between modified Fagerström scores and UADT SCC risk were detected for both men ($p<0.001$) and women ($p=0.006$) (data not shown).

Among current smokers who smoked <10 cigarettes per day, smoking within a short time after waking up was associated with an increased risk of UADT SCC (Table 3). We did not show the results for esophageal cancer due to sparse data. For former smokers, after stratifying by smoking intensity, smoking within a short time after waking up was not associated with the risk of UADT SCC regardless of smoking intensity (data not shown). In addition to stratified analyses, interaction terms between modified

Fagerström score and smoking intensity or cumulative alcohol drinking were assessed but none were detected (p=0.27 for cigarettes smoked per day and p=0.78 for cumulative alcohol drinking among current smokers; data not shown).

When stratified by cumulative alcohol drinking, we detected an association between modified Fagerström scores and UADT SCC risk among current smokers even among individuals with low cumulative alcohol drinking (<1,000 drinks in lifetime) (OR=21.17, 95% CI 3.50-128.00 for a score of 3-7, p<0.001) although the precision was low (Table 4). We were not able to examine never drinkers due to sparse data.

Discussion

Our study showed that among current smokers, smoking addiction was associated with UADT SCC risk. Similar to the previous study on all cancers by Deheinzelin et al.,[4] in our study we found an effect size of 3.83 (95%CI=2.56-5.73) for UADT SCC risk with a modified Fagerström score of 3-7. Furthermore, the ORs for UADT cancers ranged 1.65-2.22 for <60 minutes to first cigarette after waking when compared to >60 minutes, which is similar to the associations reported by Muscat et al. for head and neck cancer.[5] The association between time to first cigarette after waking and UADT SCC risk did not appear to be due to reported heavier smoking. The smoking addiction increased the risk of UADT SCC consistently regardless of the intensity of smoking. This may imply the misclassification of smoking via questionnaires or that number of pack-years is insufficient to capture all smoking characteristics that explain the association between addiction and UADT cancer risk. In our study, among current smokers we observed associations between time to first cigarette and UADT SCC risk regardless of smoking

intensity. Similarly, our stratified analysis by cumulative alcohol drinking supported the relationship between first cigarette after waking up and UADT SCC independent of cumulative alcohol drinking.

While we observed strong direct associations between addiction measures and UADT SCC risk among current smokers, these associations were not observed among former smokers. It should be noted that both direct and indirect effects among former smokers were weak, and thus they are more prone to different sources of bias, including unmeasured mediator-outcome confounding.[18] We explored the possibility of attenuation of the direct effect of addiction, where perhaps the past smokers were individuals who were less addicted to begin with and thus were able to quit successfully. Though the crude mean Fagerström scores among current smoking controls were slightly higher (2.77) compared to former smokers (2.35), the differences was small.

Based on our results, the questionnaire information on tobacco smoking and alcohol drinking could not fully explain the observed association between smoking addiction and UADT SCC risk. We observed correlation of addiction with education and with gender, both of which are potential confounding factors. However, we adjusted on these factors and the association between smoking addiction and UADT SCC was still observed. Though residual confounding from these factors is still a possibility, we do not expect that residual confounding can fully explain our observed addiction-UADT SCC risk association. Another possible pathway may be that smoking addiction might be related to risky sexual behavior via the human papillomavirus (HPV) pathway to UADT SCC. HPV is a risk factor mainly for oropharyngeal cancers,[19] and the interaction between HPV and tobacco smoking may vary by subsites.[20] However, we observed

similar addiction-cancer associations with oral cavity/oropharynx, hypopharyngeal/laryngeal, and esophageal cancers. Thus, we do not believe that the HPV pathway explains the observed association with smoking addiction. The detected addiction-cancer association may be an indication of the smoking-cancer association being stronger than that observed on questionnaire data on smoking intensity and duration. The most likely explanation for direct effects of addiction among current smokers is that pack-years do not capture all smoking characteristics (e.g. type of tobacco, smoke inhalation patterns, etc.). In other words, pack-years or duration of use could be misclassified measures of smoking as the mediator of the addiction-UADT cancer risk association.

Our study had several limitations including potential recall bias, residual confounding and sparse data. The addiction and lifestyle information was self-reported in interviews. With the knowledge of their cancer status for the UADT cancer patients, the cases might have recalled various exposures differently from the controls. This limitation might have impact on the assessment of smoking intensity, but perhaps less so for time to first cigarette after waking up since a relationship between time to first cigarette after waking up and UADT SCC risk has not been established. There could also be residual confounding by tobacco smoking intensity and alcohol drinking due to inability to stratify by finer categories of low tobacco smoking and alcohol drinking intensity or lifetime amount. Although we performed stratified analyses, sparse data were a limitation for UADT subsites, especially for esophageal cancer and for finer strata of very low tobacco smoking or alcohol drinking. Finally, we utilized only three components of the FTND to assess smoking addiction in ARCAGE because the other

three components were not available in our study. As mentioned earlier, the two items (time to first cigarette after waking up and number of cigarettes smoked per day) account for the majority of variance for FTQ scores.[3] Furthermore, the Heavy Smoking Index (HSI), which includes the number of cigarettes per day and the time of the first cigarette of the day, has been shown to have a high concordance with the FTND (Chabrol 2005). Thus, we believe our use of a modified Fagerström score was reasonable.

The possible mechanisms of an effect of the addiction score in addition to that of tobacco smoking as measured by questionnaire are complicated by the fact that cigarettes smoked per day is included in both approaches. Thus, we also attempted to focus on the other main component (time to first cigarette after waking up) of the score in our analysis. We observed that time to first cigarette after waking was associated with UADT SCC risk regardless of the number of cigarettes smoked per day. The investigation may be whether the score corrects (at least in part) the misclassification of smoking (i.e., weak smokers with strong dependence should in fact be classified as heavy smokers), or whether nicotine dependence is a marker of susceptibility to tobacco carcinogenesis (i.e., more dependent smokers are at higher risk than less dependent smokers given the same amount of tobacco smoking). The latter can happen through metabolic pathways that are in common to nicotine and tobacco carcinogens, such as tobacco-specific nitrosamines (TSN), which are derivatives of nicotine. The latter explanation might be explored through an analysis of *CYP2A6, CHRNA5-A3-B4*[21] and other genes involved in nicotine metabolism, in particular those involved in the formation of TSN.

This is the first study to examine the relationship between smoking addiction (beyond one component) and UADT SCC risk in a large multicenter case-control study. We observed that smoking addiction, especially time to first cigarette after waking up was associated with UADT SCC risk, independent of heavy smoking or alcohol drinking behaviors. These results may be consistent with a residual effect of smoking that was not captured by the questionnaire responses (on smoking intensity and smoking duration) alone since the association with time to first cigarette is not completely mediated by smoking intensity and duration (pack-years). In summary, the addiction-cancer association suggests that inclusion of addiction information when accounting for smoking effect through questionnaire information is important.

Acknowledgements and funding support

The authors thank all the participants in this study. Funding was received from European Community (5th Framework Programme) grant no. QLK1-CT-2001-00182, University of Athens Medical School (for the Athens center), and Compagnia di San Paolo and Italian Association for Cancer Research (for the Turin center). YCAL worked on this project during a post-doctoral fellows at the International Agency for Research on Cancer (IARC). None of the sponsors had any role in the design and conduct of the report; collection, management, analysis, and interpretation of the data; or preparation, review and approval of this manuscript.

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Figure 1. Illustration of mediation with smoking addiction as exposure, smoking (pack-year or duration) as mediator, and upper-aerodigestive-tract cancer as outcome.

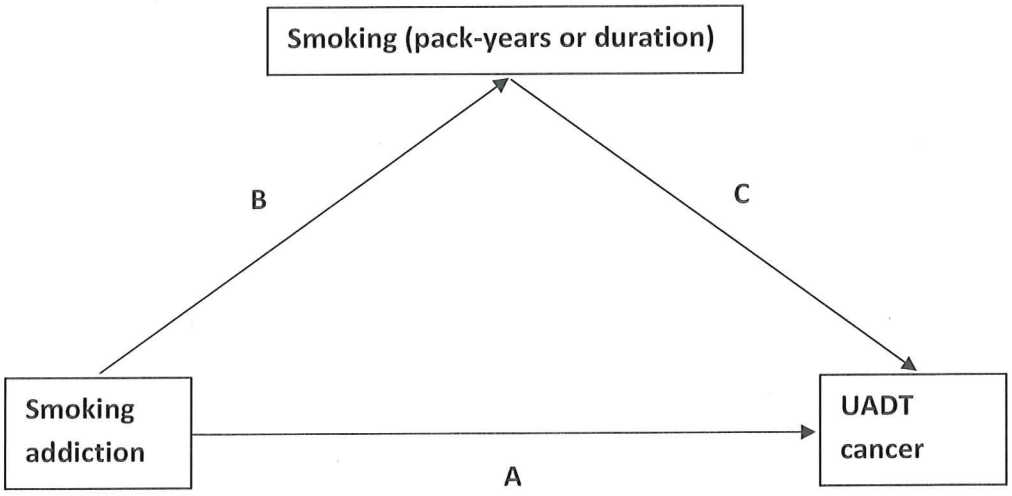

Table 1. Demographic characteristics of the UADT SCC cases and controls (ever smokers only)

		Cases n (%)		Controls n (%)	
Total		**1,586**		**1,260**	
Center	Prague	146	(9.21)	118	(9.37)
	Bremen	263	(16.58)	234	(18.57)
	Athens	187	(11.79)	134	(10.63)
	Aviano	119	(7.50)	83	(6.59)
	Padova	113	(7.12)	74	(5.87)
	Turin	125	(7.88)	130	(10.32)
	Dublin	29	(1.83)	13	(1.03)
	Oslo	116	(7.31)	115	(9.13)
	Edinburgh	82	(5.17)	47	(3.73)
	Manchester	130	(8.20)	118	(9.37)
	Newcastle	58	(3.66)	67	(5.32)
	Barcelona	172	(10.84)	95	(7.54)
	Zagreb	46	(2.90)	32	(2.54)
Age					
	<40 years	25	(1.58)	52	(4.13)
	40-44 years	57	(3.59)	64	(5.08)
	45-49 years	157	(9.90)	98	(7.78)
	50-54 years	252	(15.89)	185	(14.68)
	55-59 years	327	(20.62)	238	(18.89)
	60-64 years	273	(17.21)	183	(14.52)
	65-69 years	232	(14.63)	188	(14.92)
	70-74 years	158	(9.96)	139	(11.03)
	75+ years	105	(6.62)	113	(8.97)
	p-value	<0.001			
Sex					
	Men	1319	(83.17)	1026	(81.43)
	Women	267	(16.83)	234	(18.57)
	p-value	0.227			
Education					
	Finished primary school/worker	584	(36.82)	312	(24.76)
	Finished further school/clerks	929	(58.58)	845	(67.06)
	University degree/Manager	73	(4.60)	103	(8.17)
	p-value	<0.001			
Subsite					
	Controls			1260	(100.00)
	Oral/Oropharynx	761	(47.98)		
	Hypopharynx/Larynx	623	(39.28)		
	Esophagus	127	(8.01)		
	Overlapping	75	(4.73)		

Table 2a. Smoking addiction and UADT SCC risk

	UADT				Oral & oropharynx			Hypopharynx & larynx			Esophagus		
	Co	Ca	OR	95% CI	Ca	OR	95% CI	Ca	OR	95% CI	Ca	OR	95% CI
Current smokers													
First cigarette after waking up													
after 60 minutes	168	160	1.00		85	1.00		61	1.00		11	1.00	
31-60 minutes	98	168	1.65	(1.16-2.34)	84	1.68	(1.10-2.57)	60	1.56	(0.97-2.50)	12	2.40	(0.88-6.55)
6-30 minutes	180	449	2.11	(1.56-2.86)	209	1.94	(1.35-2.79)	178	2.10	(1.40-3.15)	43	4.74	(2.04-10.99)
within 5 minutes	109	368	2.22	(1.57-3.15)	188	2.52	(1.68-3.78)	133	1.77	(1.11-2.81)	18	2.25	(0.83-6.06)
Ptrend				<0.001			<0.001			0.005			0.022
Modified Fagerström													
0	86	50	1.00		30	1.00		13	1.00		6	1.00	
1-2	165	219	2.06	(1.34-3.15)	108	1.72	(1.03-2.88)	83	2.72	(1.39-5.30)	17	1.96	(0.65-5.87)
3-7	303	874	3.83	(2.56-5.73)	427	3.42	(2.11-5.55)	335	4.72	(2.508.93))	61	3.41	(1.24-9.40)
Ptrend				<0.001			<0.001			<0.001			0.009
Former smokers													
First cigarette after waking up													
after 60 minutes	303	125	1.00		62	1.00		47	1.00		13	1.00	
31-60 minutes	114	88	1.54	(1.05-2.24)	42	1.56	(0.96-2.53)	35	1.48	(0.86-2.53)	8	2.09	(0.70-6.21)
6-30 minutes	153	96	0.97	(0.66-1.41)	44	0.94	(0.57-1.56)	41	1.06	(0.621.82)	8	0.75	(0.23-2.44)
within 5 minutes	100	87	1.09	(0.71-1.68)	29	0.90	(0.50-1.62)	50	1.47	(0.83-2.59)	6	1.14	(0.32-4.04)
Ptrend				0.998			0.588			0.322			0.922
Modified Fagerström													
0	164	53	1.00		30	1.00		17	1.00		4	1.00	
1-2	216	125	1.31	(0.86-1.98)	64	1.35	(0.80-2.28)	44	1.15	(0.60-2.19)	15	3.80	(1.01-14.26)
3-7	286	217	1.23	(0.81-1.85)	83	0.93	(0.55-1.59)	111	1.53	(0.83-2.85)	16	2.51	(0.62-10.11)
Ptrend				0.482			0.517			0.112			0.404

*Adjusted for center, education, sex, age, alcohol drinking frequency and duration, and pack-years of smoking (duration of smoking for the Fagerström estimates)

Table 2b. Natural direct and indirect effects of addiction variables on UADT SCC.

	Natural direct effects		Natural indirect effects	
	OR	95% CI°	OR	95% CI°
Current smokers				
First cigarette after waking up *				
after 60 minutes	1.00		1.00	
within 31-60 minutes	1.64	(1.04-2.25)	1.09	(1.01-1.17)
within 6-30 minutes	2.11	(1.44-2.79)	1.15	(1.04-1.26)
within 5	2.22	(1.38-3.06)	1.27	(1.08-1.46)
Modified Fagerström^				
0	1.00		1.00	
1-2	2.06	(1.09-3.03)	1.00	(0.95-1.06)
3-7	3.83	(2.17-5.48)	1.01	(0.92-1.09)
Former smokers				
First cigarette after waking up				
after 60 minutes	1.00		1.00	
within 31-60 minutes	1.54	(0.90-2.17)	1.16	(1.05-1.27)
within 6-30 minutes	0.97	(0.59-1.36)	1.25	(1.08-1.41)
within 5	1.11	(0.57-1.64)	1.37	(1.12-1.63)
Modified Fagerström				
0	1.00		1.00	
1-2	1.31	(0.73-1.88)	1.28	(1.11-1.44)
3-7	1.22	(0.69-1.76)	1.51	(1.25-1.77)

*Exposure: first cigarette after waking up; Mediator: pack-years of smoking; Confounders: education, sex, age, alcohol drinking frequency and duration.

^ Exposure: Fagerström score; Mediator: duration of smoking; Confounders: education, sex, age, alcohol drinking frequency and duration.

° Boostrap estimation

Table 3. Smoking addiction and UADT SCC risk, stratified by sex

	Men					Women				
	Ca	**Co**	**OR**	**95% CI**		**Ca**	**Co**	**OR**	**95% CI**	
First cigarette after waking up										
after 60 minutes	230	376				55	95			
within 31-60 minutes	219	182	1.54	(1.17	- 2.04)	37	30	1.83	(0.98	- 3.44)
6-30 minutes	447	277	1.56	(1.21	- 2.02)	98	56	2.23	(1.30	- 3.83)
within 5 minutes	392	167	1.69	(1.26	- 2.25)	63	42	1.38	(0.72	- 2.64)
Ptrend				<0.001					0.086	
Modified Fagerström										
0	71	182	1.00			32	68	1.00		
1-2	276	317	1.42	(1.00	- 2.01)	68	64	2.10	(1.17	- 3.77)
3-7	938	498	2.15	(1.54	- 3.00)	153	91	2.34	(1.33	- 4.13)
Ptrend				<0.001					0.006	

*Adjusted for center, education, sex, age, alcohol drinking frequency and duration and pack-years (duration of smoking for the Fagerström estimates)

Table 34. Time to first cigarette after waking up among current smokers and UADT SCC risk, stratified by smoking intensity

	UADT overall				Oral & oropharynx				Hypopharynx & larynx			
	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI
≤ 10 cigarette/day												
After 60 minutes	51	89			30	89			14	89		
Within 31-60 minutes	16	20	1.20	(0.50 - 2.91)	6	20	0.72	(0.21 - 2.45)	5	20	2.19	(0.52 - 9.25)
Within 6-30 minutes	44	24	2.65	(1.29 - 5.46)	22	24	2.56	(1.05 - 6.21)	13	24	4.64	(1.21 - 17.81)
Within 5 minutes	17	8	2.84	(0.98 - 8.22)	11	8	5.52	(1.58 - 19.25)	5	8	5.52	(0.61 - 49.81)
Ptrend				0.004				0.004				0.015
11-20 cigarettes/day												
After 60 minutes	79	60			37	60			36	60		
Within 31-60 minutes	95	63	1.23	(0.75 - 2.00)	50	63	1.41	(0.78 - 2.56)	31	63	0.92	(0.48 - 1.77)
Within 6-30 minutes	222	96	1.78	(1.14 - 2.77)	114	96	1.85	(1.08 - 3.16)	73	96	1.59	(0.90 - 2.82)
Within 5 minutes	122	47	1.76	(1.05 - 2.94)	64	47	2.05	(1.12 - 3.78)	37	47	1.23	(0.62 - 2.41)
Ptrend				0.009				0.012				0.209
>20 cigarettes/day												
After 60 minutes	30	19			18	19			11	19		
Within 31-60 minutes	57	15	2.71	(1.13 - 6.48)	28	15	2.60	(0.93 - 7.32)	24	15	3.03	(1.01 - 9.12)
Within 6-30 minutes	183	60	2.21	(1.08 - 4.52)	73	60	1.56	(0.67 - 3.66)	92	60	2.97	(1.17 - 7.53)
Within 5 minutes	229	54	2.41	(1.15 - 5.02)	113	54	2.37	(1.00 - 5.66)	91	54	2.23	(0.86 - 5.79)
Ptrend				0.108				0.143				0.401

*Adjusted for center, education, sex, age, alcohol duration, and alcohol frequency

Table 45. Smoking addiction and UADT SCC risk, stratified by cumulative alcohol drinking

	Current smokers				Former smokers			
	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI
<1,000 drinks/lifetime								
Modified Fagerström								
0	4	18	1.00		4	20	1.00	
1-2	14	21	10.92	(1.73 - 69.08)	8	31	1.65	(0.24 - 11.43)
3-7	47	39	21.17	(3.50 - 128.00)	10	22	3.43	(0.42 - 28.06)
Ptrend				<0.001				0.233
>=1,000-<10,000 drinks/lifetime								
Modified Fagerström								
0	22	31	1.00		18	55	1.00	
1-2	57	53	1.31	(0.62 - 2.79)	29	62	1.32	(0.58 - 3.01)
3-7	128	71	2.90	(1.39 - 6.04)	30	67	0.99	(0.43 - 2.29)
Ptrend				<0.001				0.875
>=10,000 drinks*/lifetime*								
Modified Fagerström								
0	24	37	1.00		31	89	1.00	
1-2	148	91	2.32	(1.26 - 4.26)	88	123	1.39	(0.81 - 2.39)
3-7	699	193	4.39	(2.46 - 7.83)	177	197	1.25	(0.74 - 2.13)
Ptrend				<0.001				0.627

*Adjusted for center, education, sex, age, alcohol duration, alcohol frequency, and duration of smoking