An Epidemiologic Study of the Impact of Cigarette Tar Yield on the Risk of Lung Cancer

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The work described herein and the preparation of this publication was directed by the Data Oversight Committee of the Case-Control Study – Tobacco Overview of Risk (C-TOR) study that is chaired by Dr. Theodore Colton, Chairman Emeritus and Professor, Epidemiology, Boston University and made up of Prof. Dr. Karl-Heinz Jöckel, Director, Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen; Dr. Colm O'Muircheartaigh, Dean & Professor, Harris School, University of Chicago; Dr. Lechaim Naggan, Emeritus Professor of Epidemiology, Ben-Gurion University of the Negev; and Dr. Myron S. Weinberg.

Abstract

Background: Using a database assembled from a case-control study conducted at 230 sites in five European countries during the period 2005 to 2008, an analysis was undertaken to assess the effect of cigarette tar yield on risk of lung cancer, above and beyond the known effects of smoking duration and smoking intensity.

Methods: Totals of 4,450 cases and 3,605 controls met criteria for inclusion in analysis. Smoking duration and smoking intensity were assessed in each valid case and control with use of a Life Event History Calendar (LEHC) interview. Cigarette tar yield for each brand of cigarette smoked was obtained from Philip Morris International's Cigarette Information Reports (CIR). Data analyses employed a series of unconditional logistic regression models for all subjects and separately for men and for women.

Results: Analyses confirmed findings from other studies that smoking duration (years of cigarette smoking) and smoking intensity (cumulative number of cigarettes smoked) are independent risk factors for lung cancer. Furthermore, analyses also confirmed findings from other studies that lung cancer risk decreases with smoking cessation; the longer the cessation period, the greater the decrease in risk. After accounting for age, smoking duration and smoking intensity, average cigarette tar yield emerged as a statistically significant independent risk factor for lung cancer. These findings were generally consistent by gender.

Conclusions: Average cigarette tar yield is an independent risk factor for lung cancer above and beyond the effects of smoking duration and smoking intensity.

Key Words: Cigarette exposure, tar yield, lung cancer, case-control study

Introduction

It has been conclusively established that cigarette smoking causes lung cancer and that the cumulative dose of cigarette tar[1] to which a smoker is exposed is linearly related to the risk of lung cancer.[2,3] This cumulative dose is related both to the intensity of cigarette smoking, i.e. cigarettes per day, and the duration of the smoking habit. The observed dose-response relationship between lung cancer and cigarettes per day prompted a suggestion by Wynder in 1957 that the risk of lung cancer in smokers could be reduced by a number of measures including more effective filtration.[4] As a consequence, cigarette manufacturers have progressively reduced the tar yields of cigarettes. Numerous epidemiological studies have examined the risk of lung cancer comparing the use of higher tar delivery cigarettes to lower tar delivery cigarettes. Four meta-analyses have been published that determined the pooled reduction in risk of lung cancer associated with reduced tar delivery, and all four arrive at approximately the same result; namely that there is a 20-30% reduced risk associated with reduction in tar delivery.[5-8] Nevertheless, it is important to note that many, although certainly not all, of these studies compared filter cigarettes to non-filter cigarettes. Moreover, as tar values have decreased over time, a reduced delivery product in an earlier study would be a higher delivery product in a later study. This calls into question the relevance of many early epidemiological studies to the current situation.

The situation in Europe during the period of approximately 10 years prior to the study being initiated in 2005, was that the market was dominated by two categories of cigarettes. The first of these are non-reduced tar products, normally referred to as Full Flavor (FF) cigarettes yielding between 15 and 10 mg per stick as measured by International Organization for Standardization (ISO) standards,[9] while the second are so-called Low Tar (LT) cigarette products, yielding between 3 and 10 mg ISO tar. It should be noted that the provision of the 2001 Tobacco Products Directive, which mandated that cigarettes should not yield more than 10mg of came into force on January 1, 2004. A 2004 study by Harris et al., which compared the difference in lung cancer risk for European FF cigarettes to European LT cigarettes, did not find a difference between these two categories.[10]

The reason as to why no difference may have been observed between European FF and LT cigarettes in the Harris et al. study[10] is that smokers of LT cigarettes compensate. Therefore, the difference in ISO tar delivery as measured by a smoking machine does not correspond to the difference in tar delivery obtained by the average smoker. A 2005 study by Benowitz et al.[11] that investigated switching from FF to LT cigarettes observed considerable compensation, consistent with the results of Harris et al.[10] On the other hand an early paper by Benowitz et al. observed that a significant reduction in exposure was observed for smokers of Ultra-Low Tar (ULT) cigarettes,[12] a result that they confirmed in 2009.[13] ULT cigarettes (ISO machine-measured tar yield of $\leq$3 mg) were introduced in the early 1980s and since then have gained considerable popularity in some markets. No epidemiological study has ever been conducted to evaluate the risk of lung cancer associated with the use of ULT cigarettes.

In 2004, an epidemiological study, managed by The Weinberg Group LLC, Brussels, Belgium, using a case-control approach (Case-Control Study – Tobacco Overview of Risk, C-TOR), was designed to investigate the role of nominal cigarette smoke tar yield as a risk factor for the development of lung cancer. The original aim of the C-TOR study was to compare the risk of lung cancer associated with the use of ULT cigarettes with that of the use of FF cigarettes.

Using ULT cigarette market penetration data provided by the financial sponsor,[14] sample size considerations led to the recruitment goal of 13,000 cases and 13,000 controls. Subject recruitment was initiated in December 2005 and continued until the financial sponsor discontinued support for the study in October 2008. At the time of termination of financial support for the study, a large body of data had been gathered, including annual cigarette use over the lifetime of individual subjects for 4,705 cases and 3,718 controls.

The study incorporated several innovative research tools, including the use of the Life Event History Calendar (LEHC) questionnaire, a data collection instrument that supports subjects' historical recall of smoking habits by

first providing a framework of important events from the subject's own life history.[15,16] The use of this tool and others led to the creation of a very detailed database of the smoking history for subjects from five European countries, as well as their comorbidities and potential risk factors for lung cancer.

After termination of financial support for the study, The Weinberg Group requested and was granted financial support by Philip Morris International to plan and conduct analyses of the available data to determine the impact of tar yield on risk of lung cancer and to publish key findings. The Data Oversight Committee made up of independent experts external to the conduct of the study, in conjunction with the study management, The Weinberg Group, subsequently carried out this work.

The Data Oversight Committee reasoned that, despite the fact that the C-TOR study had not reached its initially proposed sample size, the available dataset contained much information about the effect of tar yield on lung cancer risk and other aspects of smoking behavior. In particular, it was determined that the C-TOR database contained sufficient numbers of smokers such that they could be classified into the following three groups: (1) those who smoked predominantly FF cigarettes, (2) those who smoked predominantly reduced tar (RT) yield cigarettes (i.e., LT and/or ULT cigarettes), and (3) those who smoked a variety of cigarettes with differing tar yields (i.e., mixed smokers of FF and RT cigarettes). In addition, exposure to tar could be represented as a continuous variable, allowing this exposure to be expressed as a lifetime average cigarette tar exposure.

This paper describes the approaches to these analyses and the findings from data collected from the 8,055 validated subjects gathered in the C-TOR study.

Methods

C-TOR is a multi-national, epidemiologic case-control study in which relevant data about the diagnosis of lung cancer (cases) and the primary hospital admission diagnosis (controls) were collected from hospital charts and physician information.

Two hundred and thirty study sites in France (73), Germany (78), Greece (35), Italy (30), and Slovenia (14) participated in the C-TOR study. These countries were selected because market penetration data indicated a relatively high use of ULT cigarettes for at least 8 years prior to the study launch.

Valid cases and controls were subjects who signed the informed consent, met a minimum level of performance (score of 18 or above) on the Standardized Mini-Mental State Examination (SMMSE),[17] and completed a specially-developed LEHC questionnaire.

Case subjects with recently (not more than 96 days before the signing of the informed consent) diagnosed, medically confirmed primary lung cancer and matching control subjects with an admission diagnosis unassociated with smoking were recruited for the study.

Controls were pair matched to cases by age (±5 years), gender, and administrative area of residence (place lived for a minimum of 6 months prior to signing informed consent form). It was intended to recruit one control per case matched for each of the three matching variables. Because of early termination in the subject recruitment phase of the study and the time lag between case and control recruitment, pairing was incomplete in the analysis dataset. Thus, data were analyzed as if they were unpaired.

Comparison of crude odds ratios estimates among the most common control diagnoses revealed similar effects, except for gender-specific diagnoses (prostate cancer and breast cancer).

Validity of the sample was assessed by comparison of crude odds ratio estimates for former-smokers and current-smokers compared to never-smokers, by gender, to those published by Simonato et al.[18] Those estimates were nearly identical.

Exposure

An interview, using a LEHC questionnaire was the main data collection tool for obtaining information about the subject's smoking behavior, confounders, and effect modifiers. The LEHC is a validated state-of-the-art

approach to data collection which uses salient life events to enhance recall.[15,16] For the analyses, annual information on number and brand of cigarettes smoked each year from the first year during which at least 100 cigarettes were smoked until 24 to 36 months prior to the date on which the informed consent was signed was used. Exclusion of the last 24 to 36 months sought to avoid the so-called quitting ill phenomena.[19]

Tar yield data corresponding to cigarettes smoked were extracted for each brand using Philip Morris International's Cigarette Information Reports (CIR) dating from 1979 to the end of the data collection period. CIRs contain historical tar yield data as printed on the cigarette pack for brands from numerous tobacco manufacturers. For brands for which no data were reported on the cigarette pack, tar yield data were extracted from the sampling results included in the CIR. The majority of CIRs and sampling information and methodologies/criteria by which data are reported are publically available and can be found at the Legacy Tobacco Documents Library website.[20] This exhaustive analysis of the CIR and supplemental analysis coming from the records of the financial sponsor is believed to make the C-TOR tar database the most comprehensive available. For time periods prior to 1979, imputation assigned the FF value of 13 mg. Even though tar values prior to 1979 were declining, 13mg is conservative i.e., it underestimates the value and hence the difference in tar yield versus ULTs.

Among those subjects for whom number of cigarettes and/or nominal tar yield were unknown during a calendar year, those values were imputed. For number of cigarettes, the unknown value in one or more years was taken as the mean of the number of cigarettes in the year before and the year after the unknown period. For tar yield imputation, tar yield of the same brand (if known) for other years or countries was used. If the brand of cigarettes smoked was unknown, mean tar yield of cigarettes smoked by the subject in the year before and the year after the unknown period was used.

Tar yield of cigarettes smoked was represented in two ways in separate analyses. One way was to classify the type of cigarettes smoked as RT (<10 mg) cigarettes or FF (≥10 mg) cigarettes. Then, lifetime tar yield was determined by identifying the type of cigarettes predominately smoked. If neither type of cigarette was smoked predominately, the subject was classified as a mixed-smoker. Table 1 summarizes these classifications and shows the numbers of cases and controls in each classification.

Table 1. Lifetime Smoking Category Definitions*.

Category	Characteristics	Cases	Controls
Never-smoker	• Smoked fewer than 100 cigarettes in lifetime	322	1,315
Ever Smoker	• Smoked more than 100 cigarettes in lifetime	4,128	2,290
Current smoker	• Smoked at least 100 cigarettes in their lifetime and smoked at least 100 cigarettes at the time of category definition	2,752	791
Former smoker	• Smoked at least 100 cigarettes in their lifetime but smoked less than 100 cigarettes at the time of category definition	1,376	1,499
All current and former smokers were also divided into:			
RT-smoker	• Smoked at least 100 cigarettes in lifetime • 70% or more of cigarettes smoked are RT cigarettes	123	79
FF-smoker	• Smoked at least 100 cigarettes in lifetime • 70% or more of cigarettes smoked are FF cigarettes	3,442	1,957
Mixed-smoker	• Smoked at least 100 cigarettes in lifetime • Fewer than 70% of cigarettes smoked are RT cigarettes • Fewer than 70% of cigarettes smoked are FF cigarettes	563	254

*The category definition of all Ever Smokers depended on their smoking behavior during the calendar year, 24 to 36 months prior to the date of signing the informed consent.

The other way tar yield was represented was as a continuous variable in which the lifetime cumulative tar yield was divided by the lifetime cumulative packs smoked.

Exposure was also classified according to the lifetime duration of smoking, the average number of packs smoked per day, smoking status at enrollment (current- vs. former-smoker), and the length of the continuous period of smoking cessation immediately prior to the time of smoking category definition as a former smoker. All of those, except smoking status, were represented by continuous independent variables. Length of smoking cessation periods was represented as a quadratic polynomial function.

Age at initiation of smoking was considered in preliminary analyses and, after consideration of other exposure variables, was found not to contribute significantly to the distinction between cases and controls. Thus, it was not included in the analyses reported here.

Analysis

Analyses were based on unconditional logistic regression models with case/control status as the dependent variable. For each analysis, three models were considered. The first model included tar yield as the only independent variable. The second included tar yield and confounders (age, gender, and country). The third included tar yield, confounders, and other aspects of cigarette exposure.

Each analysis was performed for all valid subjects and separately by gender. Also, separate analyses were carried out for all valid subjects and for only "ever smokers" (both current and former smokers). The fit of each logistic model was assessed using the Hosmer-Lemeshow goodness-of-fit test.

The contribution of each independent variable to the risk of lung cancer was summarized by odds ratios and 95% confidence intervals, except for smoking cessation periods. For cessation periods, results were summarized with the regression coefficients and standard errors for the linear and quadratic terms.

Results

A total of 5,641 cases and 4,052 controls were identified. Of these 4,705 cases and 3,718 controls were sent for data analyses. Reasons for exclusion were refusal to participate (699 cases and 273 controls), failed SMMSE (212 cases and 56 controls), consented >95 days after diagnosis (9 cases), aborted interview (13 cases and 2 controls), and missing date of birth (3 cases and 2 controls). One (1) control was excluded for reasons that were not recorded. The number of records were further reduced by data analysis team based on missing exposure information (254 cases and 113 controls), and unreasonable exposure levels (1 case). Thus, 4,450 (78.9%) cases and 3,605 (89.0%) controls were ultimately considered valid for inclusion in analyses. The characteristics of valid subjects are listed in Table 2. The six levels of education were determined by the standards in each country. Relevant occupational exposure was defined as years working in any occupation known to be associated with elevated risk of lung cancer.

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Table 2. Characteristics of valid patients for all patients and by gender. Numbers for categorical variables are frequency (percent) and numbers for continuous variables are mean ± SD.

	All Patients		Males		Females	
Variable	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
N	4,450 (44.8%)	3,605 (55.2%)	3,384 (56.0%)	2,655 (44.0%)	1,066 (52.9%)	950 (47.1%)
Age						
< 50 years	649 (14.6%)	567 (15.7%)	419 (12.4%)	343 (12.9%)	230 (21.6%)	224 (23.6%)
50–59 years	1,402 (31.5%)	1,023 (28.4%)	1,056 (31.2%)	720 (27.1%)	346 (32.5%)	303 (31.9%)
60–69 years	1,584 (35.6%)	1,352 (37.5%)	1,269 (37.5%)	1,065 (40.1%)	315 (29.6%)	287 (30.2%)
≥ 70 years	815 (18.3%)	663 (18.4%)	640 (18.9%)	527 (19.8%)	175 (16.4%)	136 (14.3%)
Country						
France	579 (13.0%)	465 (12.9%)	451 (13.3%)	353 (13.3%)	128 (12.0%)	112 (11.8%)
Germany	1,869 (42.0%)	1,774 (49.2%)	1,304 (38.6%)	1,237 (46.6%)	565 (53.0%)	537 (56.5%)
Greece	1,047 (23.5%)	599 (16.6%)	911 (26.9%)	518 (19.5%)	136 (12.8%)	81 (8.5%)
Italy	249 (5.6%)	105 (2.9%)	201 (5.9%)	73 (2.8%)	48 (4.5%)	32 (3.4%)
Slovenia	706 (15.9%)	662 (18.4%)	517 (15.3%)	474 (17.8%)	189 (17.7%)	188 (19.8%)
Education*						
None	272 (6.1%)	146 (4.0%)	221 (6.5%)	116 (4.4%)	51 (4.8%)	146 (4.0%)
Level 1	882 (19.8%)	489 (13.6%)	708 (20.9%)	362 (13.6%)	174 (16.3%)	489 (13.6%)
Level 2	1,363 (30.6%)	1,180 (32.7%)	1,013 (29.9%)	808 (30.4%)	1,364 (30.6%)	1,180 (32.7%)
Level 3	768 (17.2%)	647 (18.0%)	585 (17.3%)	478 (18.0%)	768 (17.2%)	647 (18.0%)
Level 4	699 (15.7%)	574 (15.9%)	504 (14.9%)	410 (15.4%)	699 (15.7%)	574 (15.9%)
Level 5	369 (8.3%)	478 (13.3%)	275 (8.1%)	401 (15.1%)	369 (8.3%)	478 (13.3%)
Level 6	35 (0.8%)	54 (1.5%)	26 (0.8%)	50 (1.9%)	35 (0.8%)	54 (1.5%)
Unknown	62 (1.4%)	37 (1.0%)	52 (1.5%)	30 (1.1%)	62 (1.4%)	37 (1.0%)
Occupational Exposure						
No Exposure	2,198 (43.4%)	1,970 (54.6%)	1,315 (28.9%)	1,183 (44.6%)	883 (82.8%)	787 (82.8%)
1-10 years	697 (15.7%)	621 (17.2%)	583 (17.2%)	516 (19.4%)	114 (10.7%)	105 (11.0%)
11-30 years	774 (17.4%)	557 (15.4%)	719 (21.2%)	505 (19.0%)	55 (5.2%)	52 (5.5%)
31-66 years	781 (17.6%)	457 (12.7%)	767 (22.7%)	451 (17.0%)	14 (1.3%)	6 (0.6%)
Smoking Status						
Current	2,752 (61.8%)	791 (21.9%)	2,103 (62.1%)	604 (22.8%)	649 (60.9%)	187 (19.7%)
Former	1,376 (30.9%)	1,499 (41.6%)	1,188 (35.1%)	1,289 (48.6%)	188 (17.6%)	210 (22.1%)
Never	322 (7.3%)	1,315 (36.5%)	93 (2.8%)	762 (28.7%)	229 (21.5%)	553 (58.2%)
Tar Yield (gm/pack)	0.24±0.08	0.17±0.14	0.26±0.06	0.19±0.13	0.19±0.11	0.10±0.14
Duration (yr)	34.81±14.43	16.97±16.89	37.34±12.56	19.44±17.04	26.79±16.86	10.09±14.33
Packs/Day	1.09±0.65	0.58±0.65	1.21±0.63	0.69±0.68	0.72±0.57	0.28±0.44
Cessation periods (Years)	4.27±8.85	8.50±12.88	10.23±13.65	10.23±13.65	2.03±6.32	3.67±8.76

*Levels of education determined relative to country-specific standards

Tar Yield Categories

When tar yield was represented in analyses according to the tar yield category of cigarettes predominately smoked, subjects who smoked predominately FF cigarettes had higher odds of developing lung cancer compared to RT smokers when other aspects of cigarette exposure were included for all 3 Models (Table 3). Model 3 is of considerable interest and warrants a short discussion. In this model the risk of lung cancer has been adjusted for those smoking-related parameters that could be determined from the questionnaire; namely, duration of smoking, number of cigarettes smoked, smoking status, and length of smoking cessation period. This leads to an OR which is very close to that of a non-smoker as can be seen in Table 3. These results allow a clear difference between risk of lung cancer for smokers of FF cigarettes compared to RT cigarettes.

When only ever-smokers were included in the analyses (Table 4), those who predominately smoked RT cigarettes had lower odds of developing lung cancer than persons who predominately smoked FF cigarettes. Once again, this can be most clearly seen when other aspects of cigarette exposure were adjusted for (Model 3).

Table 3. Tar yield represented as categories of the type of cigarette smoked among all patients. Values are odds ratio estimates for three models. Separate results are provided for all patients (4,450 cases and 3,605 controls), male patients (3,384 cases and 2,655 controls), and female patients (1,066 cases and 950 controls).

	Variable	Model 1[1]	Model 2[2]	Model 3[3]
All Patients	Tar Yield Category[4]			
	Never-Smoker	1.00	1.00	1.00
	RT-Smoker	6.36 (4.67- 8.65)	6.22 (4.54- 8.51)	0.94 (0.60-1.48)
	FF-Smoker	7.18 (6.28- 8.21)	8.68 (7.50-10.04)	1.50 (1.02-2.20)
	Mixed-Smoker	9.05 (7.47-10.97)	9.78 (8.02-11.92)	1.07 (0.72-1.60)
	Gender			
	Males		1.00	1.00
	Females		1.69 (1.50- 1.92)	2.04 (1.78-2.34)
	Duration			
	Per Year			1.05 (1.04-1.06)
	Number of Cigarettes			
	Per Pack/Day			1.89 (1.69-2.11)
	Smoking Status			
	Current[5]			1.00
	Former			0.62 (0.50-0.76)
	Smoking Cessation Period[5]			
	Linear Term			-0.0373±0.0115
	Quadratic Term			0.000731±0.000242
	Goodness-of-Fit	$P > 0.9999$	$P = 0.0098$	$P = 0.0041$
Male Patients	Tar Yield Category[4]			
	Never-smoker	1.00	1.00	1.00
	RT-Smoker	14.22 (8.85- 22.83)	12.44 (7.70- 20.11)	1.26 (0.65-2.44)
	FF-Smoker	13.85 (11.07-17.32)	13.62 (10.88-17.05)	1.56 (0.93-2.61)
	Mixed-Smoker	18.16 (13.71-24.05)	16.77 (12.62-22.28)	1.20 (0.70-2.06)
	Duration			
	Per Year			1.06 (1.05-1.07)
	Number of Cigarettes			
	Per Pack/Day			1.83 (1.62-2.06)
	Smoking Status			
	Current			1.00
	Former			0.62 (0.49-0.79)
	Smoking Cessation Period[5]			
	Linear Term			-0.0264±0.0127
	Quadratic Term			0.000629±0.000259
	Goodness-of-Fit	$P > 0.9999$	$P = 0.5389$	$P = 0.0201$
Female Patients	Tar Yield Category[4]			
	Never-smoker	1.00	1.00	1.00
	RT-Smoker	3.43 (2.28-5.18)	4.16 (2.72-6.37)	0.94 (0.45-1.94)
	FF-Smoker	5.29 (4.28-6.53)	6.60 (5.25-8.29)	1.81 (0.90-3.65)
	Mixed-Smoker	5.35 (4.28-6.53)	6.40 (4.68-8.75)	1.19 (0.57-2.47)
	Duration			
	Per Year			1.04 (1.02-1.06)
	Number of Cigarettes			
	Per Pack/Day			1.92 (1.39-2.66)
	Smoking Status			
	Current			1.00
	Former			0.63 (0.38-1.06)
	Smoking Cessation Period[5]			
	Linear Term			-0.0776±0.0328
	Quadratic Term			0.00165±0.000762
	Goodness-of-Fit	$P > 0.9999$	$P = 0.8104$	$P = 0.0891$

[1] Smoking classification only
[2] Smoking classification, adjusted for age, country, and gender (except for gender-specific analyses)
[3] Smoking classification, adjusted for age, country, gender (except for gender-specific analyses), duration of smoking, number of cigarettes, smoking status, and length of smoking cessation period
[4] RT-Smoker smoked predominately reduced-tar cigarettes; FF-Smoker smoked predominately full flavor cigarettes
[5] Results are reported as the regression coefficient ± SE

Table 4. Tar yield represented as categories of the type of cigarette smoked among ever smoking patients. Values are odds ratio estimates for three models. Separate results are provided for all smokers (4,128 cases and 2,290 controls), male smokers (3,291 cases and 1,893 controls), and female smokers (837 cases and 397 controls).

	Variable	Model 1[1]	Model 2[2]	Model 3[3]
All Smokers	Tar Yield Category[4]			
	FF-Smoker	1.00	1.00	1.00
	RT-Smoker	0.88 (0.66-1.18)	0.76 (0.56-1.02)	0.68 (0.49-0.95)
	Mixed-Smoker	1.26 (1.08-1.48)	1.16 (0.98-1.36)	0.74 (0.62-0.88)
	Gender			
	Males		1.00	1.00
	Females		1.35 (1.18-1.56)	1.68 (1.43-1.98)
	Duration			
	Per Year			1.06 (1.05-1.07)
	Number of Cigarettes			
	Per Pack/Day			1.82 (1.63-2.04)
	Smoking Status			
	Current			1.00
	Former			0.62 (0.50-0.76)
	Smoking Cessation Period[5]			
	Linear Term			-0.0322±0.0118
	Quadratic Term			0.000746±0.000242
	Goodness-of-Fit	$P = 0.9999$	$P = 0.6474$	$P = 0.0384$
Male Smokers	Tar Yield Category[4]			
	FF-Smoker	1.00	1.00	1.00
	RT-Smoker	1.03 (0.67-1.57)	0.90 (0.59-1.39)	0.81 (0.50-1.31)
	Mixed-Smoker	1.31 (1.08-1.59)	1.23 (1.01-1.49)	0.77 (0.62-0.95)
	Duration			
	Per Year			1.06 (1.05-1.08)
	Number of Cigarettes			
	Per Pack/Day			1.81 (1.61-2.04)
	Smoking Status			
	Current			1.00
	Former			0.62 (0.49-0.79)
	Smoking Cessation Period[5]			
	Linear Term			-0.0225±0.0129
	Quadratic Term			0.000634±0.000259
	Goodness-of-Fit	$P > 0.9999$	$P = 0.4471$	$P = 0.0822$
Female Smokers	Tar Yield Category[4]			
	FF-Smoker	1.00	1.00	1.00
	RT-Smoker	0.65 (0.43-0.98)	0.62 (0.41-0.95)	0.53 (0.33-0.84)
	Mixed-Smoker	1.01 (0.75-1.36)	0.96 (0.71-1.30)	0.65 (0.46-0.91)
	Duration			
	Per Year			1.04 (1.02-1.07)
	Number of Cigarettes			
	Per Pack/Day			1.93 (1.38-2.69)
	Smoking Status			
	Current			1.00
	Former			0.64 (0.38-1.07)
	Smoking Cessation Period[5]			
	Linear Term			-0.0771±0.0332
	Quadratic Term			0.00171±0.000762
	Goodness-of-Fit	$P = 0.9998$	$P = 0.1198$	$P = 0.6259$

[1] Smoking classification only
[2] Smoking classification, adjusted for age, country, and gender (except for gender-specific analyses)
[3] Smoking classification, adjusted for age, country, gender (except for gender-specific analyses),duration of smoking, number of cigarettes, smoking status, and length of smoking cessation period
[4] RT-Smoker smoked predominately reduced-tar cigarettes; FF-Smoker smoked predominately full flavor cigarettes
[5] Results are reported as the regression coefficient ± SE

Tar Yield Continuum

When tar yield was represented in analyses as the average tar yield of cigarettes smoked, increased tar yield was associated with higher odds of lung cancer when other aspects of cigarette exposure were included (Model 3). This was true when both smokers and never-smokers were included in the analysis (Table 5) and when only ever smokers were included in the analyses (Table 6).

Table 5. Tar yield represented as the grams of tar yielded by cigarettes smoked among all patients. Values are odds ratio estimates for three models. Separate results are provided for all patients (4,450 cases and 3,605 controls), male patients (3,384 cases and 2,655 controls), and female patients (1,066 cases and 950 controls).

	Variable	Model 1[1]	Model 2[2]	Model 3[3]
All Patients	Tar Yield			
	Grams/Pack	476.16 (307.25-737.92)	984.66 (606.65->1000)	4.53 (1.75-11.71)
	Gender			
	Males		1.00	1.00
	Females		1.70 (1.51-1.92)	1.99 (1.74-2.28)
	Duration			
	Per Year			1.05 (1.04-1.06)
	Number of Cigarettes			
	Per Pack/Day			1.88 (1.69-2.10)
	Smoking Status			
	Current			1.00
	Former			0.60 (0.49-0.74)
	Smoking Cessation Period[4]			
	Linear Term			-0.0357±0.0113
	Quadratic Term			0.000712±0.000242
	Goodness-of-Fit	$P < 0.0001$	$P < 0.0001$	$P = 0.0479$
Male Patients	Tar Yield			
	Grams/Pack	>1000 (925.90->1000)	>1000 (986.74->1000)	6.12 (1.76-21.27)
	Duration			
	Per Year			1.06 (1.05-1.07)
	Number of Cigarettes			
	Per Pack/Day			1.83 (1.62-2.06)
	Smoking Status			
	Current[4]			1.00
	Former			0.60 (0.48-0.77)
	Smoking Cessation Period[4]			
	Linear Term			-0.0266±0.0123
	Quadratic Term			0.000643±0.000258
	Goodness-of-Fit	$P < 0.0001$	$P < 0.0001$	$P = 0.1280$
Female Patients	Tar Yield			
	Grams/Pack	265.78 (125.99-560.65)	523.64 (235.29->1000)	2.73 (0.58-12.75)
	Duration			
	Per Year			1.05 (1.03-1.06)
	Number of Cigarettes			
	Per Pack/Day			1.96 (1.42-2.71)
	Smoking Status			
	Current			1.00
	Former			0.62 (0.37-1.03)
	Smoking Cessation Period[4]			
	Linear Term			-0.0656±0.0322
	Quadratic Term			0.00154±0.000759
	Goodness-of-Fit	$P < 0.0001$	$P < 0.0001$	$P = 0.1160$

[1] Tar yield only
[2] Tar yield, adjusted for age, country, and gender (except for gender-specific analyses)
[3] Tar yield, adjusted for age, country, gender (except for gender-specific analyses), duration of smoking, number of cigarettes, smoking status, and length of smoking cessation period
[4] Results are reported as the regression coefficient ± SE

Table 6. Tar yield represented as the grams of tar yielded by cigarettes smoked among ever smoking patients. Values are odds ratio estimates for three models. Separate results are provided for all smokers (4,128 cases and 2,290 controls), male smokers (3,291 cases and 1,893 controls), and female smokers (837 cases and 397 controls).

	Variable	Model 1[1]	Model 2[2]	Model 3[3]
All Smokers	Tar Yield			
	Grams/Pack	0.27 (0.10-0.75)	0.38 (0.13-1.13)	4.46 (1.34-14.77)
	Gender			
	Males		1.00	1.00
	Females		1.32 (1.15-1.52)	1.64 (1.40-1.93)
	Duration			
	Per Year			1.06 (1.05-1.07)
	Number of Cigarettes			
	Per Pack/Day			1.83 (1.63-2.04)
	Smoking Status			
	Current			1.00
	Former			0.61 (0.49-0.75)
	Smoking Cessation Period[4]			
	Linear Term			-0.029±0.0117
	Quadratic Term			0.000733±0.000241
	Goodness-of-Fit	$P < 0.0001$	$P = 0.7583$	$P = 0.7024$
Male Smokers	Tar Yield			
	Grams/Pack	0.29 (0.07-1.01)	0.36 (0.09-1.54)	7.76 (1.55-38.86)
	Duration			
	Per Year			1.06 (1.05-1.08)
	Number of Cigarettes			
	Per Pack/Day			1.82 (1.61-2.08)
	Smoking Status			
	Current			1.00
	Former			0.61 (0.48-0.77)
	Smoking Cessation Period[4]			
	Linear Term			-0.0215±0.0129
	Quadratic Term			0.000654±0.000258
	Goodness-of-Fit	$P < 0.0001$	$P = 0.0142$	$P = 0.0215$
Female Smokers	Tar Yield			
	Grams/Pack	0.39 (0.08-1.95)	0.37 (0.07-1.96)	2.09 (0.35-12.59)
	Duration			
	Per Year			1.05 (1.03-1.07)
	Number of Cigarettes			
	Per Pack/Day			1.96 (1.40-2.72)
	Smoking Status			
	Current			1.00
	Former			0.62 (0.37-1.05)
	Smoking Cessation Period[4]			
	Linear Term			-0.0639±0.0328
	Quadratic Term			0.00158±0.000758
	Goodness-of-Fit	$P = 0.0001$	$P = 0.0752$	$P = 0.7010$

[1] Tar yield only
[2] Tar yield, adjusted for age, country, and gender (except for gender-specific analyses)
[3] Tar yield, adjusted for age, country, gender (except for gender-specific analyses), duration of smoking, number of cigarettes, smoking status, and length of smoking cessation period
[4] Results are reported as the regression coefficient ± SE

Inclusion of aspects of cigarette smoking in Model 3 allowed the calculation of the contribution of each one of these factors to the risk of lung cancer. These results are discussed briefly below.

Duration of Smoking

Longer duration of smoking was associated with statistically significant higher odds of lung cancer in all analyses, regardless of whether never-smokers were included (Tables 3 and 5) or excluded (Tables 4 and 6) from the analyses.

Cigarettes Smoked

Greater number of cigarettes smoked was associated with higher odds of lung cancer in all analyses. This increase in odds was statistically significant for all groups (Tables 3-6).

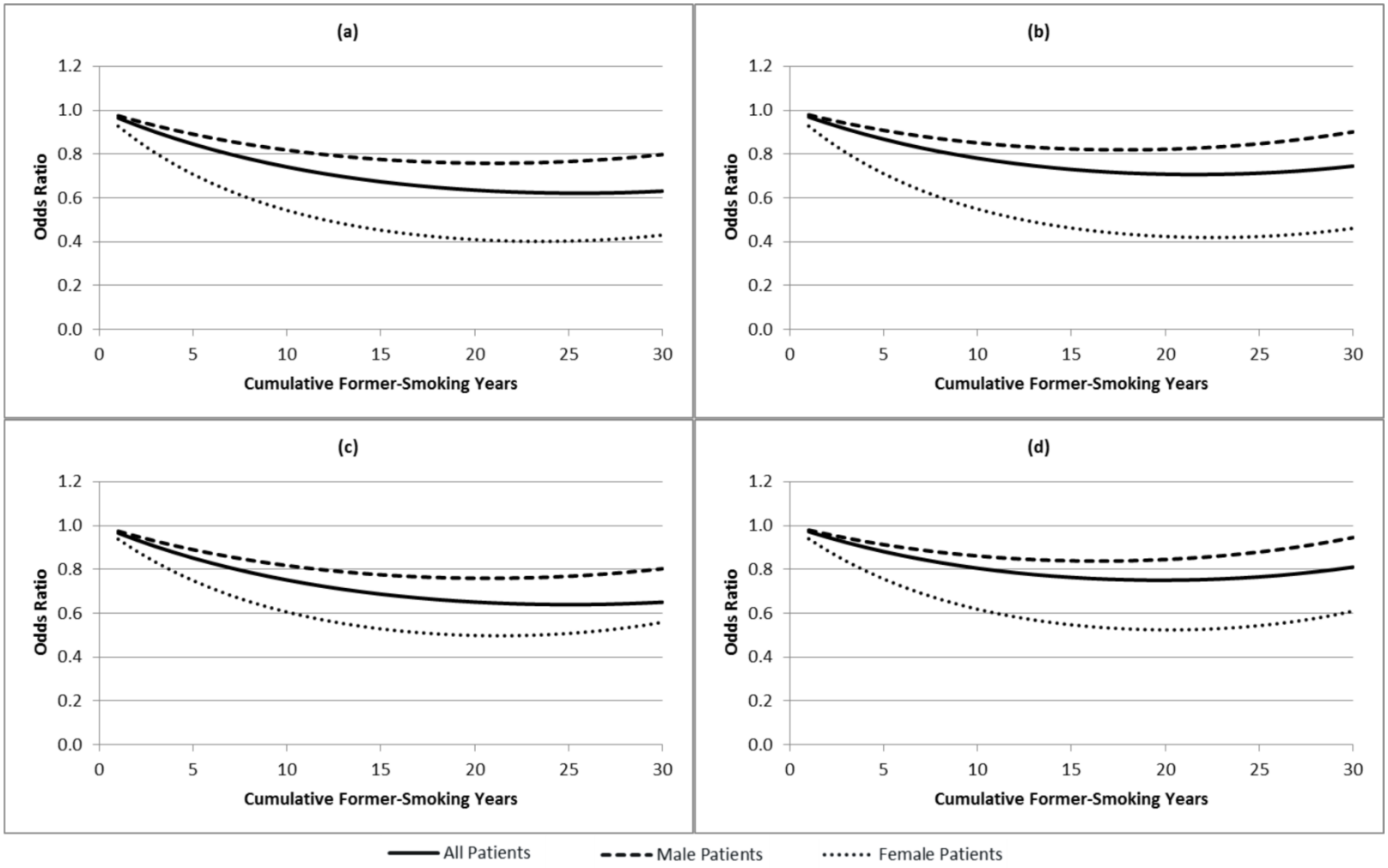
Smoking Status at Enrollment

Subjects who had quit smoking at least 24-36 months prior to enrollment had lower odds of lung cancer than other subjects. Of note, this reduction in odds was nearly identical for both genders, however statistically significant only in males, due to smaller sample size in females (Tables 3-6).

Period of Smoking Cessation among Former Smokers

To interpret the quadratic functions for the length of the continuous period of smoking cessation immediately prior to the time of smoking category definition as a former smoker, odds ratios for the smoking cessation period were compared to those for current smokers. These functions are presented graphically in Figure 1. In all cases, lower odds of lung cancer were associated with longer smoking cessation periods, as evidenced by negative regression coefficients for the linear terms.

Figure 1. Comparison of odds ratios as a function of the length of the last smoking cessation period among former smokers, compared to current smokers: (a) all subjects in which tar yield is represented as categories (Table 3), (b) smoking and former-smoking subjects in which tar yield is represented as categories (Table 4), (c) all subjects in which tar yield is represented as grams per pack (Table 5), (d) smoking and former-smoking subjects in which tar yield is represented as grams per pack (Table 6).



Discussion

Cigarette smoking is universally recognized as the cause of the vast majority of lung cancer cases which occur around the world.[2] Risk of lung cancer from cigarette smoking involves a complex mixture of chemical exposures, socio-environmental parameters, and behaviors. Many studies have been carried out in the effort to qualify and quantify these individual risks for lung cancer including age at smoking initiation,[21] smoking duration,[22] smoking intensity, impact of periodic and permanent cessation,[21,23-25] gender,[26] life styles,[27] and compensatory actions in smoking cigarettes of varying tar and nicotine yields and smoking behaviors.[28]

The findings reported here confirm many of the relationships found in other studies regarding cigarette smoking and lung cancer. In particular, the analyses have confirmed that risk of lung cancer increases with duration of smoking and cumulative number of cigarettes smoked (or pack-years of smoking). Likewise, the findings on the effects of smoking cessation are commensurate with findings in many other studies, namely, that the risk of lung cancer decreases with smoking cessation, the longer the period of cessation the greater the decrease, although the decrease in risk never reaches the reduced risk for never-smokers. Another finding of interest is the rather consistent gender difference in risk. For each of the analyses conducted by gender, women appear at lower risk than men. This finding is consistent with some, but not all, studies of gender and lung cancer risk associated with smoking.[26]

Of particular interest among the findings is the consistent effect that, after adjustment for confounders and effect-modifiers, smokers of predominantly RT cigarettes are at lower risk of lung cancer than smokers of predominantly FF cigarettes. This result clearly differs from the study of Harris et al.,[10] but there are a number of strengths associated with this study that suggest that the results obtained may be more likely to reflect the actual effect of LT cigarettes on lung cancer risk.

The first of these strengths is that the C-TOR study that provided the dataset was extremely large. Although the Harris et al. study utilized the results from the Cancer Prevention Study (CPS)II study, a massively large cohort study consisting of more than 900,000 subjects, the total number of lung cancer deaths was 4028 compared to 4450 lung cancer cases included in the C-TOR study. Secondly, because of its retrospective design, the C-TOR study was able to track changes in brands smoked over time, whereas the CPS-II study recorded the brand being smoked only at baseline. Thirdly, results in this study reflect recent smoking patterns, whereas the CPS-II study recorded brands, and thus tar level, smoked in 1982. Even LT cigarettes had not been marketed for a long period of time in 1982, while there was virtually no consumption of ULT cigarettes. As Lee and Sanders[8] pointed out, smokers of 8-14 mg tar delivery cigarettes had only been smoking their current brand for a mean of 7.2 yrs, while smokers of 0-7 mg tar delivery cigarettes for a mean of only 4.3 yrs. Although Harris et al. did present data for individuals who had been smoking 0-7 mg cigarettes for at least 10 years, there were only 31 lung cancer deaths in this group, too small a number to calculate a meaningful estimate of lung cancer risk. A further important point is that differential recall bias, always an issue with case control studies, was minimized in the C-TOR study through the use of a specially designed questionnaire to assess smoking history more accurately over a long period of time.[15,16] The LEHC questionnaire used in this study permitted the use of analytic methods to differentiate among the various risk factors involved in risk of lung cancer using types of data often not available in epidemiologic studies. This allowed for isolation of tar exposure (as indicated by tar yield) as a specific, independent risk factor.

A last important strength of this study's design was the use of the extensive historic information on tar yield of most brands of the cigarettes. The database created from this information provided detailed quantitative data on tar yield of cigarettes for the majority of C-TOR subjects who smoked. This allowed for inclusion of average tar yield of cigarettes smoked among the variables considered in the multivariate modeling of risk factors. This approach enabled the calculation of the decrease in risk of lung cancer per mg tar reduction. Only two previous studies have examined tar delivery as a continuous variable with respect to lung cancer risk. The first of these by Garfinkel and Stellman[29] showed a

reduction of the relative risk for lung cancer of 0.03 per 1 mg tar reduction, while the second, by Tang et al.[30], showed a reduction of 0.02 in lung cancer risk per 1 mg tar reduction. However, both of these studies are sufficiently old that the comparison is primarily between filter and non-filter cigarettes as opposed to being between FF and LT cigarettes.

The extensive multivariate modeling conducted on the C-TOR data has shown that average tar yield emerges as a clear independent risk factor for lung cancer in both men and women in the European population from which the data were gathered, after accounting for the known effects of age, duration of smoking, and cumulative number of cigarettes smoked. This result supports the supposition that despite extensive compensation modern LT cigarettes are associated with a lower risk for lung cancer than are modern FF cigarettes.

There are limitations as well with the C-TOR study. The cases pertain to clinical diagnoses of lung cancer. There were no data collected on histopathology of the lung cancer cases, hence it was not possible to explore relationships with particular lung cancer histopathology. The original intent of the C-TOR study was to accrue 13,000 cases and 13,000 controls matched to the cases on gender, age, and geographic area. At the time of discontinuation of the C-TOR study there was considerable imbalance in the numbers of cases and controls included in the analyses, with 845 cases that had not yet been matched to an appropriate control. Although this imbalance in numbers of cases and controls is highly atypical in case-control studies of smoking and lung cancer, it is highly unlikely that such imbalance would skew or tilt the findings of the analyses in a particular direction. This imbalance also prevented the matching of cases and control; however, the analyses did consider those variables for which matching had been planned as potential confounders. The findings with regard to tar yield are essentially across the broad spectrum of the various tar yields of all types of cigarettes smoked, not specifically the reduced tar yield of ULT cigarettes. Thus, the findings regarding the independent effect of average tar yield as a risk factor for lung cancer are suggestive of a reduction in risk by switching from the smoking of FF or LT cigarettes to the smoking of ULT cigarettes. However, the analyses conducted did not investigate directly the effect of switching the type of cigarette smoked, FF and/or LT to the smoking of solely ULT cigarettes. This is a consequence of the fact that the study was terminated well before the planned number of cases and controls had been enrolled.

The most important public health message from these findings is no different from that of the majority of epidemiologic studies of cigarette smoking and lung cancer, namely that cigarette smoking is a highly significant risk factor for lung cancer with the risk increasing with both the duration of smoking and the amount of cigarettes smoked. Secondly, for current smokers a significant reduction in risk is achieved by cessation of cigarette smoking. The findings with regard to average tar yield of cigarettes smoked, however, as an independent risk factor for lung cancer do suggest that some reduction in risk may be gained by switching to the smoking of cigarettes with lower tar yield. This reduction in risk is small, however, compared to the reduction in risk that would be achieved by quitting smoking.

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