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Cigarette smoking and male lung cancer risk with special regard to type of tobacco

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Background The mortality rate from lung cancer (LC) increased sharply in Spain between 1957 and 1986. This increase has been related to a previous increase in cigarette smoking. Certain features of cigarette smoking which were frequent among Spanish smokers (use of black tobacco and use of cigarettes without filter) have been related to a higher risk of LC.

Methods A hospital-based case-control study was conducted between December 1986 and June 1990. The 325 male patients with lung cancer included in the study (cases) were compared with 325 age-matched male controls without LC. Occupation and lifetime tobacco consumption were requested using a structured questionnaire. The LC odds ratios (OR) and 95% CI were estimated with multiple logistic regression.

Results Lung cancer risk increased with cigarette consumption and duration of the habit. After adjusting for lifetime cigarette consumption and for socioeconomic level, LC risk was greater among black tobacco smokers than among exclusive blond tobacco smokers (OR = 5.0, 95% CI : 2.0–12.7); LC risk among long-term (⩾20 years) filter-tipped cigarette users was lower compared to all other smokers (OR = 0.4, 95% CI : 0.2–0.7).

Conclusions The main results of the study (a higher LC risk among black tobacco users than in exclusive blond tobacco users, and a lower LC risk among long-term filter-tipped cigarette smokers than all other smokers) have been consistent with previous case-control studies and with ecologic studies which took into account past exposure levels.

Keywords Lung neoplasms, epidemiology, smoking, tobacco, black tobacco, filter cigarettes

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The mortality rate from lung cancer (LC) increased sharply in Spain between 1957 and 1986.[1] Although this increase has been related to a previous increase in cigarette consumption,[2] there have been few studies on LC risk in smokers from Catalonia or the rest of Spain. Furthermore, certain features of cigarette smoking which were frequent among Spanish smokers (use of black tobacco and use of cigarettes without filter) have been related to a higher risk of LC.

In regular smokers, LC risk depends mainly on the duration of the habit and there is a weaker dose-response relationship between LC and the number of cigarettes consumed daily.[3] The risk of LC is higher among smokers of non-filter cigarettes than among filter cigarette smokers; however, increases in risk with longer use of non-filter cigarettes have not been consistently detected.[3]

A recent Spanish case-control study that was restricted to female smokers showed a higher risk of developing the disease in users of black tobacco cigarettes than in users of blond tobacco cigarettes.[4] Black tobacco is obtained when *Nicotiana tabacum* plant leaves are cured in the sun or open air, and blond tobacco is obtained by curing in dryers. Black tobacco cigarettes are commonly smoked in Latin America and in the south of Europe,[5] whereas blond tobacco is consumed in North America and the UK. The majority of epidemiological studies concerning LC risk in cigarette smokers have been conducted in blond tobacco consuming areas, though somewhat more attention has

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been devoted to the effect of black tobacco smoking in recent years.[6]

Though the mortality rate from LC is greater in countries where blond tobacco is smoked,[7] results from several case-control studies from blond and black tobacco consuming areas (Argentina,[8] France,[9] Uruguay,[10,11] Brazil[12] and Catalonia[4]), have suggested that the carcinogenic effect of black tobacco products may be greater.[13]

The results of a case-control study carried out in Barcelona and focused on the effects of smoking patterns are presented here. Furthermore, as most cigarette smokers in Spain are black tobacco users,[5] we saw an opportunity to reassess the effect of this type of tobacco.

Methods

Case and control selection

Patients were obtained from a tertiary public teaching hospital. From December 1986 to June 1990, the diagnoses of male patients admitted to the hospital were checked to identify cases and controls for inclusion in the study. Only incident cases were included (a histological or cytological diagnosis of LC, made during the 6 months before the interview, was required for each case). Patients >80 years old, those in generally bad physical condition, and those with dementia were not included. Potential controls (male patients without a diagnosis of LC) were recruited from patients admitted to urology, ophthalmology, otorhinolaringology, or general surgery wards (patients admitted to traumatology were not eligible as controls); potential controls were rejected if the principal reason for hospital admittance had been a smoking-attributable pathology (chronic obstructive lung disease, ischaemic cardiopathy, bladder cancer, digestive or upper respiratory airway neoplasms).

Of the 353 potential cases interviewed, 27 were rejected because histological diagnosis was negative or could not be performed. An age-matched control was selected for each case (difference <6 years). At analysis, one case and one control were rejected due to poor information on tobacco consumption, leaving 325 cases with 325 controls.

According to the WHO criteria[14] for histological typing of lung cancers, there were 168 (51.7%) squamous cell carcinomas, 69 (21.2%) small cell carcinomas (including 29 oat cell carcinomas), 55 (16.9%) adenocarcinomas (including 5 bronchioalveolar carcinomas), 13 (4.0%) large cell carcinomas, 2 carcinoid tumours and one adenosquamous carcinoma. Histological type could not be specified in 17 cases (5.2%).

Information concerning the principal reason for hospital admittance in the 325 controls was obtained from their clinical reports and coded according to the Ninth Revision of the International Classification of Diseases (ICD-9):[15] among 87 patients (26.8%) admitted for conditions classified as disorders of male genital organs (ICD-9 600–608), 63 had hyperplasia of prostate and 14 an inflammatory disease of prostate; among 58 patients (17.8%) admitted for other disorders of kidney and urinary tract (ICD-9 590–599), 36 had calculus of kidney or ureter and 10 urethral stricture; 41 patients (12.6%) had been admitted for hernia of abdominal cavity (ICD-9 550–553); among 34 patients (10.5%) admitted for other diseases of digestive system (ICD-9 570–579), 15 had cholelithiasis and 17 other diseases of gallbladder; among 32 patients (9.8%) admitted for disorders of the eye and adnexa (ICD-9 360–379), 13 had retinal detachment and 12 cataract; 12 controls (3.7%) had been admitted for appendicitis, 8 (2.5%) for diseases of the ear and mastoid process; the remaining 53 controls (16.3%) for other diseases, each one including 7 or less individuals.

Interview

A structured interview was carried out before discharge from the hospital, with questions concerning occupation, socio-demographic data and history of tobacco consumption. Patients were asked for information on their former and present occupations and the data were coded according to the International Standard Classification of Occupations (ISCO-1968).[16] Information concerning daily cigarette consumption, duration of habit, age at which subjects had started and stopped smoking, type of tobacco smoked (only blond, only black, both), and filter or non-filter cigarette use was requested. Questions concerning weekly consumption of cigars and pipe tobacco and duration of these habits were also included. When there were breaks or changes in the smoking characteristics information was requested for each period: up to four periods for cigarette smoking and up to three periods for cigar and pipe smoking.

Definitions of the variables

Socioeconomic status was assigned according to the last occupation held, as described in the protocol of Domingo *et al.*[17] with a small modification: all farmers were assigned to level IVb and a priest was assigned to level II. Cigarette users were defined as men who had smoked one or more cigarettes daily for ⩾4 months. The cigar or pipe users were, respectively, smokers of one or more cigars or pipes weekly for the same interval. The time since cessation of cigarette use was established as the difference between the age at which cigarettes were last smoked and the age at the interview. According to their use of cigarettes, patients were classified as never smokers, ex-smokers (one or more years since stopping), or current smokers. The duration of the habit of smoking cigarettes, the total cigarette consumption (expressed in pack-years, a unit equivalent to 7300 cigarettes) and the mean daily consumption of cigarettes (the ratio between the total number of cigarettes smoked and the duration of the habit) were calculated for each patient. The duration and accumulated consumption for each period of smoking were added together. According to their later smoking habits (over the previous 20 years), smokers were classified as long-term ex-smokers (>5 years) and, if excluded from this category, they were further classified as long-term filter smokers (>20 years) or non-filter smokers.

Statistical analysis

The odds ratio (OR) was used to estimate the risk for developing LC in smokers with respect to non-smokers. The age-adjusted OR and 95% CI for lung cancer according to smoking habits were estimated using unconditional multiple logistic regression (MLR) models.[18] The estimates for type of tobacco and later smoking habits were adjusted for the variables related to tobacco dose or time; forward stepwise modelling was previously used to identify the main predictors of LC risk among the variables related to tobacco dose or time. The statistical significance of the multiplicative interaction terms was estimated for each pair of variables in the MLR models in all the

Table 1 Distribution of cases and controls according to socio-demographic factors and tobacco product smoked

	Cases		Controls	
	N	%	N	%
Age (years)				
30–39	7	2.2	7	2.2
40–44	16	4.9	15	4.6
45–49	20	6.2	19	5.8
50–54	41	12.6	52	16.0
55–59	60	18.5	51	15.7
60–64	67	20.6	76	23.4
65–69	63	19.4	53	16.3
70–74	31	9.5	31	9.5
75–79	20	6.2	21	6.5
Socioeconomic level[a]				
I–II	23	7.1	20	6.2
III	39	12.0	42	12.9
IVa	195	69.0	173	53.2
IVb	59	18.2	72	22.2
V	9	2.8	18	5.5
Tobacco product				
Never smokers	4	1.2	64	19.7
Cigarette	245	75.4	197	60.6
Pipe	1	0.3	1	0.3
Cigar	3	0.9	6	1.8
Cigarette, pipe	1	0.3	4	1.2
Cigarette, cigar	68	20.9	50	15.4
All three products	3	0.9	3	0.9
Total	325	100	325	100

[a] Socioeconomic level: I–II: Professional-intermediate occupations; III: Non-manual skilled occupations; IVa: Manual skilled occupations; IVb: Partly skilled occupations; V: Unskilled occupations (χ^2 test = 5.93, 4 d.f., $P = 0.205$).

Table 2 Distribution of cases and controls and lung cancer odds ratios (OR) according to cigarette consumption

	Cases		Controls			
	N	%	N	%	OR[a]	95% CI
Cigarette use						
Never	8	2.5	71	21.8	1	
Former[b]	129	39.7	132	40.6	8.5	3.9–18.5
Current	188	57.8	122	37.5	14.1	6.5–30.5
Duration (years)						
1–24	21	6.5	55	16.9	2.6	1.0–6.6
25–49	219	67.4	166	51.1	11.9	5.5–25.5
⩾50	77	23.7	33	10.2	26.8	11.0–65.1
Daily consumption (cig/day)[c]						
1–14	44	13.5	117	36.0	3.3	1.4–7.4
15–24	134	41.2	105	32.3	11.6	5.3–25.3
⩾25	139	42.8	32	9.8	41.2	17.8–95.0
Cumulative (pack-years)						
1–29	57	17.5	146	44.9	3.3	1.5–7.3
30–44	87	26.8	66	20.3	11.9	5.3–26.5
⩾45	173	53.2	42	12.9	40.2	17.7–91.3
Total	325	100	325	100		

[a] Adjusted on age (categorized as in Table 1) with multiple logistic regression.
[b] Former smokers: one or more years since smoking cessation.
[c] Averaged over all smoking periods.

analyses. The Epilog Plus statistical software program (version 2.10)[19] was used.

Results

The distribution of cases and controls according to socio-demographic characteristics is presented in Table 1. The majority of patients in both groups (roughly 70%) were 50–69 years old. The socioeconomic level most often found in both the cases (60%) and controls (53%) was manual skilled occupations (level IVa) and the predominant occupation at this level was bricklayer (47 cases and 32 controls). Differences in socioeconomic level between cases and controls were non-significant.

Four cases (1.2%) and 64 controls (19.7%) had never been regular smokers (Table 1); 317 cases (97.5%) and 254 controls (78.2%) had been smokers of cigarettes alone or cigarettes combined with pipes and/or cigars. The prevalence of never smokers among the controls was 25.4% in those aged 45–54 years, 22.8% in those aged 55–64 and 13.3% in those over 64.

Cigarette smoking

As shown in Table 2, 8 cases (2.5%) and 71 controls (21.8%) had never been cigarette smokers. The OR for LC among current smokers (OR = 14.1, 95% CI : 6.5–30.5) was higher than in former smokers, and the risk in former smokers was significantly higher than in never smokers, (OR = 8.5, 95% CI : 3.9–18.5). Both cigarette consumption (expressed as either average daily consumption or lifetime cumulative consumption) and the duration of the habit were greater in cases. The age-adjusted MLR models for these variables are presented in Table 2. Lifetime cumulative consumption showed the most statistically significant relationship with LC risk; the OR increased by 6% for each pack-year smoked (OR = 1.06, 95% CI : 1.05–1.07).

The distribution of smokers according to the features of their cigarette use is presented in Table 3. More cases than controls were under 17 when they acquired the habit (OR = 2.4, 95% CI : 1.7–3.3). Lung cancer risk was lower among smokers who had given up the habit ⩾6 years previously (OR = 0.3, 95% CI : 0.2–0.5). In subsequent analyses, 'current smokers' and '1–5 years since cessation' were assigned to the same category.

Filter-tipped cigarettes

As shown in Table 3, exclusive use of filter-tipped cigarettes was less frequent among the cases. More controls than cases had been long-term filter users, but their lower risk of LC was not significant (OR = 0.9, 95% CI : 0.6–1.2). It was found that 24 cases and 28 controls who had been classified as long-term filter-cigarette users were actually long-term ex-smokers (>5 years since cessation). The lower risk of LC among long-term filter users was significant when these long-term ex-smokers were excluded from the category (OR = 0.4, 95% CI : 0.3–0.7).

Type of tobacco

It was found that a larger number of cases than controls had used only black tobacco, whereas more controls had smoked

Table 3 Distribution of cases and controls and lung cancer odds ratio (OR) according to cigarette smoking features

	Cases		Controls			
	N	%	N	%	OR[a]	95% CI
Age at starting (years)						
17–45	113	35.6	144	56.7	1	
7–16	204	64.4	110	43.3	1.4	1.0–2.1
Years since cessation						
<1	188	59.3	122	48.0	1	
1–5	79	24.9	45	17.7	1.4	0.8–2.2
⩾6	50	15.8	87	34.3	0.7	0.4–1.1
Lifetime filter use						
Never	63	19.9	55	21.7	1	
Mixed	197	62.1	127	50.0	1.0	0.6–1.6
Always	57	18.0	72	28.3	0.7	0.4–1.2
Long-term filter use[b]						
No	128	40.4	94	37.0	1	
Yes	189	59.6	160	63.0	0.6	0.4–1.0
Smoking pattern[c]						
Non-filter	102	32.2	35	13.8	1	
Ex-smoker	50	15.8	87	34.3	0.3	0.2–0.6
Filter	165	52.1	132	52.0	0.4	0.3–0.7
Type of tobacco						
Blond	8	2.5	26	10.2	1	
Both	47	14.8	33	13.0	4.9	1.7–13.7
Black	262	82.6	195	76.8	5.3	2.1–13.6
Total	317	100	254	100		

[a] Adjusted for age (categorized as in Table 1) and cumulative cigarette consumption with multiple logistic regression.

[b] Long-term filter use: exclusive filter cigarette use during last 20 smoking years.

[c] Smoking pattern: ex-smoker (>5 years since cessation), filter (exclusive filter cigarette use during last 20 smoking years), non-filter (otherwise).

only blond tobacco (Table 3) with significant differences (OR = 4.4, 95% CI : 1.9–10.0). When the prevalence of exclusive black tobacco smokers among the cases was analysed according to histological type of cancer, no differences were found ($P = 0.983$). In subsequent analyses, 'exclusive black tobacco' smokers and 'both tobacco types' were assigned to the same category (black tobacco); their higher LC risk persisted after adjusting for smoking duration (OR = 4.6, 95% CI: 2.0–10.5); daily consumption (OR = 4.7, 95% CI : 1.9–11.7), lifetime cigarette consumption (OR = 5.2, 95% CI : 2.1–13.3), time since cessation (OR = 4.9, 95% CI : 2.1–11.2) or long-term filter-cigarette use (OR = 4.3, 95% CI : 1.9–9.9).

When forward stepwise modelling was used to identify the main predictors of LC risk among the variables related to tobacco dose and time, only cumulative lifetime consumption (log-likelihood ratio χ^2 test = 128.04, 2 d.f., $P < 0.001$), followed by years since cessation (χ^2 test = 4.37, 1 d.f., $P = 0.037$) were included.

As shown in Table 4, after adjusting for lifetime cigarette consumption and socioeconomic level the risk of LC was lower among long-term ex-smokers (OR = 0.3, 95% CI : 0.2–0.6) and long-term filter users (OR = 0.4, 95% CI : 0.2–0.7), and was greater among black tobacco smokers (OR = 5.0, 95% CI : 2.0–12.7); estimates were similar after adjusting for duration of cigarette use and average daily consumption instead of lifetime cigarette consumption. Estimates did not change appreciably after adjusting for cigar smoking.

Discussion

This study compares the cigarette consumption antecedents of LC cases with an age-matched, hospital-based control sample without LC. The overall results are consistent with previous studies and with the European multicentre case-control study.[20]

As most controls were patients admitted for surgery in urology, ophthalmology or general surgery wards, and potential controls admitted to the hospital for conditions known to be related to cigarette smoking were excluded, the possibility of underestimating LC risks in smokers due to a potential overrepresentation of smokers in hospital patients was minimized.[21] Furthermore, the prevalence of never smokers was consistent with the health surveys done in Barcelona in 1983 (never-smoker prevalence 14.9% among males >64 years) and 1992 (never-smoker prevalences 26.4% and 21.3% among males 45–54 and 55–64 years old, respectively).[22]

Socioeconomic level was assigned according to the last job held because education of the birth cohorts of most cases and

Table 4 Lung cancer odds ratios (OR) according to cigarette consumption features. Results of multivariate analysis

	Cases		Controls					
	N	%	N	%	OR[a]	95% CI	OR[b]	95% CI
Smoking pattern[c]								
Non-filter	102	32.2	35	13.8	1		1	
Ex-smoker	50	15.8	87	34.3	0.31	0.2–0.6	0.34	0.2–0.6
Filter	165	52.1	132	52.0	0.40	0.2–0.7	0.41	0.3–0.7
Type of tobacco								
Only blond	8	2.5	26	10.2	1		1	
Black/both types	309	97.5	228	89.8	5.04	2.0–12.7	4.68	1.9–11.8
Total	317	100	254	100				

[a] Adjusted for age (categorized as in Table 1), socioeconomic level (categorized as I–II, III, IVa, IVb–V), cumulative cigarette consumption and for the other variable in the Table.

[b] Adjusted for age (categorized as in Table I), socioeconomic level (categorized as I–II, III, IVa, IVb–V), cigarette smoking duration, average daily consumption and for the other variable in the Table.

[c] Smoking pattern: ex-smoker (>5 years since cessation), filter (exclusive filter cigarette use during last 20 smoking years), non-filter (otherwise).

controls had been interrupted by the Spanish Civil War (1936–1939).[17] Because of the characteristics of the Catalonian health care system, manual workers were over-represented in the public hospital where the study took place[17] and, therefore, differences in socioeconomic level between cases and controls were minimized. However, this fact precludes extrapolation of the results to the general population.

Among the variables related to time and dose, only cumulative consumption and years since cessation were included in the stepwise MLR model. Breslow and Day[23] have shown that if the absolute risk of LC among smokers is proportional to the daily consumption of cigarettes and to the fourth power of duration, and the baseline rates are proportional to the fourth power of age, then the relative risks of LC will be approximately equal among people with the same lifetime cumulative consumption.[23]

We found that smokers who had used filter cigarettes for ⩾20 years were at a lower risk of developing LC than all the other cigarette smokers. The risk was significant after excluding long-term ex-smokers from the analysis. In previous case-control studies, LC risk has been generally lower in filter cigarette smokers, and has been related to lower tar yields.[3] Lubin *et al.*[20] reported a significant trend between proportion of smoking time without filter use and LC risk; in a study by Benhamou *et al.*[24] the lower risk of LC among filter users was significant after excluding ex-smokers.

Type of tobacco

The most interesting finding of the present study may be the higher risk of LC among black tobacco smokers, which persisted after adjustment for cumulative consumption. Previous case-control studies have found a higher risk for the disease among black tobacco smokers than among blond tobacco smokers.[13] In a study by Joly *et al.*[25] in Cuba, the risk of LC was higher among black tobacco users in the crude analysis, but differences were reduced after stratifying by duration or intensity. The risk of LC among black tobacco smokers was about twice as high in a study performed in Argentina by Pezzotto *et al.*[8] (after adjusting for smoking duration and daily consumption), in a study carried out in Uruguay by De Stèfani *et al.* (after adjusting for age, residence, urban/rural condition, education, amount smoked, smoking duration, years since quit and filter use),[10] in another Uruguayan study by De Stèfani *et al.* (the increase in risk for black tobacco users was detected among smokers of commercially-made cigarettes, after adjusting for cumulative consumption and cessation),[11] and in a study in France by Benhamou *et al.* (after adjusting for duration, intensity, inhalation, filter use, tar yields and cessation).[9] The risk of developing LC in black tobacco smokers was three times higher than in blond tobacco smokers in a study of Catalonian women by Agudo *et al.*[4] and in a study by Suzuki *et al.*[12] in Brazil (after adjusting for cumulative consumption). In the present study, the risk for black tobacco users was significantly higher than in blond tobacco users, even after adjusting for cumulative consumption, filter use, cessation and socioeconomic level.

Death rates from LC have been found to be higher in blond-tobacco smoking countries than in black-tobacco smoking countries; however, comparisons at one point in time may be misleading if they do not take into account past exposure levels,[6] due to the strength of the relationship between previous cigarette smoking and LC risk:[23] the international correlation study by Doll and Hill[26] between cigarette consumption per adult in 1950 and LC death rates among adults aged 35–44 in the mid-1970s suggests an even stronger dose-response in Italy, France and Spain (black tobacco-using countries[5]) than in the UK and the US (blond tobacco-using countries).

Higher yields of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a tobacco-specific N-nitrosamine, have been detected in smoke from black tobacco cigarettes.[27] As reviewed by Hoffmann *et al.*,[28] NNK is metabolically activated to intermediate products which bind to DNA, and certain mutations in the *KRAS* gene in lung adenocarcinoma are consistent with the mutational spectra observed after experimental exposure to NNK.[29] Hoffmann's working hypothesis that NNK is one cause of LC in cigarette smokers[28] suggests that the higher LC risk among black tobacco cigarette users is related to the higher NNK yields of black tobacco.

Although black tobacco cigarettes have been cheaper in Spain, a confounding effect due to occupational exposures among smokers with lower income seems an unlikely explanation for the higher risk of LC detected among black tobacco smokers, since the effect persisted after adjusting for socioeconomic level. Although residual confounding might still exist, the higher risk among black tobacco users is consistent with previous studies and is biologically plausible.

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