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Clinico-pathological Features and Survival of Lung Cancer Patients in Paris, France

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We studied the clinico-pathological features of 750 lung cancers identified in Paris, France, during 1988. An internal comparison was performed between adenocarcinomas and other subtypes. Survival of 502 patients was studied. 85% of patients were males; 93% were smokers or ex-smokers. Squamous cell carcinomas, adenocarcinomas, small cell carcinomas and large cell cancers accounted for 51, 22, 15 and 12% of all cases, respectively. Differences were found for the distribution of histological subtyping according to sex ($P = 0.001$) and smoking status ($P = 0.0001$) with a greater proportion of adenocarcinomas for women and non-smokers. Median overall survival was less than one year. In multiple regression analysis, small cell lung cancer patients appeared to have a worse prognosis than other histological subtypes. This study describes patients who were treated in community practice and might be more representative of the real clinico-pathological profile of this disease in France.

Key words: lung cancer, cigarette smoking, tobacco smoke, tobacco smoke pollution, histological type, survival
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INTRODUCTION

CANCER OF the lung is the most prevalent malignant cause of death worldwide [1], and cigarette smoking accounts for an estimated 85% of lung cancers in men and 46% in women [2]. Recent epidemiological evidence supports the association between environmental tobacco smoke (ETS) exposure and the development of lung cancer in non-smokers [3]. The incidence of this tumour continues to increase in France [4]. However, no recent data are available on clinicopathological profile and survival of lung cancer patients in France.

In 1986, the Société de Pneumologie d'Ile de France (SPIF), a cooperative group of chest physicians from Paris and the Greater Paris area, was created to conduct collaborative research on pulmonary diseases. The purposes of the present study were to estimate the main characteristics of primary lung cancer patients observed for one year by the members of the SPIF, as well as to examine their survival.

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MATERIALS AND METHODS

Members of the SPIF were asked to identify all primary lung cancer cases occurring within one year (from 1 November 1987 to 31 October 1988). All cases had to be pathologically or cytologically confirmed and considered to be a primary lung cancer. For each new case, information was collected on age, sex, histological type (squamous cell, small cell, adenocarcinoma or large cell cancer) and smoking status.

Active smoking (defined as smoking of at least one cigarette a day) was assessed by noting the age at which cigarette smoking began, the average number of cigarettes smoked per day, and the cumulative tobacco consumption expressed as pack-years (PY). ETS exposure was only assessed for "never smokers" by taking into account the smoking habits of parents, spouse and fellow workers, the age at leaving the parental home and the duration of marriage and of professional activity.

Due to the higher proportion of adenocarcinomas among lifelong non-smoking patients [5, 6], an internal comparison was performed using a modified case–control approach in which adenocarcinoma cases were compared with cases of other histological subtypes (treated as controls).

Data on survival were obtained in 1992. The vital status assessment was obtained by asking directly the physician in charge of the patient, or by writing to the registry offices of birthplaces for people born in France. Follow-up was not possible for foreign-born patients; in addition, no data were available from three hospitals, which had included 149 patients in the study. In total, vital status was ascertained for 502 patients (66% of this initial cohort). Survival time was measured from the date of lung cancer diagnosis. Information on the underlying cause of death, and therapy was not collected.

Statistical comparisons were performed using the two-tailed Student's *t*-test and chi-square test. In the case–case comparison, odds ratios (ORs) of exposure to several risk factors and 95% confidence intervals (95% CIs) were computed via unconditional logistic regression [7]; regression models included sex and age as potential cofounders. The SAS statistical package was used.

Survival and death hazard curves were based on the Kaplan-Meier method, and differences in survival were tested using the log-rank test. Multiple regression survival analysis was carried out according to Cox's regression model by estimating hazard ratios and 95% CIs. Sex, age, histology, smoking status, and number of cigarettes smoked per day were the variables included in the models.

RESULTS

During the study period, 759 new lung cancer patients were diagnosed in university hospitals (n = 403; 53%), general hospitals (n = 244; 32%) and private offices (n = 112, 15%); of these, 750 had data appropriate for this analysis. Of these, 637 (85%) were males and 113 (15%) were females. Mean age at diagnosis was 62 years (standard deviation (S.D.) 11, range 26–91). Of the patients, 698 (93%) were present or ex-smokers, of these 624 were males and 74 were females. There were 52 patients (7%) who had never been smokers: of these 13 were males and 39 were females (P = 0.001).

Histopathological subtyping (Table 1) distinguished 380 (51%) squamous cell carcinomas, 168 (22%) adenocarcinomas, 115 (15%) small cell carcinomas and 87 (12%) large cell carcinomas. Squamous cell carcinoma was the most frequent tumour for men (54%), whereas for women adenocarcinoma was the main subtype (40%) (differences between sexes: P = 0.001). Compared with cigarette smokers, the histopathological diagnosis of patients who had never smoked showed a higher proportion of adenocarcinomas (48 versus 21%).

Cumulative tobacco consumption of patients who smoked was similar for both sexes (49 PY for men and 48 for women). Mean age at diagnosis for never-smoked patients was 65 years (S.D.:12), older than for smokers (62 years; P = 0.05).

Patients who did not smoke cigarettes but who were exposed to their father's smoking comprised 27 of 41 cases (66%). When known (32 cases), the mean age at leaving home was 21 years. Among the 43 non-smoking cases for whom marital status was available, 10 men were married to a non-smoking wife, and out of the 33 women, 24 were married to a smoker, with a mean length of conjugal life of 31 years. Out of a total of 52 lung cancers observed in never smoked patients, there were 5 cases (4 females and 1 male) who denied having ever been exposed to any source of ETS.

Results of case–case comparison allowing a comparison between adenocarcinoma and other histological subtypes are presented in Table 2. The risk of developing an adenocarcinoma rather than another subtype was greater for females, but consistently decreased for smokers compared with patients who had never smoked; however, no trend with increasing dose or duration of smoking was showed. The risk of having adenocarcinoma decreased with increasing age at diagnosis.

For the small subgroup of patients who had never smoked, no evidence was found of a relationship between ETS exposure and histological type (Table 3).

Overall survival and survival curves by smoking status and histological subtypes are presented in Figures 1, 2 and 3, respectively. The mean survival time was 11.9 months for the whole population (S.D.:9 months, median: 9.6 months).

The results of the Cox regression analysis are shown in Table 4. The relative risk of death did not significantly differ according to sex, age at diagnosis and age at which cigarette smoking began. However, small cell lung cancer patients exhibited a significantly worse survival compared with other subtypes. Relative risks of death of smoking patients according to their smoking characteristics are expressed relative to non-smokers, and are adjusted for histological subtype, sex and age at diagnosis. Overall, smokers showed a non-significant 16% increase in the risk of dying, compared with non-smokers, and a trend of increasing risk of death was suggested according to number of cigarettes per day, but not according to duration of smoking or pack-years. Survival of non-smokers according to ETS exposure is shown in Table 5. A non-significant increased risk of death was shown for exposure to parents' smoke; there was a trend with age at leaving the parental home (P = 0.05).

DISCUSSION

Most of the available data on clinical features and survival of lung cancer patients are obtained from university centres. It has been previously emphasised that only a small proportion of patients are entered into clinical trials [8], so that little information is published on patients who are not given active treatment [9]. Our study includes patients diagnosed in general

Table 1. Distribution of patients in the study according to smoking status and sex

	Males				Females*				
	Squamous cell carcinoma	Small cell carcinoma	Adeno-carcinoma	Large cell carcinoma	Squamous cell carcinoma	Small cell carcinoma	Adeno-carcinoma	Large cell carcinoma	Total
Never smoked	6	1	5	1	10	5	20	4	52
Cigarette smoker†	335	94	118	77	29	15	25	5	698
Total	341	95	123	78	39	20	45	9	750

* P = 0.001, for the distribution of histological subtyping according to sex. † P = 0.0001, for the distribution of histological subtyping according to smoking status.

Table 2. Relative risk of adenocarcinoma (ADC), compared with other histological subtypes, by selected variables: results of multivariate regression analysis

	ADC* (n = 168)	Other subtypes* (n = 582)	OR†	95% CI‡
Sex				
Male§	123	514	1.0	
Female	45	68	2.31	1.40–3.82
Smoking status				
Never smoked§	25	27	1.0	
Ever smoker	143	555	0.40	0.20–0.79
Pack years				
Never smoked§	25	27	1.0	
1–20	18	55	0.43	0.18–1.0
21–40	50	188	0.37	0.18–0.77
41–60	46	175	0.45	0.21–0.95
>60‖	27	132	0.35	0.16–0.78
Cigarettes per day				
Never smoked§	25	27	1.0	
1–9	4	22	0.31	0.09–1.10
10–19	23	73	0.41	0.18–0.92
20–29	29	79	0.47	0.21–1.04
⩾30¶	21	63	0.36	0.15–0.88
Age at start smoking				
Never smoked	25	27	1.0	
<18	46	152	0.44	0.21–0.95
18–20	60	255	0.36	0.17–0.74
>20**	23	85	0.44	0.20–1.0
Age at diagnosis				
<50§	35	55	1.0	
50–59	44	145	0.45	0.26–0.78
60–64	32	108	0.45	0.25–0.81
65–69	27	85	0.47	0.25–0.87
⩾70	29	179	0.21	0.12–0.39

* Number of subjects; † odds ratio, adjusted for age and sex; ‡ 95% confidence interval; § reference category; data were not available for all patients. Test for linear trend, P value: ‖ $P = 0.19$; ¶ $P = 0.42$, ** $P > 0.10$.

Table 3. Relative risk of adenocarcinoma (ADC) for the group of patients who had never smoked, compared with other histological subtypes, by smoking status of the father and the spouse: results of multivariate regression analysis

	ADC* (n = 25)	Other subtypes* (n = 27)	OR†	95% CI‡
Exposure to smoke from the spouse				
Non-exposed§	9	10	1.0	
Exposed	11	13	0.90	0.14–6.0
Exposure to smoke from the father				
Non-exposed§	6	8	1.0	
Exposed	13	14	0.92	0.19–4.52
Exposure to smoke from the spouse or father				
Non-exposed§	4	5	1.0	
Exposed	17	18	0.69	0.11–4.54

* Number of subjects; † odds ratio; ‡ 95% confidence interval; § reference category; data were not available for all patients.

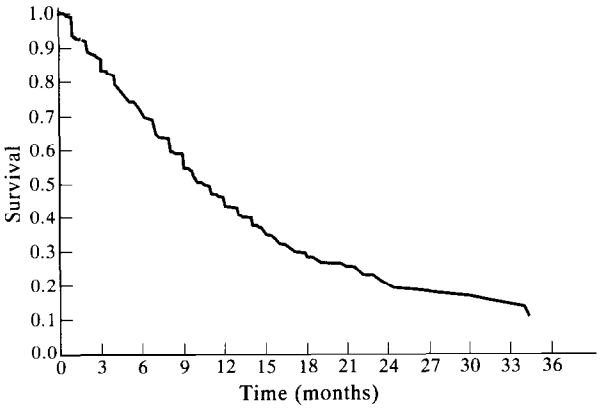

Figure 1. Overall survival of 502 lung cancer patients.

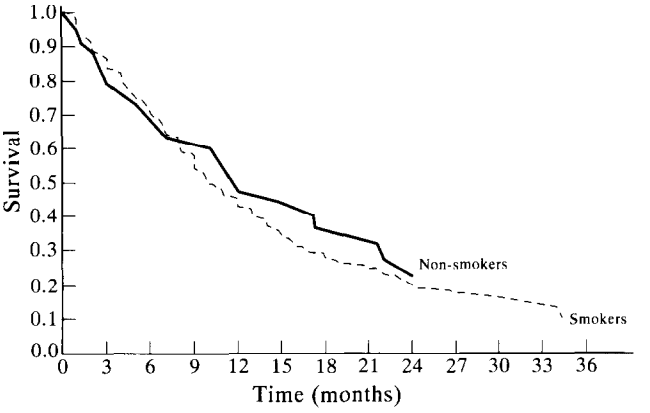

Figure 2. Survival of 502 lung cancer patients according to their smoking status.

hospitals as well as in private offices, and might be more representative of the real profile of these patients in France.

In 1990, in France, 21 617 lung cancer deaths occurred [10]. Applying the incidence rates observed by the Cancer Registry of Bas-Rhin [11], an industrialised area from Eastern France with demographic and economic characteristics similar to those of Paris, to the population of Ile-de-France [12], we calculated that the expected numbers of new lung cancer cases in Ile-de-France for 1988 were 3920 in males, and 466 in females; our cohort represents 16% of that figure in males, and 24% in females.

The histological profile of cases shows that squamous cell carcinoma is the most frequent tumour (51%). These data are not consistent with the relatively high proportion of adenocarcinoma reported among American men in recent years [13]. As for women, the predominance of adenocarcinoma has been reported consistently with little change over time. It is known that lower relative risks are observed for adenocarcinomas than for squamous/small cell cancers [14, 15].

As expected, most lung cancer patients are current or ex-smokers. In recent studies of lung cancer patients, lifelong non-smokers accounted for 2–5% [16]. We found 7% of lifelong non-smokers (95% CI: 5–9%). The questionnaire was relatively simple and was directly administered by a referring physician who was not especially trained for it. This may have caused some misclassification of smoking habits.

The analysis on survival was limited to 502 cases (66% of the initial series). There was no difference according to sex, histopathology, and smoking status between the total group and the subgroup of patients whose survival was analysed. Overall, survival curves show a rapid initial fall within the first 12 months following the diagnosis, with a median survival constantly less

Table 4. Relative risk (hazard ratio) of death during the 1988–1991 period among lung cancer patients by factors related to tobacco use

	N cases (n = 502)	HR†	95% CI‡
Histological subtype			
Squamous and large cell§	298	1.0	
Adenocarcinoma	118	1.04	0.80–1.34
Small cell cancer	81	1.49	1.13–1.96
Smoking status*			
Never smoked§	36	1.0	
Ever smoker	466	1.16	0.72–1.85
Cigarettes per day*			
Never smoked§	36	1.0	
1–9	22	1.13	0.56–2.28
10–19	68	1.20	0.69–2.09
20–29	72	1.40	0.80–2.43
30+‖	63	1.47	0.83–2.61
Pack years*			
Never smoked§	36	1.0	
1–20	46	1.21	0.69–2.13
21–40	157	1.23	0.75–2.01
41–60	156	1.07	0.65–1.74
60+¶	103	1.17	0.71–1.94

* Calculated by proportional hazards regression adjusting for sex, histological subtype and age at diagnosis; † hazard ratio; ‡ 95% confidence interval; § reference category; data were not available for all patients.
Test for linear trend, P value: ‖ $P = 0.16$, ¶ $P = 0.53$.

Table 5. Relative risk of death (hazard ratio) among the subgroup of lung cancer patients who had never smoked by environmental tobacco smoke exposure

	N cases (n = 52)	HR†	95% CI‡
Exposure to father's smoke*			
Non-exposed§	11	1.0	
Exposed	18	1.83	0.57–5.82
Age when leaving parents' home <21 years	11	1.47	0.39–5.60
Age when leaving parents' home ≥21 years	6	2.71	0.49–15.04‖
Exposure to spouse's smoke*			
Non-exposed§	15	1.0	
Exposed	17	0.90	0.28–2.90
Exposure to father or spouse's smoke*			
Non-exposed§	7	1.0	
Exposed	25	1.04	0.30–3.54

* Calculated by proportional hazards regression adjusting for sex, histological subtype and age at diagnosis; † hazard ratio; ‡ 95% confidence interval; § reference category; ‖ P = 0.05; data were not available for all patients.

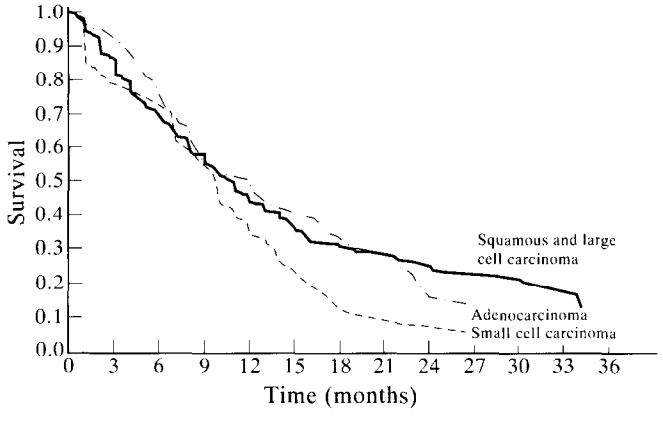

Figure 3. Survival of 502 lung cancer patients according to their histological subtype.

than one year, and are in keeping with other published series [17]. The distribution of cell types shows a persistently worst prognosis for small cell lung cancers.

Information on tumour stage, one of the most important prognostic factors for lung cancer, was not available in this study. However, the analysis on survival according to smoking status would only be invalid if stage is related to smoking status, in addition to survival, and the evidence does not suggest an association between tobacco smoking and tumour stage.

There have only been a few investigations on the effects of tobacco smoking on survival for lung cancer patients, and most have not shown a difference [18–23] whereas three studies [24–26] suggested that patients who never smoked had better survival than smokers. Our analysis suggested a slightly worse survival among smokers, although the difference was not significant. To our knowledge, this is the first study to analyse survival of lung cancer patients who have never smoked in relation to their lifelong ETS exposure. Despite the problem of the small number of patients who had never smoked, which makes it difficult to identify prognostic factors, an association was suggested between exposure to father's smoke during childhood and reduced survival. This result may be due to chance and requires confirmation.

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