Smoking and Survival from Lung Cancer

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The role of smoking in the etiology of lung cancer is well known but less is known about whether smoking also affects the pathological process. In the present analysis 290 lung cancer patients were divided into three equal-sized groups according to lifetime cigarette consumption (heavy, moderate, light/none). The age of the patient, histology, TNM and S-phase fraction of the tumor were confirmed as prognostic factors. The association between smoking and these factors was evaluated. There was a significant difference in histological type of tumor; adenocarcinomas were more common than other types among light smokers. Tumor size, nodal status and occurrence of distant metastases did not differ significantly between the smoking groups. Heavy smokers had a greater frequency of aneuploid tumors and the S-phase fraction was higher among these patients but neither of these differences was statistically significant. Survival analysis indicated no statistically significant association between survival and lifetime total cigarette consumption. Apart from histological type, smoking is not materially associated with clinical and biological prognostic factors, nor does smoking materially affect the survival of lung cancer patients. Our study material was relatively small and therefore not of sufficient power to detect small effects.

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Lung cancer is the second most common cancer among men in Finland, and among women the incidence is increasing over time. The role of smoking in the development of lung cancer is well established (1–3). Lung cancer represents a mixed group of tumors with different histology, biological aggressiveness and clinical course. An association between smoking and lung cancer cell types has been assessed in many studies: (4–9). Less is known about the effect of smoking on the biological aggressiveness of the tumor and on other prognostic factors, as well as on the survival of the patient. The aim of this study was to estimate the effect of smoking on the biological aggressiveness of the tumor and the clinical course of the disease, i.e. survival.

MATERIAL AND METHODS

All new lung cancer cases (n = 792) diagnosed in the Pirkanmaa area (population 430000) and reported to the Finnish Cancer Registry in 1983–1987 were included. Data were collected retrospectively from case notes. All patients were treated in Tampere University Hospital; smoking habits are recorded in detail in case reports. The number of cigarettes per day and the overall duration of the habit could be ascertained for 98% of the patients.

Lifetime consumption was used as an indicator of smoking (number of cigarettes per day times the duration of smoking in years). Smokers were divided into approximately equal-sized tertiles, the first group consisting of heavy smokers (lifetime consumption more than 800), the second group of moderate smokers, and the third of light or non-smokers (lifetime consumption less than 500), referred to here as light smokers. The number of non-smokers was so small that a comparison between smokers and non-smokers was not feasible.

Of all 792 cases 574 were microscopically (positive histology with sufficient sample or cytological class V) confirmed. Altogether, 277 cases were confirmed cytologically (class V), and paraffin-embedded tumor blocks with sufficient samples were available from 297 of the cases (37%). DNA flow cytometric analysis was successful in 290 cases. Of these, 171 were epidermoid carcinomas, 62 small-cell carcinomas and 26 adenocarcinomas, while the other 31 cases represented a miscellaneous group of cancers. The DNA index and S-phase fraction (SPF) were used as indicators of the biological aggressiveness of the tumor. Details of the DNA flow cytometry are described elsewhere (10). In multivariate analyses a comparison was made between heavy smokers and light smokers (n = 138).

The TNM classification (UICC) was used for stage of disease. The patients were followed-up for time of death and for causes of death up to 1992 on the basis of case

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notes from Tampere University Hospital and the Finnish Cancer Registry. The follow-up was complete, without any losses.

Statistical analysis

A BMDP statistical software package was used for statistical analysis (11). The significance of an association between survival and smoking and other prognostic parameters was tested by either the Pearson χ^2-test or Fisher's exact test (BMDP 4F). The univariate and multivariate analyses of survival and relative risk of death were calculated by the Cox proportional hazards model (BMDP 2L). Only lung cancer deaths were included in the analysis of survival; those attributable to other causes were treated as censored observations. In the multivariate analyses all prognostic variables reported in the Table 3 were forced into the model.

RESULTS

Heavy smokers (99%) tended more often to be males than light smokers (72%) but there were no differences between ages (mean 65 ± SD 9). Heavy smoking was more common among those working in agriculture, forestry, industry and traffic-related occupations (81%) than among those working in administrative posts, science, office or service (73%) work.

The proportion of small-cell cancers increased significantly ($p = 0.015$) with increasing consumption of cigarettes (15 vs. 26%) and the same trend was seen in squamous-cell cancers (55 vs. 63%), whereas adenocarcinomas had an opposite trend, being rare among heavy smokers (4%) and more common among light smokers (17%). Heavy smokers tended to have aneuploid tumors (68 vs. 58%) and higher S-phase fractions (14.0 vs. 12.8%) more often than light smokers (Table 1). These differences, however, were not statistically significant.

The survival of females was the same as that, of males, but age was correlated with survival. Patients ≥ 70 years had poorer survival rates than patients of 60 years or younger ($p = 0.01$). Stage and histological type of tumor were confirmed as factors of prognostic significance. Patients with small-cell cancer had significantly poorer survival than those with squamous-cell cancer, while the survival of adeno- and squamous-cell cancer patients did

Table 1

Numbers and percentage distributions of prognostic factors in lung cancer cases diagnosed in the Tampere University Hospital area 1983–1987 by lifetime consumption of cigarettes

Prognostic factor	Smoking								p-value
	Light		Moderate		Heavy		Total		
	N	(%)	N	(%)	N	(%)	N	(%)	
Patient-related factors									
Sex									
Male	66	(72)	93	(92)	96	(99)	255	(88)	<0.001
Female	26	(28)	8	(8)	1	(1)	35	(12)	
Mean age ± SD	65 ± 9		64 ± 8		68 ± 8		65 ± 9		0.003
Disease-related factors									
Tumor size									
T1 + in situ	19	(21)	26	(26)	14	(15)	59	(20)	0.185
T2	59	(64)	58	(57)	72	(74)	189	(65)	
T3 + 4	14	(15)	14	(14)	10	(10)	38	(13)	
Nodal status									
N0	45	(49)	59	(58)	54	(56)	158	(54)	0.432
N1	33	(36)	24	(24)	29	(30)	86	(30)	
N2 + 3	12	(13)	17	(17)	13	(13)	42	(15)	
Distant metastases									
M0	67	(73)	78	(76)	75	(78)	220	(76)	0.682
M1–2	24	(26)	23	(23)	20	(21)	67	(23)	
Histological type									
Squamous-cell carcinoma	50	(55)	60	(59)	61	(63)	171	(59)	0.015
Small-cell carcinoma	14	(15)	23	(23)	25	(26)	62	(21)	
Adenocarcinoma	16	(17)	6	(6)	4	(4)	26	(9)	
Others	12	(13)	12	(12)	7	(7)	31	(11)	
Ploidy									
Diploid	39	(42)	44	(44)	31	(32)	114	(39)	0.189
Aneuploid	53	(58)	57	(56)	66	(68)	176	(61)	
S-phase fraction									
Mean ± SD	12.8 ± 9.3		14.2 ± 10.3		14.0 ± 8.0		13.6 ± 9.5		0.564

Table 2

Relative risk of lung cancer death and 95% CI and p-value for different prognostic factors among lung cancer cases diagnosed in the Tampere University Hospital area 1983–1987

Prognostic factor	Univariate analysis			
	n	RR	95% CI	p
Patient-related factors				
Male vs. female	286	0.96	0.66–1.40	0.838
≥71 vs. ≤60	159	1.58	1.11–2.23	0.01
61–70 vs. ≤60	211	1.25	0.92–1.71	0.156
Moderate vs. light smoker	191	0.84	0.61–1.15	0.266
Heavy vs. light smoker	187	0.94	0.68–1.29	0.689
Disease-related factors				
T (2–4 vs. 1)	284	1.43	1.14–1.79	0.004
N (+ vs. −)	285	2.42	1.84–3.17	<0.001
M (+ vs. −)	283	2.85	2.10–3.86	<0.001
Small- vs. Squamous-cell carcinoma	229	1.84	1.34–2.52	<0.001
Adenocarcinoma vs. Squamous-cell carcinoma	194	0.86	0.53–1.37	0.512
Aneuploid vs. diploid	286	1.16	0.89–1.51	0.279
S-phase fraction ≤15 vs. >15%	220	1.36	1.01–1.83	0.04

not differ significantly. Patients with high S-phase fractions had a poorer rate of survival than those with low S-phase fractions ($p = 0.04$) (Table 2).

There were no statistically significant differences in lung-cancer-specific survival in terms of different lifetime histories of smoking; moderate and heavy smokers showed a trend towards a smaller risk of death from lung cancer than light smokers (Table 2). However, this small and not statistically significant difference in survival rates between the different smoking groups disappeared after adjusting for other prognostic factors (Table 3). In fact, heavy smokers had a somewhat poorer survival rate (RR = 1.13 for mortality) than light smokers, but again, this difference was not statistically significant (95% CI = 0.77–1.50).

DISCUSSION

We carried out a population-based study on the significance of smoking for the biological aggressiveness of and survival from lung cancer. All cases in a defined area (792) during a given time-span were collected and case notes scrutinized. The purpose was to establish the role of smoking in the pathogeneses of lung cancer. Some patient-related factors such as age, and disease-related factors such as tumor size, nodal status, distant metastasis, histological type, and S-phase were confirmed to be of prognostic value. More detailed analyses can be found in our earlier studies (10–12).

Histological type was associated with lifetime cigarette consumption, as also shown in other studies (4–9). The mean SPF, tumor size, nodal status, and presence of distant metastasis at diagnosis did not differ significantly for lifetime history of cigarette consumption.

There was a small trend towards survival benefit for heavy smokers in the univariate survival analysis, which is consistent with the poor prognosis of and only relatively mild correlation with smoking of adenocarcinoma patients. However, the benefit disappeared after adjusting for other prognostic factors and there was a 13% increase risk of death among the heavy smokers compared to the light smokers which, again, is consistent with the confounding effect of adenocarcinomas. The small difference was not statistically significant. To the best of our knowledge, there are no other reports on the effect of lifetime consumption of cigarettes on the prognosis of lung cancer.

Out of 792 cases, only 574 were microscopically confirmed (72%), and of these an adequate histological sample was available for only 297. DNA-flow cytometry was successful in only 290 cases (37% of total). The proportion of cases of lung cancer with microscopical verification (histology or cytology) was about 90% in Finland in the late 1980s, according to the statistics of the Finnish Cancer

Table 3

Multivariate analysis of lung cancer death for different prognostic factors among lung cancer cases diagnosed in the Tampere University Hospital area 1983–1987

Prognostic fractor	Multivariate analysis (n = 138)		
	RR	95% CI	p-value
Aneuploid vs. diploid	0.88	0.55–1.42	0.61
S-phase fraction (≤15 vs. >15%)	1.43	0.89–2.30	0.14
T (2–4 vs. 1)	1.29	0.75–2.21	0.36
N (+ vs. −)	1.91	1.19–3.06	0.01
M (+ vs. −)	1.75	1.05–2.92	0.03
Small-cell vs. non-small-cell carcinomas	2.08	1.29–3.35	0.00
Heavy vs. light smokers	1.13	0.77–1.50	0.53

Registry (13). Our material is also based on the Finnish Cancer Registry. The low proportion of histologically confirmed cases is due to the definition of confirmation and not due to selection of a sample of cases diagnosed in the Tampere area. Many of the patients were inoperable, with biopsy or cytological samples taken at bronchoscopy. Such a biopsy did not always have malignant tissue sufficient for flow cytometry, or the cytology was classified III or IV. These cases were classified in the national statistics as microscopically verified (because there was the pathology/cytology reported from the laboratory), whereas not in our material.

The strength of our study was that smoking data were available on all of these patients. Our index of cigarette-years did not take into account the potential effect of stopping smoking, and categorizing the material in approximately equal-sized tertiles resulted in substantial exposure to tobacco in all the groups. The numbers of ex-smokers and non-smokers were small and the classification used improved statistical power to detect potential differences.

Our results are consistent with those showing smoking to be inversely related to histological types of lung cancer with poor prognosis. Adjusting for this confounding effect removed the difference in survival by smoking. The material was small, however, and not of sufficient power to disclose moderate effects.

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