Lung cancer in young females

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Lung cancer in young females. T. Lienert, M. Serke, N. Schönfeld, R. Loddenkemper. ©ERS Journals Ltd 2000.

ABSTRACT: Previous studies suggested that the characteristics of young female lung cancer patients may differ from those of other patients. Using the cancer registry at the Lungenklinik Heckeshorn hospital, all female patients under the age of 46 yrs with primary lung cancer 1986–1995 were identified. The clinical records were reviewed for risk factors, stage, histology, therapy, and survival. The data were compared with those of other patients.

Of the 4,939 patients 96 (1.9%) were females aged <46 yrs. The percentage of young females doubled within ten years from 1 to 2% of all patients ($p=0.03$). The main risk factor in young females was smoking. Adenocarcinoma and carcinoids were over-represented, whereas squamous cell and small cell carcinoma were significantly rarer in the young female group. Young females and young males were more likely to have advanced disease and underwent surgery and/or combined treatment significantly more often than older patients. The overall survival was only moderately better in younger patients.

The clinical features of young female patients differed from those of young males and older females, the prognosis likewise depended on tumour stage and therapy.
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The lung cancer mortality in females in the USA and Germany is continuously rising [1, 2]. Lung cancer has replaced breast cancer as the leading cause of cancer-related death in females in the USA. In Germany, the lung cancer mortality in females doubled from 1960 to 1996, and in particular increased dramatically from 6.3 per 100,000 to 16.3% per 100,000 (plus 155%) in the group of younger females aged 45–54. In contrast, lung cancer mortality rates in males tend to decrease. In Germany, the rate declined from 73.9 per 100,000 in 1987 to 70.2% per 100,000 in 1996. These different trends are obviously due to the changing smoking habits in males and females [3, 4].

Shifts in histological types were observed during the past few years, with an increasing proportion of adenocarcinoma and a decrease in squamous-cell carcinoma [5, 6, 7]. Changes in cigarette manufacturing with low-tar and low-nicotine products may increase the risk of peripheral lung tumours, such as adenocarcinoma [5, 8]. A higher risk for female than for male smokers was found in several studies [9, 10].

The clinical records of the young females were reviewed for history of smoking, family history of cancer, occupation, duration of symptoms, applied diagnostic methods, histological or cytological tumour cell type, tumour node metastasis (TNM) stage, therapy, and survival. Almost all of the patients underwent a computed tomography (CT) scan as a routine procedure. Mediastinoscopy was performed before surgery only, for left-sided tumours. Disease staging was carried out according to MOUNTAIN [11]. Staging of tumours as determined by correlation of clinical, pathologic, and residual findings (pTNM) was performed in all patients that had been operated on.

A regular follow-up in the authors' institution was available for most of the patients. Survival was proven by inquiries at the residents' registration office. The data for the young females was compared with that from the other 4,843 patients from the cancer registry, who had been divided into groups of males and females and age groups <45 yrs or older. The data was statistically analyzed using the Chi-squared analysis, the Spearman correlation, and the Kaplan-Meier method.

Patients and methods

The retrospective analysis in the present study is based on the data of the cancer registry at Lungenklinik Heckeshorn in Berlin, Germany, 1986–1995. In this period 4,939 patients were newly diagnosed with lung cancer. All female cancer patients aged ≤ 45 (in the following referred to as "young females"), were included.

Results

The yearly number of lung cancer cases in the authors' hospital increased from 440 in 1986 to 570 patients in 1995. The percentage of female patients increased from 25.0% to 29.4% ($p=0.06$). The absolute number of young females diagnosed increased from six in 1986 to 12 in 1995 (1.1 versus 2.1%, $p=0.014$) (fig. 1). The male/female

Fig. 1. – Percentage of young females and males per year in all newly diagnosed cases at Lungenklinik Heckeshorn 1986–1995. ■: Males up to 45 yrs (n=199), $p=0.089$; ●: females up to 45 yrs (n=96), $p=0.014$; —: trend.

ratio in all patients aged <46 yrs was 2.1:1 (199 males: 96 females). In older patients, there was a more pronounced male predominance with 3,286 males *versus* 1,358 females (ratio 2.4:1).

The mean age of females <46 yrs was 39.8 yrs (range 14.1–45.9) and was significantly ($p=0.03$) below the age of young males (mean: 41.8 yrs; range: 15.6–45.9).

Of the young female patients 88% were smokers or former smokers. 80% had smoked more than 20 pack yrs, 23% were heavy smokers with more than 40 pack yrs. Median cigarette consumption was 25 pack yrs and 35% had started smoking under the age of 18. The median age of starting smoking was 19.5 yrs.

No occupational exposure to lung cancer carcinogens was found although over 97% of the young females had worked. Chronic obstructive bronchitis was present in 29 young females (30%). Nine females reported pulmonary tuberculosis in their past medical history. Only one young female had had another organ cancer (uterine cancer) before lung cancer was diagnosed. In 34% of the young female cases, a history of cancer in first degree relatives was recorded. In 13% their relatives had lung cancer.

Complaints of a cough were recorded in 48% of the young females, 32% had chest pain, 29% weight loss, 13% dyspnoea, 12% fever, and 6% haemoptysis. The diagnosis was made without symptoms and by chance in 14% of the

Fig. 2. – Distribution of stages for non-small cell lung cancer by age at diagnosis and gender at Lungenklinik Heckeshorn 1986–1995. ▨: males <45 yrs (n=73); □: females >45 yrs, (n=832); ▩: females <45 yrs, (n=135); ▤: males >45 yrs (n=2,278). $p<0.001$; n=3,318.

young females. The time between first symptoms and diagnosis varied between 1–58 months (median 2.3 months).

In the group of young females the tumours occurred significantly more often in the upper lobes (70%) and less often in the lower lobes (15%), compared to all other patients (upper lobes: 53%; lower lobes: 24%) ($p=0.007$). In only 6% of the young females a central tumour growth was recognized, while it was 15% in the other patients.

The following cell types were found in the group of young females: adenocarcinoma (38.5%); small cell lung cancer (SCLC) (14.6%); squamous cell carcinoma (14.6%); large cell carcinoma (15.6%); carcinoid tumours (9.4%); and bronchoalveolar carcinoma (6.3%) (table 1). Among young females, a significantly higher proportion of patients with adenocarcinomas, bronchoalveolar carcinomas and carcinoids were observed, while squamous cell carcinomas were significantly less frequent than in the group of all the lung cancer patients.

Of the young females 73% were diagnosed as having advanced stages IIIb or IV non-small cell lung cancer (NSCLC). This was a significantly higher proportion than in older males (47%), older females (49%), or young males (58%) (fig. 2). In small cell lung cancer (SCLC), advanced disease was present in 64% of the young females, which was not significantly different from all other SCLC patients. Young females (95%) and males with stage I to IIIa NSCLC underwent surgical resection

Table 1. – Frequency of cell types by age at diagnosis and gender for patients at Lungenklinik Heckeshorn 1986–1995

Cell types	Females		Males	
	≤45 yrs	>45 yrs	≤45 yrs	>45 yrs
Adenocarcinoma	37 (38.5)	386 (28.4)	46 (23.0)	724 (22.0)
Bronchoalveolar ca.	6 (6.3)	50 (3.4)	4 (2.0)	51 (1.6)
Squamous cell ca.	14 (14.6)	238 (17.5)	45 (22.5)	1,113 (33.9)
Small cell ca.	14 (14.6)	310 (22.8)	26 (13.0)	616 (18.8)
Large cell ca.	15 (15.6)	195 (14.4)	40 (22.0)	482 (14.7)
Carcinoid	9 (9.4)	35 (2.6)	10 (5.0)	22 (0.7)
Others*	1 (1.0)	144 (10.6)	24 (12.5)	278 (8.4)
Total	96 100%	1,358 100%	199 100%	3,286 100%

Data are presented as n (%). *: mucoepidermoid carcinoma; sarcoma of the lung; lung cancer unknown histology. ca: carcinoma $p<0.01$.

Table 2. – Therapy of non-small cell lung cancer stage I–IIIa by age at diagnosis and gender

Stage I–IIIa	Females			Males		
	≤45 yrs	>45 yrs	p-value	≤45 yrs	>45 yrs	p-value
None	5	9	0.537	2	6	0.203
Surgery	95	48	<0.001	84	48	<0.001
Chemotherapy	30	6	<0.001	14	6	0.026
Radiotherapy	50	67	0.120	61	71	0.113
Combined modality	55	27	0.024	58	29	<0.001
No. of cases	20	422		57	1,211	

Data are presented as %.

significantly more often than older patients (48%, $p<0.05$). Chemotherapy was also used much more often in young females (30%) than in older males or females (6%). Older females (67%) and males (71%) underwent radiotherapy more frequently than young females (50%) (see table 2).

Young patients with advanced NSCLC also underwent chemotherapy significantly more often (females 64%, males 71%) than older patients (37% females, 34% males) (table 3). In SCLC similar trends were observed with a higher proportion of young patients being treated with surgery when compared to older ones (28% *versus* 7%), chemotherapy (93% *versus* 77%) and/or radiation (83% *versus* 77%), but due to the small number of cases it did not reach statistical significance.

The median survival of all young women with NSCLC was 419 days (figs. 3 and 4). A significantly better chance of survival ($p<0.001$) was noted in resectable stages (I–IIIa) with 2,238 days in young females and 1,025 days in young males, compared to 609 days in females and 488 days in males aged >45 yrs. In advanced stages, the survival differences were only modest and not significant. In SCLC there were no significant differences in survival (females, 45 yrs: 368 days; >45 yrs: 370 days; males, ≤45 yrs: 367 days; >45 yrs: 322 days).

Discussion

The proportion of female lung cancer patients in Lungenklinik Heckeshorn hospital is rising, at a rate of two-fold after ten yrs in young females (2% *versus* 1% of the lung cancer patients). The male/female ratio in patients aged <46 yrs is 2.1:1, in contrast to 2.4:1 in older patients. The rising number of young female patients is due to a change in their smoking habits [4]. While only 20% of German females aged >15 yrs smoked in 1950, nearly 30% were registered in 1980 [12]. Today, 25% of male

and female children aged 15–17 yrs smoke, without any gender difference. However, males tend to predominate in those aged 18–24 yrs, with 40% of all males and 33% of all females smoking [13].

From the results of studies conducted in Europe, Japan and North America, 83–92% of lung cancer cases in males *versus* 57–80% in females are linked to smoking [14]. In the present study, 88% of young female lung cancer patients were smokers, underlining the outstanding role of tobacco smoking in lung cancer development. Whether females may be more susceptible to lung cancer is a matter of discussion [9, 10]. In particular, gender differences in nicotine metabolism [15–17], male/female variations in cytochrome P-450 enzymes [18, 19], and hormonal effects have been investigated [20–22]. Genetic [23, 24] and exogenous factors, such as passive smoking or indoor air pollution [25, 26] may also play a greater role in females. In Germany, 24% of all nonsmoking females live with a smoking male and are exposed to passive smoking [27]. A weighted average of the various relative risks for environmental tobacco calculated in 15 epidemiologic studies in different countries yielded a 25–30% higher risk for nonsmoking females living with smoking males compared to nonsmoking female partners of nonsmoking males [28].

A high percentage (34%) of the young females in the present study had a positive family history of cancer (13% of lung cancer), indicating a genetic influence on the susceptibility for lung cancer. OSANN [23] found a history of cancer in 42% of their female cases. Interestingly, women aged ≤55 yrs had a greater risk increase than older women (odds ratio, (OR) 3.8 *versus* 1.4). HORWITZ *et al.* [24] calculated that the relative risk of developing lung cancer in nonsmoking females was 6 times greater in a family with a history of cancer. The risk was 15 times higher in smoking females without a family history of cancer, and 30 times higher for smoking females with a positive family history of cancer. Other known risk

Table 3. – Therapy of non-small cell lung cancer stage IIIb–IV by age at diagnosis and gender

Stage IIIb+IV	Females			Males		
	≤45 yrs	>45 yrs	p-value	≤45 yrs	>45 yrs	p-value
None	6	14	0.100	8	11	0.344
Surgery	23	11	0.120	15	13	0.553
Chemotherapy	64	37	<0.001	71	34	<0.001
Radiotherapy	77	70	0.267	81	78	0.552
Combined modality	60	29	<0.001	68	34	<0.001
No. of cases	53	410		78	1,067	

Data are presented as %.

Fig. 3. – Survival curves for the different patient groups with non-small cell lung cancer stage I–IIIa at Lungenklinik Heckeshorn. ● : females ≤ 45 yrs ($n=20$); ○ : females >45 yrs ($n=424$); ▲ : males ≤ 45 yrs ($n=57$); △ : males >45 yrs ($n=1,207$).

factors may be a history of tuberculosis, as proposed by ZHENG *et al.* [29], or a history of chronic obstructive bronchitis [30].

The main symptoms of the young female patients did not differ from those of other lung cancer patients [31, 33–35]. The duration of symptoms (3.2 months) in the young female patients in this study before diagnosis was shorter than that reported in the literature [31–34] which may be due to age-related different diagnostic approaches, or faster tumour growth in younger patients.

In the present study, adenocarcinoma was more frequent in young females than in other patients. Many studies show that adenocarcinoma is the most frequent cell type in females and young patients and is increasing in all patients [5–7, 35, 36]. This may be due to the fact that small, previously unspecified lesions were detected by the introduction of more sophisticated diagnostic methods, such as flexible bronchoscopy with peripheral transbronchial biopsy, or CT-guided biopsy [37]. However, the shift from squamous cell carcinoma to adenocarcinoma may

be explained by changing smoking habits [5]. Filter cigarettes with a low tar content may lead to deeper inhalation. It has been hypothesized that carcinogens may thus penetrate the peripheral lung without protecting squamous cells [38, 39]. The smoke of modern cigarettes contains concentrations of tobacco-specific *N*-nitrosamines (TSNA) and lower concentrations of polynuclear aromatic hydrocarbons (PAH) [40]. *In vivo* and *in vitro* bioassays incriminate PAH as inducers of squamous cell carcinoma, while TSNA are known to elicit primarily adenocarcinoma of the lung [8].

Young females with NSCLC more frequently had advanced stages (73% stage IIIb/IV) than young males (58%) or older patients (47%). Similar results for young patients, regardless of gender, have been reported by others [41–44]. Considering the shorter duration of symptoms, this phenomenon could be explained by different biological tumour properties in young patients.

Female and male young lung cancer patients were treated more aggressively than older patients. They had a higher resection rate, received chemotherapy more frequently, and underwent radiotherapy less often than older patients. The observed better prognosis in early disease stages was probably associated with surgical therapy in these patient groups. By contrast, the more frequent use of a combination of all treatment methods in the younger patient groups with advanced disease could only be linked to a "modest" overall better prognosis. RAMALINGAM *et al.* [41] and others [43–44] found similar results and highlighted that therapy is not only guided by disease stage, histologic cell type, and patients' performance, but also by the patients' and attending physicians' "philosophic viewpoint". Young patients were treated aggressively more often due to their better overall medical condition, their desire to do everything possible, and the physicians' reluctance to accept realistic therapeutic limitations in younger individuals. Prospective studies in the future will have to clarify whether a more aggressive approach to young patients, irrespective of disease stage and histology, may be justified or not.

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Fig. 4. – Survival curves for the different patient groups with non-small cell lung cancer; stage IIIb and IV at Lungenklinik Heckeshorn. ● : females ≤ 45 yrs ($n=20$); ○ : females >45 yrs ($n=424$); ▲ : males ≤ 45 yrs ($n=57$); △ : males >45 yrs ($n=1,207$).

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