

# Lung cancer in lifelong non-smokers

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on behalf of the Edinburgh Lung Cancer Group

## Abstract

**The Edinburgh Lung Cancer Group registered 3070 new patients with lung cancer in the five years 1981-5 from a catchment population of 950 000. After review only 74 (2%) were classified as lifelong non-smokers. They differed significantly from the 2996 smokers with lung cancer in that far more were female (77% v 26%) and their mean age was higher (75.4 v 68.0 years). More were in the worst Karnofsky performance categories and fewer patients underwent surgery. The stages of disease were similarly distributed in the two groups and the five year survival was equally poor (5%). Histological cell type was determined in 59 of the 74 patients. All histological cell types were present. More non-smokers had adenocarcinoma than smokers (42% v 13%) and fewer had squamous cell carcinoma (32% v 49%) or small cell carcinoma (15% v 24%). Lung cancer in lifelong non-smokers is uncommon and the diagnosis should therefore always be questioned.**

The association between lung cancer and cigarette smoking was first reported 40 years ago<sup>1,2</sup> and a dose-response relationship has been found repeatedly since then.<sup>3</sup> In more recent series of lung cancer patients lifelong non-smokers accounted for only 2-5% of the total.<sup>3,4</sup> Doll and Peto have concluded that smoking now accounts for 95% of lung cancers in developed countries.<sup>5</sup>

Information on British non-smokers with lung cancer is scanty and conflicts to some extent with findings reported from the United States and elsewhere; the relative frequencies of cell types in smokers and non-smokers in particular are disputed. In the 1950s Kreyberg and colleagues suggested that in men four out of five squamous cell and anaplastic carcinomas ("group I") were due to smoking, whereas adenocarcinoma and alveolar cell carcinoma ("group II") were unrelated.<sup>6,7</sup> Support for the Kreyberg hypothesis was subsequently provided by the finding of a smoking dose-response relationship for both small cell carcinoma<sup>8,9</sup> and squamous cell carcinoma,<sup>10</sup> both group I tumours. Furthermore, a higher proportion of adenocarcinoma (31-85%) was observed in series of non-smokers than in smokers with lung cancer in both developed<sup>11-14</sup> and developing countries.<sup>15</sup>

The Kreyberg hypothesis has been increasingly criticised, however, for being simplistic.<sup>8,10,12,13,16,17</sup> Substantial numbers of "Kreyberg group I" tumours have been reported in non-smokers,<sup>18</sup> a dose-response relationship with smoking has been observed for adenocarcinoma, a group II cell type,<sup>10</sup> and most adenocarcinomas occur in smokers.<sup>4</sup> Additional criticism has been directed at the incomplete smoking histories in some of the earlier papers<sup>4,12,13</sup> and the wide variations in the percentage of lifelong non-smokers in lung cancer series from developed countries (from 1% to 5% in men and from 13% to 41% in women).<sup>4,11,13,14,19</sup> In contrast, the high proportion of women in various series of non-smokers with lung cancer has been fairly consistent, ranging from 62% to 79%.<sup>4,11,14,19,20</sup>

Although lung cancer now kills over 40 000 patients each year in the United Kingdom<sup>21,22</sup> there is little recent information on non-smokers with lung cancer. The Edinburgh Lung Cancer Group was formed in 1980<sup>23</sup> and members serve a catchment population of about 950 000 in south east Scotland.<sup>24</sup> We have reviewed all the non-smokers with lung cancer seen during a recent five year period.

## Methods

All patients with newly diagnosed lung cancer seen by the members of the Edinburgh Lung Cancer Group from 1981 to 1985 were recorded prospectively on a standardised registration form. Details included age, sex, occupation, smoking history, and performance score (Karnofsky index). Disease was staged according to the TNM system,<sup>25</sup> on the basis initially of clinical and radiological features, supplemented by results of laboratory investigations. The diagnosis of lung cancer was based on histological or cytological evidence in 81% of cases or, in the absence of a pathological specimen, on clear clinical and radiological appearances. The treatment for each patient was also noted: surgery, palliative (1800-2200 CGy) or radical (4250-5740 CGy) radiotherapy, chemotherapy, or symptomatic treatment only.

All 99 patients originally classified as non-smokers<sup>24</sup> were reviewed on the basis of case notes, referral letters from general practitioners, nursing records, and postmortem information. These were scrutinised to satisfy the strict definition of a "lifelong non smoker"—one who had never regularly smoked cigarettes, cigars, pipes, or any other form of tobacco. Where available pathological material

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from these patients was reviewed by two pathologists (DL and MMCI) independently without any clinical information. All specimens were assessed in the light of agreed diagnostic criteria, based on a revised and updated version of the World Health Organisation classification, and the findings were recorded on an updated Medical Research Council proforma.<sup>26</sup> The two pathologists' opinions were then compared and reviewed together with the original reports. Clinical and histological features in the smokers and non-smokers with lung cancer were compared by means of the  $\chi^2$  test or Student's *t* test as appropriate.

### Results

The total number of new patients with lung cancer registered during the five completed years 1981–5 was 3070. The 99 patients originally classified as non-smokers were reviewed and 25 were subsequently excluded: 17 patients had smoked previously and been registered erroneously as non-smokers, and for one demented patient smoking history was not recorded in any document; four patients were subsequently found to have metastases from an extrathoracic primary tumour (breast in two cases, bladder, and prostate), and three further patients had other forms of thoracic malignancy at necropsy (one lymphoma, one angiosarcoma, and one mesothelioma).

The remaining 74 patients were then classified as lifelong non-smokers with primary lung cancer. The clinical diagnosis of lung cancer was originally confirmed by pathological material in 59 of the 74 non-smokers (80%). Tissue was obtained by fiberoptic bronchoscopy with bronchial biopsy in 29 patients; by thoracotomy, lymph node biopsy, liver biopsy, or pleural biopsy in 15 patients, and from cytological material in a further 15 (sputum in 10, pleural fluid in 4, and a lymph node aspirate in 1). In the remaining 15 patients review of the

clinical and radiological features strongly suggested primary lung cancer. Pathological confirmation of lung cancer was obtained in an identical proportion (80%) of the 2996 patients in the smoking group.

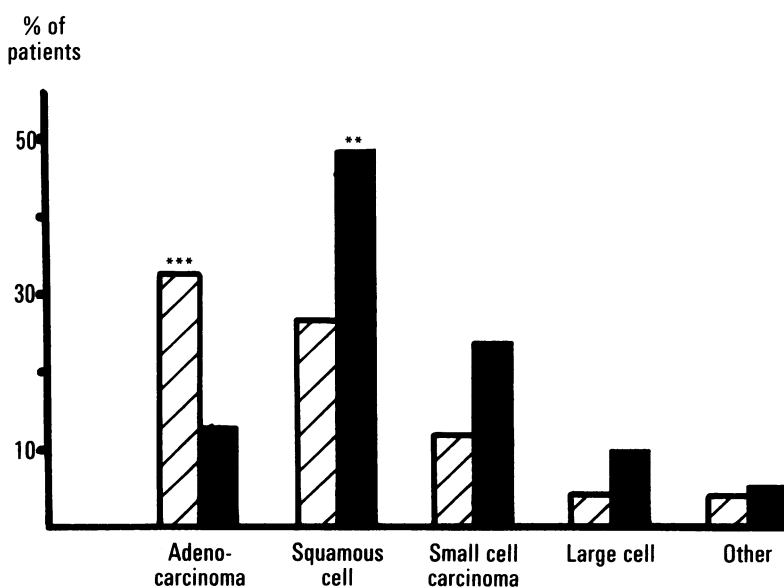
The 74 non-smokers differed significantly from the 2996 smokers in several clinical features. Far more non-smokers were female (54: 77% *v* 23% in smokers,  $p < 0.001$ ) and their mean age was 75.4 (range 28–99) years compared with 68 years in the smokers ( $p < 0.05$ ). Significantly more non-smokers were in the worst Karnofsky performance categories, 10–60 (36% *v* 26%,  $p < 0.05$ ), and correspondingly fewer underwent surgery (10% *v* 19%,  $p < 0.05$ ). The stages of disease at the time of diagnosis were similar in the two groups (62% *v* 58% stage III), and five year survival was equally poor (4/74, 5% *v* 7%).

Histological cell type was known for 59 of the 74 non-smoking patients. All cell types were represented. Adenocarcinoma was far more common than in the 2996 smokers, being present in 25 patients (42% *v* 13%,  $p < 0.001$ ). The non-smokers had correspondingly less squamous carcinoma (19 patients, 32% *v* 49%,  $p < 0.01$ ) and slightly less small cell carcinoma (nine patients, 15% *v* 24%,  $p = 0.08$ ), large cell carcinoma (three patients, 5% *v* 10%), and other types of carcinoma (three patients, 5% *v* 5%)—see figure.

### Discussion

Lung cancer in lifelong non-smokers is uncommon and represented only 2% of this prospective series of some 3000 patients. Non-smokers accounted for 0.7% of the men with lung cancer and 6.7% of the women; these figures are lower than in most earlier studies.<sup>9 11 14</sup> Thus in south east Scotland, and by implication elsewhere in the United Kingdom, smoking may now account for over 99% of lung cancers in men and over 90% in women. The role of other factors, notably occupational exposure to carcinogens, which may interact with the effects of smoking, is not clear. These percentages might increase further if figures for lung cancer due to passive smoking were also included.<sup>5 27 28</sup> The message for lung cancer prevention is clear.

Although three quarters of our non-smokers were women as in previous series,<sup>14 19</sup> our non-smoking patients differed in being somewhat older and in having correspondingly worse performance scores, lower surgical resection rates, and a five year survival rate of only 5% compared with 7% in smokers.<sup>29</sup> No occupational or domestic exposure to other recognised carcinogens had been recorded in these non-smoking patients. The female non-smokers in Kabat's series more often had a past history of pneumonia and three times as many had worked in textile industries as controls.<sup>14</sup> The previously high prevalence of tuberculosis in south east Scotland is not likely to be a factor because the contribution of tuberculosis scars to the incidence of lung cancer ("scar cancers") is now considered negligible.<sup>30 31</sup> The importance of passive smoking, however, is being increasingly appreciated.<sup>27 32</sup> Wald suggested



Comparison of histological cell types in 74 non-smokers (cross hatched columns) and 2996 smokers (solid columns). \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

Table Summary of series of non-smokers with lung cancer

Study	Total number	Non-smokers (No (%) )	Smoking history ascertained (%)	Cell type (No (%))				Comments
				Adeno- carcinoma	Squamous carcinoma	Small cell carcinoma	Other	
This study	3070	74 2% Male 20 0.7% Female 54 6.7% Female/male 77%	98.6	25 (42)	19 (32)	9 (15)	6 (11)	See text
Kabat 1984	2668	134 5% Male 1919 37 1.9% Female 749 97 13% Female/male 72%	?100	92 (69)	29 (22)	9 (7)	4 (3)	Mean age men 54 years, women 62 years
Beamish 1975	1145	Male 915 Female 230	? 78	Kreyberg II 35/60 (58)		Kreyberg I 25/60 (42)		Selected group. Used Kreyberg classification not cell typing
Vincent 1977	1682	60 3.6% Male 1404 24 1.7% Female 278 38 14% Female/male 63%	76	28 (46)	14 (23)	4 (7)	16 (27)	Pathology series
Yesner 1973	449	33 7.3% Male 396 7 1.7% Female 53 26 11% Male/female 79%	96	20 (61)	2 (6)	3 (9)	8 (24)	Small pathology series
Cooper 1968	1372	63 4.6% Male 1250 13 1% Female 122 50 41% Female/male 79%	?100	40 (63)	16 (25)	7 (11)	—	Pathology series. All slides reviewed
Wynder 1967	465	34 7.3% Male 401 8 2% Female 64 26 41% Female/male 76%	?100	17 (50)	3 (9)	3 (9)	11 (32)	Small pathology series; all reviewed
Kennedy 1973		Female 112 32 28%	67	10 (31)	7(22)	—	15(47)	Women only; % non-smokers 39% ↓ 12% by 1971
Doll 1976	Male 441	7 1.6%	98					Male doctors only; no histological details

recently that about one third of lung cancers in non-smokers who live with smokers may be attributed to environmental smoke, and one quarter of lung cancers in non-smokers overall.<sup>28</sup> Many of our non-smoking patients are likely to have been passively exposed to smoke and it will clearly be essential to record this information specifically in future studies. In our series of 99 alleged non-smokers most of the 25 who were excluded had smoked previously. An accurate smoking history may be difficult to elicit; it was unobtainable in one of our patients, compared with 22–33% of patients in some earlier studies<sup>4 12 13</sup> (table). Misclassification of ex-smokers as non-smokers clearly remains a potential source of error.<sup>14 28 33</sup>

Adenocarcinoma was the most common cell type found in our non-smokers, occurring in 42%, three times the proportion in smokers, as in a previous British series<sup>12</sup> (table). Although most American series have reported a higher percentage of adenocarcinoma (46%–69%)<sup>4 8 11 13 14 19</sup> (table), these apparent differences may simply reflect the well recognised difficulties of standardising the criteria for histological cell typing, particularly with adenocarcinoma.<sup>4 24 26</sup>

Kreyberg and colleagues originally suggested that adenocarcinoma and alveolar cell lung carcinomas (their group II) were entirely unrelated to tobacco;<sup>6 7</sup> but 267 of our 291 adenocarcinomas seen during the five years (92%) occurred in smokers, much like the 89% in Vincent's series.<sup>4</sup> Furthermore, a dose-response relationship for cigarettes has been convincingly demonstrated for adenocarcinoma.<sup>10</sup> All the principal histological cell types were represented in this large series of

non-smokers, including squamous carcinoma in 32% and small cell carcinoma in 15%. Neither can therefore be considered "rare" in non-smokers with cancer; we agree with Kabat<sup>14</sup> and others<sup>8 10 12</sup> that the Kreyberg hypothesis should now be firmly discarded.

Differentiating primary from secondary tumours may be difficult whether clinical or histological criteria are used. Any diagnosis of lung cancer based simply on pleural or lymph node biopsy is suspect, whether in smokers or non-smokers, particularly if the cell type is adenocarcinoma.<sup>34</sup> As primary lung cancer in the lifelong non-smoker is uncommon the diagnosis should always be questioned.

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