European Journal of Cancer 84 (2017) 55–59

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Increasing frequency of non-smoking lung cancer: Presentation of patients with early disease to a tertiary institution in the UK☆

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Received 5 April 2017; received in revised form 19 June 2017; accepted 24 June 2017
Available online 4 August 2017

KEYWORDS
PET-CT;
Mediastinum abnormalities;
Smoking;
Mediastinum diagnostic imaging

Abstract ***Background:*** Never-smokers with lung cancer often present late as there are no established aetiological risk factors. The aim of the study is to define the frequency over time and characterise clinical features of never-smokers presenting sufficiently early to determine if it is possible to identify patients at risk.

Methods: We retrospectively analysed data from a prospectively collected database of patients who underwent surgery. The frequency was defined as number of never-smokers versus current and ex-smokers by year. Clinical features at presentation were collated as frequency.

Results: A total of 2170 patients underwent resection for lung cancer from March 2008 to November 2014. The annual frequency of developing lung cancer in never-smokers increased from 13% to 28%, attributable to an absolute increase in numbers and not simply a change in the ratio of never-smokers to current and ex-smokers.

A total of 436 (20%) patients were never-smokers. The mean age was 60 (16 SD) years and 67% were female. Presenting features were non-specific consisting of cough in 34%, chest infections in 18% and haemoptysis in 11%. A total of 14% were detected on incidental chest film, 30% on computed tomography, 7% on positron-emission tomography/computed tomography and 1% on MRI.

Conclusions: We observed more than a double of the annual frequency of never-smokers in the last 7 years. Patients present with non-specific symptoms and majority were detected on incidental

☆ This work was presented at the IASLC 16th World Conference on Lung Cancer September 6–9 2015, Denver, Colorado.

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http://dx.doi.org/10.1016/j.ejca.2017.06.031

imaging, a modality that is likely to play an increasingly important role for early detection in this cohort that does not have any observable clinical risk factors.

Due to established aetiological role of tobacco smoking, never-smokers with lung cancer constitutes an understudied and under-represented cohort that is expected to increase due to the success of smoking prevention and efforts in establishing smoking cessation programmes. However, little is currently known of the frequency of never-smoker patients in the UK.

As there are no established aetiological factors for the development of lung cancer in never-smokers, identification of patients at risk is challenging and many present late when options for treatment are limited.

The aims of our study is to define the frequency and clinical features of never-smokers presenting sufficiently early for surgery to determine if it is possible to identify patients at risk and to understand if any differences might be attributable to a change in proportions due to the anticipated decline in smoking-related lung cancer or if it can be accounted for by differences in the absolute numbers of new never-smokers presenting annually.

1. Methods

We collated data from all patients who underwent surgery for lung cancer over a 7-year period at the Royal Brompton and Harefield NHS Trust, an institution that accounts for the highest surgical activity for lung cancer in the UK.

Smoking status was self-reported and never-smokers were defined as patients who did not ever smoke any tobacco in their lifetimes. All other patients were classified as ex-smokers or current smokers. Frequency was defined as the number (and proportion) of never-smokers versus current and ex-smokers by year.

Patient demographics were obtained from electronic databases, pathology and imaging reports and individual case records were examined to determine clinical features at presentation.

Continuous data were presented as mean with standard deviation (SD) or median with interquartile range as appropriate to the data distribution. Categorical and count data were presented as frequency and percentage (%). Pairwise comparisons were undertaken using Chi-square or Fishers exact test as appropriate to the expected frequency. The non-parametric test for tend and formal regression were utilised to formally test the statistical significance of increasing frequency with time. Kaplan–Meier plots were constructed for survival and compared using log-rank testing. Stage-adjusted survival comparisons were undertaken using Cox regression. Statistical analyses were undertaken using Stata 13 (College Station, Texas, USA) and R 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

2. Results

From March 2008 to November 2014, a total of 2170 patients underwent surgical resection for lung cancer and included in our analysis. Among them, 436 (20%) patients were never-smokers. The annual frequency of never-smokers with lung cancer increased steadily from 13, 15, 18, 19, 20, 20 to 28%, respectively. The percentage change was directly attributable to an absolute increase in numbers and not a difference in the ratio of never-smokers to current and ex-smokers (Figs. 1 and 2).

The mean age at presentation was 60 (16) years and the majority of never-smokers (67%) were women. The mean predicted forced expiratory volume in 1 second (FEV1) was 90 (23)% and forced vital capacity (FVC) was 97 (25)%. The two main histologic subtypes were 151 with adenocarcinoma (54%) and 76 with carcinoid (27%) tumours accounting for 83% of the total.

Presenting features were non-specific consisting of cough in 142 (34%), chest infections in 75 (18%) and haemoptysis in 46 (11%). Mode of presentation varied with histological type with recurrent chest infections as a predominant symptom of central carcinoid tumours (30 versus 15 percent; $P = 0.004$, Fig. 3).

The majority of patients were identified through incidentally imaging. A total of 59 (14%) were detected on incidental chest film, 127 (30%) on incidental computed tomography, 32 (7%) on incidental positron-emission tomography/computed tomography and 4(1%) on incidental MRI.

On a median follow-up of 41 months, the 5-year survival was higher for never-smokers than ex-smoker (60% vs 40%; $p < 0.001$, Fig. 4). The hazard ratio for death of smokers compared with non-smokers was 1.65 (95% confidence interval [CI] 1.29 to 2.11).

3. Discussion

We observed that the annual frequency of never-smoker patients undergoing surgery for lung cancer in our institute is increasing over the last 7 years from 13% to a 28%, attributable to an absolute increase in the number of never-smokers presenting with early disease. A similar observation was made in the USA of patients presenting with late disease [1]. If the rates continue as