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Paper

Sex-differences in lung cancer cell-types? An epidemiologic study in Ireland

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ABSTRACT

Objective: This study assesses the epidemiological pattern of lung cancer cell-types in Ireland, with identification of any underlying gender variations.

Methods: Lung cancer incidence data, including the major cell-types: squamous-cell-carcinoma (SCC), adenocarcinoma (AC), small-cell-lung-carcinoma (SCLC) and large-cell-carcinoma (LCC) were obtained from the national cancer registry (1994-2000), together with individual characteristics, such as age, gender, smoking status, and the year of diagnosis. Age-standardised incidence rates (ASIR), male-to-female (M: F) rate ratios (RR) of ASIR for SCC and AC, as well as RR of AC: SCC according to smoking status for both sexes, were estimated. Estimated-annual-percent-changes for each of the cell-types were calculated.

Results: AC incidence in females is rising annually (8.5%, $p=0.008$) from 1994 to 2000, while SCC is declining (-5.4%, $p=0.01$) in males. M: F ratios of ASIR are consistently greater than 'one', but converging recently. RR of AC: SCC is also approaching 'unity' across both sexes, irrespective of the smoking status

Conclusions: An apparent increase in lung AC incidence in females was observed in Ireland that might indicate some local environmental risk factors, in addition to changing smoking habits. The study findings do not support the hypothesis that females in general are at higher risk for lung cancer development, but tobacco and histologic-specific susceptibility cannot be ruled out.

Key words: Histology; Incidence; Lung cancer; Ireland; Smoking

INTRODUCTION

Lung cancer occurs in multiple histological cell-types. The four major cell-types include squamous cell carcinoma (SCC), adenocarcinoma (AC), large cell carcinoma (LCC), and small cell carcinoma (SCLC). Together, these four major cell-types account for >90% of lung cancer cases in the United States (US)¹. Despite extensive research, the mechanisms leading to these different types of lung cancer remain uncertain. Over recent decades there have been both geographical and temporal changes in the distribution of lung cancer cell-types²⁻⁴. Knowledge of these modifications may help to recognize any underlying new aetiological and pathological mechanisms of lung cancer.

Lung adenocarcinoma has become the leading cell-type in North America², Europe³ and Asia⁴. This increase may partly be artefactual and involve several biases, or may be a real change⁵. Geographical and temporal trends also differ in males and females. A recent birth-cohort study in the US concluded that males and females may be 'equally' susceptible to developing lung cancer from a given amount of cigarette smoking, rather than supporting the hypothesis that females are more susceptible to developing lung cancer⁶. This was reinforced in a recent prospective study⁷. Nonetheless, the gender susceptibility to developing lung cancer is debatable, and is still speculated to be associated with gender differences in their background risk profiles⁸.

To date, no such temporal variations in lung cancer incidence by major cell-types have been identified in the Republic of Ireland. Therefore, the overall aim of this study is to assess the epidemiological pattern of lung cancer cell-types in Ireland, with identification of any underlying gender and/or temporal variations.

METHODS

Source of lung cancer incidence data

The Irish National Cancer Registry Board based in Cork has been registering lung cancer incident cases from January 1st, 1994⁹. More than 90% of cancer cases are histopathologically verified, and the Registry has a centralised system of uniform data collection and quality assessment⁹. However, for lung cancer cases only 75% could be verified histo-pathologically⁹. At the time of this study, all lung cancer incident cases (on an individual basis) registered from 1994 to 2000 were

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obtained from the Registry. Specific individual covariates, such as age, gender, year of diagnosis, and smoking status (smokers, non-smoker or former smokers) were also collected for further analyses. Based on the morphology codes of the WHO International Histological Classification of Tumors¹⁰, invasive carcinomas of lung [ICD Codes: 9 (162) and 10 (C34)] were categorized into four major cell-types. They are: SCC (ICD-O: 8051-52, 8070-76), SCLC (ICD-O: 8041-45), LCC (ICD-O: 8011-12, 8020-21, 8030-33), and AC (ICD-O: 8050, 8140-246, 8260-571).

Estimation of age-standardised incidence rates (ASIR)

Incidence rates for total lung cancer cases in both sexes, together with the major cell-types, were age-standardised to the European Standard Population for better comparison. The estimated-annual-percent-changes (EAPC) in rates for each cell-type were calculated, using generalised log-linear regression model. The annual rates are adjusted for the gender and age-specific annual smoking prevalence of the Irish population for the year 1994, as the baseline year. The annual gender and age-specific smoking prevalence for the year 1994 was obtained from the publication of Lee and colleagues¹¹.

Estimation of age-standardised incidence rate ratios (RR)

Annual male-to-female RR (with 95% confidence intervals: CI) from 1994 to 2000 was estimated for SCC, AC, and for total lung cancer cases. The male-to-female ratios (with 95% CI) were calculated using a spreadsheet (quick-calc) developed by Rothman¹². Ratios more than one would generally indicate that males have higher lung cancer rates, thereby the less likelihood of supporting the hypothesis that females are more susceptible to developing lung cancer. Likewise, annual rate ratios of AC: SCC for both sexes was calculated according to their smoking status.

RESULTS

In total, 10,514 lung cancer incident cases (6,823 in males, 3,691 in females) were registered in the Republic of Ireland from 1994 to 2000. Of these, SCC was the most frequent cell-type in both males (34%) and females (22%), while AC was relatively high among female populations across all the periods studied (18% vs. 14% in males). The frequency of SCLC was also high in females (17% vs. 12% in males); LCC was the least frequent cell-type across both sexes (3%). In all our analyses where appropriate, we have combined both former and current smokers as ever-smokers for better estimates.

The overall ASIR across all the periods studied was higher in males (on an average 500 cases / 10,000 smokers) than in females (on an average 300 cases / 10,000 smokers). Total lung cancer incidence is significantly increasing annually (2%, $p=0.001$) in females, while males show an annual decline (-2.4%, $p=0.058$). In females, there is a significant annual rise (8.5%, $p=0.008$) in AC incidence, which translates into an absolute increase from 30 cases/10,000 smokers in the year 1994 to 45 cases/10,000 smokers in the year 2000 (figure 1).

Table I shows the annual male-to-female (M: F) age-adjusted population-standardised incidence rate ratios (RR) for AC, SCC and total lung cancer cases. Statistically significant higher RR was observed among ever-smokers. Also, there is gradual convergence in RR in the most recent periods, suggesting an increasing trend among the females. The ratios were relatively low among never-smokers, with very wide confidence intervals and unstable estimates, probably due to small numbers.

In table II, almost all the age-standardised incidence rate ratios (RR) of AC: SCC are less than 'one', especially in smokers of

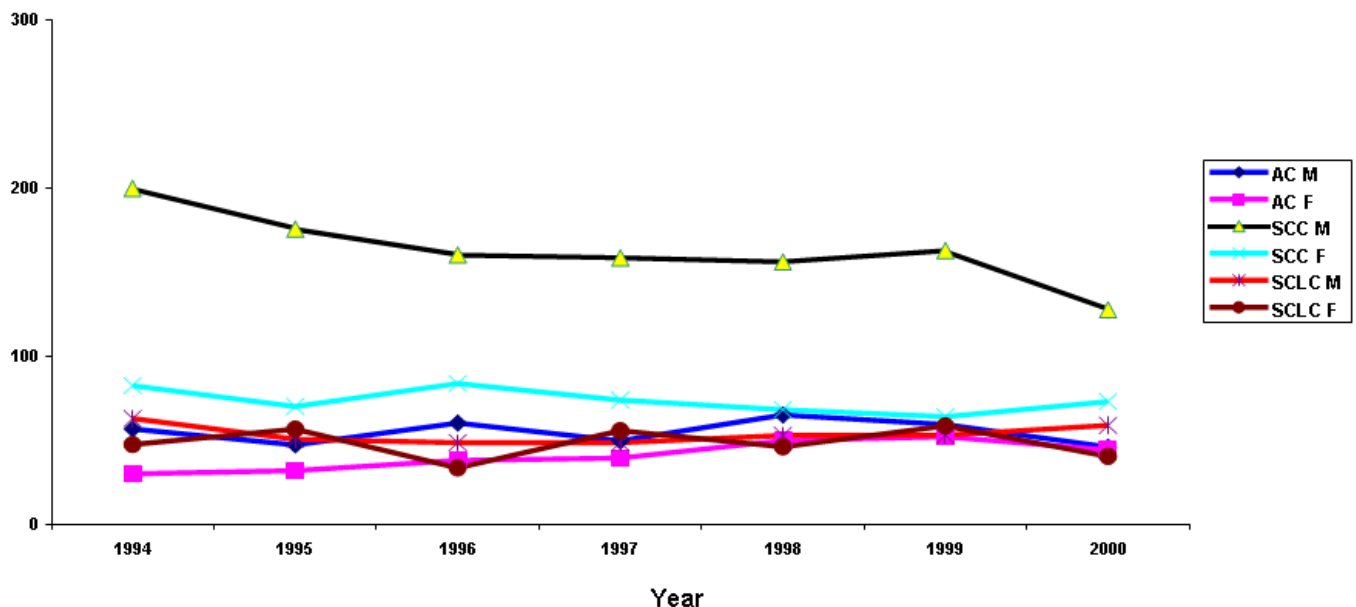


Fig 1. Age-standardised annual incidence rates of lung cancer cell-types in the Republic of Ireland from 1994 to 2000 per 10,000 smokers

AC M = Lung adenocarcinoma in males; AC F = Lung adenocarcinoma in females; SCC M = Squamous cell carcinoma in males; SCC F = Squamous cell carcinoma in females; SCLC M = Small cell lung carcinoma in males; SCLC F = Small cell lung carcinoma in females

TABLE I.

M: F Standardized Incidence Rate Ratios (age-adjusted) in ever (former and current combined) and never-smokers for total lung cancer cases, Lung Adenocarcinoma (AC) and Squamous cell carcinoma (SCC) cases.

Year	All cases	AC	SCC
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Ever-Smokers			
1994	1.94 (1.78, 2.12)	1.87 (1.42, 2.43)	2.41 (2.09, 2.78)
1995	1.70 (1.55, 1.86)	1.47 (1.07, 1.93)	2.50 (2.15, 2.90)
1996	1.66 (1.52, 1.82)	1.57 (1.19, 2.01)	1.91 (1.62, 2.23)
1997	1.55 (1.40, 1.70)	1.26 (0.93, 1.66)	2.14 (1.81, 2.49)
1998	1.62 (1.47, 1.77)	1.30 (1.00, 1.65)	2.28 (1.94, 2.67)
1999	1.54 (1.40, 1.68)	1.14 (0.87, 1.47)	2.54 (2.16, 2.96)
2000	1.40 (1.27, 1.54)	1.04 (0.76, 1.38)	1.74 (1.46, 2.08)
Never-Smokers			
1994	1.02 (0.51, 1.72)	1.43 (0.44, 3.15)	1.63 (0.51, 3.65)
1995	1.42 (0.74, 2.39)	1.47 (0.33, 4.61)	2.20 (0.41, 5.84)
1996	1.69 (0.86, 2.91)	0.71 (0.12, 3.44)	3.18 (0.99, 9.31)
1997	0.95 (0.42, 1.73)	0.39 (0.01, 3.10)	1.37 (0.33, 4.61)
1998	1.53 (0.83, 2.55)	0.74 (0.08, 2.33)	6.00 (1.56, NC*)
1999	1.14 (0.60, 2.04)	1.39 (0.13, 4.01)	4.00 (1.09, NC*)
2000	1.22 (0.68, 2.10)	1.03 (0.19, 2.74)	2.06 (0.39, 5.48)

* NC: Could not be calculated because of extreme values

TABLE II.

Age-Standardised Incidence Rate Ratios (RR) of Lung Adenocarcinoma: Squamous cell carcinoma (AC: SCC) in ever (former and current combined) and never-smokers by gender distribution.

Year	Ever-Smokers		Never-Smokers	
	Male	Female	Male	Female
Year	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
1994	0.3 (0.2, 0.4)	0.4 (0.3, 0.5)	1.0 (0.4, 2.0)	1.2 (0.3, 3.2)
1995	0.3 (0.2, 0.3)	0.5 (0.3, 0.6)	0.8 (0.2, 2.3)	1.3 (0.2, 4.8)
1996	0.4 (0.3, 0.5)	0.5 (0.3, 0.6)	0.4 (0.1, 1.8)	1.9 (0.2, 6.6)
1997	0.3 (0.2, 0.4)	0.5 (0.4, 0.7)	0.3 (0.02, 1.8)	0.9 (0.1, 3.8)
1998	0.4 (0.3, 0.5)	0.7 (0.6, 0.9)	0.5 (0.08, 1.5)	4.4 (0.9, NC*)
1999	0.4 (0.3, 0.5)	0.8 (0.6, 1.0)	0.6 (0.90, 1.6)	1.8 (0.2, 7.2)
2000	0.4 (0.3, 0.5)	0.6 (0.5, 0.7)	1.0 (0.2, 2.3)	2.0 (0.4, 5.5)

* NC: Could not be calculated because of extreme values

both sexes, suggesting that SCC incidence is still high among the Irish ever-smokers. However, the more recent rate ratios of AC: SCC is approaching 'unity' in female ever-smokers, indicating a recent annual rise in AC incidence in females (table I). Such ratios are also relatively high in female never-smokers, and are not statistically significant.

DISCUSSION

Our study has two important findings. Firstly, our findings may indicate a real increase in lung AC incidence in females from 1994 to 2000 in Ireland, consistent with other industrialised nations.²⁻⁴ The gradual convergence in ASIR (table I), with approaching 'unity' ratios between AC and SCC (table II), also suggests that the observed increase in AC incidence is less likely due to the proportionate declining SCC incidence. Secondly, all estimates (rates and ratios) indicate that females in general are unlikely to have a greater susceptibility to developing overall lung cancer, although the ratios are changing recently. This is consistent with a few of the recent observations^{6, 7}.

The main strength of our study is the analysis of lung cancer incidence data rather than lung cancer mortality data, although the trend analysis was apparently short. Our study did show that the total lung cancer incidence was significantly increasing in females, but the fact that only 75% of lung cancer cases were histologically verified using the Irish Cancer Registry Data could have had an impact on the study findings. Another weakness is the lack of comprehensive smoking data for the individual patients analysed. However, the population smoking data used in our study for the estimation of the proportions of smokers and never-smokers in Ireland for the baseline year, 1994 for analysing time-trends was from Lee and colleagues' publication¹¹, and the quality of such smoking data has recently been reviewed¹³.

The increase in lung AC incidence is also less likely due to changing diagnostic techniques or better diagnostic facilities, because the period studied was relatively short. Secondly, evidence suggests that a rise in AC incidence could be antecedent to diagnostic interventions¹⁴. Thirdly, the histopathological criteria for diagnosis and classification have not changed during the study period. Fourthly, the WHO's re-classification of LCC in 1999

is unlikely to influence the AC trend¹⁰, because our data suggest an opposite trend in AC incidence between the sexes from 1994 to 2000 (figure 1).

In Ireland, the overall survival rate in lung cancer has not improved significantly (from 8.2% in 1994 to 9.0% in 2001)⁹. However, evidence suggests that females with non-small cell lung carcinoma can have better survival, following both surgery and chemotherapy^{15,16}. This emphasises that females may respond differently to tobacco-specific carcinogens for certain cell-types^{17,18}. Several molecular studies have also suggested that sex-differences in lung cancer biology do exist. Examples include, females having higher DNA adduct levels¹⁹, an increased *CYP1A1* expression¹⁹, a decreased DNA repair capacity²⁰ and an increased incidence of *K-ras* gene mutations²¹. A novel oestrogen receptor β was also detected in lung tumours²², although both exogenous and endogenous oestrogens might be involved in lung AC development²³. All these indicate that oestrogen signalling could have a biological role in lung carcinogenesis.

Unlike the earlier notions of lung AC being more common among never-smokers, recent evidence suggests a stronger association with smoking, especially in former smokers²⁴. Because only 50% of the cigarettes in the late 1960s were 'filter-tipped' in Ireland¹¹, any underlying change in female smoking habits is less likely to contribute to the recent lung AC incidence increase, similar to a recent study²⁵. Despite small effects, potential environmental risk factor such as air quality can have some role²⁶. High residential radon levels have also been reported in Ireland²⁷. Lung AC is strongly associated with asbestos exposure levels²⁸, which also coincides with the increased mesothelioma incidence in Ireland²⁹. In summary, rapid urbanization coupled with recent lifestyle changes can potentially explain the changing lung AC incidence patterns^{30,31}.

In March 2004, the Republic of Ireland introduced a comprehensive workplace smoking ban³², with Northern Ireland being the latest to follow suit³³. If lung AC is indeed strongly associated with smoking exposure levels, then a dramatic fall in lung AC incidence over the next few years post-ban will certainly confirm the apparent increase seen in Ireland. In addition to tobacco-specific carcinogen susceptibility and gender variations in nicotine addiction levels³³, local environmental factors potentially contributing to such an apparent increase need to be identified, integrating traditional epidemiological approaches with modern molecular techniques³². To conclude, our study findings do not support the hypothesis that females are at a greater risk of developing lung cancer, but histologic-specific lung cancer susceptibility cannot be ruled out.

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