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Time trends in never smokers in the relative frequency of the different histological types of lung cancer, in particular adenocarcinoma

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ABSTRACT

The increasing proportion of lung cancers classified as adenocarcinoma has been a topic of interest and research. The main objective of the analyses reported here is to summarize how the proportion of adenocarcinoma varies in never smokers by time, sex and region based on published evidence on the distribution of lung cancer types available from epidemiological studies. Based on 219 sex- and period-specific blocks of data drawn from 157 publications, there appears to be a clear time-related increase in the proportion of lung cancers in never smokers that are adenocarcinoma, which is evident in both sexes, and not specific to any region. It is seen whether the denominator of the proportion is made up of adenocarcinoma plus squamous cell carcinoma cases, cases of the four major types combined, or all lung cancer cases. The ratio of adenocarcinoma to squamous cell carcinoma rose continuously from 1950 to 69 to be almost 4 times higher for the data from 2000 onwards. We discuss factors that may have contributed to the observed findings, including changes in lung cancer classification. Our findings argue against the hypothesis that increases in the ratio arise from changes in cigarette design and composition.

1. Introduction

The risk of developing lung cancer is strongly associated with cigarette smoking. In general, lung cancer trends tend to lag behind, but reflect trends in cigarette smoking prevalence (Devesa et al., 2005). In the United States, overall lung cancer mortality rates have been declining since 1990 (US Surgeon General, 2014). While smoking is associated with all the major histological types of lung cancer, the association varies by type. A recent meta-analysis of epidemiological evidence in the 1900s relating smoking to lung cancer (Lee et al., 2012) reported relative risks (RRs) in current smokers of 18.17 (95% confidence interval [CI] 12.92–25.56) for small cell carcinoma (SmCC), 16.43 (12.66–21.32) for squamous cell carcinoma (SqCC), 8.56 (5.29–13.86) for large cell carcinoma (LgCC) and 4.05 (3.15–5.22) for adenocarcinoma (AdC). For ex smokers, RRs were again higher for SqCC (8.74, 6.94–11.01) than for AdC (2.85, 2.20–3.70).

Time trends in lung cancer rates also vary by histological type (Devesa et al., 2005). In particular, trends in the frequency of AdC relative to SqCC have become a topic of interest and research (Wingo et al., 1999). In the late 1950s, SqCC was the dominant lung cancer type in US men, with the prevalence of AdC relatively minor by comparison (Thun et al., 1997). Over the following decades, data in the SEER tumour registries (which started in 1973), indicated that the prevalence of AdC relative to SqCC rose sharply so that, by the late 1980s, the prevalence of AdC had exceeded that of SqCC thus becoming the dominant lung cancer type in men (Thun and Heath, Jr., 1997). In women, AdC has been the dominant form of lung cancer throughout the period of data collection in the SEER registries (US Surgeon General, 2014).

The aetiological factors influencing the apparent shifts in the relative proportions of AdC vs. SqCC of the lung are complex and not clearly understood (Lewis et al., 2014). One hypothesis suggests that changes in the design and composition of cigarettes to reduce

Abbreviation: AdC, adenocarcinoma; BALC, bronchioloalveolar carcinoma; CI, confidence interval; IESLC, International Evidence on Smoking and Lung Cancer; LgCC, large cell; RR, relative risk; SmCC, small cell carcinoma; SqCC, squamous cell carcinoma.

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tar yields have resulted in an increase in the frequency of AdC, both in absolute terms, and relative to SqCC (Burns et al., 2011). This hypothesis has been questioned, however, based on the observation that the increasing rate of AdC relative to SqCC preceded the widespread use of low tar cigarettes (Chen et al., 2007b).

Changes in the distribution of smoking habits also affect the relative frequency of AdC. The pattern of RRs by histological type cited above suggests that the relative frequency of AdC to SqCC would increase as the proportion of current smokers in the population decreases, either due to an increase in smoking cessation or a reduction in initiation. This increase would, however, not be large. For example, based on these RRs one can readily calculate (details available on request) that the relative frequency of AdC to SqCC would only be 8% higher for a population with equal numbers of current smokers, ex-smokers and never smokers than for a population with 50% current smokers, 25% ex-smokers and 25% never smokers.

There is also evidence that non-smoking related factors have influenced the changing patterns of these two types of lung cancer. Although the majority of lung cancer mortality in the United States has been attributed to cigarette smoking, Samet et al. (2009) estimated that 10%–15% of lung cancer deaths are accounted for by non-smoking related factors. They also noted that, in men, the rate of AdC is increasing, whereas that of SqCC is decreasing even in never smokers. Likewise, in a meta-analysis which estimated rates among never smokers indirectly by combining data from national rates and epidemiological studies, a clear increase in rates of AdC over time was noted, with little change in rates of SqCC (Lee and Forey, 2013).

Changes in the histological classification of lung tumours may have influenced time trends in the AdC/SqCC ratio. Thus, some studies (Campobasso et al., 1993; Greenberg et al., 1984; Vincent et al., 1977; Yesner et al., 1973) found a significant increase in the numbers of AdC when the diagnoses of histological type originally made some years earlier were reviewed, though others (Butler et al., 1987, Brownson et al., 1995) did not. Also, a number of studies that used standard criteria to review cases collected over at least a 10 year period (mean 21 years) found no evident increase in the proportion of lung cancers classified as AdC (Auerbach et al., 1975; Beard et al., 1988; Butler et al., 1987; Caldwell and Berry, 1996; Chan and Maclennan, 1977; Kennedy, 1973; Tanaka et al., 1988), although a few showed some increase (Andrews, Jr. et al., 1985; Valaitis et al., 1981; Wahbah et al., 2007).

A fundamental question that could shed light on the underlying factors influencing observed rates of these two lung cancer types is whether the temporal patterns of the relative proportions of AdC vs. SqCC of the lung are similar in never smokers compared with smokers. The main objective of the analyses reported here is to summarize how the proportion of AdC varies in never smokers by time, sex and region based on published evidence on the distribution of lung cancer types available from epidemiological studies.

2. Methods

2.1. Inclusion and exclusion criteria

The analyses reported here are part of a wider project intended to answer three questions: “Has the frequency of AdC increased over time, and particularly has it increased in never smokers?”, “Has the classification and diagnosis of histological type changed over time, so as to result in an artefactual rise in the frequency of reported AdC?”, and “What risk factors other than smoking are there for AdC?” The present report addresses the first question, specifically with respect to AdC as a proportion of all lung cancers in never smokers.

For the present report, there was no restriction on location of the study. The types of epidemiological study expected to provide relevant data were case-control, prospective or cross-sectional, though other types would be considered if found. Inclusion criteria were the following: studies must report the distribution of lung cancer type in never smokers (or near-equivalent as defined elsewhere (Lee et al., 2012)); studies conducted from 1940; and studies of at least 20 lung cancer cases in never smokers. Exclusion criteria were: histological typing assessed at a time more than five years after death/diagnosis; distribution of histological type only available for a period more than 10 years long (the objective being to relate distributions to time); subjects sampled by histological type; study restricted to specific histological types, unless it included cases with at least the four main types of lung cancer (SqCC, SmCC, AdC, LgCC); study did not report AdC separately; study of persons at high risk of respiratory disease or with other co-existing diseases or conditions, or of other clearly atypical populations; and study of children or adolescents.

2.2. Literature searching and screening methods

In the initial phase, papers were extracted from a variety of in-house files, including those used for projects on the International Evidence on Smoking and Lung Cancer (IESLC) (Lee et al., 2012), on Environmental Tobacco Smoke and Lung Cancer (Lee et al., 2014), or for an earlier uncompleted similar project in 2002, and also those keyworded in our files as referring to lung cancer diagnosis or histological type, or as referring to risk of lung cancer from smoking. Secondary references (relevant papers cited in initial publications), and in some cases tertiary references (relevant papers cited in secondary references) were also sought.

Except for some papers previously identified in IESLC as having no histological confirmation, each paper was read and assessed in respect of all three questions by PNL, BAF and/or KJC. Where the assessor was in doubt about the relevance of a paper to one of the questions, other assessor(s) were consulted and a consensus decision reached. Review papers were reconsidered at the end, to ensure that any data cited were extracted if the originally cited paper had proved unavailable. For each paper rejected, a reason for rejection code was assigned. The reasons applicable to lung cancer trends in never smokers were divided into five groups: immediate rejects; publication does not provide original data; study design or outcome inappropriate; study population inappropriate; and no useful results.

Subsequently, on April 30th 2015, a Medline search was conducted using the search term (“lung neoplasms” [MeSH Terms] OR (“lung” [All Fields] AND “neoplasms” [All Fields]) OR “lung neoplasms” [All Fields] OR (“lung” [All Fields] AND “cancer” [All Fields]) OR “lung cancer” [All Fields]) AND never [All Fields] AND (smoker [All Fields] OR “smoking” [MeSH Terms] OR “smoking” [All Fields] OR “tobacco products” [MeSH Terms] OR (“tobacco” [All Fields] AND “products” [All Fields]) OR “tobacco products” [All Fields] OR “cigarette” [All Fields]) AND (histologic [All Fields] OR histological [All Fields] OR (“adenocarcinoma” [MeSH Terms] OR “adenocarcinoma” [All Fields]) OR squamous [All Fields]), and papers not already identified in the initial phase were assessed using the same inclusion/exclusion criteria to determine their relevance to study of lung cancer trends in never smokers.

2.3. Data extraction

For each paper accepted, a separate block of data was extracted for each sex, country and period for which results were available. Data for the sexes combined were extracted only when sex-specific data were not available. Data were not extracted by age or race, but