

Possible Explanations for the Observed Rise in the Incidence of Lung Adenocarcinoma relative to that of Lung Squamous Cell Carcinoma

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Abstract

The observed rise in the incidence of lung adenocarcinoma relative to lung squamous cell carcinoma has been claimed to result from changes in cigarette design associated with the shift to lower tar filter cigarettes. We present evidence that tends to undermine this claim. In particular, a recently published review based on extensive data has shown that there has been a substantial rise in the relative frequency of adenocarcinoma compared to squamous cell carcinoma in those who have never smoked.

Keywords: Lung cancer; Histological type; Diagnosis; Smoking habit; Low tar cigarettes

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In 2014, the US Surgeon General [1] noted that “the incidence of adenocarcinoma of the lung and the proportion of lung cancer that is adenocarcinoma has increased dramatically during the past several decades” and argued that this “results from changes in the design and consumption of cigarettes since the 1950s.” The argument that the switch to lower tar filtered cigarettes from the older, higher tar, plain cigarettes has been responsible for the rise in the incidence of adenocarcinoma (AdC) and in the ratio of AdC to squamous cell carcinoma (SqCC) is one that has been made previously on various occasions, [2-4] and has been supported by various researchers [5,6].

While an increase in the frequency of AdC relative to SqCC is clearly evident in many countries [7], a number of pieces of evidence suggest that changes in cigarette design do not explain the observed trends in the histological type of lung cancer.

One reason for doubting the claim lies in the observation by Chen et al. [8] that the observed increase in the frequency of AdC relative to SqCC began well before the increase in low tar filtered cigarette consumption started.

Another reason is that epidemiological studies show no overall evidence of any increase in the risk of AdC associated with filter vs. plain or lower vs. higher tar cigarettes [5,9-12]. Low tar filter cigarettes are associated with a small reduction in risk of SqCC, but not enough to explain the observed large rise over time in the frequency of AdC relative to SqCC.

Although the US Surgeon General [1] dismissed changes in diagnostic procedures as unimportant to their argument, there is in fact quite clear evidence that they are relevant. Firstly, there have been a number of changes in how certain tumour types are classified in successive published schemes for classifying histological type of lung cancer. Notably, one of the four classes of large cell carcinoma in the WHO 1967 classification [13] was reallocated to AdC in the WHO 1981 classification [14]. Second, large studies generally report a significant increase in numbers of AdC when diagnoses of histological type made some years earlier were reviewed by pathologists some years later using the latest classification schemes [15]. Third, studies using standard criteria to review cases collected over a period of at least 10 years generally (although there are exceptions) found no increase in the proportion of lung cancers classified as AdC [15,16]. Interestingly, one of those studies that did report a rise in AdC noted that this was due to the contribution of a substantial increase in the rate of bronchioloalveolar carcinoma, affecting smokers and non-smokers alike, which the authors suggested may have a viral origin.

One of the weakest links in the Surgeon General’s argument [1] is that the shift from SqCC to AdC “is confined to smokers.” Though they claimed that “neither the overall risk of lung cancer nor the risk of adenocarcinoma has changed over time among never

smokers", there has in fact been a clear change in never smokers. That there has been such a change is supported by an analysis [17] in which absolute lung cancer mortality rates by smoking habit and histological type were estimated indirectly based on relative risk estimates from studies published in the 20th century, coupled with WHO mortality data for the same country and period. It is also supported by results reported by Samet et al. [18], who noted that in men the rate of AdC was increasing over time and the rate of SqCC was decreasing, regardless of smoking habits.

That a change in never smokers has occurred has recently been demonstrated even more clearly in a study published in *Regulatory Toxicology and Pharmacology* [15]. That study investigated how the proportion of AdC varied in never smokers by time, sex and region, based on published evidence from epidemiological studies on the distribution of lung cancer types. Data were analysed from 219 sex- and period- specific blocks of data drawn from 157 publications. It was clear that there was a time-related increase in the proportion of AdC which was evident

in both sexes, all regions, and regardless of the denominator used (AdC and SqCC combined, the four main histological types combined, or all lung cancer cases). Compared to the period 1950-69, the ratio of AdC to SqCC was higher by a factor 1.67 in 1970-79, 1.97 in 1980-89, 2.35 in 1990-99 and 3.93 in 2000 onwards. The authors present arguments that the time trends could not be explained by limitations in the literature searches, changes in exposure to environmental tobacco smoke, or the inclusion of misclassified current or former smokers among the never smokers.

While the switch to lower tar filter cigarettes may somewhat have affected the relative frequency of AdC to SqCC the actual available epidemiological evidence suggests that this is because changes in cigarettes have reduced the risk of SqCC not because they have increased the risk of AdC. Also the evidence suggests that the differing trends in AdC and SqCC are due partly to changes in diagnosis and partly to other factors that affect non-smokers and smokers alike. More research is certainly needed to clarify what these factors are.

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