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The effect of time changes in diagnosing lung cancer type on its recorded distribution, with particular reference to adenocarcinoma

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ABSTRACT

Among lung cancers, a substantial shift over time has occurred in the recorded frequency of adenocarcinoma (AdC) relative to that of squamous cell carcinoma (SqCC). This is evident in many countries, and also in those who have never smoked. We attempted to address the extent to which this increase is real, or an artefact of changing diagnostic practices. We reviewed studies re-evaluating diagnoses using more up-to-date criteria, and studies applying standard criteria to cases collected over a long period. We also describe changes to classifications, and factors affecting diagnostic accuracy and consistency. While the four main types have long remained essentially unchanged, successive WHO classifications differ in how tumours are ascribed to these types. Despite refinement of classifications and technological advances, the decision is ultimately the pathologist's. In 11 studies, 189/1212(15.6%) originally diagnosed AdCs were reclassified as non-AdC on review, whereas 541/1564(34.6%) of non-AdCs were reclassified as AdC, increasing AdCs by 30%. Studies examining trends in the proportion of AdC were conflicting; three showing a declining trend, seven no trend, and six some increase. Some studies find lepidic (bronchioloalveolar) carcinoma, but not other AdC sub-types, increased. The rising AdC/SqCC ratio results at least partly from diagnostic changes.

1. Introduction[1]

Over at least the last 40 years there has been a substantial shift in many countries in the reported frequency of adenocarcinoma (AdC) of the lung relative to that of squamous cell carcinoma (SqCC) (Burns, 2014; Charloux et al., 1997; Devesa et al., 2005; US Surgeon General, 2014). This increase is evident both in smokers (US Surgeon General, 2014) and in those who have never smoked (Lee and Forey, 2013; Lee et al., 2016a).

In this paper, we attempt to address the extent to which this increase is a real one, or is an artefact of changing diagnostic practices. Our review is divided into four sections. The first two sections are descriptive, section 3.1 summarizing the various schemes used over the years to classify histological types of lung cancer, and section 3.2 discussing difficulties in implementing these. The final two sections provide more direct evidence. Section 3.3 summarizes evidence from studies that have re-evaluated diagnoses made earlier, to give insight into the magnitude of effects caused by diagnostic change. In section 3.4 we consider studies examining time trends directly by applying standard classification criteria to slides from lung cancer cases that have been collected over 10 or more years, so gaining insight into any true change in the distribution of histological type.

Except for section 3.2, publications are generally considered chronologically, so the reader sees the evidence building up over time, with conclusions summarized at the end. Few publications separate out results for smokers and nonsmokers, but relevant findings are mentioned where they do.

In the discussion section we also consider claims recently made (US Surgeon General, 2014) that the increase in the observed AdC/SqCC ratio is due to changes in the design and composition of cigarettes since the 1950s and is not due to changes in tumour classification and diagnosis.

2. Methods

Sources of publications included in-house files on lung cancer

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[1] AdC, adenocarcinoma; BalC, bronchioloalveolar carcinoma; LgCC, large cell carcinoma; SmCC, small cell carcinoma; SqCC, squamous cell carcinoma; WHO, World Health Organization.

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diagnosis type collected over many years (including publications bequeathed to PNL by the late Dr. F.J.C. Roe), papers relating to all epidemiological studies of over 100 cases on smoking and lung cancer published before 2000 (Lee et al., 2012) and many published since (Fry et al., 2013), and papers relating to a meta-analysis on environmental tobacco smoke and lung cancer (Lee et al., 2016b). Relevant secondary references are also considered. While section 3.1 (classification of lung cancer type) and section 3.2 (accuracy and consistency of diagnosis of type) are not intended to be comprehensive, section 3.3 (re-evaluation of earlier diagnoses) and section 3.4 (time changes in histological type using standard diagnostic criteria) describe all relevant studies found.

For section 3.3 we aimed to extract data from studies providing data on the two-way distribution of lung cancer type (SqCC, AdC, other) based on initial diagnosis and on a review based on standard criteria (or on diagnosis according to two differing classification schemes). Where the breakdown given was more detailed, the data were collapsed to the required 3 × 3 table, with BalC combined with AdC, for consistency with other studies. From the table, we calculated the distribution by type separately for initial diagnosis and review, the numbers of cases transferring into and out of AdC with significance of the ratio estimated using the McNemar test (Conover, 1999), and the ratio of the relative frequency of AdC to SqCC following review to that determined initially.

Section 3.4 limits attention to studies covering at least 10 years. Results are presented for each study, giving, for successive time periods, subdivided where possible by sex, numbers of cases studied and the distribution by broad categories of type. Usually this is for the same groups as before, though where available separate results are shown for BalC. Results of tests of trend over time period (Armitage, 1955) in the reported proportion of lung cancers which are AdC, SqCC, BalC or AdC-BalC are shown for each study/sex combination, where data permit. For both sections 3.3 and 3.4, the reader is referred to the source papers for any more detailed breakdown by type.

3. Results

3.1. Classification of lung cancer type

The morphological classification of lung cancer based on its microscopic characteristics formulated early in the 1900s has changed little in general structure over almost 100 years. The gradual realisation that the so-called 'oat-celled sarcoma of the mediastinum' was actually a primary lung tumour masquerading as a mediastinal lymphoma because of its early dissemination into regional lymph nodes, led, in the early 1920s, to the recognition of four basic types (Marchesani, 1924). These were *Basalzellenkrebse* basal cell carcinoma; equivalent to small cell carcinoma (SmCC) in current terminology), *Polymorphzellige Krebse* (polymorphocellular carcinoma, equivalent to large cell carcinoma (LgCC), *Verhornende Plattenepithelkrebse* (equivalent to SqCC) and *Zylinderzellige Adenokarzinome* (cylindrical cell carcinoma, equivalent to AdC). Although subsequently-recognised variants such as BalC did not fit neatly into these categories, Marchesani's classification stood the test of time so well that, when Kreyberg et al. formulated the first classification under the auspices of the World Health Organization (WHO) in the late 1950s and 1960s (Kreyberg, 1967a), it was acknowledged as being 'so comprehensive and logical that it remained substantially unchanged for some 25 years'.

The first WHO classification of lung cancer was formulated by the *International Reference Centre for the Histological Definition and Classification of Lung Tumours* established in 1958. Meetings of contributors in 1958 and 1964 were followed by its eventual publication in 1967 (Kreyberg, 1967a). Marchesani's earlier classification was recapitulated almost exactly in the categories *epidermoid carcinoma, small cell anaplastic carcinoma, adenocarcinoma* and *large cell carcinoma*, to which were added *combined carcinomas, bronchial gland tumours, mixed tumours* and *sarcomas*. A category of *unclassified* tumours was recognised as were *mesotheliomas; melanomas* were considered a final, separate group.

The 1981 revision of the first, 1967, WHO classification, actually published in 1982 (World Health Organization, 1982), changed little, certainly regarding the four major categories, although the separation of carcinoid tumours from those arising from bronchial glands presaged their recognition as tumours characterised by neuroendocrine differentiation and related in this aspect of their biology to SmCC. Notably, however, certain tumours classified as LgCC in the 1967 classification would, in the 1981 classification, be categorised as AdCs with a solid growth pattern.

The next revision of the WHO classification took almost 20 years to emerge (Travis et al., 1999). Although its structure remained essentially unchanged, the number of categories and subcategories increased significantly, with pre-invasive proliferations now included. Importantly, AdCs were sub-classified with *bronchioloalveolar carcinoma* as one of these subcategories. The 2004 WHO classification is essentially a minor revision of the 1999 scheme and did not differ significantly from it (Beasley et al., 2005).

Over the past decade, major shifts in the classification of lung cancer continue to be in the emerging recognition of sub-types of AdC, particularly early pre-invasive and minimally invasive variants. Accordingly, a new classification of AdC was formulated by the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society (Travis et al., 2013) and has recently been incorporated into the 2015 WHO classification (Travis et al., 2015).

Particularly significant in this latest scheme is that tumours previously categorised as LgCC, but which express antigens characteristic of pneumocytic differentiation, would now be classified as AdCs.

A further factor influencing lung cancer classification more recently is the use of immunochemistry to aid distinction between tumour types. Because detection in cells or tissue sections of antigens closely allied to the different types of lung cancer can aid distinction, its routine use has been driven by the pressing need for more accurate classification as a prerequisite for genomic profiling (Cagle et al., 2011). The welcome reduction in the proportion of lung cancers classified merely as 'non-small cell carcinoma, not otherwise specified' (Rich et al., 2011) has inevitably increased the proportion given a more precise diagnosis, shifting many such tumours into the AdC category.

3.2. Accuracy and consistency of diagnosis

In their early study of smoking and lung cancer, Wynder and Graham (1950) were struck by the variation between pathologists morphologically classifying lung cancer specimens, noting that 'what some pathologists would designate as an AdC, others would classify as an undifferentiated carcinoma.' Variability within and between pathologists has been evident repeatedly in numerous studies since.

In a seminal early study, for example, Feinstein et al. (1970) studied intra- and inter-observer variability in classifying lung cancer between five experienced pathologists independently studying 50 specimens on two occasions. Unsurprisingly, the greatest discrepancy related to distinguishing poorly differentiated squamous (epidermoid) from AdC, where it reached 42%. Significant disagreement between the two readings of the same slide by the same pathologist was as high as 20%. In another study (Weiss et al., 1970), of 161 specimens of lung cancer, unanimity between