The Increasing Incidence of Lung Adenocarcinoma: Reality or Artefact? A Review of the Epidemiology of Lung Adenocarcinoma

ANNE CHARLOUX,* ELISABETH QUOIX,** NORMAN WOLKOVE,* DAVID SMALL,* GABRIELLE PAULI** AND HARVEY KREISMAN*


Lung adenocarcinoma is the most common cell type in females (smokers or non-smokers) and in non-smoking males. Its incidence has been increasing in younger cohorts of males and females until very recent years. Changes in classification and in pathological techniques account for some of this increase. In females and non-smoker males, the increase could be partly due to a detection bias in former studies. Nevertheless, successive cohorts over time seem more likely to develop adenocarcinoma and less likely to develop squamous cell carcinoma. These differences between birth cohorts suggest that the increasing incidence of adenocarcinoma is not only due to changes in pathological diagnosis. Geographical differences are also observed: in Europe, the squamous cell type still predominates and an increase in incidence of adenocarcinoma has only been reported in the Netherlands. In Asia, in the 1960s and 1970s, the proportion of adenocarcinoma was higher than in North America or Europe and seems to be increasing. To what extent these differences are due to differences in establishing diagnosis remains unknown.

Despite these biases in temporal and geographical trends detailed in this review, there has probably been a true increase in incidence of adenocarcinoma. An explanation for this should be sought in studies on detailed smoking history and passive smoking exposure, occupational exposure, diet and cooking, pollution and other environmental factors.

Keywords: lung cancer; adenocarcinoma; epidemiology; tobacco smoking; environmental factors

Over recent decades there have been both geographical and temporal changes in the distribution of histological subtypes of lung cancer. Knowledge of these modifications may help to recognize the potential aetiologic and pathogenic mechanisms in lung cancer. Adenocarcinoma has become the leading lung cancer subtype in North America compared with Europe where the squamous cell carcinoma remains the most frequent subtype.\(^{1,2}\) This increase may be partly artefactual and involve several biases which are addressed in this paper.

This article, based on a computerized (Medline 1966–1996) and a manual search, reviews the epidemiology of adenocarcinoma of the lung and examines possible reasons for the differences in incidence worldwide.

GEOGRAPHICAL AND TEMPORAL DISTRIBUTION OF LUNG ADENOCARCINOMA

In the USA, the earliest studies showing that adenocarcinoma was becoming the most frequent subtype of lung cancer, exceeding squamous cell carcinoma, had been done in the 1960s and 1970s.\(^{3–5}\) These studies were hospital based and one of them\(^{3}\) included only autopsy cases of males. To avoid a classification bias or an inter-reader variability, a pathological review of histological slides had been performed in two of these series.\(^{4,5}\) More recent hospital-based and population-based studies confirmed this trend.\(^{6–9}\) The three largest studies have been published by Wu, Dodds and Travis, who gave age-adjusted incidences for each histological type, using the International Classification of Diseases for Oncology (Table 1).\(^{1,6,7}\) Through the
population-based tumour registry of Los Angeles County, Wu identified 18,108 males and 9,359 females with lung cancer from 1972 to 1981.6 During this period, the age-adjusted incidence of adenocarcinoma increased significantly, leading to a slight predominance of this subtype. Similar results have been published by Dodds7 and Travis,1 who showed through the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute that adenocarcinoma had become the most frequent subtype at the expense of squamous cell carcinoma at the beginning of the 1980s.

Geographical and temporal trends differ in males and females in previously cited studies. In the three hospital-based studies performed in the 1960s and 1970s, adenocarcinoma became the most frequent subtype in males.3–5 This predominance of adenocarcinoma in males has not been confirmed in population-based studies, although the age-adjusted incidence of adenocarcinoma increased by 30–50%, whereas the incidence of squamous cell carcinoma has remained stable over the last 20 years. In females, adenocarcinoma was already the most frequent subtype of lung cancer in the 1960s. In population-based studies, the incidence of adenocarcinoma in women increased by 75–85%, whereas the incidence of squamous cell carcinoma increased more slowly by 65% over the last 25 years.1,6

In Japan, Tanaka reviewed 282 autopsy cases from 1950 to 1983, and found a very high proportion of adenocarcinoma (46%).10 Two other authors reviewed the charts of all lung cancer patients over the periods 1966–1985 and 1970–1989 respectively.11,12 They observed an increasing number of adenocarcinoma over time, this subtype surpassing squamous cell carcinoma in the 1980s (Table 2). The WHO classification was used but there is no information about whether the second WHO classification was employed in those cases of the latest period. Moreover, there was no pathological review of slides. In these two hospital-based studies, the number of adenocarcinoma in males doubled from the beginning of the 1970s to the end of the 1980s.11,12 The number of squamous cell carcinoma remained stable in one11 and doubled in the other.12 Among males with lung cancer reported to the Osaka tumour registry, percentages of adenocarcinoma and squamous cell carcinoma were very close (35% versus 38%).2 In females, the proportion of adenocarcinoma among lung cancer increased from 52 to 69% from the 1960s to the 1980s. Squamous cell carcinoma remains an infrequent tumour in females in Japan.12

In Hong Kong, the earliest study of 228 surgical or autopsy cases from 1948 to 1962 found a high proportion (40% of lung cancers) of adenocarcinoma.13 This predominance of adenocarcinoma was not confirmed in a second hospital-based series (1960–1972).14 In a third and a fourth series, which were done in the same hospital as the second one (Table 2), the number of squamous cell carcinoma and adenocarcinoma increased dramatically and adenocarcinoma became the most frequent subtype, representing 37% of all lung cancers.

### Table 1 Distribution by histological subtypes, population-based studies, North America

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of cases by sex</th>
<th>Time period</th>
<th>Age-adjusted incidence rate per 100,000</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sq</td>
</tr>
<tr>
<td>Wu6</td>
<td>18 108 M</td>
<td>1972</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1981</td>
<td>22.6</td>
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<tr>
<td></td>
<td>9359 F</td>
<td>1972</td>
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<tr>
<td></td>
<td></td>
<td>1981</td>
<td>7</td>
</tr>
<tr>
<td>Dodd7</td>
<td>6128 M</td>
<td>1974</td>
<td>21.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1981</td>
<td>20.9</td>
</tr>
<tr>
<td></td>
<td>2769 F</td>
<td>1974</td>
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</tr>
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<td></td>
<td></td>
<td>1981</td>
<td>5.3</td>
</tr>
<tr>
<td>Travis4</td>
<td>104 116 M</td>
<td>1973–1977</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1983–1987</td>
<td>25.5</td>
</tr>
<tr>
<td></td>
<td>46 738 F</td>
<td>1973–1977</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1983–1987</td>
<td>6.6</td>
</tr>
</tbody>
</table>

M = male; F = female; Sq = squamous cell carcinoma; Adeno = adenocarcinoma; SCLC = small cell lung cancer.
cancers. Kung showed that despite an artefactual increase of adenocarcinoma due to changes in the pathological classification, there was a real increase of this subtype over the last two decades. The number of males presenting to hospital with either adenocarcinoma or squamous cell carcinoma increased. The squamous cell carcinoma/adenocarcinoma ratio decreased, yet squamous cell carcinoma remained the most frequent subtype with 39% of lung cancer cases. The proportion of adenocarcinoma in females increased from 34 to 59% from the 1960s to the 1980s. A decrease in the proportion of other subtypes was noted.

In Korea, Choi reviewed the 2229 lung cancer cases diagnosed from 1981 to 1990 in the hospital. In contrast to squamous cell carcinoma which started to decrease in number after 1987, adenocarcinoma increased and represented 28% of all lung cancers in 1990.

In Europe, lung cancer cases have been abstracted from tumour registries by Parkin for IARC. Around 1985, squamous cell carcinoma predominated in all countries (48% of lung cancers in Europe, from 36% in Denmark to 56% in Slovakia). The proportion of adenocarcinomas varied greatly from one country to another, this cell type being either the second cell type or the third one in frequency after squamous cell carcinoma and small cell lung cancer (SCLC). In males, adenocarcinoma represented 10% (Poland, Slovakia) to 23% (Denmark) of all lung cancers. In females, adenocarcinoma was the most frequent subtype in Denmark (38%), France (36%), Italy (37%), Spain (55%) and Switzerland (42%). In contrast, the squamous cell carcinoma predominated in women in the Netherlands, Poland and the UK, representing 30–35% of lung cancers. In Europe, only one longitudinal study has been published in the Netherlands, showing an increase in incidence of adenocarcinoma. Despite a decrease in incidence of squamous cell carcinoma in both sexes, this subtype remains the predominant lung cancer cell type.

### AGE-RELATED CHANGES IN THE DISTRIBUTION OF SUBTYPES

In most series, in North America and in Asia, adenocarcinoma was the most common subtype in younger males (age <45 or 55). In all series the ratio adenocarcinoma/squamous cell carcinoma decreased with age and the squamous subtype became the most common in older males. In females, adenocarcinoma was the most common subtype in all age groups in four studies, whereas in two others the ratio adenocarcinoma/squamous cell carcinoma reversed after age 55.

The predominance of adenocarcinoma in young males could reflect either a propensity for young males

### Table 2 Distribution by histological subtypes (%), Asia: hospital bases studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of cases by sex</th>
<th>Time period</th>
<th>Histological subtypes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sq</td>
</tr>
<tr>
<td>Watababe (Japan)</td>
<td>688 M</td>
<td>1981–1985</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>101 F</td>
<td>1966–1970</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>221 F</td>
<td>1981–1985</td>
<td>11</td>
</tr>
<tr>
<td>Ikeda (Japan)</td>
<td>161 M</td>
<td>1970–1973</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>42 F</td>
<td>1970–1973</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>73 F</td>
<td>1986–1989</td>
<td>22</td>
</tr>
<tr>
<td>Chan (Hong Kong)</td>
<td>576 M</td>
<td>1960–1972</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>277 F</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Kung (Hong Kong)</td>
<td>314 M</td>
<td>1973–1982</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>341 F</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Lam (Hong Kong)</td>
<td>1819 M</td>
<td>1983</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>457 F</td>
<td>1990</td>
<td>16</td>
</tr>
</tbody>
</table>

Sq = squamous cell carcinoma; Adeno = adenocarcinoma; SCLC = small cell lung cancer.
to develop this subtype or an increase in incidence of this subtype in recent years, which is reflected initially in younger cohorts. Therefore, it is of interest to study changes in histological distribution in different age groups with time (age-specific incidences). This has been done in particular by three authors. In Dodds study, over the 1974–1981 period, in males aged <65 years, the incidence of adenocarcinoma increased with time, whereas the incidence of squamous cell carcinoma decreased. In males >65 years, the number of both subtypes rose with time. This suggested that in 1981 adenocarcinoma was becoming the predominant cell type in younger patients whereas older patients were more likely to have other subtypes. In females, the incidence of adenocarcinoma increased roughly in the same proportion in the age groups over or under 65 years. The incidence of squamous cell carcinoma has been increasing with time in successive cohorts of females >65 years. However in females <65 years there has not been the dramatic reduction in incidence of squamous cell carcinoma observed in cohorts of males <65 years. These differences between age groups suggest that the increasing incidence of adenocarcinoma is not just an artefact.

Similar results have been obtained over the same period by Devesa, through five American registries, and Zheng, through the Connecticut Tumor Registry. Moreover these two authors have analysed more recent birth cohorts. The incidence of squamous cell carcinoma peaked for men born around 1920–1925, 10–20 years before the adenocarcinoma incidence which peaked for men born around 1940. Cohort peaks have been reached 10–20 years earlier for men than for women. In both studies, age-specific incidence of adenocarcinoma stabilized in recent birth cohorts in the younger age group both for men and women. This suggests a reduction in incidence of the adenocarcinoma subtype in the near future, 10–20 years later than that observed for the squamous cell carcinoma subtype.

In a prospective study conducted in 1993, a high proportion of young patients with adenocarcinoma has been found in Strasbourg as compared to Montreal where the proportion of adenocarcinoma was similar in four age categories (<60, 61–64, 65–69, >70 years). This could reflect an increase in incidence of adenocarcinoma in Strasbourg and needs to be confirmed by longitudinal studies in France.

**RISK FACTORS**

Geographical differences and temporal trends in incidence of adenocarcinoma lead to the question of changes in risk factors with time.

**Adenocarcinoma and Tobacco Consumption**

The increase in incidence of adenocarcinoma could be partly explained by an increase in tobacco smoking. Several authors have found a dose-response relationship between adenocarcinoma and cigarette smoking, however this was weaker than that between squamous cell carcinoma and smoking. This risk increased with both number of cigarettes per day and duration of smoking. Reduction of tobacco consumption in the 1960s in males has been followed by a recent decrease in incidence of squamous cell carcinoma, but not by a decrease in incidence of adenocarcinoma. Some factors could partly explain these differences in temporal trends between subtypes. Relative risk for adenocarcinoma has been found to decrease more slowly after smoking cessation than that for squamous cell carcinoma. Variations in composition of cigarette tobacco with time could have played an important role. These variations could have favoured the development of adenocarcinomas at the expense of squamous cell carcinomas. This could explain too why differences in incidence patterns between squamous cell carcinoma and adenocarcinoma are less pronounced in women, who started smoking 10–20 years later than men. For example, introduction of filter cigarettes in the 1950s has been incriminated in the increase in incidence of adenocarcinoma which occurred 20 years later, in the 1970s. Filters remove larger particles in cigarette smoke, thus reducing deposition of those particles in central airways where squamous cell carcinoma develop preferentially. This could lead to a reduction in incidence of the squamous cell type, but not of the adenocarcinoma subtype which primarily occurs in peripheral areas of the lung. Moreover, smokers, especially women, who switched from non-filter to filter cigarettes increased the number of cigarettes smoked per day, which increases the risk of lung cancer. Smokers of filter cigarettes take larger puffs and inhale more deeply than smokers of plain cigarettes. Consequently, an increased deposition of smoking particles in the small airways could result in an increased risk of adenocarcinoma. In France, smokers decreased their consumption of plain cigarettes and black tobacco much later than in the USA. These particularities may explain why no increase in the incidence of adenocarcinoma has yet been described. Impact of tar and nicotine level, additives and their variations with time on lung cancer differentiation deserve to be analysed. NNK, a tobacco specific N nitrosamine, preferentially causes adenocarcinoma in rodents. This carcinogen, which increased in cigarette smoke between 1978 and 1992 by about 45%, could be one factor responsible for the increase in incidence of adenocarcinoma.
Adenocarcinoma in Non-Smokers

Adenocarcinoma is the most common subtype in non-smokers. In North American males, adenocarcinoma accounts for 31–54% of all lung cancers in non-smokers as compared to 25–33% in smokers. In females, adenocarcinoma accounts for 49–74% of all lung cancers in non-smokers and 33–43% in smokers. In China, adenocarcinoma represents 64–80% of lung cancers in non-smoking females and only 29% of lung adenocarcinomas in females are attributable to tobacco smoke.

In the USA, a rising incidence of lung carcinoma in non-smoking women had been noticed between 1914 and 1958. Unfortunately, the distribution by subtypes was not specified. The role of detection bias in the initial increase is probably considerable but remains unknown. Some of this may be due to under-reporting of smoking by females as this habit was socially unacceptable prior to World War II. This could lead to an overestimation of cancer rates in ‘non-smokers’. No evidence of any trend in mortality rates in non-smokers has been described after 1958. Several Asian studies on the other hand found an increase in incidence of adenocarcinoma in non-smokers during the past few decades.

Adenocarcinoma and Environmental Tobacco Smoke

Although the risk due to passive smoking is probably small, there has been a large population exposed to passive smoking in the past. In Wu’s study, in non-smokers, the risk for adenocarcinoma increased with increasing years of passive smoking, but this did not reach statistical significance. In another study, after adjustment for age and cigarette smoking, a statistically significant risk for adenocarcinoma was found for females. But after further adjustment for occupation and income, the risk was no longer increased. In a multicentre population-based case-control study, Fontham found that tobacco use by spouse was associated with a 30% excess risk of lung cancer in non-smoking females. There was no statistical difference between the odds ratio (OR) for adenocarcinoma (OR = 1.29) and the OR for other primary lung carcinoma (OR = 1.37). Thus, this would not explain the change in distribution by histological subtype. On the other hand if sidestream smoke contains many gaseous components which penetrate deeper into the lung than mainstream smoke with more particulate matter, more adenocarcinomas would be expected in passive smokers.

Other Environmental Factors

An excess of adenocarcinomas has been described after exposure to asbestos, arsenic or polyvinyl chloride. However, because of difficulties in methodology (small sample size, lack of non-exposed controls, inadequate source of pathological material) in such studies, no definitive conclusion can be given about the relationship between a carcinogen and a particular lung cancer subtype. Most authors who tried to evaluate the relationship between occupational categories and adenocarcinoma found no or slight increased relative risk of adenocarcinoma. However, these series have small numbers of subjects in each occupational category. Sankila, linking information on occupations obtained in Finland’s 1970 census (including information on 4.6 million people) with the files of the Finnish Cancer Registry described a high risk of adenocarcinoma of 2.41 in the miners and quarryers groups as compared to all other economically active Finnish men, however lower than the risk for small cell lung cancer (SCLC).

In the USA, the number of lung cancers due to radon exposure has been estimated to be 5000–20 000 per year, taking into account the hypothesis that there was a multiplicative effect of smoking. All non-small cell lung cancer (NSCLC) subtypes have been observed in patients exposed to this carcinogen. However, the risk was higher for SCLC.

Two recent large studies found a relationship between lung cancer mortality and outdoor pollution. The adjusted relative risk was however weak (1.15) as compared to the relative risk for smoking. Katsouyanni studied a small series of females in Athens and described an interaction between smoking and air pollution but only in NSCLC other than adenocarcinoma. There was no effect of air pollution on non-smokers. In Trieste (Italy), the risk of lung cancer has been found to increase with increasing level of pollution. The risk of adenocarcinoma was increased in the industrial area (RR = 2.1), especially in the proximity of the shipyard (exposure to asbestos?) but not in the centre of the city. In China, where the rate of lung cancer in non-smoking women is one of the highest in the world, indoor pollution due to coal burning has been implicated in the genesis of lung cancer. The effect of indoor pollution was stronger for squamous cell carcinoma than for adenocarcinoma in one study, and similar for the two subtypes in another one.

Three case-control studies showed that there is an inverse relationship between intake of beta carotene, a precursor of vitamin A, and adenocarcinoma, albeit weaker than for squamous cell carcinoma. One of these and two other studies showed a stronger inverse relationship between fruit intake and lung cancer than between beta carotene and lung cancer. This relation existed for squamous cell carcinoma as well as for adenocarcinoma. This suggests that other nutrients or
confounding variables may have a protective effect against lung cancer. In China, non-smoking females in the lowest tertile of fresh fruit or fresh fish consumption had a statistically significant increased risk of lung cancer (odds ratio 2.4 and 2.8 respectively). There was a trend for a dose-response relationship for this protective effect of fresh fruit or fish. This effect was greater for adenocarcinoma than for squamous cell carcinoma or small cell lung cancer. A high fat intake, especially a high cholesterol intake, has been associated with an increased risk of lung cancer. However, the distribution by histological subtype was not specified.

Pre-existing lung diseases have been significantly related to lung cancer. Adenocarcinoma accounted for 62% of these lung cancers in one study which however included only non-smoking women. A significant increase of the risk of adenocarcinoma was reported in patients with a history of asthma and tuberculosis. Pneumonia and chronic bronchitis were associated with non-adenocarcinoma subtypes.

At present, despite interesting physiopathological hypotheses, there is no epidemiological argument in the literature to incriminate environmental factors other than tobacco smoking in the greater increase in incidence of adenocarcinoma as compared to other subtypes. However, large studies focused on NSCLC subtypes are necessary before drawing conclusions.

RISING INCIDENCE OF ADENOCARCINOMA: POSSIBLE BIASES
Several factors could affect the reported change in distribution of lung cancer subtypes. These include detection bias, technological advances, changes in classification and a true increase in certain subtypes.

Detection Bias
Investigations for a diagnosis of lung cancer tend to be made in smokers, particularly males with pulmonary symptoms. McFarlane in an autopsy series found that 43 of 153 lung cancers (28%) had not been diagnosed antemortem. The proportion of non-smokers was higher in the undiagnosed group than in those patients having an antemortem diagnosis of lung cancer (30% versus 8%, *P* < 0.001). This study also revealed a predominance of females in the undiagnosed group. A case-control study showed that sputum cytology was ordered in patients with chronic cough, recent cough, male sex and smokers. This leads to a detection bias in non-smokers, asymptomatic individuals and in females. As adenocarcinoma is the most common subtype in these groups, its incidence may have been previously underestimated. Correction of this detection bias might lead to the conclusion that the incidence of lung cancer in general and adenocarcinoma in particular is increasing with time.

As a corollary, distribution by histological subtypes in various countries should be compared with caution because the proportion of specified histology can vary greatly. In a country such as The Netherlands or Switzerland, more than 90% of lung cancers have a pathological diagnosis. In Poland, Hong Kong, only 40–50% of histological subtypes are specified.

Historically in Europe, the origin of adenocarcinoma in the lung was debated and adenocarcinomas were often considered as metastatic from an unknown primary. The proportion of patients with adenocarcinoma in the lung considered as an adenocarcinoma of unknown primary rather than a primary adenocarcinoma of the lung may vary between institutions or countries. How much a change in this diagnostic classification contributed to the increase of the incidence of adenocarcinoma has not been evaluated.

Changes in Diagnostic Technique
Because the clinical presentation differs from one histological type to another, the distribution by cell type in series of patients diagnosed by bronchoscopy, trans-thoracic needle aspirate (TTNA), transbronchial needle biopsy, autopsy or surgery may vary significantly. In radiological series, 52–75% of adenocarcinomas present as a peripheral nodule. This explains why there might be an underestimate of the proportion of adenocarcinomas in bronchoscopy series. However, the increased use of flexible bronchoscopy has facilitated access to the lung periphery; this may have led to an increase in the proportion of adenocarcinoma. Whitwell compared the histological distribution in 1329 bronchial biopsies, 907 surgical specimens and 128 autopsies. The proportion of adenocarcinoma cases was 2% in bronchoscopy series, 10% in the surgical and 28% in the autopsy series. In contrast, squamous cell carcinoma accounted for 42% of all lung cancers diagnosed by bronchoscopy, 54% by surgery and 35% by autopsy. In two series comparing the distribution by histological type in patients with positive bronchoscopy to all patients with a final diagnosis of lung cancer, the proportion of adenocarcinoma increased by 7 or 8% whereas the proportion of squamous cell carcinoma and small cell carcinoma, which usually present as central tumours, decreased significantly.

Since the 1980s, TTNA has been widely used for the diagnosis of peripheral lesions and may result in a pathological diagnosis in inoperable patients. As expected, in these series, the proportion with adenocarcinoma and large cell carcinoma is high.
Adenocarcinoma might be expected to constitute a high proportion of surgical cases. Nevertheless, in such series, the rate of adenocarcinoma is often lower than expected.\(^8\)\(^8\)\(^–\)\(^9\)\(^0\) This could be explained by the significantly greater incidence of unresectability due to N2 or M1 disease in adenocarcinoma as compared to squamous cell carcinoma, for an equivalent size of tumour.\(^9\)\(^1\)\(^,\)\(^9\)\(^2\)

**Change of Classification and in Pathological Techniques**

Several authors have evaluated the impact of changing classification on distribution of cell types by rereading the slides of patients previously diagnosed using the original classification. In three of these studies, there was a 6–11% increase in rate of adenocarcinoma when using the first WHO classification, at the expense of the other histological types (Table 3).\(^4\)\(^,\)\(^3\)\(^7\)\(^,\)\(^9\)\(^3\) The first WHO classification of lung tumours was published in 1967 and revised in 1981.\(^9\)\(^4\)\(^,\)\(^9\)\(^5\) In the initial classification, solid tumours with mucin production were classified as large cell carcinoma, whereas in the current classification they are categorized as adenocarcinoma. The influence of this second change in classification has been evaluated by Kung who found an increase in the proportion of adenocarcinoma from 34 to 41% after having reviewed the slides using the second WHO classification.\(^1\)\(^5\)

Since the 1980s, histological specimens have been routinely stained for presence of mucin by Periodic Acid Schiff (PAS), PAS diastase, mucicarmine or alcian blue stains. Valaitis reviewed the impact of staining using mucicarmine and PAS and/or PAS-diastase in 219 cases of lung cancer.\(^5\) He noted a reduction in number of undifferentiated carcinomas with an increase of adenocarcinomas. Between 40% and 47% of cancers initially categorized as undifferentiated carcinomas were reclassified as adenocarcinomas. Similarly, in another study, the proportion of adenocarcinomas increased from 11 to 29% after slides were reviewed using special stains for mucin.\(^9\)\(^6\)

**Inter-Reader Variability**

Even when using the same classification, there is an inter-reader difference in pathological diagnosis. In one study, in which five pathologists reviewed 50 lung cancers, inter-reader variability ranged from 2% for well-differentiated squamous cell carcinoma, 5% for well-differentiated adenocarcinoma to 42% for poorly differentiated adenocarcinoma.\(^9\)\(^7\) In another study, all three pathologists agreed on classification of 67% of 476 lung cancers, and two agreed in 94% of cases.\(^9\)\(^8\) The rates of agreement were 86% for squamous cell carcinoma, 89% for small cell carcinoma, 76% for adenocarcinoma and only 40% for large cell carcinoma. Similar results have been reported by Campobasso who noted a high agreement for squamous cell carcinoma, SCLC and adenocarcinoma (κ = 0.87, 0.89 and 0.85 respectively) in contrast to that for large cell (κ = 0.71) and adenosquamous carcinoma (κ = 0.56).\(^9\)\(^9\) In a review of 161 lung cancers by three pathologists, Weiss reported a 47% agreement rate for adenocarcinoma; the lower the degree of differentiation, the lower was the degree of agreement.\(^1\)\(^0\)\(^0\) The differences in interpretation reported in these studies would potentially apply in a hospital-based study with a small number of pathologists interpreting the slides. In a population-based

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**Table 3 Impact of changing classification on distribution of lung cancer cell types**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of cases</th>
<th>Classification</th>
<th>Histological subtypes (%)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sq</td>
</tr>
<tr>
<td>Yesner(^3)(^7)</td>
<td>449</td>
<td>Original</td>
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Sq = squamous cell carcinoma; Adeno = adenocarcinoma; SCLC = small cell lung cancer.
trial the large number of pathologists involved would likely dilute individual differences in interpretation of histology. Whether there are differences in diagnosis between pathologists from different countries remains unknown.

In summary, even if adenocarcinoma is worldwide the most common cell type in women and non-smoking men, there are international differences. The percentage with this type is higher in Asia than in North America or Europe. The proportion of adenocarcinoma is increasing with time in Asia and North America. Such a trend has been described only in the Netherlands in Europe. There are several biases that may account for some but certainly not all of the observed increase. Further studies should assess the role of passive smoking, occupational exposure, diet, pollution, other environmental factors and potential newer risk factors as viruses.

ACKNOWLEDGEMENTS
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