Implications of Evolving Medical Science for Proof of Lung Cancer Causation *

by

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CONFLICT OF INTEREST STATEMENT

LCF is a partner and JM a senior research analyst in the Geneva, Switzerland, offices of the law firm Shook, Hardy & Bacon LLP. They work on tobacco litigation and regulatory matters for Philip Morris International (PMI). Neither PMI nor any other entity has provided financial support for or has participated in any way in the development or drafting of this article. The views expressed in the article should be attributed exclusively to the authors.

SUMMARY

Causal determination in cases of diseases involving multiple risk factors and long development time poses formidable challenges to judges and juries. Numerous scientific, medical and legal questions are involved. For example, is the mere presence of a factor known to be associated with elevated disease risk sufficient for a causal determination? If not, what level of exposure should be deemed sufficient, and how can that exposure be measured with adequate confidence over an extended period? In the presence of two or more factors associated with elevated disease risk, how can causation be demonstrated and apportioned among these factors, particularly when the potential effects of their interaction are unknown? With increasing knowledge of the molecular and genetic changes involved in disease development, what level of comprehension and proof is sufficient to implicate a specific risk factor in the complex causal mechanism of an individual's disease? Lung cancer,

notwithstanding its strong association with cigarette smoking, represents a group of diseases associated with both a variety of risk factors and relatively long development time. Both the published scientific literature and current clinical practice for the treatment of lung cancer, particularly lung adenocarcinoma, reflect the rapid changes that have occurred in this field over the past decade. These medical advances, in addition to promising better prognosis for some lung cancer patients, have implications for the proof of lung cancer causation in litigation in which plaintiffs contend that tobacco smoke exposure caused their disease. This is particularly true in cases arising in many European countries and other jurisdictions in which little or no histological or cytological information has been produced by plaintiffs. This paper examines the rapidly evolving science underpinning lung cancer diagnosis and treatment and its forensic implications. [Beitr. Tabakforsch. Int. 26 (2015) 298–311]

ZUSAMMENFASSUNG

Die Ermittlung der Ursachen von Erkrankungen, bei denen mehrere Risikofaktoren und eine lange Entwicklungszeit vorliegen, stellt Richter und Gerichte vor beträchtliche Herausforderungen. Dabei ist eine Vielzahl von wissenschaftlichen, medizinischen und rechtlichen Fragen zu klären. Zum Beispiel, ob das bloße Vorliegen eines Faktors, von dem eine Assoziation mit einem erhöhten Krankheitsrisiko bekannt ist, ausreicht, um einen kausalen Zusammenhang festzustellen. Wenn dies nicht der Fall ist, welcher

Grad der Exposition sollte als ausreichend gelten und wie kann man diese Exposition hinreichend zuverlässig über einen längeren Zeitraum messen? Wie kann bei Vorliegen von zwei oder mehr Faktoren, die mit einem erhöhten Krankheitsrisiko verbunden sind, der ursächliche Zusammenhang nachgewiesen und diesen Faktoren anteilig zugerechnet werden, insbesondere wenn die potenziellen Effekte ihrer Wechselwirkungen nicht bekannt sind? Welche Kenntnisse und welche Nachweise reichen angesichts des vermehrten Wissens über die molekularen und genetischen Veränderungen im Laufe der Entwicklung einer Krankheit aus, um zu schlussfolgern, dass ein bestimmter Risikofaktor im komplexen Kausalmechanismus der Erkrankung eines Menschen eine Rolle gespielt hat? Ungeachtet seiner starken Assoziation mit dem Rauchen von Zigaretten stellt Lungenkrebs eine Gruppe von Erkrankungen dar, die mit einer Vielzahl von Risikofaktoren verbunden ist und eine relativ lange Entwicklungszeit hat. Sowohl die veröffentlichte Fachliteratur als auch die aktuelle klinische Praxis in der Behandlung von Lungenkrebs, insbesondere der Adenokarzinome der Lunge, spiegeln die rasanten Veränderungen des vergangenen Jahrzehnts auf diesem Gebiet wider. Dieser medizinische Fortschritt verspricht nicht nur eine bessere Prognose für manche Lungenkrebspatienten, sondern hat auch Auswirkungen für den Nachweis der Ursache von Lungenkrebs in Rechtsstreitigkeiten, in denen Kläger behaupten, die Exposition gegenüber Tabakrauch sei Ursache ihrer Erkrankung. Das trifft besonders auf die Fälle zu, die in vielen europäischen Ländern und anderen Rechtsgebieten auftreten, in denen von den Klägern keine bzw. kaum histologische oder zytologische Informationen vorgelegt wurden. In der vorliegenden Arbeit werden die rasanten Entwicklungen der Wissenschaft zur Unterstützung der Diagnose und Behandlung von Lungenkrebs sowie ihre rechtsmedizinischen Auswirkungen beleuchtet. [Beitr. Tabakforsch. Int. 26 (2015) 298–311]

RESUME

La détermination du lien de cause à effet dans le cas de pathologies impliquant de multiples facteurs de risque et un long temps d'évolution place les juges et les jurés devant de redoutables défis. Un grand nombre de questions d'ordre scientifique, médical et juridique se pose. A titre d'exemple, la seule présence d'un facteur notoirement associé à un risque pathologique élevé suffit-elle à déterminer une causalité? Si tel n'est pas le cas, quel est le niveau d'exposition réputé suffisant et comment est-il possible de mesurer cette exposition avec un niveau de confiance adéquat sur une longue période? En présence d'au-moins deux facteurs associés à un risque pathologique élevé, comment le lien de causalité peut-il être démontré et réparti parmi ces facteurs, notamment lorsque les effets potentiels de leur interaction demeurent inconnus? Compte tenu de l'approfondissement des connaissances relatives aux changements génétiques et moléculaires participant au développement d'une pathologie, quel est le niveau de compréhension et de preuve qui suffit à impliquer un facteur de risque spécifique dans le complexe mécanisme de causalité de la pathologie d'un individu? Indépendam-

ment de sa forte association avec le tabagisme, le cancer du poumon représente un groupe de pathologies associé tant à une multitude de facteurs de risque qu'à un temps d'évolution relativement long. Tant la littérature publiée que les pratiques cliniques actuelles dans le traitement du cancer du poumon, et particulièrement de l'adénocarcinome pulmonaire, reflètent les changements rapides qui se sont produits, dans ce domaine, au cours de la décennie écoulée. Ces avancées médicales, couplées à une amélioration prometteuse du pronostic pour certains patients atteints d'un cancer du poumon, ne sont pas sans avoir des implications sur la production de la preuve des causes du cancer du poumon dans le cadre de litiges durant lesquels les plaignants font valoir que l'exposition à la fumée de cigarette est la cause de leur maladie. Ceci vaut particulièrement dans les affaires entendues dans de nombreux pays européens et sous d'autres juridictions, au cours desquelles les plaignants ne produisent que peu de données cytologiques ou histologiques, voire aucune. Le présent article analyse l'évolution rapide de la science qui sous-tend le diagnostic du cancer du poumon, son traitement et ses implications médico-légales. [Beitr. Tabakforsch. Int. 26 (2015) 298–311]

GENERAL CONSIDERATIONS

Lung carcinogenesis is a complex, multi-step process in which numerous molecular pathways and corresponding mutations are implicated, with some of these mutations occurring late in the tumor-development process (1). The timeframe necessary for potentially harmful exogenous exposures to combine with individual susceptibility factors to eventually produce the genetic changes that result in clinically diagnosed lung cancer is measured in decades rather than years (2). The generic term "lung cancer" encompasses numerous distinct diseases (3). In addition to many relatively minor types of lung cancer, four major lung cancer histological or cell types exist: small cell carcinoma, squamous cell carcinoma, adenocarcinoma, and large cell carcinoma (3). Squamous cell carcinoma, large cell carcinoma, and adenocarcinoma are collectively termed non-small cell lung cancer (NSCLC), a term that has significant meaning with respect to lung cancer treatment and that is discussed in greater detail below. Large cell lung cancer (LCC) is the least common and most poorly characterized of the four major histological types of lung cancer and will consequently often be ignored in this discussion, as it is in many publications dealing with lung cancer incidence and treatment. Despite their distinct biology and morphology, all four major cell types are associated with cigarette smoking, i.e., epidemiological studies dating back several decades have established that smokers have a higher risk of developing these types of lung cancer than nonsmokers (4). On the other hand, some types of lung cancer are not associated with cigarette smoking, e.g., typical and atypical carcinoids, which are neuroendocrine tumors sometimes mistakenly diagnosed as small cell lung carcinoma. In a case litigated in California, USA, in 2005, the plaintiff alleged that he had developed small cell lung cancer from smoking. A jury found in favor of the defendant cigarette manufacturer, who argued that the plaintiff's cancer was an

atypical carcinoid and not small cell lung cancer. Small cell lung cancer is particularly virulent, with a relatively short average survival time following diagnosis. Consequently, the defendant's case was facilitated by the fact that the plaintiff who alleged small cell lung cancer was alive in the courtroom several years following diagnosis (5).

The relative risk of a smoker to develop squamous cell or small cell lung cancer when compared to a never-smoker is much higher than the relative risk to develop adenocarcinoma (6). The relative risk (RR) is the ratio of lung cancer developed by smokers compared to nonsmokers: $RR = \text{lung cancer incidence in smokers} / \text{lung cancer incidence in nonsmokers}$. Adenocarcinoma is the most common type of lung cancer diagnosed in never-smokers (7), and thus the ratio of adenocarcinoma in smokers relative to never-smokers is lower than for the other two major cell types. For example, depending on the duration of smoking and number of cigarettes smoked, some epidemiological studies demonstrate that the risk that a smoker will develop squamous cell or small cell lung carcinoma compared to the risk of a never-smoker is 20 or more times higher (8). In contrast, the risk that the same smoker might develop adenocarcinoma compared to a never-smoker is far lower, generally falling in the range of three to ten times, depending on the gender and smoking history of the individual (8). A marked shift in the prevalence of the major lung cancer cell types has occurred over the past several decades (9). In the mid-20th century, small cell and squamous cell carcinoma were the most common types of lung cancer diagnosed in many parts of the world (9). At that time, many researchers and clinicians even doubted whether adenocarcinoma was associated with cigarette smoking (10). Over time, the prevalence of adenocarcinoma has increased markedly to the point where it is now the most common major lung cancer cell type throughout much of the world (11), regularly diagnosed in both smokers and never-smokers. This histological shift has occurred relatively rapidly and without adequate explanation. While some observers contend that changes in cigarette design since the 1950s are responsible for this phenomenon (12, 13), no solid proof currently exists to sustain this hypothesis (14). Some researchers have observed that the increase in adenocarcinoma began well before the advent of cigarette filters and other supposedly pertinent cigarette design changes (15). Moreover, FRY *et al.* (16) recently concluded that "[t]he slower decline in quitters for adenocarcinoma, evident in subgroups by sex, age and other factors, may be one of the factors contributing to the reported rise in the ratio of adenocarcinoma to squamous cell carcinoma".

In addition to cigarette smoking, several other risk factors are associated with the development of lung cancer (17). These include environmental factors such as exposure to radon, asbestos, diesel exhaust, and various other substances commonly found in ambient air or the workplace, or specific dietary components. In addition, a family history of lung cancer – which suggests the existence of mutations and other genetic factors in an individual's germ cells favoring the development of lung cancer, as opposed to subsequent somatic mutations in oncogenes or tumor-suppressor genes – can also play a role in the development of disease (18). While the strength of the association between lung cancer and most other risk factors might be

weaker than the association between lung cancer and cigarette smoking, relative risks used for such comparisons are determined in population studies that cannot serve as the basis for a determination of the complex interactions that occur among exogenous and endogenous lung cancer risk factors in the case of a specific individual (19). Moreover, the presence of a specific risk factor in an individual's history – even cigarette smoking as a risk factor for the development of lung cancer – does not mean that risk factor was part of the causal mechanism responsible for the development of the disease (19–21). No methods currently exist to accurately characterize the complex biological mechanisms that give rise to lung cancer and most other diseases with long development times and multiple risk factors (19, 22, 23).

Smokers who quit smoking reduce their risk of developing lung cancer over time (24–26). The relative risk of developing small cell and squamous cell carcinoma declines more rapidly than the risk of developing adenocarcinoma following smoking cessation (27). For a long time, the general assumption was that 10–15 years after cessation most of the excess lung cancer risk in smokers compared to never-smokers had disappeared (28). More recent studies tend to indicate that 20 or more years are required before the elimination of most of the excess lung cancer risk is attained (29). Notably, the decline in lung cancer risk following smoking cessation, just as in the case of the risk of developing lung cancer, is closely associated with both the duration and intensity of cigarette smoking over time, with duration tending to be the more important factor, according to most epidemiological studies (30, 31).

Some 10–40% of lung cancer cases in many countries of the world are diagnosed in never-smokers (32). That figure is even higher when considering the prevalence of adenocarcinoma among non-smoking women, particularly in Asian countries (32, 33). While numerous researchers have opined that lung cancer in smokers and nonsmokers represents distinct diseases, based on specific genetic mutations commonly found among the two groups (34), other researchers have recently observed considerable overlap among the many genetic mutations and other changes that occur in the tumors of smokers and never-smokers (35, 36). Careful analysis of the histological and genetic characteristics of lung cancer arising in smokers and never-smokers can play an important role in cases in which plaintiffs contend that their lung cancer was caused by smoking.

CLINICAL ISSUES

When a patient presents at a hospital with symptoms consistent with lung cancer, a chest X-ray, CT (computer tomography) scan or other imaging study will invariably be performed. Should thoracic imaging reveal the presence of a suspicious lesion or infectious process, a biopsy will ensue. Depending on the size and location of the suspected lesion, a variety of options are available, including an open surgical biopsy, endobronchial biopsy, or fine needle aspiration (FNA). The material obtained from the biopsy can be lung/tumor tissue (histology), individual lung or tumor cells suspended in fluid (cytology), or a combination

of the two. In the presence of an adequate biopsy specimen a diagnosing pathologist can generally determine the presence of malignancy and the major cell type and grade (cellular differentiation/aggressiveness) of cancer.

FNA biopsies are commonly performed, particularly if a suspected tumor resides in the lung periphery, as is often the case with adenocarcinoma. In fact, an estimated 70% of lung cancers are diagnosed via small tissue specimens or cytology (11). An FNA involves the insertion of a needle through the chest wall, generally guided by CT scan, to obtain a small sample. Cytology is most commonly obtained via FNA, though, on occasion, some tissue might also be extracted. Because of the small amount of diagnostic material obtained via FNA and other lung biopsy methods, and the resulting diagnostic uncertainty, a surgical pathologist will sometimes limit his/her diagnosis to one of two broad categories: small cell or non-small cell lung cancer (NSCLC). As noted above, the NSCLC category includes squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.

The small cell/NSCLC diagnostic dichotomy was, until recently, sufficient in most cases for treatment purposes because small cell carcinoma is not usually amenable to surgical treatment due to its virulence and propensity for early, distant metastases (3). Thus, small cell lung cancer is generally treated with palliative chemotherapy. On the other hand, squamous cell, large cell and adenocarcinoma, when detected at an early stage, are candidates for surgical intervention and possible clinical cure, i.e., five-year disease-free survival. Recent advances in lung cancer treatment have, however, necessitated changes to the former status quo, requiring surgical pathologists to move beyond the simple small cell/NSCLC dichotomy, as discussed in greater detail below.

Among the four major lung cancer cell types, adenocarcinoma has received the most research attention over the

past 15–20 years. This is likely due in part to the growing worldwide importance of adenocarcinoma vis-à-vis the other major lung cancer cell types. Numerous lung cancer screening and imaging studies conducted in recent years have probably also contributed to the focus on adenocarcinoma because most of the lesions detected in such studies are small, peripheral adenocarcinomas that lend themselves to surgical resection and clinical study. Adenocarcinoma has traditionally been quite common among Asian populations, and many of the important studies analyzing adenocarcinoma have been conducted by Asian researchers (37).

The collective results of much of the recent research on lung adenocarcinoma have given rise to a revised classification of lung adenocarcinoma histological subtypes produced jointly by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) (11). This reclassification supersedes the current World Health Organization (WHO) adenocarcinoma classification scheme, last updated in 2004 (38). The IASLC/ATS/ERS revised lung cancer classification is based on input from a broad spectrum of medical specialists, including pathologists, radiologists, thoracic surgeons, molecular biologists, and oncologists. Table 1 compares the WHO and IASLC/ATS/ERS lung adenocarcinoma classifications.

According to the authors of the revised lung adenocarcinoma classification, “[a] widely divergent clinical, radiological, molecular, and pathologic spectrum exists within lung adenocarcinoma. As a result, confusion exists, and studies are difficult to compare.... This classification is needed to assist in determining patient therapy and predicting outcome” (11). The source of much of the confusion that the revised classification seeks to address is the imprecise use of the term bronchioloalveolar carcinoma (BAC) over the past several decades.

Table 1. Comparison of WHO (38) and IASLC / ATS / ERS (11) revised lung adenocarcinoma classifications.

World Health Organization (WHO) adenocarcinoma classification, 2004	IASLC / ATS / ERS revised lung adenocarcinoma classification
	<i>Preinvasive lesions</i>
	• Atypical adenomatous hyperplasia
	• Adenocarcinoma <i>in situ</i>
	<i>Minimally invasive lesions</i>
	• Minimally invasive adenocarcinoma
	<i>Invasive lesions</i>
	• Lepidic predominant
Acinar adenocarcinoma	• Acinar predominant
Papillary adenocarcinoma	• Papillary predominant
	• Micropapillary predominant
Solid with mucin production	• Solid predominant with mucin production
Adenocarcinoma, mixed subtype	• [80–90% of adenocarcinomas are mixed; “predominant” designation to be used]

The authors of the revised adenocarcinoma classification list five different histological variations for which the term BAC had been used over time, some of which are associated with distinctly disparate prognoses. Adenocarcinoma that metastasizes to the lung can also produce a BAC-like appearance. One of the more common presentations denominated BAC has been a peripheral lung tumor with a lepidic growth pattern, little or no invasion into surrounding lung parenchyma, and almost 100% five-year survival when surgically resected (38). Lepidic growth refers to tumor cells that line alveolar walls and replace normal bronchioalveolar epithelium while conserving alveolar architecture (20). A so-called “ground glass” appearance on CT studies has also been commonly associated with BAC (11).

The revised adenocarcinoma classification identifies two “pre-invasive” or “minimally invasive” tumor subtypes that generally correspond to this former BAC classification, along with five “invasive” histological variations. Adenocarcinoma *in-situ* (AIS) and minimally invasive adenocarcinoma (MIA) now occupy the category formerly denominated BAC. AIS is composed exclusively of lepidic growth along alveolar septa, while MIA represents much the same, combined with minor extension into surrounding lung parenchyma of no more than 5 mm in any direction. Both tumor types result in almost 100% five-year survival when resected, according to numerous studies dating back to the seminal study by NOGUCHI *et al.* (37) published in 1995.

The invasive subtypes of adenocarcinoma include the following: (i) lepidic (ii) acinar, (iii) papillary, (iv) micropapillary, and (v) solid. Because 80–90% of lung adenocarcinomas are composed of two or more histological subtypes (39), the authors of the revised classification recommend that the subtype comprising the largest percent of tumor growth be designated “predominant,” e.g., papillary predominant, and that the presence of additional tumor components be described in increments as precise as 5% of total tumor mass. Because lepidic growth is, by definition, restricted to the alveolar walls, the term “lepidic predominant adenocarcinoma” is intended to refer to AIS > 3.0 cm, or MIA that includes more than 5 mm of invasive growth into surrounding lung parenchyma, which growth is composed of one or more of the other invasive adenocarcinoma subtypes. This characterization goes a long way toward resolving much of the confusion formerly associated with the term BAC.

The acinar, papillary, and solid adenocarcinoma subtypes (often to be characterized as “predominant”) in the revised classification are also included in the 2004 WHO classification. The micropapillary subtype is new to the revised classification owing to significant research conducted in recent years indicating that it is an important variant associated with aggressive growth and poor prognosis, even when representing only a relatively small percentage of total tumor volume (40). The solid adenocarcinoma subtype, more common than micropapillary adenocarcinoma, is also associated with aggressive growth and poor patient outcome (20).

The precision required in the revised adenocarcinoma classification to parse lung tumor surgical resection specimens in 5% increments stands in marked contrast to the

imprecise small cell/NSCLC dichotomy that has been commonly used by surgical pathologists with poorly differentiated small biopsies to determine suitability for surgical intervention. The revised classification specifically provides that “NSCLC be further classified into a more specific histologic type, such as adenocarcinoma or squamous cell carcinoma, whenever possible” (11). When such a determination is not possible with light microscopy alone, as has often been the case with many poorly differentiated lesions, “special studies” are recommended, such as the use of immunohistochemical staining for the markers TTF-1 (positive for lung adenocarcinoma in 75–85% of cases) and p63 (generally positive for squamous cell carcinoma) (11).

While immunohistochemical testing can provide greater certainty when analyzing poorly differentiated small biopsy specimens, it cannot alone resolve the problem of overall tumor heterogeneity, which requires more diffused tumor sampling from larger specimens. Even when immunohistochemical staining is conducted to help clarify a histologic diagnosis, some tumors can evade accurate characterization in a small biopsy specimen. For example, approximately 0.4–4% of NSCLCs are adenosquamous carcinomas (41), which reflect the characteristics of both histological types of lung cancer. Small biopsy specimens pose a heightened risk of missing one histological type or the other that co-exist in such tumors (3).

The insistence on the part of the authors of the revised classification that surgical pathologists avoid whenever possible the generic NSCLC classification in favor of an adenocarcinoma/squamous cell carcinoma distinction stems from recent advances in the treatment of lung adenocarcinoma that require a clearer diagnosis as their starting point (20). Such treatments include the folate antimetabolite pemetrexed and the monoclonal antibody bevacizumab for cases of advanced adenocarcinoma. Prior to the use of these drugs, however, a diagnosis of squamous cell carcinoma must be excluded to help ensure treatment efficacy (pemetrexed, when used with cisplatin) and to avoid possible fatal hemorrhaging (bavacizumab) (3, 20).

Other advances in the treatment of adenocarcinoma are based on the presence of so-called genetic “driver mutations” or chromosome rearrangements identified when molecular testing is conducted on tumor specimens. Driver mutations are those “that confer a selective growth advantage to the tumor cell,” and are to be contrasted with so-called “passenger mutations,” which have no apparent effect on the neoplastic process (2). In their review from 2013, VOGELSTEIN *et al.* (2) provided information on approximately 140 driver mutations revealed in all types of human cancers. A typical tumor contains two to eight driver mutations that can affect as many as 12 key cellular signaling pathways. Reported genetic alterations for lung adenocarcinoma include: *EGFR* (32, 42–47), *KRAS* (42, 48–52), *BRAF* (53–56), and *ERBB2* (formerly *HER2*) (45, 56–60) driver mutations; *ROS1* (32, 61–63), *KIF5b-RET* (32, 64, 65), and *EML4-ALK* rearrangements (20, 45, 57, 61, 66–70); and other gene amplifications (20).

An estimated 50% of lung adenocarcinomas in patients in Western populations have either an *EGFR* or *KRAS* driver mutation (42). The two mutations are mutually exclusive (52). In approximately 30–40% of patients with adeno-

carcinoma a driver mutation has not been identified (20), which leaves substantial room for the development of additional targeted treatments for these tumors.

Some of the early studies of *EGFR* mutations in lung adenocarcinoma seemed to indicate that such mutations occurred almost exclusively in nonsmoking Asian women (47, 71–73). That initial impression has given way to more recent data demonstrating that *EGFR* mutations are not so narrowly confined and that they also commonly occur in male smokers from Western countries (74, 75).

While the frequency of identifiable driver mutations in lung adenocarcinoma varies substantially from one study to the next (75–77), those tumors that do test positive for *EGFR* and some other less frequent driver mutations can often benefit significantly from treatment with tyrosine kinase inhibitors, such as erlotinib, gefitinib, and afatinib (20). Tumors containing an *ML4-ALK* rearrangement tend to respond to crizotinib treatment. The targeting of *EGFR* mutations with tyrosine kinase inhibitors represents one of the most important non-surgical advances in lung cancer treatment discovered to date. These therapies appear promising with respect to eventually improving overall five-year survival rates for lung cancer, which have stalled at around 15% for many years (77). Similar therapies for *KRAS* and other driver mutations in lung adenocarcinoma are at present the focus of extensive study (78). While targeted therapies for squamous cell carcinoma have lagged when compared to adenocarcinoma, research proceeds on this front, as well (3, 35).

The revised adenocarcinoma classification cautions that “when morphology or immunohistochemical findings are equivocal, pathologists need to keep in mind that a diagnosis of squamous cell carcinoma or NSCLC, favor squamous cell carcinoma, will exclude [patients] from histologically driven molecular testing or chemotherapy” (11). Clearly, absent a definite showing of squamous cell carcinoma, a diagnosis of adenocarcinoma is currently favored, owing to the enhanced treatment options now possible for an important subset of this lung cancer cell type compared to squamous cell carcinoma.

ADENOCARCINOMA SUBTYPES, DRIVER MUTATIONS, AND SMOKING

The diagnosis, treatment, and analysis of lung cancer, particularly adenocarcinoma, has progressed over time from a focus on major histological type (small cell, squamous cell, large cell, adenocarcinoma) to adenocarcinoma subtypes (AIS, MIA, lepidic, acinar, papillary, micropapillary, and solid) including genetic driver mutations, such as *EGFR*, *ALK* and *KRAS* (20). In fact, the analysis of adenocarcinoma subtypes and driver mutations now occurs simultaneously in some studies (79). This progression represents a logical refinement in human understanding of lung cancer, as articulated by VOGELSTEIN and KINZLER (18): “The revolution in cancer research can be summed up in a single sentence: cancer is, in essence, a genetic disease”. Consequently, an in-depth understanding of the complex mechanisms that give rise to lung cancer must decipher the changes in the genome that occur over time in the progression from non-cancerous cells

to frank carcinoma and the relative roles of endogenous and exogenous factors in that process. In light of the prominent role cigarette smoking plays in the development of lung cancer generally, some recent research has examined the association between adenocarcinoma histological subtypes and smoking, progressing thereafter to an analysis of the link between specific driver mutations, adenocarcinoma subtypes, and smoking. The following discussion provides a sample of the papers published in this area.

Adenocarcinoma histological subtypes

Specific lung adenocarcinoma subtypes are associated to a greater or lesser extent with smoking. For example, MAEDA *et al.* (80) analyzed 320 smoking and nonsmoking patients with stage I lung adenocarcinoma that was surgically resected in 2004–2006 at a cancer treatment center in Kashiwa, Chiba, Japan. They analyzed histological subtypes in each resection specimen according to the WHO classification (38), and included reference to all subtypes composing 10% or more of each specimen. Those patients with a solid tumor component had poorer three-year survival than patients with BAC, acinar and papillary tumor components. Smoking was significantly associated with the presence of a solid tumor component and not associated with BAC (now AIS or MIA, as discussed above). Acinar and papillary tumor components were less associated with smoking than a solid component.

SAKAO *et al.* (81) reported a negative correlation between amount of cigarette smoking and the presence of a BAC tumor component in a group of 121 patients with small (< 2 cm) lung adenocarcinomas, using a modified version of the 2004 WHO adenocarcinoma classification that included (i) BAC, (ii) adenocarcinoma with little or no BAC component, and (iii) mixed BAC with other adenocarcinoma histological subtypes. Twenty-seven percent of patients with BAC were smokers; 43.2% of patients with mixed BAC and other adenocarcinoma subtypes were smokers; 74.6% of patients with little or no BAC component were smokers. The difference between the BAC group and little/no BAC group was statistically significant.

HU *et al.* (82) analyzed 1,015 lung adenocarcinomas for driver mutations according to the IASLC/ATS/ERS classification and correlated these data with clinico-pathological characteristics. The results indicate that 83.1% of patients with lepidic predominant, 71.3% with acinar predominant, 66.5% with papillary predominant, and 70.8% with micropapillary predominant adenocarcinoma were never-smokers. Smoking was, however, significantly associated with the presence of a solid tumor component. Based on the studies of MAEDA *et al.* (80), SAKAO *et al.* (81), HU *et al.* (82), and MIYOSHI *et al.* (83), smoking is consistently associated with the solid predominant subtype but not with the other subtypes. Table 2 provides a sample of those studies that have examined the relationship between adenocarcinoma histological subtypes and smoking. Apart from an association or lack of association with smoking, determination of adenocarcinoma subtypes in a tumor specimen is important for determining patient prognosis, as initially demonstrated in 1995 by NOGUCHI *et al.* (37).

Table 2. IASLC / ATS / ERS lung adenocarcinoma histological subtypes and their association with smoking.

IASLC / ATS / ERS revised lung cancer classification	Not associated with smoking	Associated with smoking
<i>Preinvasive lesions</i>		
• Atypical adenomatous hyperplasia		
• Adenocarcinoma <i>in situ</i>	(80)	
<i>Minimally invasive lesions</i>		
• Minimally invasive adenocarcinoma	(80, 92)	
<i>Invasive lesions</i>		
• Lepidic predominant	(82)	
• Acinar predominant	(80, 82)	
• Papillary predominant	(80, 82)	
• Micropapillary predominant	(82, 83)	
• Solid predominant		(80, 82, 83)

Driver mutations

LI *et al.* (77) examined adenocarcinoma histological subtypes and the presence or absence of six “well identified” driver mutations in a cohort of 230 Chinese lung cancer patients, all current or former smokers. The driver mutations/rearrangements analyzed were *EGFR*, *KRAS*, *BRAF*, *HER2*, *EML4-ALK* rearrangement, and *PIK3CA*. These researchers reported that 43.5% of patients had an *EGFR* mutation, 16.5% a *KRAS* mutation, 3.5% a *PIK3CA* mutation, 3.0% a *BRAF* mutation, and 3.0% an *EML4-ALK* rearrangement. No *HER2* mutations were detected in the patient population. Approximately one-third of resected tumors had none of the six driver mutations, with 80% of these patients having a smoking history of more than 20 pack-years. All eight *PIK3CA* mutations occurred concurrently with either *EGFR* or *KRAS* mutations. All other driver mutations were mutually exclusive. *EGFR* mutations were associated with the presence of micropapillary, lepidic, and papillary predominant adenocarcinoma subtypes. *EGFR* was negatively associated with the solid predominant subtype. Other studies have also indicated that *EGFR* mutations are associated with the absence of a solid tumor component and never-smoking status (79, 80, 82, 84). *EGFR* mutations were significantly more frequent among smokers of 20 pack-years or less, as well as patients aged 60 years or more. Nonetheless, among patients with smoking histories of 31–40, 41–50, and > 50 pack-years, 39.1%, 30.4%, and 15.1%, respectively, had *EGFR* mutations. While *KRAS* mutations were associated with a smoking history greater than 20 pack-years, the tumors resected from almost 10% of patients with smoking histories of 10 pack-years or less had *KRAS* mutations. DOGAN *et al.* (42) examined the frequency of *EGFR* and *KRAS* mutations among 3,026 patients treated for adenocarcinoma at Memorial Sloan-Kettering Cancer Center in 2004–2009. 20% of the patients (593) tested positive for *EGFR* mutations, while 26% (670) tested positive for *KRAS* mutations. *EGFR* mutations were

detected in 43% of never-smokers (352 of 828) and 11% of former or current smokers (241 of 2,198); *KRAS* mutations were found in 34% of former or current smokers (627 of 1,860) and 6% (43 of 669) of never-smokers. *EGFR* mutations among smokers were most common for those with less than a 10 pack-year smoking history. Among smokers with a 10 pack-year smoking history or less, *EGFR* mutations were more common than *KRAS* mutations. The authors observed that “[a]lthough typically seen in the absence of smoking history, a significant minority (11%) of former and current smokers harbor *EGFR*-mutated tumors, arguing against excluding smokers from *EGFR* testing.” Notably, the authors also described *EGFR*-mutated tumors as “non-smoking associated cancers.” They concluded, “our observations strengthen the notion that careful consideration of histologic subtypes (focusing on adenocarcinoma instead of mixing all lung cancer types) and molecular subtypes defined by distinct, nonoverlapping driver mutations (*EGFR*, *KRAS*) can help to clarify epidemiologic associations that may otherwise remain elusive. This approach, which recognizes the possible etiologic diversity represented by different histologic and molecular subtypes, has recently been termed molecular pathological epidemiology.”

The studies of LI *et al.* (77) and DOGAN *et al.* (42) characterize the frequency of driver mutations in two distinct populations: Chinese and Western patients, respectively. Most studies conducted to date have demonstrated a higher rate of *EGFR* mutations among Asian patients than Western patients, and these studies are consistent with those findings. Nonetheless, the LI and DOGAN studies, among others (42, 45, 57, 77, 85, 86), establish that a significant number of smoking patients harbor *EGFR* mutations in their tumor specimens. These findings stand in contrast to those reported in some of the early *EGFR* studies (47, 71–73), which seemed to indicate that an *EGFR* mutation occurred exclusively in nonsmokers. Table 3 provides a sample of those studies that have examined the relationship between specific driver mutations/ rearrangements and smoking.

Table 3. Driver mutations / rearrangements and their association with smoking.

Driver mutations / rearrangements	Not associated with smoking	Associated with smoking
<i>EGFR</i>	(32, 42–47)	
<i>KRAS</i> transition	(42, 48, 50)	
<i>KRAS</i> transversion		(42, 48, 50)
<i>BRAF</i>		(55, 56)
<i>BRAF</i> V600E	(54)	(53)
<i>BRAF</i> NON-V600E		(53, 54)
<i>ERBB2</i>	(45, 56–60)	
<i>EML4-ALK</i>	(45, 57, 61, 66, 68–70)	
<i>ROS1</i>	(32, 61–63)	
<i>RET</i>	(32, 64, 65)	

Lung cancer in a smoker is not inherently different from lung cancer in a nonsmoker

Numerous researchers in recent years have asserted that lung cancers diagnosed in smokers and never-smokers represent inherently different diseases (32). For example, THU *et al.* (75) have written that “[i]t is a well established concept that lung tumors in smokers and NS are distinct disease entities”. Such statements appear to be based on early trials of *EGFR* mutations and tyrosine kinase inhibitor treatment that seemed to indicate that these mutations occurred almost exclusively in never-smokers (47, 71–73), while *KRAS* mutations are more common in current and former smokers. Smoking status is not, however, the important distinguishing factor in these cases, as *EGFR* and *KRAS* mutations commonly occur in both smokers (42, 48, 77) and nonsmokers and are at the same time mutually exclusive (52). The key distinction is that *EGFR* mutations, even when identified in current or former smokers, are not caused by smoking (20, 87), while two different *KRAS* mutations – one associated with smoking, the other not associated with smoking – have been identified in the published literature.

In a study of *KRAS* mutations in 482 smokers and never-smokers, RIELY *et al.* (50) reported that “[n]ever smokers were significantly more likely than former or current smokers to have a transition mutation (G > A) rather than the transversion mutations known to be smoking-related (G > T or G > C; P < 0.0001) ... Based on our data, *KRAS* mutations are not rare among never smokers with lung adenocarcinoma and such patients have a distinct *KRAS* mutational profile”. A number of other studies have reported similar results (42, 48–50).

On the other hand, several statements in the published literature by researchers examining adenocarcinoma histological subtypes and driver mutations support the conclusion that *EGFR*, *ALK* and other less common driver mutations are not part of a causal pathway influenced by smoking. The quotation by DOGAN *et al.* (42) noted in the preceding section on page 304 is important in this respect: “[C]areful consideration of histologic subtypes ... and ... driver mutations (*EGFR*, *KRAS*) can help to clarify ... the possible etiologic diversity represented by different histologic and molecular subtypes”. This statement is supported by the data presented by DOGAN *et al.* (42), who reported that 11% of smokers in their study population of over 3,000 patients tested positive for *EGFR* mutation. The authors explicitly describe *EGFR*-mutated adenocarcinomas as “nonsmoking-associated cancers.” Consequently, the tumors diagnosed in the 11% of smokers in the study of DOGAN *et al.* (42) that had *EGFR* mutations were not caused by smoking, according to these researchers, despite the patients’ smoking histories.

This same research group from Memorial Sloan-Kettering Cancer Center (88), analyzing a later cohort of 675 lung adenocarcinoma patients treated in 2009–2010, found that the driver mutation – either *EGFR*, *ALK* or *KRAS* – not smoking status, determined favorable response to tyrosine kinase inhibitor treatment and overall survival benefit. According to the authors,

we observed no significant differences in the [overall survival] of never-smokers and former/current smokers who had identical genotypes. ... We note that former/current smokers with *EGFR* mutations and *ALK* arrangements in our analysis were not light tobacco consumers, with median pack-years smoked of 18 and 15, respectively. These data are particularly compelling when placed beside those from recent whole genome sequencing of smoking-related lung adenocarcinoma tumor, suggesting that high somatic mutation rate caused by smoking may not substantially alter the course of tumors driven by certain oncogenes, such as *EGFR* and *KRAS*.

PAIK *et al.* (88) concluded,

our data demonstrate that never smokers and former/current smokers with lung adenocarcinomas are not homogenous subgroups. Each group is made up of individuals with a set of disparate mutations that, in sum, generates an overall prognosis. Never-smokers carry a higher proportion of *EGFR* mutations, but this should not lead to reflexive treatment of never smokers with *EGFR* TKIs. All patients with lung adenocarcinoma, regardless of smoking history, should undergo testing for *EGFR* mutations...

In a recent review of the IASLC/ERS/ATS/ revised adenocarcinoma lung cancer classification, KERR (20) provided perhaps the clearest statement concerning *EGFR* mutations, adenocarcinoma causation, and smoking to be found in the published literature:

With the exception of *KRAS* mutation, and probably *MET* amplification, those other mutations shown in figure 3 [*EGFR*, *ROS1*, *KIF5B-RET*, *HER2*, *BRAF*, *ALK*] are unrelated to tobacco carcinogenesis. While these mutations are much [sic] common in never-smokers with adenocarcinoma, there is no known reason why a tobacco smoker should be any less likely than a never-smoker to develop such a tumour. The causes and risk factors for these mutations are unknown. If adenocarcinoma testing is limited to non-smokers, up to half of *EGFR* mutations will be missed. The higher levels of *EGFR* mutation observed in adenocarcinomas in women and those of East Asian ethnicity at least in part reflects a population in which smoking is uncommon and therefore, adenocarcinomas with these driver mutations are less diluted by tobacco carcinogen induced cases, as may be seen in a European patient cohort.

STAAL *et al.* (36) conducted an extensive analysis of gene expression in lung adenocarcinomas diagnosed in both smokers and never-smokers. They found substantial overlap between the two groups. The authors observed,

although lung cancer in never-smokers has been suggested to represent a different disease entity compared to cancers arising in smokers, numerous reports of gene expression derived AC [adenocarcinoma] subtypes have reported consistent lack of a never-smokers’ or a never-smoker predominant AC subtype.

They continued,

results from the current study in combination with previous reports on different AC subtypes indicate that never-smokers cannot be completely separated from smokers based on transcriptional differences, and consequently, that AC arising in never-smokers do not appear to represent a distinct entity based on transcriptional patterns. Instead, this may suggest a shared biology between AC arising in never-smokers and in a subgroup of smokers, the latter thus perhaps representing tumors that arose in smokers “by chance”, i.e., possibly independent/or less dependent of a positive smoking history, which warrants further investigation.

In a subsequent publication (89), this same Swedish research group observed that “the genomic and transcriptional landscape of lung adenocarcinomas of smokers and never-smokers is not . . . distinct, and that there are common mechanism[s] in the tumorigenesis in never-smokers and smokers.”

They concluded that

[a]lthough smoking increases the overall incidence of lung cancer, tumors unrelated to smoking can still occur in heavy smokers as smoking does not prevent the incidence of such cancers.

YANO *et al.* (87), in a review paper examining lung cancer among never-smokers, made the following observation:

Tobacco smoking remains the predominant risk factor for the occurrence of lung cancer. On the other hand, recent interest in lung cancer in patients without a history of tobacco smoking has led to the classification of a distinct disease entity of “nonsmoking-associated lung cancer”. . . . Non-smoking associated lung cancer does not only occur in never smokers, but also in current and former smokers. However, in order to investigate the etiology and clinical features specific to “non-smoking-associated lung cancer”, it is best to examine the tumors present only in never smokers.

Finally, researchers from Singapore recently conducted whole-genome sequencing of 30 Asian lung cancer specimens (90). The authors concluded that

[a]lthough patients self-reported as smokers or ex-smokers, the molecular signature of a subgroup of patients with smoking history resembles that of never-smokers, despite having cigarette consumption similar to the smokers with the “smoker-only” signature. . . . Thus, a higher fraction of the ex-smokers/smokers in the “never-smoker-like” group carry a driver mutation in *EGFR*. This raises the possibility that people who smoke or have a smoking history may have a driver mutation, and regardless of smoking status, have the never-smoker-like signature.

To summarize, specific adenocarcinoma histological subtypes and driver mutations, not individual smoking

history, reflect the primary causal mechanisms implicated in the development of any given lung adenocarcinoma (35).

IMPLICATIONS OF EVOLVING SCIENCE ON LUNG ADENOCARCINOMA IN SMOKING-AND-HEALTH LITIGATION

Plaintiffs in smoking-and-health litigation invariably assert that smoking was the cause of an individual’s lung cancer based on numerous published epidemiologic studies demonstrating a consistent association between smoking and all major histological types of lung cancer. Unlike U.S. litigation, however, most European courts have been reluctant to compel plaintiffs to produce complete historical medical records to support their claims, reasoning that plaintiffs shoulder both the burden of proving their claims and the risk of failing to do so should they produce inadequate evidence that smoking caused their disease. Some courts have cited a plaintiff’s right to privacy to support such decisions.

Defendants counter plaintiffs’ claims by contending that epidemiology, a population-based assessment of disease risk factors, cannot alone sustain a claim for individual injury. They insist that the court focus instead on smoker-specific medical issues and possible alternative lung cancer risk factors apparent in the smoker’s social, employment, and residential histories. While the possibility always exists that a smoker’s lung cancer was metastatic from a distant site to the lung rather than a lung primary – the lungs are the most common destination for metastatic disease (91) – such cases have been uncommon in European litigation. Plaintiffs invariably have the upper hand in establishing lung cancer causation when a court fails to order production of complete medical records and employment and residential histories because the only lung cancer risk factor that is adequately supported by the record in such cases is cigarette smoking.

Currently evolving medical science examining adenocarcinoma histological subtypes, driver mutations, and smoking could alter the medical causation status quo in smoking-and-health litigation in Europe and other jurisdictions where the production of medical records and diagnostic and treatment materials is often not mandated. Among the currently recognized lung adenocarcinoma histological subtypes, only the solid predominant variant demonstrates a consistent association with smoking (80–84). According to MIYOSHI *et al.* (83), “[i]t is well established that less differentiated adenocarcinomas are related to smoking, tobacco carcinogens producing tumors with solid growth.” The three lepidic subtypes: adenocarcinoma *in situ* (92), minimally invasive, and lepidic predominant adenocarcinoma are not associated with smoking, an observation consistent with the negative association between smoking and bronchioloalveolar carcinoma (BAC) (81), an adenocarcinoma subtype from the WHO 2004 classification that roughly encompasses the three lepidic subtypes in the revised classification. The recently recognized subtype micropapillary predominant adenocarcinoma, despite its aggressive nature, is also not associated with smoking according to recently published studies (82, 83). Both acinar- and papillary predominant

adenocarcinoma have also been shown to be negatively associated with smoking (80, 82).

Of potentially even greater import due to its application to small biopsy specimens, rapidly expanding testing of driver mutations for purposes of patient treatment could provide enhanced insight in some cases as to whether smoking was part of the causal mechanism of disease. The published literature has now established that specific driver mutations, particularly *EGFR* and *ALK*, are not associated with cigarette smoking (69), even when detected in smokers. Only *KRAS* transversion mutations and possibly one type of *BRAF* mutation are associated with smoking among currently recognized driver mutations for adenocarcinoma (Table 3). Moreover, 40–50% of lung adenocarcinomas do not test positive for any of the currently recognized driver mutations, leaving open the possibility that additional driver mutations not linked to smoking will be identified in the coming years (85).

The increasing availability of lung adenocarcinoma histological subtype and genetic information in smoking-and-health litigation provides both opportunities and risks for plaintiffs and cigarette manufacturers. Plaintiffs who choose to grant access to lung cancer biopsy or surgical resection materials could in some cases more firmly establish the role of smoking in the development of disease. A histological evaluation demonstrating solid predominant adenocarcinoma would tend to support the role of smoking in the development of a given tumor. A similar inference could be drawn in the case of a positive finding of a *KRAS* transversion mutation in a patient with lung adenocarcinoma and a significant smoking history. In fact, in the only judicial decision of its kind rendered to date in Europe, an Italian appellate court in the *Stalteri* case ruled in favor of appellants, the heirs of a deceased smoker, after a panel of court-appointed experts concluded that a positive finding for a *KRAS* codon 12 mutation in the decedent smoker's lung tumor specimen proved that the tumor was caused by smoking.

On the other hand, several histological subtypes of adenocarcinoma are not associated with smoking, including AIS, MIA, and micropapillary predominant. The presence of these subtypes in a surgical resection specimen would tend to support the defense case in many instances. *EGFR* amplifications or mutations and *ALK* rearrangements are also not associated with smoking, even when identified in smokers. Both plaintiffs and defendants will need to carefully assess the relative strengths and weaknesses of their respective cases prior to determining whether histological subtyping, when possible, or genetic testing represents a potential advantage.

In cases seemingly posing the greatest uncertainty or risk of an adverse finding, plaintiffs and defendants might attempt to enter into a confidentiality agreement prior to testing so that either party can privately conduct the testing it deems appropriate without divulging the results unless they prove helpful. Such agreements have been forged by U.S. litigants in the past. In any event, a presiding court in most jurisdictions would have to approve (i) the parties' access to lung cancer histology or cytology, (ii) destructive testing, and (iii) the parties' intentions concerning use or withholding of testing results.

Even with plaintiffs' agreement, some courts might be

unwilling to permit such testing, particularly if the issue of ownership of pathology specimens has never been addressed in a given jurisdiction. In some cases litigated in the United States, for example, hospitals that retain pathology specimens following surgery or biopsy have proven reluctant to release them for such testing, arguing that the specimens are property of the hospital and not the plaintiff. One of the most difficult challenges for plaintiffs and defendants going forward will be to educate the courts hearing smoking-and-health cases about the potential importance and interpretation of adenocarcinoma histological subtypes and driver mutations for causal determinations.

While the medical and scientific issues addressed herein could play an increasingly important role in international smoking-and-health litigation, most cases to date have been decided in defendants' favor based on judicial findings that (i) the smoker was aware of the risks of smoking and chose to smoke despite those risks, and (ii) smokers can quit smoking when sufficiently motivated. These defenses will likely predominate for the foreseeable future.

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