Carcinoma of the Lung

7

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7.1 Introduction

During the past 50 years, the USA and other industrialized nations have witnessed a remarkable increase in mortality from carcinoma of the lung. Today, this disease is the number one cause of cancer mortality in the USA, accounting for more than 180,000 deaths annually [1]. Unraveling the various causes of this increased risk has required painstaking epidemiologic studies, but it has become apparent that cigarette smoking is the single largest preventable cause of lung cancer in the world today [2]. It has been estimated that between 85 and 95 % of deaths from lung cancer are directly attributable to smoking [1, 2]. Cigarettes are the leading offenders, but pipe and cigar smokers are also at risk, though only if they inhale the smoke [1–3]. Asbestos workers are also at increased risk for lung cancer, particularly those who smoke tobacco products [4, 5]. It is the purpose of this chapter to review the characteristics of asbestos-associated lung cancers and to discuss the role of the pathologist in recognizing asbestos as a causative factor. The historical context in which asbestos was recognized to be a carcinogen for the lower respiratory tract will first be reviewed, followed by a discussion of the epidemiologic features of asbestos-related lung cancer, including the role of asbestosis, synergism with cigarette smoking, and asbestos fiber type. The role of cytopathology in the diagnosis of lung cancer in asbestos workers is discussed in Chap. 9, experimental models of pulmonary carcinogenesis in Chap. 10, and lung fiber burdens in asbestos workers with lung cancer in Chap. 11.

7.2 Historical Background

The first report of carcinoma of the lung in an asbestos worker was that of Lynch and Smith in 1935, a squamous carcinoma in a patient with asbestosis [6]. In 1943, Homburger reported three additional cases of bronchogenic carcinoma associated with asbestosis, bringing the world total reported to that date to 19 cases [7]. In his annual report for 1947 as chief inspector of factories in England and Wales, Merewether noted that among 235 deaths attributed at autopsy to asbestosis, 13 % had a lung or pleural cancer [8]. During the 20-year period following Lynch and Smith's initial case report, some 26 reports were published covering approximately 90 cases of carcinoma of the lung found at autopsy in asbestos workers [9]. Then in 1955, Sir Richard Doll published his classic study, which was the first systematic combined epidemiologic and pathologic study of lung cancer among asbestos workers [10]. Doll concluded that carcinoma of the lung was a specific industrial hazard of asbestos workers. Also in 1955, Breslow published a

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case-control study of asbestosis and lung cancer from California hospitals [11]. In 1968, Selikoff published data from a cohort of asbestos insulation workers which showed that insulators who smoked had a 92-fold increased risk of carcinoma of the lung over non-asbestos-exposed, nonsmoking individuals [12]. This was also the first study to suggest that there is a multiplicative, or synergistic, effect between cigarette smoking and asbestos exposure in the production of pulmonary carcinomas. Buchanan noted that more than half of all patients with asbestosis would eventually die of respiratory tract cancer [13]. Since these pioneering studies, there have been numerous reports confirming the association between asbestos exposure and carcinoma of the lung [14–23].

7.3 Epidemiology

7.3.1 Asbestos or Asbestosis?

Epidemiologic studies have demonstrated a dose-response relationship between asbestos exposure and lung cancer risk, and there is a long latency period between initial exposure and manifestation of disease, usually beginning more than 15 years after initial exposure [4, 5, 9, 19]. There are three primary hypotheses that have been put forward to describe the relationship between asbestos exposure and lung cancer risk [24]. The first hypothesis [H1] is that there is only an increased risk of lung cancer in asbestos workers who also have asbestosis. The second hypothesis [H2] is that it is the dose of asbestos rather than the occurrence of fibrosis that is the determinant of lung cancer risk. The third hypothesis [H3] is that there is a no threshold, linear dose-response relationship between asbestos exposure and subsequent lung cancer risk, with any level of exposure potentially increasing one's risk of disease. Whether or not there is a threshold for asbestos-induced carcinoma of the lung and whether or not asbestosis is a prerequisite precursor lesion are issues of more than academic importance [25], since the number of individuals exposed to low levels of asbestos greatly exceeds the numbers of individuals with asbestosis.

All investigators are in agreement that there is a dose-response relationship between asbestos exposure and lung cancer risk [26, 27] and that the highest risk occurs among those workers who also have asbestosis. Proponents of [H1] believe that only those with asbestosis have an increased lung cancer risk [28–32]. In the original study by Doll [10], all 11 of the asbestos workers dying of carcinoma of the lung had pathologically confirmed asbestosis. Furthermore, in the review by An and Koprowska of asbestos-associated carcinoma of the lung reported from 1935 to 1962, all 41 cases occurred in individuals with asbestosis [33]. Published mortality data reveal a close correlation between relative risks of death from lung cancer and from asbestosis [14, 16, 34–39]. In addition, a longitudinal study of Quebec chrysotile miners indicated that most of the observed cancers have occurred in subgroups of workers with prior radiographic evidence of asbestosis [40].

Further support for this hypothesis includes studies of Louisiana asbestos-cement workers, South African asbestos miners, insulators, and individuals with non-asbestos-related interstitial lung disease. The Hughes-Weill study of 839 asbestos-cement workers found a statistically significant increased risk of lung cancer among workers with radiographic evidence of asbestosis (International Labor Organization score $\geq$1/0), but not among those with pleural disease only or with no radiographic abnormality [19]. Sluis-Cremer and Bezuidenout reported on an autopsy study of 399 amphibole miners, in which increased lung cancer rates were observed in cases with pathologic asbestosis, but not in those lacking asbestosis [41]. Kipen et al. studied 138 insulators with lung cancer and tissue samples available for histologic review and found evidence for asbestosis in all 138 cases [42]. In addition, there is an increased risk of lung cancer among patients with interstitial lung disease other than asbestosis [43–45].

There are a number of weaknesses in the hypothesis that asbestosis is a prerequisite for asbestos-induced lung cancer. First of all, the Hughes et al. [19] study lacks the statistical power to detect an increased risk of lung cancer among patients without radiographic

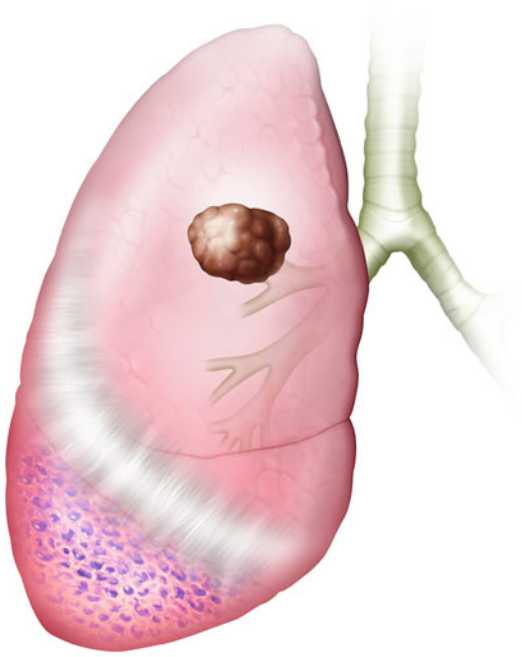

Fig. 7.1 Artist's rendering of the location of the typical lung cancer in an asbestos worker (central and upper lobe) versus the location of fibrosis in most cases of asbestosis (peripheral lower lobe). This distribution of disease is difficult to reconcile with the hypothesis that fibrosis is the precursor of asbestos-induced lung cancers

evidence of asbestosis [46]. Second, the studies by Sluis-Cremer and Bezuidenout [41] and Kipen et al. [42] have unconventional definitions for the histologic diagnosis of asbestosis [47, 48]. For example, the Kipen study diagnosed asbestosis in eight cases lacking asbestos bodies in histologic sections [42]. Third, the rates of lung cancer among individuals with asbestosis (from 40 % to more than 50 %) are much higher than the rates in cases with idiopathic pulmonary fibrosis (pooled estimate from 14 studies of 17 %) [45]. Notably, patients with idiopathic pulmonary fibrosis usually die of their disease in 3–5 years from the time of diagnosis as compared to patients with asbestosis who frequently live decades. Thus, it is not too surprising that patients with idiopathic pulmonary fibrosis develop less cancer as they have much less time to develop cancer than patients with asbestosis. Fourth, the vast majority of lung cancers among asbestos workers are bronchogenic carcinomas not distinguishable on the basis of their morphology or histologic features from those occurring in nonexposed smokers and not the peripheral adenocarcinomas typically associated with diffuse interstitial fibrosis. It is difficult to reconcile the requirement for the peripheral fibrosis of asbestosis with the proximal bronchogenic carcinomas seen in the majority of asbestos workers (including those with asbestosis) (Fig. 7.1) [49]. Finally, it is difficult to explain the synergistic effect between asbestos exposure and cigarette smoking in lung cancer induction on the basis of [H1] [25].

Proponents of [H2] believe that lung cancer and asbestosis are independent manifestations of asbestos exposure, each following a dose-response relationship with exposure. Hence, both diseases are likely to occur among individuals with the heaviest exposures. Accordingly, it is the dose of asbestos rather than the development of fibrosis per se that is the determining factor. Asbestosis is not invariably present in cohorts of asbestos workers with a demonstrable excess risk of lung cancer [25, 40, 50, 51]. In addition, studies with greater statistical power than that of the Hughes et al. study [19] have shown an increased risk of lung cancer among asbestos workers without radiographic evidence of asbestosis [52–55]. Furthermore, studies have shown an increased risk of lung cancer based on the fiber burden within the lung, independent of asbestosis and cigarette smoking [56, 57]. For example, Karjalainen et al. studied 113 surgically treated male lung cancer patients versus 297 autopsy cases on males as referents [57]. For subjects with amphibole fiber counts exceeding one million/g of dry lung, the adjusted odds ratio was 4.0 for adenocarcinoma and 1.6 for squamous cell carcinoma. The odds ratio for a lower-lobe carcinoma was 2.8 for patients with a fiber count between one and five million and 8.0 for those with fiber concentrations greater than or equal to five million/g of dry lung.

There are several weaknesses to the hypothesis that fiber burden rather than asbestosis is the primary determinant of lung cancer risk among asbestos workers. First, studies with an increased lung cancer risk but no radiographic evidence of asbestosis do not exclude the possibility that the patients actually had subclinical asbestosis that would have been detected histologically. Second,

it is difficult to reconcile the preferential association between fiber burden and a specific histologic type (i.e., adenocarcinoma) and location (i.e., lower-lobe tumors), when studies have not consistently shown an association between any histologic pattern or tumor location and asbestos exposure (see below). Third, there are few epidemiologic studies that have examined the relationship between fiber burden and lung cancer risk [58–60]. Finally, the fiber burden levels in patients without asbestosis did not have a statistically significant odds ratio for lung cancer in the Karjalainen study [57]. However, the study did show a trend from a low to a higher odds ratio with transition from an intermediate- to a higher-level fiber count. Furthermore, the odds ratio for adenocarcinoma did show a statistically significant elevation with fiber burden greater than one million, even when all cases with any fibrosis were excluded [46].

Proponents of [H3] believe that asbestos exposure rather than asbestosis is the key element in lung cancer induction by asbestos and that any level of exposure increases one's risk for cancer. Hence there is no threshold for asbestos exposure and increased lung cancer risk according to this hypothesis. In published cohorts with the steepest dose-response relationship, excess lung cancers were detected even in the groups with the very lowest level of exposure [34, 50]. Although some investigators have suggested that there is a threshold level of exposure to asbestos below which no excess deaths from carcinoma of the lung will occur [17, 61], investigation of the consequences of low-level exposures is the Achilles' heel of epidemiologic studies because it requires large cohorts followed for extended periods of time in order to detect statistically significant associations [62, 63]. Nonetheless, the consensus based on a number of cohort mortality studies as well as studies of populations with environmental asbestos exposure is that there is some level of exposure below which no statistical excess of lung cancers can be demonstrated [25, 64–72].

Experimental animal studies also bear on the issue of the mechanism of asbestos-induced carcinogenesis [25], and this subject is reviewed in detail in Chap. 10. It is the author's view that the literature in this regard indicates that fibrogenesis and carcinogenesis are separate and distinct effects of asbestos pathobiology, which have as a common denominator a dose-response relationship with respect to asbestos exposure and a dependence upon fiber length.

In summary, the weight of the evidence at this time seems to favor [H2]: asbestos-induced lung cancer is a function of fiber dose (and hence fiber burden) with a threshold for increased lung cancer risk [73, 74]. Therefore, in order to attribute a substantial contributing role for asbestos in the causation of lung cancer, asbestosis must be present clinically or histologically, or there should be a tissue asbestos burden within the range of values observed in patients with asbestosis [75] (see Chap. 11). The mere presence of parietal pleural plaques is not sufficient to establish causation (see Chap. 6) [76, 77]. Furthermore, studies have shown a very close correlation between fiber burden levels associated with an increased lung cancer risk and the presence of histologically confirmed asbestosis. A fiber burden in the range determined by Karjalainen et al. [57] to be associated with an increased lung cancer risk was found in 82 % of 70 cases with histologic asbestosis but in only 6 % of 164 cases without asbestosis [75]. Hence it is unlikely that the distinction between [H1] and [H2] can be resolved by epidemiologic studies [78].

7.3.2 Cigarette Smoking and Synergism

Epidemiologic studies have indicated that there is a synergistic effect between cigarette smoking and asbestos exposure in the production of lung cancer [5, 12, 79, 80]. This concept is well illustrated in the study by Hammond et al. [5] in which cancer mortality in 17,800 asbestos insulators was compared with cancer death rates in the general population. In this study, it was noted that cigarette smoking increases one's risk of lung cancer approximately 11-fold, whereas asbestos exposure increases the risk about fivefold, when compared to a nonsmoking, nonexposed reference population. If these two effects were merely

additive, one would expect an approximately 16-fold increase in lung cancer risk among cigarette-smoking asbestos insulators. Instead, what is actually observed is a 55-fold increased risk, indicating that the two effects are multiplicative rather than additive [5]. Other investigators have also indicated that the interaction between asbestos and cigarette smoke in increasing the lung cancer risk is a synergistic or multiplicative effect [14, 81–93]. Some studies have reported an additive effect [94, 95] or an effect that was intermediate between additive and multiplicative [80, 95, 96]. More recent studies favor a model that is more than additive and less than multiplicative [97–99]. Possible mechanisms for synergism are discussed in Chap. 10.

The US Surgeon General's report on the effects of smoking cessation on the risk of developing carcinoma of the lung indicates that ex-smokers have a risk which is intermediate between that of current smokers and nonsmokers [100]. The magnitude of the decrease in risk is related to a number of factors, including the age when the patient started smoking, total duration and intensity of smoking, the age at cessation of smoking, and the time elapsed since the individual quit smoking. In this regard, studies have indicated that the risk of developing lung cancer in an ex-smoker is still greater than that of a lifelong nonsmoker even 20 or more years after cessation of smoking [99, 100]. These factors must be considered in the evaluation of the role of asbestos exposure in the development of carcinoma of the lung in an ex-smoker.

Since most lung cancers among asbestos-exposed individuals occur in workers who also smoke, it is difficult to obtain information regarding the lung cancer risk among nonsmoking asbestos workers. Hammond et al. [5] reported four such cases among their asbestos insulators, with an expected value of 0.8, hence their calculation of a fivefold increase in risk among nonsmoking asbestos workers. Berry et al. [95]. reported four additional cases of lung cancer among nonsmoking asbestos factory workers. They concluded that after allowance had been made for the effect of smoking on lung cancer, the relative risk due to asbestos was highest for those who had never smoked, lowest for current smokers, and intermediate for ex-smokers ($p < 0.05$). More recently Berry and Liddell report that the relative risk due to asbestos was higher for light smokers than for heavy smokers [101]. Lemen [102] reported four more cases of lung cancer among nonsmoking women in a predominantly chrysotile asbestos textile plant.

The author has also observed 23 additional cases of lung cancer in nonsmokers with some history of asbestos exposure in which fiber burden analyses had been performed. Sixteen of these cases have been reported previously [75, 103]. Twenty of the twenty-three were adenocarcinomas, including 3 bronchioloalveolar carcinomas, 1 pseudomesotheliomatous carcinoma, and 1 adenosquamous carcinoma. The other three were large cell carcinoma, squamous cell carcinoma, and pleomorphic carcinoma. Two cases occurred in the setting of idiopathic pulmonary fibrosis (usual interstitial pneumonia), including one bronchioloalveolar carcinoma. Six of the patients had pleural plaques, including one pseudomesotheliomatous carcinoma. One patient with adenocarcinoma had asbestosis. Only the latter case of the 23 had a fiber burden within the range described by Karjalainen et al. as being associated with an increased odds ratio for lung cancer [57]. In a review of lung cancer in nonsmokers, no evidence for a role of asbestos was identified [104]. Carcinoma of the lung is quite rare among nonsmokers [105]. In such cases, one must consider other possible factors such as the effects of passive smoking [1, 106] and of household radon gas exposure [1, 107].

7.3.3 Role of Fiber Type and Fiber Dimensions

Epidemiologic data indicate that carcinoma of the lung may develop in response to exposure to any of the types of asbestos [4, 9, 14, 34, 85, 108]. However, there is considerable controversy regarding the relative potency of the various fiber types for the production of pulmonary neoplasms [25]. Individuals who believe that chrysotile is less potent as a lung carcinogen than the

amphiboles amosite and crocidolite cite as evidence the relatively low rate of carcinoma of the lung among chrysotile miners and millers [64, 109, 110], asbestos-cement workers [17, 111], and friction-product manufacturers [65, 66]. On the other hand, some chrysotile asbestos textile plants have reported extremely high lung cancer rates, with exceptionally steep dose-response curves [34, 36, 112]. Although it has been suggested that contamination of the asbestos fibers with mineral oil might explain the high rate of carcinoma of the lung among asbestos textile workers [9], the steep dose-response relationship among these workers also holds for asbestosis, which is difficult to explain on the basis of contaminating oil. One major difficulty for studies trying to assess the relative potency of asbestos fiber types is the inaccuracy of historical estimates of asbestos exposure [25, 113]. In this regard, Newhouse [114] noted that chrysotile textile plants were particularly dusty when compared with other types of occupational exposure to chrysotile. Furthermore, in comparing the cancer mortality for two different asbestos textile plants, Finkelstein concluded that the risk of death from asbestos-associated cancer in factories manufacturing similar products is unrelated to the type of asbestos fiber used [36, 112, 113].

The author suspects that much of the variation in lung cancer rates among chrysotile workers can be explained on the basis of dose and relative fiber size, with longer fibers being more potent. For example, the low rate of lung cancer among automotive maintenance and brake repair workers [115] can be explained on the basis of relatively low dust levels, the low proportion of asbestos in the dust generated, and the preponderance of very short chrysotile fibers in brake dust [116, 117]. The relative ability of fibers to penetrate the bronchial mucosa may also be an important factor. Churg and Stevens in a study of smokers and nonsmokers with similar exposure histories and similar fiber burdens in the lung parenchyma examined this question [118]. These investigators found that the amosite content was six times greater in the bronchial mucosa of smokers as compared to nonsmokers and the chrysotile content was 50 times greater. Thus there is evidence that cigarette smoking increases the penetration of fibers into the bronchial mucosa, and this effect appears to be greater for chrysotile than for the amphiboles.

The issue of relative potency of chrysotile versus amphiboles in lung cancer production has been addressed in great detail by Hodgson and Darnton [119] and Berman and Crump [120, 121]. The former concluded that the relative potency of amphibole fibers (amosite and/or crocidolite) as compared to chrysotile for lung cancer was between 10:1 and 50:1. The latter proposed a model for predicting risk of lung cancer based on fiber dimensions and fiber type, with amphiboles more potent than chrysotile and long fibers more potent than short. Recent studies of lung cancer in asbestos textile workers lend support to the importance of fiber length in this regard [122, 123]. Differences in relative potency of fiber types is reflected in levels of exposure associated with a doubling of the risk of lung cancer: 25 fiber/cc-yrs for amphibole exposure versus 40 fiber/cc-yrs for mixed exposures [73, 74].

7.4 Pathology of Asbestos-Related Carcinoma of the Lung

7.4.1 Gross Morphology

Lung carcinomas have been classically divided into the proximal bronchogenic carcinomas, which arise from a mainstem, segmental, or subsegmental bronchus and typically present as a hilar mass, and peripheral carcinomas, arising from small airways (i.e., bronchioles or peripheral bronchi) and presenting as a "coin" lesion on chest roentgenogram [124]. Asbestos-related lung cancers can assume either of these gross appearances. In fact, there are no discernible differences between the macroscopic appearance of carcinomas of the lung among asbestos workers and those in individuals not exposed to asbestos [29, 49, 124, 125]. One possible exception to this observation is the lobar distribution, with carcinomas among cigarette smokers from the general population occurring about twice as often in the upper as compared to the lower lobes,

Table 7.1 Tumor location in 312 lung cancer cases with and without asbestosis

	Asbestosis	PPP[a]	Others[b]
Upper lobe	26	45	78
Lower lobe	18	23	33
Right lung	36	52	91
Left lung	24	43	69

[a]*PPP* parietal pleural plaques, no evidence of asbestosis
[b]No evidence of asbestosis or plaques or uninformative cases

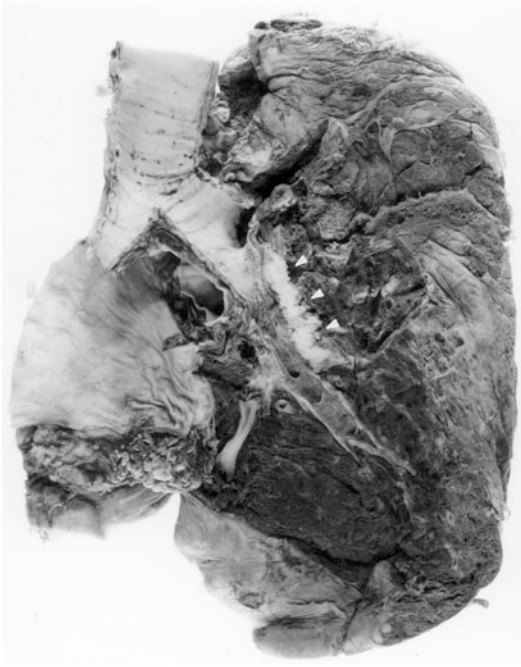

Fig. 7.2 Gross photograph showing infiltrating carcinoma involving the bronchus intermedius of the right lung (*arrowheads*). The patient was a guard in a plant which manufactured amosite pipe insulation for 7 years (Reprinted from Ref. [128], with permission)

whereas the reverse is true for carcinomas among asbestos workers [56, 57, 126]. However, more recent studies have failed to confirm this observation and have found instead that lung cancers in asbestos workers occur more commonly in the upper lobe (Table 7.1) [75, 127]. At any rate, the overlap is great enough that the lobar distribution is hardly sufficient to assign attribution to asbestos exposure in the individual case [75, 126].

Typical examples of carcinoma of the lung in asbestosis patients are illustrated in Figs. 7.2, 7.3, and 7.4. One shows a proximal bronchogenic

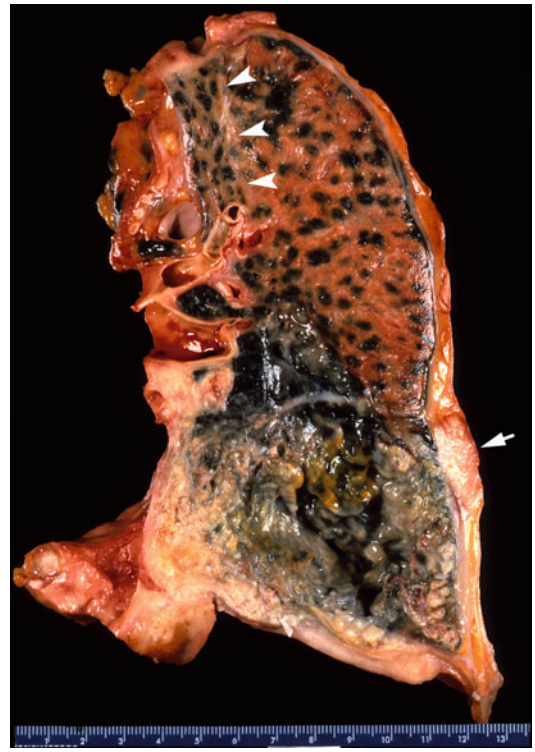

Fig. 7.3 Gross photograph showing a cavitating carcinoma of the right lower lobe (*arrow*). The patient was an asbestos insulator in a shipyard for 30 years (same case as Fig. 4.4). Radiation fibrosis is present in the medial aspect of the right upper lobe (*arrowheads*), and a few scattered silicotic nodules were also palpable in the right upper lobe

carcinoma (Fig. 7.2) from a Tyler asbestos plant worker who was a guard at the Tyler plant for 7 years and developed the neoplasm 21 years after initial exposure. This plant made pipe insulation material from amosite asbestos [128, 129]. The second example is a lower-lobe cavitating cancer (Fig. 7.3) from a shipyard insulator and boiler scaler for 30 years. The third example shows a massively enlarged hilar lymph node secondary to metastatic bronchogenic carcinoma (primary tumor not visible in the section). Very fine interstitial fibrosis was just visible to the unaided eye in the lower lobes (Fig. 7.4). This patient was admitted comatose and died shortly thereafter, without providing any occupational history; asbestosis was confirmed upon histologic examination. All three examples are squamous cell carcinomas (Fig. 7.5), and two of the individuals also smoked cigarettes (180 and 50 pack-years, respectively). The smoking history of the third is unknown.

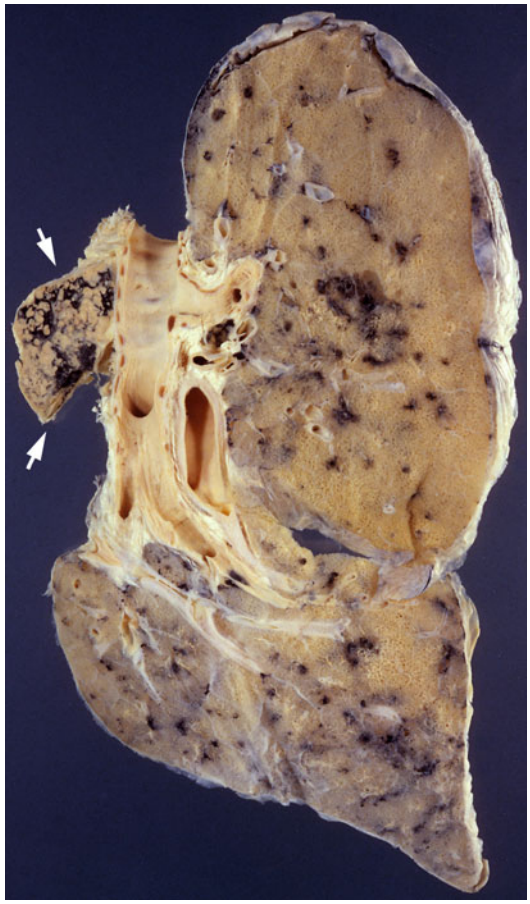

Fig. 7.4 Metastatic bronchogenic carcinoma in a hilar lymph node (*arrows*). Asbestosis was present in histologic sections

7.4.2 Histopathology

Carcinomas of the lung have conventionally been categorized into four histologic patterns: squamous cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma [124, 130–132]. These patterns are illustrated in Figs. 7.6 and 7.7. The most recently revised WHO classification for the more common lung cancer types is summarized in Table 7.2 [133]. Squamous cell carcinomas are characterized by keratinization or intercellular bridges. In well-differentiated tumors, keratinization manifests in the form of keratin pearls and, in more poorly differentiated tumors, as individual cell keratinization (Fig. 7.6a). Squamous cell carcinomas account for about 30 % of primary lung carcinomas and usually present as proximal hilar masses. Small cell carcinomas have scant amounts of cytoplasm with high nuclear-to-cytoplasmic ratios. The nuclei are often hyperchromatic or else have finely stippled chromatin with inconspicuous nucleoli (Fig. 7.6b). Small cell carcinomas account for about 10–15 % of primary lung carcinomas and also present as proximal tumors. Large cell carcinomas consist of sheets or nests of tumor cells with moderately abundant cytoplasm, anaplastic nuclei, and prominent nucleoli (Fig. 7.6c). They do not keratinize, form glandular or papillary structures, or

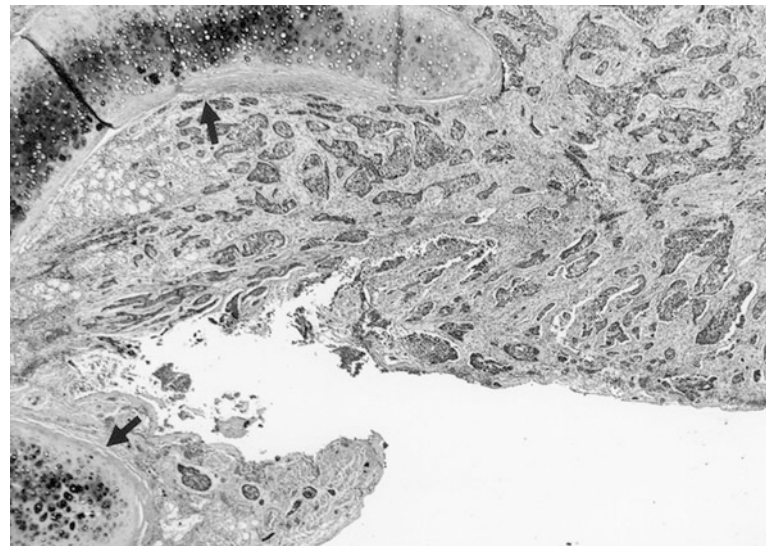

Fig. 7.5 Squamous cell carcinoma of the right lung invading the wall of the bronchus intermedius in close proximity to the bronchial cartilages (*arrows*). Same case as Figure 7.2. Hematoxylin and eosin, ×39 (Reprinted from Ref. [129], with permission)

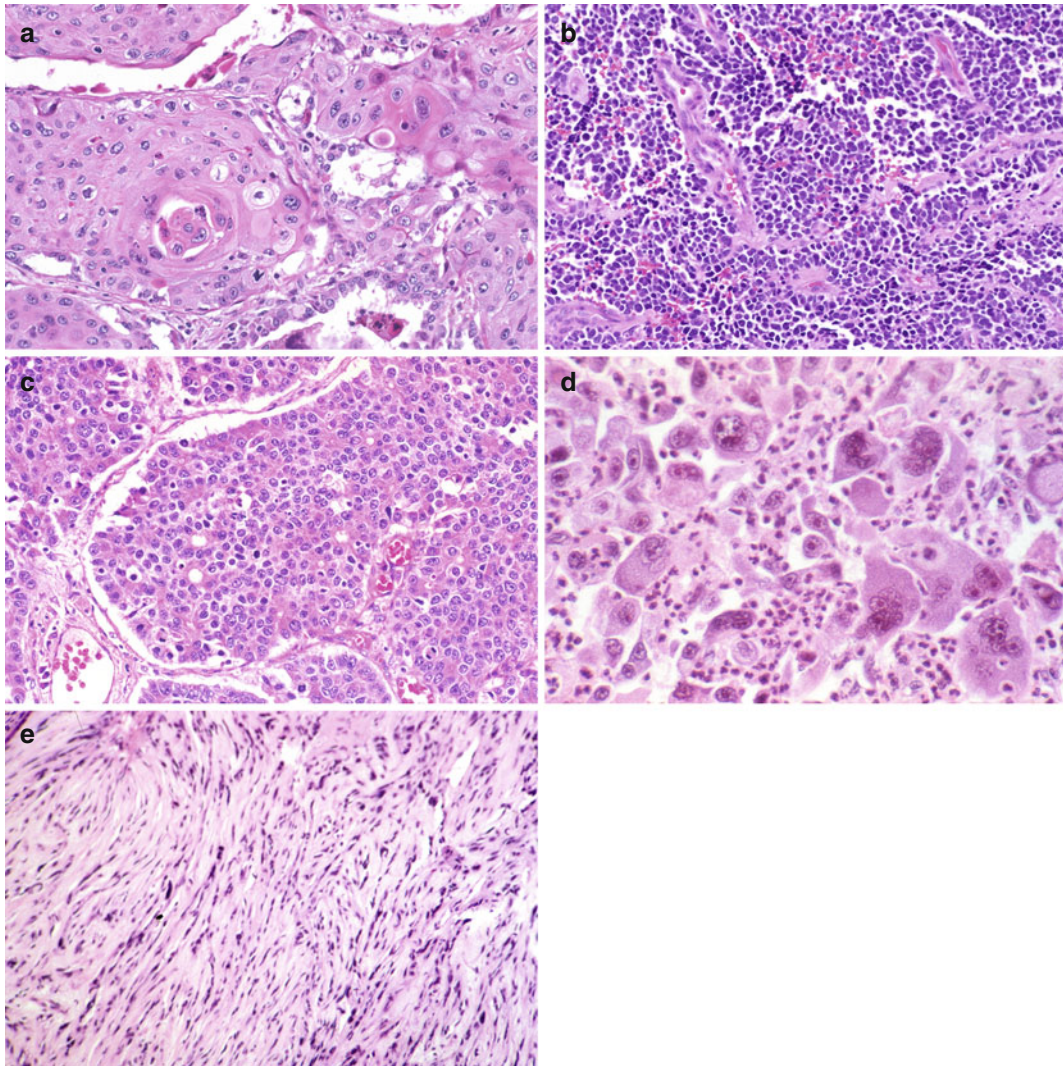

Fig. 7.6 High-magnification photo micrographs illustrating major cell types of carcinoma of the lung—(**a**) squamous carcinoma, (**b**) small cell carcinoma, (**c**) large cell neuroendocrine carcinoma, (**d**) giant cell carcinoma, and (**e**) sarcomatoid carcinoma. Hematoxylin and eosin, ×600

produce mucosubstances. Large cell carcinomas account for about 15 % of primary lung carcinomas and more often present as a peripheral mass.

The classification of adenocarcinomas has undergone extensive revision in recent years [134]. These tumors are recognized by their tendency to form glandular, acinar, or papillary structures (Fig. 7.7). In some cases, the tumor cells form solid sheets and can only be distinguished from large cell carcinoma by means of special stains for mucosubstances or by immunohistochemistry [134]. Adenocarcinomas account for about 40 % of primary lung carcinomas and usually present as peripheral nodules or masses. An uncommon variant of adenocarcinoma, formerly known as bronchioloalveolar cell carcinoma, consists of tall columnar tumor cells which tend to grow along intact alveolar septa (Fig. 7.7e). These tumors are now referred to as mucinous adenocarcinoma and are nearly always accompanied by focal areas of invasion [134]. This variant accounts for about 1–2 % of

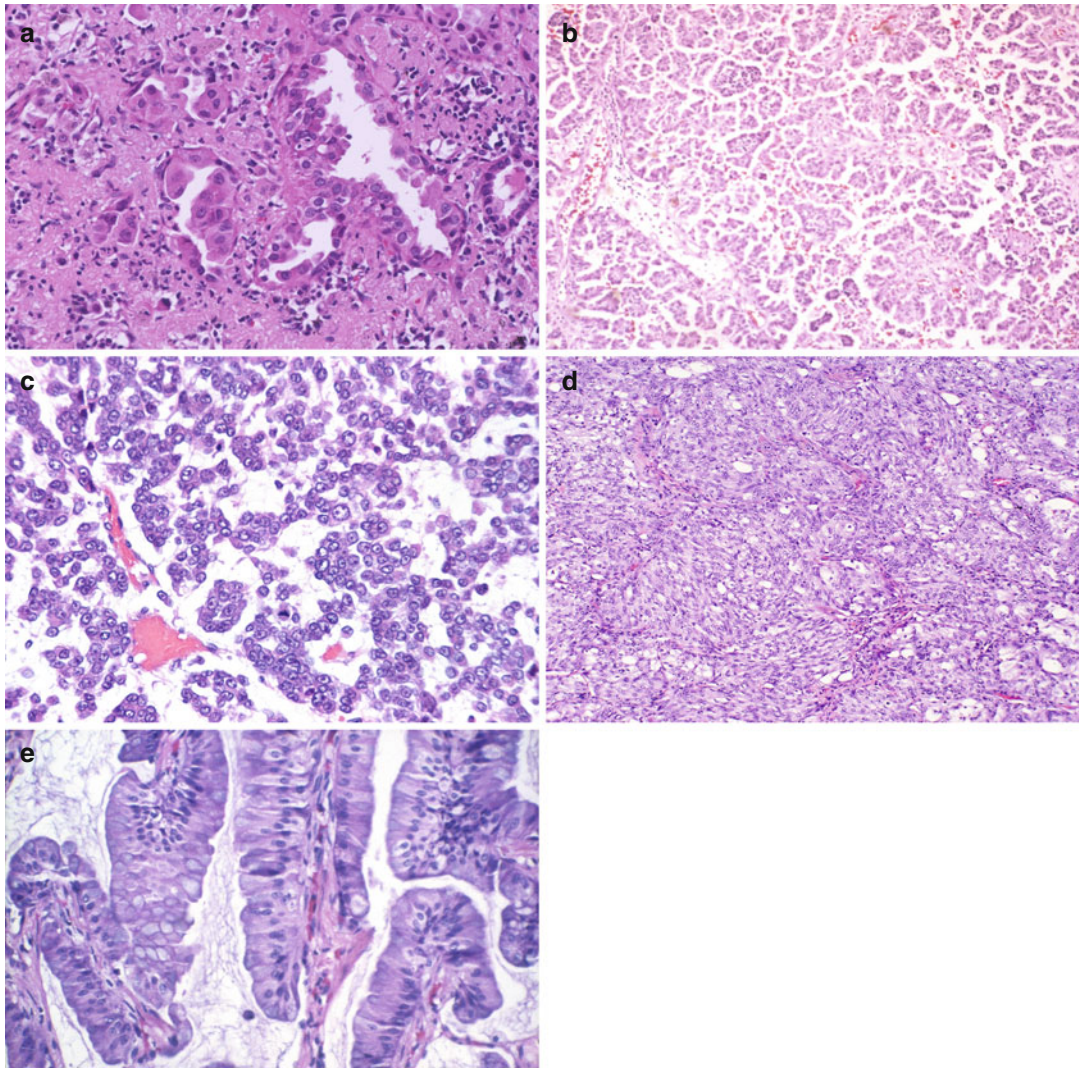

Fig. 7.7 High-magnification photomicrographs illustrating the most common variants of adenocarcinoma—(**a**) acinar or glandular type, (**b**) papillary type, (**c**) micropapillary type, (**d**) solid type, and (**e**) mucinous adenocarcinoma (formerly bronchioloalveolar cell carcinoma). Hematoxylin and eosin, ×130 (**a**–**d**), ×600 (**e**)

lung cancers. All of the major lung cancer histologic types are associated with cigarette smoking, although adenocarcinoma is the type most likely to occur in a nonsmoker (Fig. 7.8) [105].

Some pulmonary carcinomas may have a pleomorphic or sarcomatoid appearance (Fig. 7.6e) [135, 136]. We have seen examples of such carcinomas in asbestos workers presenting as superior sulcus (Pancoast) tumors (Fig. 7.9) or as proximal hilar masses (Fig. 7.10). These tumors may invade the pleura or chest wall and thus must be distinguished from sarcomatoid or biphasic malignant mesotheliomas (see below). Mixtures of the major histologic cell types may also occur, resulting in a heterogeneous histologic appearance of many primary carcinomas of the lung. With thorough sampling, various combinations of the four major histologic patterns can be found in almost half of the cases [137]. In addition, the authors have encountered examples of asbestos workers with synchronous primary lung neoplasms of differing histologic type (e.g., a patient

with asbestosis and adenosquamous carcinoma and small cell carcinoma in the same lung) [75].

All of the histologic patterns of lung cancer described above may occur in asbestos workers [29, 75, 124, 125, 138, 139]. However, there is some confusion in the literature regarding the distribution of histologic types in asbestos workers as compared to nonexposed individuals. A number of studies described an excess of adenocarcinomas among asbestos workers with carcinoma of the lung [13, 57, 140–143]. Other investigators have reported that the distribution of histologic types of lung cancer was similar for asbestos workers and members of the general population [75, 127, 144–148]. Possible reasons for these discrepancies include selection bias for surgical resection (with patients with peripheral adenocarcinomas more likely to be surgical candidates) or referral bias. In the author's opinion, the histologic features of a lung tumor are of no particular value in deciding whether or not it is an asbestos-related malignancy [75, 125].

Table 7.2 Histologic typing of lung cancer

I. Squamous cell carcinoma
II. Small cell carcinoma
III. Adenocarcinoma
A. Acinar type
B. Papillary type
C. Micropapillary type
D. Solid adenocarcinoma
E. Mucinous adenocarcinoma (formerly bronchioloalveolar cell carcinoma)
IV. Large cell carcinoma
A. Large cell neuroendocrine carcinoma
B. Basaloid carcinoma
C. Lymphoepithelioma-like carcinoma
D. Clear cell carcinoma
E. Rhabdoid phenotype
V. Adenosquamous carcinoma
VI. Sarcomatoid carcinoma
A. Pleomorphic carcinoma
B. Spindle cell carcinoma
C. Giant cell carcinoma
D. Carcinosarcoma
E. Pulmonary blastoma

Modified after WHO classification of lung tumors [133]

The distribution of histologic types of lung cancer in 1,258 patients from the author's series is shown in Table 7.3. The first column includes patients with carcinoma of the lung in which asbestosis was confirmed histologically, whereas the second column includes patients with parietal pleural plaques but without asbestosis. The third column includes cases with no histologic evidence of asbestosis or cases for which only a biopsy of the tumor was available (no lung tissue sampled). The fourth column includes 100 consecutive lung cancer resections or autopsies

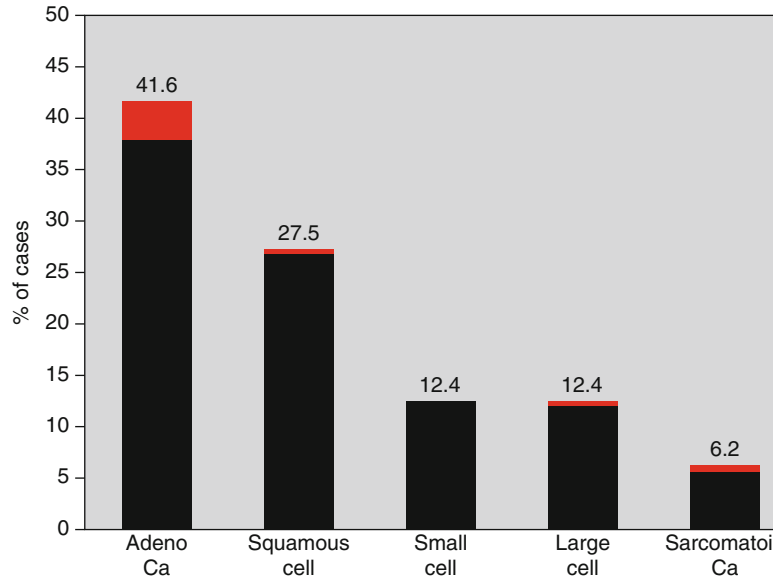

Fig. 7.8 Histogram showing the percentage distribution of histologic types and percentage of lifetime nonsmokers in a series of 1,051 lung cancers for which smoking status was available. *Red bars* indicate the percentage of cases by histologic types that were reportedly nonsmokers. Adenocarcinoma group includes adenosquamous carcinoma and mucinous adenocarcinomas (formerly known as mucinous bronchioloalveolar cell carcinomas). Large cell carcinoma group includes cases categorized as non-small cell carcinoma

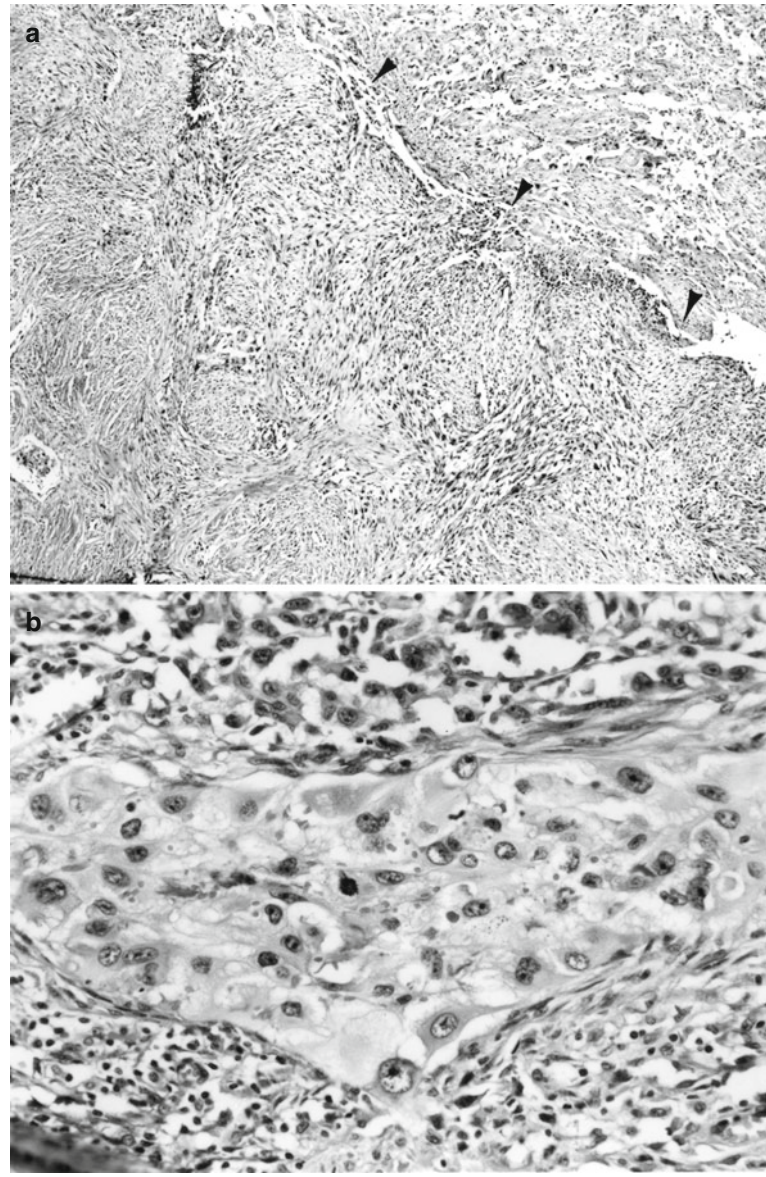

Fig. 7.9 (**a**) Predominantly spindle cell carcinoma of right upper lobe of an asbestos worker, presenting as a superior sulcus tumor. The margin of tumor invading the underlying lung parenchyma can be discerned (*arrowheads*). (**b**) Higher magnification elsewhere in the tumor shows epithelial component composed of large anaplastic cells with abundant cytoplasm. Hematoxylin and eosin, (**a**) ×40, (**b**) ×250

collected at Baylor Affiliated Hospitals, Houston, TX, from 1979 to 1980 [137]. The percentage of adenocarcinoma cases is similar across all four groups (39–43 %). The data in Table 7.2 are consistent with the proposition that most carcinomas of the lung occurring in asbestos workers are histologically similar to those occurring in nonexposed cigarette smokers. Adenocarcinomas derived from the scarring process account for only a small proportion of cases, resulting in a statistically insignificant increase in the percentage of adenocarcinomas.

7.4.3 Differential Diagnosis

Primary lung carcinomas must be distinguished from pulmonary metastases and from other primary intrathoracic malignancies. Knowledge of the clinical information and radiographic

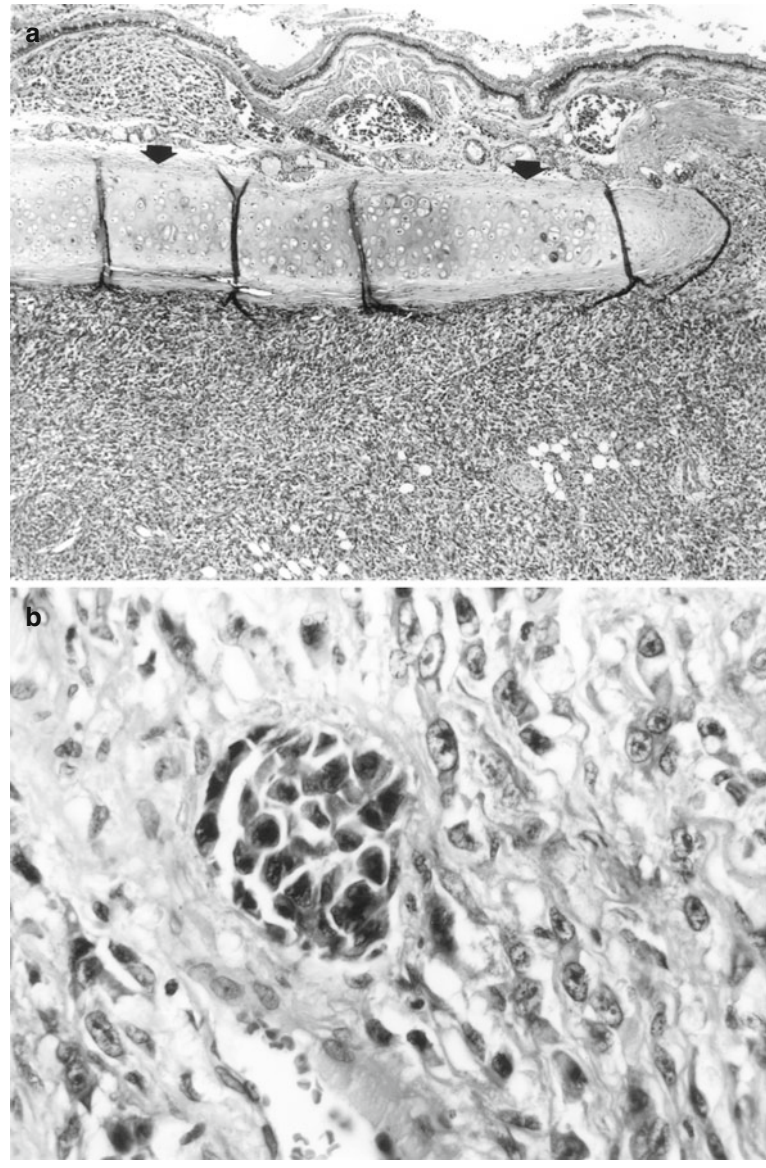

Fig. 7.10 (**a**) Predominately spindle cell carcinoma invading the right mainstem bronchus in close proximity to the bronchial cartilages (*arrows*). Asbestosis was confirmed histologically in the pneumonectomy specimen. (**b**) Higher magnification elsewhere in the tumor shows epithelial component composed of a nest of loosely cohesive polygonal-shaped tumor cells which were strongly positive for cytokeratins. Hematoxylin and eosin, (**a**) ×40, (**b**) ×400

Table 7.3 Distribution of histologic types in 1,258 lung cancer cases with and without asbestosis

	Asbestosis	PPP[a]	Others[b]	Ref. pop.[c]
Squamous cell carcinoma	64 (30 %)	74 (31 %)	197 (28 %)	31 (31 %)
Small cell carcinoma	28 (13)	28 (12)	76 (11)	11 (11)
Adenocarcinoma	85 (40)	103 (43)	303 (43)	39 (39)
Large cell carcinoma	27 (13)	30 (12)	116 (16)	19 (19)
Adenosquamous carcinoma	9 (4)	7 (3)	11 (2)	–
Total	213	242	703	100

[a]*PPP* parietal pleural plaques, no evidence of asbestosis
[b]No histologic evidence of asbestosis or biopsy of tumor only (no lung tissue sampled)
[c]100 consecutive lung cancer cases collected at Baylor Affiliated Hospitals, 1979–1980 [137]

findings is often useful in this regard. Primary lung carcinomas usually present as a solitary pulmonary mass or nodule, whereas metastatic disease most often manifests as multiple and bilateral nodules of similar size, most numerous in the lower lobes. A history of a primary malignancy in an extrapulmonary location is of obvious significance in this regard. The histologic appearance of the tumor is of limited use in determining whether a lung neoplasm is primary or metastatic. Most small cell carcinomas are primary to the lung, whereas adenocarcinomas are common histologic patterns in a number of primary sites, and histologic features alone (especially on a small biopsy) usually are not indicative of a primary site of origin. Immunohistochemistry can be useful in sorting out primary versus metastatic adenocarcinomas. For example, primary lung adenocarcinomas typically stain positive for TTF-1 and cytokeratin 7 but negative for cytokeratin 20 [134]. In contrast, metastatic colon cancer typically stains positive for cytokeratin 20 and CDX2 but negative for TTF-1 and cytokeratin 7. For tumors with a prominent clear cell component, a renal primary source needs to be excluded. Here again, immunohistochemistry may be of assistance.

Primary lung carcinomas must also be distinguished from other pulmonary neoplasms, most of which are distinctly uncommon [149]. Peripheral carcinomas which invade the pleura must be distinguished from malignant mesothelioma (see Chap. 5). The gross features of the tumor may be of limited utility in this regard [150, 151], and the pathologist must rely on histologic, histochemical, immunohistochemical, or ultrastructural features of the tumor to make this distinction. Uncommonly, a pulmonary carcinoma with a prominent spindle cell component may occur in the lung periphery and invade the pleura, mimicking a biphasic or sarcomatoid pleural mesothelioma (Figs. 7.9 and 7.10). The localized nature of the tumor with a prominent pulmonary parenchymal component, or the presence of a hilar mass with prominent involvement of a proximal bronchus, are useful differentiating features in this regard. Immunohistochemistry plays a rather limited role in making this distinction [152, 153].

7.5 The Pathologist's Role in Identification of Asbestos-Associated Carcinomas of the Lung

It has been estimated that in the 25-year period from 1985 to 2009, 76,700 deaths from asbestos-related carcinomas of the lung would occur in the USA alone [154]. In contrast, there are 180,000 lung cancer deaths annually (or 4.5 million over the above time period), the great majority of which are related to cigarette smoking [1, 2]. These observations are consistent with other estimates indicating that 2–3 % of lung cancers are asbestos related [155–157]. Thus it is clear that a major challenge for the medical profession and society in general will be to determine which lung cancers are related to asbestos exposure in order that appropriate compensation may be provided where indicated. This will require careful consideration of clinical, radiographic, and pathologic data in the individual case, as well as epidemiologic and relevant experimental animal studies. The challenge is all the greater considering that the percentage of asbestos-related lung cancers appears to be decreasing and modification of workplace conditions has resulted in lower exposures with decreasing rates of asbestosis [103, 158, 159].

As noted in the previous discussion, there are no pathologic features of carcinoma of the lung in asbestos workers that permit their distinction in the individual case from the much more common tobacco-related cancers in non-asbestos-exposed individuals. Therefore, the primary role of the pathologist is to render an accurate and precise diagnosis of carcinoma of the lung based on available pathologic materials and to help exclude other differential diagnostic considerations. Another important aspect of the pathologists' role has been referred to as the "second diagnosis" [160], that is, the identification of other abnormalities that are related to inhalation of asbestos fibers. These include the

identification of benign asbestos-related pleural diseases, such as parietal pleural plaques or diffuse pleural fibrosis (Chap. 6), asbestosis (Chap. 4), and asbestos bodies in histologic sections [161]. Similarly, the pathologist should search for evidence of tissue injury related to inhalation of tobacco smoke, including centrilobular emphysema, chronic bronchitis, and small airways disease [162, 163]. This requires adequate sampling of lung parenchyma at a distance well removed from the primary tumor and its effects on immediately adjacent tissues [125, 164]. These changes are best observed with lungs that have been fixed by intratracheal instillation of formalin [47, 162], which procedure should be employed when feasible on lobectomy or pneumonectomy specimens. In addition, lung cancer cases for which a role for asbestos is suspected should have portions of formalin-fixed lung tissue uninvolved by tumor preserved for possible tissue asbestos analysis at some subsequent time if indicated (Chap. 11). Such analyses should preferably be performed at specialized centers with experience with these procedures, since proper interpretation of results requires determination of a normal range of expected values.

It has been suggested that in the future, molecular genetic markers may be found that specifically link a lung cancer to asbestos exposure [165]. Since asbestos acts primarily as a promoter for cigarette smoke carcinogens, it is likely that molecular changes in patients with asbestos-related cancers would be the same as those in tobacco-induced cancers but accumulate at a higher rate following exposure to a cocarcinogen such as asbestos [166]. There is evidence that asbestos causes specific molecular changes that could accelerate the progression of lung cancer. For example, loss of 3p21 and EGFR activation are more common in asbestos-exposed patients. Asbestos-exposed workers with lung cancer can have mutations in the k-ras gene at codon 12 in the absence of radiographic evidence of asbestosis, indicating that these two events are not necessarily linked [167]. In addition, a variety of asbestos-related microRNAs are either overexpressed or under-expressed in asbestos-induced lung cancers, and DNA copy number alterations correlated with the deregulated microRNAs [168]. More work is required in this area, both to improve our understanding of the mechanisms by which asbestos induces malignancy and to identify markers that are specific for asbestos carcinogenesis.

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