Introduction

During the past fifty years, the United States 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 United States, accounting for 170,000 deaths annually. 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. It has been estimated that between 85% and 95% of deaths from lung cancer are directly attributable to smoking. Cigarettes are the leading offenders, but pipe and cigar smokers are also at risk, though only if they inhale the smoke. Asbestos workers are also at increased risk for lung cancer, particularly those who smoke tobacco products. This chapter will review the characteristics of asbestos-associated lung cancers and 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 be reviewed first, 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 Chapter 9, experimental models of pulmonary carcinogenesis in Chapter 10, and lung fiber burdens in asbestos workers with lung cancer in Chapter 11.

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. In 1943, Homburger reported three additional cases of bronchogenic carcinoma associated with asbestosis, bringing the world total reported to that date to 19 cases. 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 case control study of asbestosis and lung cancer from California hospitals.\(^11\) In 1968, Selikoff published data from a cohort of asbestos insulation workers that showed that insulators who smoked had a 92-fold increased risk of carcinoma of the lung over nonasbestos-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, numerous reports have confirmed the association between asbestos exposure and carcinoma of the lung.\(^14\)–\(^23\)

**Epidemiology**

**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.\(^4\)–\(^5\),\(^9\),\(^19\) Three primary hypotheses 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 there is a threshold for asbestos-induced carcinoma of the lung and whether asbestosis is a prerequisite precursor lesion are issues of more than academic importance,\(^25\) because the number of individuals exposed to low levels of asbestos greatly exceeds the numbers of individuals with asbestosis.

All investigators are in agreement that a dose-response relationship exists between asbestos exposure and lung cancer risk,\(^26\) 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.\(^27\)–\(^31\) In the original study by Doll,\(^10\) all 11 of the asbestos workers dying of carcinoma of the lung had pathologi-