CHAPTER 1

Overview

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Introduction

Lung cancer is one of the most commonly occurring cancers in the United States, with an estimated 221,130 new cases developing in 2011. Cancers of the breast and prostate occur slightly more frequently, with estimates of 232,620 and 240,890 cases, respectively. Lung cancer is associated with the highest cancer-related mortality, with an estimated 156,940 deaths occurring in 2011. This far outweighs deaths from breast (39,970) and prostate (33,720) cancers (Siegel, Ward, Brawley, & Jemal, 2011).

The five-year survival for lung cancer is approximately 15%. Treatment of early-stage disease can produce cures, with the five-year survival for treated stage I lung cancers as high as 70%. Unfortunately, less than 15% of lung cancers are localized at the time of diagnosis. Most lung cancers are diagnosed in advanced stages, and five-year survival in patients with locally advanced and metastatic disease is less than 10% (Siegel et al., 2011). Late diagnosis is attributed to multiple factors. Until recently, there has not been a proven method for screening or early detection in high-risk individuals, and no guidelines currently exist. Although most patients present with symptoms, symptoms such as cough and exertional dyspnea often are subtle and attributed to chronic symptoms of smoking. These topics will be explored further in this publication.

According to data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program (2010), the age-adjusted rate for lung cancer for all race and sex groups combined has risen sharply since 1950. From 1969 to 1991, the overall incidence almost doubled, with rates diminishing over the last decade. Lung cancer rates for African American and White men peaked and began to decrease around 1984. Although incidence for women of both races continues to rise, the overall incidence rate for the general public is decreasing. The lag in this trend is attributed to the historical difference in cigarette smoking between men and women, which peaked in women 20 years later than in men (Siegel et al., 2011).

Lung cancer was thought to be a disease of older men until the last half of the 20th century, when incidence in women rose sharply. Women now represent almost half of all new cases, with 2011 estimates of 115,060 for men versus 106,070 for women (Siegel et al., 2011). In addition, lung cancer surpassed breast cancer in 1987 as the leading cause of cancer-related deaths in women and currently accounts for more deaths than breast and all gynecologic cancers (e.g., ovarian, vulvar, vaginal, uterine) combined, as well as breast and colorectal cancer, the other leading causes of death, combined. Lung cancer is expected to account for 26% of all female cancer deaths in 2011 (Siegel et al., 2011) (see Table 1-1).

Most lung cancers are attributed to tobacco exposure. At least 79% of lung cancer cases in women are related to smoking. Although smoking rates have declined since the 1960s, the current prevalence of smoking among U.S. women is still high—estimated at 22%—and mortality from lung cancer in women rose 600% from 1930 to 1997 as a result of smoking prevalence (U.S. Department of Health and Human Services, 2001). Whether the association between smoking and lung cancer is stronger for women than men is unclear. Many epidemiologic studies have provided evidence that women are more susceptible than men to the adverse effects of

Table 1-1. Estimated Leading Cancer Incidence and Mortality by Sex, 2011

Sex	Cancer Type	Incidence	Mortality
Male	Prostate	29%	11%
	Lung	14%	28%
	Colorectal	9%	8%
Female	Breast	28%	15%
	Lung	14%	26%
	Colorectal	10%	9%

Note. Based on information from Siegel et al., 2011.

tobacco smoke as a result of molecular influences, hormones, and genetics (O'Keefe & Patel, 2008). These findings will be discussed in Chapter 3.

The magnitude of the effect of smoking on lung cancer risk may not differ between the genders, but smoking appears to have an impact on the type of lung cancer that develops in each gender. Female smokers have a greater risk of developing small cell lung cancer than male smokers. Also, women are more likely than men to develop adenocarcinoma, and the bronchoalveolar carcinoma subtype of adenocarcinoma is two to four times more common in women (Patel, 2005). The inclusion of women in lung cancer screening and treatment trials has not been adequate in the past. Active recruitment of women for trials with specific reference to gender is needed to investigate this phenomenon further.

African American men experience higher lung cancer incidence and mortality rates than all other male racial groupings, including Whites, Asian Americans/Pacific Islanders, American Indians/Alaska Natives, and Hispanics/Latinos. Incidence and death rates are similar between White and African American women with significantly lower incidence and mortality in the other female ethnic groups (Siegel et al., 2011).

Histologic Classification

The World Health Organization (WHO) classification of lung cancer includes four major histologic types: squamous cell carcinoma, adenocarcinoma, small cell lung carcinoma, and large cell carcinoma (Travis, Brambilla, Müller-Hermelink, & Harris, 2004). These classes are further subdivided, and other less common lung tumors also exist, such as sarcomatoid carcinoma and carcinoid. For clinical purposes, the histologic classes are grouped into two main categories of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC includes a category called combined small cell carcinoma. NSCLC includes squamous cell carcinoma (SCC), large cell carcinoma, and adenocarcinoma (Franklin, Noguchi, & Gonzalez, 2010) (see Table 1-2).

Table 1-2. Histologic Groups of Lung Cancers

Category	Histologic Groups
Non-small cell lung cancer	Adenocarcinoma Large cell carcinoma Squamous cell carcinoma
Small cell lung cancer	Combined small cell carcinoma
Sarcomatoid carcinoma	
Carcinoid	

Note. Based on information from Franklin et al., 2010; Travis et al., 2004.

Non-Small Cell Lung Cancer

Approximately 75%–80% of all lung cancers in the United States are NSCLCs (Franklin et al., 2010). Although the subtypes may differ in incidence according to sex, race, and age, they are grouped because of similarities in course and response to treatment. SCC arises most frequently in the proximal segmental bronchi and is associated with squamous metaplasia. Tumors are composed of sheets of epithelial cells, which may be poorly or well differentiated. At one time, SCC was the most frequently occurring lung cancer in North America, but its incidence is decreasing and has been surpassed by adenocarcinoma for reasons that are thought to be related to changes in tobacco use (Govindan et al., 2006). SCC can be detected by cytologic examination of exfoliated cells in its earliest form, carcinoma in situ, where stratified squamous epithelium is replaced with malignant squamous cells. Unchecked, the tumor eventually invades and obstructs the bronchial lumen. SCC tends to be slow growing and can take years to develop from a carcinoma in situ to a clinically evident tumor (Franklin et al., 2010).

Adenocarcinoma is the most common form of lung cancer in North America, accounting for almost 40% of all lung cancers (Franklin et al., 2010). It presents as a peripheral tumor, arising from the alveolar surface epithelium or the bronchial mucosal glands. Tumors also can arise from areas of previous infections or scars. Adenocarcinoma tumors are mucin producing and form glands. Other than very early stage tumors, adenocarcinoma appears to have a worse prognosis than SCC. Bronchoalveolar carcinoma is a subclassification of adenocarcinoma that appears to have distinct clinical and pathologic properties (Franklin et al., 2010). Bronchoalveolar carcinoma and its properties will be described more extensively later in this book.

Large cell lung carcinoma is the least common of all NSCLC tumors, representing about 10% of all lung tumors (Franklin et al., 2010). As diagnostic techniques have improved, tumors originally thought to be large cell lung carcinomas have been more appropriately diagnosed as poorly differentiated adenocarcinomas or SCCs.

Small Cell Lung Cancer

SCLC is less common than NSCLC, representing about 13% of all lung cancer cases per year in the United States (Govindan et al., 2006). A slow decline has occurred over the past 30 years as a result of changing patterns in cigarette smoking. The WHO classification of SCLC includes a variant known as combined small cell carcinoma, which is defined as a small cell carcinoma with a component of any histologic subtype of NSCLC. SCLC is a neuroendocrine tumor that routinely occurs in the central airways. Among the subtypes of lung cancer, the highest association between the extent of

tobacco exposure and risk occurs in SCLC and SCC (Franklin et al., 2010).

Although SCLC officially is staged according to the International System for Staging Lung Cancer, a more common clinical staging introduced by the Veterans Administration Lung Cancer Study Group generally is used. SCLC is staged as either limited or extensive disease. Nearly one-third of patients present with limited-stage disease, which is defined as disease that is confined to one hemithorax, without pericardial or pleural effusion, and encompassed in a single radiotherapy port. *Extensive* is the term applied to all other presentations of the disease. SCLC is an aggressive disease, and limited-stage disease is more curable than extensive-stage disease. Prior to the use of chemotherapy, patients diagnosed with limited-stage disease survived about three months. Survival rates have improved modestly but significantly with current therapies. Median survival with chemotherapy is 10–14 months with a five-year survival of 10% (Huang, Shepherd, & Kelly, 2010). SCLC exhibits a high degree of neuroendocrine differentiation with expression of a wide variety of neuropeptides and neuropeptide receptors. Several of these neuropeptides have mitogenic potential and have been shown to be mediators of SCLC proliferation.

Staging of Lung Cancer

Staging is a major indicator of prognosis and treatment for lung cancer. The purpose of clinical stage classification is to facilitate the accurate, concise description of the extent of disease in a way that can be communicated and replicated (the tumor, node, metastasis [TNM] classification) and to facilitate comparison of differing therapeutic approaches by combining patients with certain common attributes (TNM subsets) into groups or stages with generally similar prognoses and treatment options. Four stages of lung cancer have been identified depending on the presentation at diagnosis, and treatment is prescribed accordingly. The primary tumor is subdivided into four categories (T1–T4) and reflects size, site, and local involvement. Lymph node spread is subdivided into bronchopulmonary (N1), ipsilateral mediastinal (N2), and contralateral or supraclavicular disease (N3). Metastatic spread is either absent (M0) or present (M1) (Edge et al., 2010; Rusch et al., 2009).

The American Joint Committee on Cancer and the International Union Against Cancer adopted the International System for Staging Lung Cancer in 1986 as a means of unifying variations in definitions and providing consistent meaning and interpretation among clinicians and scientists throughout the world. The system was revised in 1996 to improve the rules for TNM subsets and incorporate a new schema for regional lymph node mapping. In 2009, the International Association for the Study of Lung Cancer (IASLC) proposed revisions to the lymph node maps to reconcile differences in nomenclature and provide precise anatomic definitions for all lymph node stations, now grouped as zones. Implementation of the IASLC lymph node map is intended to provide the basis for research and to resolve the controversies related to nodal status that currently affect patient care and clinical trials (Edge et al., 2010; Rusch et al., 2009).

Prognostic Factors

Clinical stage is the most important prognostic indicator for lung cancer survival. The size and location of the tumor at the time of diagnosis is tied directly to the ability to achieve cure. Other factors have been known to affect survival. Male gender and age older than 60 years have been found to adversely affect survival. Numerous studies have shown that women generally survive longer than men (Patel, 2005). Tumor expression of mucin, seen in adenocarcinoma, has been identified as an adverse factor in early-stage disease because mucin may facilitate formation of metastases. In those with advanced stages at diagnosis, poor performance status, weight loss, and elevated serum lactate dehydrogenase have been associated with poor outcomes (Wozniak & Gadgeel, 2010).

Advances in molecular testing have produced a variety of novel and potentially useful prognostic factors. The connection between activated oncogenes and loss of tumor suppressor gene function offers targets for determining prognostic outcomes. These targets include the significance of the presence of epidermal growth factor receptors on lung cancer cells, neuroendocrine markers, blood group antigens, and genetic markers such as *K-ras* mutations, *TP53* mutations, *bcl-2* expression, *Fas* expression, and angiogenic indicators, to name a few (Miller, 2008).

Pathogenesis

Lung cancer arises from malignant changes to the epithelial cells in the lung. As a protective layer, the epithelium is continually damaged, shed, and replaced. Cellular abnormalities occur as the epithelium is chronically exposed to irritating inhaled substances. Exposure of the cell results in various combined genetic mutations that contribute to malignant transformation, taking a normal cell through the morphologic evolution of hyperplasia; metaplasia; mild, moderate, and severe dysplasia; carcinoma in situ; and invasive carcinoma (Schottenfeld, 2010). It is not known whether all epithelial cells are susceptible to malignant transformation or only a subset of cells. Lung cancer is a heterogeneous disease, and its cause reflects changes in cells with potential for differentiation (squamous versus adenomatous) and molecular changes. Multiple oncogenes, tumor suppressor genes, signaling pathways, and other cellular processes contribute to lung cancer pathogenesis (Larsen, Spinola,

Gazdar, & Minna, 2010). In addition, an inherited variability in genes that activate and detoxify carcinogens may contribute to a genetic susceptibility to developing lung cancer (Amos & Bailey-Wilson, 2010). The biologic influences on lung cancer development are discussed throughout this book. Chapter 2 describes in greater detail the molecular mechanisms of lung cancer. The chapters on each major cell type include discussion of the specific genetic mutations involved in their pathogenesis and the related treatment targets.

Summary

As our knowledge of the pathologic and molecular features has evolved, lung cancer can now be thought of as a heterogeneous disease. Identification of specific genetic activity has led to more customized therapeutic interventions that interfere with tumor initiation, progression, and metastasis and can be matched to individual disease presentations and mutational analysis. The following chapter on the lung cancer biology provides an in-depth review of the current genetic properties of lung cancer and a basis for a greater understanding of the evolving direction of treatment.

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