53.1 Introduction

Lung cancer is one of the most common malignancies and is the leading cause of cancer mortality in the Western World. In the USA, the disease has been the leading cause of cancer deaths in men for years, and since 1988 it has also become the number one cause of cancer death in women. It is estimated that in the year 2005, approximately 172,570 people will be diagnosed with lung cancer and 163,510 will die of the disease, surpassing the combined death rates from breast, prostate, and colon cancers [1].

In addition to being the biggest cancer killer, lung cancer is one of the few cancers with a well defined etiology, namely, the inhalation of tobacco smoke. Cigarette smoking is estimated to be responsible for approximately 87% of lung cancer cases, and evidence for this link is indisputable [2]. Estimates of the relative risk of disease in the long-term smoker vary from 10- to 30-fold. The cumulative lung cancer risk among heavy smokers may be as high as 30% compared with a lifetime risk of 1% or less in non-smokers [3, 4]. The risk of carcinoma increases with the number of cigarettes smoked, years of smoking, earlier age of onset, degree of inhalation, tar and nicotine content, and use of unfiltered cigarettes. Other risk factors for lung cancer include exposure to asbestos, haloethers, polycyclic aromatic hydrocarbons, nickel, arsenic, genetic factors, and the presence of underlying benign forms of parenchymal lung disease, especially pulmonary fibrosis. Recent interest has focused on the potential roles of exposure to environmental tobacco smoke (passive exposure to second-hand smoke) and to radon.

Two major subdivisions are recognized: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). This is due to the major clinical differences in presentation, metastatic spread, and response to therapy. SCLC accounts for 15–25% of all lung cancers and although the disease is sensitive to both chemotherapy and radiotherapy, the duration of response is usually short-lived. The majority of patients of SCLC patients die from progressive disease [5–8].

Non-small cell lung cancer accounts for the remaining cases and composes a heterogeneous aggregate of at least three histological subtypes including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [9]. About 30% of patients with NSCLC present with stage I and II disease. Surgery is currently the treatment of choice for these patients and represents the best chance of a cure. Despite apparent complete resection, however, patients with pathologic stage Ia disease have an 80% survival rate after resection, whereas 5-year survival rates are 60% in those with stage Ib disease and 40–50% in those with stage IIa/IIb disease [10].

A further 25–30% of patients have locally advanced or stage IIIa and IIIb disease at presentation. While multimodality therapy is routinely recommended for this patient group, its exact nature and sequence remain controversial. In the past, radiation therapy was considered standard of care, however long-term survival with this approach was poor, in the range of 5–10%, with poor local control and early development of distant metastatic disease. Recent studies indicate that the addition of chemotherapy improves survival in these pa-
tients, however the magnitude of improvement is small [11–15].

The outcome for patients with stage IV disease is particularly bleak. Systemic chemotherapy has been used in an attempt to prolong symptom-free survival. Treatment with modern cisplatin-containing regimens improves median survival by a modest 6–12 weeks and 1-year survival from 5% to 15% with best supportive care alone to 30–40% in treated patients [16]. Therefore, despite improvements in diagnostic imaging, surgery, radiotherapy, and chemotherapy, the overall survival for NSCLC remains poor with only about 14% of patients surviving 5 years from the date of diagnosis. Furthermore, it appears unlikely that additional marked improvements with these practices alone will occur in the near future. This grim overview argues powerfully for new, emerging approaches such as biologic or molecularly targeted therapy and chemoprevention for controlling lung cancer.

53.2 Chemoprevention

Dr. Michael Sporn is widely credited with launching the modern era of cancer chemoprevention and prevention research. He was the first to put forward the notion that the goals and objectives of clinical efforts in the treatment of some types of cancers should be the process rather than the state of carcinogenesis. He intensely promoted the concept of treatment of precancerous conditions and coined the term chemoprevention to describe “the use of specific natural or synthetic chemical agents to reverse, suppress or prevent carcinogenic progression to invasive cancer” [17, 18]. Although at first regarded with skepticism, this approach has led to significant advances in cancer prevention. Clinical validation for the cancer prevention concept was provided by a randomized trial using the selective estrogen receptor modulator tamoxifen in women who are at high risk for breast cancer development based on age, lobular carcinoma in situ, or the Gail model [19]. In women who received tamoxifen, there was a highly statistically significant reduction in the risk of both invasive and non-invasive breast cancers. Studies in colon and head and neck cancers have provided further proof of principle for the concept of chemoprevention as a serious and practical approach to the control of cancer in humans [20–22].

This article will focus on several issues related to lung cancer chemoprevention including current and new chemopreventive agents and endpoint biomarkers. Also, the results of completed clinical chemoprevention trials are reviewed.

53.3 Lung Cancer Biology and Chemopreventive Approaches

Primary carcinoma of the lung appears to develop from a pluripotent stem cell involved in the generation of the bronchial epithelium and capable of differentiation along several pathways [6]. The biology of this process is based on two themes: field carcinogenesis and multistep carcinogenesis [23–25]. Field carcinogenesis denotes diffuse epithelial injury resulting from carcinogenic (e.g., tobacco smoke) exposure in an entire epithelial field or region, setting off a chronic pattern of tissue damage and wound healing where changes can be detected at the gross, microscopic, and molecular levels [26]. The clinical importance of this phenomenon is best illustrated in aerodigestive cancers for which both synchronous and metachronous second primary tumors are common.

Chronic carcinogenic insults set off a multistep process characterized by the occurrence of initiation, promotion, and progression events occurring over latent periods of a decade or more. These events produce an accumulation of genetic and epigenetic alterations of at least three groups of genes: proto-oncogenes, tumor suppressor genes, and mutator genes resulting in imbalances between cellular proliferation, apoptosis, and shedding. Imbalance in cellular population kinetics promotes a build-up of cells that, if sufficiently abnormal, have malignant capability. Numerous systems including repair, replacement, recruitment, replication, and redundancy mechanisms become operational to help restore structural and functional integrity. In some instances, however, these mechanisms fail or are overwhelmed and unrepaired injury not only occurs but also is propagated, resulting in the triggering of a transformation from normal to premalignant cells and eventually to invasive carcinoma.

The essence of chemoprevention is intervention within the multistep carcinogenic process and throughout the tobacco/carcinogen-damaged field. Using pharmacologic or natural compounds, chemoprevention is meant to interrupt this clonal propagation of aberrant cells by blocking DNA damage, retarding or reversing malignant phenotype, or inducing apoptosis in the damaged cells of premalignant lesions. Chemopreventive approaches can be considered at three different major levels: primary, secondary, and tertiary (Table 53.1). Primary prevention is defined as an intervention intended to delay the development of cancer or hinder its progression. Normal “healthy” individuals represent the population at which primary prevention is directed. Smoking prevention and cessation treatments or the use of chemoprevention drugs in a group of asymptomatic smokers are good examples of this strategy. Secondary chemoprevention is aimed at persons with evidence of early disease, but without well-established can-