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WORLD CANCER REPORT

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LUNG CANCER

SUMMARY
Lung cancer is the second most common cause of death in men, and the third in women, worldwide. While the exact cause of death is not yet known, it is generally accepted that smoking is the main cause of death. Smoking causes lung cancer. The highest incidence of lung cancer is in the United Kingdom and the Netherlands. The lowest incidence is in Africa and Southern Asia (Fig. 5.1). Rates are higher in men than in women. The lowest rates are in women in Europe, Japan, and Spain. In which the prevalence of smoking in men has increased only recently. The lowest rates (<3 cases per 100,000 population) are recorded in Africa and India. In most countries, lung cancer incidence is greater in lower socioeconomic classes; to a large extent, this pattern is explained by differences in the prevalence of smoking. Having risen dramatically since the turn of the century, lung cancer mortality amongst males is now abating in several countries, including the USA, the UK and Finland (Fig. 5.4).

Etiology
The geographical and temporal patterns of lung cancer incidence are overwhelmingly determined by consumption of tobacco.

USA and Maoris from New Zealand and are followed by those in the United Kingdom and the Netherlands. The lowest incidence rates are reported from Africa and Southern Asia (Fig. 5.1). Rates in women are higher in the USA, Canada, Denmark and the UK, but are lower in countries such as France, Japan and Spain, in which the prevalence of smoking in women has increased only recently. The lowest rates (<3 cases per 100,000 population) are recorded in Africa and India. In most countries, lung cancer incidence is greater in lower socioeconomic classes; to a large extent, this pattern is explained by differences in the prevalence of smoking. Having risen dramatically since the turn of the century, lung cancer mortality amongst males is now abating in several countries, including the USA, the UK and Finland (Fig. 5.4).

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tobacco smoking: age at start, average consumption, duration of smoking, time since quitting, type of tobacco product and inhalation pattern, with duration being the dominant factor. While lung cancer risks rise sharply with increasing numbers of cigarettes per day, the trends have been reported to be even stronger with duration of smoking. Such findings are essentially consistent in men from diverse communities, including those of the USA, UK and China. In populations with a long duration and heavy intensity of cigarette usage, the proportion of lung cancer attributable to smoking is of the order of 90% [9].

As compared to continuous smokers, the excess risk sharply decreases in ex-smokers approximately five years after quitting, but a small excess risk persists in long-term quitters throughout life. The risk of lung cancer is slightly lower among smokers of low-tar and low-nicotine cigarettes than among other smokers, although "low-tar smokers" tend to compensate for lower yields of nicotine by deeper inhalation or greater consumption. A relative reduction in risk has also been observed among long-term smokers of filtered cigarettes compared to smokers of unfiltered cigarettes. Smokers of black (air-cured) tobacco cigarettes are at a two to three-fold higher risk of lung cancer than smokers of blond (flue-cured) tobacco cigarettes. A causal association with lung cancer has also been shown for consumption of cigars, cigarillos, pipe, bidis and water pipe.

An association between exposure to passive smoke and lung cancer risk in nonsmokers has been shown in a number of case-control and cohort studies (Fig. 5,9). In general, such studies involve exposure to environmental tobacco smoke in the home or the workplace or both. In many instances, the increased risk recorded is at the margin of statistical significance, and in some cases less than that. However, a causal relationship has been recognized on the basis of consistent findings and taking account of biological plausibility (that is, the established carcinogenic activity of tobacco smoke). The magnitude of the risk is in the order of 15-20% [4].

Occupational exposures have been associated with increased risk of lung cancer more than of any other tumour type (Occupational exposures, p.33). For many workplace exposures associated with a high risk of lung cancer, the specific agent(s) responsible for the increased risk has been identified. Risk of lung cancer and mesothelioma (a malignant tumour of the pleura) is increased in a variety of occupations involving exposure to asbestos of various types. A characteristic of asbestos-related lung cancer is its synergistic relationship to cigarette smoking; risk is increased multiplicatively amongst persons who both smoke and are exposed to asbestos. Such a phenomenon has been recorded in relation to other occupational lung cancers.

Atomic bomb survivors and patients treated with radiotherapy are at increased risk.
Detection

Sputum cytology and radiology (chest X-ray and computed tomography (CT)) scans are the only non-invasive methods of detecting early lung cancer. Sensitivity can be variable dependent on histological type (greater for small cell and squamous cell carcinomas), tumour size and location [10]. Sputum cytology may be appropriate for certain clearly defined groups or individuals at risk of lung cancer. Currently, however, there are no practical and effective procedures available to provide population-based screening for lung cancer.

The signs and symptoms of lung cancer depend on the location of the tumour, the spread and the effects of metastatic growth. Many patients are diagnosed on the basis of an asymptomatic lesion discovered incidentally on X-ray. Symptoms indicative of the primary tumour include cough, decreased activity, persistent cough, chest pain, decreased appetite and weight loss. Hoarseness as a result of recurrent laryngeal nerve injury may be provoked by left-sided lesions, and superior vena cava syndrome by right-sided lesions. Wheeze or stridor may also develop in advanced stages. Continuous tumour growth may result in collapsed lung, pneumonitis and abscess formation.

In some patients with lung cancer, metastatic deposits lead to the first symptoms; the majority of patients with lung cancer already have locally advanced disease or distant metastases at diagnosis; common metastatic sites are mediastinal and supraclavicular lymph nodes, liver, adrenal glands, brain, lungs, pleura and pericardium. Less commonly, a patient may be diagnosed on the basis of a paralysisplastic syndrome (signs and symptoms not produced by the direct effect of a tumour or its metastasis), such as the syndrome of inappropriate secretion of antidiuretic hormone in small cell lung cancers. Diagnostic procedures involve chest X-ray, bronchoscopy and sputum analysis, as well as CT and magnetic nuclear resonance. CT imaging is used for the detection of liver and adrenal gland metastases. Clinical and Image-based
diagnosis is usually confirmed by histological examination of biopsies obtained by fibre-optic endoscopy or surgical specimens. Percutaneous fine needle aspiration may be used to diagnose peripheral tumours, or in the event of inconclusive bronchoscopy results. The complementary use of spiral CT in screening may improve the robustness with which lung cancer of any cell type can be detected early [11]. However, many cases of lung cancer, especially at older ages and in low resource countries, are diagnosed only on the basis of clinical and X-ray evidence.

**Pathology and genetics**

Principal histological types of lung cancer are squamous cell carcinomas, adenocarcinoma, large cell carcinoma and small cell carcinoma. The first three are also referred to as "non-small cell" lung carcinomas. In North America and Europe over the last 20 years, the proportion of squamous cell carcinoma, previously the predominant type, has been decreasing, while an increase of adenocarcinoma has been recorded in both genders. Squamous cell carcinoma arises most frequently in proximal segmental bronchi and is associated with squamous metaplasia. This tumour type is very strongly associated with smoking and represents the most common type of lung cancer in many populations. It tends to grow slowly, three to four years being required for development from an *in situ* lesion to a clinically apparent tumour. Adenocarcinoma is less strongly associated with smoking. This tumour is often peripheral in origin and may present as a solitary peripheral nodule, multifocal disease, or a rapidly progressive pneumonic form, spreading from lobe to lobe. These tumours form glands and produce mucin. Early metastasis is common, particularly to the brain, pleura and adrenal glands. Large cell carcinoma often appears in the distal bronchi and is generally undifferentiated. Small cell carcinoma typically arises in the central endobronchial location and is commonly aggressive and invasive; frequently metastases are present at diagnosis. Although the histogenesis and the putative precursor lesions of lung cancer are largely unknown for the different histological types, the presence of putative precursor lesions (dysplasia, metaplasia and carcinoma *in situ*) are commonly reported in resection specimens and/or cytology for squamous cell carcinoma [12].

A positive familial history of lung cancer has been identified as a risk factor. Increased risk of lung cancer has been associated with certain polymorphisms of the cytochrome P450 genes and with deficiencies in DNA repair capacity [13]. Genetic changes associated with progression of premalignant lesions to malignant tumours have been identified [14] (Table 5.1). Mutations in the *p53* gene are frequent events in lung cancer, although adenocarcinoma shows a lower prevalence of *p53* mutations than other histological types. Among lung cancer cases, the proportion of *p53* mutations increases with duration and amount of tobacco smoking. A wide distribution and a variety of types of *p53* mutation have been observed following different environmental exposures; their analysis is likely to elucidate different mechanisms involved in lung carcinogenesis [15].

Activating point mutations in the *KRAS* oncogene (mainly at codon 12) occur in adenocarcinoma, with a prevalence ranging from 15% to 40%. This alteration, which is more prevalent in tumours from smokers than from non-smokers, may be a relatively early event in lung carcinogenesis. Frequent loss of heterozygosity and aber-

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**Fig. 5.7** A lung tumour viewed by computed tomography. T= tumour, M= mediastinum.

**Fig. 5.8** Biopsy of a small cell lung carcinoma, showing a monomorphic proliferation of small tumour cells with dense nuclei and poorly-defined cytoplasm, invading the deep parts of the bronchial wall.

**Fig. 5.9** Relative risk of lung cancer (odds ratios) among non-smokers by cumulative exposure to environmental tobacco smoke from the spouse and workplace. Pooled analysis of data from two studies in the USA and in Europe.