

WORLD HEALTH ORGANIZATION



International Agency for Research on Cancer

# WORLD CANCER REPORT

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# LUNG CANCER

## SUMMARY

- > Lung cancer is the most common tumour worldwide, with 900,000 new cases each year in men and 330,000 in women. It is the leading cause of death from cancer.
- > In men, more than 80% of lung cancer cases are caused by smoking; in women, the attributable risk is less (about 70% in Northern Europe; 45% worldwide).
- > Some occupational exposures and air pollution (including environmental tobacco smoke) make a minor contribution to incidence.
- > No population-based screening procedures have been established.
- > No effective treatment is available; the five-year survival rate for lung cancer patients is less than 15%.

## Definition

Lung cancer almost exclusively involves carcinomas, these tumours arising from epithelia of the trachea, bronchi or lungs. There are several histological types, the most common being squamous cell carcinoma, adenocarcinoma and small (oat) cell carcinoma.

## Epidemiology

Lung cancer is the most common malignant disease worldwide, and is the major cause of death from cancer, particularly amongst men. It was a rare disease until the beginning of the 20<sup>th</sup> century. Since then, the occurrence of lung cancer has increased rapidly and it now accounts for an estimated 901,746 new cases each year among men and 337,115 among women [1].

The highest incidence rates (>100 cases per 100,000 population) are recorded among Afro-Americans from New Orleans,

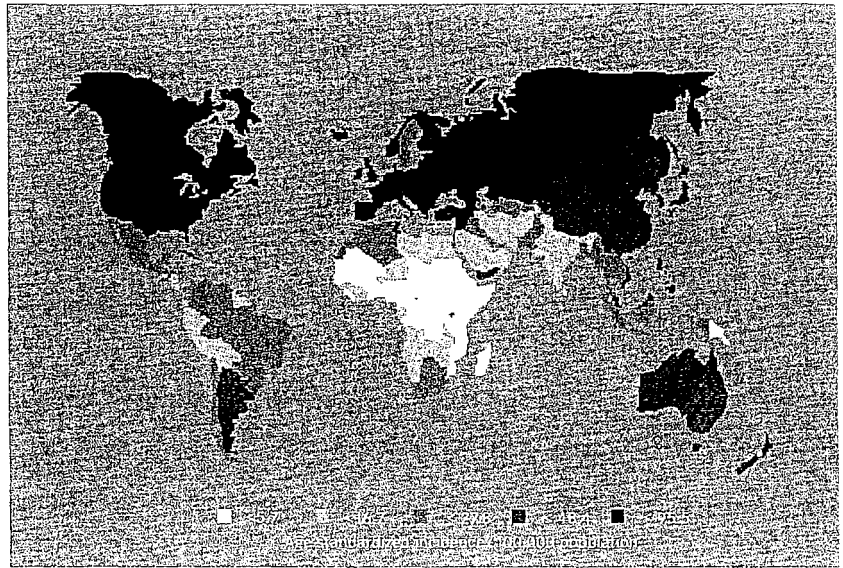


Fig. 5.1 The global incidence of lung cancer in men. Incidence is highest in Europe, especially Eastern Europe, and in North America and Australia.

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 [2] (Fig. 5.1). Rates in women are high 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).

## Etiology

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

The association between lung cancer and smoking is probably the most intensively investigated relationship in epidemiology. Smoking causes lung cancer. An increase in tobacco consumption is paralleled some 20 years later by an increase in the incidence of lung cancer, and a decrease in consumption (e.g. a large proportion of smokers who quit) is followed by a decrease in incidence. In both men and women, the incidence of lung cancer is low before age 40, and increases up to at least age 70. The situation in China appears to be different, given the relatively high rates of lung cancer (particularly adenocarcinoma) recorded among Chinese women, despite a low prevalence of smoking. The association between lung cancer and smoking was demonstrated in the 1950s and has been recognized by public health and regulatory authorities since the mid-1960s. The risk of lung cancer among smokers relative to the risk among never-smokers is in the order of 8-15 in men and 2-10 in women. This overall risk reflects the contribution of the different aspects of

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% [3]. 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 non-smokers 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*, p33). 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



Fig. 5.2 The incidence of smoking-induced lung cancer in women is increasing in many countries at an alarming rate.



Fig. 5.3 Smoking is the primary cause of lung cancer. "Every cigarette is doing you damage" campaign, Australia.

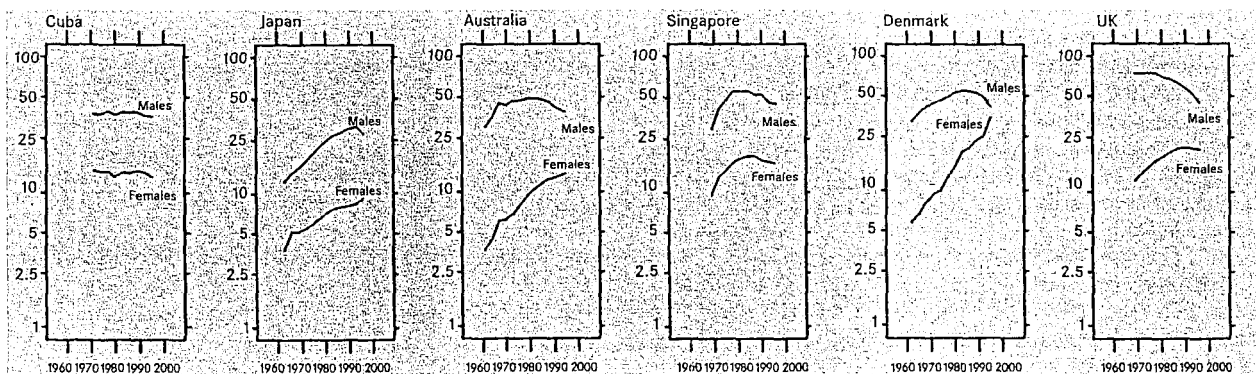


Fig. 5.4 Trends in mortality from lung cancer in men and women. Countries in which the smoking habit was first established are also the first to show decreases in mortality following reduction in the prevalence of smoking. D.M. Parkin et al. (2001) *Eur J Cancer* 37 Suppl. 8: S4 - 66.

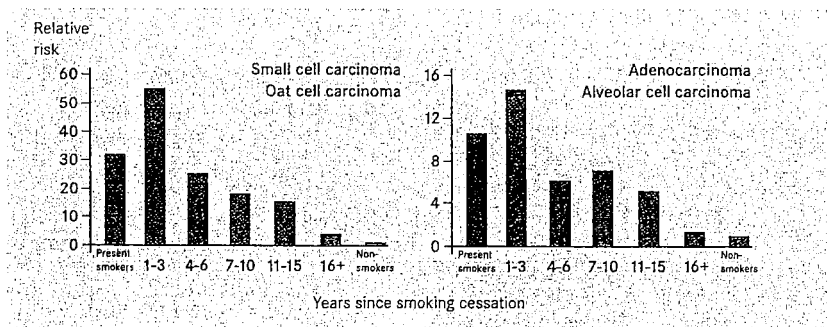


Fig. 5.5 The relative risk of lung cancer is markedly lower five years after quitting, and decreases further with time (by comparison with those who continue to smoke).

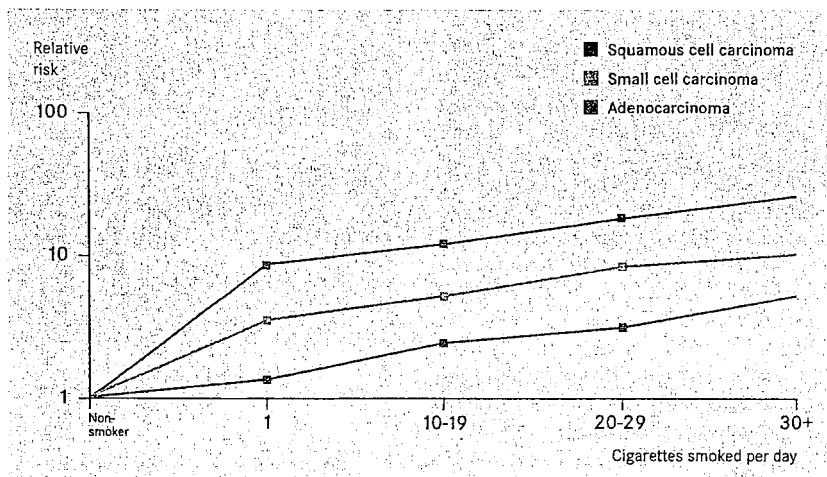


Fig. 5.6 The relative risk of major histological types of cancer by average cigarette consumption.

of lung cancer. Although the magnitude of the increased risk is moderate (relative risk, 1.5 to 2 for cumulative exposure in excess of 100 rads), the number of extra cases of lung cancer exceeds that of other neoplasms. Underground miners exposed to radioactive radon and its decay products have been found to be at an increased risk of lung cancer [5,6]. Indoor exposure to radon has been associated with a marginal increase in risk of lung cancer.

There is abundant evidence that lung cancer rates are higher in cities than in rural settings [7]. Urban air pollution is a risk factor for lung cancer and the excess risk may be in the order of 50% (*Environmental pollution*, p39). Two particular sources of indoor air pollution are the use of coal-

burning heaters without proper exhaust emission (e.g. *kang* in North-Eastern China) and high-temperature cooking using unrefined vegetable oils, such as rapeseed oil (common in several parts of China). Indoor levels of benzo[a]pyrene have been reported to be very high in such circumstances [8]. Indoor air pollution is a major cause of lung cancer in Chinese women, who experience very high lung cancer rates despite a low prevalence of smoking.

There is convincing evidence that a diet rich in vegetables and fruits exerts a protective effect against lung cancer [9]. Subjects in the categories of highest consumption experience about 50% of the risk of lung cancer compared with subjects in the categories of lowest consumption.

## 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 practicable 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 fatigue, decreased activity, persistent cough, laboured breathing, 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, pneumonia 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 paraneoplastic 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 carcinoma, 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 defi-

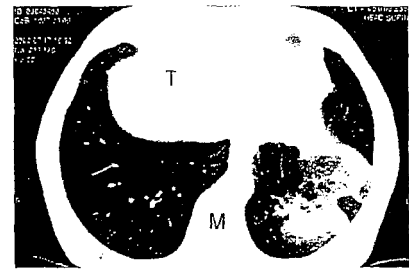


Fig. 5.7 A lung tumour viewed by computed tomography. T= tumour, M= mediastinum.

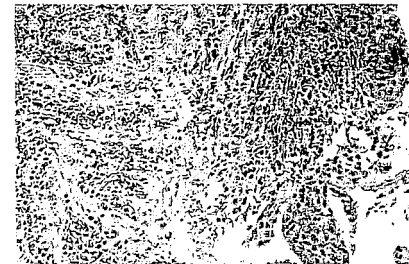


Fig. 5.8 Biopsy of a small cell lung carcinoma, showing a monomorphic proliferation of small tumour cells with dense nuclei and poorly-defined cytoplasm, invading the deep parts of the bronchial wall.

ciencies 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 60%. 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-

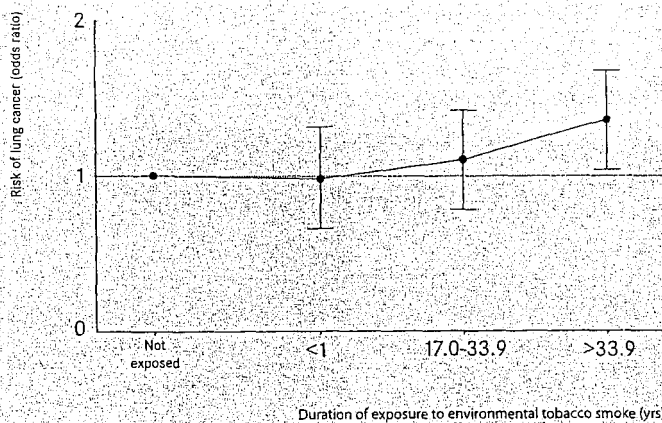


Fig. 5.9 Relative risk of lung cancer (odds ratio) among non-smokers by cumulative exposure to environmental tobacco smoke from the spouse and workplace. Pooled analysis of data from two studies in the USA and in Europe.