



# LUNG CANCER

**A multidisciplinary approach**

Edited by

**Alison Leary**



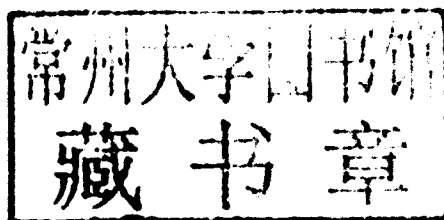
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# Lung Cancer

A Multidisciplinary Approach

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*Alison Leary*

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# Chapter 1

# Introduction to Lung Cancer and Mesothelioma

Alison Leary

## Key points

- Lung cancer is the most common cause of cancer worldwide and the most common cause of cancer death in the UK.
- The causes of lung cancer are multifactorial but there is a strong and established link with tobacco. Increasingly women who are never smokers are being diagnosed with lung cancer.
- Despite high levels of service improvement in cancer, there remains variability in the level of care provided to people with lung cancer.

## Introduction

*Malignant disease of the lung is a rare condition. The Middlesex Hospital Reports show only 890 cases of cancer of the Lung, 317 found at post mortem examination since records began.... As for prognosis a fatal termination is inevitable with average duration of the disease [life expectancy] to be 13.2 months.*

Fowler and Rickman (1898), *Diseases of the Lung*

*Lung cancer is currently the most common form of cancer worldwide...life expectancy is usually between three to seven months from diagnosis.*

From Boyle et al. (2000), *Textbook of Lung Cancer*

From being a virtually unknown disease at the end of the nineteenth century, lung cancer has become the most common worldwide cancer. In just over 100 years lung cancer has become a modern epidemic. Thought to account for over 3 000 000 deaths each year worldwide and 33 400 deaths in the UK

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from the 39 000 diagnosed (Cancer Research UK (CRUK) 2010a) and with a 5-year survival rate of only 8-11% overall.

Five-year survival from lung cancer has barely improved in the last 30 years (Spiro and Silvestri 2005) but there has been a decline in deaths in the male population and an increase in female deaths. In contrast, 1-year survival has improved to some degree. In England and Wales 1-year survival in men with advanced non-small-cell lung cancer (NSCLC) rose from 15% in the 1970s to 25% in 2000/2001 (Coleman *et al.* 2004).

Average 5-year survival in the UK is 8.95%, which can be broken down by country:

- England (8.6%)
- Scotland (8.0%)
- Northern Ireland (10.2%)
- Wales (9.0%)

This is compared with 12.3% average in Europe (Berrino *et al.* 2007) and 15% in the USA (Reis *et al.* 2004). Surgical resection of lung cancer is the primary management, but the vast majority of patients with lung cancer present at a stage that is too advanced for surgery. Surgical resection rates are lower in the UK (11%) than Europe (17%) and North America (21%) (CRUK 2010a).

It is hoped that development of targeted therapies, earlier detection and increased opportunity for surgical intervention may improve the survival rate in lung cancer.

### Epidemiology and causes of lung cancer

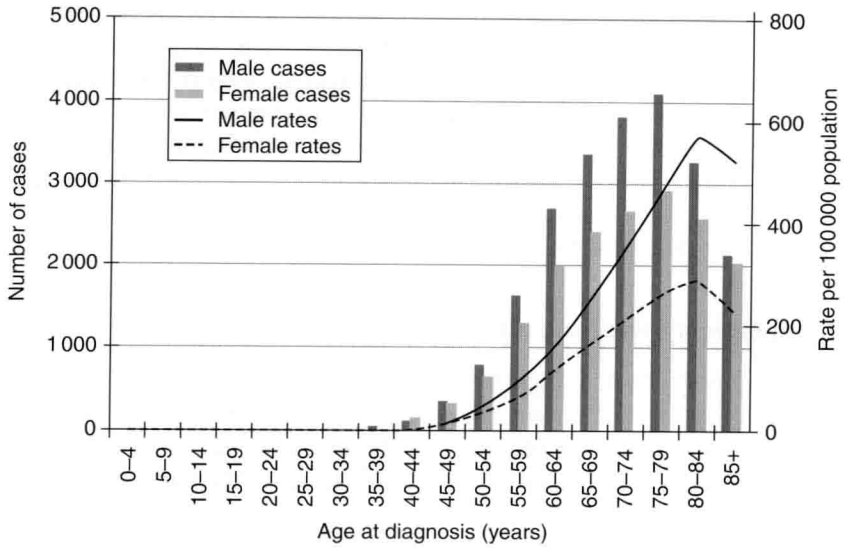
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Until recently - as late as the 1990s - lung cancer was the most frequently occurring cancer in the UK. It has now been overtaken by breast cancer but is still the cause of 1 in 7 of all new cancer cases and 1 in 5 cancer deaths. In 2007, 39 473 people were diagnosed with lung cancer (CRUK 2010b). Most cases of lung cancer (approximately 86%) occur in people over the age of 60 years; the peaking age is 75-84 years (Fig. 1.1). Lung cancer accounts for 15% of all new male cancers and 12% of all new female cancers in the UK (CRUK 2010b). Lifetime risk of developing lung cancer is 1 in 14 for men and 1 in 21 for women in the UK.

### Lung cancer incidence and social deprivation

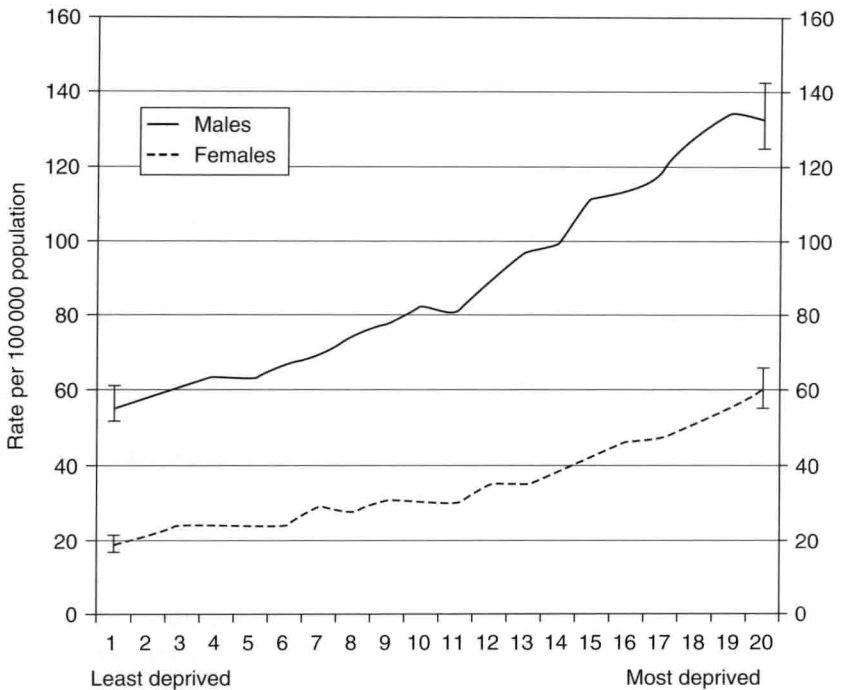
Higher incidence of lung cancer has also been linked to areas associated with higher economic deprivation. Data from the 1990s shows that the incidence of lung cancer was thought to be three times higher in women in deprived areas and 2.5 times higher in men compared with the least-deprived areas (Fig. 1.2).

Lung cancer remains a cancer prevalent in areas of socioeconomic deprivation. Data from the National Cancer Intelligence Network (NCIN) in 2008 on



**Fig. 1.1** Lung cancer: numbers of new cases and age-specific incidence rates by sex, UK 2007.

(Source: CRUK 2010b, reproduced with kind permission.)



**Fig. 1.2** Age-standardised incidence rates by deprivation category, England and Wales 1993.

(Source: CRUK 2010b, reproduced with kind permission.)

the years 2000–2004 demonstrated that if the incidence of lung cancer were the same in the most deprived groups as in the least deprived this would account for 11250 fewer cases of lung per year (NCIN 2008). Rates of lung cancer in Scotland are among the highest in the world, reflecting the history of high smoking prevalence. Many authors now comment that lung cancer is endemic in society (Boyle *et al.* 2000). The increase in incidence of lung cancer in the last hundred years has certainly been recognised. One of the causes of this rise is the now axiomatic link with smoking, particularly of tobacco.

### Lung cancer incidence and smoking

From the mid-1950s there was an increase in the understanding of the aetiology of lung cancer and also the growing awareness that lung cancer was becoming more prevalent, reaffirming a causal link to smoking tobacco. This was in part due to the benchmark studies of Doll and Hill (1950, 1952, 1954). The body of evidence was so strong that in the USA the surgeon general was moved to produce an official statement on smoking and health that caused a worldwide reaction. After the publication of these documents, a more descriptive epidemiology of lung cancer occurred with the publishing of large cohort studies, for example the work of the National Cancer Institute in the USA.

From the 1960s onwards more epidemiological research into the rise of smoking-related diseases, of which non-small-cell lung cancer is just one, also charted the way in which smoking habits have changed. For example, in the 1970s consumers were made aware of tar levels and encouraged to smoke low-tar products. Some authors contend that this merely seems to have changed the histological subtype of lung cancer without reducing its incidence. Although tobacco smoking is thought to account for the majority of lung cancer deaths (CRUK 2010b) some authors, particularly from studies in the United States, cite as many as 10–20% of all newly diagnosed lung cancers being in those who have never smoked (never-smokers).

The link between lung cancer and smoking established in the 1950s and subsequent health promotion campaigns have influenced the public perception of lung cancer as a disease of smokers. In a recent survey by the UK Lung Cancer Coalition it was found that 40% of the population considered lung cancer to be a self-inflicted cancer, despite the fact that 1 in 8 lung cancer patients are never-smokers. The belief that lung cancer was a self-inflicted cancer was higher (50%) in higher socioeconomic groups and lower (35%) in lower socioeconomic groups (UK Lung Cancer Coalition (UKLCC) 2005), and so whereas other patients with cancer are seen as victims by society, patients with lung cancer are seen as at least partly culpable for their disease. This then affects their perception of their own disease and some authors contend that lack of investment in research and other areas of lung cancer care stem from the less vocal nature of the lung cancer population and that as a group lung cancer patients tend to come from lower socioeconomic backgrounds with more limited access to education. Previous educational background influences how the cancer is perceived by the patient and family and also influences the subsequent

information needs of the patient (Chapple *et al.* 2004; Jacobs-Lawson *et al.* 2009) Because of the established epidemiological link with tobacco use, lung cancer patients often experience feelings of stigmatisation and guilt (Chapple *et al.* 2004), which gives an added dimension to their suffering.

### **Lung cancer incidence and ethnicity**

Data recently published by the National Cancer Intelligence Network on cancer incidence by survival in major ethnic group illustrates the difficulty of looking at ethnicity incidence. Data in this area is limited as it is only in recent years that routine data on ethnicity has been collected. However, from these data we can see that the rate of lung cancer in all non-white ethnic groups is significantly lower than in the white ethnic group, with people of all ages ranging from 23.1 to 37.2 per 100 000 in the Asian ethnic group, from 30.1 to 48.9 per 100 000 in the black ethnic group, from 22.4 to 48.6 per 100 000 in the Chinese ethnic group, and from 21.9 to 43.1 per 100 000 in the mixed ethnic group. In the white ethnic group the rate was 61.1 to 62.6 per 100 000 (NCIN 2009).

A standardised relative survival for the Asian ethnic group was significantly higher than the white ethnic group, for both 1 and 3 years; there is no significant difference in a standardised relative survival between black and white ethnic groups. For males aged 15–64 years at diagnosis, relative survival for the Asian ethnic group was significantly higher than for the white ethnic group at both 1 and 3 years. Given that the majority of lung cancers occur after the age of 60, these data have to be viewed in that context. For males aged 65–99 years, relative survival was significantly higher than in the white ethnic group for both Asian and black ethnic groups at both 1 and 3 years.

### **The causes of lung cancer**

Although the link between smoking and lung cancer was established in the 1950s, the smoking or direct consumption of tobacco-related products is thought not to be the sole cause of lung cancer. It is estimated that exposure to passive smoking in the home causes around 11 000 deaths every year in the UK, from not only lung cancer but also stroke and ischaemic heart disease (CRUK 2010b).

Other causes of lung cancer are thought to include radon gas, which is a naturally occurring gas that increases the chance of developing lung cancer, particularly among smokers. Radon is present throughout the UK, but in some areas geological conditions can lead to higher than average levels. Some of the highest levels are found in the south west of England. Radon is thought to account for 50% of the exposure to radiation for the average UK adult (Health Protection Agency 2010) and thus is thought to contribute overall to the incidence of lung cancer.

Other risk factors for lung cancer include industrial carcinogens; for example, arsenic, asbestos, polycyclic hydrocarbons or nonferrous metals. More recently, air pollution is now also thought to make a small contribution to the

lung cancer risk burden. There is some evidence to suggest that an increase in risk of lung cancer caused by exposure to nitrogen oxides, particularly those in traffic fumes (Vineis *et al.* 2006). Despite these other risk factors, smoking remains the largest one. Current smokers are 15 times more likely to die from lung cancer than lifelong non-smokers. The risk of developing lung cancer is affected by the level of consumption and the length of time for which a person has smoked.

### Overview of the types of lung cancer

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Lung cancer is divided broadly into two types; non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). Non-small-cell lung cancers were historically grouped together as treatment offered was often the same for each type of NSCLC but different from that for SCLC. Increasingly, however, NSCLC is thought of as much more variable. It has three main variants and this is reflected in the different treatment regimes, survival rates and range of symptoms on presentation.

In addition, another disease affecting the lung, but not a primary tumour of the bronchus or lung tissue, is malignant pleural mesothelioma (MPM). Mesothelioma can affect the pleura or peritoneum and is often managed by the same multidisciplinary team as those with lung cancer.

### Non-small-cell lung cancers (NSCLC)

Non-small-cell lung cancers are divided broadly into three types by histology. This was because historically all non-small-cell lung cancer patients were offered a limited set of treatment options. Now, with new agents and the increasingly precise nature of staging of this cancer in recent years, this has changed and is explored in more detail in Chapters 2 and 3.

Most of the patients who present with NSCLC do so as a result of progression of the tumour either locally in the chest or by metastatic spread. Such progression can precipitate the symptoms of dyspnoea, cough, chronic respiratory illness, haemoptysis and pain. Direct tumour invasion to the left laryngeal nerve may cause hoarseness of voice as a presenting symptom. Other presenting symptoms may be due to the spread of distant metastases; for example, pain at the site of bone metastasis.

The following are the main histological groupings of non-small-cell lung cancer.

- **Squamous** cell carcinoma is the most common type, accounting for 20-25% of lung cancers. Squamous cell carcinoma is usually a tumour arising from bronchial squamous epithelium and has several variants. It is the most common lung cancer in smokers.
- **Adenocarcinoma** of the lung arises from the secretory (glandular) cells located in the epithelium lining the bronchi. It is increasing in incidence and

it is likely to surpass squamous cell carcinoma in the near future as the most common type of NSCLC. Although adenocarcinoma occurs often in smokers, it is becoming the more prevalent variant of NSCLC in non-smokers and is also becoming the most common type of lung cancer in women. It can arise centrally or in the lung periphery.

- **Large-cell carcinoma** is composed of large-sized cells that are anaplastic and often arise in the bronchi.

In addition there are also bronchoalveolar carcinoma and others variants such as mixed and undifferentiated pulmonary carcinomas. It is more common these days to pursue the subtype of NSCLC histology as this can now inform treatment decisions. It is not uncommon to find mixed histological subtypes in lung cancer.

Around 80% of lung cancers in the UK are non-small-cell lung cancers (CRUK 2010b).

### Small-cell lung cancer (SCLC)

Small-cell lung cancer (also known as oat cell) is a primary lung cancer that usually arises centrally in the chest (large airways or lymph nodes). It makes up the remainder of primary lung cancers in the UK.

SCLC is associated with paraneoplastic syndromes at presentation such as inappropriate secretion of antidiuretic hormone (ISADH) as small-cell tumours contain dense neurosecretory granules that can then give this tumour endocrine/paraneoplastic syndrome components. SCLC is generally more sensitive to chemotherapy and radiation, but it often presents with metastasis in areas such as the brain or liver and usually carries a worse prognosis. Small-cell lung cancers have traditionally been staged into limited and extensive stage disease. There is recent research, however, to revise the staging system for SCLC (Shepherd 2007). This type of lung cancer is strongly associated with smoking.

### Carcinoid tumours

Carcinoid tumours are occasionally found in the lung and have been defined by the World Health Organisation (Solcia *et al.* 2000). They are divided into typical and atypical and can grow either in the airways or the lung periphery. Like SCLC, carcinoid tumours are neuroendocrine tumours and can present with local signs and symptoms such as haemoptysis or systemic symptoms such as carcinoid syndromes (flushing, wheezing, shortness of breath, tachycardia). The most common site of carcinoid tumours is the gastrointestinal tract, but occasionally they occur in the lung. Resection is the primary means of treatment.

### Malignant pleural mesothelioma

Mesothelioma is a cancer of the mesothelium and peritoneum; the most common form of this is pleural mesothelioma, also known as malignant pleural mesothelioma or MPM. Pleural mesothelioma causes the pleura to thicken.



Lung expansion can become compromised and pleural effusion, pain, weight loss or breathlessness can be some of the presenting symptoms.

Approximately 2000 people are diagnosed with mesothelioma in the UK each year (Macmillan Cancer Support 2010). In pleural mesothelioma the pleura thicken and it is thought that exposure to asbestos is responsible for 90% of all mesothelioma cases (Mesothelioma UK 2010).

### **Delivering cancer services and the multidisciplinary team**

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The years since the late 1990s have seen significant changes in the way cancer services in the UK are delivered. A programme of investment and reform with the aim of equitable and timely care delivery has taken place, with significant investment in cancer care. A fundamental part of this reform was the launch in 2000 by the Department of Health (DH) of the NHS Cancer Plan (DH 2000). The NHS Cancer Plan essentially had four aims: to save more lives; to ensure that people with cancer got the right professional support and care as well as the best treatments; to tackle the inequalities in health that mean unskilled workers are twice as likely to die from cancer as professionals; and 'to build for the future for investment in the cancer workforce through strong research and through the preparation for the genetics revolution so that the NHS never falls behind on cancer care again' (DH 2000).

In the 10 years in which the NHS Cancer Plan was launched in England there was significant improvement in the way services were delivered. One of the most significant changes was the assurance that implementation of the plan would reduce waiting times for diagnosis and treatment of any cancer. The NHS Cancer Plan recognised the inequalities in cancer care in England and became a foundation to its improvement. In 2007 the Department of Health published the Cancer Reform Strategy (DH 2007). This work reviewed the progress of the Cancer Plan with the aim of increasing cancer prevention, further speeding up the diagnosis and treatment of cancer, continuing to reduce inequalities, improving the experience of people living with and beyond cancer, ensuring that care is delivered in the most appropriate setting, and ensuring that patients can access effective new treatments quickly (DH 2007).

Many of the improvements made as a result of cancer reform in England are now included in the NHS Constitution. This includes the pledge of a maximum two-week wait to see a specialist referred for suspected cancer by their GP and that all patients referred with a suspected cancer by their GP will wait no more than 62 days from referral to treatment.

Despite many improvements in cancer care as a result of these initiatives, the recent National Lung Cancer Audit (NHS IC 2009) demonstrated that, although there have been improvements in lung cancer care, there is still variation in services offered. For example, nationally 54% of patients with lung cancer were offered an anti-cancer treatment (chemotherapy, radiotherapy, surgery) in 2008 but this varied between hospital trusts and was as low as