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Lung cancer

Introduction

Key points

- Lung cancer is the biggest cancer killer in Europe, accounting for approximately 20% of all cancer deaths and for the loss of 3.2 million disability-adjusted life-years annually in Europe.
- More than a quarter of lung cancer cases occur among the under-60s.
- Despite recent advances in surgery, chemotherapy and radiotherapy, seven out of eight patients die within 5 years of diagnosis. However, recent advances in understanding the biology of lung cancer are resulting in promising new targeted therapies.
- Smoking is by far the most important cause of lung cancer, accounting for 90% of cases in men and 80% in women. Reducing smoking and therefore eventually reducing the incidence of lung cancer requires sustained government action.

Lung cancer was a rare disease at the start of the 20th century, but exposure to new causative agents and an increasing lifespan have contributed to make lung cancer a pandemic of the 20th and 21st centuries. Lung cancer is the biggest cancer killer in Europe, accounting for approximately 20% of total cancer deaths. It remains the leading cause of cancer deaths worldwide, with 1.38 million deaths in 2008 (376 000 in Europe alone). Even though an extensive list of risk factors has been well characterised, and lifestyle changes have occurred regarding tobacco consumption, particularly in men in western Europe, lung cancer remains a huge health problem. The relevant International Classification of Disease (ICD) codes (used to code and classify mortality data from death certificates) are ICD-10 C33 (neoplasm of the trachea) and ICD-10 C34 (neoplasm of bronchus and lung).

Unfortunately, lung cancer usually becomes manifest late in its natural history, so that curative treatment is not possible in up to 90% of cases. In Europe, the overall 5-year survival for men with lung cancer is only 11.2% and for women it is 13.9%. Research has aimed to identify patients with early-stage disease in the hope of improving survival and developing individualised therapies for patients with advanced disease. Prolonging survival and improving quality of life for patients presenting with inoperable lung cancer are also subjects of current research.

> *It is now recognised that patients with different subtypes of cancer respond differently to treatment, and it is possible to tailor treatment according to the tumour subtype*

Epidemiology

Incidence

The World Health Organization (WHO) and the Organisation for Economic Cooperation and Development (OECD) provide comprehensive data on the epidemiology of lung cancer in Europe and worldwide. In 2008, there were an estimated 1.6 million new cases worldwide, representing 12.7% of all new cancers. Men are more frequently affected worldwide (1.1 million *versus* 0.5 million cases in women), with higher rates in central–eastern and southern Europe, North America and eastern Asia. In some Western countries where the tobacco epidemic reached its peak by the middle of the 20th century (*e.g.* the UK, Finland, and the USA), lung cancer rates have been decreasing slowly in men and plateauing in women.

Lung cancer is the second most common malignancy following prostate cancer in men of OECD countries. Figure 1 shows lung cancer incidence across Europe for men and women combined; figure 2 illustrates the marked difference in incidence between the sexes. In men in the European Union (EU), the highest rates are seen in Hungary (109.5 cases per 100 000 males), Poland (104.5 per 100 000) and Estonia (91.5 per 100 000). In women, Denmark (49.5 cases per 100 000 females), Hungary (39.8 per 100 000) and the UK (38.7 per 100 000) have the highest rates. Among non-EU countries, the highest reported incidence is seen in Armenia (111.1 per 100 000) in men and in Iceland (48.0 per 100 000) in women (figure 2).

Even though lung cancer incidence in women is generally lower than that in men, worldwide, lung cancer is now the fourth most common cancer in women (513 000 cases in 2008, 8.5% of all cancers) and the second most common cause of death from cancer (427 000 deaths, 12.8% of total cancer deaths). It has been estimated that in the UK in 2008, the lifetime risk of developing lung cancer was one in 14 for men and one in 19 for women. The incidence of lung cancer also varies within countries: in the UK, it is higher in Scotland and northern England, reflecting the historically higher rates of smoking in these areas. In Europe, the 388 753 lung cancer cases in 2008 had the following age distribution at diagnosis: approximately 6% were below 50 years of age, 20% were 50–59 years of age, 29% were 60–69 years of age, and 44% were over 70 years of age.

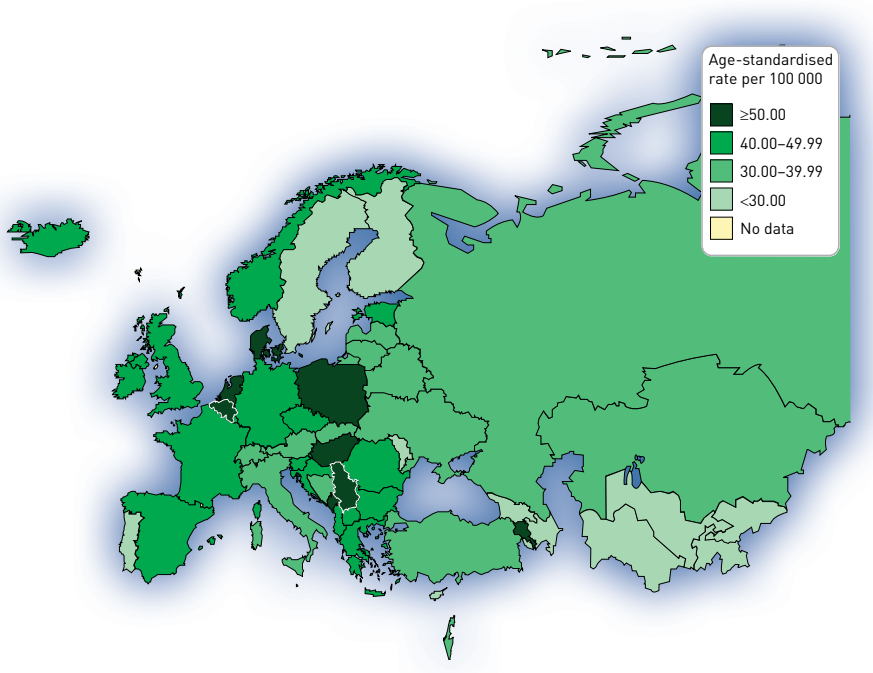

Figure 1 – Incidence rate of lung cancer. Data from Ferlay *et al.*, GLOBOCAN 2008 v2.0, 2010.

Annual mortality

Figure 3 shows lung cancer mortality in Europe. Hungary showed the highest mortality rate of all European countries with an average of 65.9 deaths per 100 000 population, followed by Denmark with 52.3 deaths per 100 000 and Serbia with 51.3 deaths per 100 000. The lowest death rates in the EU were seen in Portugal and Cyprus (23.8 per 100 000). Lower mortality rates were reported in Tajikistan (6.5 per 100 000) and Uzbekistan (8.9 per 100 000); however, the efficiency of case reporting systems in those countries is unclear.

Morbidity from lung cancer

Most patients with lung cancer presenting to healthcare settings have symptoms or signs of the disease. However, these clinical features are nonspecific in their onset and are often attributed initially to benign causes by both patients and healthcare providers. This often results in a delay before patients seek medical attention and a further delay before the practitioner initiates any diagnostic tests.

The most common symptoms and signs are cough, weight loss and dyspnoea, followed by chest pain, haemoptysis, bone pain, finger clubbing and hoarseness. Less common are weakness, superior vena cava obstruction, dysphagia, wheezing and stridor.

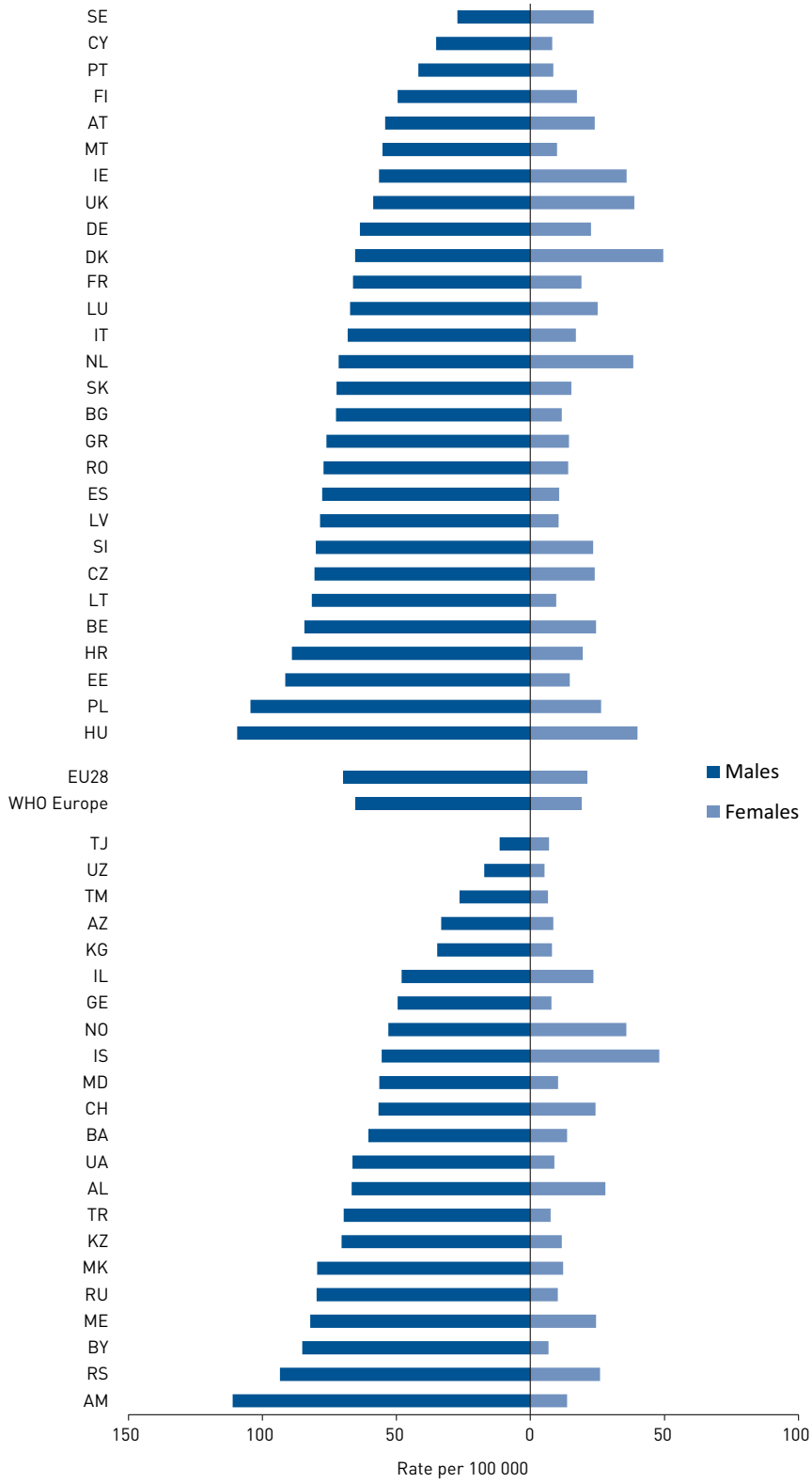

Figure 2 – Age-standardised incidence of lung cancer by sex, 2008. Data from Ferlay *et al.*, GLOBOCAN 2008 v2.0, 2010.

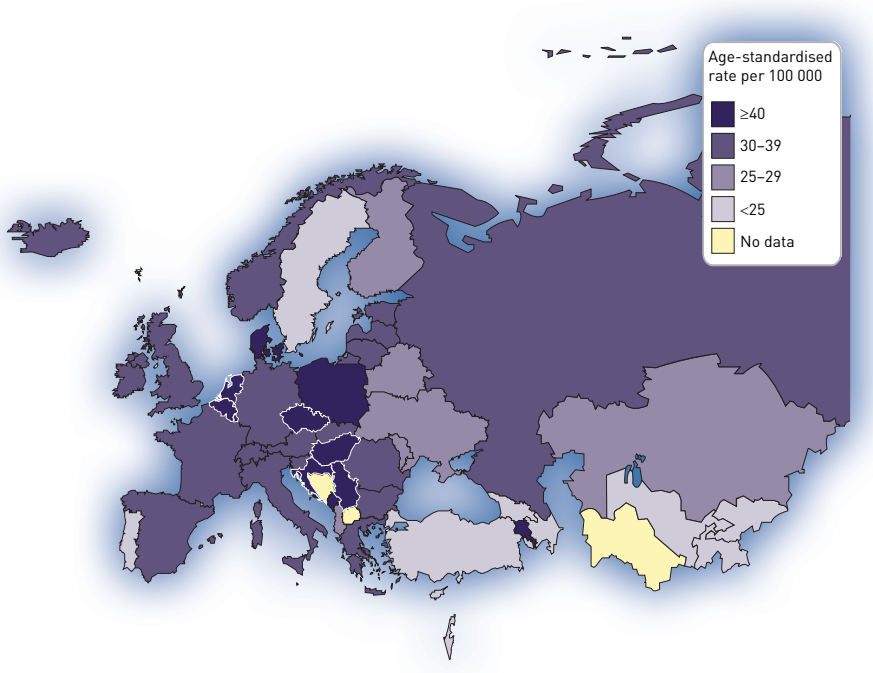

Figure 3 – Mortality rate for lung cancer. Data from the World Health Organization World and Europe Detailed Mortality Databases, November 2011 update.

A commonly used index of the burden of a disease is the loss of disability-adjusted life-years (DALYs). This is a term developed by the WHO and the World Bank to measure the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. Due to its high prevalence and mortality, lung cancer causes the highest losses of DALYs of all the cancers: in Europe, lung cancer accounts for approximately 3.2 million DALYs lost annually.

Causes

Table 1 summarises the risk factors for lung cancer. Smoking is by far the most important cause, accounting for 90% of cases in men and 80% in women. Tobacco smoke contains more than 7000 chemicals, at least 70 of which are known to cause cancer in humans or animals (see chapters 8 and 9). People who smoke are 15–30 times more likely to be diagnosed with lung cancer or die from it than those who do not smoke, and the risk increases with the quantity and duration of smoking. Chronic obstructive pulmonary disease (COPD) is also a risk factor for lung cancer and patients with airflow limitation are more likely to develop lung cancer than those with normal airway function, independent of smoking status. Asbestos exposure is another important risk factor,

Risk factors for lung cancer		
Smoking	COPD	Asbestos
Radon	Chromium	Arsenic
Beryllium	Diesel exhaust	Pulmonary fibrosis
Head/neck/oesophageal cancer	Genetic susceptibility	Lymphoma or breast cancer treated with thoracic radiotherapy
Family history of lung cancer	Air pollution	Coal smoke, indoor emissions from other fuels

Table 1 – Lung cancer risk factors. COPD: chronic obstructive pulmonary disease.

with lung cancer developing in 20–25% of heavily exposed asbestos workers (see chapters 7 and 24). Asbestos is particularly found in insulation, pipe lagging and brake pads. Exposure to radon, chromium, arsenic and beryllium are further risk factors, and recently, diesel exhaust was added to the list. Other factors that may predispose to lung cancer include pulmonary fibrosis and a medical history of cancer of the head and neck or oesophagus. Genetic susceptibility plays a contributory role in the development of lung cancer, especially in those who develop the disease at a younger age and those who are nonsmokers. A family history of lung cancer has been implicated in conferring a higher risk. Smokers who have previously had lymphoma or breast cancer treated with thoracic radiotherapy also appear to be at increased risk.

Prevention

It is widely accepted that smoking is the leading cause of lung cancer and smoking cessation remains the most effective method of reducing its incidence. Although attempts to reduce smoking rates have been relatively successful in the Western world, there is a lag of 20 years or so between reducing smoking and reducing the incidence of lung cancer. Despite the recent reduction in smoking rates seen in some countries (particularly in men), further education on the harmful effects of smoking as well as smoking-cessation programmes are urgently required and efforts need to be intensified (see chapter 8). It is recognised that exposure to environmental tobacco smoke is also associated with lung cancer risk (see chapter 9). Therefore, uniform policies on the banning of smoking in public places are required and their implementation needs to be assured in all countries.

Asbestos is a known carcinogen and its combination with cigarette smoking confers a greater than 40 times increased risk of lung cancer. Despite this, a worldwide ban on asbestos use is not in force and is urgently required (see chapter 7).

Management

Treatment options are determined by the histological cell type, the stage of cancer at diagnosis, patient performance status and the patient's wishes. Socioeconomic

deprivation, depression, comorbidities and late diagnosis all result in lung cancer being difficult to treat. Treatments include surgery, chemotherapy and radiotherapy.

Over the past 10 years, surgical techniques have trended towards minimal invasiveness. This offers comparable or sometimes better results in terms of patient outcome than the classical, more invasive procedures. Video-assisted thoracic surgery (VATS) is a form of keyhole surgery on the lung; its use in the management of patients with lung cancer was initially met with much scepticism. However, VATS-guided excisions and lobectomies have become established in the management of patients with early-stage lung cancer. VATS has an important role in patients with significant comorbidities and borderline pulmonary function, since recovery is usually quicker than after thoracotomy. Consequently, more patients with lung cancer are able to have operations. In addition, in order to improve the prognosis, adjuvant (post-operative) or neo-adjuvant (pre-operative) chemotherapy and/or radiotherapy may be useful (this is known as multimodal therapy).

"Lung cancer usually becomes manifest late in its natural history, so that curative treatment is not possible in up to 90% of cases"

Significant advances have also been made in chemotherapy. It is now recognised that patients with different subtypes of lung cancer respond differently to treatments and it is possible to tailor treatment according to the tumour subtype. For example, patients with advanced adenocarcinoma of the lung will benefit from pemetrexed plus platinum, while those with squamous cell carcinoma of the lung will benefit from gemcitabine plus platinum.

Recent advances in understanding the biology of lung cancer have resulted in newer targeted therapies, such as the tyrosine kinase inhibitors (erlotinib or gefitinib), which are known to be particularly beneficial in patients with advanced lung cancers that harbour a mutation in the epidermal growth factor receptor. Oral tyrosine kinase inhibitors are now licensed for the first-line treatment of patients with advanced lung cancer. In genetically selected patients with advanced lung cancer, these oral agents have been shown to be superior to conventional chemotherapy. In 2012, the European Medicines Agency approved the oral agent crizotinib for patients with advanced lung cancer and this may be preferred to standard chemotherapy when the lung cancer is shown to have an EML4-ALK fusion gene.

Radiotherapy techniques for lung cancer are also continuing to evolve. Modern radiotherapy employs techniques to spare surrounding tissues from the damage-enabling higher radiation doses applied to the cancer. The advent of

stereotactic radiotherapy has allowed patients with poor lung function, who previously may not have received treatment, to receive radiotherapy.

Interventional bronchoscopic techniques are useful in the palliative care of patients with cancers that obstruct major airways.

Prognosis

Lung cancer survival rates are a measure of the proportion of people who remain alive with lung cancer after a certain amount of time. Survival rates for lung cancer vary depending on the subtype of cancer and at what stage the illness is diagnosed. The 1-year relative survival for lung cancer in the USA increased from 35% in 1975–1979 to 43% in 2003–2006, largely due to advances in surgical techniques and chemoradiotherapy. However, the prognosis also depends upon the histological type: for example, small cell lung cancer usually has a worse prognosis than nonsmall cell lung cancer.

The TNM (Tumour, Nodes, Metastases) system, which was updated for nonsmall cell lung cancer in 2010, is used by health professionals as a common way of staging cancer. In individual patients, the TNM system is used in decisions about treatment and prognosis. It is also used on a population basis to inform and assess treatment guidelines, cancer research and planning. The individual T, N and M scores are based, respectively, on the size and situation of the primary tumour (T1–T4), the extent of lymph node involvement (N0–N4), and recognition of the presence of metastases (M0 or M1). These scores are combined to give a stage (I–IV) for the cancer, with higher stages associated with shorter survival (table 2).

Treatment of lung cancer: current needs

- Lung cancer patients should be investigated and treated as outpatients whenever possible. This should reduce the financial burden of the disease and decrease the psychological impact of the disease on patients and families.
- Staging of lung cancer is critical to determine the prognosis and treatment options. Novel staging techniques (positron emission tomography (PET) scans, endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS)) should increasingly be made available in cancer centres as they will offer quick and accurate outpatient diagnosis and staging of the disease. Hospital admissions will be reduced and shorter time intervals from presentation until treatment decision will be achieved.
- Targeted therapy: advances in tailoring chemotherapy to the type of lung cancer must be matched by the availability of diagnostic services for lung cancer phenotyping and genotyping.
- The availability of lung-sparing radiotherapy techniques should increase in treatment centres throughout Europe. Intensity modulation radiation therapy (IMRT), gamma knife and image-guided radiation therapy are all high-precision modalities that allow tracking of respiratory movement during treatment, sparing of healthy lung tissue and reduced risk of radiation-induced lung toxicity.

Stage	T	N	M	5-year survival %
Ia	T1a	N0	M0	50
	T1b	N0	M0	
Ib	T2a	N0	M0	43
IIa	T1a	N1	M0	36
	T1b	N1	M0	
	T2a	N1	M0	
	T2b	N0	M0	
IIb	T2b	N1	M0	25
	T3	N0	M0	
IIIa	T1	N2	M0	19
	T2	N2	M0	
	T3	N2	M0	
	T3	N1	M0	
	T4	N0	M0	
	T4	N1	M0	
IIIb	T4	N2	M0	7
	T1	N3	M0	
	T2	N3	M0	
	T3	N3	M0	
	T4	N3	M0	
IV	T Any	N Any	M1a or 1b	2

Table 2 – The new TNM (Tumour, Node, Metastases) classification in nonsmall cell lung cancer with corresponding 5-year survival rates per stage. Ta and Tb refer respectively to larger and smaller primary tumours and M1a and M1b respectively to intrathoracic and distant metastases. Modified from International Union against Cancer, 2010 and see also details in Detterbeck *et al.*, 2009.

"The advent of low-dose helical computed tomography has revolutionised the landscape of lung cancer screening"

The 5-year survival rate for patients with lung cancer of all stages combined remains poor, at only 12.6%. Figure 4 shows the age-adjusted 5-year relative survival, reported in 2008, of patients diagnosed in 2000–2002 in various European countries. Detailed comparisons between countries suggest that some differences (for example, the low survival rate in the UK) may be explained in part by presentation with more advanced disease due to poor population awareness and consequent late access to healthcare, but an effect of differences in diagnostic and therapeutic activity cannot be excluded.

Future developments

- A further reduction in smoking prevalence in all groups may be achieved by government campaigns with the longer-term goal of reducing lung cancer incidence.

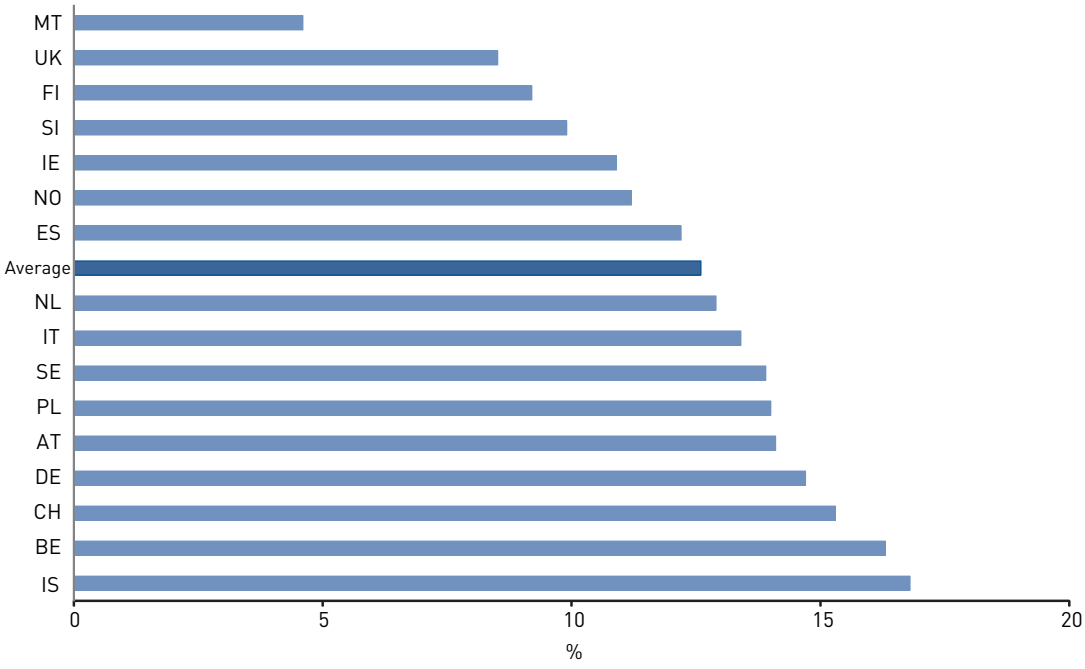

Figure 4 – Age-adjusted 5-year survival from lung cancer in selected European countries among patients diagnosed 2000–2002 relative to that of the general population. Survival for the UK has been derived from estimates for England, Scotland, Wales and Northern Ireland and the average independently calculated. Data from EUROCARE-4 study (www.eurocare.it).

However, this will require intensification and further funding of smoking-cessation programmes.

- Genetic profiling of lung cancer may become routinely available or be encompassed in clinical trials, and will enable therapy to be personalised using targeted agents according to the genetic profile of the tumour.
- Standardised and universal data collection for patients with lung cancer across Europe must be a priority.
- Positron emission tomography-computed tomography (PET-CT), endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) will play a prominent role in diagnosing and staging lung cancer.
- Lung-sparing radiotherapy techniques will become more widely available.
- The clinical effectiveness and cost-effectiveness of lung cancer screening with low-dose computed tomography (CT) will be clarified, as will patient selection.
- There will be a focus on quality of life of patients with advanced lung cancer as well as survival.
- Patients will have improved access to palliative care resources.

Research needs

In patients with advanced nonsmall cell lung cancer, drugs against newer molecular targets (*e.g.* Ros1) are currently being evaluated in early-phase clinical trials. It is a priority that these agents are then tested in later-phase trials so that any benefits discovered can be translated into better patient outcomes as soon as possible.

Refining radiotherapy techniques also holds considerable promise, while there is ongoing work in the area of biomarkers for the early diagnosis of lung cancer. Novel staging tools (for example, newer PET ligands and magnetic resonance imaging (MRI)) may improve the accuracy of lung cancer staging, thereby leading to more appropriate treatment for patients.

Lung cancer screening is another promising research field. Since the majority of lung cancer patients present late in the natural history of the disease, the concept of screening high-risk asymptomatic people to detect early-stage (curable) disease is attractive. The advent of low-dose helical CT has revolutionised the landscape of lung cancer screening and has made this a possibility. In 2011, the National Lung Screening Trial (NLST) in the USA demonstrated that screening with the use of low-dose CT reduces mortality from lung cancer by 20%. The challenge is now to determine whether results from this trial can be reproduced in trials in Europe and whether the intervention is cost-effective. Currently, there is optimism about screening with low-dose CT scanning, with results awaited from ongoing lung cancer screening trials in western Europe (NELSON and the UK Lung Cancer Screening (UKLS) trial). Further research is required on identifying high-risk patient groups using phenotypic or genetic characteristics or biomarkers. Finally, studies of pre-malignant lesions may offer insight into cancer formation and provide targets for preventing the development of lung cancer.

There is a great need to establish well-organised and reliable lung cancer databases with a uniform design and standardised collection of (and ready access to) epidemiological data across Europe. This would allow trends to be identified, and prompt investigation at a public health level to clarify the reasons for differences in survival between countries. In addition, reporting of the disease and its impact on patients would be improved.

Lung cancer in never-smokers is of particular interest, and these patients comprise a growing proportion of adults with lung cancer in economically developed countries. It is important to identify epidemiological, clinical and molecular patterns of this disease and, in particular, the relevant risk factors. A uniform database of patients with lung cancer would be an important step forward in achieving these goals.

Further reading

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