

## ERS School Course Early-stage lung cancer

# What's new in the epidemiology of lung cancer: the female aspect



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## Educational aims

- ▶ To describe the incidence of lung cancer in the USA and Europe.
- ▶ To identify the epidemiological specificities of lung cancer in females.
- ▶ To correlate some of these specificities with genetic and hormonal factors.

## Summary

There has been a tremendous increase in lung cancer incidence in females, which is mainly due to the increase in tobacco consumption by females after the Second World War in the USA and from the end of the 1960s in Europe.

However, there are more non-smoking females developing lung cancers than non-smoking males, and lung cancer can be attributed to active tobacco smoking only in ~70% of female lung cancer cases in Europe. Even if the female patients who develop lung cancer are smokers, the amount smoked is consistently less than that of males, thus suggesting an increased susceptibility to carcinogens of smoke. This increased susceptibility is still controversial, but there are several genetic differences that may account for such an increased susceptibility.

## Key points

- ▶ Lung cancer is more frequent in non-smoking females than in non-smoking males.
- ▶ Although the main reason for the tremendous increase in lung cancer incidence in females is tobacco, there are several other potential risk factors.
- ▶ There are genetic factors that could explain different susceptibility to lung cancer development in both sexes.

The main epidemiological novelty in lung cancer is the tremendous increase in its incidence in females over recent years. This phenomenon began in the USA several years ago, and has lately been observed in Europe. An increase in tobacco-smoking rates appears to be the main cause of this rise in lung cancer incidence in females. However, smoking habits in females are quite different to males, and other risk factors that are specific to females also appear to play a role. Genetic differences and hormonal factors underlie these epidemiological features.

## Lung cancer incidence and prevalence

Lung cancer is the most common cancer in the world and has been since 1985. In 2002, there were 1.35 million new cases of lung cancer diagnosed, which represented 12.4% of all new cancers [1]. Lung cancer is also the most frequent cause of death by cancer, accounting for 1.18

million deaths in 2002 (a value comparable to the incidence) [1]. Figure 1 shows the position of lung cancer in the ranking of new cancer cases for males and females, together with the corresponding numbers of deaths in the developing and developed regions of the world. In females, the incidence rate is globally 12.1 cases per 100,000, compared with 35.5 cases per 100,000 in males. The 5-year survival rate in patients with lung cancer is about 15% in the USA, 10% in Western Europe and 9.8% in developing countries.

In Europe, lung cancer is the most frequent cause of death by cancer in males (figure 2). The highest rates of incidence and mortality in 2000 were observed in Belgium (76.43 and 70.85 cases per 100,000, respectively) and the Netherlands (62.04 and 59.71 cases per 100,000, respectively), whereas the lowest rates were in Sweden (21.41 and 22.64 cases per 100,000, respectively) [2, 3].

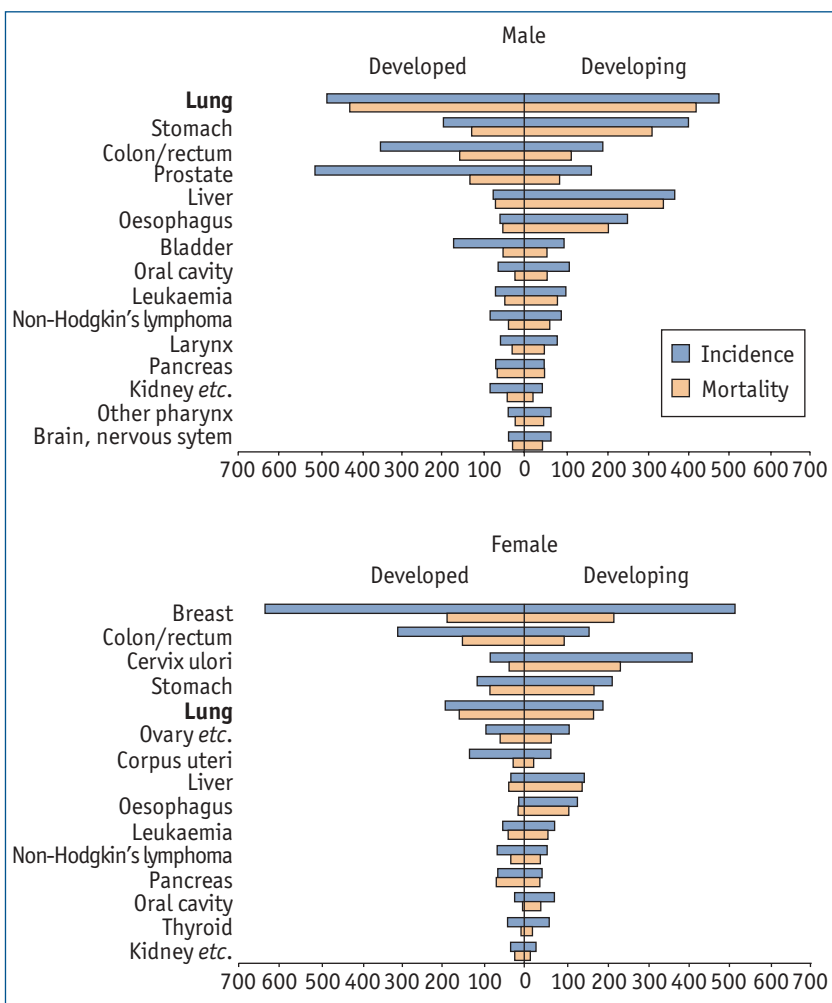
Sex ratios for lung cancer are quite different according to the European country from which the data are taken, which reflects differences in smoking habits. The lowest sex ratio (male/female) is 1.7 in Denmark and the highest is 13.4 in Spain. The sex ratio is 2.4 in Northern Europe, whereas it is 7.4 for Southern Europe and 5.0 for Western Europe. While stabilisation or even a decrease in the number of lung cancers in males has begun in most countries in Europe, mortality due to lung cancer is increasing in females [3].

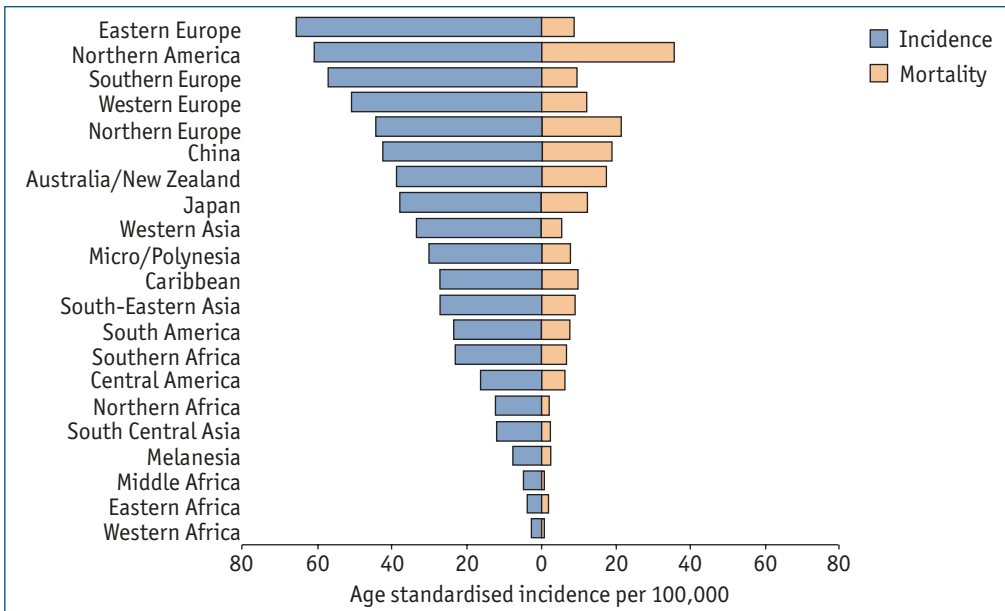
In the USA, incidence and mortality standardised rates in 2000 were 58.6 and 53.2 in males and 34.0 and 27.2 in females, respectively, with a sex ratio of 1.7 [2]. Since 1987, mortality due to lung cancer in females has surpassed mortality from breast cancer [4]. In parallel with tobacco consumption increase, the mortality rate due to lung cancer in females increased by 600% in the time period between 1990 and 1997 [5]. In France, between 1985 and 1995, the incidence of lung cancer in females almost doubled, with 1,892 diagnosed cases in 1985, 3,578 in 1995 and 4,591 in 2000 [6, 7]. As a consequence, lung cancer, which was the 6th highest cause of cancer death in females in 1985, was ranked 3rd in 1995.

## Changes in tobacco consumption in Europe

Importantly, there has been a decrease in tobacco consumption in the UK, Sweden and Finland from 1970 until 1994. However, there has been

**Figure 1**  
Estimated numbers of new cancer cases (incidence) and deaths (mortality) in 2002. Reproduced with permission from [1].





**Figure 2**  
Age-standardised incidence rates for lung cancer. Reproduced with permission from [1].

an increase in consumption in other countries such as Portugal. In France, the prevalence of smoking has decreased in males, whereas it has increased in females, particularly in the age range of 20–50 years. This is probably explained by the tremendous increase in tobacco consumption that occurred at the end of the 1960s, 20 years later than the same trend in the USA, paralleling the women's lib movements.

## Histological distribution in males and females

Adenocarcinoma is the main histological subtype in female lung cancer cases, and this is not dependent on smoking status (figure 3). The second most frequent is small cell lung cancer, whereas squamous cell carcinoma is still the main histological subtype in males, at least in Europe [8, 9]. An increase in adenocarcinoma incidence

might be due to the type of cigarette used: filters induce a deeper inhalation and, thus, more peripheral distribution of the smoke where adenocarcinomas arise [10].

## Factors that influence lung cancer in females

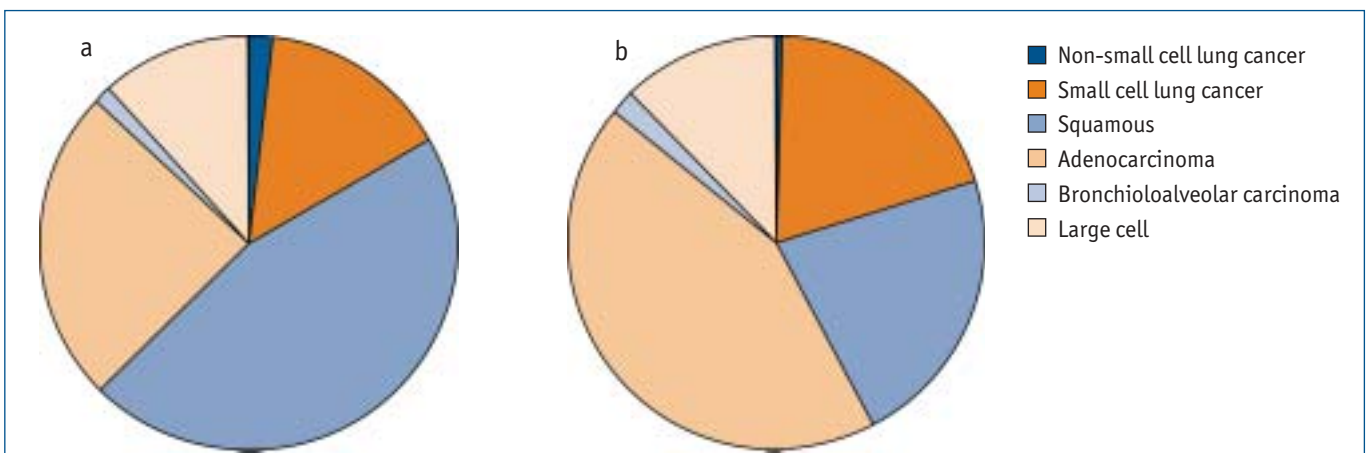
### Age

Some studies have shown a higher age at diagnosis in females with lung cancer when compared with males [11, 12]. However, a lower age has been reported in other studies [13].

### Smoking

Even if tobacco is the main cause of lung cancer in females, the attributable risk is lower in females when compared with males. For example, worldwide in 2000, an estimated 85% of lung cancers were attributed to tobacco smoking in males,

**Figure 3**  
Histological distribution of lung cancer in males (a) and females (b).



compared to 47% in females [1]. In Europe, ~70% of lung cancers in females are attributed to an active smoking habit *versus* 85% in males [7].

The proportion of non-smoking females with lung cancer is significantly higher when compared with males [12–14]. In addition, several studies have shown that the mean consumption of tobacco in females with lung cancer is much less than males with lung cancer [13–15]. Hence, it has been concluded that females have a higher sensitivity to tobacco-smoke carcinogens than males. This can be explained by several factors, including a lower capacity for DNA repair in females [16]. DNA adducts due to tobacco smoke are more frequent in females than in males, whatever the level of smoking, and *CYP1A1* (a gene involved in the first phase of the metabolism of polycyclic aromatic hydrocarbons) expression is higher in females [17]. *K-Ras* mutations are also more frequent in female smokers than in male smokers [18], and have been observed in non-smoking females [19].

Even taking the above into account, there is no agreement with the concept of higher risk in females [20, 21] and several biases need to be taken into account, such as the absolute risk being higher in non-smoking females compared to non-smoking males; the reluctance of females to express their true smoking habits; and the heightened importance of environmental tobacco smoke (ETS) exposure in females.

Genetic polymorphisms may explain some individual variations in risk due to smoking habits. The role of glutathione *S*-transferase M1 (*GSTM1*) has been demonstrated in lung cancer: a lack of activity is associated with an increased risk of lung cancer in smokers [22]; deletion of the gene results in a greater increase in risk of lung cancer in female smokers than in male smokers [23];

and the combination of the null genotype of *GSTM1* with a mutation of *CYP1A1* also results in an increase in lung cancer risk for females [24]. The null genotype of *GSTM1* also seems to result in an increase in lung cancer risk due to ETS exposure in females [25].

The expression of receptors to gastrin-releasing peptides plays an important role in proliferation stimulation in lung cancer. This receptor has been shown to be expressed in 55% of non-smoking-female cases *versus* 0% of non-smoking males, and in 75% of smoking females with <25 pack-years *versus* 20% of males [26]. The receptors are mainly found in epithelial cells and fibroblasts with a high affinity for nicotine. Hyperexpression in females could be attributed to the location of the receptor gene, which is located on the part of the X chromosome that escapes inactivation.

## Hormones

It is well established that oestrogens may act as direct carcinogens by means of chromosomal alterations and genetic mutations [27]. Hormone-replacement therapy and oral contraception have controversial effects on the risk of developing lung cancer [28].

Receptors ( $\alpha$  and  $\beta$ ) to oestrogens have also been found in bronchial tumour cells, with a more frequent expression in females [29]. Thus, oestrogens could play an additional role in carcinogenesis through these receptors in addition to its direct carcinogenic actions.

## Dietary factors

Fruit and vegetable consumption has been reported to be a protective factor against lung cancer [30]; however, whether a difference in the level of protection between males and females exists is controversial.

## Other factors

A previous history of respiratory disease is more frequently reported in females with lung cancer than in controls [31]. Occupational risk is, of course, less frequent in females. The role of radon in the home has been controversial for many years, but it is now recognised that there is a small added risk of getting lung cancer with radon exposure [32]. In developing countries, the role of fossil fuel combustion and cooking fumes is already well established [33, 34].

ETS exposure has been extensively studied for several years with controversial results that probably relate to measuring difficulties. The results of meta-analyses have concluded that there is an



increased risk of developing lung cancer in females exposed to tobacco smoke from their spouses [35]. More recent studies have confirmed the increased risk linked to ETS [36, 37].

## Conclusion

Lung cancer remains the most frequent cause of death by cancer throughout the world, representing a heavy burden for humankind. In

developed countries, a peak seems to have been attained in males, but the tremendous increase in frequency in females is the main and most worrying recent epidemiological trend. This increase in female cases of lung cancer should be seriously considered, as it will subsequently lead to changes in the general age of onset of the disease and the histological subtype distribution, as well as the clinical features, therapeutic management and, ultimately, prognosis.

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