

# Epidemiology of Lung Cancer

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## Abstract

### Keywords

- lung cancer
- lung neoplasms
- tobacco
- epidemiology
- etiology

Incidence and mortality attributed to lung cancer has risen steadily since the 1930s. Efforts to improve outcomes have not only led to a greater understanding of the etiology of lung cancer, but also the histologic and molecular characteristics of individual lung tumors. This article describes this evolution by discussing the extent of the current lung cancer epidemic including contemporary incidence and mortality trends, the risk factors for development of lung cancer, and details of promising molecular targets for treatment.

**Objectives:** Upon completion of this article, the reader will be able to identify the etiology, epidemiology, and molecular therapeutic targets of lung cancer.

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## History

Incidence and mortality attributed to lung cancer has risen steadily since the 1930s, predominantly due to the popularity of cigarette smoking.<sup>1</sup> In the past 100 years, lung cancer has therefore been transformed from a rare disease<sup>2</sup> into a global problem.<sup>1</sup> Efforts to improve outcomes have not only lead to a greater understanding of the etiology of lung cancer but also the histologic and molecular characteristics of individual lung tumors.

Accounts of lung cancer in the scientific literature date back to the early 1400s, when up to 50% of miners working along the border of Germany and the Czech Republic died of a

pulmonary disease called *bergkrankheit* (mountain disease).<sup>3,4</sup> In 1879 Harting and Hesse performed 20 autopsies on miners and described pulmonary sarcoma in 75% of these patients diagnosed with *bergkrankheit*. It was hypothesized that dust inhalation was a causative factor of this illness, which was later identified as squamous cell carcinoma of the lung.<sup>5</sup> Investigators in the 1920s and 1930s proposed radiation and radon gas as potential etiologic agents. With the incidence of lung cancer increasing in the 1930s, Ochsner and DeBaakey reviewed the increasing number of lung cancers among their patients and concluded that cigarette smoke inhalation was a probable responsible factor.<sup>6</sup>

Sir Richard Doll and Austin Hill's landmark article in 1950 described mounting evidence that lung cancer was associated with cigarette smoking.<sup>7</sup> The 1962 report by the Royal College of Physicians and the 1964 warning by the surgeon general of the United States firmly established the correlation between cigarette smoking and lung cancer.<sup>8,9</sup> It is now known that most deaths from lung cancer—80 to 85%—which is now the leading cause of cancer mortality in the United States, are directly attributable to smoking.<sup>10,11</sup>

## Incidence

Six million new cases of lung cancer, or 12.7% of the world's total cancer incidence, were diagnosed in 2008.<sup>12</sup> Lung cancer was estimated to cause 160,340 deaths in the United States in 2012, potentially accounting for 28% of all cancer deaths in the country.<sup>1</sup> The global geographic distribution of lung cancer

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demonstrates marked regional variation, with age-standardized incidence rates ranging >60-fold in men and 30-fold in women.

Lung cancer is the most common cancer in men worldwide with an age-standardized rate (ASR) of 33.8 per 100,000, and it is the fourth most frequent cancer in women (13.5 per 100,000).<sup>12</sup> In men, the highest incidence rates are observed in North America, East Asia, central-eastern and southern Europe (48.5 to 56.5 per 100,000). In less developed countries, the highest rates are seen in West Asia, South Africa, and the Caribbean (25.7 to 32.2 per 100,000).<sup>12</sup> In women, the worldwide incidence rates of lung cancer are lower; the highest rates are seen in North America and in Northern Europe (35.8 to 37 per 100,000).

In men, several nations have now passed the peak of the tobacco-related epidemic, and incidence and mortality rates are now decreasing. For example, in the United States, the ASR has declined from 102 cases per 100,000 in men in 1984 to 69 cases per 100,000 in 2009. In women, however, the incidence has increased over this time period but has plateaued in the past decade, most recently calculated to be 51 per 100,000 in 2009 compared with 39 per 100,000 in 1984.<sup>13</sup> The lifetime probability of developing lung cancer in men in the United States is 1 in 13; for women it is 1 in 16.<sup>14</sup> The long-term trends in the age-adjusted lung cancer incidence among men and women are consistent with the historic pattern of tobacco use. Incidence rates of lung cancer also differ by ethnicity. In 2009, African Americans had the highest incidence rates of 69 per 100,000, whereas Hispanics had the lowest rate of 30 per 100,000.<sup>14</sup>

Conversely, incidence rates for men in southern and eastern European countries, Japan and China, and for women from most developed countries continue to increase or have recently begun to plateau.<sup>15–19</sup> Trend data are scarce for less developed countries, but evidence suggests that lung cancer rates among women in Latin America are increasing,<sup>20</sup> and lung cancer incidence is predicted to increase in Asia and Africa, particularly among men.<sup>21</sup>

## Mortality

Lung cancer has been the leading cause of cancer deaths among men since the early 1950s, and in 1987 it surpassed breast cancer to become the leading cause of cancer deaths among women in the United States.<sup>12</sup> In 2008, worldwide lung cancer mortality amounted to 1.38 million deaths (18.2% of the total).<sup>12</sup> Although lung cancer mortality in the United States has risen since the 1950s, recent data reports a 1.9% annual percentage decrease in the mortality rate for men from 1993 to 2005, and a 0.9% decrease for women in the same time period.<sup>22</sup> Lung cancer accounts for more deaths than any other cancer in both men and women. In the United States, an estimated 160,340 deaths, ~28% of all cancer deaths, were expected to occur in 2012. Death rates began declining in men in 1991, and between 2004 to 2008 rates decreased by 2.6% per year; death rates for men were most recently reported to be 61.9 per 100,000.<sup>13</sup> Improvements in lung cancer death rates in women lagged behind but started

to decrease in 2003, and between 2004 and 2008, rates decreased by 0.9% per year. Lung cancer mortality rates for women was most recently reported to be 38.5 per 100,000.<sup>13</sup>

Globally, lung cancer is the most common cause of death from cancer, with 1.38 million deaths recorded in 2008 (18.2% of the total) of cancer deaths.<sup>12</sup> Global lung cancer mortality does not differ significantly by region, with 43% of deaths occurring in more developed countries and 57% occurring in less developed countries.<sup>12</sup> Gender differences in lung cancer mortality patterns reflect historical differences between men and women in the increase and reduction of cigarette smoking over the past 50 years.<sup>1</sup>

## Survival

The 1-year relative survival rate for lung cancer increased from 35% in 1975–79 to 42% in 1988–2008. The overall 5-year survival rate for lung cancer of all stages was 16.8% in 2004. This rate has slightly improved over time, compared with a 13.3% 5-year survival rate in 1982.<sup>13</sup> This rate varies considerably depending on the stage at diagnosis: 52.2% for localized disease, to 25% for regional disease, to 4% for distant disease.<sup>13</sup> Unfortunately, only 15% of lung cancers are discovered in the early localized stage.

Although the overall prognosis for lung cancer remains poor, women have better survival compared with men across all ages, irrespective of histologic subtype. The 5-year survival for women with lung cancer is 19% compared with 14% for men (based on data from 1999 to 2006).<sup>13</sup> The explanation for this gender discrepancy is not clear, but it suggests that lung cancer may not be a biologically identical disease in men and women.<sup>23</sup>

## Women and Lung Cancer

Although the smoking prevalence among women in the United States has been stable for the past few years, the U.S. Surgeon General 2001 report on women and smoking described a 600% increase since 1950 in women's death rates for lung cancer, a disease primarily caused by cigarette smoking, as a "full-blown epidemic."<sup>24</sup> Due to the increase in lung cancer deaths between 1930 and 2000, lung cancer has moved from the seventh most common to the most common cancer cause of death in U.S. women. Lung cancer surpassed breast cancer as the leading cause of cancer death in 1987 and in 2012 was expected to account for 26% of all cancer deaths among women.<sup>1</sup>

Important differences exist among men and women with lung cancer. Controversy exists as to whether women are more or less susceptible to the carcinogenic effects of cigarette smoke. Several studies have argued that women are more vulnerable to tobacco carcinogens than men.<sup>25–27</sup> Studies suggest that women may be more predisposed than men to molecular aberrations resulting from the carcinogenic effects of tobacco smoke.<sup>28</sup> Women smokers are more likely than men to develop adenocarcinoma of the lung, and those women who have never smoked are more likely to develop lung cancer than men who have never smoked. This

phenomenon suggests a role for estrogen signaling.<sup>29</sup> Bronchioloalveolar carcinoma (now considered a subtype of adenocarcinoma and referred to as a lepidic growing tumor)<sup>30</sup> is reported to be two to four times more common in women, particularly never smokers, compared with men.<sup>31</sup>

## Risk Factors

### Tobacco

Cigarette smoking is by far the most important risk factor in the development of lung cancer. It is estimated that ~90% of lung cancer deaths in men and 75–80% of lung cancer deaths in women in the United States each year are caused by smoking.<sup>32,33</sup> There is a consistent association between cigarette smoking and lung cancer as a cause of death. There are at least two ways that smoking is associated with lung cancer. First, polycyclic aromatic hydrocarbons, carcinogenic compounds present in tobacco smoke, induce mutations in the *p53* gene that are crucial for cell cycle dysregulation and carcinogenesis.<sup>34</sup> G to T transversions within the gene have been linked to a molecular signature of tobacco mutagens in smoking-associated lung cancers. Second, the N-nitroso compounds are another major group of chemicals found in tobacco smoke, several of which are potent animal carcinogens. These compounds can be found in the urine of smokers.<sup>35</sup>

Over the past few decades, the incidence of adenocarcinoma of the lung increased much more rapidly than that of squamous cell carcinoma in men and women. At the same time, filtered cigarettes with substantially reduced “tar” and nicotine yields have dominated the market.<sup>36</sup> The smoke of modern cigarettes contains higher concentrations of nitrosamines that primarily predispose to adenocarcinoma as opposed to other cell types.<sup>36</sup> The decrease in tars and the increase in nitrosamines appear to be the cause of the recent change of dominant cell type from squamous cell to adenocarcinoma. Since the 1970s in the United States, adenocarcinoma as a percentage of all lung carcinomas has nearly doubled in men and increased from ~25% to ~33% in women, among whom adenocarcinoma has long been the most commonly diagnosed histologic type.<sup>37,38</sup> A recent study demonstrated there is no difference in the risk of lung cancer between people who smoke medium tar filter, low tar filter, and very low tar filter cigarettes.<sup>39</sup> Addicted smokers who switch from a higher to lower tar cigarette maintain their nicotine intake by blocking ventilation holes, increasing the puff volume or the time during which the smoke is retained in the lungs, and smoking more cigarettes. These deeper and more frequent inhalations, described as compensatory smoking, can result in increased distribution of carcinogens to the periphery of the lung and the increased prevalence of adenocarcinoma.<sup>40</sup>

### Radon

The U.S. Environmental Protection Agency has determined radon to be the second leading cause of lung cancer after cigarette smoking.<sup>41</sup> The increased risk attributed to radon is from domestic exposure, due to diffusion of radon from the soil. High radon concentrations have been linked to an

increased risk of lung cancer in underground miners.<sup>4</sup> More recent epidemiological studies of residential radon exposure also identify it as a risk factor for lung cancer. Inhaled radon can have a carcinogenic effect on the lung due to its emission of  $\alpha$  particles upon decay,<sup>42,43</sup> and additionally it has a synergistic effect with tobacco smoke inhalation.<sup>44</sup>

### Secondhand Smoke Exposure and Other Environmental Factors

National committees and organizations have concluded that exposure to environmental tobacco smoke is a cause of lung cancer.<sup>45,46</sup> Experimental exposure of nonsmokers to tobacco smoke leads to an increased concentration of a tobacco-specific carcinogens in the blood and urine.<sup>47</sup> A 24% excess lung cancer risk has been shown in nonsmokers who have lived with a smoking spouse.<sup>48</sup> A significant dose–response relationship for both the number of cigarettes smoked by the spouse and the duration of exposure has also been shown.<sup>48</sup>

Occupational exposure to carcinogens accounts for ~5% of all lung cancers in the United States.<sup>49</sup> Asbestos accounts for a large number of these cases. Exposure to asbestos at high levels can cause lung cancer and mesothelioma. Because mesothelioma is so rare, asbestos-induced cases of lung cancer significantly outnumber cases of mesothelioma among asbestos-exposed workers. Other environmental agents that have been associated with lung cancer are radon, silica, chromium, cadmium, nickel, arsenic, and beryllium.<sup>50</sup>

### Other Predisposing Risk Factors

The risk of developing a second lung cancer in patients who survive lung tumor resection is ~1 to 2% per patient per year for non–small cell lung cancer (NSCLC), and 6% for small cell lung cancer.<sup>51</sup> Ten years after initial treatment of small cell lung cancer, cancer risk increases from ~2% to >10% per patient per year. This risk of developing a second primary lung cancer can translate into an important cumulative risk and is a common cause of death in lung cancer survivors.<sup>51</sup>

Lung cancer risk is also higher in the human immunodeficiency virus (HIV)-infected population than in the general population, and it is the most common non-acquired immunodeficiency syndrome defining malignancy.<sup>52</sup> Although 60 to 80% of the HIV infected population smoke, increased tobacco use is not sufficient to account for this excess of lung cancers.<sup>53</sup> HIV-infected patients are also diagnosed with lung cancer a median of 18 years earlier than those without a diagnosis of HIV.<sup>53,54</sup> The relationship between immunosuppression and lung cancer is uncertain, and the role of this and other co-factors in the etiology of lung cancer in HIV-infected individuals remains to be fully elucidated.

Studies have also shown a marked increased risk of lung cancer in breast cancer survivors treated with radiotherapy who smoke cigarettes. The combination of smoking and radiation exposure enhances the risk of lung cancer compared with radiation exposure in nonsmoking breast cancer survivors.<sup>55</sup> The lung cancer risk appears to be proportional to the radiation dose administered and the extent of irradiated lung tissue. A detailed analysis of patients who received extensive

postmastectomy radiation to the chest wall and regional lymphatic node areas were shown to have a greater risk of developing lung cancer than patients who had undergone more conservative postlumpectomy breast irradiation.<sup>56</sup>

## Tobacco Use Trends

Preventing initiation of tobacco use is a public health priority. Approximately 80% of persons in the United States that use tobacco begin before the age of 18 years.<sup>57</sup> The Centers for Disease Control and Prevention analyzed data from the national youth risk behavior survey and found that although student cigarette smoking rates declined from 43% in the late 1990s to 26% in 2007, this rate of decline slowed from 2007 to 2011, and currently rests at 23.4%.<sup>57</sup>

Between 1965 and 2004, cigarette smoking in adults 18 years and older decreased by half from 42% to 21%. Since 2004, the previous declines in smoking prevalence have stalled and, in 2010, 19% of U.S. adults were current cigarette smokers.<sup>58</sup>

Worldwide, tobacco is the second most common cause of death, currently responsible for the death of 1 in 10 adults, amounting to ~5 million deaths per year. If current smoking patterns continue, the World Health Organization estimates that tobacco use will cause 10 million deaths in 2025, with lung cancer expected to contribute at least 30% of that total.<sup>59</sup>

## Molecular Targets

Current research into lung cancer therapy is largely focused on molecular therapies for NSCLC. Mutational profiling of lung tumors has demonstrated distinct somatic mutations that can be used as molecular targets and biomarkers of response to anticancer agents: *Epidermal growth factor receptor* (*EGFR*), *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*), and *anaplastic lymphoma kinase* (*ALK*) mutations have shown particular promise in the treatment of lung adenocarcinoma.

*EGFR* is a tyrosine kinase receptor commonly altered in epithelial tumors. Many tumors demonstrate increased activity of the *EGFR*; resultant amplification of the *EGFR* signaling pathway drives cell proliferation and tumor growth. *EGFR* mutations are more common in adenocarcinoma than in lung cancers of other histologies (30% compared with 2%), and more common in lung cancer in never-smokers than in ever-smokers (45% compared with 7%).<sup>60</sup> Lung cancers with *EGFR* mutations occur more frequently in women and in East Asian patients irrespective of their geographic location.<sup>60</sup> Somatic mutations in the tyrosine kinase domain of the *EGFR* gene in NSCLC are associated with clinical responses to *EGFR* inhibitors gefitinib and erlotinib.<sup>61,62</sup> The therapeutic potential of *EGFR* inhibition was demonstrated by the Iressa Pan-Asia Study that analyzed Asian nonsmoking patients with adenocarcinoma histology treated with first-line gefitinib.<sup>63</sup> It confirmed an improvement in progression-free survival compared with chemotherapy. In those patients with *EGFR* mutations, progression-free survival after receiving gefitinib was twice that of patients without an *EGFR* mutation, thus identifying a group that would benefit from tyrosine kinase inhibition. Although *EGFR* mutations are more common in Asian populations, the therapeutic effect of tyrosine kinase inhibition in a non-Asian population with *EGFR*

mutations was also observed when erlotinib was compared with chemotherapy as a first-line treatment for European patients with advanced lung cancer.<sup>64</sup>

*KRAS* oncogenes encode a GTPase downstream of *EGFR*. *KRAS* mutations result in Ras proteins with impaired GTPase activity and constitutive activation of Ras signaling.<sup>65</sup> *KRAS* mutations are also more common in lung adenocarcinomas than other NSCLCs. Unlike *EGFR* mutations, *KRAS* mutations show no sex predilection, are more frequent in white populations than Asians, and are most commonly identified in former or current cigarette smokers.<sup>66,67</sup>

Because *KRAS* is a downstream effector of *EGFR*, therapeutic agents that inhibit *EGFR* have been shown to be ineffective against *KRAS* mutant tumors across multiple cancer types such that the presence of a *KRAS* mutation in NSCLC is a negative predictor of clinical benefit from both adjuvant chemotherapy and anti-*EGFR* directed therapies.<sup>68</sup>

*ALK* encodes a receptor tyrosine kinase. *ALK* gene rearrangement is a mutation also implicated in the oncogenesis of NSCLC, especially adenocarcinoma. Patients with *ALK* rearrangements tend to be younger than those without the rearrangement, have little or no exposure to tobacco, and have adenocarcinoma histology.<sup>69</sup> Crizotinib is a selective inhibitor of the *ALK* and *Met* tyrosine kinases, and it has been shown to result in tumor shrinkage or stability in most treated patients with an *ALK* rearrangement.<sup>69</sup>

Mutations in *EGFR* and *ALK* rearrangements are typically not present in squamous cell lung carcinoma, and targeted agents developed for adenocarcinoma are therefore largely ineffective against squamous cell carcinoma.<sup>70</sup> Recent advances in the genetic profiling of squamous cell carcinoma have identified 11 recurrent mutations that are distinct from those identified in lung adenocarcinoma including mutations of *TP53* and *human leukocyte antigen A* (*HLA-A*), thus revealing a possible future role for genotypic selection of patients with squamous cell carcinoma for molecular therapy.<sup>71</sup>

## Conclusion

Lung cancer is unique among leading cancers in that it has an obvious environmental etiology and therefore the potential for risk reduction. Because disease control efforts throughout the world have plateaued, lung cancer is likely to remain the world's leading cause of cancer-related disease burden. Smoking cessation programs should remain an important aspect of the long term efforts to reduce the incidence of lung cancer.

The elucidation in recent years of individual genetic susceptibility for lung cancer has been a step forward in the understanding of lung cancer biology, facilitating development of targeted therapies and providing prognostic predictors of treatment response and outcome.

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