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Sex and Gender in Lung Cancer

How Big is the Problem?

Historically, lung cancer has mostly affected men and was considered rare in women. Although lung cancer mortality is still high in men accounting for 36 in 100,000 deaths, it is now also becoming a much more important cause of cancer death in women, accounting for about 13 in 100,000 deaths. The incidence rate across Europe is just over 290 per 100,000 for men and 119 per 100,000 for women.¹ It is predicted that lung cancer will cause nearly 187,000 male deaths and 93,000 female deaths in 2015, accounting for over 20% of cancer deaths in Europe.^{2,3}

Over the last decades there has been a decline in men's lung cancer dropping by 8% across Europe from 2000-2004 to 2005-2009. Despite this drop, lung cancer remains the principle cause of cancer death in men. There are marked country by country variation with the eastern European countries showing the highest mortality rates at over 50 per 100,000 in much of Eastern Europe as compared to 35-40 per 100,000 in western Europe.³ The rate of new cases of lung cancer in men is leveling off or decreasing in nearly all countries across Europe with an overall decline in smoking, but there are exceptions to this trend, with Belgium, Bulgaria, Iceland and Romania all seeing increases between 2000-2004 and 2005-2009.³ The fall in lung cancer is greatest in younger men; it is now estimated that only about 25% of young European men ages 20 to 25 years smoke as compared to 60% in the 1980s.

For women, there has been an overall increase in female lung cancer of 50% between the mid 1960s and the early 2000s across Europe.^{3,4} While there are indications that in some countries rates of lung cancer in women have started to fall in recent years, the overall rates continue to climb across the EU, rising to 14 in 100,000 deaths by 2015. Female lung cancer rates in the 35 to 64 age range are now greater than male rates in Denmark, Iceland and Sweden.⁵ The female lung cancer epidemic is expanding in countries of western and southern Europe, particularly in France, Portugal and Spain due to a recent uptake of smoking by women.⁴

Cancer of the lung/bronchus is the third most common cancer among women (7.4%) and second for men (15.9%).⁹ In women, lung cancer death has overtaken that of breast in many European Countries including Denmark, Hungary, Iceland, Ireland, Poland, Sweden and the UK.¹ A recent study estimates that in the UK, for example, lung cancer death is expected to quadruple in women in the next 30 years.⁶ However, while women fear breast cancer, they seem to be unaware of their lung cancer risk. The poor prognosis for lung cancer leads to similar incidence and mortality patterns throughout the world. Relatively low survival rates mean that despite high incidence rates there are fewer patients surviving. Lung cancer is one of the most lethal cancers with only 13% average relative survival at 5 years in Europe with better survival for women than for men at 16% and 12% respectively.⁷ Although this has long been recognised,⁸ the reasons are still not fully understood. However, the effect seems to be mostly limited to early stage adenocarcinoma; sex does not affect survival of patients with squamous carcinoma.⁹

Prevention of Lung Cancer

Smoking

Although lung cancer is deadly, it is highly preventable. The most important cause of lung cancer is smoking, accounting for 85% of lung cancer cases in men and 80% of cases in women in the UK.¹⁰ Across Europe, men still are heavier smokers than women, but the gap has been narrowing due to a decrease in male smokers and increase in female smokers in some countries. Women stopping smoking well before the age of 30 avoids more than 97% of the excess mortality caused by continuing smoking, but those who have smoked at some point in their life retain a 1.2 greater risk of death than those who have never smoked.¹¹ The most effective approach is to persuade young women not to start smoking, but if they are smoking, the earlier they stop the better. A high percentage of lung cancer in both men and women is smoking-related, though not all.¹² Despite lung cancer's strong association with tobacco use, one in five people who develops the disease has never smoked. Non-smoking women appear to be at two to three times greater risk for developing lung cancer than men, suggesting that other factors such as passive or environmental smoke play a role.¹³

Smoking (continued)

The Tobacco industry has long targeted young people in the promotion of their products.²⁸ Their aggressive marketing strategies are increasingly aimed at women who are considered to be a lucrative, unexplored market. Creating women-only brands, their packaging plays on the appeal of glamorous images such as cigarettes as party accessories, sponsored events, like women's tennis games and dances. Female-targeted branding includes light or slim cigarettes, low prices, easy availability and free samples.²⁹ Despite the industry aggressively targeting women with their promotional activities, few anti-smoking initiatives have taken a gender-based approach.³³

Smoking is more common in lower socio-economic groups. Women on average are poorer than men, have a lower employment status, and often are economically dependent. Increasingly, they are heading single parent and low-income households. Their lower-paid work may expose them to a smoking environment through part-time house or hospitality work. Maternal smoking has a devastating effect on their offspring, causing miscarriages, birth defects, premature births etc. Smoking cessation programmes for vulnerable women must offer a way out of breaking the cycle of deprivation and tobacco dependency.

There is a strong link between socio-economic factors and smoking for men too, which brings a higher burden of cancer and further negative impact on struggling families.²⁶ With men being numerically much more at risk of lung cancer in these settings and smoking-attributed mortality accounting for nearly half of total male mortality in the lowest social stratum of each country continued action must be taken to target socially disadvantaged men with smoking cessation programmes.³⁴

Why Gender Matters: Biological Differences

Researchers are just beginning to understand the differences in lung cancer between women and men. Lung cancer results from the interactions between genetic, hormonal, behavioural and environmental factors. For example, the odds of lung cancer in women who have ever smoked heavily compared with those who had never smoked were increased 19-fold, which is more than men for the same number.¹⁵ The gender difference in cancer susceptibility is one of the most consistent findings in cancer epidemiology, although findings are often questioned.^{14,16,17} Additional research into the gender and biological differences needs to be urgently encouraged and funded.

Studies suggest that lung cancer differs biologically between men and women^{1:6, 18-22}

- Women's genes may make them more vulnerable to the harmful effects of smoking.
- Women's bodies may metabolise the chemicals in tobacco differently.
- Various genetic associations with lung cancer are specific to either males or females, which either increase their risk of developing the disease or being protected from it.
- Elderly women with early lung cancer have better risk adjusted survival than men, both when treated and untreated
- A lowered ability to repair DNA damage may aid in cancer development.
- Women's hormones, such as estrogen, may directly or indirectly influence cancer progression
- Some treatments may work better in women than men

Why Gender Matters: Biological Differences

Though men are more likely to develop and die from lung cancer, many are still unaware of the risk and the signs and symptoms they should be reporting. In part, this is due to an overall lower understanding of health and being less likely to seek health information in men compared to women.²⁴ This view of men being unlikely to present with what they consider 'trivial' conditions is reinforced by the negative response from health professionals some men receive on self referral.²⁵ More men die of lung cancer because they are more likely to smoke, so more effort needs to be made in getting smoking prevention programmes in place.²⁶

Few studies have explored the differences between women and men in the procedures and outcomes of lung cancer screening. Studies have found that women were less likely to undergo surgery to treat lung cancer than men. Radiation therapy is more frequently administered to men than women.

Women have better survival rates than men following surgery even when adjusting for confounders for both non-small cell and small cell lung cancers as well as various types of treatments (surgery, chemotherapy, radiation therapy, no treatment)—although the reasons for the difference are unknown. Targeted therapies, adjusting for tumor characteristics, are improving lung cancer treatment. One of the most promising molecular targets to-date in lung cancer treatment focuses on the epidermal growth factor receptor gene (EGFR). Mutations in this gene are more common in women who have never smoked and in those with adenocarcinoma of the lung than in other populations.²²

ABOUT THE EUGENMED PROJECT

Research addressing sex and gender (S&G) in biomedical sciences and health research is emerging as a novel and highly promising field. This interaction between S&G leads to different manifestation of diseases—such as infarction, heart failure, diabetes, rheumatic disease—in women and men. Research in the area will lead to novel, better targeted and, therefore, to more efficient treatment strategies than the previous global approaches, creating additional opportunities for prevention and increased healthy life expectancy.

The EUGenMed Project is coordinated by Charité, Universitätsmedizin Berlin in partnership with the European Institute of Women's Health and the University Maastricht. The Project is funded by the European Commission under the Seventh Framework Programme and began on October 1st 2013. The Project aims to create a multi-sectorial source of knowledge based on consensus of experts.

The EUGenMed Project will produce an innovative roadmap for implementation of S&G in in biomedicine and health, based on the generation of material and results from four workshops and the final project conference.

For more information, please visit the EUGenMed website: <http://eugenmed.eu>.



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