

Gender-specific aspects of epidemiology, molecular genetics and outcome: lung cancer



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ABSTRACT

Lung cancer remains the leading cause of cancer-related deaths worldwide in women and men. In incidence, lung cancer ranks second, surpassed by breast cancer in women and prostate cancer in men. However, the historical differences in mortality and incidence rate between both sexes have changed in the last years. In the last decades, we have also witnessed an increased number of lung cancer in female never-smokers. These disparities have grown our interest in studying the impact of the gender and sex in the presentation of lung cancer. The aetiology is yet to be fully elucidated, but the data are clear so far: there is a growing divide between lung cancer presentation in women and men that will change our management and study of lung cancer. This article aims to review the sex and gender differences in lung cancer.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths for men and women globally.¹ Despite of the encouraging overall cancer mortality predictions for 2020 in the European Union pointed out by Carioli *et al*, the highest cancer mortality rates were predicted for lung cancer for both sexes. The authors revealed a narrowing of male–female gap in lung cancer rates in the last 5 years with a decrease among men (9.2%) whereas an increase of rates among women is reported (6.0%).² Nevertheless, recent reports of US National Institutes of Health (NIH) highlighted a decrease of lung cancer death rates (–4.8%) per year among men and (–3.7%) per year among women.³

Both the incidence and mortality of lung cancer are strongly connected to cigarette smoking. Thus, both had risen for several years before starting to decline for men and plateauing for women in the first tobacco epidemic countries, mirroring the different smoking history between both sexes.⁴ It is worth remembering as the societal roles of women began to closely epitomise those of men, the risk for women rose significantly, reaching similar levels.⁵ Likewise, this tendency follows the initiation of comprehensive smoking control programmes and

campaigns.⁴ These trends occurred earlier in industrialised countries than in the developing ones, where the tobacco epidemic occurred later following the adoption of western lifestyle. In the USA and most of Western Europe, male lung cancer incidence and mortality rates have indeed been dropping since the 1990s.¹ Furthermore, economically emerging nations (eg, Brazil, Russia, India, China and South Africa states) and low/middle-income countries showed varied incidence rates depending on religious background, environmental and occupational factors, consumption of smokeless tobacco including dip, snuff, snus and chewing tobacco, and life expectancy, among others. Unfortunately, high lung cancer incidence countries exhibit higher related mortality burden compared with wealthier countries.¹

However, an in-depth analysis of the lung cancer incidence related to tobacco consumption in many western countries revealed the existence of deep inequalities regarding to tobacco use, with vulnerable populations such as certain racial/ethnic groups, low educational and/or socioeconomic level groups, people with mental diseases, lesbian, gay, bisexual and transgender community, among others being more exposed to smoking.^{6,7}

In addition, Jemal *et al*, focused on lung cancer incidence among young adults, finding sex-based incidence divergences with higher incidence among young women not attributed to smoking habits; particularly among the adenocarcinoma (ADC) subtype.⁸

Furthermore, numerous studies have been conducted in order to analyse smoking habits among teenagers, evoking risk factors such as the search of social recognition and approval among their smoker peers; close relatives and family smoking; parental educational status, parental control and relationship, socioeconomic level, secondhand exposition leading to nicotine dependence, ads by their idols, curiosity, attention troubles, stress, psychological burden and parenteral rivalry, as well

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as low perceived risk, among others.^{9–11} In 2017, Arrazola *et al* revealed in their Global Youth Tobacco Survey across 61 countries that smoking prevalence among students between 13 and 15 years was about 11%, with a median of 14.6% among males and 7.5% among females.¹²

Different national initiatives aimed at decreasing adolescent smoking have already been implemented. These include increasing the minimum age of sale for tobacco products as well as the selling prices of tobacco products; carrying out public campaign to decrease tobacco promotions, buoying up the establishment of tobacco-free places, involving their idols in these programmes and forbidding smoking in indoor and mutual places.¹³ Furthermore, performing instructive programmes about negative consequences of tobacco use; implicating parents and families in these programmes; and supplying available therapeutic options and counselling for tobacco dependence.

Another subject of further consideration, it is lung cancer among never-smokers. Never-smoker is an individual who has never smoked or who has smoked fewer than 100 cigarettes in their lifetime and does not currently. Several studies have shown an increased rate of never-smoker female lung cancer cases (over 50% of lung cancer women). In contrast, men had an incidence of about 15%. In Asia, this incidence is higher, reaching about 80% of cases.^{14–18} Despite of this increased incidence, never-smoker lung cancer has lower mortality rates than former-smoker and current-smoker lung cancer.^{18,19} In fact, never-smoker lung cancer is deemed a different pathology taking into account its distinct epidemiological, clinical, histological, molecular and prognostic features.²⁰ The aetiology of never-smoker lung cancer is yet to be clarified. Nevertheless, several risk factors have been evoked such as genetic, occupational, hormonal, microbiological and environmental factors.^{21–24}

Here, we will discuss the epidemiology of lung cancer and the impact of sex and gender in these setting, and possible hypotheses explaining oncological disparities between males and females.

Sources and selection criteria

We identified references for this review by performing a PubMed, Cochrane Library electronic databases, and Google Scholar search for years 1970 to 2020. Search terms used in strategic combination to identify germane articles included “cancer”, “lung cancer”, “women”, “incidence”, “mortality”, “Europa”, “sex”, “gender”, “sex hormones”, “oncogenic drivers”, “immunotherapy”, “chemotherapy”, “survival”, “screening”, “teenagers”, “smoking”, “nicotine”, “genetic alterations”, “virus”, “histology”, “occupation” and “psychosocial”. We included *in vitro*, animal and human studies, including meta-analyses. Only articles published in English were reviewed. In all cases, we used the highest level of evidence available to inform this review, with more recent studies cited where possible.

We also acceded WHO, American Society of Clinical Oncology (ASCO), European Society for Medical

Oncology and Centers for Disease Control and Prevention (CDC) websites for current cancer statistics and guidelines. The recent presentation performed by Gonzaga at 2019 annual Canadian Cardiovascular Congress was also reviewed.

The final reference list was based on relevance to the topics covered in the review and was modified on the basis of comments from peer reviewers.

Gender and sex differences

Over the course of the last 25 years, there has been a growing interest in the possible differences in the presentation of lung cancer in women compared with men: age at diagnosis, incidence, biology and natural history, response to anticancer therapy, immune responses and mortality. This interest is obvious, considering well-known divergences in sex as determined by our physiological and anatomical features, as well as, in gender conditioned by our behaviour and actions regulated by society, religious or cultural backgrounds. Furthermore, these differences became more ostensible when the characteristics of oncogene addicted non-small-cell lung cancer (NSCLC) patients were highlighted.

Despite a vast research, the landscape is intricate, not entirely understood and inconclusive. Multiple statements have emerged from countless studies which are not always consistently observed; most remain speculative. These statements include higher susceptibility to lung cancer in women compared with men, inferior cessation rates among female smokers compared with their male counterparts, the predominance of ADC in women, different tumour responses and immune responses between men and women, and the higher frequency on never-smoking among female lung cancer.^{1,25}

As discussed later, all these issues have been attributed to several causes such as the metabolism of carcinogens, genetic differences, social roles, environmental exposures, hormonal factors and oncogenic viruses.

SEX-RELATED ITEMS

Sex differences involve biological, physiological, hormonal and genetic factors. This topic has been broadly studied and has generated controversial results. Differences between sexes are inconsistent across studies. Here, we expose some theories evoking metabolic, genetic, hormonal, viral, immune and histological causes.

Tobacco-related carcinogens metabolism

There is a theory that females are biologically more susceptible to the effects of carcinogens than males. This is supported by epidemiological data showing that female smokers have a higher likelihood of developing lung cancer compared with male smokers. Females with an estimated 40 pack-year smoking history had a threefold higher ORs (27.9% vs 9.3%) of developing lung cancer compared with males with the same smoking habits.²⁶

Tobacco smoke is a mixture of more than 7000 chemical compounds, among them, 70 are known to cause

cancer, based on evidence for carcinogenicity from either laboratory, animals or humans research. There are various classes of chemicals such as polycyclic aromatic hydrocarbons, aza-arenes, N-nitrosamines, volatile hydrocarbons, ethyl carbamate, ethylene oxide, nickel, chromium, cadmium, polonium-210, arsenic and hydrazine.²⁷

The polycyclic aromatic hydrocarbons are activated by the phase I carcinogen-activating enzymes (ie, cytochrome P450, mono-oxygenases) which are coded by cytochrome P450, family 1, subfamily A, member 1 (CYP1A1) genes. Phase II enzymes contend with phase I enzymes, inhibiting the formation of free radicals and catalysing the conversion of reactive intermediates to inactive conjugates. If these metabolites are not inactivated, they bind to DNA, constructing DNA adducts.²⁸

It must be emphasised that nicotine is not a carcinogen, but it is the addictive constituent of smoke, inhibiting the smoking cessation due to compulsive drug-seeking behaviour, even in the face of negative health consequences.²⁹ According to CDC in 2010, only 6.2% of smokers give up definitively smoking.³⁰

Subsequently, numerous studies have indicated that women metabolise smoke carcinogens differently from men. These studies are inconclusive, those on animals showed a lower nicotine metabolism.^{31 32} By contrast, Klein and Gorrod conducted a study on a group of smokers in the UK that found no gender difference in nicotine exposure.³³ These results were confirmed by Rubinstein *et al* who did not find significant differences either by gender or self-reported hormone use.³⁴

Two potential mechanisms may explain these findings. First, the imbalance between metabolic activation and detoxification of carcinogens.^{35 36} Second, a defective DNA repair system.³⁷

In fact, gene expression studies provide a possible rationale for the increased risk of lung cancer among female smokers. Female smokers have a higher expression of CYP1A1 genes in the lungs than males, resulting in greater carcinogen activation.³⁸ This increased expression might be hormone induced, as mentioned below.³⁹

Furthermore, women exhibit a more prominent polymorphism in the phase II detoxification enzymes, mainly glutathione S-transferase M1 null genotype gene deletion induced.⁴⁰ This could again favour the accumulation of free radicals and carcinogenic metabolites.

Additionally, other studies have shown that women have higher levels of DNA adducts than men. High levels of stable adducts in lung tissue are believed to play a role in the initiation of carcinogenesis.⁴¹

Finally, it is well known that a reduced capacity for DNA repair is associated with an increased risk of lung cancer. Preclinical data suggest that women have lower DNA repair capacity than men.⁴²

Genetic factors

Several studies have reported a higher frequency of more critical driver genes among women, such as tumour protein 53 (TP53) suppressor gene and the V-Ki-ras2

Kirsten rat sarcoma viral oncogene homolog (KRAS); this is explained by a higher predisposition to molecular aberrations among women as a consequence of the carcinogenic effects of tobacco smoke.⁴³

Some studies have found an earlier activation and higher expression of peptide stimulating cell proliferation, the gastrin-releasing peptide receptor (GRPR) explaining the greater risk of lung cancer among women. Shriver *et al* detected GRPR messenger RNA (mRNA) expression more frequently in female non-smokers than in male non-smokers (55% and 0%, respectively).⁴⁴

In addition, a major lung cancer susceptibility locus was also found to map to chromosome 6q23-25. Even light smoke exposure greatly increased the risk in individuals with inherited susceptibility.⁴⁵

Furthermore, among northeast Chinese female non-smokers, two single nucleotide polymorphisms, rs4787050 and rs8045980 were associated with a significantly increased risk of lung cancer, a risk further exacerbated by exposure to cooking oil fumes.⁴⁶

A subset of lung ADC is related to the activation of potent proto-oncogenes, called drivers. Somatic driver genetic alterations, including epidermal growth factor receptor (EGFR) mutations, occur more frequently in non-smokers, and particularly, women with ADC. Exon 18 mutations have been linked to genetic polymorphisms associated with oestrogen biosynthesis and metabolism in never-smoking females with ADC. Mutations in human epidermal growth factor receptor 2 (HER-2) exon 20 occur in 1%–5% of patients, particularly young never-smoker women. By contrast, there are no sex differences among other oncogene-addicted tumours such as anaplastic lymphoma kinase (ALK) or ROS proto-oncogene 1 receptor tyrosine kinase (ROS-1) addicted lung carcinomas.⁴⁷

Hormonal factors

There remains a controversy about the potential influence of reproductive and hormonal factors involving parity, age at menarche and menopause on lung cancer.

Data regarding the impact of hormonal replacement therapy (HRT) on the risk for lung cancer in women is inconsistent. An increased risk associated with HRT disappears after adjusting for smoking and other confounding factors. In a study by Chlebowski *et al*, HRT in postmenopausal women did not increase incidence of lung cancer, yet it increased the mortality of women already affected by NSCLC.^{48 49}

The controversy remains, another analysis of more than 36 000 perimenopausal and postmenopausal women showing, after adjusting certain possible confounding factors, an association between HRT use and lung cancer incidence in a duration-dependent manner, with an approximate 50% increased risk for use of 10 years or longer.⁵⁰

A prospective, observational study, the French Collaborative Intergroup for Thoracic Cancer Research, (IFCT-1002) BioCAST study, in 260 female never-smokers with

lung cancer showed that reproductive factors were associated significantly with specific lung cancer mutations. In particular, EGFR mutations were correlated significantly with increasing age at menarche and age at first birth. In addition, ALK alterations were associated with both parity and number of pregnancies.⁵¹

In terms of the association between risk of lung cancer and reproductive factors, the American NIH-American Association of Retired Persons cohort including 185 017 women, suggested late menarche was a protective factor, while early menopause was identified as a risk factor for lung cancer.⁵² While correlation has been demonstrated, there is yet to be clear causality.

The relevance of oestrogen receptors (ER) expression in lung ADC appears minimal. Lee *et al* investigated the expression of the female sex hormone receptors, ER alpha, ER beta, and progesterone receptor in lung ADCs. The expression of each receptor exhibited associations with certain clinic-pathological features and prognostic factors; however, in multivariate analysis, none of the female sex hormone receptors were significantly associated with patient survival.⁵³

In vitro studies are inconsistent regarding the potential role of oestrogen. It may be involved in lung carcinogenesis through promotion of cellular proliferation, both acting on fibroblasts and activating intermediates that produce DNA adducts.⁵⁴ Moreover, in vitro studies have reported that ER and EGFR pathways have operating synergy.⁵⁵ These observations have led to in vivo studies and clinical trials evaluating the association of an ER antagonist (fulvestrant) and EGFR-tyrosine kinase inhibitors (EGFR-TKI). Stabile *et al* found that the combination decreased cell proliferation and incremented apoptosis.⁵⁶ Nevertheless, the phase II IFCT-1003 LADIE Trial reported this association does not improve the outcome compared with EGFR-TKI regardless of EGFR status.⁵⁷

Viral factors

Human papillomavirus (HPV) infection has been suggested to participate in lung carcinogenesis. Asian studies have reported a prevalence of pulmonary HPV infection in lung ADC of 9%–42%. In contrast, western studies show a lower prevalence. The small cohorts and diverse diagnostic methods with variable ranges of sensitivity/specificity, as well as the heterogeneous expression of HPV prevent any firm conclusions to be made.⁵⁸

Immune factors

Germane dissimilarities in immune response between men and women have been disclosed in many studies, mirroring tangled interplay among the factors mentioned above. The stronger immune responses reported in women have been attributed to sex chromosome linked genes and miRNA, coding for proteins involved in the regulation of the innate and acquired immunity; differences in microbial composition, in programmed death-ligand 1 (PD-L1) expression, hypothetically modulated in an oestrogen-dependent manner (evidence-based in

preclinical studies); and proportion of intratumoural immune infiltrates.^{59 60}

Histological factors

ADC has become the most common histological variant in both sexes, but more women than men are diagnosed with ADC. This switch in the incidence of histological subtypes is mainly related to the change in cigarette manufacturing with the introduction of filtered cigarettes (smaller particles were able to travel deeper in the lungs, where they cause ADC, rather than more proximal squamous cell carcinoma), the reduction of smoking prevalence among men, and the later onset of smoking filtered cigarettes among women.⁶¹

Another theory is based on the unequal reduction in different histological subtypes following smoking cessation. For example, data have shown that after quitting smoking, the risk of developing small cell carcinoma decreases by about 17% per year, while the decrease in ADC is only 8% per year potentially revealing why there may be increased incidence rates of ADC among female populations.⁶²

GENDER-RELATED ITEMS

Our gender features are conditioned by our behaviour and actions regulated by society, religious or cultural background. These behaviours can determine our occupation, lifestyle, smoking's age onset, smoking ways, type of cigarettes, among others.

Occupational and residential factors

It has been accepted for a long time that certain employments predispose to greater risk of lung cancer. In fact, occupational exposures are the second most significant risk for lung cancer. Unfortunately, most studies evaluating occupational lung carcinogens have been performed in traditionally predominantly male occupations. Consequently, we know that occupations in metallurgy, mining and building are sources of lung carcinogens. With the advent of female emancipation, during the second world war, many women engaged in several professional activities and, a few studies emerged in order to analyse this topic in the female population. Risky female occupations are different from risky male occupations. In fact, some studies have found a higher risk of lung cancer in hairdressers, nails salon workers, housemaids, laundry/dry cleaners and, catering and cooking.⁶³

Aside from specific occupations, women spend more time in the home, therefore, they are more exposed to indoor pollution, for example, to high levels of radon; another important risk factor of lung cancer.⁶⁴

Psychosocial factors

Psychosocial hypotheses have been put forward to explain the gender differences on smoking and tobacco cessation. This remains a sensitive topic, subject to pre-existing stereotypes, and data should be taken with caution.

Several studies observe a poorer rate of smoking cessation among women, although some did not find differences. Anxiety, depression, high levels of stress, both professional and at home (childcare) are thought to be likely causal factors.⁶⁵

Recently, Gonzaga presented the results of a study of more than 200 smokers at the 2019 Canadian Cardiovascular Congress: showing that women are half as likely to quit smoking as men. In her study, women had a higher prevalence of anxiety or depression than men (41% vs 21%, respectively), which potentially affected the smoking cessation process.⁶⁶

On other hand, a study published by Martin showed that smokers who were partnered at baseline were more likely to quit than those who were not partnered and; those who had a non-smoking partner throughout were more likely to give up. Those who had a partner who smoked at baseline but stopped smoking in the following 4 years were even more likely to drop out.⁶⁷

It has been hypothesised that men and women smoke for different reasons. Women smoke to improve frame of mind, self-esteem, to lose weight or responding to tobacco-related cues. Men smoke in order to increase reward effects of nicotine.⁶⁸

Another risk factor importantly influenced by gender is secondhand smoke, which increases the risk of lung cancer by about 20%. It has been reported that women are more affected by this problem, including in their own homes where they often lack the power to negotiate smoke-free spaces. In addition, women, as well as children, are more exposed to thirdhand smoke (residual nicotine and other chemicals left on indoor surfaces by tobacco smoke).⁶⁹

Historically, tobacco companies have developed advertising tactics tailored particularly towards women in order to make cigarette smoke more palatable or addictive. Examples include the introduction of menthol as a cigarette additive, filtered and low-tar versions, cigarettes with fashionable names and sophisticated colours, and even alleging its powerful role on the control of weight gain or its relaxing and antidepressant powers.

IMPLICATIONS OF SEX DIFFERENCES

Sex and gender differences have implications on screening, response to therapy and prognosis.

On screening

Large randomised trials on low-dose CT screening such as the Dutch-Belgian lung-cancer screening (Nederlands-Leuven Longkanker Screenings Onderzoek, NELSON) trial and National Lung Screening Trial (NLST) have demonstrated a meaningful decline in lung cancer mortality of 26% and 20%, respectively. Women have been under-represented in these trials. However, despite of not being included in the primary endpoint population and consequently leading to an underpowered subgroup analysis, the reduction of mortality was 61% in

females in NELSON trial and 26% in NLST. Although, post hoc analyses from the NLST showed slight difference after adjusting by histological subtype; an extended follow-up (12 years) study of the NLST cohort revealed a lung cancer mortality risk ratio (RR) lower for women (RR=0.86) than for men (RR=0.97).⁷⁰

In the German Lung Cancer Screening Intervention trial, Becker *et al* showed a significant reduction in lung cancer mortality among women (HR=0.31) but not among men (HR=0.94). According the authors, this curious difference could be explained either by the tumour histological heterogeneity between both sexes, or it could be due to chance.⁷¹

On the other hand, a retrospective cohort study analysed the application of current screening guidelines among more than 200 women diagnosed of lung cancer. Around 80% of female lung cancer patients did not meet the lung cancer screening criteria: this leads us to rethink our screening criteria considering that 20% of lung cancers are not attributed to tobacco.⁷²

Multiples efforts are being carried out in order to deploy an international uniform screening programme. These items related to sex differences should be taken into account. Probably, women have to be screened at lower pack-years than men and at a younger age; taking into account the findings of the updating of International Early Lung Cancer Action Programme (I-ELCAP), which indicate that women are at higher risk of lung cancer than men at a similar age and smoking history.⁷³

Up until now, the screening criteria involve adults aged 55–80 years who have a 30 or more pack-year smoking history and currently smoke or have quit within the past 15 years.

On response to therapy and prognosis

A myriad of studies have demonstrated that women have a better response to therapy regardless of therapeutic modality, stage, histological subtype, smoking status, even after adjusting for gender-specific life expectancy.⁷⁴

Evidence has long suggested that there are sex differences in chemotherapy toxicity and cytotoxic response. For instance, Wakelee *et al* evaluated whether sex affected survival in the Eastern Cooperative Oncology Group E1594 trial. Patients with stage IIIB or IV were randomised to receive different platinum based chemotherapy treatment arms. Women had a 1.9-month statically significant improvement in median survival compared with men, despite similar response rates and greater toxicity.⁷⁵

The influence of sex dimorphism in microbiome composition is suggested as another cause of the dissimilarity on response and toxicity to anticancer therapies, between women and men.⁶⁰ However, it is extremely difficult to draw conclusions about the influence of microbiome in therapeutic response, taking into account myriad items influencing in the microbiota's composition and tumour response to anti-cancer therapies.

Additionally, these observations could be attributed to differences in drug metabolism, toxicity and diminished



DNA repair capacity (which could explain their higher sensitivity to platinum drugs).

The sex differences on immune responses could influence on response to immunotherapy, though no firm conclusion can be drawn at this time regarding immune checkpoint inhibition in cancer.

A meta-analysis by Conforti *et al* including 20 randomised trials in which anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death 1 (PD-1) antibodies were administered alone or with other agents such as chemotherapy or other immunological agents and compared with placebo or non-immunological agents, reported a greater overall survival in male compared with female patients.⁷⁶

These results should be interpreted with caution given the high heterogeneity in tumour types. A recent update of this meta-analysis but including only randomised controlled trials testing anti-PD-1 or PD-L1 given either alone or combined with chemotherapy, as first-line systemic treatment for patients with advanced NSCLC showed that women with advanced lung cancer derived a statistically significantly larger benefit from the addition of chemotherapy to anti-PD-1/PD-L1 than men. The authors ascribed these findings to the ability of chemotherapy to increase the mutational burden and neoantigenic load of lung cancer in women.⁷⁷

In a similar analysis, Wallis *et al* disclosed no statistically significant association between sex and overall survival in more than 13 000 patients with solid tumours from 23 randomised clinical trials treated by anti-PD-L1 checkpoint inhibitors.⁷⁸

Regarding prognosis, a Swedish population-based cohort study concluded that women have a better prognosis after adjustments for several factors in early stage NSCLC and lung ADC.⁷⁹ Additionally, Albain *et al* showed, in a prospective case series intergroup study of Southwest Oncology Group (SWOG S0424), that women, regardless of smoking history, type of therapy, hormonal factors or mutational status, had significantly better overall survival rates compared with men.⁸⁰

Recently, the updated I-ELCAP found that women's survival rates were 87.3% higher than the men's survival rates, after adjusting for age, smoking history, disease stage, histology and resection.⁷³

Similarly, given the increased incidence of EGFR and HER-2 oncogene addicted lung cancers in women and the effective therapeutic arsenal for these diseases, an improved prognosis is expected.

Recently, a Spanish study presented at the 2019 ASCO Annual Meeting showed that the median overall survival was 12 months for men and 19 months for women diagnosed with NSCLC. Women with stage IV NSCLC harbouring an EGFR sensitising mutation were found to outlive men as well, with men and women having median survival of 19 and 32 months, respectively.⁸¹

CONCLUSIONS

In recent years, there has been much focus on the impact of sex and gender differences in lung cancer. While genetic and

biological difference between men and women could explain the disparity in incidence and mortality of lung cancers, much remains unanswered. The degree which gender-associated habits, genetics and environmental exposure to carcinogenic agents participate in these differences is unclear.

The data so far are clear: there is a growing divide between lung cancer incidence in women and men. Future studies should investigate the potential demographic, environmental and behavioural factors that may be driving these findings, with the aim of tailoring interventions or programmes to reduce the incidence of lung cancer among females.

A review of the screening criteria will in particular be necessary to take account of female smoking history and lung cancer diagnosis. Further research including prospective clinical trials is warranted to customise our therapeutic decision making based on sex and gender.

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