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Gender differences in lung cancer

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Summary. In the early 20th century, lung cancer was diagnosed in a few hundred cases, but the progressive spread of tobacco consumption caused an increasing incidence of this disease firstly among male and later among female smokers, and is now the leading cause of cancer death for both sexes in developed countries. The higher percentage of lung cancer in non-smoking women, as compared with non-smoking men, suggests distinctive biological aspects in female patients. Hormonal status is one of the possible explanations: estrogens are involved in lung tumorigenesis through cell proliferation induced by ligand-estrogen receptor (ER) interaction and cross-talks between ERs and growth factor receptors. From a prognostic point of view, mainly retrospective data evidence greater survival rates in women compared with men regardless of stage, histology or treatment modality, thus implying the need for gender-based prospective confirmative trials. Increasing knowledge of sex-differences in lung cancer pathogenesis and biology will be the background for further investigations aiming to identify genetic alterations or hormonal profiles, which could be targeted by personalized sex-based therapies.

Key words: lung cancer, women, gender differences, cigarette smoking, hormones.

Differenze di genere nel tumore del polmone

Riassunto. Agli inizi del XX secolo la neoplasia polmonare veniva diagnosticata raramente, tuttavia la progressiva diffusione del consumo di tabacco ne ha causato una crescente incidenza tra i fumatori prima e tra le fumatrici poi, e ora è la principale causa di morte per cancro in entrambi i sessi nei paesi sviluppati. Il maggior riscontro di neoplasia polmonare nelle non-fumatrici rispetto ai non-fumatori suggerisce inoltre un differente comportamento biologico della malattia e fra le possibili cause a supporto di questa condizione vi è sicuramente l'assetto ormonale. Gli estrogeni sono infatti coinvolti nella tumorigenesi attraverso la proliferazione cellulare indotta dall'interazione ligando-recettore estrogenico (ER) e *cross-talks* tra ERs e recettori del fattore di crescita. Dal punto di vista prognostico, dati principalmente retrospettivi riportano tassi di sopravvivenza maggiori nelle donne rispetto agli uomini, indipendentemente da stadio di malattia, istologia o trattamenti, e questo nuovamente indica differenze di genere sebbene con necessità di studi prospettici confermativi. Una più approfondita conoscenza delle differenze di genere nella patogenesi e biologia del tumore polmonare consentirà l'identificazione di alterazioni genetiche o ormonali, quali possibili bersagli di terapie personalizzate, genere-specifiche.

Parole chiave: neoplasia polmonare, donne, differenze di genere, fumo di sigaretta, ormoni.

Introduction

In the early 20th century, only a few hundred cases of lung cancers were diagnosed yearly, but the progressive huge spread of tobacco consumption caused an increased incidence of this disease first among men and then later among female smokers in Western countries[1].

Nowadays, cigarette smoking accounts for more than 90% of lung cancers in men and 75-85% of them in women in the United States (US) and the European Union, being the most well-established risk factor for this disease[2].

Furthermore, 20% of women with lung cancers have never smoked: it has been known that women have a 1 in 16 lifetime risk of developing lung cancer, regardless of smoking status and the higher percentage of lung cancer in non-smoking women, as compared with non-smoking men, suggests that lung cancer behaves differently in female patients[3].

Literature data suggest gender differences concerning clinical presentation and biology of lung cancer, arguing that this disease should be considered a specific entity in women, where adenocarcinoma is the most common histological subtype and prognosis and response to treatment were described to be dissimilar[4-7].

In line with these findings, hormonal receptors have been evaluated in lung cancer tissues: estrogen receptors (ERs) interaction with growth-factor-receptor signalling is an emerging area of investigation and, considering the potential impact of hormonal factors, lung carcinogenesis is hypothesized to have distinctive aspects in women[8,9].

Despite these concerns, no "gender-driven" diagnostic or therapeutic approaches are currently available. Improving knowledge of lung cancer in women will permit to identify specific genetic alterations or hormonal profiles, which could be targeted by therapy, enhancing personalized sex-based investigations.

Epidemiology

In 2012, the estimated number of new lung cancer cases was 1.8 million, accounting for about 13% of total cancer diagnoses. Lung cancer was the leading cause of cancer death among males in both developed and developing countries; while, among females, it was the

foremost cause of cancer death in more developed countries, and the second one in less developed countries, after breast cancer[2].

In men, the highest lung cancer incidence rates (age-standardized per 100,000) were in Central and Eastern Europe (53.5), East Asia (50.4), Southern Europe (46.4) and North America (44.0), with a lower incidence in Middle and Western Africa (2.0 and 1.7 per 100,000 respectively). Among women, they were generally lower, mainly reflecting different historical exposure to tobacco smoking: the highest ones were evidenced in Northern and Western Europe (33.8 and 23.7), North America (33.8), Australia/New Zealand (21.7), Eastern Asia (19.2) while the lowest were described in Western and Middle Africa (1.1 and 0.8 respectively)[2] (Figure 1).

Lung cancer was estimated to account for almost one in five cancer deaths (1.59 million deaths, 19.4% of the total), worldwide. Because of its high fatality (the overall ratio of mortality to incidence is 0.87) and the relative lack of variability in survival in different world regions, the geographical distribution of mortality followed the same incidence data: the highest lung cancer mortality was evidenced in Australia/New Zeland (age standardized rates: 43.3 for males, 15.4 for females), in Europe (40.3 and 11.3, respectively) and in females in America (15.5)[2,10]. Considering Asian Countries, lung cancer mortality rates were 14.2 for males and 5.2 for females: in East Asia, China presented the highest rates (18 per 100,000), even more elevated than those among women in some European countries (Germany: 14.5, France: 12.9, per 100,000 respectively) despite a relatively lower prevalence of female smoking. This is likely due to higher exposure to secondhand smoke, outdoor and indoor air pollution from unventilated combustion of coal used for heating and cooking purposes[11-13].

In Europe, almost 75% of lung cancer deaths in men and over 80% in women were evidenced, with the majority of them (38% for men and 27% for women) in Central and Eastern Europe. The highest lung cancer mortality in women was observed in Northern and Western Europe (19.1 and 14.8, respectively), with the most elevated rates in Denmark (43) and Netherlands (36). In Southern Europe lung cancer mortality rates were lower: 39.1 for males and 10.0 for females[2].

In Italy, according to "Pool Airtum 2007-2011" data, lung cancer is the second neoplasm in terms of incidence (after prostate cancer) in men, with a 1.4% decrease in the last few years; on the contrary, it ranked third (after breast and colorectal cancer) in women with a 2.7% increase in recent years (1996 to 2014)[14]. These data reflect a progressive reduction of tobacco consumption among males (from 55% to 28% between 1970-2011 - according to Istituto Nazionale di Statistica, ISTAT, data) with a constant increase among females (from 12% to 17% - according to ISTAT data). The highest density region for male smokers in Italy is Campania and the lowest is Trentino-Alto-Adige. For female smokers, the highest density region is Lazio, while the lowest ones are Basilicata and Calabria[15].

Lung cancer death worldwide will increase from 1.6 million in 2012 to 3 million in 2035. It will almost double in both men (1.1 million in 2012 to 2.1 million

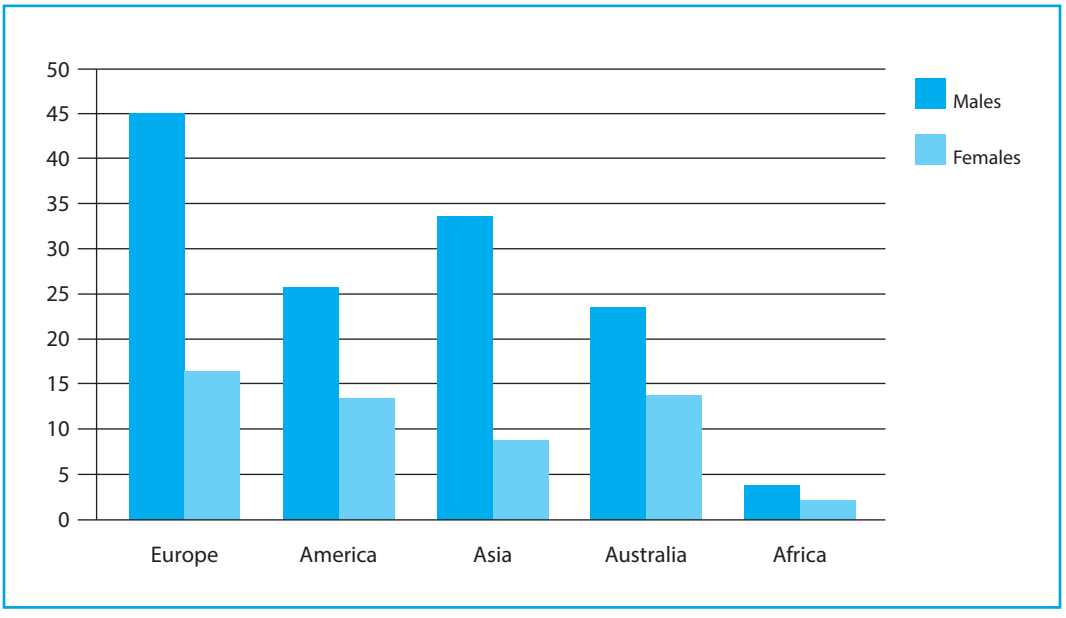

Figure 1. Median global lung cancer incidence rates in 2012 per continent.
Data extrapolated and elaborated from Torre et al[2].

in 2035) and women (0.5 million in 2012 to 0.9 million in 2035). A progressive increase is predicted worldwide, but its scale is different: the lowest increase is expected for Europe (37%); in the Western Pacific Region, America and South-East Asia it is predicted to double (by 97%, 91% and 95%, respectively), while in the East Mediterranean region and Africa the estimated increase is expected to be the highest (123% and 108%, respectively)[2].

Smoking trends and lung cancer risk

The observed variations in lung cancer rates and trends across countries or between males and females within each country, largely reflect differences in tobacco spread and consumption. In US, California has been a leader in introducing public policies designed to reduce cigarette smoking. It was the first state in the US to establish a comprehensive state-wide tobacco-control program in 1988 through increased excise taxes on cigarettes, and as early as the mid-1970s, issued local government ordinances for smoke-free work places. As a result, progress in reducing smoking prevalence and mortality associated with smoking-related diseases, including lung cancer, was evidenced and it was much greater in California than in the rest of the US[16].

Some Northern European countries were able to substantially reduce smoking prevalence in both men and women; consequently, in some of them, such as the United Kingdom and Denmark, lung cancer mortality rates decreased for several decades, first among men and then later among women. Many other high-income nations in Europe, such as Germany and the Netherlands experienced a major decrease in prevalence of smoking in men, but with only a recent and modest decrease in female smoking[17,18].

Italy was among the first large European States to introduce a comprehensive smoking ban, in 2005: this resulted in a further acceleration of a decreasing trend of smoking prevalence in both sexes with an estimated reduction from 27.6% in 2010 to 23.1% in 2025, among men, and from 17.6% in 2010 to 16.3%, in the same projected year, for women[19,20,21].

By contrast, in those countries where tobacco epidemic has been established more recently and smoking has just peaked or continues to increase, such as in China, Indonesia, or several countries in Africa, lung cancer rates will probably rise at least for the next few decades without interventions to accelerate smoking cessation and avoid initiation[2].

Considering previous data, tobacco smoking is confirmed as the most well-established risk factor for lung cancer; however, if women are more or equally susceptible to the carcinogenic effects of cigarette smoke on the lungs compared with men, is still a matter of controversy[22].

Several case–control studies suggested a higher relative risk among women compared with men for the same level of smoking exposure[23-26]. By contrast, other cohort studies did not evidence any higher smoking-related risks, suggesting that the incidence of lung cancer among female smokers was about the same as that of male smokers, after standardizing for the amount smoked[27-29].

In this context, the ICARE study, a multicenter case-control study, compared lung cancer risks associated with smoking between genders, suggesting that heavy smoking might confer to women a higher risk of lung cancer as compared with men. The study included 2276 male and 650 female cases and 2780 male and 775 female controls. Lifetime smoking exposure was represented by the comprehensive smoking index (CSI), which combines duration, intensity and time since cessation of smoking habits. Results varied according to histological type: overall lung cancer risk was similar among men and women, but women had a two-fold greater risk associated with a one-unit increase in CSI than men of developing either small cell carcinoma (Odds Ratio [OR] 15.9, 95% Confidence Interval [CI] 7.6-33.3 and 6.6, 95% CI 5.1-8.5, respectively; $p < 0.05$) or squamous cell carcinoma (OR 13.1, 95% CI 6.3- 27.3 and 6.1, 95% CI 5.0-7.3, respectively; $p < 0.05$)[30].

Despite previous studies, De Matteis et al, with the evaluation of 2100 cases and 2120 controls, evidenced a negative female sex-smoking interaction (OR = 0.39, 95% CI: 0.24, 0.62; $p < 0.0001$) in all subjects and no interaction (OR 0.63, 95% CI 0.29, 1.37; $p = 0.24$) among non-smokers[31].

Moreover, a recent Chinese meta-analysis of 47 studies found that males had higher susceptibility for cigarette smoking-attributable lung cancer than females. Compared with non-smokers, male to female Relative Risk Ratio (RRR) was 1.61 (95% CI 1.37, 1.89) among current smokers. The analysis involved more than 400,000 individuals of which 44.8% were Asians and 35.8% were Europeans. The prevalence of smoking was higher in men than in women, particularly in Asians[32]. Estimates of the sex-specific associations between smoking and lung cancer varied across studies, possibly because of differences in study design, region, classification of smoking status, and adjustment for confounders. For examples, the number of cigarette packs smoked per year and the years of smoking were generally higher in males than in females. This might also result in overrating the risk of lung carcinoma in males. Additionally, a specific biomarker of nicotine absorption suggested that more females than males underreported their smoking behavior[32].

Environmental tobacco smoke and additional risk factors

Passive smoking is also another established risk factor for lung cancer: approximately 20% of women with lung cancer are non-smokers and women married to men who smoke have been shown to have a 25%-29% increased risk of developing lung cancer[33-37].

Wang et al recently evaluated the relationships between active and passive smoking with lung cancer incidence in a prospective cohort of more than 90,000 US postmenopausal women, the Women's Health Initiative Observational Study (WHI-OS). Compared with non-smokers, lung cancer incidence was greatly higher in current (Hazard Ratio [HR] 13.44, 95% CI 10.80–16.759) and former smokers (HR 4.20, 95% CI 3.48–5.08) in a dose-dependent manner. Current and former smokers had a significantly increased risk for all lung cancer subtypes, particularly small-cell and squamous cell carcinomas. In WHI-OS study, among non-smokers, lung cancer incidence did not differ between non-smokers with passive exposure compared with non-smokers without passive exposure (HR 0.88, 95% CI 0.52-1.49). However, borderline significant increased lung cancer risk was seen in non-smokers with adult home exposure ≥ 30 years when compared with women with no adult home exposure (HR 1.61, 95% CI 1.00-2.58)[38].

In a cohort of 91.540 Japanese non-smoking wives, women with smoker husbands were at a higher risk (Rate Risk, [RR] 1.8) for lung cancer when compared to women with non-smoker husbands[39].

Environmental tobacco smoke exposure is one of the most important risk factors for non-smoking females, but it is only one of a well-characterized set of risk factors that include: occupational exposure to lung carcinogens such as asbestos, pesticides, radon, outdoor and indoor air pollution (e.g. coal-fuelled stoves and cooking fumes), diet, pre-existing lung disease, family history and infections[12,40,41].

A case-control study carried out in Missouri on occupational risk factors in never-smoking women, described an increased risk for lung cancer among women exposed to asbestos (OR 3.5; 95% CI 1.2-10) and pesticides (OR 2.4; 95% CI 1.1-5.6)[42].

Exposure to high levels of radon is also associated with an enhanced risk for developing lung cancer. In fact, radon, the first identified environmental cause of lung cancer, is not only of concern for underground miners, but for the population generally, as a ubiquitous contaminant of indoor air[43].

In non-smokers, smoke from domestic fuel (i.e., coal, wood, biomass) used for cooking and heating has been associated with lung cancer, particularly among Asian females using coal[44]. In addition, housing characteristics related to poor ventilation - including less window area, absence of a separate kitchen, lack of a ventilator and limited time with windows open - were associated with lung cancer in a Chinese case-control study. This study included 399 lung cancer cases and 466 controls, of which 164 cases and 218 controls were female non-smokers[45].

A protective effect against lung cancer has been suggested for consumption of vegetables, fruit and β-carotene among never-smoking women[46,47]. A cohort study of Finnish men and women found an inverse relation between Vitamins E, C and β-carotene and lung cancer risk in non-smokers[48]. However, other cohort studies from US found non-significant decreased risks for fruit consumption among non-smokers and no association between Vitamins E, C, carotenoids, or vegetable and fruit intake and lung cancer risk among non-smokers[49,50]. More recently, over 71,000 Chinese women with no history of smoking or cancer at baseline were prospectively evaluated for their dietary intake with a follow-up time exceeding 11 years. Dietary riboflavin intake was inversely associated with lung cancer risk (HR 0.62; 95% CI 0.43–0.89; p trend = 0.03 for the highest quartile, compared with the lowest)[51].

Pre-existing lung diseases such as asthma and chronic obstructive pulmonary diseases can represent additional potential risk factors for lung cancer[52]. Even after controlling for active and passive tobacco exposure, some studies have shown an increased risk for lung cancer among these patients[53]. Literature studies showed that people with tuberculosis had as much as a 50% increase in lung cancer risk: interestingly, a study by Hinds et al, examining lung cancer risk among smokers and non-smokers with tuberculosis, found that female non-smokers with tuberculosis had approximately an eightfold increase in lung cancer risk, whereas there was no association among female smokers[54]. Wu et al. found that the risk for lung cancer was increased for non-smoking women with previous lung disease (adjusted OR 1.56; 95% CI 1.2-2.0) and this finding was mainly driven by the prevalence of tuberculosis in this population[55].

Patients with a family history of lung cancer have an increased incidence of lung cancer, even in non-smoking families. It has been shown that non-smoking women in non-smoking families with a history of lung cancer have a greater risk in the development of lung cancer compared with non-smoking men with a similar family history[56].

Finally, Human Papillomavirus (HPV) is known to be associated with different types of cancer and has been proposed to be also one of the etiological factors for lung cancer, especially in Asia[57]. Since the virus infects the oral mucosa and subsequently the larynx and bronchial tissue, this may be the main source of HPV

detected in the lungs[58]. A meta-analysis on HPV in non-smokers with Non-Small-Cell-Lung Cancer (NSCLC) evaluated 46 articles, of which 23 were from Asian countries. The prevalence of the virus in non-smokers was significantly higher in East Asia (33.9%; 95% CI, 29.2–38.9, N = 392) than in Europe (14.8%; 95% CI, 6.6–27.1, N = 58, p = 0.005). While HPV prevalence in East Asia was similar between never- and ever- smokers (33.9% vs 39.2%, p = 0.080), it was significantly higher in never-smokers than in ever-smokers (14.8% vs 2.9%, p <0.001) in Europe[59]. A recent population-based study showed a significant increase in lung cancer risk among Taiwanese women, who were exposed to HPV infection. The study included 24.162 individuals with HPV infection from 2001 to 2004 and 1.026.986 uninfected individuals. Lung cancer incidence among infected and uninfected individuals was compared using univariate and multivariate regression models. After adjusting for age, gender, low income, residential area, and comorbidity, the risk of lung cancer was higher in women (HR 1.26; 95% CI 1.01-1.57), while all cancer risks were high in both men and women with corresponding HR of 1.16 (95% CI, 1.08-1.24) and 1.24 (95% CI 1.15–1.33), respectively. Cigarette smoking, the modifiable risk factor for lung cancer, was not adjusted, due to the lack of this information in the database[60]. However, other studies have yielded different results. In a retrospective evaluation of 223 lung cancer cases, HPV infection had no role in the pathogenesis of primary lung cancer, whereas HPV positivity was indicative of pulmonary metastasis from a primary HPV-associated cancer elsewhere in the body[61]. Considering controversial data emerged from literature studies, this information needs further confirmations.

Hormonal influences

Hormonal status is one of the potential explanations for differences in lung cancer between men and women. Estrogens may be involved in lung tumorigenesis through numerous mechanisms, such as cell proliferation induced by ligand-estrogen receptor interaction and the cross-talk between ERs and other growth factor receptors (i.e. epidermal and insulin growth factor receptors)[62].

As for ER-β, immunohistochemical positivity has been commonly observed for both the nucleus and cytoplasm in lung cancer. ER-β nuclear positivity has been related with a favorable clinical outcome in most studies, whereas the opposite is true for cytoplasmic positivity[63]. Compared with ER-β, ER-α shows great variability in its expression frequency. ER-α positivity is more usually observed in the cytoplasm than the nucleus, and ER-α cytoplasmic positivity has been related with poor clinical outcome[63].

The presence of ERs on lung cancer cells raises the question of exogenous estrogen influence on lung cancer presentation. At present, it is still unclear whether or not exposure to oral contraceptives (OC), hormone replacement therapy (HRT) or hormonal therapy may influence positively lung cancer incidence and survival (Table 1).

The International Lung Cancer Consortium (ILCCO) meta-analysis results revealed an interaction between hormone use and lung cancer risk in women (1961 cases, 2609 controls): a reduced lung cancer risk for both oral OC use and HRT was found, independent of smoking status[64]. A reduced risk of lung cancer was also observed in an EAGLE study for HRT (OR 0.63, p = 0.03) and OC use (OR 0.67, p = 0.05)[65]. While in the Maryland Lung Cancer Study (n = 1041) no significant associations for OC or HRT use, including long-term use, and NSCLC cancer risk were evidenced[66].

Table 1. Hormonal therapy and lung cancer survival correlations (selected retrospective studies highlighting controversial results).

Author	Study design	Years	Patients n	Results
Ganti et al[98]	Retrospective	1994-1999	498 (86 HRT users)	Improved OS among no HRT users (HR, 1.97; 95% CI, 1.14–3.39)
Ayeni et al[99]	Retrospective	1999-2003	397 (115 HRT users)	No effect of HRT on OS observed.
Huang et al[100]	Retrospective	1995-2005	648 (114 HRT users)	Non-significant improved OS among HRT users (HR, 1.09; 95% CI, 0.82-1.44)
Katcoff et al[71]	Retrospective	2001-2005	485 (230 HRT users)	Improved OS among HRT users (HR, 0.69; 95% CI, 0.54-0.89).

HRT: Hormone Replacement Therapy; OS: Overall Survival; HR: Hazard ratio; CI: Confidence Interval.

A recent meta-analysis of 14 cohort studies did not show a statistically significant association between HRT and lung cancer risk in women[67]. However, a significant increase in lung cancer incidence associated with HRT use was observed in the Vitamins and Lifestyle (VITAL) study (n = 36.000 postmenopausal women). The use of an estrogen plus progesterone (E+P) combination for more than 10 years was associated with an increased risk of lung cancer in comparison with no use of HRT (HR 1.48, p = 0.03)[68].

The Women's Health Initiative, a randomized, placebo-controlled trial, in which more than 16,000 postmenopausal women received placebo or daily HRT for 5 years, reported a strong negative effect on survival after a lung cancer diagnosis in women on the HRT arm in 2009, and recently, after 6 years' additional post intervention follow-up, the increase in lung cancer deaths was found to be attenuated (p = 0.042) after discontinuation of combined hormone therapy[69].

Finally, in the California Teachers Study (CTS) (n = 133.479), no effect of E+P use on female lung cancer was observed. Decrease of lung cancer mortality rates was determined among women who used estrogen-only therapy (ET) compared to non-users. The median survival time of lung cancer patients and ET users was 20.2 months vs 15.6 months for ET non-users (p = 0.008)[70]. In the Katcoff H et al study, E+P use was associated with a significantly improved survival for women with NSCLC taking combined HRT for 11 years or longer (p <0.0001)[71].

With regard to the expression of specific gene alterations, there are relevant sex differences and correlations with hormonal status. Molecular details of the interaction between ER and Epidermal Growth Factor Receptor (EGFR) are emerging, suggesting that a reciprocal control mechanism exists between the two pathways: EGFR protein is down-regulated in response to estrogens and is up-regulated in response to anti-estrogens[72]. Estrogen can directly stimulate the transcription of estrogen-responsive genes in the nucleus of lung cells and can also transactivate growth factor signaling pathways, such as EGFR pathway[72]. He et al. evidenced, in a recent meta-analysis, a correlation between high nuclear expression of ER-β and EGFR mutations in NSCLC and no significant correlation with ER-α or progesterone[73].

Finally, several reports found little or no progesterone Receptor (PR) in NSCLC and there are also data indicating lower PR levels in lung tumors compared to matched normal lung tissue[74-76]. Skjefstad et al. analyzed PR expression in 335 stage I–IIIA lung cancer and found that positive PR expression in stromal tissue correlates with favorable survival, on the contrary positive PR expression in tumor tissue correlates with poor survival in females[77].

Enzymes capable of synthesizing PR were also detected in many NSCLC tumors. A positive correlation was observed between intratumoral levels of progesterone and the presence of three enzymes participating in progesterone synthesis. Progesterone treatment led to growth inhibition of tumor xenografts and induction of apoptosis, in agreement with clinical data suggesting that the presence of PR was correlated with longer overall survival in NSCLC patients[75].

Genetic alterations, innovative evaluations and research approaches

It is now well known that sex differences influence specific gene alterations: EGFR mutation is found at a much higher frequency in adenocarcinomas, women, Asians and non-smokers[78]. Mazieres et al observed differential genetic alteration repartition in women, according to their tobacco status: 50.8% of non-smokers displayed an EGFR mutation versus 10.4% of smokers (p <0.001)[79].

Ongoing research has been adding new data towards specificities of lung cancer in women.

Although the Human Epidermal growth factor Receptor 2 (HER2) is well-known as a prognostic and predictive marker in patients with breast cancer, its role in lung cancer patients is far less understood[35]. In NSCLC, HER2/neu gene mutations occur in exons 18-21 of the tyrosine kinase domain, they are not seen in breast cancer and occur mostly in lung adenocarcinoma[80]. These mutations are identified in approximately 2% of NSCLC and in a recent publication, Mazierès et al. identified a high proportion of women (45 women versus 20 men; 69%) and a high proportion of non-smokers (n = 34; 52.3%)[81].

V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations have been primarily observed in smokers and are historically associated with male sex, but Dogan et al. genotyped 3026 lung adenocarcinomas for the major EGFR (exon 19 deletions and L858R) and KRAS (G12, G13). From these data emerged that KRAS G12C, the most common G >T transversion mutation in smokers, was more frequent in women (p = 0.007) and these women were younger than men with the same mutation (median 65 versus 69, p = 0.0008) and had smoked less[82].

C-ros oncogene 1, receptor tyrosine kinase (ROS1) fusions have been identified in about 1-2% of lung adenocarcinomas[83]. Warth A. et al. analyzed a cohort of 1478 NSCLC patients and a significantly higher rate of ROS1 translocations was observed in females (1.3%) than in males (0.3%). ROS1 positivity in tumor (in 68/1478 cases) was significantly more likely in females with low pathologic tumor size (pT) (7.8%) than in males (3.2%, p <0.001)[83].

To gain insights into the etiology of lung cancer in never-smoking women, the Female Lung Cancer Consortium in Asia (FLCCA) was founded including China, South Korea, Japan, Singapore, Taiwan, and Hong Kong. A multi-stage genome-wide association study (GWAS) on this population (6,609 cases, 7,457 controls) identified novel susceptibility loci at 10q25.2, 6q22.2, 6p21.32, and confirmed two previously identified loci at 5p15.33 and 3q28.6. Lately, data from studies participating in FLCCA were analyzed with available information (n = 3; 1731 cases; 1349 controls) in order to evaluate the gene–household air pollution interactions associated with lung cancer in loci independent of smoking. The risk of lung cancer associated with coal exposure varied with the respective alleles for two SNPs (HLA Class IIrs2395185, p = 0.02; TP63 rs4488809 (rs4600802), p = 0.04) providing evidence that genetic variation in HLA Class II and TP63 may modify the association between household air pollution and lung cancer risk. The roles played in the cell cycle and inflammation pathways by the proteins encoded by these two genes provide biological plausibility for these interactions[84]. Furthermore, a meta-analysis of four imputed GWAS of lung cancer in never smoking Asian women has yielded three new genetic susceptibility alleles for lung cancer at loci 6p21.1, 9p21.3 and 12q13.13[85].

Finally, recent studies investigated the role of telomere shortening in lung cancer. A 2015 report from FLCCA indicates that a genetic background that favors longer telomere length may increase lung cancer risk, consistently with earlier prospective studies relating longer telomere length with increased lung cancer risk. The dataset consisted of a sample of 5457 lung cancer cases and 4493 controls from a population of never-smoking Asian females. A genetic risk score, based on seven telomere-length associated variants, was used as instrumental variables to predict longer telomere length and it was associated with increased lung cancer risk (OR 1.51; 95% CI 1.34-1.69 for upper vs lower quartile of the weighted genetic risk score, p value = 4.54 x 10e14)[86].

Prognostic implications

Women exhibit greater survival rates regardless of stage, histology, treatment modality, or smoking status, even after adjusting for gender-specific life expectancy[87-89].

As for early-stage disease, data on a cohort of 10,908 patients with NSCLC (6665 men and 4243 women) from the Manitoba Cancer Registry showed a significantly better survival rate for women, independent of treatment, age, year of diagnosis, and histology (p <0.001). The adjusted HR for death for men compared with women was 1.13 (95% CI 1.04-1.23; p = 0.004). Sex modified the effect of surgical treatment on survival (HR 1.26; 95% CI 1.13 to 1.40]; p <0.001)[90].

In a recent retrospective analysis on 8016 adults with NSCLC who underwent lobectomy with or without adjuvant chemotherapy for pathologic T2 tumors measuring at least 4 cm, with no lymph node involvement, gender appeared to be a significant factor in determining which patients would benefit from adjuvant chemotherapy. Data were obtained from the National Cancer Data Base, a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The cohort included 4617 men (58%) and 3399 women (42%). Overall, women had improved 5-year survival relative to men (60% vs 47%, p <0.0001). However, there were groups of older women who experienced no benefit from adjuvant chemotherapy: specifically, those older than age 72 years (5-year survival: 53% vs 56%, p = 0.57), and those aged 65–72 years with medical comorbidities (5-year survival: 51% vs 58%, p = 0.29). By contrast, all groups of men identified by recursive partitioning analysis demonstrated improved survivals with adjuvant chemotherapy[91]. In this setting, also the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) JBR.10 trial evidenced remarkable gender differences: in this trial, adjuvant chemotherapy was found to confer a significant survival benefit for patients with completely resected stage IB or II NSCLC. In a stratified analysis, male gender was predictive of poorer survival regardless of treatment (p = 0.03)[92].

The Surveillance, Epidemiology, and End Results Database (31,226 patients) of lung cancer has been analyzed for prognostic factors and has identified the following as favorable prognostic factors: low-stage disease, surgical therapy, age <50 years, and female sex[93].

A Polish population-based study, 77 of 20,561 cases of lung cancer between 1995 to 1998 revealed that female patients had a better prognosis than males regardless of treatment modality, with an RR of death of 1, compared to 1.21 (p <0.001) in male patients by univariate analysis. More women were non-smokers compared to men (18.8% vs 2.4%, p <0.001). A multivariate analysis of absolute survival in this series showed that the RR of death was significantly higher for men (1.15; p <0.001)[94].

One potential explanation for better survival among women is a gender difference in DNA-repair capacities, which make tumors in women more responsive to platinum-based chemotherapies. DNA-repair machinery has been shown to be more defective in women, making them more susceptible to respiratory carcinogens but also more sensitive to DNA- interfering agents, however further prospective studies will clarify these suggestive hypotheses[95-97].

Conclusions

All the exciting findings and progressive improvements in gender-based research discussed above will provide further evidence for the specificities of lung cancer in women. The differential expression of specific biomarkers, which could be targeted by therapy, will stimulate the development of further gender-based approaches and therapeutic tools which could be hopefully applied in clinical practice.

Key messages

- After the huge spread of tobacco consumption, lung cancer incidence increased. Lung cancer is currently the first cause of cancer-related death in both men and women in developed countries.
- Cigarette smoking is the major risk factor for lung cancer in both sexes. Many studies reported a greater risk for female-smokers than for male-smokers, even though the higher female susceptibility for tobacco carcinogens is still controversial.
- Considering environmental risk factors in non-smokers, Human Papilloma Virus (HPV) infection and household air pollution have been associated with lung cancer, especially among Asian females.
- Lung cancer is a result of complex interplaying factors including carcinogen exposure, metabolism and genetics.
- Hormonal status is one of the possible explanations for differences in lung cancer between men and women; hormonal pathways are promising targets for lung cancer therapy.

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