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Women and lung cancer

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epidemiology

In the early 1900s lung cancer was reported to be rare in women, but has, starting from the 1960s, progressively reached epidemic proportion, surpassing breast cancer in 1987 and becoming the leading cause of cancer deaths among women. Over the past 30 years there has been a four-fold increase in lung cancer in women (altering the male/female ratio of the disease) and it is estimated that this rise will not plateau until after 2010 [1]. Observational studies suggest differences in the histologic presentation [2–4] and age distribution of lung cancer between men and women (Table 1). Lung cancer kills more women in the United States each year than in any other country in the world: over 170 000 patients die from lung cancer and over 70 000 are women (29% of all cancer deaths), that means more deaths than breast, ovarian and uterine cancer combined together. Small cell lung cancer and adenocarcinoma are more common in women than in men (26.6% vs. 19.9%, P <0.001 and 21.6% vs. 9.6%, P <0.001, and younger lung cancer patients are more likely to be female than male (age <50 years: 23.3% vs. 12%, P <0.001) [4].

risk factors

Controversy exists as to whether women are more or less sensitive to the carcinogenic effect of tobacco smoke. Several case-control studies seem to suggest that women are more vulnerable to tobacco carcinogens than men. In 1993, Risch et al. investigated the male–female differences in more than 800 patients with lung cancer and they showed that, compared with a non-smoking population, the relative risk of developing lung cancer was 27.9 in women vs. 9.6 in men at the same level of lifelong exposure (40 pack-year) [5]. An American Health Foundation case-control study including 1108 men with lung cancer, 781 women with lung cancer and 2070 controls, found that, given the same level of exposure to cigarette smoke, women had approximately 1.5-fold higher estimated relative risk of developing lung cancer than men. The sex difference, in estimated relative risk, was statistically-significant for all histological subtypes of lung cancer although slightly greater for adenocarcinoma and small cell lung cancer than for squamous cell carcinoma [6]. On the contrary, cohort studies have reported that there are no significant differences in susceptibility between females and males [7].

However, important differences exist between the sexes: women who smoke are more likely to develop an adenocarcinoma, and never-smoking females are more likely to develop lung cancer than men who have never smoked. Several studies showed that women may be more predisposed to molecular aberrations caused by the carcinogenic effects of tobacco smoke. Kure et al. found a higher frequency of G:C→T:A mutation in the p53 gene and a higher average of DNA adduct level in lung tumors from women even if the level of exposure to carcinogens was lower among women than men [8]. In the lung of female smokers an increased expression of the CYP1A1 gene has been found [9]; the CYP1A1 gene codes for an enzyme (phase 1 enzyme) that metabolizes the polycyclic aromatic hydrocarbons and leads to DNA forming adducts. Although the CYP1A1 gene activates carcinogens metabolically, phase 2 enzymes compete with phase 1 to inhibit the formation of free radicals. The most common polymorphism, in phase 2 detoxification enzymes, is the glutathione S-transferase M1 (GSTM1) null genotype, which is present in 40 to 60% of the general population owing to a gene deletion. Expression of the null phenotype may be a marker of susceptibility to lung cancer, and the effects of GSTM1 gene deletion may be heightened among female smokers: the effects of polymorphisms in both genes could contribute to an increase risk of lung cancer in women [10]. However, women may have other underlying predispositions to lung cancer: they appear to have lower DNA repair capacity and K-*ras* mutations are more common in NSCLC from female than from male smokers [11]. The gastrin-releasing peptide (GRP) is a bombesin-like peptide which stimulates cell proliferation through an interaction with its receptor (GRPR). The gene for GRPR is X-linked, located on chromosome Xp22, near a cluster of genes that escape X-inactivation. Therefore, women can have two actively transcribed alleles of the GRPR gene compared with only one in men. Shiver and colleagues reported that the GRPR mRNA expression was observed in airway cells and tissues more frequently in female than male nonsmokers (55% vs. 0%) and short-term smokers (1–25 pack-years) (75% vs. 20%) (P =.01) [12]; in addition, the activation of the GRPR gene occurs earlier in women in response to tobacco exposure. The same author also showed an increase in the GRPR gene expression when human airway cells were exposed to estrogens, suggesting a role in lung carcinogenesis for these hormones. Stabile and colleagues have shown that β-Estradiol induced proliferation of cultured non small cell lung cancer cells and that anti-estrogens could block these effects [13]. Taioli and Wynder [14] also presented evidence that estrogens may play a role in the development of lung adenocarcinoma

Table 1. Distribution of lung cancer by histology and gender

Histologic type	Males n = 1156	Females n = 831
Squamous/epidermoid	397 (34%)	165 (20%)
Small-cell	182 (16%)	142 (17%)
Large-cell	111 (10%)	90 (11%)
Adenocarcinoma	418 (36%)	384 (46%)
Brocho-alveolar	17 (1.5%)	30 (3.6%)

in women. Using case-control data they showed that: (i) early age and menopause (40 years or younger) is associated with reduced risk of adenocarcinoma of the lung ([Odd Ratio] OR=0.3); (ii) the use of estrogen replacement therapy is associated with a higher risk of adenocarcinoma of the lung (OR=1.7); (iii) a positive interaction between estrogen therapy, smoking, and development of adenocarcinoma of the lung (OR=32). (iv). The estrogen-related effects in the lung might be mediated mainly through the functional estrogen receptor ERβ.

More recently, activating mutations in the tyrosine kinase domain of the Epidermal Growth Factor Receptor (EGFR) have been identified; these mutations correlate with the radiological response to Tyrosine-kinase Inhibitors (TKIs) such as gefitinib and erlotinib. These mutations often occurred in tumors from non-smoker females with adenocarcinoma [15]. Some authors observed that the EGFR protein expression is down-regulated in response to estrogen and up-regulated when estrogen is depleted, suggesting a cross-talk between these two pathways. The potential role of estrogens in lung cancer tumorigenesis is intriguing and should be further investigated.

It is still unclear if lung cancer in women has intrinsic behaviour and a natural history different from men: however, women having lung cancer experienced better survival time in comparison with men. This has important implications in the design and interpretation of clinical trials where females are more and more represented. Sex migration could be confusing even in carefully designed clinical trials and a stratification by sex could be necessary in the next future.

therapeutic outcomes

The 5-year survival rate for women who have lung cancer is 15.6% compared with 12.5% for men and this improved survival has important implications in the design and interpretation of lung cancer trials. From 1990 to 2003 there was a 60% increase in the number of new cases of lung cancer in American women, while the number of men diagnosed with lung cancer remained stable. This increase was reflected in clinical trial participation by women, causing a survival improvement and suggesting the need of stratification by sex in future studies.

Women have superior responses to therapy regardless of stage, therapeutic modalities or histology (Tables 2 and 3). A Surveillance analysis among 31.226 patients published in 1998 showed the female sex as favourable prognostic factor. Among 20 561 patients in the Polish cancer registry from 1995 to 1998 women had an RR of death of 1, compared to 1.21 ($P = 0.001$) in male by univariate analysis [4]. In a French cohort of 208 patients, when the data was adjusted for stage, women lived significantly more at each stage [16]. In a retrospective review of 7553 patients treated for NSCLC between 1974 and 1998 there is an overall median survival of 12.4 months for women and 10.3 for men ($P < 0.001$) and the advantage is present for all stages ($P < 0.001$) [17]. In the evaluation of the above mentioned three studies, two factors have to be taken into account: the lack of information about smoking habit and lack of data about cause-specific mortality. However there is a prospective trial which confirms the female sex as an independent predictor of survival including in the multivariate analysis age at diagnosis, histology, stage, smoking attitude and treatment and, despite the greater number of comorbidities in the male cohort, the survival was not negatively impacted for men [18].

In localized NSCLC women will experience superior survival after either surgical resection or radiation as single modalities. In a retrospective study done by de Perrot et al., women had an hazard ratio of 0.72 (95% CI, 0.56–0.92) among 1046 patients who underwent surgery for NSCLC from 1977 to 1996. In this analysis the rate of pneumonectomy was higher in men (32% vs. 22%), but the difference in mortality was not statistically significant and this fact confirm that early operative deaths are not the cause of lower survival in men [19].

Another retrospective analysis done by Ferguson et al. showed a median survival of 41.8 months in women versus 26.9 months in men ($P = 0.007$) among 451 cases resected and this gap was particularly present for stage I disease (109.8 months vs. 50.3 months, $P = 0.0008$) [20].

In United Kingdom a prospective analysis among 833 patients undergoing lung resection between 1990 and 2000 showed a 5 year survival of 48% in women compared with 36.5% in men ($P = 0.01$) and this survival advantage was maintained also considering the higher prevalence of cardiovascular comorbidities in men that are not entirely responsible for lower survival [21].

Similar results are reported in the adjuvant setting. At equivalent stages of lung cancer, women live longer than men. In the Adjuvant Lung Project Italy (ALPI) trial there was no advantage for patients randomized to chemotherapy (mitomycin-vindesine.cisplatin), but there was an advantage in term of overall survival in favour of female sex [22].

Female sex is an independent positive prognostic factor also in the SWOG study of multimodality therapy (chemotherapy, radiotherapy, surgery) : the median survival for women was 21 months vs. 12 months for men ($P = 0.08$) [23].

In advanced disease there is evidence of survival advantage for women described in a large review of 13 SWOG trials with a database of 2531 women enrolled between 1974 and 1987. Median survival ratio for females/males was 5.7/4.8 with 1-year survival rates of 19% vs. 14% ($P < 0.01$) [24]. Similar results were reported by the European Lung Cancer Working Party (ELCWP) among 1052 patients evaluating 23 pretreatment variables: female sex was one of eight variable significantly associated with superior survival [25].

Similar outcomes emerge for small cell lung cancer: the analysis of four consecutive prospective trials showed the superior survival for women compared with men [26]. A total of 2580 patients from 10 SWOG trials with limited (LD) and

Table 2. Treatment in NSCLC

Author	No. of patients	Female %	Stage of disease	Therapy	MST female:male	HR	*P* value
O'Connell [32]	378	30	III-IV	Chemot.	12.4:8.8	0.71	0.001
Mitsudomi [33]	492	27	I-IV	Surg	60:38	0.63	0.00036
Ferguson	299	45	I-IV	All modalit.	12.1:9.1	0.75	0.044
Sorenson	259	46	III-IV	Chemot.	6.8:6.8	1.0	0.5
Albain	2531	23	III-IV	Chemot.	NS:NS	0.77	<0.00005
Paesmans	1052	10	III-IV	Chemot.	NS:NS	0.70	0.003

Table 3. Treatment in SCLC

Author	No. of patients	Female %	Stage of disease	Therapy	MST female:male	HR	*P* value
Johnson	378	28	LD & ED	Ch/RT	13:10	0.77	0.002
Albain	1363	32	LD	Ch/RT	NS:NS	0.77	0.00001
Paesmans	763	11	LD & ED	Chemot.	11.1:10.2	0.91	0.16

extensive disease (ED) were analyzed for prognostic factors and, only for LD, female sex ($P \leq 0.0.001$) was significant favourable independent predictor [27].

Many data regarding epidermal growth factor receptor tyrosine kinase inhibitors are in favour of female sex. In second line therapy the studies IDEAL 1 and 2 evaluated gefitinib in patients with advanced non-small cell lung cancer previously treated with one or two lines of chemotherapy and showed the female sex as predictor of improved outcomes [28, 29]. In the IDEAL 2 in 50% of women there was an improvement of symptoms compared with 31% in men and eighty-two percent of partial response occurred in women. The improved prognosis observed in women may be due to differences in frequency of mutations in tyrosine kinase domain of the epidermal growth factor receptor: 20% in women versus 9% in men [30].

In broncho-alveolar carcinoma gefitinib is more effective in women as demonstrated in a SWOG study in which 138 patient with bronchoalveolar carcinoma were treated with gefitinib as first or second line. In this trial there was a prolonged survival in females with a statistical significance in the previously untreated population ($P = 0.04$) [31].

conclusion

Lung Cancer is not only a man's disease. Women do not realize this fact because their awareness of other cancers (e.g. breast cancer) is much higher. We have to try to help them to understand that lung cancer is their top cancer killer. Over 20 000 patients diagnosed with lung cancer each year have never smoked. Of these lung cancer patients, a disproportionate number are women.

AIDA^{CP} (Associazione Italiana Donne anti Cancro del Polmone) has been set up an initiative among professionally invoved women (namely doctors, social workers, nurses and others involved in thoracic oncology), sharing the peculiar issues of the neoplastic disease in women and facilitating the possibility to gather together all women who believe it is important to put their ideas into practice in an association that can serve to disseminate information in our country and transfer the data within the context of programmes and social initiatives of pragmatic intervention.

Another European association is in the planning stage following a similar association, that already exists in the United States, called Women Against Lung Cancer (WALC). This is a non-profit organization of leading scientists, physicians, nurses and advocates dedicated to treat lung cancer as a public health threat to women. From a Spanish and Italian idea we are planning to create a European Group named WALCE (Women Against Lung Cancer in Europe). We would like WALCE to represent a valid working tool aimed at supporting, both socially and scientifically, a challenge that we cannot miss.

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