New Aspects in the Epidemiology of Lung Cancer – The Women’s Epidemic

a report by

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Lung cancer is the most common cancer in the world and, by 2002, there were 1.35 million new cases, representing 12.4% of all new cancers. It is also the most frequent cause of death by cancer, with 1.18 million deaths. In women, the global incidence rate is 12.1 per 100,000 compared with 35.5 per 100,000 in men.

In the US, incidence and mortality standardised rates in 2000 were, respectively, 58.6 and 53.2 in males and 34.0 and 27.2 in females, with a sex ratio of 1.7. In females, mortality due to lung cancer has been greater than mortality due to breast cancer since 1987. In Europe, lung cancer is the most frequent cause of death by cancer in males. Sex ratios differ significantly between the European countries, reflecting differences in smoking habits. The lowest sex ratio is in Denmark (1.7), and the highest in Spain (13.4). While stabilisation or even a decrease in the number of lung cancers in males is emerging in most European countries, mortality due to lung cancer in females is increasing. In western Asia, the age-standardised incidence is 33.1 in males and 5.5 in females (sex ratio: 1.6).

Lung Cancer – Attributable to Active Tobacco

Smoking habits vary within the different countries in Europe, with a significant decrease in tobacco consumption in the UK, Sweden and Finland between 1970 and 1994 and a significant increase in Portugal (+64.2%).

Even if active tobacco smoking is the main cause of lung cancer in females, the attributable risk is inferior to that noted in males.

Worldwide, in 2000 an estimated 85% of lung cancer cases in men and 47% in women were attributable to tobacco smoking. In the US, the proportion attributable to tobacco smoking in females is pretty much the same as in males. Moreover, there is now a convergence between lung cancer incidence in the youngest birth cohorts, reflecting the convergence in cigarette use in males and females.

In Europe, about 70% of lung cancer cases in females are attributable to an active smoking habit versus 85% in males, whereas in Asia very few lung cancer cases in females are attributable to tobacco smoking. Even if the incidence of lung cancer in male non-smokers is consistently higher than in female non-smokers, the proportion of non-smokers in females with lung cancer is rather significant compared with males in all studies.

Higher Tobacco-smoke Susceptibility in Females

Some case-control studies suggest a higher susceptibility to tobacco for females. A 1993 analysis found an odds ratio of 27.9 (95% confidence interval (CI) 14.9–52) for women who have smoked 40 pack-years (one pack a day for 40 years or two packs a day for 20 years, etc.) relative to lifelong non-smokers, versus 9.6 (95% CI 5.64–16.3) for males. Also, in an American Health Foundation case-control study, the relative risk of female smokers was estimated to be 1.5 times that of males. On the other hand, cohort studies demonstrated either no difference between genders regarding the risk linked to tobacco-smoke exposure or a higher risk in men. There are many differences between genders that could favour a higher susceptibility to tobacco in females. Capacity of DNA repair is inferior in females. DNA-adduct formation due to tobacco smoke is more frequent in females than in males, regardless of the level of smoking, and CYP1A1 (a gene involved in phase I of the metabolism of polycyclic aromatic hydrocarbons) level of expression is higher in females.

In men, the Glutathione S-transferases, the µ isoenzyme has been extensively studied. A lack of activity is associated with an increased risk in smokers. Deletion of the gene results in a higher increase of the risk in female smokers than in male smokers. Gastrin-releasing peptides (GRPs) are involved in the development of normal human lung and cell proliferation. They act through a receptor, GRP-R. The receptors are mainly in epithelial cells and fibroblasts with a high affinity for nicotine. It has been demonstrated that in non-smoking females this receptor is expressed in 55% of cases versus none in non-smoking males. In smokers of less than 25 pack-years, it is expressed in 75% of females versus 20% of males.

Hyperexpression in females could be due to the fact that the receptor gene is in a part of the X-chromosome escaping inactivation.

Also, hormonal factors, especially oestrogens, are involved in lung cancer risk, especially for adenocarcinomas. Hormone-replacement therapy has controversial effects on the risk of developing a lung cancer, with some studies indicating an excess of risk and others showing no influence or even a protective effect. All of these studies were case-control studies and prospective studies are needed to allow for a clear conclusion. Receptors α and β to oestrogens have been demonstrated in bronchial tumour cells, as well as in the bronchiolar epithelium.
with more frequent expression in females.24 Thus, oestrogens could play a role through activation of the receptors. They also act as a direct carcinogen after metabolic activation to catechol oestrogens, which can form DNA adducts but can also induce the CYP1A1 gene.25,27

Some gender differences – genetic – are more involved in prognosis than in susceptibility. For example, K-ras mutation of codon 12 in adenocarcinoma is more frequent in female smokers with lung cancer than in males,28 but epidermal growth factor receptor (EGFR) mutations of the intracellular domain gene are more frequent in females, accounting for higher response rates with inhibitors of tyrosine kinase observed in females with lung cancer (especially adenocarcinoma and in Asian people).29,30 Of interest is the fact that K-ras mutations and EGFR mutations are mutually exclusive, the former having a negative impact on survival and the latter having a positive impact.31 Although there are many biological differences between the genders regarding the susceptibility to tobacco-smoke carcinogens, there is still controversy around the potentially higher risk in females.32,33 There are several susceptibility to tobacco-smoke carcinogens, there is still controversy about the potential carcinogenic risk between the genders regarding the many biological differences between the genders.34 More recent studies confirm the increased risk of their spouse or partner.35 Among the other risk factors, ETS has been extensively studied, with controversial results probably related to the difficulties in measuring exposure.36

Age and Histological Distribution in Males and Females

Age at diagnosis has been considered as higher in females in some studies,11,47 whereas in other studies authors report a lower age.3 These discrepancies might be due to the proportion of non-smokers in these series. Non-smokers are older at lung cancer diagnosis than smokers.48 Adenocarcinoma is the main histological subtype in females whether or not they are smokers. The second in frequency is small-cell lung cancer. Even if adenocarcinoma is increasing in frequency in males, squamous cell carcinoma is still the main histological subtype in males, at least in Europe.49,50 An increase in adenocarcinoma incidence in males might be due to the type of cigarette used: filters and blonde blend induce a deeper inhalation and thus more peripheral distribution of the smoke, which is where adenocarcinomas arise.51

Conclusion

The main epidemiological novelty in lung cancer is the tremendous increase of its frequency in females. This phenomenon has already been observed for several years in the US but is more recent in Europe. Even if tobacco smoking appears to be the main cause, other risks seem to be rather specific in females even if smoking habits are quite different. Genetic differences and hormonal factors underlie these epidemiological features.
ZOMETA® 4 MG POWDER AND SOLVENT FOR SOLUTION FOR INFUSION. PRESENTATION: Zoledronic acid. Vial containing 4 mg of zoledronic acid supplied as a powder together with ampoules containing 5 mL of water for injections for reconstitution.

INDICATIONS: Prevention of skeletal-related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone. Treatment of hypercalcaemia of malignancy (HCM). DOSAGE: For “prevention of skeletal-related events in patients with advanced malignancies involving bone,” the recommended dose is 4 mg (reconstituted and diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution) given as an intravenous infusion for no less than 15 minutes every 3 to 4 weeks. Dose reduction is recommended in patients with preexisting mild to moderate renal impairment. For “treatment of HCM,” the recommended dose is 4 mg given as a single intravenous infusion for no less than 15 minutes. No dose adjustment in patients with mild to moderate renal impairment. Patients without hypercalcaemia should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.

CONTRAINDICATIONS: Pregnancy, breast-feeding women, patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates, or any of the excipients in the formulation of ZOMETA. PRECAUTIONS/WARNINGS: Patients must be assessed prior to administration of ZOMETA to assure that they are adequately hydrated. Monitoring of standard hypercalcaemia-related metabolic parameters such as serum levels of calcium, phosphate and magnesium, and particularly, serum creatinine should be performed infrequently in patients taking bisphosphonates. In view of the potential impact of bisphosphonates on renal function and the lack of extensive clinical safety data in patients with severe renal impairment with ZOMETA, its use in this population is not recommended. Dose reduction in patients with preexisting mild to moderate renal impairment. In patients requiring repeated administration of ZOMETA, serum creatinine should be evaluated prior to each dose. If renal function has deteriorated, the dose should be withheld. Limited clinical data in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population. Overhydration should be avoided in patients at risk of cardiac failure. No experience in children. Patient should inform the dentist while under dental treatment or if dental surgery is foreseen. INTERACTIONS: Zoledronic acid shows no appreciable binding to plasma proteins and does not inhibit human P450 enzymes in vitro, but no formal clinical interaction studies have been performed. Caution is advised when bisphosphonates are administered with aminoglycosides since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required. Caution is asked when used with other potentially nephrotoxic drugs. Attention should also be paid to the possibility of hypermagnesaemia developing during treatment. In multiple myeloma patients, the risk of renal dysfunction may be increased when IV bisphosphonates are used in combination with thalidomide. ADVERSE REACTIONS: Usually mild and transient and similar to those reported for other bisphosphonates: most commonly reduction in renal calcium excretion is accompanied by a fall in serum phosphate levels; hypocalcaemia; commonly flu-like syndrome consisting of fever, fatigue, chills, and bone, joint, and/or muscle pain; headache; elevation of serum creatinine and blood urea; renal impairment; anaemia; conjunctivitis; gastrointestinal reactions such as nausea and vomiting, anorexia; serum calcium may fall to asymptomatic hypocalcaemic levels; uncommonly thrombocytopenia, leukopenia, hyperamylasemia reactions; hypertension, hypotension, resulting very rarely in syncope or circulatory collapse; shortness of breath, cough, dizziness, paraesthesia, taste disturbance, hyperaesthesia, hypoaesthesia, tinnitus, anxiety, sleeping disturbances; blurred vision; diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth, local reactions at the infusion site such as redness or swelling; dermatitis, peripheral oedema, weight increase, chest pain; rash and pruritus, increased sweating; muscle cramps, osteonecrosis (primarily of the jaw); acute renal failure, haematuria, proteinuria, hypermagnesaemia, hyperkalaemia; rarely pancreatitis, confusion, bradycardia, angioneurotic oedema, “hyperkalaemia, hypermetraemia” very rarely urticaria and epidermictis. PACKS AND PRICES: Country-specific. NOTE: Before prescribing, please read full Prescribing Information.


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