Editorial Commentary

Lung cancer screening: think pink!

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Lung cancer is one of the leading causes of death worldwide, and its annual incidence continues to grow especially in women and in the developing countries (1). In 2019, the estimates for Italy showed that 13.076 new women were diagnosed with lung cancer, equal to the 30.6% of all new diagnosis (2). Indeed, lung cancer represents the third cancer diagnosed in female cohort (6.9% of all cancer), with a probability to develop it during lifetime of 1:39. Compared to male incidence, which has been decreasing since the early 1990s, the risking trend in female incidence is steadily increasing (+2.2%), mostly related to tobacco habits (3). Besides, the lung cancer-related women death accounts approximately 14% of all death (second only to breast cancer death) (3), with a 10-year survival estimated of 15%.

Smoking prevention and cessation are the best strategies for reducing lung cancer mortality and all deaths due to tobacco-related diseases, but it is still not enough considering that even if the prevalence of tobacco smoking continues to decrease, the incidence of lung cancer among non-smokers seems to be increasing (4). Thus, screening for both men and women has been proposed as a strategy for reducing lung cancer mortality.

Controlled trials have already shown that chest radiography (CXR) and sputum cytology are ineffective screening tests (4), whereas screening the population with low-dose computed tomography (LDCT) could significantly reduce lung cancer mortality (5-7). Indeed, LDCT could anticipate diagnosis through the detection of lung nodules, which may also be of few millimeters in diameter, with low radiation exposure, limited costs, and without the need of contrast.

The large-scale randomized National Lung Screening Trial (NLST) on 53,000 high-risk volunteers (subjects aged 55–74 randomized to either LDCT or CXR in a 1:1 ratio) with high smoking exposure (>30 packs/year) was the first trial to demonstrate a mortality reduction of 20% in subjects screened by LDCT, compared to those screened by CXR (5,8). In particular, analyses of NLST data stratified by sex, smoking history, and lung cancer histology had showed a lung cancer-mortality benefit more evident in the subgroup of women than among men (risk ratio of 0.73 *vs.* 0.93, respectively; P interaction =0.08) (8).

Even, the Nelson trial (15,882 participants) showed a significantly lower lung-cancer mortality (24%) among those who underwent volume LDCT screening compare to those without screening, and confirmed the more favorable effect of screening on women (9). Moreover, the analysis of a small subgroup of women showed a reduced risk of lung cancer death of 33% at 10 years of follow-up (9).

Recently, the German Lung Cancer Screening Intervention Trial (LUSI) (4,052 long-term smokers) compared LDCT screening (n=2,029) to a control arm without screening intervention (n=2,023), over an average observation time of 8.8 years post-randomization, showing an overall hazard ratio for lung cancer mortality of 0.74 (95% CI: 0.46–1.19), which although not statistically significant, was in line with overall mortality reductions reported by the NLST. Besides, a significant benefit with respect to lung-cancer mortality was evident especially in the small subgroup of women (hazard ratio 0.31; 95% CI: 0.10–0.96) (7). These outcome data are also consistent with differences between the sexes in the screening-detectable preclinical period (i.e., the period in which the lung cancer is detectable through CT screening but has not yet clinically manifested itself through symptoms) (10).

Contrary, the Multicentric Italian Lung Detection (MILD) study, as well as other European randomized control trials such as DLCST and DANTE trials (6,11,12), failed to demonstrate the efficacy of the LDCT screening in term of reduction of lung-cancer 5-years mortality (13). This is probably due to a relatively small population, and to an insufficient length of follow-up as well as various heterogeneities between the arm groups (e.g., different radiological criteria, population differences, and imperfect randomization). However, a subsequent pooled analysis of MILD and DANTE showed a reduction of the lung cancer mortality of 17% at 8 years, which was similar (even not statistically significant) to the NLST data (14). In particular, 10-year results of MILD, empowered by the prolonged LDCT screening at 10 years, reversed the earlier negative 5-year results (15), showing a statistically significant 39% reduction of lung-cancer mortality of the LDCT arm (hazard ratio 0.61; 95% CI: 0.39–0.95) compared with control arm, and a non-significant 20% reduction of overall mortality (HR 0.80; 95% CI: 0.62–1.03) (6). Nevertheless, no mention was done on gender-difference, and new-pooled analyses of the European data should be done to provide further clues in screening efficacy in term of lung-cancer mortality by sex and/or histologic tumor subtype.

All these studies underlined the benefit of the screening for lung cancer in older high-risk smokers, and showed how this was dependent on a number of factors related to the screening participants (gender, ethnicity, comorbidities, operability and life expectancy), and to the type and biology of the tumor at the diagnosis (stage, histology and aggressive biology). However, the evidence of differential benefit by gender is still weak and probably related to the more prevalence of adenocarcinoma in women than in men. A recent study (16) has demonstrated that women had a longer disease-free survival compared to matching male patients (i.e., patients with similar disease stage, histological subtype and demographics characteristics), with adenocarcinoma as the most frequent histology (50%), followed by the squamous carcinoma (12%).

However, Pinsky *et al*. (17) performed a post-hoc analysis to examine whether the benefit was affected by various baseline factors, including gender, showing a borderline significant difference in overall mortality between men and women [relative risk (RR) 0.92 in men and 0.73 in women, with a p-value for interaction of 0.08]. In particular, the gender-difference in mortality was not evident in the adenocarcinoma cohort, where the RR mortality was essentially the same for men as for women (RR 0.77 and 0.73, respectively). Instead it was significant in the setting of small cell carcinoma (RR =0.90) or squamous carcinoma (RR =1.23), in which usually the screening effect was less evident and the variations across arm and gender could be chance occurrences (17).

Thus, the reason why women with NSCLC have a better survival, and why there is a gender-related disparity in the timing of recurrence is not completely understood, and still very much debated. The fact that women have good outcomes is not necessarily attributed to the high rates of histological subtypes associated with a long disease free interval, such as adenocarcinoma or stage IA disease among women but it might be also related to hormonal status. The exact mechanism by which estrogens may be involved in lung carcinogenesis is not clear, but some researchers have reported that estrogens and its receptors may play an important role in the pathogenesis of lung cancer (18,19). This was also reflected in early diagnosis biomarkers study, which identify a 2% differences between men and women, reflecting the genome gender-specific differences (20). Besides, Watanabe *et al*. suggested that sex-dependent differences in the recurrence patterns could be explained by the gender difference in the interval during which residual tumor cells proliferated and micro metastases developed after entering a transient state of dormancy (16). The sex-related inner milieu of the host might act differently on residual tumor cells in men and women, resulting in different durations of the micro metastatic dormancy phase and the different timing of the recurrence peak (16).

In conclusion, LDCT screening could be considered a valuable approach for reducing lung-cancer mortality, especially in women even if the reason is not yet completely understood. New pooled data analysis, in particular from the European trials, are essential to better the gender-related different effect of the lung cancer screening on population.

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