Editorial

Tobacco cessation in lung cancer screening—do we have the evidence?

Emily Stone[1], Henry Marshall[2]

[1]Department of Thoracic Medicine and Kinghorn Cancer Centre, St Vincent's Hospital Sydney, University of New South Wales, Sydney, Australian; [2]University of Queensland Thoracic Research Centre, Department of Thoracic Medicine, The Prince Charles Hospital, Brisbane, Australian

Correspondence to: Emily Stone. Department of Thoracic Medicine and Kinghorn Cancer Centre, St Vincent's Hospital Sydney, University of New South Wales, Sydney, Australian. Email: estone@meshastele.com.au.

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The field of lung cancer screening with low-dose CT scan (LDCT) has witnessed a surge of research and interest, particularly with the publication of the National Lung Screening Trial (NLST) in 2011 (1), showing for the first time, a reduction in lung cancer mortality related to LDCT screening. Allied to this, a growing number of recent papers have investigated the links between tobacco cessation and screening, exploring the effect of screening itself on smoking rates, additional tobacco cessation interventions and the impact of better quit rates on lung cancer outcomes. Studies report on various tobacco cessation interventions including face to face counselling, telephone counselling, the addition of varenicline and primary-care based interventions. The protocol for a planned study describes randomization of current smokers presenting for screening to usual care or a digital cessation intervention (web-based education tool plus daily cessation text messages) with or without referral to a tobacco treatment specialist (2). Much of the recent published data emanate from the NLST and most studies that examine prospectively collected smoking data perform secondary analyses although two recent papers included randomization to a specific smoking cessation intervention versus control (3,4). A number of uncertainties remain for tobacco cessation in the context of lung cancer screening with LDCT. Optimal selection and timing of interventions have not been defined. Candidates for aggressive tobacco cessation, such as highly-dependent smokers who may struggle to quit smoking and who may be at particular risk of developing lung cancer, are not routinely identified or described. Important outcomes beyond cessation, such as lung cancer rates and survival as well as cost-related outcomes, are not routinely reported.

A number of papers published over the last 5 years have analysed prospectively collected smoking data from various lung cancer screening studies. Nearly half of the studies (5-8) draw upon data from the National Lung Screening Trial (1) while other studies include data from Danish (9), British (10), Australian (3), Italian (11,12), German (13) and US (4) trials. Several of these studies include specific smoking cessation interventions, including single session counselling (3), counselling at multiple visits (9,12), behavioural interventions in primary care (6) and the use of varenicline (11,12). A number of studies have randomized lung cancer screening participants to smoking cessation interventions, finding little effect from self-help materials (14) or computer-based intervention (15) but some impact from pre-scan tobacco-dependence treatment (16). Two further studies have randomized participants to different tobacco cessation counselling treatments. An Australian study involving 55 patients (9) randomized participants to single session face-to-face counselling with a physician on the day of screening plus audiomaterial, printed materials and Quitline referral compared with printed materials and Quitline referral alone. The primary outcome, smoking status at 12-months according to the question, "Do you now smoke cigarettes (one or more cigarettes per week)?" was biochemically verified by measurement of exhaled carbon monoxide in just four participants. Baseline characteristics including

demographics, details of smoking history, symptoms, previous smoking cessation therapies and measurements of readiness to quit were similar between groups apart from a possible higher alcohol intake in the intervention group. At 12-months, assuming that 5 participants with missing data were smokers (3 intervention, 2 controls), the quit rates were not significantly different between groups: 14.5% in the intervention group, 18.5% in control and 16.4% overall. Moderate levels of nicotine dependence were recorded according to the Fagerström Test for Nicotine Dependence (FTND) (17). The study concluded that while single-session counselling was feasible in the context of lung cancer screening with LDCT, it did not appear to affect smoking cessation rates. The other randomized trial of smoking cessation intervention in lung cancer screening (4) compared 3-month abstinence in a control group who received usual care with that in an intervention group who received telephone-based counselling. Findings also indicated a muted effect of counselling. Ninety-two participants were randomized, the intervention group received up to six brief counselling calls (completing an average of 4.4) during which the screening result was used as a motivator for cessation. Self-reported 7-day point prevalence abstinence at 3 months was biochemically verified by salivary analysis (kit sent by mail) or exhaled carbon monoxide. The groups were broadly similar for demographics, smoking history, nicotine dependence and readiness to quit. At 3 months, in the control group 9 subjects reported abstinence and (based on study supplementary material) 7 completed biochemical verification. In the intervention group 10 subjects reported abstinence and 9 completed biochemical verification. There was no difference between groups on reported abstinence via intention-to-treat analysis; there was a difference in abstinence with biochemical verification (8/46, 17.4% intervention *vs.* 2/46, 4.3% control). Neither of these studies provided pharmacotherapy but participants were encouraged to discuss NRT with their family doctor. From the larger recent studies, a number of inferences can be drawn. Screening itself, with or without counselling, appears to reduce smoking rates over time, above that of background population rates (9,10), influenced by screening results (5,7) and with positive effects on longer term lung cancer outcomes (8). Methods that may help include delivery of particular behavioural interventions in the primary care setting (6), offering counselling to all participants and the use of varenicline (11,12). The evidence-base for management of smoking cessation in the general population is strong and well-articulated in many national guidelines. How generalizable this evidence is to lung cancer screening participants is yet to be confirmed. Lung cancer screening trial participants present some paradoxes in that they are healthy volunteers, exhibit some degree of volunteer bias and are clearly interested in the health of their lungs, yet at the same time, are of an older age with extensive smoking histories, suggesting a hard-core smoking phenotype. Questions that still remain about the impact of lung cancer screening on smoking cessation (18) and on screening as a "teachable moment" (19,20) include the best tobacco cessation interventions for a screening program, optimal timing of interventions, the best ways to measure smoking cessation (including biochemical validation), the impact of screening results across all settings and identification of candidates most likely to benefit, including measurements of nicotine dependence. The results from screening trials may be optimistic when applied to less selected, general screening populations and the environment in which the screening program is set (e.g., background level of tobacco control, access to standard behavioural and pharmacotherapeutic measures) may be an important modulator of outcome.

Rojewski *et al.* (21) add to the literature with a well-conducted secondary analysis of NLST-ACRIN data, exploring the relationship between nicotine dependence, cessation rates and health outcomes in a screening population. The study also addresses the practical question of how to measure nicotine dependence by using three related self-report tools—the FTND (17), the Heaviness of Smoking Index (HSI) (22) (based on time to first cigarette and number of cigarettes per day) and the Time to First Cigarette (TTFC); the HSI and TTFC are both subsets of the FTND. The study analysed data from 7,057 current smokers at the time of randomization, measured nicotine dependence according to the above three tools and evaluated four clinical outcomes: smoking cessation following LDCT, rates of lung cancer, all-cause mortality and lung cancer-specific mortality using regression analysis controlling for sex, age, race, pack-years, treatment arm, and presence of lung nodule (yes/no) but not education level or marital status. Participants were evenly randomized to LDCT and CXR arms but had some slight differences compared to the full NLST cohort (23) (positive CT scan result 19.5% *vs.* 24.2% LDCT and 6.9% CXR over all three rounds; female proportion 45.9% *vs.* 41.0%, married proportion 58.5% *vs.* 66.6%; completed more than high school proportion 32.6% *vs.* 29.9%).

Nicotine dependence levels were moderate to high (34% reported TTFC of less than 5 minutes). Smoking cessation

was stratified according to levels of dependence and showed a reduction in likelihood of cessation with incremental increases in severity of dependence across all three measures of dependence. Overall, 34.2% of participants reported abstinence over 6 years of follow-up, but those who smoked within 5 minutes of waking had a much lower likelihood of cessation than those who smoked after more than an hour (OR 0.5, 95% CI, 0.42–0.60). Higher levels of nicotine dependence were also associated with poorer health outcomes with significantly higher hazard ratios for lung cancer diagnosis, lung-cancer mortality and all-cause mortality. For low and medium levels of dependence, the associations were weaker, with trends (but not statistical significance) recorded for mortality outcomes.

The authors note that tobacco cessation is mandated in the US within lung cancer screening programs as part of Medicare and Medicaid Services and that cost savings may be significant, with the cost of a quality-adjusted life year (QALY) put at $81,000 for LDCT and $1,100 for tobacco cessation. However, the NLST cost-effectiveness analysis underestimates the cost-effectiveness of screening as it assumed that screening had no affect on smoking status (24). Apart from being sensitive to assumptions, cost analysis may not translate to other health-care settings. In Australia for example, the cost per QALY for lung cancer screening using NLST criteria has been modelled at AUD $233,000 (25) (US$ 197,793 at the time of writing).

There are limitations to this study (21); the analysis is secondary, does not examine specific smoking cessation interventions and includes only a small proportion of NLST participants. The analysis relies on self-reported smoking behaviours and the results were different between groups, more robust for the highly nicotine-dependent participants than for those with lower levels of dependence. The regression analyses did not account for certain sociodemographic variables such as marital status and education level which were found to be important predictors in the NLST-LSS subgroup analysis (5). There was also a difference in the association of TTFC with cessation and lung cancer outcomes compared with cigarettes per day (CPD) (the second question in the 2-question HSI) that was not explained. Given that pack-years (accounted for in the regression analysis) is a composite of CPD and years of smoking, the differential association is confusing and requires explanation.

Nonetheless, the results do point to ongoing smoking as a crucial variable for clinical outcomes, highlight the utility of TTFC (easily incorporated into screening and the clinic) as a single measure to identify high nicotine dependency and the potential importance of recognising high-risk, highly-dependent subjects as targets for intensive tobacco cessation therapy.

Lung cancer screening by LDCT focuses on candidates with significant smoking histories. Previous concerns that lung cancer screening may result in decreased smoking cessation are not supported by published data (18,26) and secondary analyses suggest a positive effect overall. Studies of smoking cessation in lung cancer screening indicate favourable smoking cessation outcomes in lung cancer screening populations, perhaps more so in participants with an abnormal screen result and possibly improved by multiple sessions of counselling. Limited randomized data illustrate the difficulties in confirming both the extent of effect and the best interventions in screening programs. Given that smoking abstinence may have as much impact on lung cancer outcomes as LDCT screening (16), full exploitation of opportunities to maximize smoking cessation in screening participants may prove both cost-effective and powerful. That continued smoking leads to poorer clinical outcomes is no surprise. Smoking cessation has many well-established benefits including reduction in lung cancer risk (27), improved lung cancer survival (28) and, particularly before the age of 40, significant gain in life-expectancy (29). The introduction of a simple assessment tool, like the one-question TTFC, or two-question HSI to help identify screening participants most likely to struggle with smoking cessation has the potential to improve cessation rates, improve outcomes and raise the impact of lung cancer screening programs.

The study by Rojewski *et al.* (21) provides a novel approach to assessment of nicotine dependence in lung cancer screening subjects. The simple, 1-step tool to identify high-risk, highly nicotine dependent candidates is easy to implement and understand. While appealing, the TTFC is not yet widely reported in lung cancer screening literature and deserves to be further explored. Participants with high-nicotine dependence may benefit from more aggressive, tailored and targeted tobacco cessation programs integrated into lung cancer screening. The results of this study emphasize the utility of clinical trial data and the possible high impact of successful translation in clinical practice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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