JECH Online First, published on August 19, 2014 as 10.1136/jech-2014-204293

Lung cancer screening with low-dose CT (LDCT), or when a public health intervention is beyond the patient's benefit

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Lung cancer is the main cause of cancer death in the developed world. It is also the second most incident cancer in males and the third in females. Tobacco is its main risk factor, with 90% of all LC deaths attributable to tobacco consumption. It has a 13% 5-year survival,[1] and more than 60% of all LCs are diagnosed in advanced stages. To reduce the burden of disease, it would be very important to have a screening test that is able to: (1) detect LC at an early stage to modify its prognosis, (2) present a low percentage of false-positives, to avoid unnecessary harms, (3) minimise adverse effects for the patient (ie, cancer-induced radiation) and (4) be cost-effective for the health system.

Screening effectiveness is being assessed in randomised trials. There are seven ongoing trials comparing low-dose CT (LDCT) with usual care.[2] The only trial which has published final incidence and mortality results is the National Lung Screening Trial (NLST), which compared LDCT versus chest X-ray (CXR).[3] The NLST has the highest sample size to date and there are no forthcoming trials with higher sample sizes. It included individuals aged between 55–74 years who had smoked at least 30 pack-years, and ex-smokers with less than 15 years since quitting. It found a 20% relative risk reduction in LC mortality and a 6.7% reduction in all-cause mortality. For each 1000 participants in the trial, LDCT avoids 5 deaths of which 3 are due to LC. The NLST was a well-designed study including more than 53 000 participants with three screening rounds and an extra follow-up of 5 years after the screening stopped.

These results have encouraged many scientific societies to recommend LC screening for individuals fulfilling the NLST selection criteria. Despite these apparently promising results, implementing a screening programme is very complicated and harms are always present. Health managers should leverage the expected benefits with expected harms, which in the case of LC screening with LDCT might overcome the benefits. Some of these harms are summarised below.

SCREENING-RELATED HARMS

LC screening with LDCT can lead to a very high number of false-positives. Although LDCT is non-invasive, false positives entail psychosocial distress, unnecessary radiation exposure due to further imaging, and they can lead to unnecessary invasive diagnostic work-up. For example, using data from the NLST, we can estimate that for each 1000 people having three rounds of screening, 242 would have experienced a false-positive[4] and four would have had a surgery for something later shown to be benign.[3]

Overdiagnosis is the detection of cancers that would not progress to symptoms or death, and would not be discovered if it were not for screening. Overdiagnosed cancers cannot be distinguished from life-threatening LC on pathology. They can only be measured indirectly in randomised trials as the excess number of cancers in the screened arm after accounting for lead time. Overdiagnosed cancers also bias the screening results when survival is used as an outcome measure. To add overdiagnosed cancers in the screening process—which by definition are not lethal—will pull survival upwards. Overdiagnosis also increases the screening costs. In the NLST, there was an excess of 119 cancers in the CT group that could not be explained by lead time. This means that 119 of the 649 screen-detected cancers (18%) could be overdiagnosed.[5] In other words, per 1000 participants in the trial, there were four people with overdiagnosed LC. This figure is probably higher since the control group received CXR and the Mayo Lung Project reported an overdiagnosis with CXR versus standard practice.[6]

LDCT increases the risk of a radiation-induced LC. The average dose estimated for the NLST was 1.5 mSv per scan, and a positive result is usually followed by a full CT (8 mSv).[3] During a LC screening programme where current or ex-smokers would be screened from 55 to 74 years of age, modelling studies have suggested that an average individual might receive an accumulated dose of 280 mSv, considering the addition of the standard screening procedures plus those due to false-positives. This radiation dose is much higher than that estimated for atomic bomb survivors or nuclear plant workers.[7] There is a direct relationship between radiation dose and LC risk and it is plausible that there is a potential synergism between radiation and tobacco and a higher cancer risk due to breast and bone marrow exposure to radiation.

WHEN SCREENING IS NOT EFFECTIVE

LC screening with LDCT is not always effective. This situation comprises false negatives and individuals with interval cancers. The NLST had a 6.3% false–negative rate. Sixty-six per cent of LCs detected after a negative screening had IIIB and IV stages, suggesting an extremely quick growth.

Perhaps the most striking issue related to LC screening with LDCT is the low downstaging observed in the incidence rounds regarding the prevalence round. The percentage of LCs at stages IIIA, IIIB and IV was 37.8% at the prevalence round, compared with 30.4% in the third round. These figures were, for stages IA and IB, 54.6% and 63.9%, respectively, for the prevalence and third rounds. These results strongly suggest that approximately 30% of screen detected LCs would not benefit from screening since surgical resection is not possible or is of doubtful usefulness. One of the most important objectives of a screening programme, if not the most, is to achieve a modification of the clinical outcome of the disease in the sense that the intervention (surgery plus other treatments) is more effective for early detected cancers.

OTHER ISSUES

Many scientific societies have recommended LC screening with LDCT, even broadening the inclusion criteria used by the NLST to individuals where LDCT has

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not demonstrated its effectiveness. This is the case of the American Association of Thoracic Surgeons.[8] The US Preventive Services Task Force has recommended LC screening with CT, but only if screening is accompanied by an intervention against tobacco consumption.[9] This last aspect is of paramount importance and is currently neglected in the available recommendations. LC screening should be used (if performed) to reduce tobacco burden in current smokers. Some studies have observed no effect of screening on smoking rates.[10 11]

The external validity of the NLST has been criticised. Although it has a robust design to assess the effectiveness of LC screening, there are some issues that would affect its external validity. The screening adherence was very high, perhaps related to the fact that, on average, the participants had a higher education than the general population pointing to a possible selection bias. The participating centres had extensive skills in CT imaging interpretation and also had a very low surgical mortality following LC resection. Finally, only 26.6% of all participants were 65 or older. These characteristics mean that the NLST was performed under different conditions than those observed in real clinical settings, where worse screening results would be expected.

From the NLST, we can estimate that for every 1000 people screened, LDCT-screening reduces 5 deaths (3 from LC), leads to 4 cases of overdiagnosis, 242 people experience a false-positive and an undefined number of individuals will develop radiation-induced cancers. Costs are an important problem, given the need to have dedicated CT facilities and full-time trained personnel, with the extremely high rate of false-positives and overdiagnosis.[12] So what should we do with LC screening with LDCT? First, we should wait for the final mortality and incidence results in the European trials, which are expected in 2015.[2] Multiple trials with clinical and statistical heterogeneity will provide information of how reproducible the NLST results are. Also, the European trials—all of which used usual care as the control group—are the only ones that can provide reliable estimates of the most important harm of screening: overdiagnosis. While we wait, resources can be directed towards ensuring that all smokers wishing to quit have access to effective smoking cessation therapy and studying how healthcare services can reach the same standards of care that were provided in the screening trials. Health managers should consider if they have to allocate resources to LDCT LC screening or reimburse pharmacological therapies for smoking cessation, with this second option probably being the most cost-effective one.

Acknowledgements The authors are grateful to Dr Peter Bach, from the Memorial Sloan Kettering Cancer Center, for providing critical input to the first version of this manuscript.

Contributors AR-R had the idea of the Editorial. All authors provided critical comments to the first draft, approved the final version of the manuscript and are accountable for its content.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

To cite Ruano-Ravina A, Heleno B, Fernández-Villar A. *J Epidemiol Community Health* Published Online First: [*please include* Day Month Year] doi:10.1136/jech-2014-204293

Received 17 June 2014
Revised 1 August 2014
Accepted 4 August 2014

J Epidemiol Community Health 2014;**0**:1–2. doi:10.1136/jech-2014-204293

REFERENCES

1 De Angelis R, Sant M, Coleman MP, *et al*. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE—5-a population-based study. *Lancet Oncol* 2014;15:23–34.
2 Field JK, van Klaveren R, Pedersen JH, *et al*. European randomized lung cancer screening trials: Post NLST. *J Surg Oncol* 2013;108:280–6.
3 Aberle DR, Adams AM, Berg CD, *et al*.; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
4 Kramer BS, Berg CD, Aberle DR, *et al*. Lung cancer screening with low-dose helical CT: results from the National Lung Screening Trial (NLST). *J Med Screen* 2011;18:109–11.
5 Patz EF Jr, Pinsky P, Gatsonis C, *et al*. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med* 2014;174:269–74.
6 Marcus PM, Bergstralh EJ, Zweig MH, *et al*. Extended lung cancer incidence follow-up in the Mayo Lung Project and overdiagnosis. *J Natl Cancer Inst* 2006;98:748–56.
7 McCunney RJ, Li J. Radiation risks in lung cancer screening programs: a comparison with nuclear industry workers and atomic bomb survivors. *Chest* 2014;145:618–24.
8 Jaklitsch MT, Jacobson FL, Austin JHM, *et al*. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. *J Thorac Cardiovasc Surg* 2012;144:33–8.
9 Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: US. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014;160:330–8.
10 Ashraf H, Saghir Z, Dirksen A, *et al*. Smoking habits in the randomised Danish Lung Cancer Screening Trial with low-dose CT: final results after a 5-year screening programme. *Thorax* 2014;69:574–9.
11 Van der Aalst CM, van Klaveren RJ, van den Bergh KAM, *et al*. The impact of a lung cancer computed tomography screening result on smoking abstinence. *Eur Respir J* 2011;37:1466–73.
12 Rasmussen JF, Siersma V, Pedersen JH, *et al*. Healthcare costs in the Danish randomised controlled lung cancer CT-screening trial: a registry study. *Lung Cancer* 2014;83:347–55.