Cost-effectiveness of model-based eligibility for lung cancer screening in the routine clinical practice

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Provenance: This is a Guest Editorial commissioned by Section Editor Bingrong Zhou, MD, PhD (Department of dermatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Comment on: Kumar V, Cohen JT, van Klaveren D, *et al.* Risk-Targeted Lung Cancer Screening: A Cost-Effectiveness Analysis. Ann Intern Med 2018;168:161-9.

Submitted Jun 27, 2018. Accepted for publication Jul 20, 2018.
doi: 10.21037/atm.2018.07.24
View this article at: http://dx.doi.org/10.21037/atm.2018.07.24

In the 2018 the American Cancer Society estimates about 234,030 new cases of lung cancer (121,680 in men and 112,350 in women) and about 154,050 deaths from lung cancer (83,550 in men and 70,500 in women) in the US (1).

Since the burden of lung cancer is going to rise remarkably during the coming years (2) and this malignancy is curable only if diagnosed in early stage, the prevention of deaths has become a public health priority, even if the role of screening is yet unclear.

Effective and efficient screening programmes for breast and bowel cancer are already well established in many countries, but only US and Canada have approved a national lung cancer screening program based on findings from the US National Lung Screening Trial (NSLT) (3).

NLST enrolled from August 2002 through April 2004, 53,454 persons at high risk for lung cancer at 33 US medical centers. Eligible participants were between 55 and 74 years, had a history of heavy smoking and were 1:1 randomly assigned to undergo three annual screenings, once a year, with either low-dose computed tomography (LDCT) (26,722 participants) or single-view posteroanterior chest radiography [26,732]. They were then followed for 3.5 additional years without any screening exam. The NLST demonstrated that annual CT scan for 3 years compared with annual chest radiography allows to decrease mortality from both lung cancer and all causes, 20% and 6.7%, respectively.

Previous experiences with randomized trials investigating the role of chest radiography and LDCT as screening test showed a high risk of false positive findings with the more expensive exam. Overdiagnosis is a constant well-known concern in all cancer screening programmes. For this reason in NLST rigorous inclusion criteria were considered, in order to select only individuals at very high risk for the development of lung cancer during the entire specified follow-up period. Despite these precautions, also in NLST after 6 years of follow-up data showed that 18% of detected cancers were false positives, although future perspectives seem to estimate a reduction of that overdiagnosis to 9%. Overdiagnosis could be considered inextricably linked to any screening method. Screening usually allow to diagnose both cancers that never progresses or cancers that progresses slowly enough that the patient dies of other causes before the cancer becomes symptomatic (4). Although trial results were welcomed positively by most of the scientific community and used in the US and Canada to build an approved national screening for lung cancer, just the overdiagnosis could in part explain the improved survival advantage showed by LDCT.

In a recently published paper (5) Kumar and colleagues examined the cost-effectiveness of the NLST risk-based screening tool evaluating the increases in quality adjusted life-years (QALYs) in the screened group.

The results showed that, during the first 7 years,

LDCT provided a reduction of lung cancer mortality in comparison to chest X-ray ranging from 1.2 lung cancer deaths prevented per 10,000 person-years, in subjects at the lowest decile of prescreening risk for lung cancer mortality, to 9.5 lung cancer deaths prevented in the group at highest decile.

The incremental benefit on lung cancer mortality according to baseline risk, however, was attenuated in terms of life-years and QALYs. Moreover, the incremental cost effectiveness ratios (ICERs) varied between $75,000 per QALY in the lowest risk decile to $53,000 per QALY in the highest risk decile.

Although these costs fell below the $100,000-per-QALY threshold that is considered reasonable for health services in USA, the highest- and lowest-risk groups had a difference in cost-effectiveness ratio of 30% in comparison to a nearly 90% difference in terms of lung cancer deaths, as correctly pointed out in the editorial accompanying this article (6). The implications for routine clinical practice is that preventing a death in a higher-risk individual translates to fewer QALYs gained than preventing a death in subjects at lower risk.

In this trial the cost effectiveness of screening with LDCT is measured over a short-term time period. These data do not account for the effect in long-term surviving and this is a limitation. In addition it should be noted that lung cancer mainly occurs in older people. Most people diagnosed with lung cancer are 65 or older, with an average age at the time of diagnosis of about 70 (7). Therefore, people who are most likely destined to die of lung cancer have *per se* a shorter life expectancy and lower quality of life irrespective the occurrence of lung cancer. In many of these patients the potential benefit of screening is questionable.

Thus, more refined risk stratification, looking for the best screen interval, eligible age and smoking history is of paramount importance to provide the best trade-off among lifetime health benefits, harms, sustainability and reproducibility in real life.

No universally accepted guidelines or management protocols are yet available for diagnosis and treatment of screen-detected nodules and the access to smoking cessation programmes are not worldwide offered to all current smokers.

The Dutch-Belgian Nelson lung cancer screening final results may generate almost conclusive data about the advantages to screen some people for this malignancy.

It is important to underline that trial participants had high education compared to a group of smokers with a similar age (8), that they were not patients but healthy volunteers enrolled through simple but strict inclusion and exclusion criteria and that the study was performed by highly skilled radiologist. All these conditions are not reproducible in everyday clinical practice.

Despite many questions remain with regard to the implementation of lung cancer screening, a gradually larger amount of data suggests that lung cancer screening with low-dose CT could be a cost-effective way to save lives. For this reason, any effort should be done to ensure the successful implementation of low-dose CT lung cancer screening in Europe (9).

Moreover, recent findings may open new, maybe unforeseen, future scenarios in the way to increase the value of a lung cancer screening program.

In the last years, the knowledge of tumorigenesis process and tumor microenvironment became clearer and usually these data harnessed to develop targeted therapies. CANTOS trial results (10) investigated the use of canakinumab, a monoclonal antibody anti IL-1β in the secondary prevention of major adverse cardiovascular events (MACE) and secondary cardiovascular endpoint of MACE + Unstable Angina Requiring Unplanned Revascularization (MACE+). CANTOS study randomized 10,061 subjects with history of previous recent myocardial infarction, a C-Reactive Protein (CRP) greater than 2 mg/L at entry to 3 doses of canakinumab (50, 150 and 300 mg subcutaneous administration every 3 months) *vs.* placebo. Results demonstrated a clinically and statistically significant effect in reducing the risk of MACE. Even more interesting from an oncologic point of view, given the increasing evidence of the role of inflammation in development of tumors (11), are data about lung cancer. Trial showed a dose dependent risk reduction with canakinumab in lung cancer incidence of 67%, in all fatal cancer incidence of 51% and in lung cancer mortality incidence of 77% (300 mg). In addition, CRP baseline levels correlate with risk of lung cancer development and increase with non-small cell lung cancer (NSCLC) progression.

If these results will be confirmed in a prospective large prevention and screening phase III trial, unexpected and fascinating scenarios could be unwrapped and it will be necessary to find new approaches to face unavoidable economic challenges.

Acknowledgements

The study was supported by donations of “gli Amici di

Carlo" in memory of Carlo Ridon, "gli Amici di Andrea" in memory of Andrea Gadeschi and the amateur dramatics group "Attori non per caso", parish church of Collio Valtrompia (Brescia). The donations provided support for editorial work and review.

Footnote

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

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Cite this article as: Intagliata S, Roca E, Cosentini D, Berruti A. Cost-effectiveness of model-based eligibility for lung cancer screening in the routine clinical practice. Ann Transl Med 2018;6(18):369. doi: 10.21037/atm.2018.07.24

