INESSS
LE SAVOIR PREND FORME

APRIL 2019

Relevance of low-dose computed tomography lung cancer screening

English summary

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

Direction des services de santé et de l'évaluation des technologies

Québec

This is the English summary of the guidance entitled Pertinence du dépistage du cancer du poumon par la tomographie axiale à faible dose published in April 2019.

The complete version of this guidance (in French) is available on the website of INESSS in the Publications section.

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SUMMARY

Since the publication, in 2011, of the results of a randomized clinical trial (RCT) on low-dose computed tomography (LDCT) lung cancer screening, divergent recommendations regarding the relevance of screening have been published. The Ministère de la Santé et des Services sociaux (MSSS) asked the Institut national d'excellence en santé et en services sociaux (INESSS) to assess the performance, clinical efficacy and safety of LDCT lung cancer screening. The organizational impact of implementing lung cancer screening in Québec and the oversight mechanisms to be put in place in the event of such implementation are also discussed in this report.

The RCT National Lung Screening Trial (NLST) recruited a total of 53,454 adults aged 55 to 74 years who had a history of smoking at least 30 pack-years (or 24 Canadian pack-years) and, if former smokers, had quit within the previous 15 years. This large, high-quality RCT showed that LDCT lung cancer screening has the potential to reduce the risk of lung cancer deaths in heavy smokers when compared to chest radiography screening. The group assigned to three annual LDCT screening rounds had a 15% lower risk of death after a 7.4-year follow-up than the control group. This means that approximately 3 lung cancer deaths were avoided per 1000 participants. No statistically significant difference was reported for the risk of lung cancer death in four other, smaller RCTs of average to low quality, while other RCTs are still in progress. A meta-analysis found a reduction in the relative risk of lung cancer death of approximately 15%, but the approximately 7% reduction in the risk of all-cause mortality observed in the NLST did not translate into a statistically significant effect in the meta-analysis.

The lung cancer mortality benefits can be explained by a reduction in the number of cancers detected at a late stage, since the prognosis for patients treated for advanced lung cancer is poor. Based on NLST data, approximately 4 fewer advanced-stage and 8 more early-stage cancers can be expected per 1000 screening participants. Most studies have shown a statistically significant increase in the number of cancers detected at an early stage, but this observation may also reflect a certain degree of overdiagnosis. The extent of overdiagnosis is, however, difficult to quantify, since the calculation methods vary from study to study. Of importance with respect to risks is the high number of false-positive results observed in the NLST and several other RCTs as well as implementation studies. The investigations following abnormal screening results can be invasive and lead to serious complications or even death. According to three meta-analyses, about 20 to 25% of LDCT screening tests yield a false-positive result, whereas in the NLST, more than 1 participant in 3 had at least one abnormal result by the end of the third screening round. The observed variability is attributed to the differences in positivity criteria used in the studies. For the purposes of the NLST protocol, a very sensitive criterion was chosen by setting the threshold for abnormal lesions at 4 mm in diameter. Based on the NLST, the number of LDCT screening participants who undergo a minor invasive procedure for a benign condition was estimated at 12 per 1000, the number of those who undergo a major invasive procedure for a benign condition at 7 per 1000. Furthermore, according to

modeling based on NSLT data, approximately one death would be caused by radiation in 2500 in LDCT lung cancer screening participants, and this would occur with a delay of 10 to 20 years.

The variability in the screening protocols, the positivity criteria, the diagnostic protocols and the follow-up protocols between the 10 selected RCTs and the lack of consistency in the results obtained, both in terms of efficacy, safety and performance of the screening procedures, have raised some uncertainty about the balance between the benefits and risks of screening. Furthermore, several aspects regarding the design and conduct of the NLST, such as the choice of chest radiography screening as the comparator and the high participation and retention rates, have cast doubt on the transferability of the benefits and risks to other practice settings. The clinical practices themselves have changed since the NLST was published in 2011, notably with regard to the use of risk prediction models and nodule classification systems.

By including other risk factors besides the age and smoking criteria used in RCTs, the risk prediction models are aimed at better targeting individuals at high risk of cancer, with a view to maximizing benefits for screening participants. The $PLCO_{m2012}$ model is under study in Canada, and various risk thresholds have been proposed. In order to minimize the drawbacks of screening, several nodule classification systems aimed at harmonizing LDCT results interpretation and better identifying results requiring diagnostic investigations have been developed. Among these, the Lung-RADS system was tested retrospectively on the NLST data, yielding a considerable reduction in the number of false-positive results. In either case, a prospective evaluation of the impact on morbidity and mortality would be desirable.

According to data from the 2013-2014 cycle of the Canadian Community Health Survey (CCHS), close to 380,000 Quebecers met the NLST eligibility criteria for lung cancer screening. They were overrepresented in the lowest socioeconomic strata and in certain regions. The number of people eligible for screening should decrease over the next few years if the smoking uptake and cessation trends in Québec persist. However, the proportion of the eligible population that would avail itself of lung cancer screening is not known. The experts consulted by INESSS felt that achieving a participation rate of about 40% by the end of a 10-year deployment period would be realistic. Using OncoSim modeling, these assumptions were used to estimate what the population and organizational impact would be of implementing a LDCT lung cancer screening program in Québec. Thus, if the screening started in 2020, maximum participation would be achieved in 2029 with slightly more than 100,000 participants. Since the screening strategy targets a high-risk population that accounts at most for 5% to 6% of the Québec population, the cancers diagnosed in screening participants would constitute only a minority of all diagnosed cancers. Consequently, at the level of the Québec population, the proportion of cancers identified by screening would reach 12.5% in 2029 and decrease thereafter. Deaths avoided by screening would result in a reduction in the number of lung cancer deaths of about 3% in 2029.

The OncoSim microsimulation model has several limitations, but it does offer the advantage of yielding estimates of clinical outcomes, diagnostic and therapeutic procedure volumes, and costs for the Québec population with and without screening. This approach enabled us to estimate numbers of additional investigations that could be compared to the numbers of procedures currently performed in Québec, in order to anticipate the additional workload that various services involved in the lung cancer care trajectory would be faced with should screening be implemented. Relative to the procedure volumes reported in the RAMQ's databases in 2016-2017, the volume of additional procedures anticipated in Québec in 2029 would constitute an increase of 5% or less for bronchoscopies and PET and could exceed 7.5% for biopsies. The anticipated workload for thoracic surgeries would constitute an increase of approximately 20% relative to the total number of mediastinotomies and thoracotomies billed for in 2016-2017. However, with the advent of EBUS, the use of these different procedures could evolve over time. The anticipated workload for CT scans in 2029 would exceed by close to 40% the number of chest and chest/abdominal CT scans billed for in 2016-2017 or by 8% the total number of CT scans recorded in Québec in 2016. If the service corridors and the current organizational structures remain unchanged, considerable regional differences in the demand for additional services and in the expected pressure on service provision are to be expected for thoracic surgery and CT scans. It is noteworthy that, on the one hand, the additional workload due to false-positive results could be cut down since this modeling exercise is based, to a large extent, on NLST data and that clinical practice have evolved. On the other hand, the organizational consequences of the large number of incidental findings were not taken into account in the model.

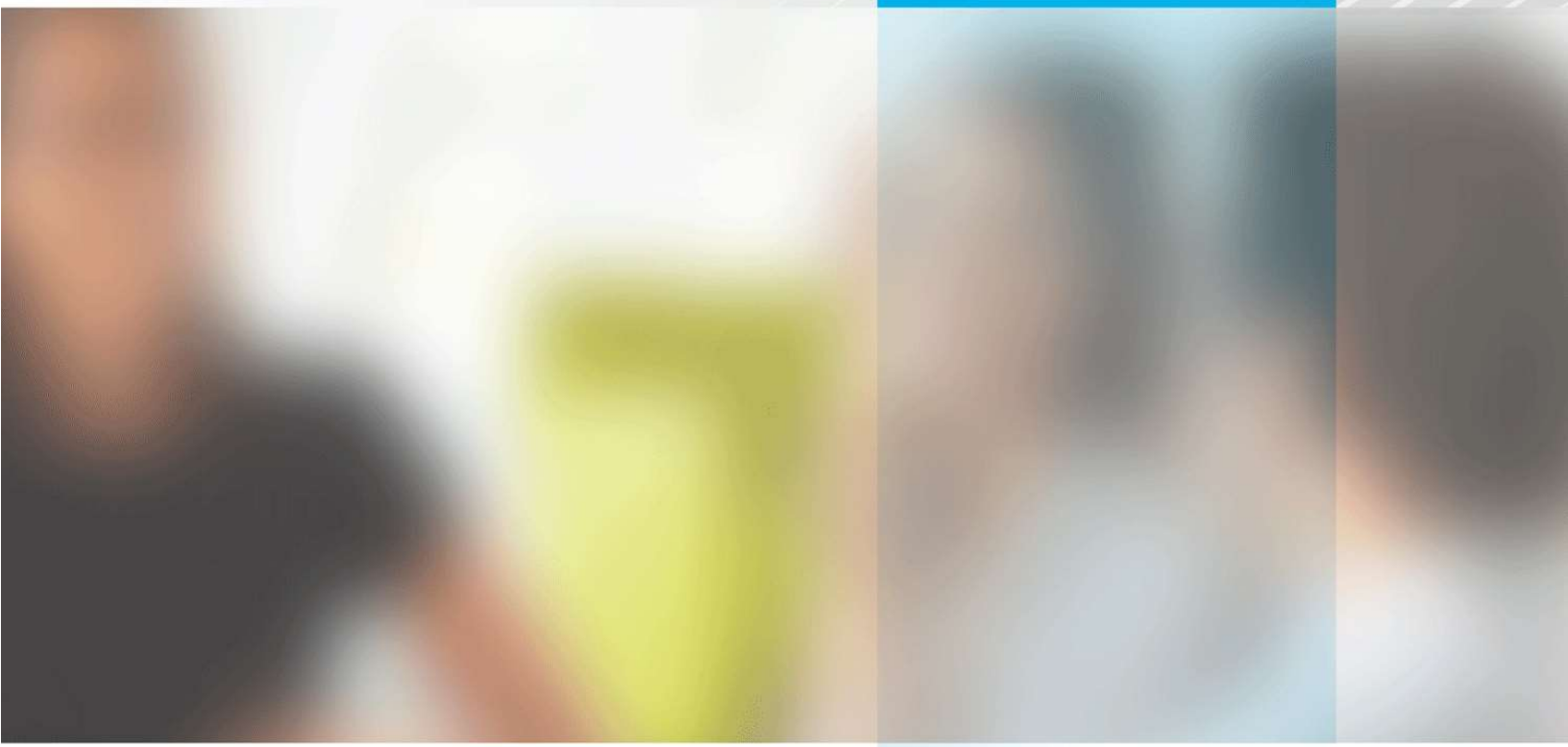
According to literature data, the uncertainties regarding the incremental cost-effectiveness ratio of screening compared to no screening are high, with some estimates below and other above the thresholds considered socially acceptable. It is the same with the budget impact estimations, which sometimes show savings, sometimes increased health-care costs. Depending on the parameters and assumptions underlying the OncoSim modeling, implementing screening could cost Québec approximately CAD$11.5 million in 2020 and up to CAD$37.3 million in 2029. These estimates do, however, have certain major limitations and depend on the organizational structures chosen. A proper budget impact analysis should be able to rely on up-to-date data on the use of investigations like EBUS or that of treatments like immunotherapy, with respect to which practices are changing quickly.

INESSS conducted public consultations, including with a group of people potentially eligible for lung cancer screening, and discussed the evidence and issues raised by screening with the members of several advisory committees. These consultations brought to light the sensitive situation in which lung cancer screening would be implemented. The socioeconomic and geographic distribution of smoking is uneven, which would present organizational challenges and create tensions between equality, equity of access and service quality. The difficulty in reaching the most vulnerable populations and a possibly weaker participation on their part raises certain concerns over

the potential exacerbation of health inequalities. The acceptability of screening by the target population could depend on the mechanisms put in place to maximize the benefits and minimize the risks of screening and to facilitate informed decision-making, but would also depend on personal factors, such as attitude towards health and smoking. The social acceptability of screening might be influenced by the issue of personal responsibility, but also by the opportunity to help populations with vulnerability factors. The importance of investing in smoking prevention and tobacco cessation strategies was stressed repeatedly.

Many of the people consulted brought up the uncertainty regarding the ability to reproduce, in the Québec clinical context, the lung cancer mortality reduction benefits observed in the NLST and to mitigate the risks. The importance of minimizing the consequences of false-positive results by properly targeting invasive procedures and that of ensuring continuity of the services were stressed. With regard to organizational issues, certain concerns were expressed about a possible lack of physical, human and financial resources. Concern over services being unduly overstrained and over resources being shifted to the detriment of other patients was also mentioned as a fundamental issue, even if many recognize that efforts to rationalize requisitions could free up resources. These concerns show that LDCT lung cancer screening, which is considered a promising intervention, should be integrated in such a way as to limit the potential risks as much as possible, while at the same time respecting the health-care system's capacity. There is a consensus about the need to proceed cautiously, to implement oversight mechanisms and to assess its impact.

In short, integrating the scientific and contextual data and the data obtained during consultations revealed a number of concerns regarding the balance between the benefits and risks of screening; the feasibility of recruiting the target population; the costs; the equity of access at the regional level; the possible bottlenecks in the offer of services; and the social acceptability of and relevance time window for LDCT lung cancer screening. In a context where the benefits and risks strongly depend on the organizational and societal context, the wide-scale introduction of LDCT lung cancer screening is clearly not desirable. INESSS recommends that low-dose computed tomography lung cancer screening be available and accessible only within the context of a rigorous evaluation in a real-world care setting. Such an evaluation would make it possible to estimate the performance of screening, to assess its impact on the health-care system and, ultimately, to rule on the relevance of implementing or not implementing a lung cancer screening program in Québec. Specific recommendations have been made regarding the execution and monitoring of this evaluation phase.



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