Reviewer’s report

Title: Do we know enough about the effect of low dose computed tomography screening for lung cancer on survival to act? A systematic review, meta-analysis and network meta-analysis of randomised controlled trials.

Version: 1 Date: 21 Aug 2019

Reviewer: Valentijn de Jong

Reviewer's report:

General comments

Overall, I think the author's conclusion that currently there is still uncertainty regarding the effectiveness of these screening strategies is an important one, that needs to be heard. Though, the review still lacks elaboration in some places; see specifics below. But first two general issues:

In the abstract, the authors state "There was a non-statistically significant increase in all-cause mortality." This is a confusing statement: it suggests that the increase was significant, but not statistical. If the notion of significance is to be used, it is to be stated as "There was a statistically non-significant increase …". The same goes for similar statements throughout the text.

The abstract is missing more information regarding the interpretation of the results. For instance, the conclusion of the abstract does not mention all-cause mortality, which is mentioned as a primary outcome in the text. See more below.

I'll start with some specific issues that have remained after the first round of reviewal, and continue with more issues.

Comment 5.

I agree with reviewer 1 that issues such as harms and overdiagnosis need to be considered when making statements such as "CXR screening had a 99.7% probability of being the worst intervention with usual care intermediate." Though, I also agree with the authors that it is still important to look at mortality outcomes in isolation.

Yet, the conclusions, including those in the abstract, need to make clear that these issues have not been considered, i.e. that any statements are made only with respect to lung cancer or all-cause mortality. For instance, I suggest rephrasing this example sentence to: "The results showed that in terms of lung cancer mortality reduction LDCT was ranked as the best screening strategy,
CXR screening as the worst strategy and usual care intermediate." and preferably include statements regarding the uncertainty of these ranks.

Comment 6.

Considering that the research question is "Do we know enough about…" solely estimating a RR is not enough. Instead, I believe it certainly is necessary to grade the level of evidence, as this is precisely what the research question entails. I believe GRADE is the preferred method here.

Comment 9.

Several elements have remained unclear regarding the NMA.

1. The authors mention it was a multivariate NMA, but does this mean they took the multivariate NMA approach (in contrast with the hierarchical approach or the meta-regression approach, see (2) ), or does this mean they analyzed the two outcomes simultaneously? Or the multivariate NMA approach for both outcomes simultaneously?

2. Did the NMA method take within-study correlations into account?

3. On what level of measurement has the meta-analysis been performed? No link function is mentioned.

Line 48. Is it "CT has developed" or "CT has been developed"?

Page 4

Lines 8 -11 mention a study on LDCT and CXR. Then lines 12-14 state: "Investigators concluded that screening with LDCT reduces mortality from lung cancer." What happened to CXR? Does that mean LDCT reduces mortality from lung cancer compared to CXR? And then lines 14-15 mention only screening. Does that include CXR? Please clarify the text.

Page 5

Lines 25 - 27. Please note that the Dersimonian and Laird method is not recommended. It is recommended to estimate the variance by REML, and apply the HKSJ modification to the confidence interval of the effect estimate instead.(1) Though, as REML has been used in the NMA I don't consider this a major issue.

Page 8, line 8
"a highly borderline non-statistically significant decrease". The p-value happens to be equal to the decision boundary. It cannot be "highly borderline" to the boundary. I suggest to remove "highly".

Page 8 "The main findings of this systematic review are a non-statistically significant decrease in lung cancer mortality (...) and a non-statistically significant increase in all-cause mortality outcome (...)") for what intervention and comparators? Also which method is used to estimate this RR, is it the MA or the NMA?

Page 9

"The network meta-analysis confirms the likelihood that". The NMA was performed on largely the same data as the direct MA, making this a misleading statement. I would rather say the results from the NMA were in agreement with those from the direct MA.

In "This translates to a number needed to screen to avoid one lung cancer death of 357 (95% CI 82 to -113[...])" the point estimate falls outside the confidence interval, which makes no sense.

Lines 10-13. The authors note in the manuscript that due to the possible ineffectiveness of CXR, the evidence from the NLST study that found a higher efficacy for LDCT (vs CXR) may not be considered evidence in the comparison of LDCT vs no screening. This has serious implications for the validity of the comparisons in the direct MA, and thereby the conclusions made in the manuscript and especially the abstract.

Lines 17-19. The authors mention statistical heterogeneity. This is at least partially a result of the mixing of the comparator: If the effect for LDCT vs CXR is truly different from the one for LDCT vs no screening, then the effect for LDCT vs (CXR or no screening) is guaranteed to be heterogeneous for a large enough number of studies.

Prisma chart

394 assessed - 230 excluded yields 164 eligible articles. The next step mentions 18 + 128 (or is it 18 + 12 + 128) studies or reviews. What happened to the remaining eligible articles?

References


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