

Peer Review File

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Reviewer A

Comment #1: The Introduction section lacks of a background and updating on the current smoking interventions in lung cancer screening recommended by European and US guidelines/statements.

Reply: The United States Preventive Services Task Force and National Comprehensive Cancer Network recommend smoking cessation services for those participating in lung cancer screening, actually this is in line with the general guidelines for tobacco use. Although in Europe there are no nationwide population screening programmes so far, the importance of a combined approach of lung cancer screening and tobacco treatment according to smoking cessation guidelines is recognised by the European Respiratory Society and European Society of Radiology. We have included the endorsement of a combined strategy by these organizations in the text:

“...Although it is evident that smoking cessation should be offered to lung cancer screening participants, which is reflected by current guidelines and recommendations (9-14), there is still limited evidence on how to integrate (effective) smoking cessation services for both high- as well as low-risk smokers in a CT lung cancer screening context (15,16)...” (Lines 72-74)

Comment #2: The present review lacks of recent (published in 2019, see for example the Italung study) original papers on smoking cessation interventions in randomized-controlled trials (RCTs) of lung cancer screening by low dose computed tomography. Was it due to having chosen as selection criterion the availability of (online free?) full text?

Reply:

Only papers that were available in English as full text were included in this review. Thereby, a search strategy was used for this review based on title, abstract and/or keywords. It might

be possible that a specific article was not identified due to the combination of title/abstract/keywords.

The study related to the ITALUNG and smoking cessation of August 2019 was included in our search. Our apologies that we did not include this paper in our review correctly. We have now included the paper of the ITALUNG trial as published in 2019, also in table 1 and 2. If there are other specific papers that you are missing, please let us know. If we have a full text of a relevant paper, we can add the article in question.

We updated the main text:

“...The database search yielded 19 publications that evaluated the impact of enrolment in a lung cancer screening program on smoking behaviour (Table 1). Data used for these publications derived from the following European or US-American randomized-controlled studies: the Danish Lung Cancer Screening Trial (DLCST) (21,22), the Early Detection of Cancer in the Lung Scotland (ECLS) (23), the Italian Lung Cancer Screening Trial (ITALUNG) (24),[...]” (lines 139-144)

“... In the UKLS trial, cessation rates were found to be higher for the screen arm than for the control arm two weeks up to two years after the screening (24% vs. 21%) using ITT-analysis. In the most recently published trial, the ITALUNG trial, the cessation rates were also higher for the screen arm than the control arms four years after baseline screening (20.8% vs 16.7%; p=0.029). When using ITT-analyses, one found still a trend in more favourable outcomes in screen arm participants (16.04% vs 14.64%; p=0.059) ...” (lines 166-171)

“UKLS and ITALUNG data showed that participants with a positive baseline scan were more likely to quit smoking compared to participants in the control arm, while no significant differences between the control group and those with a negative baseline scan were observed (24, 31).” (lines 186-189)

“The database search yielded 11 publications that evaluated smoking cessation (SC) interventions incorporated in lung cancer screening trials (Table 2). Data used for these studies derived from five randomized-controlled studies (ITALUNG (24),

LUSI (26), the Multicentric Italian Lung Detection trial [MILD] (40), NELSON (41) and NLST (42) [...]” (lines 212-215)

“Three Italian observational studies based on the ITALUNG, MILD and COSMOS-II trial examined the effect of clinician-delivered behavioral counselling combined with pharmacological treatment on SC (24,40,45). (lines 240-242)

“In the ITALUNG study, participants who voluntarily entered a structured smoking cessation intervention consisting of behavioral counselling and pharmacotherapy (varenicline, bupropion, NRT or a combination of these agents, n = 119) were compared to baseline smokers enrolled at the same screening site who did not enter the smoking cessation program (n= 306)(24). The results showed that participation in the smoking cessation program was associated with a threefold increase in the odds of smoking cessation. Furthermore, those ITALUNG participants who completed all counseling visits (n=76) had higher cessation rates than smokers from routine practice who did not undergo CT-screening but participated in the same smoking cessation intervention (n =66) across a 12-month follow up period. For example, at 12 months follow-up, the cessation rates were 28.9% and 13.6% respectively.” (lines 242-252)

“In the three studies, around 40% of participants (36.2%, 42.9%and 38.9% respectively) interrupted the treatment (24,40,45)”. (lines 259-261)

“While higher cessation rates in the screen than in the control arm were found in the UKLS and ITALUNG trial, the NELSON-trial found a reversed effect and the DLSCST and LUSI trials found no effect” (lines 294-296)

“Moreover, participants in the NELSON, DLSCST, UKLS, ITALUNG or LUSI received all different type of interventions[.]” (lines 299-300)

Comment #3: More specific description of the methods applied to perform the search strategy should be provided, for example, which specific key words were used. A figure with the algorithm of the results of the search strategy might be helpful. If this is a non-systematic review it should be stated.

We added the search strategy as appendix to this response. However, we think that this is too extensive to include this in the main text. Therefore, we would like to suggest that we provide these details as appendix.

We add some more details about the review in the main text:

*“... For this overview, a search strategy was used that selects papers **based on search terms in keywords, title and abstract that related to a) lung cancer screening or the early detection of lung cancer, b) smoking or tobacco use and c) behavioural effect (cessation, behavioural, quit smoking, smoking abstinence, tobacco dependence).** We performed the search with assistance of a medical research librarian in MEDLINE (Pubmed), Embase, Web of Science, the Cochrane Central Register of Controlled Trials and Google Scholar. **The initial search yielded 568 articles.** After removing duplicates, we obtained 236 **unique** records.*

*Only original articles that were available online (full text) and published in English until July 2020 were selected. We looked at the references of selected papers to check whether relevant articles were missed. The included articles should to be relevant to **smoking cessation in the context of lung cancer screening, which implies an asymptomatic adult (50-80 years) population who are at high risk for developing lung cancer.** **Two reviewers independently reviewed the articles based on title, abstract and full text respectively. Any discrepancies were resolved by discussion.** Based on evaluations of abstract **we selected 94 articles** and after reviewing the full text, we included **32 publications in the study.** **These articles were grouped into some relevant main topics: effect of smoking cessation, impact of lung cancer screening on smoking behaviour, impact of the screening result on smoking behaviour and impact of a smoking cessation intervention in the context of lung cancer screening. A total of 2 articles were added based on the reference lists of selected publications.** ... “ (lines 81-100)*

Comment #4: Results from recent (published in 2019, see for example Cadham et al., Zeng et al., Iaccarino et al.) systematic reviews and meta-analyses on the topic of the present paper should be discussed.

Reply: Thank you for your suggestion. We have now linked our results to the findings of Cadham and Iaccarino in our discussion.

“In line with findings of a meta-analysis among populations eligible for lung cancer screening and a systematic review on the effectiveness of smoking cessation interventions embedded within lung cancer screening (54,55), our results suggest that more intensive interventions such as clinician-delivered interventions combined with pharmacologic cessation aids delivered across multiple sessions appear to be more successful in influencing smoking behaviour” (lines 383-388)

Comment #5: The table 2 should be completed by providing the methods of selection of the subjects enrolled in the various considered studies (e.g., media campaigns, randomization from GPs' lists of patients, etc.). This information is important to interpret/speculate on the smoking cessation intervention in relation to the source of enrolment of the screening subjects.

Reply: Thank you for this suggestion, we added the information on the recruitment method as detailed as possible in table 2 in the second column (‘trial type and recruitment method’). The exact methods are not always specified in the articles or (published) original protocols; in these cases we stuck to more general descriptions (e.g. volunteers).

Comment #6: When reporting results on the rates of smoking abstinence/cessation, it should be always specified if they are based on point prevalence or intention to treat analysis, wherever is appropriate, including in table 1.

Reply: There is still great variety in how authors measure and report smoking behaviour. Authors did not always specify how they measured smoking status (e.g. which time window was used), so we could not always specify if it concerns point prevalence. We mentioned point prevalence in table 1 whenever it was applicable and added more specific information on the smoking outcome for the articles of Balata, Clark (2019) and Borondy.

We added in the text and table 1 that Ashraf et al. (2009, 2014) and Brain et al. (2017) used ITT-analysis to compare smoking cessation between screen and control arm. In the Dutch-

Belgian RCT NELSON the primary analysis was done both without and with ITT-analysis, this was already explicated in the text and table 1. The new text passage and table entry concerning the added ITALUNG paper also include information about the ITT-analyses.

“In the DLCST, no differences between screen and control arm were found in 1-month point prevalence of cessation (11.9% vs 11.8%) one year after randomization using Intention-To-Treat (ITT) analysis (17)” (lines 157-160)

“In contrast, in NELSON, prolonged abstinence was lower for the screen arm (14.5%) than for the control arm (19.1%) two years after randomization, although after ITT-analysis, the difference was no longer observed (22). In the UKLS trial, cessation rates were found to be higher for the screen arm than for the control arm two weeks up to two years after the screening (24% vs. 21%) using ITT-analysis (25)” (164-169)

Minor

- Lines 130-138. References of the mentioned studies should be reported.
- Lines 193-197. References of the mentioned studies should be reported.

Reply: We inserted all the references for the mentioned studies (which can now be found in lines 142-150 and 214-218). Please be aware that the numbering of the references changed a lot throughout the article.

Reviewer B

Comments #1: I have with interest read the MS. It is generally a well written MS, which touches upon a highly relevant topic. It provides an overview of the current knowledge concerning smoking cessation in relation to screening programs. An intervention with potential to improve outcome for patients with lifestyle that carries a high risk for increased morbidity and mortality.

I find that the MS is ready for publication. I do miss a sentence or two in the methods section concerning the review process. Were the articles reviewed by one, two or all the authors. What was the method in case of discrepancies?

Reply: Thank you for your feedback. The articles were reviewed by two researchers and discrepancies were discussed. A third reviewer to discuss potential unsolved discrepancies was not needed. We will add this information to the text.

“Two reviewers independently reviewed the articles based on title, abstract and full text respectively. Any discrepancies were resolved by discussion.” (lines 92-94)