

Diminishing marginal cost-effectiveness in risk-targeted lung cancer screening

Szu-Chun Yang^{1,2}, Jung-Der Wang^{1,2}

¹Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; ²Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Correspondence to: Jung-Der Wang, MD, ScD. Department of Public Health, College of Medicine, National Cheng Kung University, No.1, University Road, 701 Tainan, Taiwan. Email: jdwang121@gmail.com.

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 Aug 17, 2018. Accepted for publication Aug 22, 2018. doi: 10.21037/tcr.2018.08.33 View this article at: http://dx.doi.org/10.21037/tcr.2018.08.33

The article, entitled "Risk-Targeted Lung Cancer Screening: A Cost-Effectiveness Analysis," published in the Annals of Internal Medicine (1), is the first to report that the marginal gain in cost-effectiveness would be modest using risk-targeted lung cancer screening. Intuitively, using a predictive risk model to select high-risk participants for lung cancer screening may not only achieve superior efficacy, but might also improve cost-effectiveness. Several studies have attempted to identify high-risk individuals for lung cancer screening (2-4). But such models usually considered multiple risks factors and their combinations, which complicate the cost-effectiveness during implementation into clinical practice. One of the most influential studies was conducted by Kovalchik et al., who assessed participants in the National Lung Screening Trial (NLST) according to the quintile of the 5-year risk of lung cancer death (5). They found a decrease in the number of participants with false positive results and an increase in the number of lung cancer deaths prevented per 10,000 person-years across risk quintiles. Specifically, screening the highest-risk participants with low-dose computed tomography (CT) was reported to prevent the greatest number of deaths. These findings seem to support risk-targeted lung cancer screening. However, because the observation period was only 6.5 years, it remains uncertain whether the effect would persist if follow-ups continued over the participants' lifetime. A related study examined the cost-effectiveness of this risk-targeted strategy and performed subgroup analyses (6). The incremental cost-effectiveness ratio (ICER)

appeared to be lower for the two highest-risk quintiles when compared with the three lowest-risk quintiles. Nevertheless, given the small numbers of lung cancers reported in the subgroups, the ICER values were unstable across quintiles due to the trend related to risk being uneven.

Kumar et al. (1) applied a multistate regression model comparing the cost-effectiveness of risk-targeted versus NLST-based screening. During the first 7 years of observation, although the health benefits of prevented mortality from lung cancer climbed from 1.2 in the lowestrisk decile to 9.5 per 10,000 person-years in the highestrisk decile, estimates of health benefits based on life-years and quality-adjusted life-years (QALYs) did not show a similar trend. Namely, after extrapolation to lifetime, the ratios of lifetime survival and utility benefits of the highestversus the lowest-risk deciles (extreme decile ratios: 3.6 and 2.4, respectively) were not as high as that of 7-year survival (extreme decile ratio: 7.9). The diminishing effectiveness may result from older age and related comorbidities in the highest-risk participants, which would be accompanied by a shorter life expectancy and worse quality of life (QoL). Thus, when we extrapolate the survival to lifetime, the quality-adjusted life expectancy (QALE) of the highest-risk participants would be much shorter than that of the lowestrisk ones. As mentioned in Kumar et al.'s article, selection of higher-risk participants also incurred higher screeningrelated costs, which further lowered the cost-effectiveness of screening (US\$53,000/QALY in the highest-risk decile versus US\$75,000/QALY in the lowest-risk decile). In other

Translational Cancer Research, Vol 7, No 5 October 2018

words, although there would be some gain in effectiveness when the focus is placed on people with high risks, the marginal improvement of cost-effectiveness declines as efforts are made toward identifying a higher-risk group of participants; that is, there is "diminishing marginal costeffectiveness in risk-targeted lung cancer screening." This phenomenon could be explained by at least the following reasons: The major health benefit of CT screening is the stage shifting in diagnosing patients at an earlier stage, which results in fewer lung cancer-related deaths. However, this benefit tends to be diluted by an increased mortality unrelated to lung cancer, such as chronic obstructive lung disease, acute myocardial infarction, etc., in higher-risk participants, while the incremental costs increase from recruiting people with the lowest risk to the highest risk groups. Consequently, the marginal improvement in ICER diminishes.

The comparison of CT screening versus chest radiography (CXR) within each decile in Kumar et al.'s article was conducted with a post-hoc analysis. Although randomization in a trial usually leads to an even distribution of age and sex in the long run for the two comparison groups, the final distributions of participants with lung cancer detection may still be different if stage shifting occurred in the CT group, namely, they would usually be younger in age. Consequently, potential lead-time bias may exist, particularly if we directly regard the difference in life expectancies between the two groups as gained health benefit. Alternatively, we could estimate the incremental lifeyears gained or compare the saving of expected years of life lost (EYLL) (7), which is the difference of life expectancies between participants with lung cancer detection and their age- and sex-matched general population. The saving in EYLL, or the difference in differences between lung cancer detected in the CT and CXR groups and their corresponding age- and sex-matched referents, would account for the difference in age because of stage shifting, or the lead-time bias. Similarly, loss-of-QALE is the difference in QALE between participants with lung cancer detection and their age- and sex-matched general population, which would be the net savings of loss-of-QALE for the CT group in comparison with the CXR group after adjustment for lead-time bias. In the era of big data, we have improved access to longitudinal datasets regularly collected by related governmental and non-governmental agencies, and interlinkages between them is possible. Thus, a viable alternative to constructing a conventional Markov model for cost-effectiveness assessment is to directly estimate

the lifetime survival function, EYLL, loss-of-QALE, and corresponding lifetime costs through real world data (7,8), which would require fewer assumptions and already be adjusted for lead-time bias resulting from stage shifting. In terms of over-diagnosis bias, we would also be able to have control by analyzing the sub-cohort of suspected "indolent cancer" from long-term data (7).

In conclusion, there appears to be a diminishing trend for marginal cost-effectiveness from low to high risktargeted lung cancer screening. From the health care sector's perspective, applying a complicated risk model in lung cancer screening may not necessarily yield substantial improvement in cost-effectiveness. Moreover, it is recommended that future cost-effectiveness analyses account for the potential lead-time bias resulting from stage shifting to ensure a fair comparison.

Acknowledgments

Funding: We are grateful for the following grants from the Ministry of Science and Technology (No. MOST106-2627-M-006-015 and No. MOST107-2320-B-006-069).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/tcr.2018.08.33). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

Yang and Wang. Diminishing returns in risk-targeted screening

References

- 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.
- 2. Fu M, Travier N, Martin-Sanchez JC, et al. Identifying high-risk individuals for lung cancer screening: Going beyond NLST criteria. PLoS One 2018;13:e0195441.
- Ten Haaf K, Jeon J, Tammemagi MC, et al. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. PLoS Med 2017;14:e1002277.
- 4. Katki HA, Kovalchik SA, Berg CD, et al. Development and Validation of Risk Models to Select Ever-Smokers for

Cite this article as: Yang SC, Wang JD. Diminishing marginal cost-effectiveness in risk-targeted lung cancer screening. Transl Cancer Res 2018;7(5):1310-1312. doi: 10.21037/tcr.2018.08.33

CT Lung Cancer Screening. JAMA 2016;315:2300-11.

- Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lungcancer death. N Engl J Med 2013;369:245-54.
- Black WC, Gareen IF, Soneji SS, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. N Engl J Med 2014;371:1793-802.
- Yang SC, Lai WW, Lin CC, et al. Cost-effectiveness of implementing computed tomography screening for lung cancer in Taiwan. Lung Cancer 2017;108:183-91.
- 8. Hwang JS, Hu TH, Lee LJ, et al. Estimating lifetime medical costs from censored claims data. Health Econ 2017;26:e332-44.