HHS Public Access

Author manuscript

Lancet Respir Med. Author manuscript; available in PMC 2021 April 06.

Published in final edited form as:

Lancet Respir Med. 2021 January ; 9(1): 7–9. doi:10.1016/S2213-2600(20)30553-1.

Overdiagnosis in lung cancer screening

Matthew E J Callister[1], **Peter Sasieni**[2], **Hilary A Robbins**[3]

[1]Department of Respiratory Medicine, Leeds Teaching Hospitals, St James's University Hospital, Beckett Street, Leeds, LS9 7TF, UK

[2]School of Cancer & Pharmaceutical Sciences, King's College London, London, UK

[3]International Agency for Research on Cancer, Lyon, France

Overdiagnosis in cancer screening reflects the detection of cancers that would not have become clinically apparent if the person had not been screened. Diagnosis of cancer causes anxiety, and treatment often causes physical harm. For individuals with overdiagnosed cancer, these harms occur without any benefit. There are two major contributors to overdiagnosis: indolent cancers and competing causes of death. In practice, there is a spectrum of interaction between these two factors.

Explaining overdiagnosis to people considering whether to be screened is challenging. People want to know what might happen to them if they undergo screening, or if they do not. Here, we can derive a health communication strategy from an unlikely source: the 1998 romantic comedy "Sliding Doors" starring Gwyneth Paltrow. The movie portrays a scenario whereby two possible outcomes in an individual's life are compared, following two parallel story lines depending on whether the lead character catches or misses an underground train. In the storyline where she boards the train, she discovers her boyfriend's infidelity, but in the counterfactual storyline she remains unaware.

Consider a sequel to the film in which the same cinematic gimmick causes the character to attend a low-dose CT lung screening appointment in one storyline, but not the other. In the screening thread, her scan reveals a pure ground glass nodule which is resected and classified as a minimally invasive adenocarcinoma. The non-screened character continues life unaware of this abnormality. Fast-forward a few years, and both continue to lead healthy lives, with one perceiving that screening has saved her life. This would constitute overdiagnosis due to indolent disease.

Long-term follow-up after screening ends is necessary to accurately quantify overdiagnosis in a randomised trial. The initial estimate of overdiagnosis in the National Lung Screening Trial,[1] with mean of 4.5 years follow-up from the last screen, estimated that 18.5% of

Corresponding Author: Matthew E J Callister.

Conflicts of Interest

None

screen-detected cancers were overdiagnosed.[2] However, with longer follow-up of approximately 9 years after the last screen, this proportion fell to only 3%.[3] Results from the NELSON trial were similar, estimating 19.7% overdiagnosis at 4.5 years after the final screening round, and 8.9% at 5.5 years.[4] Modelling studies are needed to estimate the magnitude of overdiagnosis at the population level, accounting for changes in lung cancer risk and screening eligibility over time.[5] They can also be used to estimate overdiagnosis in clinical trials when post-screening follow-up is short.[6]

Does the long-term NLST result mean that real-world lung cancer screening is only minimally affected by overdiagnosis? Unfortunately, the answer may well be no, due to the second contributor to overdiagnosis: competing causes of death. Unlike other screening programmes, LDCT screening is targeted to those at highest risk of lung cancer, largely defined by age and smoking history. However, these individuals also have high risk for other causes of death, particularly cardio-respiratory comorbidities. This effect might be exacerbated by the use of lung cancer risk models to define eligibility for screening.[7]

Returning to possible story-lines for “Sliding Doors: The Sequel,” consider instead a scenario where the lead character is screened and diagnosed with a T1bN1M0 adenocarcinoma. She undergoes lung resection and adjuvant chemotherapy, but unfortunately suffers an unrelated myocardial infarction a year later and dies. The unscreened counterpart suffers the same fate, and has metastatic lung cancer diagnosed post-mortem. This is clearly biologically aggressive disease, but here overdiagnosis was caused by a competing cause of death.

In the NLST, 80% of control arm participants remained alive after 12 years of follow-up, and ‘healthy volunteer’ effects were documented.[3,8] A comparison of outcomes in patients with stage I non-small cell lung cancer (NSCLC) detected by screening in the NLST versus those diagnosed in routine clinical practice in a Surveillance, Epidemiology, and End Results (SEER)-Medicare dataset showed that 5-year all-cause survival (but not 5-year cancer-specific survival) was significantly worse in the SEER versus NLST group, especially in patients with greater comorbidities.[9] Another recent study comparing screening participants between a US urban academic hospital and the NLST demonstrated that the ‘real-world’ participants were older and had more comorbidities, with 2-3 times higher rates of asthma, COPD, diabetes, heart disease and hypertension than in the NLST.[10] These comorbidities increase the likelihood that treatment of biologically aggressive early lung cancer will not prevent lung cancer death because the patient will die of another disease before the lung cancer progresses.

Additional indicators of comorbidity in a screening population are the investigation and treatment of screen-detected cancers. Non-surgical treatment of patients with early-stage screen-detected lung cancers usually reflects comorbidity that precludes surgery. Similarly, treatment without pathological confirmation of cancer suggests that the patient wasn’t fit enough for surgery or percutaneous biopsy (for example, due to emphysema). The NLST showed 99% pathological confirmation of screen-detected lung cancer and 91% surgical resection for patients with stage I/II cancer.[1] The ‘real-world’ Manchester Lung Health Check screening programme showed lower rates, specifically 87% pathological confirmation

and 65% surgery for early-stage disease.[11,12] In a screening programme in Gateshead, pathological confirmation occurred in 79%, and only 3 (25%) of 12 patients with early-stage disease had surgery.[13]

It is therefore possible that some of the participants diagnosed with screen-detected lung cancer in real-world studies would not have lived long enough for their cancer to present if they had not been screened, and thus were overdiagnosed. Even for participants for whom lung cancer screening did extend life, comorbidities will likely attenuate their individual life-years gained, which will decrease the cost-effectiveness of screening. The 5-year survival of those patients with stage I disease treated with radiation (and not surgery) in the SEER-Medicare database referenced above was only 25%.[9]

What therefore is the solution? The bluntest tool to address this issue is the upper age limit of screening. The US Preventive Services Task Force recommends screening up to 80 years, [14] but reducing the age-to-stop screening could reduce the likelihood of overdiagnosis due to competing comorbidity. The downside is that healthy older patients miss out on the benefits that lung screening might afford them. Another potential approach is to define a frail population who may experience net harm from screening and exclude them from the invitation process (e.g. using tools such as the Electronic Frailty Index[15]). Most recently, novel risk prediction tools have been proposed to choose individuals for screening based on how many life-years they are predicted to gain on an individual basis.[16]

A comprehensive review on incorporating comorbidities into lung screening decisions was provided by an American Thoracic Society Research Statement published in 2018.[17] The review highlighted a need to identify the best method to quantify the burden of comorbidities among people considering lung screening, and to define what types of information to include in models of competing mortality. Clearly, research is needed not only to quantify comorbidities and competing risks, but also to quantify how these interact with individualized lung screening benefit and patient preferences. Both prospective studies and retrospective analyses are needed to evaluate the tools that have been proposed. In due course, information about comorbidity will need to be incorporated into resources aimed to facilitate shared decision making such as shouldiscreen.com.[18] However, one important concern about these approaches is their potential to exacerbate existing disparities between socioeconomic or ethnic groups.

Overdiagnosis is a complex phenomenon that can only be understood in a population. Long-term follow-up of the National Lung Screening Trial showed very low levels of overdiagnosis, but these estimates may not apply to the ‘real world’ if the people recruited to screening differ from those in the trials. As implementation of lung screening proceeds, many studies have aimed to refine estimation of lung cancer risk to maximise the number of lung cancers detected by screening. However, there is a parallel need to define who not to screen, with the goal of minimising overdiagnosis to find an optimal balance of benefits and harms.

Acknowledgments

Funding

MEJC was part-funded by Yorkshire Cancer Research (through the Yorkshire Lung Screening Trial - L403).

HAR was partially supported by the US National Cancer Institute (R03 CA245979 and U19 CA203654).

References

1. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011 Aug 4;365(5):395–409. [PubMed: 21714641]
2. Patz EF, Pinsky P, Gatsonis C, Sicks JD, Kramer BS, Tammemägi MC, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med. 2014 Mar 1;174(2):269–74. [PubMed: 24322569]
3. Black WC, Chiles C, Church TR, Gareen IF, Gierada DS, Mahon I, et al. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. J Thorac Oncol. 2019 Jul 3;
4. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med. 2020 Jan 29;10.1056/NEJMoa1911793.
5. Blom EF, Ten Haaf K, de Koning HJ. Trends in lung cancer risk and screening eligibility affect overdiagnosis estimates. Lung Cancer. 2020 Jan;139:200–6. [PubMed: 31816564]
6. Ten Haaf K, de Koning HJ. Overdiagnosis in lung cancer screening: why modelling is essential. J Epidemiol Community Health. 2015 Nov;69(11):1035–9. [PubMed: 26071497]
7. Lebrett MB, Balata H, Evison M, Colligan D, Duerden R, Elton P, et al. Analysis of lung cancer risk model (PLCOm2012 and LLPv2) performance in a community-based lung cancer screening programme. Thorax. 2020 Aug;75(8):661–8. [PubMed: 32631933]
8. Aberle DR, Adams AM, Berg CD, Clapp JD, Clingan KL, Gareen IF, et al. Baseline characteristics of participants in the randomized National Lung Screening Trial. J Natl Cancer Inst. 2010 Dec 1;102(23):1771–9. [PubMed: 21119104]
9. Tanner NT, Dai L, Bade BC, Gebregziabher M, Silvestri GA. Assessing the generalizability of the National Lung Screening Trial: Comparison of patients with stage 1 disease. Am J Respir Crit Care Med. 2017 Sep;196(5):602–8. [PubMed: 28722466]
10. Iaccarino JM, Steiling KA, Wiener RS. Lung cancer screening in a safety-net hospital: Implications of screening a real-world population versus the National Lung Screening Trial. Ann Am Thorac Soc. 2018 Dec;15(12):1493–5. [PubMed: 30199643]
11. Crosbie PA, Balata H, Evison M, Atack M, Bayliss-Brideaux V, Colligan D, et al. Implementing lung cancer screening: baseline results from a community-based “Lung Health Check” pilot in deprived areas of Manchester. Thorax. 2018 Feb 13;74(4):405–9. [PubMed: 29440588]
12. Crosbie PA, Balata H, Evison M, Atack M, Bayliss-Brideaux V, Colligan D, et al. Second round results from the Manchester “Lung Health Check” community-based targeted lung cancer screening pilot. Thorax. 2018 Nov 12;74(7):700–4. [PubMed: 30420406]
13. Grover H, Ross T, Fuller E. Implementation of targeted screening for lung cancer in a high-risk population within routine NHS practice using low-dose computed tomography. Thorax. 2020 Apr;75(4):348–50. [PubMed: 32127463]
14. Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive Services Task Force recommendation. Ann Intern Med. 2013 Sep;159(6):411–20. [PubMed: 23897166]
15. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing. 2016 May;45(3):353–60. [PubMed: 26944937]
16. Cheung LC, Berg CD, Castle PE, Katki HA, Chaturvedi AK. Life-gained-based versus risk-based selection of smokers for lung cancer screening. Ann Intern Med. 2019 Oct 22;
17. Rivera MP, Tanner NT, Silvestri GA, Detterbeck FC, Tammemägi MC, Young RP, et al. Incorporating coexisting chronic illness into decisions about patient selection for lung cancer

screening. An official American Thoracic Society Research Statement. Am J Respir Crit Care Med. 2018 Jul;198(2):e3–13. [PubMed: 30004250]

18. University of Michigan. shouldiscreen.com [Internet]. 2017 [cited 2019 Apr 10]. Available from: www.shouldiscreen.com