CT Lung Cancer Screening of Female Never Smokers

Katrina Steinsultz, MPH, R.T.(R)(M)

Lung cancer is a leading cause of morbidity and mortality with 2.21 million new cases reported globally in 2020.[1] In the United States alone, more than 238 000 new cases of lung cancer and 127 000 deaths will be reported for 2023.[2] Lung cancer is the third most common type of cancer in the United States, after female breast and prostate cancer, accounting for 12.2% of new cancer diagnoses.[2] However, lung cancer is the most common cause of mortality among cancers, accounting for 20.8% of cancer deaths.[2] Although survival rates of lung cancer are improving, 356 deaths occur daily in the United States due to lung cancer, which carries a 5-year survival rate of 22.9% (all stages).[3] Tobacco use in the form of cigarette smoking has been widely established as the primary risk factor in the development of lung cancers with various sources reporting tobacco use in up to 90% of new cancer diagnoses.[3-10] Other reported risk factors that contribute to lung cancer include[6,11-13]:

- environmental and occupational exposure to hazardous materials
- gender differences
- genetic factors
- geographic location
- other lung diseases
- therapeutic radiation exposure

Lung cancer's onset creates challenges in early detection, which is when the cancer is more treatable.[3,14,15] Common signs of lung cancer include nonspecific presentations such as a chronic cough, difficulty breathing, and wheezing.[10,14,15] The presence of a chronic cough, casually referred to as *smoker's cough*, in individuals with a history of cigarette use can mask early symptoms.[16] At diagnosis, more than half of all lung cancers are at the distant (metastasized) stage with a 5-year survival rate of 8.2% (see **Figure 1**).[2] In 2014, the cost of treating lung cancer was $21.1 billion and was projected to increase to $23.8 billion in 2020. Only colorectal cancer and breast cancer have higher expenditures than lung cancer.[16] Even with Medicare coverage, in 2019, lung cancer patients had an average cost of care burden ranging from $10 866 at initial diagnosis to $13 852 at death.[17]

Lung Cancer Among Smokers and Nonsmokers

Gender differences in smoking status, tobacco use, and reported lung cancer incidence have been reported widely in the literature. In 1964, 51.9% of men in the United States reported current cigarette use, while approximately 33.9% of women smoked, which is attributed to past societal norms having less acceptance for smoking in women (see **Figure 2**).[18,19] As a result, incidence of lung cancer in women also lagged behind men in the mid-1960s as reported in the 1964 Surgeon General's report, *Smoking and Health*.[10] The number of women who reported smoking cigarettes peaked in the mid-1970s, after which a steady and slow decline

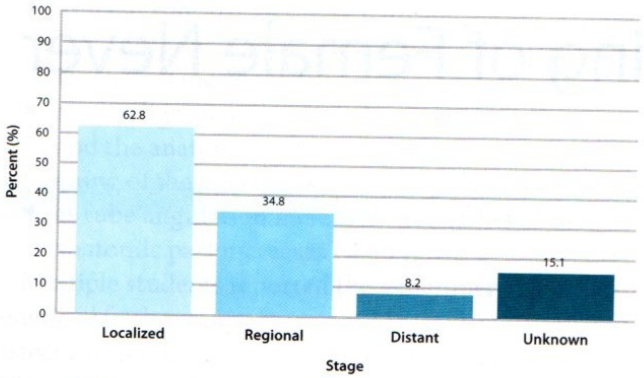

Figure 1. *Five-year relative survival rates for lung cancer by stage. Public domain figure from Surveillance, Epidemiology, and End Results (SEER) program.*

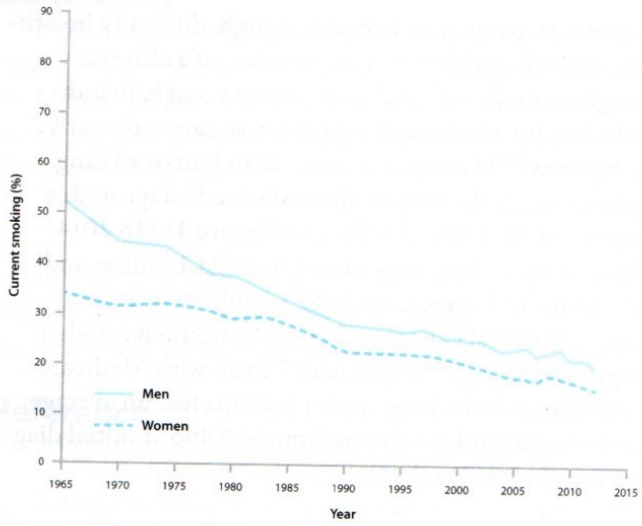

Figure 2. *Prevalence (%) of cigarette smoking among adult men and women. Public domain figure from the Centers for Disease Control and Prevention.* The health consequences of smoking - 50 years of progress: a report of the surgeon general.

began.[10] During this time, the incidence of lung cancer among young women as increased and currently approaches the incidence of lung cancer among young men.[2] Cigarette use among men was already declining in the mid-1960s and continued to drop more rapidly than in women between 1965 and 2015.[10] Although smoking prevalence among women has varied throughout time, their proportions have consistently remained below men, and their smoking patterns have historically been different from their male counterparts. Compared with men, women smoked fewer cigarettes per day, smoked menthol cigarettes, and did not tend to use other forms of tobacco (eg, chewing tobacco).[20]

Although tobacco use is identified as the primary risk factor for developing lung cancers, some lung cancers occur among individuals who have never smoked. Aggregated rates of lung cancer in the United States among never-smokers account for 10-15% of all lung cancers and has a significantly higher incidence in women than in men.[4,19-23] In women, 15-20% of reported lung cancers in the United States occur in never-smokers, while in men, that percentage drops to 7-10%.[19,24,25] Internationally, 25% of lung cancer diagnoses occur in never-smokers, with 53% of women who have never smoked receiving a lung cancer diagnosis, compared with 15% of men who have never smoked.[19] The incidence of lung cancer in never-smokers is increasing, especially among women. One study performed in the United States found that the incidence of lung cancer among never-smokers rose from 8% between 1990 and 1995 to 14.9% between 2011 and 2013.[19] The United Kingdom has also reported a similar rise in the incidence of lung cancers among never-smokers in a retrospective study from 2008-2014 with annual cases of lung cancer rising from 13% to more than 28%, and 67% of the lung cancer cases among never-smokers occurring in women.[19] Studies focusing on the sex-related disparity of lung cancer incidence among never-smokers is ongoing. Previous and current literature has reported possible relationships among groups of patients, such as histological differences between smokers versus never-smokers, genetic and molecular differences between the sexes, environmental versus occupational exposures, and risks of developing lung cancer after breast cancer.[19,20] Never-smokers with lung cancers have better outcomes at any stage of the cancer or type of treatment and an improved 5-year survival rate as compared with patients with lung cancer who have a history of smoking.[19]

Lung Cancer Screening With Low-Dose Computed Tomography

With the rise in the number and proportion of lung cancers diagnosed among never-smokers worldwide,

some research has focused on whether using low-dose computed tomography (LDCT) as a screening tool for never-smokers is feasible. For any screening tool to be successful, it must be effective at accurately identifying a disease or condition in early stages, easy to administer with minimal patient discomfort, and it must have a high number of true positives with a low number of false negatives.[26] Screening tests must also consider the psychological distress accompanying a positive test result, regardless of whether future exploration of a positive test confirms a diagnosis.[27]

The benefit of LDCT screening among current and former smokers has been established by the National Lung Cancer Screening Trial (NLCST), which enrolled over 50 000 participants (current and former smokers) in 33 different locations between 2002 and 2004 in the United States.[28,29] Findings published in 2011 demonstrated that more lung cancers were diagnosed and fewer deaths occurred in participants that received LDCT screening as compared with participants who were screened with chest radiography, reducing the mortality rate from lung cancer in those screened with LDCT by 20%.[29] The NLCST research team continued to monitor the participants after their 2011 publication through passive means, adding 5 years of follow-up for incidences of lung cancer and 6 years of follow-up for mortality.[30] They found that the reduction in mortality from lung cancer from the original NLCST was maintained during the additional follow-up time, thereby concluding that LDCT screening reduced or prevented lung cancer mortality or prevented mortality for at least 10 years.[30] In 2020, researchers conducting the Dutch-Belgian Nederlands-Leuvens Longkanker Screening Onderzoek (NELSON) trial, which performed LDCT scanning in more than 15 000 randomized current and former smoker participants at 1-, 3-, and 5-year intervals with a follow-up of 10 years, published results of their study. They found that with LDCT screening, lung cancer mortality was reduced by 24% in men and 33% in women.[11]

In response to the evidence gathered and presented by the NLCST and other screening trials, in 2013, the U.S. Preventive Services Task Force (USPSTF) began recommending annual screening with LDCT for adults aged 55-80 years with a 30-pack-year smoking history that were either current smokers or quit in the previous 15 years.[31,32] In 2021, this criterion was expanded to include screening with LDCT for adults aged 50-80 years with a 20-pack-year smoking history that currently smoke or have quit in the past 15 years.[33] In 2015, the Centers for Medicare and Medicaid Services began to cover the cost of LDCT screening for high-risk individuals.[34] Uptake of LDCT as a screening tool has been slow, with less than 4% of eligible individuals screened in 2015,[35] increasing marginally to 6.5% of eligible individuals in 2020.[36] Despite evidence for the benefits of LDCT, 8.5% of adults at high risk for lung cancer due to their smoking status undergo chest radiography instead.[11] Poor uptake of LDCT screening is estimated to result in 12 000 lung cancer deaths per year.[34] Reported reasons for the lack of LDCT screenings include lack of provider education on the effectiveness of LDCT over chest radiography and screening guidelines, strained resources in the management of patients with comorbidities or complex medical needs, complex data collection and shared decision-making requirements, and concerns about access and costs.[11,37-39] Patients report a fear of results, the perception that screening will not affect the outcome, mistrust in health care or the health care system, and barriers to resources.[11,37,39]

LDCT screening has an additional risk to consider—exposure of a healthy, asymptomatic individual to ionizing radiation. Although the benefit of LDCT screening for individuals at high risk for lung cancer (smoking history) immensely outweighs the risks received from the radiation dose, the same risk to benefit scenario applied to individuals not at high risk for lung cancer is not as favorable.[40] According to the American College of Radiology, nonscreening chest CT has an approximate effective radiation dose of 6.1 mSv, which is equivalent to 2 years of comparable time of background radiation exposure.[41] A chest CT for lung cancer screening has approximately a 1.5 mSv dose (which varies in clinical practice), and 25% of the radiation dose of nonscreening chest CT; it is comparable to approximately 6 months of natural background radiation exposure.[40,41] Considering the recommendation to screen annually through LDCT and the potential for additional radiation doses from further investigation

of any identified nodules of concern, the cumulative effects of radiation dose from screening and investigation are of concern, especially when patients begin screenings at an earlier age or when a clear benefit has not been established.[40] Using radiation models and a dose of 8.5 mSv (estimated from the NLCST), it is predicted that 1 cancer death per 2500 individuals screened might occur, however, any carcinogenesis due to radiation exposure likely would not manifest for at least another decade.[40]

Current Research on Effectiveness of LDCT as a Screening Tool Among Never-Smokers

Recent studies in some Asian countries have produced mixed results on the effectiveness of LDCT screening among never-smokers (see **Table**).[21,42,43] Although the American College of Radiology recommends continual annual LDCT screening in individuals with negative results, this might not be applicable to low-risk individuals such as female never-smokers.[21] A retrospective cohort in Korea followed 4365 female never-smokers through the Korea Central Cancer Registry who had an initial LDCT screening between 2002 and 2007, with follow ups until the end of 2013.[21] They found lung cancer in 0.5% of these individuals after a median follow-up of 9.69 years, most commonly Lung-RADS category 4. Researchers inferred that LDCT screening for never-smokers might not be useful but recognized that there is a gradual increase in risk of lung cancer among never-smokers as individuals age.[21] Consistent with previous documentation that lung cancers more often are discovered on initial scans than in annual follow-up, researchers concluded that performing routine LDCT lung cancer screenings every 5 years or longer would be reasonable among female never-smokers after initial negative findings, similar to recommendations of colon cancer screenings.[21]

Table

Summary of Selected Studies

Authors	Study type	Summary	Recommendation
Kim et al[22]	Retrospective	LDCT performed between 2002-2007 with follow up until 2013. 0.5% of female never-smokers diagnosed with lung cancer after initial LDCT in a median follow up of 9.69 years.	Reasonable to perform screening LDCT every 5 years or more.
Kakinuma et al[43]	Observational	Participants with variable smoking status. 2-day cancer screening including LDCT. Lung cancer identified in 133 participants, with 66 cases in never-smokers (50 women, 15 men).	Never-smokers should be included in screening populations.
Gao et al[44]	Population-based ecological cohort study	Study performed between 2004-2018 Researchers assumed no overdiagnosis before 2004, late-stage lung cancer is not overdiagnosed, and lung cancer occurrence is stable. No. of diagnosed early-stage lung cancers increased from 2.3 to 14.4 while no increase in late-stage detection. Researchers conclude that the increase in early-stage lung cancers is indicative of diagnosis.	LDCT only for populations with history of heavy smoking.

Abbreviation: LDCT, low-dose computed tomography.

Another observational study conducted in Japan recruited 12 114 participants (6090 smokers and 6021 nonsmokers), aged 40 years or older with variable smoking status to undergo a 2-day cancer screening that included a LDCT lung cancer screening.[42] For the duration of this study, lung cancer was identified in 133 patients, with 66 of the cancers occurring in never-smokers.[42] Among the never-smokers, a disproportionate number of cancers occurred in women, with 50 cancers in women versus 16 in men.[42] In further investigation of the 50 cancers in female never-smokers, 17 reported a history of daily exposure to second-hand smoke for 30 years and 16 indicated exposures to second-hand smoke several times a month, while the rest reported little exposure to second-hand smoke.[42] Detection rates of lung cancer in never-smokers was calculated to be at 1.1%, which is the same detection rate that was identified in the smoking population.[42] Researchers concluded that due to the consistent detection rates of lung cancers on LDCT lung screening among never-smokers and smokers, never-smokers should be included in the population screened for lung cancers in Japan.[42]

A population-based, ecological cohort study in Taiwan, whose female population consists of 95% never-smokers, examined the effects of the introduction of LDCT lung screening in 2004 on approximately 12 million women.[43] As part of this study, researchers assumed that no overdiagnosis of lung cancer occurred before 2004, late-stage lung cancer is not overdiagnosed, and that lung cancer occurrence is stable. This study determined that from 2004 to 2018, the number of early-stage lung cancers identified increased from 2.3 per 100 000 population (pre-2004 level) to 14.4 per 100 000 population while late-stage cancer diagnosis remained consistent with pre-2004 levels.[43] Researchers applied these data to the assumptions and determined that this increase in early-stage detection is indicative of overdiagnosis of lung cancer among women, especially because of the lack of an expected decrease in identification of late-stage lung cancers. An alternative explanation of increased lung cancer diagnosis due to environmental toxin exposure was rejected by the researchers because of significant reductions in environmental toxins in Taiwan between 1990 and 2017.[43] Researchers also noted an increase in total thoracotomies after 2006, which they contend is a downstream effect of the increased number of overdiagnosed lung cancers.[43] The researchers concluded that LDCT lung cancer screenings should be performed for individuals with a history of heavy smoking and include patient education during the decision-making component.[43]

Conclusion

Lung cancer among never-smokers is on the rise, especially among women. Although many possible etiologies have been suggested, none alone can conclusively explain the reason behind this rise. With significant numbers of never-smokers at risk for lung cancer, identifying a viable and low-risk screening tool is crucial to detecting lung cancer at the earlier stages. Most published studies of LDCT effectiveness have concentrated on and established a benefit of mortality reduction among smokers, but the same has not been definitively determined for the never-smoker population.[21] Exploration of LDCT as a screening tool for never-smokers has yet to establish a benefit of mortality reduction and has mixed results in the literature. Concerns of the psychological impact of screening, radiation dose and carcinogenesis, and follow-up testing with rare complications must be considered by researchers as they continue to pursue LDCT as an effective screening tool in female never-smokers.

Katrina Steinsultz, MPH, R.T.(R)(M), is clinical assistant professor for the University of North Carolina at Chapel Hill.

References

1. Cancer. World Health Organization. February 3, 2022. Accessed September 13, 2022. https://www.who.int/news-room/fact-sheets/detail/cancer
2. Cancer stat facts: lung and bronchus cancer. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. Accessed February 26, 2024 https://seer.cancer.gov/statfacts/html/lungb.html#content
3. State of lung cancer 2023 report. American Lung Association. Published November 14, 2023. Accessed February 27, 2024. https://www.lung.org/getmedia/186786b6-18c3-46a9-a7e7-810f3ce4deda/SOLC-2023-Print-Report.pdf

4. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33. doi:10.3322/caac.21708
5. Lung cancer: what are the risk factors? Centers for Disease Control and Prevention. Reviewed July 31, 2023. Accessed February 26, 2024. https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm
6. Ten Haaf K, van der Aalst CM, de Koning HJ, Kaaks R, Tammemägi MC. Personalising lung cancer screening: an overview of risk-stratification opportunities and challenges. *Int J Cancer*. 2021;149(2):250-263. doi:10.1002/ijc.33578
7. Jin J. Screening for lung cancer. *JAMA*. 2021;325(10):1016. doi:10.1001/jama.2021.1799
8. Faselis C, Nations JA, Morgan CJ, et al. Assessment of lung cancer risk among smokers for whom annual screening is not recommended. *JAMA Oncol*. 2022;8(10):1428-1437. doi:10.1001/jamaoncol.2022.2952
9. Yang D, Liu Y, Bai C, Wang X, Powell CA. Epidemiology of lung cancer and lung cancer screening programs in China and the United States. *Cancer Lett*. 2020;468:82-87. doi:10.1016/j.canlet.2019.10.009
10. *The health consequences of smoking - 50 years of progress: a report of the surgeon general*. Centers for Disease Control and Prevention; 2014.
11. Houston T. Screening for lung cancer. *Med Clin North Am*. 2020;104(6):1037-1050. doi:10.1016/j.mcna.2020.08.005
12. Jonas DE, Reuland DS, Reddy SM, et al. Screening for lung cancer with low-dose computed tomography: an evidence review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality (US); 2021. Accessed October 18, 2022. https://www.ncbi.nlm.nih.gov/books/NBK568576/
13. Peddireddy V. Lung cancer incidence in never smokers: genetic and gender basis. *Gene Rep*. 2016;4:198-207. doi:10.1016/j.genrep.2016.06.003
14. United States Public Health Service. Office of the Surgeon General. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. U.S. Dept. of Health and Human Services, Public Health Service, Office of the Surgeon General; 2010.
15. VanMeter KC, Hubert RJ. *Gould's Pathophysiology for the Health Professions*. 7th ed. Elsevier; 2023.
16. Financial Burden of Cancer Care. National Cancer Institute. Published April 2022. Accessed September 14, 2022. https://progressreport.cancer.gov/after/economic_burden
17. Yabroff KR, Mariotto A, Tangka F, et al. Annual report to the nation on the status of cancer, part 2: patient economic burden associated with cancer care. *J Natl Cancer Inst*. 2021;113(12):1670-1682. doi:10.1093/jnci/djab192
18. Centers for Disease Control and Prevention. Woman and smoking: a report of the Surgeon General (Executive Summary). *MMWR*. 2002;51(RR-12).
19. Tanoue LT. Women and lung cancer. *Clin Chest Med*. 2021;42(3):467-482. doi:10.1016/j.ccm.2021.04.007
20. Jemal A, Miller KD, Ma J, et al. Higher lung cancer incidence in young women than young men in the United States. *N Engl J Med*. 2018;378(21):1999-2009. doi:10.1056/NEJMoa1715907
21. Kim HY, Jung KW, Lim KY, et al. Lung cancer screening with low-dose CT in female never smokers: retrospective cohort study with long-term national data follow-up. *Cancer Res Treat*. 2018;50(3):748-756. doi:10.4143/crt.2017.312
22. Pelosof L, Ahn C, Gao A, et al. Proportion of never-smoker non-small cell lung cancer patients at three diverse institutions. *J Natl Cancer Inst*. 2017;109(7):djw295. doi:10.1093/jnci/djw295
23. Torres-Durán M, Curiel-García MT, Ruano-Ravina A, et al. Small-cell lung cancer in never-smokers. *ESMO Open*. 2021;6(2):100059. doi:10.1016/j.esmoop.2021.100059
24. Siegel DA, Fedewa SA, Henley SJ, Pollack LA, Jemal A. Proportion of never smokers among men and women with lung cancer in 7 U.S. states. *JAMA Oncol*. 2021;7(2):302-304. doi:10.1001/jamaoncol.2020.6362
25. Henschke CI, Yip R, Boffetta P, et al; I-ELCAP Investigators. CT screening for lung cancer: importance of emphysema for never smokers and smokers. *Lung Cancer*. 2015;88(1):42-47. doi:10.1016/j.lungcan.2015.01.014
26. Herman C. What makes a screening exam "good"? *Virtual Mentor*. 2006;8(1):34-37. doi:10.1001/virtualmentor.2006.8.1.cprl1-0601
27. Tanoue LT, Tanner NT, Gould MK, Silvestri GA. Lung cancer screening. *Am J Respir Crit Care Med*. 2015;191(1):19-33. doi:10.1164/rccm.201410-1777CI
28. Aberle DR, Berg CD, Black WC, et al; National Lung Screening Trial Research Team. The National Lung Screening Trial: overview and study design. *Radiology*. 2011;258(1):243-253. doi:10.1148/radiol.10091808
29. Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395-409. doi:10.1056/NEJMoa1102873
30. National Lung Screening Trial Research Team. Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. *J Thorac Oncol*. 2019;14(10):1732-1742. doi:10.1016/j.jtho.2019.05.044
31. Lung cancer: screening. U.S. Preventative Services Task Force. Published December 31, 2013. Accessed October 11, 2022. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lung-cancer-screening-december-2013
32. Silvestri GA, Goldman L, Burleson J, et al. Characteristics of persons screened for lung cancer in the United States: a cohort study. *Ann Intern Med*. 2022;175(11):1501-1505. doi:10.7326/M22-1325
33. U.S Preventative Services Task Force. Lung Cancer: Screening. Published March 9, 2021. Accessed February 27, 2024. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lung-cancer-screening
34. Hall DL, Lennes IT, Carr A, Eusebio JR, Yeh GY, Park ER. Lung cancer screening uncertainty among patients undergoing

LDCT. *Am J Health Behav.* 2018;42(1):69-76. doi:10.5993/AJHB.42.1.7

35. Jemal A, Fedewa SA. Lung cancer screening with low-dose computed tomography in the United States–2010 to 2015. *JAMA Oncol.* 2017;3(9):1278-1281. doi:10.1001/jamaoncol.2016.6416
36. Fedewa SA, Bandi P, Smith RA, Silvestri GA, Jemal A. Lung cancer screening rates during the COVID-19 pandemic. *Chest.* 2022;161(2):586-589. doi:10.1016/j.chest.2021.07.030
37. Smits SE, McCutchan GM, Hanson JA, Brain KE. Attitudes towards lung cancer screening in a population sample. *Health Expect.* 2018;21(6):1150-1158. doi:10.1111/hex.12819
38. Carter-Harris L, Gould MK. Multilevel barriers to the successful implementation of lung cancer screening: why does it have to be so hard? *Ann Am Thorac Soc.* 2017;14(8):1261-1265. doi:10.1513/AnnalsATS.201703-204PS
39. Jonas DE, Reuland DS, Reddy SM, et al. Screening for Lung Cancer With Low-Dose Computed Tomography: An Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 198. AHRQ Publication No. 20-05266-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2021.
40. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA.* 2012;307(22):2418-2429. doi:10.1001/jama.2012.5521
41. Radiation dose to adults from common imaging examinations. American College of Radiology. Published May 2022. Accessed October 18, 2022. https://www.acr.org/-/media/ACR/Files/Radiology-Safety/Radiation-Safety/Dose-Reference-Card.pdf
42. Kakinuma R, Muramatsu Y, Asamura H, et al. Low-dose CT lung cancer screening in never-smokers and smokers: results of an eight-year observational study. *Transl Lung Cancer Res.* 2020;9(1):10-22. doi:10.21037/tlcr.2020.01.13
43. Gao W, Wen CP, Wu A, Welch HG. Association of computed tomographic screening promotion with lung cancer overdiagnosis among Asian women. *JAMA Intern Med.* 2022;182(3):283-290. doi:10.1001/jamainternmed.2021.7769