

Lung Cancer Screening
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. <i>CA Cancer J Clin.</i> 2018;68(1):7-30.	Review/Ot her-Dx	N/A	Each year, the American Cancer Society estimates the numbers of new cancer cases and deaths that will occur in the United States and compiles the most recent data.	Each year, the American Cancer Society estimates the numbers of new cancer cases and deaths that will occur in the United States and compiles the most recent data on cancer incidence, mortality, and survival. Incidence data, available through 2014, were collected by the Surveillance, Epidemiology, and End Results Program; the National Program of Cancer Registries; and the North American Association of Central Cancer Registries. Mortality data, available through 2015, were collected by the National Center for Health Statistics. In 2018, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in the United States. Over the past decade of data, the cancer incidence rate (2005-2014) was stable in women and declined by approximately 2% annually in men, while the cancer death rate (2006-2015) declined by about 1.5% annually in both men and women. The combined cancer death rate dropped continuously from 1991 to 2015 by a total of 26%, translating to approximately 2,378,600 fewer cancer deaths than would have been expected if death rates had remained at their peak. Of the 10 leading causes of death, only cancer declined from 2014 to 2015. In 2015, the cancer death rate was 14% higher in non-Hispanic blacks (NHBs) than non-Hispanic whites (NHWs) overall (death rate ratio [DRR], 1.14; 95% confidence interval [95% CI], 1.13-1.15), but the racial disparity was much larger for individuals aged <65 years (DRR, 1.31; 95% CI, 1.29-1.32) compared with those aged ≥65 years (DRR, 1.07; 95% CI, 1.06-1.09) and varied substantially by state. For example, the cancer death rate was lower in NHBs than NHWs in	4

**Lung Cancer Screening
EVIDENCE TABLE**

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				Massachusetts for all ages and in New York for individuals aged ≥ 65 years, whereas for those aged < 65 years, it was 3 times higher in NHBs in the District of Columbia (DRR, 2.89; 95% CI, 2.16-3.91) and about 50% higher in Wisconsin (DRR, 1.78; 95% CI, 1.56-2.02), Kansas (DRR, 1.51; 95% CI, 1.25-1.81), Louisiana (DRR, 1.49; 95% CI, 1.38-1.60), Illinois (DRR, 1.48; 95% CI, 1.39-1.57), and California (DRR, 1.45; 95% CI, 1.38-1.54). Larger racial inequalities in young and middle-aged adults probably partly reflect less access to high-quality health care.	
2. American College of Radiology. ACR–STR Practice Parameter for the Performance and Reporting of Lung Cancer Screening Thoracic Computed Tomography (CT). Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/ct-lungcasr.pdf?la=en .	Review/Other-Dx	N/A	Guidance document to promote the safe and effective use of diagnostic and therapeutic radiology by describing specific training, skills and techniques.	No abstract available.	4

**Lung Cancer Screening
EVIDENCE TABLE**

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<p>3. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 365(5):395-409, 2011 Aug 04.</p>	<p>Observational-Dx</p>	<p>53,454 persons</p>	<p>To determine whether screening with low-dose computed tomography (CT) could reduce mortality from lung cancer.</p>	<p>The rate of adherence to screening was more than 90%. The rate of positive screening tests was 24.2% with low-dose CT and 6.9% with radiography over all three rounds. A total of 96.4% of the positive screening results in the low-dose CT group and 94.5% in the radiography group were false positive results. The incidence of lung cancer was 645 cases per 100,000 person-years (1060 cancers) in the low-dose CT group, as compared with 572 cases per 100,000 person-years (941 cancers) in the radiography group (rate ratio, 1.13; 95% confidence interval [CI], 1.03 to 1.23). There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; P=0.004). The rate of death from any cause was reduced in the low-dose CT group, as compared with the radiography group, by 6.7% (95% CI, 1.2 to 13.6; P=0.02).</p>	<p>3</p>

**Lung Cancer Screening
EVIDENCE TABLE**

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4. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Baseline characteristics of participants in the randomized national lung screening trial.[Erratum appears in J Natl Cancer Inst. 2011 Oct 19;103(20):1560]. J Natl Cancer Inst. 102(23):1771-9, 2010 Dec 01.	Observational-Dx	53,456 persons	To present characteristics of the study population.	The National Lung Screening Trial (NLST) enrolled 53 456 persons, with 26 733 randomly assigned to chest radiograph screening and 26 723 to computerized tomography screening. Characteristics of the participants were as follows: 31 533 (59%) were men, 39 234 (73%) were younger than 65 years, 25 779 (48%) were current smokers, and 16 839 (32%) had a college or higher degree. Median cigarette exposure was 48 pack-years. Among Tobacco Use Supplement respondents who met NLST age and smoking history criteria, 59% were men, 65% were younger than 65 years, and 57% were current smokers. Median cigarette exposure among this group was 47 pack-years, and 14% had a college degree or higher.	3
5. National Lung Screening Trial Research Team, Aberle DR, Berg CD, et al. The National Lung Screening Trial: overview and study design. Radiology. 258(1):243-53, 2011 Jan.	Review/Other-Dx	N/A	To provide a concise but comprehensive description of the National Lung Screening Trial (NLST).	No results stated in abstract.	4

**Lung Cancer Screening
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6. Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung Screening Trial. <i>N Engl J Med.</i> 369(10):920-31, 2013 Sep 05.	Experimental-Dx	53,454 participants	To determine whether 3 annual screenings (rounds T0, T1, and T2) with low-dose helical CT, as compared with chest radiography, could reduce mortality from lung cancer.	At the T1 and T2 rounds, positive screening results were observed in 27.9% and 16.8% of participants in the low-dose CT group and in 6.2% and 5.0% of participants in the radiography group, respectively. In the low-dose CT group, the sensitivity was 94.4%, the specificity was 72.6%, the PPV was 2.4%, and the NPV was 99.9% at T1; at T2, the PPV increased to 5.2%. In the radiography group, the sensitivity was 59.6%, the specificity was 94.1%, the PPV was 4.4%, and the NPV was 99.8% at T1; both the sensitivity and the PPV increased at T2. Among lung cancers of known stage, 87 (47.5%) were stage IA and 57 (31.1%) were stage III or IV in the low-dose CT group at T1; in the radiography group, 31 (23.5%) were stage IA and 78 (59.1%) were stage III or IV at T1. These differences in stage distribution between groups persisted at T2.	1
7. Black WC, Gareen IF, Soneji SS, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. <i>N Engl J Med.</i> 371(19):1793-802, 2014 Nov 06.	Observational-Dx	53,302 participants	To examine the cost-effectiveness of screening with low-dose computed tomography (CT) in the National Lung Screening Trial (NLST).	As compared with no screening, screening with low-dose CT cost an additional \$1,631 per person (95% confidence interval [CI], 1,557 to 1,709) and provided an additional 0.0316 life-years per person (95% CI, 0.0154 to 0.0478) and 0.0201 quality-adjusted life-years (QALYs) per person (95% CI, 0.0088 to 0.0314). The corresponding incremental cost-effectiveness ratios (ICERs) were \$52,000 per life-year gained (95% CI, 34,000 to 106,000) and \$81,000 per QALY gained (95% CI, 52,000 to 186,000). However, the ICERs varied widely in subgroup and sensitivity analyses.	3

Lung Cancer Screening
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8. National Lung Screening Trial Research Team, Church TR, Black WC, et al. Results of initial low-dose computed tomographic screening for lung cancer. <i>N Engl J Med</i> . 368(21):1980-91, 2013 May 23.	Experimental-Dx	53,439 participants : 26,715 in low-dose CT group and 26,724 in radiography group	To describe the screening, diagnosis, and limited treatment results from the initial round of screening in the National Lung Screening Trial (NLST) to inform and improve lung-cancer-screening programs.	A total of 7191 participants (27.3%) in the low-dose CT group and 2387 (9.2%) in the radiography group had a positive screening result; in the respective groups, 6369 participants (90.4%) and 2176 (92.7%) had at least one follow-up diagnostic procedure, including imaging in 5717 (81.1%) and 2010 (85.6%) and surgery in 297 (4.2%) and 121 (5.2%). Lung cancer was diagnosed in 292 participants (1.1%) in the low-dose CT group versus 190 (0.7%) in the radiography group (stage I in 158 vs. 70 participants and stage IIB to IV in 120 vs. 112). Sensitivity and specificity were 93.8% and 73.4% for low-dose CT and 73.5% and 91.3% for chest radiography, respectively.	3
9. Clark MA, Gorelick JJ, Sicks JD, et al. The Relations Between False Positive and Negative Screens and Smoking Cessation and Relapse in the National Lung Screening Trial: Implications for Public Health. <i>Nicotine Tob Res</i> . 18(1):17-24, 2016 Jan.	Observational-Dx	18 840 participants	To examine (1) five-year follow-up rates of quitting and relapse; (2) the relation between screening result and quitting and relapse behaviors, and (3) the relation between screening and current smokers' motivation to quit.	During five years of follow-up, annual point prevalence quit rates ranged from 11.6%-13.4%; 48% of current smokers reported a quit attempt and 7% of long-term former smokers relapsed. Any false positive screening result was associated with subsequent increased point (multivariable hazard ratio HR = 1.23, 95% CI = 1.13, 1.35) and sustained (HR = 1.28, 95% CI = 1.15, 1.43) abstinence among smokers. Recent quitters with ≥ 1 false positive screen were less likely to relapse (HR = 0.72, 95% CI = 0.54, 0.96). Screening result was not associated with relapse among long-term former smokers or among baseline smokers who quit during follow-up.	2

**Lung Cancer Screening
EVIDENCE TABLE**

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10. Croswell JM, Baker SG, Marcus PM, Clapp JD, Kramer BS. Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial.[Erratum appears in Ann Intern Med. 2010 Jun 1;152(11):759]. Ann Intern Med. 152(8):505-12, W176-80, 2010 Apr 20.	Observational-Dx	4828 patients	To quantify the cumulative risk that a person who participated in a 1- or 2-year lung cancer screening examination would receive at least 1 false-positive result, as well as rates of unnecessary diagnostic procedures.	By using a Kaplan-Meier analysis, a person's cumulative probability of 1 or more false-positive low-dose CT examinations was 21% (95% CI, 19% to 23%) after 1 screening and 33% (CI, 31% to 35%) after 2. The rates for chest radiography were 9% (CI, 8% to 11%) and 15% (CI, 13% to 16%), respectively. A total of 7% of participants with a false-positive low-dose CT examination and 4% with a false-positive chest radiography had a resulting invasive procedure. LIMITATIONS: Screening was limited to 2 rounds. Follow-up after the second screening was limited to 12 months. The false-negative rate is probably an underestimate.	2
11. Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med. 369(3):245-54, 2013 Jul 18.	Experimental-Dx	26,604 participants in the CT group and 26,554 in the radiography group	To assess the variation in efficacy, the number of false positive results, and the number of lung-cancer deaths prevented among 26,604 participants in the NLST who underwent low-dose CT screening, as compared with the 26,554 participants who underwent chest radiography, according to the quintile of 5-year risk of lung-cancer death (ranging from 0.15 to 0.55% in the lowest-risk group [quintile 1] to more than 2.00% in the highest-risk group [quintile 5]).	The number of lung-cancer deaths per 10,000 person-years that were prevented in the CT-screening group, as compared with the radiography group, increased according to risk quintile (0.2 in quintile 1, 3.5 in quintile 2, 5.1 in quintile 3, 11.0 in quintile 4, and 12.0 in quintile 5; P=0.01 for trend). Across risk quintiles, there were significant decreasing trends in the number of participants with false positive results per screening-prevented lung-cancer death (1648 in quintile 1, 181 in quintile 2, 147 in quintile 3, 64 in quintile 4, and 65 in quintile 5). The 60% of participants at highest risk for lung-cancer death (quintiles 3 through 5) accounted for 88% of the screening-prevented lung-cancer deaths and for 64% of participants with false positive results. The 20% of participants at lowest risk (quintile 1) accounted for only 1% of prevented lung-cancer deaths.	1

**Lung Cancer Screening
EVIDENCE TABLE**

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12. Kruger R, Flynn MJ, Judy PF, Cagnon CH, Seibert JA. Effective dose assessment for participants in the National Lung Screening Trial undergoing posteroanterior chest radiographic examinations. <i>AJR Am J Roentgenol.</i> 2011(1):142-6, 2013 Jul.	Review/Other-Dx	73,733 chest radiographic examinations	To determine the effective radiation dose associated with individual chest radiographic screening examinations.	This study showed that the mean effective dose assessed from 66,157 postero-anterior chest examinations was 0.052 mSv. Additional findings were a median effective dose of 0.038 mSv, a 95th percentile value of 0.136 mSv, and a fifth percentile value of 0.013 mSv.	4
13. Patz EF Jr, Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer.[Erratum appears in <i>JAMA Intern Med.</i> 2014 May;174(5):828]. <i>JAMA Intern Med.</i> 174(2):269-74, 2014 Feb 01.	Observational-Dx	1089 lung cancers	To estimate overdiagnosis in the National Lung Screening Trial (NLST).	During follow-up, 1089 lung cancers were reported in the low-dose computed tomography (LDCT) arm and 969 in the chest radiography (CXR) arm of the National Lung Screening Trial (NLST). The probability is 18.5% (95% CI, 5.4%-30.6%) that any lung cancer detected by screening with LDCT was an overdiagnosis, 22.5% (95% CI, 9.7%-34.3%) that a non-small cell lung cancer detected by LDCT was an overdiagnosis, and 78.9% (95% CI, 62.2%-93.5%) that a bronchioalveolar lung cancer detected by LDCT was an overdiagnosis. The number of cases of overdiagnosis found among the 320 participants who would need to be screened in the NLST to prevent 1 death from lung cancer was 1.38.	2

Lung Cancer Screening
EVIDENCE TABLE

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14. Pinsky PF, Church TR, Izmirlian G, Kramer BS. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. <i>Cancer</i> . 119(22):3976-83, 2013 Nov 15.	Observational-Dx	26,722 patients	To examine whether the benefit was affected by various baseline factors, including age, sex, and smoking status, and whether it differed by tumor histology.	The overall mortality RR was 0.92 in men and 0.73 in women, with a P value for interaction of .08. RRs were similar for individuals aged < 65 years versus those aged ≥ 65 years (0.82 vs 0.87), and for current versus former smokers (0.81 vs 0.91). By tumor histology, mortality RRs were 0.75 for adenocarcinoma, 0.71 for all non-small cell lung cancers except squamous, 1.23 for squamous cell carcinoma, and 0.90 for small cell carcinoma. RRs were similar for men and women for nonsquamous non-small cell lung cancers (0.71 and 0.70, respectively); women were found to have lower RRs for small cell and squamous cell carcinoma.	2
15. Pinsky PF, Gierada DS, Hocking W, Patz EF Jr, Kramer BS. National Lung Screening Trial findings by age: Medicare-eligible versus under-65 population. <i>Ann Intern Med</i> . 161(9):627-33, 2014 Nov 04.	Observational-Dx	19 612 participants	To examine the results of the NLST (National Lung Screening Trial) low-dose computed tomography (LDCT) group by age (Medicare-eligible vs. <65 years).	he aggregate false-positive rate was higher in the 65+ cohort than in the under-65 cohort (27.7% vs. 22.0%; P < 0.001). Invasive diagnostic procedures after false-positive screening results were modestly more frequent in the older cohort (3.3% vs. 2.7%; P = 0.039). Complications from invasive procedures were low in both groups (9.8% in the under-65 cohort vs. 8.5% in the 65+ cohort). Prevalence and positive predictive value (PPV) were higher in the 65+ cohort (PPV, 4.9% vs. 3.0%). Resection rates for screen-detected cancer were similar (75.6% in the under-65 cohort vs. 73.2% in the 65+ cohort). Five-year all-cause survival was lower in the 65+ cohort (55.1% vs. 64.1%; P = 0.018).	3

Lung Cancer Screening
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16. Tanner NT, Kanodra NM, Gebregziabher M, et al. The Association between Smoking Abstinence and Mortality in the National Lung Screening Trial. Am J Respir Crit Care Med. 193(5):534-41, 2016 Mar 01.	Observational-Dx	50,263 participants	To quantify the effects of smoking history and abstinence on mortality in high-risk individuals who participated in the NLST (National Lung Screening Trial).	Measurements included self-reported demographics, medical and smoking history, and lung cancer-specific and all-cause mortality. Cox regression was used to study the association of mortality with smoking status and pack-years. Kaplan-Meier survival curves were examined for differences in survival based on trial arm and smoking status. Current smokers had an increased lung cancer-specific (hazard ratio [HR], 2.14-2.29) and all-cause mortality (HR, 1.79-1.85) compared with former smokers irrespective of screening arm. Former smokers in the control arm abstinent for 7 years had a 20% mortality reduction comparable with the benefit reported with low-dose computed tomography (LDCT) screening in the NLST. The maximum benefit was seen with the combination of smoking abstinence at 15 years and LDCT screening, which resulted in a 38% reduction in lung cancer-specific mortality (HR, 0.62; 95% confidence interval, 0.51-0.76).	3

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17. Infante M, Cavuto S, Lutman FR, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. <i>Am J Respir Crit Care Med.</i> 180(5):445-53, 2009 Sep 01.	Observational-Dx	2,811 subjects	To explore the effect of screening with low-dose spiral computed tomography (LDCT) on lung cancer mortality. Secondary endpoints are incidence, stage at diagnosis, and resectability.	A total of 2,811 subjects were randomized and 2,472 were enrolled (LDCT, 1,276; control, 1,196). After a median follow-up of 33 months, lung cancer was detected in 60 (4.7%) patients receiving LDCT and 34 (2.8%) control subjects (P = 0.016). Resectability rates were similar in both groups. More patients with stage I disease were detected by LDCT (54 vs. 34%; P = 0.06) and fewer cases were detected in the screening arm due to intercurrent symptoms. However, the number of advanced lung cancer cases was the same as in the control arm. Twenty patients in the LDCT group (1.6%) and 20 controls (1.7%) died of lung cancer, whereas 26 and 25 died of other causes, respectively.	2
18. Infante M, Cavuto S, Lutman FR, et al. Long-Term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with Spiral Computed Tomography. <i>Am J Respir Crit Care Med.</i> 191(10):1166-75, 2015 May 15.	Observational-Dx	1,264 subjects	To explore the effect of low-dose spiral computed tomography (LDCT) screening on lung cancer mortality compared with no screening. Secondary endpoints included incidence, stage, and resectability rates.	A total of 1,264 subjects were enrolled in the LDCT arm and 1,186 in the control arm. Their median age was 64.0 years (interquartile range, 5), and median smoking exposure was 45.0 pack-years. The median follow-up was 8.35 years. One hundred four patients (8.23%) were diagnosed with lung cancer in the screening arm (66 by CT), 47 of whom (3.71%) had stage I disease; 72 control patients (6.07%) were diagnosed with lung cancer, with 16 (1.35%) being stage I cases. Lung cancer mortality was 543 per 100,000 person-years (95% confidence interval, 413-700) in the LDCT arm versus 544 per 100,000 person-years (95% CI, 410-709) in the control arm (hazard ratio, 0.993; 95% confidence interval, 0.688-1.433).	2

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EVIDENCE TABLE**

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19. Infante M, Chiesa G, Solomon D, et al. Surgical procedures in the DANTE trial, a randomized study of lung cancer early detection with spiral computed tomography: comparative analysis in the screening and control arm. <i>J Thorac Oncol.</i> 6(2):327-35, 2011 Feb.	Observational-Dx	72 patients	To summarize the surgical management experience in the setting of a randomized trial of lung cancer early detection with spiral computed tomography (CT) and discuss results in the screening and the control arm in the light of available data from other current screening trials.	In the low-dose spiral computed tomography (LDCT) arm, 77 suspicious lesions were surgically managed in 72 patients. A benign lesion was diagnosed in 17 cases (22%). Major video-assisted thoracoscopic surgery resection was carried out in five lung cancer cases (7%) and segmentectomy in 11 (19%). Complete resection was achieved in 93%, and stage I rate was 73%. Two patients had a local recurrence after open lobectomy, and three had a resectable new primary. In the control group, 28 patients underwent 31 surgical procedures, in five cases (16%) for benign lesions. No major video-assisted thoracoscopic surgery resections were carried out. Resectability rate was 88%, and stage I rate was 52%. Five patients had a local recurrence and two had a second primary.	2
20. Infante M, Lutman FR, Cavuto S, et al. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. <i>Lung Cancer.</i> 59(3):355-63, 2008 Mar.	Observational-Dx	2472 subjects	To present the baseline results of a randomized trial comparing screening for lung cancer with annual spiral computed tomography (CT) versus a yearly clinical review.	2472 subjects were randomized (1276 spiral CT arm, 1196 controls). Age, smoking exposure and co-morbid conditions were similar in the two groups. In the spiral CT group, 28 lung cancers were detected, 13 of which were visible in the baseline chest X-rays (overall prevalence 2.2%). Sixteen out of 28 tumours (57%) were stage I, and 19 (68%) were resectable. In the control group, eight cases were detected by the baseline chest X-rays (prevalence rate 0.67%), four (50%) were stage I, and six (75%) were resectable.	2

Lung Cancer Screening
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21. Goffin JR, Flanagan WM, Miller AB, et al. Cost-effectiveness of Lung Cancer Screening in Canada. JAMA Oncol. 1(6):807-13, 2015 Sep.	Review/Other-Dx	24700 patients	To assess the cost-effectiveness of low-dose computed tomographic (LDCT) scans scan screening for lung cancer within the Canadian health care system.	Compared with no screening, the reference scenario saved 51,000 quality-adjusted life-years (QALY) and had an incremental cost-effectiveness ratio of CaD \$52,000/QALY. If smoking history is modeled for 20 or 40 pack-years, incremental cost-effectiveness ratios of CaD \$62,000 and CaD \$43,000/QALY, respectively, were generated. Changes in participation rates altered life years saved but not the incremental cost-effectiveness ratio, while the incremental cost-effectiveness ratio is sensitive to changes in adherence. An adjunct smoking cessation program improving the quit rate by 22.5% improves the incremental cost-effectiveness ratio to CaD \$24,000/QALY.	4
22. Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. J Thorac Oncol. 4(5):608-14, 2009 May.	Observational-Dx	179 persons	To present the design and results from the prevalence round of the randomized Danish Lung Cancer Screening Trial (DLCST).	At baseline 179 persons showed noncalcified nodules larger than 5 mm, and most were rescanned after 3 months: The rate of false-positive diagnoses was 7.9%, and 17 individuals (0.8%) turned out to have lung cancer. Ten of these had stage I disease. Eleven of 17 lung cancers at baseline were treated surgically, eight of these by video assisted thoracic surgery resection.	3

Lung Cancer Screening
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23. Saghir Z, Dirksen A, Ashraf H, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. <i>Thorax</i> . 67(4):296-301, 2012 Apr.	Observational-Dx	69 lung cancers	To report lung cancer specific mortality and all-cause mortality at the end of the 4-year screening period.	Participation rates were high in both groups (screening: 95.5%; control: 93.0%; $p < 0.001$). Lung cancer detection rate was 0.83% at baseline and mean annual detection rate was 0.67% at incidence rounds ($p = 0.535$). More lung cancers were diagnosed in the screening group (69 vs. 24, $p < 0.001$), and more were low stage (48 vs 21 stage I-IIb non-small cell lung cancer (NSCLC) and limited stage small cell lung cancer (SCLC), $p = 0.002$), whereas frequencies of high-stage lung cancer were the same (21 vs 16 stage IIIA-IV NSCLC and extensive stage SCLC, $p = 0.509$). At the end of screening, 61 patients died in the screening group and 42 in the control group ($p = 0.059$). 15 and 11 died of lung cancer, respectively ($p = 0.428$).	3

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<p>24. Wille MM, Dirksen A, Ashraf H, et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. <i>Am J Respir Crit Care Med.</i> 193(5):542-51, 2016 Mar 01.</p>	<p>Observational-Dx</p>	<p>4,104 participants</p>	<p>To explore the effect of computed tomography (CT) screening.</p>	<p>Follow-up information regarding date and cause of death, lung cancer diagnosis, cancer stage, and histology was obtained from national registries. No differences between the two groups in lung cancer mortality (hazard ratio, 1.03; 95% confidence interval, 0.66-1.6; P = 0.888) or all-cause mortality (hazard ratio, 1.02; 95% confidence interval, 0.82-1.27; P = 0.867) were observed. More cancers were found in the screening group than in the no-screening group (100 vs. 53, respectively; P < 0.001), particularly adenocarcinomas (58 vs. 18, respectively; P < 0.001). More early-stage cancers (stages I and II, 54 vs. 10, respectively; P < 0.001) and stage IIIa cancers (15 vs. 3, respectively; P = 0.009) were found in the screening group than in the control group. Stage IV cancers were nonsignificantly more frequent in the control group than in the screening group (32 vs. 23, respectively; P = 0.278). For the highest-stage cancers (T4N3M1, 21 vs. 8, respectively; P = 0.025), this difference was statistically significant, indicating an absolute stage shift. Older participants, those with chronic obstructive pulmonary disease, and those with more than 35 pack-years of smoking had a significantly increased risk of death due to lung cancer, with nonsignificantly fewer deaths in the screening group</p>	<p>3</p>

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<p>25. Horeweg N, Scholten ET, de Jong PA, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. <i>Lancet Oncol.</i> 15(12):1342-50, 2014 Nov.</p>	<p>Observational-Dx</p>	<p>15,822 participants</p>	<p>To assess the effect of screening with increasing screening intervals on lung cancer mortality.</p>	<p>15,822 participants were enrolled in the NELSON trial, of whom 7915 were assigned to low-dose CT screening with increasing interval between screens, and 7907 to no screening. We included 7155 participants in our study, with median follow-up of 8.16 years (IQR 7.56-8.56). 187 (3%) of 7155 screened participants were diagnosed with 196 screen-detected lung cancers, and another 34 (<1%; 19 [56%] in the first year after screening, and 15 [44%] in the second year after screening) were diagnosed with 35 interval cancers. For the three screening rounds combined, with a 2-year follow-up, sensitivity was 84.6% (95% CI 79.6-89.2), specificity was 98.6% (95% CI 98.5-98.8), positive predictive value was 40.4% (95% CI 35.9-44.7), and negative predictive value was 99.8% (95% CI 99.8-99.9). Retrospective assessment of the last screening CT and clinical CT in 34 patients with interval cancer showed that interval cancers were not visible in 12 (35%) cases. In the remaining cases, cancers were visible when retrospectively assessed, but were not diagnosed because of radiological detection and interpretation errors (17 [50%]), misclassification by the protocol (two [6%]), participant non-compliance (two [6%]), and non-adherence to protocol (one [3%]). Compared with screen-detected cancers, interval cancers were diagnosed at more advanced stages (29 [83%] of 35 interval cancers vs 44 [22%] of 196 screen-detected cancers diagnosed in stage III or IV; p<0.0001), were more often small-cell carcinomas (seven [20%] vs eight [4%]; p=0.003) and less often adenocarcinomas (nine [26%] vs 102 [52%]; p=0.005).</p>	<p>3</p>

**Lung Cancer Screening
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
26. Horeweg N, van der Aalst CM, Thunnissen E, et al. Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial. <i>Am J Respir Crit Care Med.</i> 187(8):848-54, 2013 Apr 15.	Observational-Dx	200 participants	To determine the effect of stringent referral criteria and increasing screening interval on the characteristics of screen-detected lung cancers, and to compare this across screening rounds, between sexes, and with other screening trials.	In the first three screening rounds, 200 participants were diagnosed with 209 lung cancers. Of these lung cancers, 70.8% were diagnosed at stage I and 8.1% at stage IIIB-IV, and 51.2% were adenocarcinomas. There was no significant difference in cancer stage, histology, or tumor localization across the screening rounds. Women were diagnosed at a significantly more favorable cancer stage than men. Compared with other trials, the screen-detected lung cancers of the NELSON trial were relatively more often diagnosed at stage I and less often at stage IIIB-IV.	3
27. Nawa T, Nakagawa T, Mizoue T, et al. A decrease in lung cancer mortality following the introduction of low-dose chest CT screening in Hitachi, Japan. <i>Lung Cancer.</i> 78(3):225-8, 2012 Dec.	Review/Other-Dx	N/A	To report the trend of lung cancer mortality among Hitachi citizens in relation to the timing of screening implementation.	Results suggest that wide implementation of low-dose chest computed tomography (CT) screening may decrease lung cancer mortality in the community 4-8 years after introduction of the screening.	4
28. Oudkerk M, Heuvelmans MA. Screening for lung cancer by imaging: the Nelson study. <i>JBR-BTR.</i> 96(3):163-6, 2013 May-Jun.	Review/Other-Dx	N/A	To review the detection rate, morbidity, mortality, recall rate, and cost-effectiveness of lung cancer screening, compared to other approaches.	Mortality results are still pending, but the knowledge already gained in the NELSON trial and its side-studies provide valuable information in the field of screening for lung cancer.	4

**Lung Cancer Screening
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
29. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). Int J Cancer. 120(4):868-74, 2007 Feb 15.	Review/Other-Dx	335,441 subjects	To describe a method to come to an optimum selection and recruitment of the eligible population for a lung cancer screening trial, taking into account available resources and screening capacity and the influence that selection criteria have on the estimated lung cancer mortality and the power of such a trial.	Selection criteria were chosen so that the required response among eligible subjects to reach sufficient sample size was minimised and the required sample size was within our capacity. Inviting current and former smokers (quit \leq 10 years ago) who smoked >15 cigarettes/day during >25 years or >10 cigarettes/day during >30 years was most optimal. With a power of 80%, 17,300-27,900 participants are needed to show a 20-25% lung cancer mortality reduction 10 years after randomisation. Until October 18, 2005 11,103 (first recruitment round) and 4,325 (second recruitment round) (total = 15,428) participants have been randomised. Selecting participants for lung cancer screening trials based on risk estimates is feasible and helpful to minimize sample size and costs. When pooling with Danish trial data (n = +/-4,000) NELSON is the only trial without screening in controls that is expected to have 80% power to show a lung cancer mortality reduction of at least 25% 10 years after randomisation.	4

Lung Cancer Screening
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Van't Westeinde SC, Horeweg N, De Leyn P, et al. Complications following lung surgery in the Dutch-Belgian randomized lung cancer screening trial. <i>Eur J Cardiothorac Surg.</i> 42(3):420-9, 2012 Sep.	Observational-Dx	198 subjects	To assess the complication rate in participants of the screen arm of the NELSON lung cancer screening trial who underwent surgical resection and to investigate, based on a literature review, whether the complication rate, length of hospital stay, re-thoracotomy and mortality rates after a surgical procedure were different from those of the non-screening series, taking co-morbidity into account.	In total, 182 thoracotomies, 5 thoracotomies after video-assisted thoracoscopic surgery (VATS) and 11 VATS procedures were performed. In these patients, 36% had chronic obstructive lung disease, 16% coronary artery disease, 14% diabetes mellitus and 11% peripheral vascular disease. Following thoracotomy, 47% (88/187) had ≥ 1 minor (7-57% in literature) and 10% (18/187) ≥ 1 major complication (2-26% in literature); following VATS, 38% (6/16) had ≥ 1 minor complication, but no major complications. Seventeen per cent (3/18) of major complications and 21% (20/96) of minor complications were seen in subjects operated for benign disease. The re-thoracotomy rate was 3% and there was no 30-day mortality after thoracotomy or VATS (0-8.3% in literature). The mortality rate of 0% after surgical procedures is low when compared with the non-screening series (0-8.3%); the rate of complications (53%) is within range when compared with the non-screening series (8.5-58%).	2

**Lung Cancer Screening
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Wattson DA, Hunink MG, DiPiro PJ, et al. Low-dose chest computed tomography for lung cancer screening among Hodgkin lymphoma survivors: a cost-effectiveness analysis. <i>Int J Radiat Oncol Biol Phys.</i> 90(2):344-53, 2014 Oct 01.	Review/Other-Dx	N/A	To estimate the merits of annual low-dose computed tomography (LDCT) screening among Hodgkin lymphoma (HL) survivors.	Annual low-dose computed tomography (LDCT) screening was cost effective for all smokers. A male smoker treated with mantle RT at age 25 achieved maximum quality-adjusted life year (QALY) by initiating screening 12 years post-HL, with a life expectancy benefit of 2.1 months and an incremental cost of \$34,841/QALY. Among nonsmokers, annual screening produced a QALY benefit in some cases, but the incremental cost was not below the WTP threshold for any patient subsets. As age at HL diagnosis increased, earlier initiation of screening improved outcomes. Sensitivity analyses revealed that the model was most sensitive to the lung cancer incidence and mortality rates and expected stage-shift from screening.	4
32. Yousaf-Khan U, Horeweg N, van der Aalst C, Ten Haaf K, Oudkerk M, de Koning H. Baseline Characteristics and Mortality Outcomes of Control Group Participants and Eligible Non-Responders in the NELSON Lung Cancer Screening Study. <i>J Thorac Oncol.</i> 10(5):747-53, 2015 May.	Observational-Dx	7453 persons	To investigate the generalizability of the NELSON lung cancer screening trial to the Dutch population.	Participants had better self-reported health ($p = 0.02$), were younger, more physically active, higher educated, and more often former smokers compared with eligible nonresponders (all $p < 0.001$). No differences were seen in self-reported outcomes of pulmonary tests, history of lung cancer, and smoked pack-years. Mortality due to all-causes ($p < 0.001$) and mortality classification separately was lower among participants. However, the proportion of subjects death due to cancer was higher among participants (62.4% vs. 54.9%).	3

**Lung Cancer Screening
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
33. Chien CR, Liang JA, Chen JH, et al. [(18)F]Fluorodeoxyglucose-positron emission tomography screening for lung cancer: a systematic review and meta-analysis. [Review]. Cancer Imaging. 13(4):458-65, 2013 Dec 14.	Meta-analysis	12 studies	To describe the role of positron emission tomography (PET) in lung cancer screening.	Among the identified studies (n = 3497), 12 studies were included for analysis. None of the studies evaluated the efficacy of primary PET screening specific to lung cancer. Eight studies focused on primary PET screening for all types of cancer; the detection rates of lung cancer were low. Four studies reported evidence of lung cancer screening programs with selective PET, in which the estimated pooled sensitivity and specificity was 83% and 91%, respectively.	Good
34. Minamimoto R, Senda M, Jinnouchi S, et al. Detection of lung cancer by FDG-PET cancer screening program: a nationwide Japanese survey. Anticancer Res. 34(1):183-9, 2014 Jan.	Observational-Dx	854 cases	To analyze the lung cancer detection rate in asymptomatic individuals by the Fluorine-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) cancer screening program in Japan.	Among the 854 cases, 319 were verified as lung cancer. The relative sensitivity and positive predictive value (PPV) of FDG-PET were 86.5% and 38.9% for lung cancer, respectively. The sensitivity of PET/computed tomography (CT) scanner was higher than that of dedicated PET (100.0% vs. 63.2%), indicating that CT imaging was effective for lung cancer screening. The majority of lung carcinomas detected by FDG-PET screening were UICC stage IA or IB, but detection of smaller or less invasive carcinomas was limited.	3

**Lung Cancer Screening
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Hocking WG, Hu P, Oken MM, et al. Lung cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. J Natl Cancer Inst. 102(10):722-31, 2010 May 19.	Observational-Dx	77 464 participants	To determine whether screening would reduce mortality rates from Prostate, Lung, Colorectal, and Ovarian (PLCO) cancers.	Compliance with screening decreased from 86.6% at baseline to 78.9% at the last screening. Overall positivity rates were 8.9% at baseline and 6.6%-7.1% at subsequent screenings; positivity rates increased modestly with smoking risk categories (P(trend) < .001). The PPVs for all participants were 2.0% at baseline and 1.1%, 1.5%, and 2.4% at years 1, 2, and 3, respectively; PPVs in current smokers were 5.9% at baseline and 3.3%, 4.2%, and 5.6% at years 1, 2, and 3, respectively. A total of 564 lung cancers were diagnosed, of which 306 (54%) were screen-detected cancers and 87% were non-small cell lung cancers. Among non-small cell lung cancers, 59.6% of screen-detected cancers and 33.3% of interval cancers were early (I-II) stage.	2
36. Hocking WG, Tammemagi MC, Commins J, et al. Diagnostic evaluation following a positive lung screening chest radiograph in the Prostate, Lung, Colorectal, Ovarian (PLCO) Cancer Screening Trial. Lung Cancer. 82(2):238-44, 2013 Nov.	Observational-Dx	308 patients	To evaluate the diagnostic approach following a positive lung screening examination in Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO).	Of 308 screen-detected cancers, the diagnosis was established by thoracotomy/thoracoscopy in 47.7%, needle biopsy in 27.6%, bronchoscopy in 20.1% and mediastinoscopy in 2.9%. Eighty-four percent of screen-detected lung cancers were diagnosed within 6 months. Diagnostic evaluations following a positive screen were conducted in a timely fashion. Lung cancer was diagnosed by tissue biopsy or cytology in all cases. Lung cancer was excluded during evaluation of positive screening examinations by clinical or radiographic evaluation in all but 1.4% who required a tissue biopsy.	3

**Lung Cancer Screening
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA. 306(17):1865-73, 2011 Nov 02.	Experimental-Dx	154,901 participants	To evaluate the effect on mortality of screening for lung cancer using radiographs in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.	Screening adherence was 86.6% at baseline and 79% to 84% at years 1 through 3; the rate of screening use in the usual care group was 11%. Cumulative lung cancer incidence rates through 13 years of follow-up were 20.1 per 10,000 person-years in the intervention group and 19.2 per 10,000 person-years in the usual care group (rate ratio; 1.05, 95% CI, 0.98–1.12). A total of 1,213 lung cancer deaths were observed in the intervention group compared with 1,230 in usual care group through 13 years (mortality rate ratio, 0.99; 95% CI, 0.87–1.22). Stage and histology were similar between the 2 groups. The rate ratio of mortality for the subset of participants eligible for the NLST, over the same 6-year follow-up period, was 0.94 (95% CI, 0.81–1.10).	1
38. Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR. Lung cancer screening: the Mayo program. J Occup Med. 28(8):746-50, 1986 Aug.	Review/Other-Dx	N/A	To review the lung cancer screening.	Results of the three trials suggest that sputum cytology alone detects 15% to 20% of lung cancers, almost all of which are squamous cancers with a favorable prognosis; and chest roentgenography may be a more effective test for early-stage lung cancer than previous reports have suggested. Nevertheless, results of the randomized trial conducted at the Mayo Clinic showed that offering both procedures to high-risk outpatients every 4 months conferred no mortality advantage over standard medical practice that included recommended annual testing	4

**Lung Cancer Screening
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
<p>39. Melamed MR, Flehinger BJ, Zaman MB, Heelan RT, Perchick WA, Martini N. Screening for early lung cancer. Results of the Memorial Sloan-Kettering study in New York. Chest. 86(1):44-53, 1984 Jul.</p>	<p>Observational-Dx</p>	<p>10,040 subjects</p>	<p>To review the Screening for early lung cancer</p>	<p>Over 40 percent of the 288 who developed lung cancer were diagnosed in stage I, and their survival was 76 percent at five years; overall survival was 35 percent. Nearly one third of the lung cancers detected on first examination on the dual screen, and 14 percent of those on subsequent examinations were found by cytologic examination. The same number of cancers developed in the x-ray screen only group, and were diagnosed at a later date. Despite the delay, survival and mortality were the same, suggesting that the squamous carcinomas detected by cytologic examination alone are very slow growing and tend to remain localized until detectable by x-ray examination.</p>	<p>3</p>

**Lung Cancer Screening
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. . Screening (lung cancer). Chest. 89(4 Suppl):324S-326S, 1986 Apr.	Review/Ot her-Dx	53,454 people	To determine whether screening with low-dose computed tomography (CT) could reduce mortality from lung cancer.	The rate of adherence to screening was more than 90%. The rate of positive screening tests was 24.2% with low-dose CT and 6.9% with radiography over all three rounds. A total of 96.4% of the positive screening results in the low-dose CT group and 94.5% in the radiography group were false positive results. The incidence of lung cancer was 645 cases per 100,000 person-years (1060 cancers) in the low-dose CT group, as compared with 572 cases per 100,000 person-years (941 cancers) in the radiography group (rate ratio, 1.13; 95% confidence interval [CI], 1.03 to 1.23). There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; P=0.004). The rate of death from any cause was reduced in the low-dose CT group, as compared with the radiography group, by 6.7% (95% CI, 1.2 to 13.6; P=0.02).	4

**Lung Cancer Screening
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. Doria-Rose VP, Marcus PM, Szabo E, Tockman MS, Melamed MR, Prorok PC. Randomized controlled trials of the efficacy of lung cancer screening by sputum cytology revisited: a combined mortality analysis from the Johns Hopkins Lung Project and the Memorial Sloan-Kettering Lung Study. <i>Cancer</i> . 115(21):5007-17, 2009 Nov 01.	Observational-Dx	10,386 eligible subjects	To combine the data for the purpose of calculating 1 joint estimate of screening efficacy.	Over (1/2) of squamous cell lung cancers diagnosed in the dual-screen group were identified by cytology; these cancers tended to be more localized than squamous cancers diagnosed in the X-ray only arm. After 9 years of follow-up, lung cancer mortality was slightly lower in the dual-screen than in the X-ray only arm (rate ratio [RR], 0.88; 95% confidence interval [CI], 0.74-1.05). Reductions were seen for squamous cell cancer deaths (RR, 0.79; 95% CI, 0.54-1.14) and in the heaviest smokers (RR, 0.81; 95% CI, 0.67-1.00). There were also fewer deaths from large cell carcinoma in the dual-screen group, although the reason for this is unclear.	2
42. American College of Radiology. ACR Appropriateness Criteria® Radiation Dose Assessment Introduction. Available at: https://www.acr.org/-/media/ACR/Files/Appropriateness-Criteria/RadiationDoseAssessmentIntro.pdf .	Review/Other-Dx	N/A	Guidance document on exposure of patients to ionizing radiation.	No results stated in abstract.	4

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
 - a. The study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
 - b. The study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
 - c. The study is an expert opinion or consensus document.
- Meta-analysis
 - a. *Good quality* – the study design, methods, analysis, and results are valid and the conclusion is supported.
 - b. *Inadequate quality* – the study design, analysis, and results lack the methodological rigor to be considered a good meta-analysis study.

Abbreviations Key

Dx = Diagnostic

Tx = Treatment