| Bibliographic Cite | PMID Link | Literature Type | Level of Evidence | Purpose | Population | Intervention and Outcome Measures | Results/ Recommendations | Study Limitiations |
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| Hoffman RM, Atallah RP, Struble RD, Badgett RG. Lung cancer screening with low-dose CT: A meta-analysis. J Gen Intern Med. 2020; 35(10):3015-3025. | 32583338 | Meta-analysis | Moderate | To evaluate the association of LDCT lung cancer screening with early-stage cancer diagnoses, lung cancer mortality, overall mortality, and screening harms, including false positive results, complications from invasive procedures among subjects with false positive results, overdiagnsis, and significant incidental findings. | Included were randomized controlled trials of computed tomography (CT) that reported lung cancer and/or overall mortality data. Included were 9 studies that enrolled a total of 96,559 subjects. The mean and median age was around 60, 64.1% were male, 51.7% were current smokers, and the mean and median pack-years of smoking was usually about 40 or more. | After identification of studies, the authors abstracted data on study design features, stage I LC diagnoses, LC and overall mortality, false positive results, harm from invasive diagnostic procedures, overdiagnosis, and significant incidental findings. Study quality was assessed using the Cochrane risk-of-bias tool. Authors used random-effects models to calculate relative risks and assessed effect modulators with subgroup analyses and meta-regression. | The risk of bias across studies was judged to be low. Overall, LDCT screening significantly increased the detection of stage I LC, RR = 2.93 (95%CI, 2.16–3.98), I2 = 19%, and reduced LCmortality, RR = 0.84 (95% CI, 0.75–0.93), I2 = 0%. The number needed to screen to prevent an LC death was 265. Women had a lower risk of LC death (RR = 0.69, 95% CI, 0.40–1.21) than men (RR = 0.86, 95% CI, 0.66–1.13), p value for interaction = 0.11. LDCT screening did not reduce overall mortality, RR = 0.96 (95%CI, 0.91–1.01), I2 = 0%. The pooled false positive rate was 8%(95%CI, 4–18); subjects with false positive results had < 1 in 1000 risk of major complications following invasive diagnostic procedures. The most valid estimates for overdiagnosis and significant incidental findings were 8.9% and 7.5%, respectively. The authors conclude that LDCT screening significantly reduced LC mortality, though not overall mortality, with women appearing to benefit more than men. The estimated risks for false positive results, screening complications, overdiagnosis, and incidental findings were low. | Long-term mortality data were available only for studies conducted in Europe and North America, which may limit the generalizability of results based on screening just older, high-risk current or former smokers. Lung cancer incidence and mortality rates vary around the world, particularly in emerging economies and developing countries, related to differences in genetics, tobacco use, environmental exposures, and access to care. The Chinese AME trial enrolled substantial proportions of subjects whose lung cancer risk was defined as exposure to second-hand smoke, cooking oil fumes, or occupational carcinogens. Additionally, the observed efficacy of LDCT screening as conducted in randomized clinical trial settings may not translate into community practice. |
| Jonas DE, Reuland DS, Reddy SM, et al. Screening for lung cancer with low-dose computed tomography: Updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2021; 325(10):971-987. | 33687468 | Systematic review | High | To review the evidence on screening for lung cancer with low-dose computed tomography (LDCT) to inform the US Preventive Services Task Force (USPSTF). | English-language studies of adults aged 18 years or older conducted in countries categorized as "very high" on the Human Development Index, rated as fair or good quality, and published in or after 2001 were included. For all key questions (KQs), randomized clinical trials (RCTs) and nonrandomized controlled intervention studies were eligible. Cohort studies based on prospectively collected data that were intended to be used for evaluations relevant to this review were also eligible for KQs on harms of screening or workup (KQs 4 and 5) and treatment (KQs 6 and 7). | PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published through May 2019. Two investigators independently reviewed titles, abstracts, and full-text articles to determine eligibility using prespecified criteria. Disagreements were resolved by discussion and consensus. For each included study, 1 investigator extracted pertinent information about the populations, tests or treatments, comparators, outcomes, settings, and designs, and a second investigator reviewed this information for completeness and accuracy. Two independent investigators assessed the quality of studies using predefined criteria developed by the USPSTF. The overall strength of the evidence for each KQ was assessed as high, moderate, or low. | A total of 223 publications were included. Seven randomized clinical trials (RCTs) (N = 86 486) evaluated lung cancer screening with LDCT; the National Lung Screening Trial (NLST, N = 53 454) and Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON, N = 15 792) were the largest RCTs. The NLST found a reduction in lung cancer mortality (incidence rate ratio [IRR], 0.85 [95%CI, 0.75-0.96]; number needed to screen [NNS] to prevent 1 lung cancer death, 323 over 6.5 years of follow-up) with 3 rounds of annual LDCT screening compared with chest radiograph for high-risk current and former smokers aged 55 to 74 years. NELSON found a reduction in lung cancer mortality (IRR, 0.75 [95%CI, 0.61-0.90]; NNS to prevent 1 lung cancer death of 130 over 10 years of follow-up) with 4 rounds of LDCT screening with increasing intervals compared with no screening for high-risk current and former smokers aged 50 to 74 years. For every 1000 persons screened in the NLST, false positive results led to 17 invasive procedures (number needed to harm, 59) and fewer than 1 person having a major complication. Overdiagnosis estimates varied greatly (0% 67%chance that a lung cancer was overdiagnosed). Incidental findings were common, and estimates varied widely (4.4%-40.7%of persons screened). | This review has several limitations. First, non–English-language articles were excluded, as were studies with sample size less than 500 or 1000 for some KQs to focus on the best evidence. Doing so omitted some smaller studies that reported on harms of screening. Second, the KQ on risk prediction models was limited to how well risk prediction models perform vs current recommended risk factor–based criteria for lung cancer screening. KQ2 complements the decision analysis report by evaluating previously published studies that apply risk prediction models to cohorts or representative samples of the US population rather than simulated populations. Third, for accuracy, some included studies did not report accuracy metrics; rather, when sufficient data were reported, values were calculated from the study data. This approach introduces uncertainty and may account for variability. |
| Li Z, Huang Y, Song H, et al. The value of 18F-FDG-PET/CT in the diagnosis of solitary pulmonary nodules: A meta-analysis. Medicine (Baltimore). 2018; 97(12):e0130. | 29561412 | Meta-analysis | Low | To investigate the value of 18F-FDG-PET/CT in the diagnosis of malignant solitary pulmonary nodules (SPNs). | Included studies met the following criteria: patients with SPN were from outpatient or inpatient department; 18F-FDG-PET/CT imaging was performed in all patients; the number of patients and information about the sensitivity and specificity of 18F-FDG-PET/CT for the diagnosis of SPN was complete; there were clear diagnostic criteria and sizes of the nodule were provided; and the articles were written in English. Exclusion criteria included unpublished data, case reports, letters to the editor, abstracts, and review articles. | Two reviewers independently assessed study eligibility in accordance with the inclusion/exclusion criteria. Methodological quality of the studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist. Published data on sensitivity, specificity, and other measures of diagnostic accuracy were meta analyzed. Statistical analyses were undertaken using Meta-DiSc 1.4 software and Stata version 12.0. The measures of accuracy were pooled using random-effects models. Deeks' funnel plots were used to test for the potential presence of publication bias | A total of 20 publications reporting 21 studies were identified. Pooled results indicated that 18F-FDG PET/CT showed a diagnostic sensitivity of 0.89 (95% CI, 0.87–0.91) and a specificity of 0.70 (95% CI, 0.66–0.73). The positive likelihood ratio was 3.33 (95% CI, 2.35–4.71) and the negative likelihood ratio was 0.18 (95% CI, 0.13–0.25). The diagnostic odds ratio was 22.43 (95% CI, 12.55–40.07). Deeks test gave a P value of .26, suggesting that our analysis had no significant risk of publication bias. The authors conclude that 18F-FDG-PET/CT showed insufficient sensitivity and specificity for diagnosing malignant SPNs; it cannot replace the "gold standard" pathology by resection or percutaneous biopsy. Larger studies are required for further evaluation. | First, only studies identified in a few databases were included, possibly leading to the exclusion of high quality non-English research. Second, the SUVmax and size of the nodules in the studies were not exactly the same, leading to increased heterogeneity. In addition, other important factors contributed to the pooled result, such as past history and environmental exposure; these issues could not be precisely explained due to insufficient information. |

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| Liu H, Chen R, Tong C, Liang X. MRI versus CT for the detection of pulmonary nodules: A meta-analysis. Medicine (Baltimore). 2021; 100(42):e27270. | 34678861 | Meta-analysis | Low | To compare the diagnostic accuracy of MRI versus CT for detecting pulmonary nodules. | Studies were eligible for inclusion if the following criteria were met: patients with pulmonary lesions or with high risk of pulmonary nodules; patients with MRI and CT for detecting pulmonary nodules; and the study provided true positive, false positive, false negative, true negative for MRI, and CT diagnostic results. | A literature search was independently undertaken by 2 authors using a standardized approach to identify studies in which CT/MRI was used to diagnose pulmonary nodules. According to true positive, true negative, false negative, and false positive extracted from the included studies, authors calculated the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and area under the curve (AUC) using Stata version 14.0 software (STATA Corp, TX). Heterogeneity between studies was investigated by using the Q statistic. Deeks asymmetry tests for MRI and CT were calculated and presented as funnel plots. | A total of 8 studies involving a total of 653 individuals were included. The pooled sensitivity, specificity, PLR, NLR, and AUC were 0.91 (95% CI: 0.80–0.96), 0.76 (95%CI: 0.58–0.87), 3.72 (95%CI: 2.05–6.76), 0.12 (95%CI: 0.06–0.27), and 0.91 (95%CI: 0.88–0.93) for MRI respectively, while the pooled sensitivity, specificity, PLR, NLR, and AUC for CT were 1.00 (95% CI: 0.95–1.00), 0.99 (95%CI: 0.78–1.00), 79.35 (95%CI: 3.68–1711.06), 0.00 (95%CI: 0.00–0.06), and 1.00 (95%CI: 0.99–1.00), respectively. Further, authors compared the diagnostic accuracy of CT versus MRI and found that compared with MRI, CT shows statistically higher sensitivity (odds ratio [OR] for MRI vs CT: 0.91; 95%CI: 0.85–0.98; P value .010), specificity (OR: 0.82; 95%CI: 0.69–0.97; P value .019), PLR (OR: 0.29; 95%CI: 0.10–0.83; P value 0.02), AUC (OR: 0.91; 95%CI: 0.89–0.94; P value<.001), and lower NLR (OR: 8.72; 95%CI: 1.57–48.56; P value .013). The authors conclude that both CT and MRI have a high diagnostic accuracy in diagnosing pulmonary nodules, while CT was superior in sensitivity, specificity, PLR, NLR, and AUC. In terms of the currently available evidence, MRI could not replace CT in diagnosing pulmonary nodules. | The limitations of the study are as follows: the diagnostic performance based on size of pulmonary nodules of MRI versus CT were not calculated because most of the included studies did not report the diagnostic performance based on size of pulmonary nodules for MRI or CT; different diagnostic techniques in MRI and CT might affect the diagnostic accuracy for detecting pulmonary nodules; in a meta-analysis of published studies, publication bias is an inevitable problem; the meta-analysis is based on study level results but not original data of an individual patient, which restricted authors to present a more comprehensive result. Therefore, more future studies are required to prove these conclusions. |
| Martucci F, Pascale M, Valli MC, et al. Impact of 18F-FDG PET/CT in staging patients with small cell lung cancer: A systematic review and meta-analysis. Front Med (Lausanne). 2020; 6:336. | 32118000 | Systematic review and meta-analysis | Low | To provide quantitative data about the impact of 18F-FDG PET/CT in staging SCLC. | Inclusion criteria were studies or subsets of studies investigating the impact of 18F-FDG PET/CT in staging patients with SCLC histologically proved. The exclusion criteria were (a) articles outside the field of interest of this review (including articles evaluating the role of 18F-FDG PET/CT for treatment response assessment or restaging after treatment); (b) review articles, letters, comments, editorials, and conference proceedings; and (c) case reports or small case series. | Two authors performed a comprehensive literature search of three different bibliographic databases. Two researchers independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. The overall quality of the studies included in the systematic review and meta-analysis was performed using the revised “Quality Assessment of Diagnostic Accuracy Studies” tool. Pooled analyses were performed using a random-effects model. Publication bias was assessed through the Egger’s test | Nine articles including 721 patients with SCLC were included in the systematic review. Compared to conventional staging, a superior diagnostic accuracy of 18F-FDG PET/CT was found. A change of binary SCLC staging using 18F-FDG PET/CT was demonstrated in 15%(95%CI, 9–21%) of patients with SCLC. Currently, it is not clearly demonstrated that the use of 18F-FDG PET/CT for staging may improve the survival outcome of patients with SCLC. The authors conclude that 18F-FDG PET/CT is a useful molecular imaging method for staging patients with SCLC because it can change the management in a significant number of patients. More large prospective studies on the impact of 18F-FDG PET/CT in staging patients with SCLC are needed. | The first limitation is the low number of included studies on the impact of 18F-FDG PET/CT in staging SCLC. Another limitation is the heterogeneity among the included studies likely based on differences of patient characteristics, methodological aspects, and study quality. Based on the data reported in our systematic review, the authors suggest a need to perform more large multicentric and prospective studies on the impact of 18F-FDG PET/CT for SCLC staging to strengthen its role in this setting. |
| Passiglia F, Cinquini M, Bertolaccini L, et al. Benefits and harms of lung cancer screening by chest computed tomography: A systematic review and meta-analysis. J Clin Oncol. 2021; 39(23):2574-2585. | 34236916 | Systematic review and meta-analysis | Moderate | To combine and analyze randomized clinical trials comparing CT lung screening (CTLS) versus either no screening (NS) or chest x-ray (CXR) in subjects with cigarette smoking history, to provide a precise and reliable estimation of the benefits and harms associated with CTLS. | Authors included randomized controlled trials comparing CTLS with either NS or CXR in a high-risk population with a cigarette smoking history of at least 15 pack-years, including former smokers who had quit within the previous 15 years. | Subgroup analyses by comparator (NS or CXR) were performed. Pooled risk ratio (RR) and relative 95% Cis were calculated for dichotomous outcomes. The certainty of the evidence was assessed using the GRADE approach. The primary outcome was lung cancer–related mortality. Secondary outcomes assessed were any cause-related mortality, resectability rate, diagnosis of early-stage tumors, diagnosis of late-stage tumors, and overdiagnosis. Two authors independently assessed for risk of bias. | Nine eligible trials (88,497 patients) were included. Pooled analysis showed that CTLS is associated with: a significant reduction of lung cancer–related mortality (overall RR, 0.87; 95% CI, 0.78 to 0.98; NS RR, 0.80; 95% CI, 0.69 to 0.92); a significant increase of early-stage tumors diagnosis (overall RR, 2.84; 95% CI 1.76 to 4.58; NS RR, 3.33; 95% CI, 2.27 to 4.89; CXR RR, 1.52; 95% CI, 1.04 to 2.23); a significant decrease of late-stage tumors diagnosis (overall RR, 0.75; 95% CI, 0.68 to 0.83; NS RR, 0.67; 95% CI, 0.56 to 0.80); a significant increase of resectability rate (NS RR, 2.57; 95% CI, 1.76 to 3.74); a nonsignificant reduction of all-cause mortality (overall RR, 0.99; 95% CI, 0.94 to 1.05); and a significant increase of overdiagnosis rate (NS, 38%; 95% CI, 14 to 63). The analysis of lung cancer–related mortality by sex revealed nonsignificant differences between men and women (P = .21; I-squared = 33.6%). The authors conclude that, despite there still being uncertainty about overdiagnosis estimate, this meta-analysis suggested that the CTLS benefits outweigh harms, in subjects with cigarette smoking history, ultimately supporting the systematic implementation of lung cancer screening worldwide. | The main limitation of the analysis includes the lack of blinding for the majority of included studies, which may have increased the risk of potential detection bias. Also of note is the heterogeneity of included trials and population, in terms of eligibility criteria and follow-up duration, as well as the differences regarding nodule evaluation methods and screening positivity criteria or intervals. Finally, as partially discussed above, the lack of extended follow-up data regarding yearly screening and overdiagnosis rate among the majority of included studies may have negatively conditioned the results of the analysis, likely leading to an underestimation of benefits along with an overestimation of harms associated with the CTLS. |

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| Sadate A, Occean BV, Beregi JP, et al. Systematic review and meta-analysis on the impact of lung cancer screening by low-dose computed tomography. Eur J Cancer. 2020; 134:107-114. | 32502939 | Systematic review and meta-analysis | Moderate | To evaluate the efficacy of screening by LDCT compared with any other intervention in populations who reported tobacco consumption for more than 15 years on lung cancer and overall mortality. | Inclusion criteria for the systematic review and meta-analysis were topics about lung cancer screening, RCT study design, LDCT compared with any other intervention, population who reported an average smoking history over 15 pack-years (corresponding to the lowest criteria of the European RCTs on lung cancer screening) and the report of data on all-cause mortality or lung cancer-specific mortality. | The search was made using the Medline and Cochrane Library databases. Two double-blind reviewers selected the publications by screening the titles and abstracts first and then on the full-text articles. Discrepancies were resolved by consensus between the two readers. The critical appraisal of each eligible RCT was made by two reviewers using a CONSORT checklist. The extraction of the data for the meta analysis was made independently by two double-blind reviewers. Results on all-causes and lung cancer- specific mortality of the studies included were combined for meta- analysis. Possible publication biases were explored through visual analysis of funnel plots. | A total of 7 RCTs were included. The symmetric distribution of the relative risk across the global effect paired with the standard deviation of the screening effect confirmed the studies included did not present major biases. A total of 84,558 participants were included in the meta-analysis. There was no heterogeneity in the data (I2 = 0%, tau2 = 0, p Z =.67). A relative reduction of overall mortality of 4% was observed in the experimental screening group versus control group (risk ratio [RR] = 0.96, 95% CI: 0.92-1.00). Concerning lung cancer-specific mortality, a significant relative reduction of 17% was observed in the experimental screening group (RR = 0.83, 95% CI: 0.76-0.91). To prevent one lung cancer-related death, 294 patients needed to be screened. The authors conclude that, In populations highly exposed to tobacco, screening by LDCT reduces lung cancer mortality. | Limitations of our study include the partial heterogeneity of the protocols studied, in particular the interventions in the control arm, either prevention or clinical examination in all the studies except the NLST (annual CXR) and DANTE (CXR at inclusion) studies. Also, heterogeneity among studies concerning smoking history of patients was found to be much higher in the NLST study than in other RCTs included. |