Review Article

A narrative review of lung cancer screening: risks of lung cancer screening

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Abstract: Low-dose chest CT (LDCT) screening for lung cancer in high-risk individuals is the current standard of care in the United States and European countries. LDCT has been shown to reduce lung cancer mortality. However, potential "side effects" and "risks" of lung cancer screening should be concerned and weighed against its benefits. To provide a summary of the risk of lung cancer screening as performed with LDCT. The potential risks of LDCT screening are generally considered to be outweighed by the benefit of reducing the risk of lung cancer death in the high-risk population. The studies on harm of LDCT screening varied on definition of positive test and study protocol. However, using current nodule protocols guidelines defining positive nodule based on consistency, size, and round of screening with certain management protocol as Lung-RADS would have reduced in the false positive rate in baseline and subsequent rounds, prevented invasive procedures and complications associated with false positive exams and decreased the overdiagnosis rate. Currently, there are no epidemiological evidence supporting increased cancer incidence or mortality from radiation dose of the LDCT screening for lung cancer which below 100 mSv. While the risks are generally considered to be outweighed by the benefit of reducing the risk of lung cancer death in the screening-eligible population, it is important to understand these potential risks, especially given the requirements for shared decision making.

Keywords: Lung cancer; screening; early detection; low-dose chest CT (LDCT); harm; risk

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Introduction

Rationale and objective

Low-dose chest CT (LDCT) screening for lung cancer in high-risk individuals is the current standard of care in the United States and European countries. LDCT has been shown to reduce lung cancer mortality in multiple prospective randomized, controlled trials, including the National Lung Screening Trial (NLST) (1), Multi-centric Italian L Detection trial (MILD) (2), and Nederlands–Leuvens Longkanker screenings Onderzoek study (NELSON) (3). There remains, however, a concern that there are potential "side effects" and "risks" of lung cancer screening that should be weighed against its benefits, and these can be evaluated through the results of the same large trials as well as systematic and meta-analysis reviews. The U.S. Preventive Services Task Force (USPSTF) and others specifically recommend practitioners thoroughly discuss with their patients the benefits, limitations, and known and uncertain harms of screening with LDCT (4-6). We present

the following article in accordance with the narrative review checklist (available at: http://dx.doi.org/10.21037/ccts-2020-lcs-08).

Objective

This review is intended to provide a summary of available evidence regarding the risk of lung cancer screening as performed with LDCT.

Methods

We reviewed of the literature by collecting the information from authorship, meta-analysis, systematic analysis, and narrative overview retrieved from searches of computerized databases. One investigator reviewed the literature systematically using the search terms lung cancer, screening, early detection, low- dose CT, and review through August 2020 and additional hand searches of the references of retrieved literature with sources agreed on by co-authors. We included the review studies or articles that addressed at least one of the following risks of the LDCT screening for lung cancer: (I) false positive results, (II) harms of false positive evaluations, (III) false negative results or missed lung cancers, (IV) overdiagnosis, and (V) risks of radiation exposure.

Discussion

Potential risks of LDCT screening

Potential effects of LDCT that are considered risks primarily concern one of several categories: (I) false positive results leading to tests and invasive procedures considered unnecessary, (II) false negative results leading to missed cancers, (III) identification of indolent cancers leading to treatment of cancers that might not otherwise clinically warrant treatment and (IV) the impact of cumulative radiation exposure on other cancer risk. While these risks are generally considered to be outweighed by the benefit of reducing the risk of lung cancer death in the screening-eligible population, it is important to understand these categories, especially given the requirements for shared decision making. We will discuss the specific evidence for each of these risks and summary the risks from systemic reviews and meta-analyses in *Table 1*.

False positives exams

False positive exams are defined as any CT finding precipitating additional evaluation that does not result in the diagnosis of cancer. The false positive rate is calculated by dividing the number of false positives by the number of individuals screened with LDCT. Reported false positive rates vary among studies in the literature, ranging from 0.6% to 96% among systematic reviews and meta-analyses (7-10,13,14). This variability is largely due to differences in the definition of a positive exam. For example, a trial in which the cut-off for nodule size considered positive is smaller would result in a higher rate of positive screens, and ultimately false positives, as the absolute number of lung cancers would not change compared to a trial with a higher size cut-off. Additional variability results from differences in screening protocols (e.g., the number of screening rounds and intervals), scan slice thickness (as smaller slice thicknesses will detect more nodules), lung cancer risk of trial participants (false positive proportion has been shown to be higher with increased age, pack-years and concomitant chronic obstructive pulmonary disease), prevalence of granulomatous disease (leading to increased prevalence of benign disease among study populations), and whether the analysis reflects baseline or follow-up rounds of imaging (6,7,14,16,17).

In a collaboration among the American Cancer Society (ACS), the American College of Chest Physicians (ACCP), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN), Bach and colleagues (7) summarized literature from 1996–2012 to form the basis for the clinical practice guideline of the ACCP and ASCO. The average nodule detection rate per round of screening was 20%, but varied from 3–30% in RCTs and 5–51% in cohort studies. Most studies reported that >90% of nodules were benign. Based on this review, the National Cancer Institute (NCI) (16) described a median false positive rate of 20.5% (range, 1–49%) on baseline screens and 9.5% (range, 1–42%) on follow-up screens. False positive rates are generally lower on post-baseline screens because a nodule's growth rate can be assessed when there is a previous screen available, and stable nodules are often denoted as negative screens in subsequent rounds.

Humphrey *et al.* (8) summarized 63 papers including 7 RCTS (1,18-23) in an updated review of lung cancer screening for the USPSTF in 2013, focusing on

Table 1 Summary of systematic reviews and meta-analyses on harm of LDCT for lung cancer screening

Author	Published year	Study year	Studies included	Radiation exposure (mSv/scan)	Overdiagnosis, %	False positive, %, (range)			Invasive procedure following a false positive result	Major complications from invasive work up		Death after invasive procedures	
						Overall	Baseline	Follow-up		Overall	With benign result	Overall	With benign result
Bach (7)	2012	1996–2012	20 (7 RCT)	NLST:1.5, (~8 mSv/participant over 3 years)	Cannot yet be estimated	N/A	20.5 (range, 1–49)	9.5 (range, 1–42)	N/A	LDCT: 1.5/10,000; CXR: 0.7/10,000 (1 study: NLST)	Included noninvasive work up: LDCT - 0.36%, 4.5/10,000; CXR - 1.5/10,000 (1 study: NLST)	LDCT: 3.4/10,000; CXR: 2.2/10,000 (1 study: NLST)	Included noninvasive work up: LDCT - 0.06%, 4.1/10,000; CXR -1.1/10,000 (1 study: NLST)
Humphrey (8)	2013	2000–2012	63 (7 RCTs)	0.61–1.5 (4 studies)	Insufficient follow up to fully evaluate	N/A	79–96 (in cohort studies)	N/A	N/A	N/A	N/A	N/A	N/A
Usman Ali (9)	2016	Through 2015	31 for harm (13 RCTs for benefit)	N/A	10.99–25.83 (4 studies)	N/A	25.53 (7.90–26.23) (3 studies)	23.28 (0.64–69.0) (9 studies, multi rounds)	Minor procedure: 9.74 (95% CI: 4.34–15.15) per 1,000 screened; Major procedures: 5.28 (95% CI: 3.94–6.62) per 1,000 screened	52.03 (95% CI: 15.77–88.28) per 1,000 patients undergoing invasive procedures	N/A	11.18 deaths (95% CI: 5.07–17.28) per 1,000 patients undergoing invasive testing (7 studies)	N/A
Coureau (10)	2016	2003–2014	10 (Only RCT)	N/A	N/A	7–23% (overall)	N/A	N/A	Surgery, 9–32% of interventions	N/A	N/A	N/A	N/A
Fu (11)	2016	1994–2013	5 (Only RCT)	N/A	N/A	LDCT *vs*. control (OR 8.7, 95% CI: 7.43–10.19)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mazzone (6)	2018	Through 2017	59	N/A	N/A	N/A	N/A	N/A	Surgery: LDCT - 4.7 per 1,000 screened, CXR - 2.6 per 1,000 screened	LDCT: 0.8–3.1 per 1,000 screened (3.7–8.2% of procedures)	N/A	7.7 deaths per 1,000 patients undergoing invasive procedures	N/A
Huang (12)	2019	Through 2019	9 (Only RCT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Death (2 studies) - LDCT: 19/2129 (0.89%) invasive procedures; CXR 11/792 (1.4%) invasive procedures, RR 0.64 (95% CI: 0.30–1.33)	N/A
Hoffman (13)	2020	2011–2020	9 (Only RCT)	N/A	33 (6 studies)	8% (95% CI: 4–15)	N/A	N/A	17 in 1,000 subjects with a false positive LDCT	N/A	0.4 in 1,000	N/A	N/A
Jonas (14)	2020	2012–2019	223	0.65–2.36	0–67	N/A	Overall:7.9–49.3; RCTs: 7.9–26.9; Cohort: 9.6–49.3	Overall: 0.6–28.6; RCTs: 0.6–27.2; Cohort: 5.0–28.6	Needle biopsy 0.09–0.56%; Surgery 0.5–1.3%; Surgical resection 0.1–0.5% of all screened	N/A	Needle biopsy 0.03–0.07% of all screened	N/A	N/A
Brodersen (15)	2020	No restrictions	5 (Only RCT)	N/A	Overall: 38% (95% CI: 14–63%); Sensitivity analysis: 49% (95% CI: 11–87%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

LDCT, low-dose computed tomography; CXR, chest X-ray; NLST, National Lung Screening Trial; RCT, randomized control trial; RR, risk ratio; T0, baseline round; Tfu, follow up round, N/A, not applicable.

effectiveness as well as potential risks and harms. The number of positive examinations on baseline screens ranged from 9.2–39% in the RCTs and 9.8–51% in the cohort studies (24-27), with most in the 10–20% range. The positive predictive value (PPV) for an abnormal baseline finding showing cancer ranged from 2.2–36% in the RCTs. Among the cohort studies, the PPV of abnormal baseline scans requiring further evaluations ranged from 4–21%, such that 79–96% of positive baseline scans did not result in a diagnosis of cancer.

Ali and colleagues (9) evaluated evidence for the Canadian Task Force on Preventive Health Care (CTFPHC) lung cancer screening guidelines with a systematic review focused on benefits and harms of screening in average-to-high-risk adults for lung cancer using chest X-ray (CXR), sputum cytology (SC) and LDCT. Thirty-four studies were included, 13 RCTs for benefits and 31 studies for harms. There was a median false positive rate of 25.53% (range, 7.90–26.23%) for baseline screen/once-only screening (3 studies) and 23.28% (range, 0.64–69.0%) for multiple rounds (9 studies). In a similar effort for the French National Authority for Health, Coureau and colleagues (10) reviewed 10 RCTs on the effectiveness, acceptability and safety of lung cancer screening with LDCT in smokers. False positives among LDCTs ranged from 7% to 23%. Among positive screening LDCTs, 91–96% were false positives, corresponding to a positive predictive value between 4% and 9%.

In a formal meta-analysis, Fu *et al.* (11) investigated the effect of LDCT on screening for lung cancers in smokers over age 49 years in studies from 1994-2013. Five RCTs (DLCST, DANTE, Garg, ITALUNG, and LSS) showed that the odds of false positive for LDCT compared to CXR or usual care was 41.77 (95% CI: 5.18–336.95); although, there was significant heterogeneity in the data (chi^2=186.98, I^2=98%, P<0.001). In a more modern meta-analysis of 9 RCTs (96,559 patients) (13) conducted between January 2011 to April 2020, Hoffman demonstrated a pooled false positive rate of 8% (95% CI: 4–18%), with <1 in 1,000 risk of major complication following invasive diagnostic procedures performed in these false positive cases.

Currently, "the USPSTF Recommendation Statement on Lung Cancer Screening is being updated, but it and its supporting Evidence Review are still in draft form". Jonas *et al.* (14) evaluated LDCT in the U.S. primary care setting for the U.S. Preventive Services Task Force, summarizing 27 publications. The range of overall false positives was 7.9–49.3% for baseline screening and 0.6–28.6% for follow-up screens. For the RCTs, the false positive rates ranged from 7.9–26.9% for baseline screening, and 0.6–27.2% for incidence screening. For cohort studies, the rates ranged from 9.6–49.3% for baseline screening and 5.0–28.6% for follow-up screens. False positive rates generally decreased with each screening round.

The NLST classified CTs with at least one noncalcified nodule larger than 4 mm in greatest transverse dimension as positive and reported false positive rates of 26.3% at baseline and 27.2% and 15.9% for the two subsequent screening rounds, respectively (1). Patients age 65 years or older had false positives rate in baseline, 1st and 2nd subsequent rounds of 30.3%, 31.5%, 19.5%, respectively, all higher than the rates of 24.8%, 25.7% and 14.6%, respectively in younger patients (28). However, according to the NLST protocol nodules that remained unchanged at one year after discovery were still considered false positive until they were found to be stable for 2 years and were then considered to be benign, thus raising the rates of false positive exams for annual rounds compared to protocols that did not consider stable nodules at one year from discovery as false positives.

Further analyses have suggested that the false positive rate in the NLST would have been reduced by using a larger nodule size threshold (17,29-33) or by not rounding the size up to the nearest whole mm (34). The International Early Lung Cancer Action Program (I-ELCAP) investigators demonstrated the impact on false positive rates on baseline CT using increasing thresholds of 5.0, 6.0, 7.0, 8.0, and 9.0 mm for solid or part-solid noncalcified nodules in I-ELCAP (29) and NLST databases (30). Using 6 mm instead of 5 mm would decrease false positive rates from 15.5% to 9.7%, and from 14.4% to 9.2%, for I-ELCAP and NLST data, respectively, decreasing evaluations for positive results by 36%, and 33.8% in each dataset, respectively. These threshold increases would not have resulted in delays in the diagnosis of lung cancer as corresponding delays up to 9 months would have occurred in 0% and 0.9% cases for I-ELCAP and NLST, respectively (14,29,30). The I-ELCAP investigators also demonstrated that rounding size up to the nearest whole mm increased false positive rates up to 28.9% and 22.3% for baseline and repeat rounds, respectively in their database (34).

Other adjustments to the cut-off for a positive nodule based on consistency, size, and whether it is a baseline or subsequent screen can likewise impact false positive rates. For example, the Lung CT Screening Reporting and Data System (Lung-RADS) version 1.0 classification system

defined a positive baseline screen as a solid/part-solid nodule ≥6 mm or non-solid nodule ≥20 mm and a positive follow-up screen as a new solid nodule ≥4 mm, any size new part-solid nodule or a new non-solid nodule ≥20 mm. Using these criteria for the NLST population, Pinsky *et al.* (31) demonstrated reduction in the false positive rate in baseline rounds from 26.6% (95% CI: 26.1–27.1%) to 12.8% (95% CI: 12.4–13.2%) and in subsequent rounds from 21.8% (95% CI: 21.4–22.2%) to 5.3% (95% CI: 5.1–5.5%).

Harms of false positive evaluations

In addition to patient and provider anxiety over a positive finding, the potential physical harm of a false positive result manifests as result of the evaluation of a nodule found on LDCT. The rate of actual harm from evaluation of a positive finding varies in the literature depending on nodule management protocol, operator expertise, and comorbid conditions of the screening population included. Options for management of a positive screen include surveillance with serial CT, non-surgical biopsy, and surgical diagnosis. Each approach has advantages and disadvantages and the choice of strategy depends on the finding and risk of malignancy in an individual patient (pre-test probability) (35). The USPSTF draft (14) summarized current data (1,14,24,26,28,36-45) on the percentage of screening patients undergoing invasive testing for false positive exams. The percentage of all screened patients undergoing needle biopsy for a false positive result ranged from 0.09–0.56%. Complication rates from needle biopsy for false positives ranged from 0.03–0.07%. Surgical procedures and surgical resections for false positives were 0.5–1.3% and 0.1–0.5%, respectively, for all screened participants.

False positive results led to invasive procedures (needle biopsy, thoracotomy, thoracoscopy, mediastinoscopy, and/or bronchoscopy) in 1.7% of patients screened in the NLST. Complications occurred in 0.1% of those screened, with 0.03%, 0.05%, and 0.01% for major, intermediate, and minor complications, respectively (1). The risk of major complications following invasive procedures for a false positive in the NLST was 4.1 per 10,000 screening participants in the LDCT arm and 0.37 per 10,000 screening participants in the CXR arm (6). Patients 65 years or older had a higher rate of invasive procedures after false positives, 3.3% compared to 2.7% for younger patients (P=0.039) (28). Death within 60 days of the most invasive procedure performed occurred in 0.007% of those screened (1). The risk of death following invasive procedures for a false positive finding was 2.2 per 10,000 screening participants in the LDCT arm (6). As not all of these deaths were directly related to the procedures, this is the upper limit of risk of death. Moreover, using Lung-RADS criteria for the same data-set as described above would have prevented 23% of all invasive procedures associated with false positive exams (31). This is because, based on Lung-RADS criteria, 180 cases of the NLST false positives had at least one finding that would have been followed with 3–6 months surveillance CT rather than intervention. Among these 180, 13 would have ultimately required an invasive procedure to rule out lung cancer, 0.4 (1 in 2,500 screened) would have had a major complication from an invasive procedure, and 0.2 (1 in 5,000 screened) would have died within 60 days of an invasive procedure from any cause (33).

Usman Ali and colleagues (9) summarized the consequences of false positives in multiple studies. Among 40,569 patients screened with LDCT in 8 studies (28,38,41,46-50), 403 with benign conditions underwent minor invasive procedures as part of diagnostic follow-up; resulting in an absolute number of 9.74 patients with benign conditions undergoing minor invasive procedures (95% CI: 4.34–15.15) per 1,000 screened. Among 66,535 patients in 17 studies (18,19,26,28,38,41,46,47,50-58) that reported data on major invasive procedures, 411 underwent major invasive procedures as part of the diagnostic evaluation of false positive findings, resulting in an absolute number of 5.28 patients with benign conditions undergoing major invasive procedures (95% CI: 3.94–6.62) per 1,000 screened.

The risk of death or major morbidity associated with invasive testing (including both lung cancer cases as well as false positives) was also reported (9). Among 1,502 patients in 7 studies (1,23,26,52,55,59,60) reporting 30- and 60-day death, death within 60 days or due to postoperative complications, 20 deaths were reported resulting in an absolute number of 11.18 deaths (95% CI: 5.07–17.28) per 1,000 patients undergoing invasive follow-up testing. For 1,465 patients in 4 studies (1,26,57,60) including this information, the rate of major complications following invasive procedures in response to LDCT findings, 109 had major complications or morbidity, resulting in an absolute number of 52.03 major complications (95% CI: 15.77–88.28) per 1,000 patients undergoing invasive follow-up procedures.

Huang *et al.* (12) performed a meta-analysis of 9 RCTs that included 97,244 patients, only 2 of which [NLST (1) and DANTE (56)] reported the mortality rate from diagnostic invasive procedures resulting from lung cancer screening. Nineteen deaths occurred after 2,129 invasive procedures in patients screened by LDCT and 11 deaths after 792 invasive procedures in the control group; NLST compared LDCT and CXR (RR 0.60 (95% CI: 0.27–1.31) and DANTE compared LDCT and usual care (RR 0.75 (95% CI: 0.07–8.02) for a combined RR 0.64 (95% CI: 0.30–1.33) for mortality after invasive procedures following LDCT compared to control groups.

False negatives exams and missed lung cancers

False negatives exams are defined as CTs in which the diagnosis of lung cancer is made after a negative CT screen, resulting in missed lung cancer. This is infrequent but can occur with very rapidly growing cancers especially those that are endobronchial, and also as result of detection and interpretation errors. Slice thickness, interval between exams, and familiarity with lesions in blind spots (such as cystic airspaces with thickened walls or consolidative masses imitating pneumonia) are vital to accurate CT interpretation (61,62).

In the NLST (1,62), 44 of 56,980 negative CT screens over 3 annual screening rounds (0.08%), or 7.7 per 10,000 negative screens, were diagnosed with an interval lung cancer within one year of a negative CT screen and before the next annual screen. Retrospective review revealed 91% (40/44) met the NLST criteria for a positive screen. The most frequent of the retrospectively identified abnormalities were: (I) noncalcified lung nodule larger than 4 mm (n=16), (II) mediastinal mass or lymph node enlargement (n=8), (III) hilar mass or lymph node enlargement (n=6) and (IV) bronchial lesion (n=6). Among missed lung nodules, most were located in hidden areas, such as a peripheral region (n=11), near a vessel (n=4) or near the hilum (n=2). Three missed nodules were associated with a cystic air-space. Most patients (32/44, 73%) had stage III or IV lung cancer at the time of diagnosis. Lung cancer mortality for these 44 cases was 80% (35/44), compared to 35% (225/649) for all screen-detected cancers within the NLST follow-up period (P<0.0001). The authors suggested that interval cancers that developed between annual scans may have been more aggressive (evolved more quickly due to faster doubling-time) or been of a higher pathological grade. Awareness of frequently missed abnormalities and interpretation errors may decrease the rate of false negative CT screens (62).

The NELSON study (63) required the use of nodule detection software, and interval cancers were diagnosed in 34 of the 7,155 CT-screened patients after the first 3 screening rounds: baseline, 1 and 3 years after baseline. Among a total of 20,100 negative scans out of total 20,563 scans over the 3 rounds with different screening intervals, the false negative was 0.17%, or 16.9 per 10,000 negative screens. A suspicious abnormality was retrospectively identified in 22 of 34 (65%) interval cancers. Commonly missed findings in these 22 cases were: (I) thickened walls of bullae (n=5), (II) endobronchial lesions (n=5), (III) nodules with pleural attachment (n=4) and (IV) lymph node enlargement (n=3). In contrast to screen-detected cases, interval cancers were associated with higher proportion of stage III/IV disease (83 *vs.* 22%, P<0.0001), small-cell carcinomas (20% *vs.* 4%; P=0.003) and histology other than adenocarcinoma (74% *vs.* 48%; P=0.005) (63,64).

Many interval lung cancers diagnosed in studies from 1999–2002 occurred due to large (10-mm) slice thickness resulting in missed lung cancers, most often in the setting of faint nodules, sub-solid nodules, and/or laying adjacent to normal structures (65,66). Kakinuma *et al.* (65) reported the findings from 7 missed lung cancers at initial spiral CT screening with 10-mm collimation of 1,443 patients undergoing screening between 1993–1996. Minute missed lung cancers included a nodule among shadows of old tuberculosis (n=2), a faint nodule with high attenuation in the center of the nodule (n=1), an increase in attenuation just adjacent to an axial peripheral pulmonary vessel (n=1) and adjacent to a craniocaudal peripheral pulmonary vessel (n=1), and a minute faint nodule (n=2). Six (86%) cancers were stage I. The authors concluded that minute nodules representing lung cancer near the threshold of detectability may be missed by spiral CT screening if the collimation is large. It is important to examine noncalcified nodules with thin-section CT even when lesions from prior disease exist and to evaluate the shadows of pulmonary vessels carefully. A study from the late 1990s by Li *et al.* (66) examined 32 cases of missed lung cancers on 39 CT scans with 10-mm collimation, and a 10-mm reconstruction interval. Most (88%) lung cancers were stage IA with a subtle or very subtle lesion (25/39), small faint nodules (ground-glass opacity (27/39), overlapping normal structures (19/23), or opacities in a complex background of other disease (14/16).

Humphrey *et al.* (8) reported the sensitivity of LDCT for detecting lung cancer from one RCT, NELSON (21), as 96% in both baseline and incidence screens and from 5

cohort studies (21,24,42,67,68) ranging from 80–100%, implying a false negative ranging from 4–20%, with no harms associated with false negative tests. In the draft of the updated USPSTF review (14) they reported a mean sensitivity among 9 RCTs (3,39,41,56,69-72) and 8 cohort studies (24-26,42,67,68,73,74) of 80.3% (range, 59–95%) and 93.3% (range, 87.7–100%), respectively.

Overdiagnosis

Overdiagnosis is defined as the diagnosis of a condition that would not have become clinically significant had it not been detected by screening. In the case of screening with LDCT, overdiagnosis could lead to unnecessary treatment for lung cancer that would not have had clinical impact, such as surgery, chemotherapy, immunotherapy and/or radiation therapy (14,16). Overdiagnosis is difficult to quantify because a tumor cannot truly be called "clinically insignificant" unless it is observed indefinitely without treatment, causes no symptoms, and the patient ultimately dies of another cause, a situation that is unlikely to be permitted. The slow growth rate of tumors starting as non-solid (pure ground-glass) nodules represents the indolent behavior of lesions corresponding histologically as lepidic-predominant adenocarcinomas. These are the cancers that are most at risk for "overdiagnosis" (6). The rate of overdiagnosis varied depending on the duration of follow-up as cancers prove to be clinically more significant over time (14).

The NLST (75) demonstrated 120 excess lung cancer cases in the LDCT group compared with the chest radiograph group (1,089 *vs.* 969) after a median follow-up of 6.5 years and suggested that the probability was 18.5% (95% CI: 5.4–30.6%) that any lung cancer detected by screening with LDCT was an overdiagnosis, and 78.9% (95% CI: 62.2–93.5%) that a sub-solid adenocarcinoma detected by LDCT was an overdiagnosis. With an "overdiagnosis" probability of 18.5%, Robbins *et al.* (33) estimated that using Lung-RADS version 1.0 in the NLST (41 per 1,000 diagnosed with lung cancer), 4 cases could represent overdiagnosis, and 3 could represent lung cancer deaths prevented by screening. The NLST (76) reported cases of overdiagnosis decreased when, after a median follow-up 11.3 years for incident cancer, only 20 excess cumulative lung cancer cases were detected in the LDCT group (1,701 *vs.* 1,681) with no statistically significant rate of overdiagnosis for CT compared to CXR arms (RR=1.01, 95% CI: 0.95–1.09). In the subset of sub-solid adenocarcinomas, the RR of overdiagnosis for LDCT was measured as 2.6 (95% CI: 1.9–3.7) (76). The USPSTF draft (14) noted important methodologic limitations for ascertaining lung cancer incidence and overdiagnosis in the NLST. These included using different methods of verification during trial years and post-trial years; lack of information on any post-trial screening with LDCT; missing data for lung cancer incidence for 11 out of 33 centers that did not have a home state cancer registry available for linkage; and risk of biasing overdiagnosis estimates toward the null because the comparison group received CXR.

An excess of 40 lung cancers (344 *vs.* 304 from LDCT and control group, respectively) were found in the NELSON trial 10 years after randomization (3), which suggests an overdiagnosis rate of 19.7%. After 11 years of follow-up, however, the number of excess cases reduced to 18, yielding an excess incidence overdiagnosis rate of 8.9% (3).

The rate of estimated ranges from 0–67% in the literature (9,13-15). Usman Ali *et al.* (9) reported an overdiagnosis rate of 10.99–25.83% depending on the thresholds used to determine overdiagnosis across studies (44,75,77,78): lead time 5.5 years with mean sojourn time 2 years, lead time ≥5 years, tumor size 30 mm, and tumor volume doubling time ≥400 days. Hoffman's meta-analysis (13) calculated an overdiagnosis rate of 33% from 6 studies comparing LDCT with usual care, with an excess of 171 cancers in the LDCT cohort among 515 screen-detected lung cancers. Based on 5 studies examining overdiagnosis (44,75,79-81) and 7 studies reporting differences in cancer incidence between LDCT and control groups (1,3,19,20,82-84), Jonas *et al.* (14) estimated anywhere from 0–67% chance that a screen-detected lung cancer was overdiagnosed.

In a meta-analysis of 5 RCTs (2,3,79,82,85) reporting lung cancer incidence in LDCT compared to no imaging ("usual care"), Brodersen and colleagues (15) estimated that at least 3.6 years of follow-up from last screening round was required to avoid lead-time bias as this is the estimated mean sojourn time in a preclinical phase before clinical manifestation of a non-lepidic adenocarcinoma by using convolution model (95% CI: 3–4.3 years) in a study of overdiagnosis in LDCT screening for lung cancer by Patz *et al.* (75) Of screen-detected cancers, 38% (95% CI: 14–63%) may have been overdiagnosed for all studies and 49% (95% CI: 11–87%) in a sensitivity analysis restricted to the two trials (DLCST and LUSI) at low risk of bias in all

domains of Cochrane's Bias tool 2.0.

"Overdiagnosis" only confers harm if it renders "overtreatment," which is the actual treatment of cancers that would otherwise not be clinically significant. By identifying indolent tumors, modern screening protocols include measures for conservative non-interventional management of indolent-appearing lesions. For example, the I-ELCAP protocol recommends that non-solid nodules of any size be followed with annual repeat CT and LungRADs recommends that non-solid nodules ≥20 mm (version 1.0) and ≥30 mm (version 1.1) be followed with repeat CT in 6 months. By including strategies for management that include ongoing surveillance for specific indolent lesions, such measures mitigate overtreatment and therefore minimize overdiagnosis.

Risks of radiation exposure with lung cancer screening

While many of the other "risks" of lung cancer screening may be overstated as result of improper thresholds or misinterpretation of data, the actual risk of radiation exposure is objective and quantifiable. This must be calculated and risks adequately mitigated through use of low-dose imaging.

The quantity most relevant for assessing the carcinogenic risk of LDCT is the "effective dose," measured in millisieverts (mSv). The average annual dose from environmental radiation in the U.S. is 3.1 mSv. The patient's body habitus plays an important role in designing CT protocols. Scanning parameters such as tube current and voltage must be higher for larger patients in order to attain acceptable image quality (86). The American College of Radiology (ACR) guidelines (87) specify that the volumetric CT dose index ($CTDI_{vol}$) for lung cancer screening in average-sized patients (170 cm, 70 kg, BMI 24.1 kg/cm^2) should be ≤3 mGy/m^2. For comparison, a typical effective dose for screening CT is ≤1.0 mSv. According to the U.S. Food and Drug Administration (FDA) (88), a CT examination with an effective dose of 10 mSv may be associated with an increase in the possibility of fatal cancer of approximately 1 in 2000. Comparison to the natural incidence of fatal cancer in the U.S. population, about 400 in 2000, the risk of radiation-induced cancer is much smaller than the natural risk of cancer, and extremely small relative to the risk of death from lung cancer in patients (e.g., smokers) requiring lung cancer screening (88).

The radiation associated with one LDCT scan ranged from 0.65 to 2.36 mSv in LDCT screening studies (1,14,27,42-44,73,89-91). Recent LDCT lung cancer-screening trials, including ITALUNG, NELSON, UK Lung Cancer Screening trial (UKLS), and NLST, have specified patient weight-based adjustments of tube parameters (86). The $CTDI_{vol}$ in ITALUNG was 3.4–3.6 mGy (22), $CTDI_{vol}$ in NELSON (92) & UKLS (93) varied from 0.8 mGy in <50 kg to 3.2 mGy in >80 kg, and $CTDI_{vol}$ in NLST (94) was 2.9±1 mGy (86). Moreover, with recently available iterative reconstruction techniques, it is possible to reduce radiation dose to well under 1.0 mSv, with $CTDI_{vol}$ and DLP values as low as 0.46mGy and 16mGy, respectively (95).

ITALUNG (96) and COSMOS (91) evaluated the cumulative radiation exposure of LDCT for screening patients. The USPSTF draft (14) estimated cumulative radiation exposure for 25 years of annual screens from age 55–80 based on these studies for a total of 20.8–32.5 mSv. The ITALUNG trial (96) examined total exposure cumulative over 4 annual LDCT examinations and related further images including follow-up LDCT, 2-[^{18}F]flu-2-deoxy-D-glucose positron emission tomography (FDG-PET) and/or CT-guided fine needle aspiration biopsy. The mean collective effective dose of radiation ranged between 8.75 and 9.36 Sv and the mean effective dose to a single patient over 4 years was between 6.2 and 6.8 mSv (range, 1.7–21.5 mSv). Of this total, 77.4% was associated with the annual LDCT and 22.6% related to further investigations. The estimated mean number of radiation-induced cancers ranged between 0.12 and 0.33 per 1,000 subjects.

The COSMOS trial (91) followed 5,203 patients enrolled between 2004-05 for at least 10 years with 42,228 LDCT and 635 PET-CT scans performed. The median cumulative effective dose at the 10th year of screening was 9.3 mSv for men and 13.0 mSv for women. The numbers of lung cancer and major cancer cases induced by 10 years of screening in this cohort were 1.5 and 2.4, respectively, which corresponded to an additional risk of induced major cancers of 0.05% (2.4/5,203). With 259 lung cancers diagnosed in 10 years of screening, 1 radiation-induced major cancer would be expected for every 108 (259/2.4) lung cancers detected through LDCT screening.

Many investigators have modeled the risk of radiation exposure from LDCT on the development of radiation-induced lung cancer. Bach *et al.* (7) calculated 1 cancer death per 2,500 screens in those participating in a screening program such as the NLST. Brenner (97)

estimated that a 50-year-old female smoker who undergoes annual CT lung screening until age 75 would incur an estimated radiation-related lung cancer risk of 0.85% in addition to her otherwise expected lung cancer risk of approximately 17%. Frank *et al.* (98) estimated the lifetime attributable risk of radiation-related lung cancer mortality, assuming annual LDCT examinations from age 55–74 years, to be approximately 0.07% for men and 0.14% for women. Gierada *et al.* (61) estimated that after 20 annual screening CT examinations, the increased risk of cancer would be 0.22% in women and 0.12% in men, and that of a fatal cancer attributable to screening CT of 0.1%. Jonas *et al.* (14) estimated the number of radiation-induced cancers to be 0.26–0.81 major cancers for every 1,000 people screened with 10 annual LDCTs. These models, however, are based on hypothetical risk and the American Association of Physicists in Medicine (99) have stated that the epidemiological evidence supporting increased cancer incidence or mortality from radiation doses below 100 mSv is inconclusive as below:

"At the present time, epidemiological evidence supporting increased cancer incidence or mortality from radiation doses below 100 mSv is inconclusive. As diagnostic imaging doses are typically much lower than 100 mSv, when such exposures are medically appropriate, the anticipated benefits to the patient are highly likely to outweigh any small potential risks.

Given the lack of scientific consensus about potential risks from low doses of radiation, predictions of hypothetical cancer incidence and mortality from the use of diagnostic imaging are highly speculative. The AAPM, and other radiation protection organizations, specifically discourages these predictions of hypothetical harm. Such predictions can lead to sensationalistic stories in the public media. This may lead some patients to fear or refuse safe and appropriate medical imaging, to the detriment of the patient."

Conclusions

With the support of several decades of medical literature, most clinicians and investigators consider the potential risks of LDCT screening to be outweighed by the benefit of reducing the risk of lung cancer death in high-risk populations. The wide range of values for each of the "harms" described makes coherent discussion with participants in screening programs challenging. This is in large part based on how findings such as false positives and overdiagnosis are defined. Risk from radiation is especially challenging given that the most prestigious society evaluating its potential for harm explicitly warns against making assumptions about low-dose radiation causing death or leading to cancer. While it may be prudent to take a cautious approach towards explaining harms, this review strongly points towards the need to define better how we quantify risks so that a more meaningful measure can be provided to potential.

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Footnote

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