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Review Article

Combining smoking cessation interventions with LDCT lung cancer screening: A systematic review

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ABSTRACT

Providing smoking cessation treatment with annual low dose CT (LDCT) screening offers an opportunity to reduce smoking-related morbidity and mortality. However, the optimal approach for delivering cessation interventions in the LDCT screening context is unknown. We searched for randomized controlled trials and observational studies with a control group testing a smoking cessation intervention among adults undergoing LDCT screening through May 1, 2018 using MEDLINE, the Cochrane Library, Web of Science, EMBASE, PsycINFO, and ClinicalTrials.gov. Two reviewers independently reviewed each study to assess eligibility and extracted information using pre-specified protocols for included studies. Given significant differences in the interventions in each study, meta-analyses for the included studies could not be performed. Of 2513 identified studies, 9 met inclusion criteria. Five of the included studies were randomized controlled trials while 4 were observational studies with a control group. Studies were of varying quality, but overall were of poor to fair quality with significant potential for bias and limited generalizability. Based on the available studies, there was insufficient data to suggest a particular approach to smoking cessation counseling in the LDCT screening setting. While no studies compared combined pharmacotherapy and counseling to counseling alone or compared the various pharmacologic agents, we identified several studies underway investigating new approaches during LDCT screening. The optimal strategy for smoking cessation in patients undergoing LDCT screening remains unclear. Future studies should focus on evaluating effectiveness and implementation of combined counseling and pharmacotherapy to optimize smoking cessation during LDCT screening.

1. Introduction

The National Lung Screening Trial (NLST) demonstrated a 20% relative reduction in lung cancer mortality with annual low-dose computed tomography (LDCT) screening of current and former smokers (National Lung Screening Trial Research T et al., 2011). While LDCT screening has great potential for improving patient outcomes, quitting smoking remains the most effective intervention in reducing lung cancer death (Villanti et al., 2013). Promoting smoking cessation has been identified as an essential component of a lung cancer screening program, with Medicare requiring information about tobacco cessation interventions be offered to current smokers in order to receive reimbursement for LDCT screening (Decision Memo for Screening for Lung Cancer With Low Dose Computed Tomography (LDCT) (CAG-00439N), 2015; Wiener et al., 2015; Mazzone et al., 2015; Fucito et al., 2016).

Smokers eligible for LDCT screening have at least a 30 pack-year smoking history and thus often have a high degree of nicotine dependence, potentially creating significant obstacles to quitting smoking (Donze et al., 2007; National Lung Screening Trial Research T et al., 2010). LDCT screening has been identified as a potential "teachable moment" when smokers may be more aware of the risks related to smoking and consequently more receptive to smoking cessation interventions (McBride et al., 2003; McBride and Ostroff, 2003). However, quit rates among smokers undergoing LDCT screening have been estimated to be as low as 11%, in part due to a lack of delivery of guideline-based cessation interventions provided by screening programs (Slatore et al., 2014; Ostroff et al., 2016).

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Providing smoking cessation counseling in the context of LDCT screening is an opportunity to further optimize the benefit of LDCT screening; current smokers who underwent annual LDCT screening and successfully quit smoking had the greatest reduction in mortality in the NLST (Tanner et al., 2016). Identifying effective approaches to tobacco dependence treatment in the context of LDCT screening has been identified as a priority by the NIH (RFA-CA-15-011: Smoking Cessation Within the Context of Lung Cancer Screening (R01), 2016), the National Academy of Science (National Academies of Sciences, Engineering, and Medicine, 2016), the Society for Research on Nicotine and Tobacco (Fucito et al., 2016), and the American Thoracic Society (Wiener et al., 2015; Kathuria et al., 2017). We performed a systematic review to determine effective strategies for smoking cessation interventions in the LDCT screening setting.

2. Materials and methods

2.1. Search strategy

We searched MEDLINE (1950-May 1, 2018) to identify studies relevant to our research question. We used exploded Medical Subject Headings in the following search strategy: *x-ray computed tomography* or *LDCT* or *CT scan* or *lung cancer screening*; and *tobacco use* or *tobacco use disorder* or *tobacco dependence* or *tobacco products* or *tobacco use cessation* or *smoking cessation* or *smoking* or *electronic cigarettes* or *e-cigarettes;* and *early detection of cancer* or *early diagnosis of cancer* or *cancer screening*. Using similar search terms, we also searched Web of Science, EMBASE, PsycINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL). We reviewed reference lists of relevant articles to identify additional studies overlooked by our search. We used a similar search strategy on ClinicalTrials.gov to identify ongoing clinical trials relevant to our research question.

2.2. Study selection

2.2.1. Inclusion criteria

Given the vast majority of published clinical research are observational studies, we included both randomized controlled trials (RCTs) and observational studies with a comparison group to include all potential studies that might provide important insight on smoking cessation strategies in LDCT screening. Studies that met each of the following criteria were included: 1) patients were active smokers undergoing LDCT screening, 2) the intervention group received a smoking cessation intervention (pharmacologic therapy, counseling, *etc.*), 3) the comparison group received "usual care" as defined by the study, 4) the primary or secondary end points included smoking abstinence at 6 months or greater (primary end point), smoking abstinence at 1 month, reduction in tobacco use, quit attempts, and change in readiness to quit.

2.2.2. Exclusion criteria

Studies were excluded if the smoking cessation intervention was not paired with LDCT lung cancer screening, if patients underwent a different modality of screening (*e.g.*, chest x-ray, sputum cytology), or if the study was not published in the English language.

2.2.3. Missing data

We contacted investigators of unpublished or currently active studies identified on clinicaltrials.gov to assess eligibility based on the inclusion and exclusion criteria as well as to obtain additional study data.

2.3. Data extraction and quality assessment

Two co-authors (J.M.I. and H.K.) independently reviewed all titles and abstracts and examined each full text study to determine final inclusion or exclusion. Discrepancies were resolved by consensus discussion among co-authors. Data were abstracted by two non-blinded reviewers (H.K. and C.D.) in duplicate using a standardized, predefined form. Recorded data included study methodology, baseline patient characteristics, smoking cessation intervention, definition of usual care/control group, primary and secondary outcomes, abstinence measures, and follow-up. Study quality of RCTs was assessed using criteria developed by the United States Preventive Services Task Force, rating quality of studies as "good," "fair," or "poor" based upon subject selection, maintenance of comparison groups, rates of follow-up, intervention and outcome definitions, and quality of analysis (U.S. Preventive Services Task Force, 2015). Observational study quality was assessed using the Newcastle-Ottawa Scale, rating studies based upon subject selection, comparability, and outcomes/exposures (Wells et al., n.d.).

2.4. Outcome measures

2.4.1. Primary outcome

We considered smoking abstinence at 6 months or greater to be the most important beneficial outcome of a smoking cessation intervention. Six-month smoking abstinence was defined by absence of cigarette smoking at 6 months following the smoking cessation intervention. Measure of abstinence could include continuous abstinence, prolonged abstinence, or point prevalence measured by self-report and/or biochemical validation using biomarkers such as cotinine or exhaled carbon monoxide (Hughes et al., 2003; West et al., 2005). For each study, we utilized intention-to-treat analyses when available, with participants missing from follow-up data considered continued smokers.

2.4.2. Secondary outcomes

We also evaluated the association of smoking cessation interventions compared with usual care for other potential benefits: smoking abstinence at 1 month, reduction in tobacco use, quit attempts, and change in readiness to quit. These outcomes were chosen to show possible efficacy of the intervention. We defined smoking abstinence at 1 month as absence of cigarette smoking at 1 month following the smoking cessation intervention, by self-report and/or biochemical validation, as recommended by the Society for Research on Nicotine and Tobacco and the Russell Standard (Hughes et al., 2003; West et al., 2005). We defined reduction in tobacco use as a decrease in the number of cigarettes smoked per day based on self-report. Quit attempts referred to the number of patient-reported attempts at quitting smoking following the smoking cessation intervention. Change in readiness to quit was defined as an increase or decrease in a patient's motivation to quit based on a readiness scale or ladder.

2.5. Statistical analyses

When *p*-values were not reported within the included studies, we performed statistical analyses using chi-square and Fisher's exact test as appropriate. Of note, meta-analysis pooling study results could not be performed given the significant differences in sample characteristics, comparison and intervention arms, and outcomes across studies.

3. Results

Of the 2513 initial studies found in our search, we identified 1656 unique potentially eligible studies (Fig. 1). The majority were excluded because they were non-comparative studies (*i.e.* single arm observational studies, case reports, *etc.*), tested an intervention unrelated to smoking cessation, were non-English articles, or did not occur in the context of LDCT lung cancer screening. After detailed review of the remaining 20 studies, 9 met all inclusion criteria and were considered as appropriate for inclusion (Appendix).

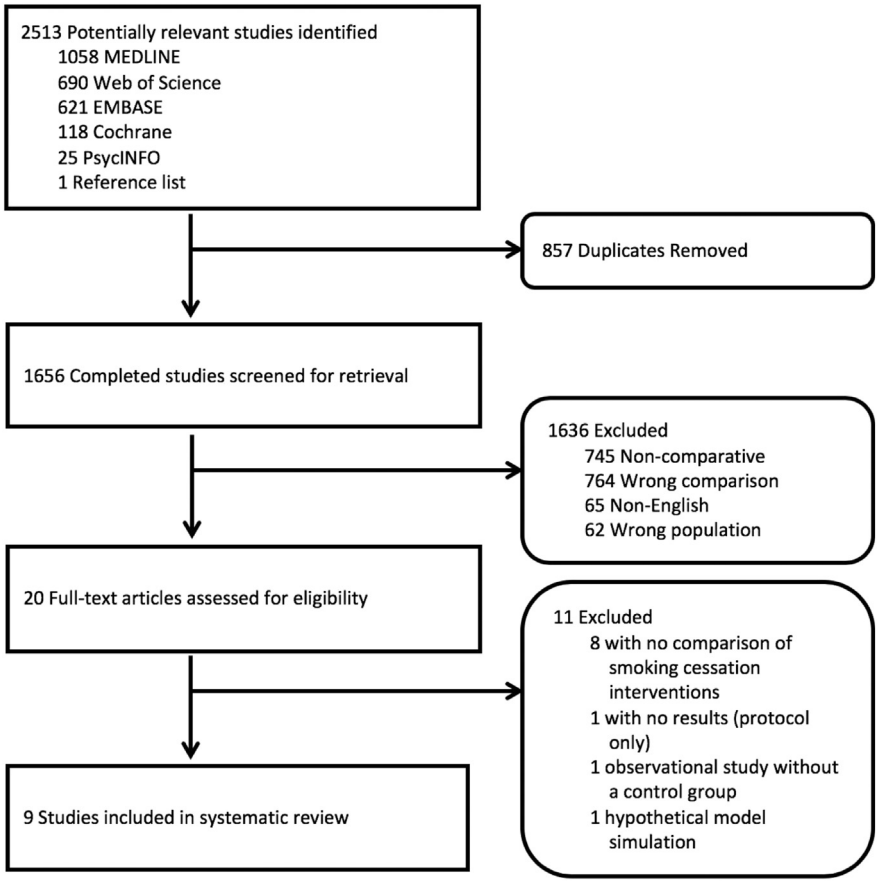

Fig. 1. PRISMA diagram of process used to select relevant studies.

3.1. Randomized controlled trials

We identified 5 RCTs that evaluated the effect smoking cessation interventions in the setting of LDCT screening (Table 1).

Clark et al. compared 12-month 7-day point prevalence smoking abstinence, biochemically confirmed by exhaled carbon monoxide, and change in readiness to quit among 85 patients who were given internet-based cessation resources (intervention) to 86 patients given written self-help materials from the NCI (control) (Clark et al., 2004). At 12-month follow-up, 5% of patients receiving internet-based resources had biochemically confirmed smoking abstinence compared to 10% of patients receiving standard written resources ($p = 0.166$). There was also no difference between the groups in change in readiness to quit (internet resources 30%, written resources 27%, $p = 0.704$). More patients receiving internet-based resources made an attempt to stop smoking (68%) than patients receiving standard written resources (48%, $p = 0.011$).

Using a subgroup of the Dutch-Belgian lung cancer screening trial (NELSON trial), Van der Aalst et al. compared 642 patients given tailored, computer-generated self-help materials (intervention) to 642 patients given a standard written cessation brochure (control) (Aalst et al., 2012). At 24 months follow-up, there was no significant difference in point prevalence of smoking abstinence between patients receiving the computer-tailored information (13.2%) and the standard brochure (15.9%, OR 0.81, 95% CI 0.59–1.10). There was similarly no significant difference in prolonged smoking abstinence between the two groups (computer-tailored 12.5%, standard brochure 15.6%, OR 0.77, 95% CI 0.56–1.06). While this study utilized intention-to-treat analysis, there was poor penetration of the intended interventions with 25.1% of patients accurately recalling receiving the computer-tailored materials and 38.8% of patients accurately recalling receiving the brochure ($p < 0.001$).

Ferketich et al. was intended as a pilot study to determine feasibility of providing counseling in combination with pharmacotherapy for smoking cessation in the context of LDCT screening. This RCT compared 7-day point prevalence in smoking abstinence at 4 and 6 months among 9 patients receiving cessation counseling from a medical oncologist prior to LDCT screening to 9 patients receiving the same counseling after LDCT screening was performed (Ferketich et al., 2012). Per patient preference, counseling was followed by either 12 weeks of varenicline or 8 weeks of nicotine replacement therapy in both arms. There was no significant difference in abstinence rates in patients receiving counseling before LDCT (4 months: 33.3%, 6 months: 22.1%) compared to those receiving counseling after LDCT (4 months: 22.2%, 6 months: 11.1%, p-values from our analysis: $p = 1.0$ and $p = 1.0$, respectively).

Marshall et al. performed an RCT randomizing 28 patients to receive a single face-to-face tailored counseling session from a physician, take-home audio quit educational materials, printed materials, and telephone helpline referral (intervention) and 27 patients to receive printed materials and telephone helpline referral only (control) (Marshall et al., 2016). There was no significant difference in quit rates at 12 months, determined by self-reported point prevalence, in patients who had received the intervention (14.3%) compared to control (18.5%, $p = 0.74$).

Taylor et al. performed an RCT randomizing 46 patients after receiving their LDCT screening results to receive usual care (written smoking cessation materials, link to a smoking cessation app and website, local cessation resources, text messaging link) and 46 patients to usual care plus 6 weekly proactive telephone counseling calls (Taylor et al., 2017). There was no significant difference in 7-day point prevalence of abstinence at 3 months based on self-report (telephone

Table 1
Randomized controlled trials evaluating smoking cessation interventions during LDCT screening.

Study	Sample size	Age	Male %	Smoking history	Comparison	Intervention	Measure of abstinence	Summary of findings	Study quality
Clark et al. (2004) (United States)	171	57.4 (mean)	51	≥20 pack-years[a]	Written self-help materials from the NCI	Internet-based resources – patients provided 10 links to different smoking cessation websites	Self-report, exhaled carbon monoxide	No significant difference in 12 month quit rates or change in readiness to quit. Increased number of quit attempts in intervention group ($p = 0.011$)	Fair
Aalst et al. (2012) (Netherlands)	1284	57.0 (median)	100	38 pack-years (median)	Standard brochure with smoking cessation information for different stages of readiness to quit.	Computer-generated, tailored self-help material based on input of individual smoking behaviors and history.	Self-report	No significant difference in point prevalence, quit attempts, or prolonged smoking abstinence at 24 months follow-up.	Fair
Ferketich et al. (2012) (United States)	18	56.4 (mean)	28	28 pack-years	Smoking cessation counseling with a medical oncologist occurring after LDCT performed followed by 12-week tobacco dependence protocol.	Smoking cessation counseling with a medical oncologist occurring before LDCT performed followed by 12-week tobacco dependence protocol.	Exhaled carbon monoxide	No difference in 7-day point prevalence at 4 and 6 months	Poor
Marshall et al. (2016) (Australia)	55	63 (mean)	64	25 cigarettes per day (median) 46-Year smoking duration (median)	Nontailored printed smoking cessation materials and telephone helpline referral.	Single face to face tailored counseling session (thoracic physician) with take-home audio education materials, printed materials, and telephone helpline referral.	Self-report, exhaled carbon monoxide	No significant difference in quit rates at 12 months for patients receiving counseling intervention compared to the control group.	Fair
Taylor et al. (2017) (United States)	92	60.3 (mean)	44	≥20 pack-years	Resource list: Booklet, website, contact information for local resources, text messaging link	Resources list and 6 weekly, proactive counseling calls	Self-report, carbon monoxide, saliva test	Higher 7-day point prevalence cessation at 3-months in patients who received telephone counseling	Fair

[a] There was a median smoking history of 45 pack-years in the 1520 patient cohort from which the sample was obtained.

Table 2
Observational studies with a control group evaluating smoking cessation interventions during LDCT screening.

Study	Study type	Sample size	Age	Male %	Smoking history	Comparison	Intervention	Measure of abstinence	Summary of findings	Study quality
Park et al. (2015) (United States)	Case-control	3336[a]	61.0 (mean)	52	≥30 pack-years	Continued smokers who received provider-delivered cessation counseling using the 5As	Patients who quit smoking after receiving provider-delivered (primary care provider) cessation counseling using the 5As.	Self-report	Assist and arrange were associated with a significant increase in the odds of quitting at 12 months	Poor
Bade et al. (2016) (Germany)	Observational	1206	50–59: 69.9% 60–69: 30.1%	62[b]	Daily: ≤20 cigarettes: 55.3% > 20 cigarettes: 44.7% Duration: ≤35 years: 40.3% > 35 years: 59.7%	Non-attendance to smoking cessation counseling that was offered at time of LDCT screening.	Attendance to smoking cessation counseling offered at time of LDCT screening; performed by trained psychologists based on readiness to quit smoking.	Self-report	Higher rates of smoking cessation in patients who attended smoking cessation counseling compared to those who did not attend at 1 and 2 years follow-up	Fair
Luh et al. (2016) (Taiwan)	Quasi-experimental	489	≤50: 19.6% 51–64: 24.3% ≥65: 56.1%	100	Age started smoking: ≤20: 56.6% > 20: 38.4%	Smoking cessation leaflet given to patients at time of screening. Second comparison group did not receive any smoking cessation advice.	Clinician-provided (MD and nurse) counseling tailored to willingness to stop smoking and degree of smoking addiction.	Self-report	Significant advancement in patients' readiness to quit smoking in those receiving clinician-provided counseling.	Poor
Zeliadt et al. (2017)	Observational	83	64.3 (mean)	93	≥30 pack-years	LDCT screening letters providing information for quitline and tobacco treatment services	Telephone counseling provided prior to receiving LDCT screening results, using motivational interview and tailored counseling approach	Self-report	Significantly higher use of behavioral cessation support. No significant difference in 7-day abstinence 4 weeks after intervention	Fair

[a] Patients from NLST, including both LDCT and radiography arms.
[b] Proportion of males in entire cohort from which the sample was selected.

Table 3
Ongoing studies comparing smoking cessation interventions in the setting of LDCT screening.

Study	Primary investigator	Comparison	Intervention	Primary outcome	Secondary outcomes
Alberta Lung Cancer Screening Program (NCT02431962) (n.d.) (Canada)	Tremblay, A.	Providing general information on available cessation resources	Trained smoking cessation counselors offering cessation support and advice	Smoking status at 12 months post-randomization	Health economics analysis
SMART for Smoking Cessation in Lung Cancer Screening (NCT02597491) (n.d.) (United States)	Joseph, A.	Arm 1: 8 weeks evidence-based first-line smoking cessation treatment	Arm 2: Telephone-based tobacco longitudinal care (TLC) Arm 3: TLC with pharmacist-administered medication therapy management	6 months abstinence from smoking at 18 months post-randomization	None reported
Benefits of Tobacco Free Cigarette (BETOFREE) (NCT02422914) (n.d.) (Italy)	Lucchiari, C.	Arm 1: Smoking cessation counseling program	Arm 2: Smoking cessation counseling program and tobacco-free cigarettes without nicotine Arm 3: Smoking cessation counseling program and tobacco-free cigarettes with nicotine	Pulmonary health index	Psychological well-being, number of daily cigarettes, expired air carbon monoxide concentration, cough-related quality of life questionnaire, daily activity, lifestyle changes
Capitalizing on a Teachable Moment to Promote Smoking Cessation (NCT02276664) (n.d.) (United States)	Brandon, T.	Clearing the air smoking-cessation manual	Self-help intervention developed with input from focus groups	7-Day abstinence measured at several follow-up periods	Degree of practicality, rate of intervention demand
Implementation of Smoking Cessation Services Within NCI NCORP Community Sites (NCT03291587) (n.d.) (United States)	Foley, K.	Usual care	Implementation of a multi-faceted training program and toolkit for integrating cessation strategies in LDCT screening	Quit attempts, 3- and 6-month smoking cessation rates, strategies used for quitting	None reported
Smoking Cessation Intervention During Low Dose CT (LDCT) Screening for Lung Cancer (NCT03059940) (n.d.) (United States)	Cinciripini, P.	Arm 1: Referral to quitline and NRT	Arm 2: Referral to quitline and pharmacotherapy provided by LDCT screening provider Arm 3: Referral to tobacco treatment program including 4–8 counseling sessions and 10–12 weeks pharmacotherapy.	6-Month smoking cessation rates	None reported
The Lung Screening, Tobacco, and Health Project (NCT03200236), (n.d.) (United States)	Taylor, K.L.	3 telephone counseling sessions with NRT	8 telephone counseling sessions with NRT	7- and 30-Day abstinence at 3, 6, and 12 months	Intervention fidelity and feasibility for implementation Cost-effectiveness of intensive telephone counseling
Implementing Tobacco Treatment in Low Dose CT Lung Cancer Screening Sites (NCT03315910) (n.d.) (United States)	Ostroff, J.	Arm 1: Motivational interviewing	A combination of nicotine patch, nicotine lozenge, and/or gain-framed messages	6-Month smoking cessation rates	None reported
Personalized Smoking Cessation Tool Based on Patient Lung CT Image (NCT03087617) (n.d.) (United States)	Keith, L.	Usual care ± counseling	Usual care and an individualized smoking cessation report ± counseling	Quit attempts and use of quitline number	None reported
Low Dose Computed Tomography for Lung Cancer Screening (LDCT) (NCT03084835) (n.d.) (United States)	Hays, J.	Brief cessation counseling	Arm 1: Digital cessation intervention combining web and text messaging Arm 2: Digital cessation intervention combined with specialist counseling	12-month smoking abstinence	None reported
Promoting smoking cessation in lung cancer screening through proactive therapy (PROACT) (Implementing Smoking Cessation Into Delivery of Lung Cancer Screening, n.d.) (United States)	Zeliadt, S.	Unstructured, usual care	Tailored screening results, mailed starter pack of NRT, 2 proactive calls from quitline	Smoking cessation rates	Resource utilization

counseling 21.7%, usual care 19.6%, $p = 0.8$). However, using biochemically verified abstinence at 3 months, telephone counseling (17.4%) had a significantly greater abstinence rate compared to usual care (4.3%, $p = 0.04$).

3.2. Observational studies with a control group

We identified 4 observational studies (a case-control study, a quasi-experimental untreated control study, and 2 observational studies) evaluating various smoking cessation interventions in the setting of LDCT screening (Table 2).

Park et al. evaluated the effect of counseling using the 5As approach (Ask about smoking, Advise to quit, Assess readiness to quit, Assist with tobacco dependence treatment, and Arrange follow-up) on smoking cessation (self-reported point prevalence) at 12 months among a subset of smokers enrolled in the NLST. (Park et al., 2015) While the NLST itself did not include smoking cessation interventions, Park et al. evaluated 5As delivery from primary care providers during the study period based on patient self-report. In this matched case-control study, 1668 patients who had quit smoking (cases) were compared to 1668 patients who continued smoking (controls). There was no significant change in the odds of quitting at 12 months in patients reportedly receiving the 'ask, advise, or assess' steps of 5As counseling. There was a significant increase in the odds of quitting at 12 months in patients who reported receiving the assist (OR 1.4, 95% CI 1.21–1.63) and arrange (OR 1.46, 95% CI 1.19–1.79) steps of 5As counseling.

Bade et al. evaluated smoking cessation rates among patients who underwent LDCT screening compared to those who did not undergo screening, reporting 12-month smoking abstinence among patients who underwent screening as a subgroup analysis (Bade et al., 2016). In this observational study, patients in both arms were offered smoking cessation counseling performed by trained psychologists. Among patients in the LDCT screening arm, 595 (47.6%) current smokers attended the offered counseling and 654 (52.4%) current smokers chose not to attend. Within the LDCT screening arm, there were significantly higher smoking cessation rates in patients attending counseling at 12 months (14.6%) and 24 months (12.9%) compared to those who did not attend counseling (12 months: 6.7%, 24 months: 7.6%, p-values from our analysis: $p < 0.0001$ and $p = 0.002$, respectively). These analyses did not control for confounding variables.

Luh et al. was a quasi-experimental study that did not provide data on our primary outcome of 6-month smoking abstinence but did report data on our secondary outcomes (Luh et al., 2016). This study evaluated advancement in readiness to quit among 46 patients receiving physician and nurse-provided counseling during an in-person visit to discuss LDCT screening results compared to 53 patients who did not return for the in-person visit, instead receiving a smoking cessation leaflet by mail. An additional 390 patients received neither in-person counseling nor a mailed leaflet (control). Patients who received clinician-provided counseling had greater odds of advancing in readiness to quit compared to control (multivariable adjusted OR 2.27, 95% CI 1.07–4.84). Patients who received a smoking cessation leaflet had no significant difference in the odds of advancing in readiness to quit compared to control (multivariable OR 0.99, 95% CI 0.44–2.25). Quit rates were not reported in this study.

Zeliadt et al. performed a pilot feasibility trial looking at the effect of a proactive outreach telephone counselor on use of behavioral counseling resources and 7-day quit rates at 1 month (Zeliadt et al., 2017). This study was similar to a waitlist control study design with the control group of 56 patients being current smokers who underwent screening and had already received their results. The intervention group of 27 patients were contacted by telephone prior to receiving their screening results and given tobacco cessation counseling that included motivational interviewing and an individually tailored cessation plan. Patients who received the intervention had higher rates of using behavioral cessation support programs (44% *vs.* 11%, RR 4.1, 95% CI 1.7–9.9) than the control group. While more patients in the intervention group reported 7-day abstinence 4 weeks after intervention (19% *vs.* 7%), the study was underpowered for this secondary outcome and this was not statistically significant ($p = 0.1$).

3.3. Ongoing trials of smoking cessation in LDCT screening

Through our search of clinicaltrials.gov, we identified 11 RCTs currently underway comparing various smoking cessation interventions in the setting of LDCT screening (Table 3; Appendix). The tested strategies for improving smoking cessation vary widely across these studies, with most evaluating various methods for counseling patients to quit smoking (*e.g.* type of message framing, intensity of counseling, delivery platforms). While several studies will include pharmacotherapy in their intervention arms, none of the studies will directly compare different pharmacotherapy strategies. Several studies are set up to assess implementation of interventions as well as their effectiveness.

4. Discussion

In this systematic review, we sought to identify the optimal approach for delivering smoking cessation interventions for patients undergoing LDCT screening. Although we identified several studies in this area, we found insufficient and low-quality data to support one particular approach to smoking cessation over another in this patient population. Overall, it appeared that less intensive interventions, such as providing brochures or performing brief counseling, were insufficient for making significant impact on smoking cessation rates or patient readiness to quit. More intensive interventions that including several counseling visits with or without various pharmacologic therapies appeared to be more effective in these studies, although with insufficient evidence to support a particular approach to be used for patients during LDCT screening. Given that LDCT screening is an opportune time to counsel patients on smoking cessation, it is critical that clinicians and researchers aim to identify more effective interventions for facilitating smoking cessation among these high-risk patients.

A prior systematic review by Slatore et al. evaluated the impact of LDCT screening on patient smoking behaviors (Slatore et al., 2014). This review demonstrated that undergoing LDCT screening in and of itself does not achieve long-term abstinence, although a positive screening result was associated with increased quit rates (Slatore et al., 2014). Slatore et al. did not evaluate adjunctive tobacco treatment strategies for improving smoking cessation surrounding LDCT screening, instead assessing the impact of screening itself on smoking behavior. Another systematic review by Pineiro et al. assessed smoking cessation interventions during LDCT screening that were published prior to July 1, 2015 (Pineiro et al., 2016). This review included observational and non-randomized controlled studies and ultimately concluded that smoking cessation interventions can be successfully implemented in screening settings (Pineiro et al., 2016). Our review aimed to evaluate the efficacy of smoking cessation interventions in the LDCT screening setting and included only RCTs and observational studies with a comparison group that were published before May 1, 2018. Four studies were included that were not evaluated as part of Pineiro's prior review and 2 studies were excluded from this prior review that did not meet our inclusion criteria.

The importance of providing effective smoking cessation interventions in the context of LDCT screening cannot be understated. Quitting smoking would improve both the mortality benefit and cost-effectiveness of LDCT screening (Villanti et al., 2013; MacMahon et al., 2005). It is estimated that doubling the quit rate in screening-eligible patients would decrease the cost of LCDT screening nearly in half (based on cost per quality-adjusted life-year [QALY] gained) (MacMahon et al., 2005). A simulation model suggested the addition of a behavioral cessation intervention to LDCT screening could reduce the cost per QALY by approximately 25%, while addition of pharmacologic therapy in

addition to behavioral therapy for smoking cessation could reduce cost per QALY by nearly 50% (Villanti et al., 2013).

Several of the studies in our review suggest some potential benefit in smoking cessation with more intensive counseling, particularly when providers directly offer or initiate smoking cessation interventions during LDCT visits. However, these studies lack generalizability and have significant bias or flaws in study design. For instance, Park et al. and Bade et al. both showed higher smoker cessation rates in the intervention groups (Park et al., 2015; Bade et al., 2016). In Park et al., there was improvement in the odds of quitting smoking when clinicians used the five-step algorithm of the 5As (ask, advise, assess, assist, and arrange) compared to 3 (ask, advise, assess) or less. This study may have been inherently biased given the final two steps of this algorithm (assist and arrange) are largely dependent on whether a patient is assessed as being ready to quit. Additionally, this study reported aggregate outcomes from both the chest x-ray and LDCT arms from the NLST and it is unclear if the intervention was actually delivered during the LDCT discussion. Bade et al. showed higher rates of cessation for patients who chose to attend offered smoking cessation counseling compared to those who chose not to attend counseling sessions (Bade et al., 2016). However, this study had several flaws likely was influenced by selection bias, with patients attending counseling sessions inherently more motivated and likely to quit smoking than those who chose not to attend. Luh et al. compared patients receiving counseling after returning for an in-person visit to discuss LDCT screening results to those who did not return for in-person visit (therefore, not receiving counseling) and found patients who underwent counseling had an increase in patient readiness to quit (Luh et al., 2016). This study also had a high risk of bias given that patients who did not return for the in-person visit may have had inherently lower interest and motivation for quitting. Zeliadt et al. found patients who had telephone counseling had higher use of behavioral cessation support but was underpowered to assess smoking abstinence rates at 1 month. Additionally, as a pilot feasibility study, patients were not randomized and data analysis did not adjust for potential confounders. Taylor et al. showed a difference in smoking abstinence at 3 months with biochemical verification using proactive telephone counseling over 6 weeks, but the sample size for this study was relatively small with very small numbers of patients with biochemical data available (Taylor et al., 2017).

With insufficient data from available studies in providing smoking cessation counseling during LDCT screening, clinicians are faced with the challenge of providing an intervention without the guidance of how to best do so. What is particularly challenging is these patients are the most highly tobacco dependent and addicted patients given the extent of their smoking history. We propose that an aggressive two-pronged approach is necessary to optimize the likelihood of success with smoking cessation for this patient population. Counseling is essential to motivating patients to quit, identifying potential barriers and obstacles to quitting, and aiding patients in developing an individualized quit plan. However, counseling on its own will likely be insufficient in treating the physiologic dependence of smoking. This is where pharmacotherapy is needed to complement patient quit efforts and treat physiologic dependence while psychological dependence is managed with counseling. Two single-arm studies (therefore excluded from this systematic review) have demonstrated high quit rates with combined pharmacotherapy and counseling. Filippo et al. demonstrated a 57.1% smoking cessation rate in a single arm study using behavioral counseling and pharmacological therapy during LDCT screening (Filippo et al., 2015). Similarly, Pozzi et al. found a 33.7% 6-month abstinence rate in a single arm study when behavioral counseling was combined with varenicline during LDCT screening (Pozzi et al., 2015). Prior studies have validated the use of combined pharmacotherapy and behavioral counseling in the general population (Stead et al., 2015) and in reducing cigarette consumption in patients unable or unwilling to quit entirely (Ebbert et al., 2015). However, it is unclear how effectiveness of these methods will differ in the highly addicted, specialized patient population undergoing LDCT screening. It will be critical for future studies to evaluate both effectiveness and implementation of combined tobacco counseling and pharmacotherapy interventions in the opportune LDCT screening context.

Among ongoing studies, several studies are taking this combined approach and analyzing effectiveness and/or implementation of various smoking cessation strategies (Gain-framed Messages and NRT for Lung Cancer Screening Patients (NCT03069924), n.d.; Smoking Cessation Intervention During Low Dose CT (LDCT) Screening for Lung Cancer (NCT03059940), n.d.; The Lung Screening, Tobacco, and Health Project (NCT03200236), n.d.; Implementing Tobacco Treatment in Low Dose CT Lung Cancer Screening Sites (NCT03315910), n.d.; Implementing Smoking Cessation Into Delivery of Lung Cancer Screening, n.d.). Among the 5 studies currently investigating a combined counseling and pharmacotherapy approach, 4 are combining various forms of counseling with NRT (Gain-framed Messages and NRT for Lung Cancer Screening Patients (NCT03069924), n.d.; The Lung Screening, Tobacco, and Health Project (NCT03200236), n.d.; Implementing Tobacco Treatment in Low Dose CT Lung Cancer Screening Sites (NCT03315910), n.d.; Implementing Smoking Cessation Into Delivery of Lung Cancer Screening, n.d.). The other study allows the choice of pharmacotherapy to be decided based on patient and clinician preference (Smoking Cessation Intervention During Low Dose CT (LDCT) Screening for Lung Cancer (NCT03059940), n.d.). Another study will look at a more novel approach, evaluating the potential role of tobacco-free cigarettes with counseling (Benefits of Tobacco Free Cigarette (BETOFREE) (NCT02422914), n.d.). Of note, no current studies compare effectiveness of different pharmacotherapies in this patient population.

Our study has limitations. Of the 9 studies included in our review, only 5 were RCTs (Clark et al., 2004; Aalst et al., 2012; Ferketich et al., 2012; Marshall et al., 2016; Taylor et al., 2017). The other 4 studies were observational studies and with potential for bias given analyses may not have been adjusted for all relevant confounders (Park et al., 2015; Bade et al., 2016; Luh et al., 2016). Additionally, variability between interventions and settings made it difficult to pool results and meta-analysis could not be performed. Finally, in an effort to be inclusive across contexts, we included several studies from screening programs in Europe, Asia, and Australia; however, these findings may have limited generalizability to the United States (Aalst et al., 2012; Marshall et al., 2016; Bade et al., 2016; Luh et al., 2016).

5. Conclusions

While LDCT screening represents a valuable opportunity to deliver smoking cessation interventions, the optimal strategy for these patients with high tobacco dependence remains unknown. Our review found insufficient data to suggest an optimal approach. While further research in this area is ongoing, it is important future efforts in this area combine counseling to treat the psychologic impact of addiction with pharmacotherapy to treat physiologic dependence.

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Author contributions

JMI and HK had full access to all the data and take responsibility for the integrity of the data and accuracy of the analysis. All authors contributed to study design and interpretation of data. JMI performed the statistical analysis. JMI and HK drafted the manuscript and all authors critically revised the drafted manuscript for important intellectual content.

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Conflict of interest

The authors do not have any conflict of interests to disclose.

Disclaimer

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