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Psychological Burden Associated with Lung Cancer Screening: A Systematic Review

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Abstract

Introduction—Lung cancer screening (LCS) with low dose computed tomography (LDCT) reduces mortality and is recommended for high-risk current and former smokers. Several potential harms associated with LCS have been identified, including the potential for psychological burden. To summarize the current state of the scientific knowledge on psychological burden associated with LCS, we performed a systematic search of the contemporary quantitative and qualitative research literature.

Methods—We included randomized controlled trials and cohort studies that evaluated the impact of LCS with LDCT on psychological burden and health-related quality of life (HRQOL) as assessed by validated and non-validated measures. PubMed, CINAHL, PsychINFO, and Scopus were searched for English language articles published between 2004 and January 2015. Data abstraction and quality assessment were conducted by two independent reviewers.

Results—Thirteen studies were included that met our inclusion criteria. Overall, results were variable with some studies reporting worse psychological burden for patients with indeterminate results at pre-screening, post-screening and short-term follow-up (<6 months post-screen). These adverse effects diminished or resolved at long-term follow-up (>6 months post-screen).

Conclusion—LCS may be associated with short-term adverse psychological burden, particularly after a false positive result. However, these adverse effects diminished over time. The current evidence is small, with limitations in study design and use of outcome measures. More high-quality research is needed to determine the frequency, duration, and overall magnitude of LCS-related psychological burden in non-clinical trial settings.

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Keywords

Lung cancer screening; psychological distress; anxiety; health-related quality of life; shared decision-making

Introduction

Lung cancer is the leading cause of cancer mortality for both men and women in the United States and worldwide.[1] An estimated 158,040 Americans will die from lung cancer in 2015, more than colon, breast, and pancreatic cancers combined.[2] Compared to other leading cancer sites such as colon and breast, which have better outcomes due to successful screening, the 5-year survival rate for lung cancer is only 16.6%.[3] In contrast, the ten-year survival of screen-detected lung cancers may be as high as 88%.[4] The National Lung Screening Trial (NLST) demonstrated that annual low-dose radiation computed tomography (LDCT) scans for three years improved lung cancer mortality by 20% when compared to chest x-ray.[5] This finding has led the US Preventative Services Task Force (USPSTF) and a number of professional medical organizations, including the Centers for Medicare and Medicaid Services (CMS), to support LCS with LDCT in high risk current and former smokers.[6–8]

One of the risks of LCS highlighted by most screening guidelines is the potential for psychological burden, such as anxiety related to false positive or, synonymously, indeterminate results.[9] Screening may result in anxiety and psychological distress, which can potentially impact more multidimensional outcomes such as overall health-related quality of life (HRQOL). Psychological burden can potentially occur at various time points throughout the screening process (before screening, after screening while waiting for screen results, after a positive result, after a positive workup), and can vary by severity (mild to severe).[10] Twenty-four percent of patients undergoing LDCT in NLST had pulmonary nodules identified, although 96% of these were benign. While advances in nodule management such as Lung Imaging Reporting and Data System (Lung-RADS) have minimized the number of positive studies to 10%, the high rate of false positive exams suggests that many patients are at risk for screen-related distress. However, the magnitude, duration, frequency, and trajectory of LCS-related psychological burden is largely unclear. Therefore, we performed a systematic search of the contemporary research literature to summarize the current state of the scientific knowledge on psychological burden associated with LCS. We focused on gathering information on the number of published studies and select study characteristics, including follow-up period and findings. Special attention was given to describing the type of outcome measures used to assess psychological burden in each study. Finally, we classified study findings on the potential impact of LCS on psychological burden pre-screen (baseline) and post-screen (short-and long-term).

Materials and Methods

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) were followed for this review.[11] We conducted a systematic literature search using PubMed, PsychINFO, CINAHL and Scopus electronic databases. In an effort to more efficiently identify relevant studies that reflect the most current practices in LCS with LDCT, we restricted our search to English language articles published in the last 10 years between January 2004 and January 2015. A research librarian with experience and expertise in cancer worked with the authors to develop a list of terms and Medical Subject Heading (MeSH) to further refine the search procedures. Key words included psychology, psychosocial, psychiatric, quality of life, distress, depression, anxiety, fear, risk perception, lung, early detection of cancer, cancer screening, and neoplasm (search strategies for the databases are available on request).

Review Process

Inclusion criteria for articles in the final full-text review included the following: 1) report results of an empirical study, 2) relate to LCS using LDCT, and 3) present findings on patient self-report of psychological burden and related outcomes (eg HRQOL, psychological distress, depression). We chose to include studies that utilized both validated and non-validated outcome measures of psychological burden to examine the impact of selected measures on study findings. All other studies that did not meet the criteria described were excluded, including case reports, commentaries, systematic reviews and meta-analyses. Two authors (GW, VS) independently reviewed all titles and abstracts from the initial search and reached agreement on whether selected abstracts should be retained. Where discrepancies occurred, the titles and abstracts were reviewed and discussed collectively until consensus was reached. Full text versions of the articles retained from the initial review were obtained. The full-text articles were reviewed by two authors (GW, VS) independently. The bibliography of each reviewed article was also perused for other relevant studies. Consensus was reached on articles that should be included in the final full text review.

Data Abstraction

Study characteristics from articles that met the inclusion criteria and selected through the two-stage review process were obtained. One author (VS) recorded the following details of each included study: year, location, patient population, sample size, study design, screening procedure and results, outcome measures, and key findings. A second author (GW) reviewed all abstractions for verification, completeness, and accuracy. Any discrepancies between reviewers were resolved by further discussions until a consensus was reached. Selected articles were further classified based on timing of outcome assessment. Outcome measures recorded less than 6 months after initial screening were considered short-term impact of LCS whereas those taken 6 months or more after screening were considered long-term impact of LCS.

Results

Figure 1 presents the flow diagram that outlines the approach for stepwise selection of articles included in the final full-text review. From an initial total of 2,113 articles, 13 studies that assessed the psychological burden of LCS and met the inclusion criteria were selected for review. Study characteristics of the 13 reviewed articles are summarized in Table 1. The majority of studies were derived from three large randomized controlled trials evaluating the utility of LDCT for LCS. Five studies were based from Denmark, Belgium, and the Netherlands as part of the NELSON trial which compared LDCT with no screening in current or former smokers (quit less than 10 years) aged 50 to 75 who smoked more than 15 cigarettes/day for more than 25 years, or more than 10 cigarettes/day for more than 30 years.[12] One study was based from the NLST which recruited participants between 55 and 74 years of age with at least a 30 pack-year smoking history and if a former smoker, had quit within 15 years, and randomized patients to LDCT or chest radiography.[13] Another four studies were derived from the Dutch Lung Cancer Screening Trial (DLCST) which compared LDCT to no screening for 5 rounds and included current and former smokers (quit after age 50 and <10 years prior) aged 50-70 years with 20 or more pack-years.[14]

Table 1 presents study characteristics and findings from the articles included in the final full text review. Three articles included in our review were based on cohort studies evaluating LCS. One study was derived from the Pittsburg Lung Screening study (PLuSS) which included a cohort of 50-79 year-old current and former smokers (quit within 10 years) who smoked more than a half pack a day for more than 25 years and were screened with LDCT. Vierriko et al. evaluated the psychological burden of using spiral chest CT for LCS in 633 asbestos-exposed workers from Finland with variable smoking history. Lastly, 60 individuals with extensive family history of lung cancer (three blood relatives with lung cancer with at least one first degree relative) who underwent spiral CT for LCS were surveyed regarding their risk perception and concern for lung cancer before and after the process.

Baseline (Pre-Screen) Psychological Burden

Most studies measured baseline pre-screen anxiety and demonstrated varied results. With the exception of NLST HRQOL study participants who were more likely to be female, white, more educated, and unmarried compared to controls[15], the screening groups of the remaining studies did not differ significantly in patient characteristics from control groups.[16–20] Pre-screen assessments from the NELSON trial (T0 = pre-randomization; T1 = post-randomization screening group) did not demonstrate statistically significant differences among subjects who eventually received negative CT scan results and those who eventually received indeterminate results in all measures of HRQOL, general anxiety, and lung cancer specific distress.[18] At T1, screening group subjects had HRQOL and general anxiety scores that were comparable to those of the Dutch general population.[17] However, all respondents had certain HRQOL scores that were significantly worse after randomization than before ($P<0.05$ for EQ-5D, $P<0.001$ for STAI 6 and IES).[18] In addition, a subset of patients who reported most discomfort while awaiting screening results had significantly worse lung cancer specific distress at randomization than those that found other aspects of CT scanning most discomforting.[17] When baseline perceived risk was evaluated in the NELSON trial

population, 14.6% (n = 47/324) of participants reported high affective risk 1 day before screening and these participants had significantly worse measures of lung cancer-specific distress and general HRQOL than those in the low affective risk group ($p<0.01$).[21] In a separate study on the same patient population, it was concluded that pre-screen informed decision-making, defined as adequate knowledge and a positive attitude toward LCS, had no effect on any measures of HRQOL except a better mental component score for those who made an informed decision ($p=0.003$).[19] In the United States, NLST screened and control participants did not report significant differences in baseline HRQOL and anxiety measures.[15]

Rasmussen et al. reported that DLCST participants in the control group had significantly worse psychosocial consequences when compared to the screened group at baseline ($p<0.022$).[22] Another study comparing DLCST participants to a sample of the general population at baseline found significantly higher negative psychosocial scores in the latter group in all psychological burden measures. This was attributed to significant differences between the trial participants and a comparable population control, including more women, higher socio-economic status, longer education, higher employment rate, and more central urban location in the trial group.[23] In contrast, two separate DLCST-based studies evaluated trial participants and equivalent general population controls at baseline and found no statistically significant differences in the outcomes measures utilized, including consequences of screening (COS)[16] and use of anxiolytics or antidepressants.[20]

A study derived from the PLuSS demonstrated lower baseline anxiety and fear of cancer in individuals who were eventually found to have a suspicious screening result compared to those who eventually received an indeterminate or negative result.[24] In a population at high-risk for lung cancer (based on family history), 64-74% had high pre-screen lung cancer risk perception and 94% of participants reported thoughts and concerns about developing lung cancer that did not affect mood or interfere with daily activity.[25] One third of asbestos workers undergoing LCS thought that they were at risk for lung cancer at baseline. Additionally, baseline anxiety was higher in the false positive group than in the negative group.[26]

Short-Term (Immediate and <6 Months Post-Screen) Psychological Burden

Short-term (immediate post-screen and <6 months) LCS-related psychological burden also varied by trial and screening results. The NLST did not demonstrate significant difference in HRQOL or anxiety among LCS participants that received false positive, significant incidental or negative results at 1 month after screening. However, patients who had true positives had lower scores on the mental component aspect of the SF-36 compared to baseline (OR 3.95 CI -5.87, -2.04 $p<0.001$), which signified worse anxiety, as well as higher STAI ratio (OR 1.47 CI 1.16–1.88, $p<0.01$), or worse HRQOL, than those with false positive, incidental, and negative results.[15] The NELSON trial reported that 46.4% of participants reported discomfort and 50.5% reported dread or fear while waiting for results, and this subgroup had significantly worse measures of HRQOL and lung cancer-specific distress as measured by STAI-6 and IES, respectively ($P<0.01$). In addition, 76% of respondents reported the most discomfort while awaiting CT scan results, and had worse

STAI-6 and IES scores immediately post-screen compared with those who reported most discomfort with other aspects of CT scanning ($p<0.05$ and <0.01, respectively).[17] In a separate study from the same trial, there was no significant difference immediately post-screening in any measures of HRQOL or anxiety between the negative and indeterminate result groups. However at 2 months follow up, participants with indeterminate results had higher IES scores, indicating worse lung cancer specific distress than in the negative result group ($P<0.01$). In the negative result group, IES scores improved at two months compared to post-screen and to baseline scores ($P<0.01$ for both). In the indeterminate group, EQ-5D scores measuring HRQOL and IES scores worsened at 2 months compared to post-screen and baseline scores ($P<0.01$ for both). Likewise, STAI-6 scores suggested increased anxiety from baseline to 2 months in those with indeterminate results ($P<0.05$).[18]

Similar short-term findings were reported from the PLuSS cohort that demonstrated increased general anxiety measures with indeterminate or suspicious screening results immediately following and up to 1 month after screening. Fear of cancer scores (PCQ) increased after LDCT for screenees with suspicious results and were relatively unchanged for the negative or indeterminate groups. Perceived risk of cancer decreased in short-term follow up for those with negative screen results and increased for those with indeterminate or suspicious results. For all categories, perceived risk of cancer was higher than objective risk. However, perceived risk of cancer was accurately estimated to be high by those who had a suspicious screening result, while the negative and intermediate groups estimated much higher perceived risk than their actual objective risk. Additionally, higher education and married status were associated with lower anxiety while current smoking status was associated with higher anxiety. Current smokers and women experienced higher fear of cancer whereas the opposite was true for those with higher education.[24] Similarly, for subjects undergoing screening for extensive family history of lung cancer, short-term evaluation at 1 month after screening demonstrated increased levels of worry, concern and perceived risk of cancer.[25] In contrast, asbestos workers who received a negative or false positive LDCT screening result experienced decreased anxiety ($p<0.001$) compared to baseline. There were also no differences in post-screening perceived risk of or worry for lung cancer among participants with negative or false positive results.[26]

Long-Term (>6 Months Post-Screen) Psychological Burden

Long-term adverse psychological burden of LCS was reduced or absent in most studies. At 6 months follow-up, only NLST HRQOL participants who received true positive results had worse HRQOL and anxiety measures from baseline. There was no difference in HRQOL or anxiety among the negative, false positive, or significant incidental finding groups from baseline to 6 months after screening.[15]

HRQOL and anxiety also did not change 6 months after baseline for participants in the NELSON trial and were not significantly different between the negative and indeterminate groups.[17] Long-term assessment of lung cancer specific distress in low and high perceived risk groups showed that although IES scores were significantly lower at 6 months than at baseline for both groups, the high affective risk group had worse IES scores than the low affective risk group ($p<0.01$). However, there were significantly fewer subjects in the high

affective risk group at 6 months than at pre-screen baseline.[21] At 2 years, HRQOL and anxiety scores were not different between screen and control groups and any discrepancies in IES scores between indeterminate and negative result groups had resolved to baseline levels by the second round of screening.[27] Long term follow up of PLuSS subjects at 6 months demonstrated that the short-term increase in anxiety in the indeterminate group had resolved and that the elevated perceived risk and fear of cancer experienced by those with suspicious screening results had diminished.[24] By 6 months after screening, the same return to baseline of short-term increased worry, concern and perceived risk occurred in high risk screenees with extensive family history of lung cancer.[25] In the screened population of asbestos workers, no significant long-term psychological differences were identified based on screening result.[26]

In assessing long-term psychosocial consequences of screening in DLCST participants, one study found significant increases in COS-LC scales in both control and screening groups 1 year after baseline CT. In addition, while no significant differences in COS-LC measures were found between the control and screen group at baseline, there were several significant differences in scores for anxiety, dejection, and self-blame at 1 year with the control group scoring worse than the screening group. This may be attributed to the significantly higher response rate of participants in the screening group (97%) compared to that of the control group (91.8%) in the prevalence screening round after randomization ($p<0.0001$), or to the fact that individuals with false positive results were excluded from analysis.[16] Rasmussen et al. also reported significant increases in COS-LC scores for behavior, dejection, and poor sleep for both the screen and control groups after each annual screening up to 4 years. However, by years 3 and 4 (screening rounds 4 and 5), the scores for the screening group were closer to baseline. In general, the control group reported significantly worse psychosocial consequences compared to the screening group at all 5 rounds over 4 years. The control group also had more lung-cancer-specific negative psychosocial consequences compared to the screen group at 1, 2, and 4 years.[22] Lastly, there was no difference in the use of anxiolytics or antidepressants after 3-year follow-up between the screen and control groups in this trial population.[20]

Outcome Measures Utilized

The selected articles utilized both validated and non-validated measures that were either general or condition-specific. Some studies used interviews to assess the effects of LCS on anxiety, fear, or worry of screening procedures, false positive results, and perceived risk. Outcome measures are summarized in Table 2 and include: the European Quality of Life (EQ-5D) with the visual analogue scale (VAS) for ranking self-impression of health; the two-component 36-item Short Form questionnaire (SF-36) with its shorter version the SF-12, both of which measure generic HRQOL (MCS = mental component summary and PCS = physical component summary); the State-Trait Anxiety Inventory (STAI-20 and STAI-6) with 20 and 6 questions, respectively, that measure generic anxiety; the impact of event scale (IES) which measures lung cancer specific distress; the consequences of screening (COS) and the lung-cancer-specific consequences of screening in Lung Cancer (COS-LC) which was developed and validated in the NELSON trial and the Dutch Lung Cancer Screening Trial (DLCST) and assesses the psychological burden of LCS [22,28]; the

Psychological Consequences Questionnaire (PCQ) adapted from a validated measure in breast cancer screening to measure lung cancer fear.

Discussion

This systematic review identified and reviewed 13 studies that examined the impact of LCS on psychological burden. Ten of the studies were derived from three large randomized control trials evaluating the efficacy of LCS (NELSON, NLST, DLCST) while three studies reported psychological outcomes in smaller cohorts undergoing LCS (PLuSS, asbestos workers, individuals with lung cancer family history). Collectively, the current scientific evidence suggests that LCS has the potential to cause short-term psychological burden in individuals with an indeterminate scan result, although the adverse effects do not appear to persist long-term. This is in contrast to the current evidence in mammography screening for breast cancer, where indeterminate results requiring further investigation resulted in short-term increased anxiety which persisted long-term for up to three years.[29,30] Additionally, most of the reviewed studies did not report differences in psychological burden among individuals with false positive and true negative results. In some cases, a negative result led to decreased distress and anxiety while a true positive resulted in increased anxiety and worse HRQOL.[15,26] Furthermore, individuals with indeterminate or suspicious results who endorsed high perceived risk of lung cancer or who experienced the most discomfort while waiting for CT screening results had increased anxiety, lung cancer-specific distress, and fear of lung cancer.[17,21,24]

There are several characteristics to the current body of evidence that warrants further discussion. First, our search yielded a small total number of studies evaluating psychological burden in LCS. This may perhaps be a result of the perception that psychological burden is trivial compared to the potential physical harms from screening, or the lack of a clear conceptual framework to guide high-quality studies on LCS-related psychological burden. Harris and colleagues recently proposed a framework to guide research examining the potential harms associated with LCS. The framework includes four key domains: physical harm, psychological harm, financial strain, and opportunity costs.[31] Psychological harm, as proposed within this framework, can potentially occur at any step of the “screening cascade,” but may be heightened at specific timepoints, such as receiving scan results or undergoing additional workup for a positive screen.[31,32] Development and further refinement of conceptual frameworks on the psychological burden of LCS can potentially yield more high-quality evidence in future research.

The majority of studies selected in our review were conducted in the context of clinical trials that evaluated the effectiveness of LCS, comparing outcomes between screened versus nonscreened populations. Although these studies provide some evidence on LCS-related psychological burden, the findings may be biased because trial participation itself may have psychological effects.[32] Furthermore, characteristics of trial participants are usually different from community nonparticipants; therefore the true magnitude of psychological burden may not be fully detected. Another important factor to consider is the context of the screening situation. Current recommendations are focused on screening high risk populations of current and former smokers. These individuals may already be experiencing feelings of

guilt, shame, and anxiety based on factors such as perceived risk of developing lung cancer.[31] Only six studies from our review included the assessment of these potential moderating factors.

Another important characteristic in our selected studies is the heterogeneity in outcome measures utilized to capture psychological burden. The majority of measures used were general rather than condition-specific. The use of general measures of psychological burden and HRQOL alone may not be as responsive to the subtle changes in psychological burden as condition-specific measures.[10] There are few condition-specific measures in LCS with strong psychometric properties, with the exception of the COS-LC, which was used primarily in the European LCS trials. The addition of a more condition-specific measure may have resulted in differences in psychological burden outcomes in the European and US trials in our review. There is a need to develop and refine condition-specific psychological burden measures that are reliable and relevant to LCS populations.

The current Medicare coverage guidelines put forth by the Center for Medicare and Medicaid Services (CMS) includes a counseling and shared decision-making visit on the benefits and potential harms of LCS. Extensive counseling on LCS harms is a potentially promising strategy to decrease short-term psychological burden associated with LCS. Analysis of HRQOL and state anxiety data from the NLST study revealed no differences in these outcomes by screen-results (false-positive, true-positive, significant incidental findings), which the authors attributed partially to the extensive counseling that trial participants received.[15] Quality counseling and shared decision-making can be guided by tools such as patient decision aids, which are designed to help individuals participate in complex decision-making related to health care options and to improve decision quality.[33] Decision aids prepare patients to make informed, value-based decisions by providing quality information on the options available in easily understandable formats and coaching patients on communicating personal value to providers.[33] As demand for LCS with LDCT increases, the provision of high quality information on the benefits and harms of screening is needed to promote informed decision-making, eliminate misperceptions, and reduce screen-related psychological burden.

Our review has some limitations. First, the small body of literature limits the ability to comment on the quality of data currently available. Second, our review focused only on psychological burden in the context of LCS; therefore, the findings may not be generalizable to other cancer screening settings. Finally, as previously discussed, our review yielded primarily studies that were conducted in an LCS clinical trial context; therefore, findings may be biased and not generalizable to non-participants.

In summary, based on our review, LCS did not appear to have substantial long-term impact on psychological burden, but potential short-term psychological burden was observed. More high-quality research conducted in non-clinical trial settings are needed to determine the frequency, duration, and overall magnitude of psychological burden associated with LCS.

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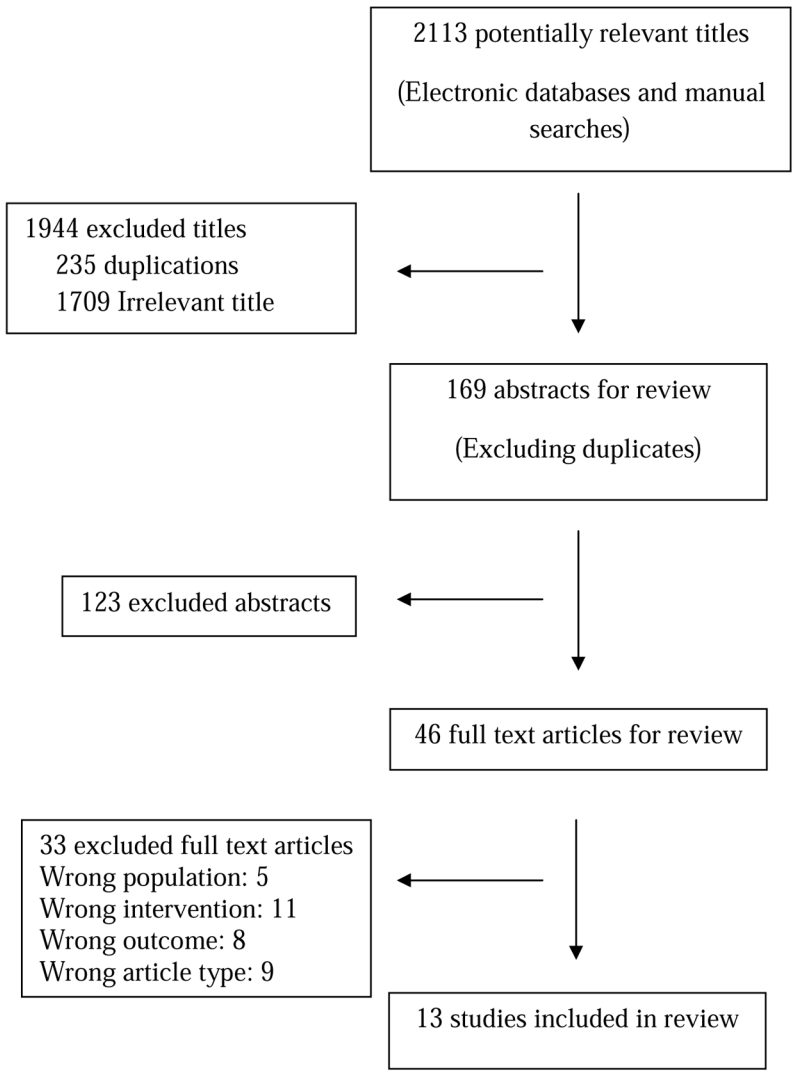

Figure 1.
Flow Diagram Representing Selection of Studies

Table 1

Characteristics of Selected Studies

Study, year	Location	Trial Population	Sample Size	Follow-up Period	Response rate %	FP[1]/IR[2]%	Outcome Measures	Findings
van den Bergh et al., 2007[14]	Denmark Belgium	NELSON[3]	351	T1= pre- screen T2= post- screen T3= 6 months	92.3 94.4 90 All surveys 76.9	17	Discomfort SF-12 EQ-5D STAI-6 IES	*Baseline:* Screening population had similar HRQoL and anxiety scores as general population. *Short-term:* not reported. *Long-term (6 months):* No significant change in any outcome measures from baseline. *Other:* 46% reported discomfort while awaiting results and a subset of these with IR had worse STAI-6 and IES scores (p<0.01)
Bunge et al., 2008[15]	Netherlands	NELSON	351	Pre-screen 6 months	92.3 90	17	Affective Risk IES SF12	*Baseline*: Those with high lung cancer risk perception had increased IES and lower MCS score than those with low risk perception (p<0.01) *Short term*: not reported *Long term (6 months):* IES was less but still significantly higher in those with high lung cancer risk perception compared to those with low risk perception (p<0.01) Difference in MCS score not present

Study, year	Location	Trial Population	Sample Size	Follow-up Period	Response rate %	FP[1]/IR[2]%	Outcome Measures	Findings
van den Bergh et al., 2010[16]	Denmark Belgium	NELSON	630	T0= baseline T1= pre-screen T2= post-screen T3= 2 month	91 93.6 93 87.7 All surveys 71.4	22.4	SF-12 EQ-5D STAI-6 IES	*Baseline:* Prescreen HRQoL scores worse than baseline (p<0.05) Postscreen STAI-6 and IES scores better than prescreen (p<0.01) *Short term (2 months):* NR[4] group: IES scores better from baseline (p<0.01) IR group: Worse IES, EQ-5D than at baseline and post ,l-screen (p<0.01); worse STAI-6 scores than at baseline (p<0.05) *Long-term:* not reported
van den Bergh et al., 2010[17]	Netherlands Belgium	NELSON	288	T0= deciding to participate T1= before randomization T2= after results	93 89	22	SF-12 EQ-5D STAI-6 IES COS-LC	*Baseline:* Pre-randomized subjects who made informed decision had better MCS[5] scores than those who did not (p =0.003) IR group: no differences in any outcome measures after receiving results between subjects with and without an informed decision *Short term/long term:* not reported
van den Bergh et al., 2011[18]	Netherlands Belgium	NELSON	1466	T0= pre-screen T1= 2 months T2= 2 year	87.9 87.7 78.9	20.5	SF-12 EQ-5D STAI-6 IES	*Baseline:* IR and NR groups: no difference in IES or EQ-5 *Short-term (2 months):*

Study, year	Location	Trial Population	Sample Size	Follow-up Period	Response rate %	FP[1]/IR[2]%	Outcome Measures	Findings
								IR group: worse IES compared to baseline and at 2 years (p<0.01) *Long-term (2 years):* Screen and control groups: no difference in HRQoL from baseline IR and NR groups: no difference in HRQoL from baseline
Gareen, et al., 2014[19]	United States	NLST[1]	2812	Baseline 1 month 6 months	82.4 70.8	24.5 9.5 (SIF[2])	SF-36 STAI	*Baseline:* not reported *Short-term (1 month):* FP, SIF, NR groups: No difference in HRQoL or anxiety scores from baseline TP[3] group: Worse outcomes from baseline (p<0.001) *Long-term (6 month):* FP, SIF, NR groups: No difference in HRQoL or anxiety scores from baseline TP group: Worse outcomes from baseline (p<0.001 for SF-36, p<0.05 for STAI)
Hestbech, et al., 2011[20]	Denmark	DLCST[4]	4,104(DLCST) 673[5]	Pre-screenonly	99.5(DLCST) 77.4 (CPS)	NR[6]	COS-LC	*Baseline:* Trial participants: from better social groups, had longer education (p<0.0001 for both), and better COS-LC scores than the control group for all scales (p<0.01) and single items (p<0.02)

Study, year	Location	Trial Population	Sample Size	Follow-up Period	Response rate %	FP[1]/IR[2]%	Outcome Measures	Findings
								Short term and long term: not reported
Aggestrup et al., 2011[21]	Denmark	DLCST *Excluded TP/FP	4104	Pre-screen 1 year	97 (screen) 91.8 (control)	3.9	COS COS-LC	*Baseline:* Control and NR group: no significant difference in COS measures *Short term:* not reported *Long term (1 year):* Control group: worse COS and COS-LC scores than screening group (p<0.05) Control and screening groups: Worse COS-LC and single item scores compared to prescreen (p<0.05)
Kaerlev et al., 2012[22]	Denmark	DLCST	4104	Baseline Once in 3 years	94.1	NR	Use of AD[7] or AX[8]	*Baseline:* LCS and control groups: no difference in use of AD or AX *Short term:* not reported *Long term (up to 3 years):* LCS group: No increase in use of AD and AX (HR 1.00, 95% CI (0.90-1.12)
Rasmussen et al., 2015[23]	Denmark	DLCST	4104	Pre-screen 1 year (round 2) 2 year (round3) 3 year (round 4) 4 year (round 5)	95.5 (screen) 73.6 (control)	NR	COS-LC	*Baseline:* Control group reported worse core scores than screen group for dejection (p<0.0001) *Short term:* not reported *Long term (1–4 years):* Screen and control groups: worse measures of behavior, dejection, and negative

Study, year	Location	Trial Population	Sample Size	Follow-up Period	Response rate %	FP[1]/IR[2]%	Outcome Measures	Findings
								impact on sleep at 1 year compared to pre-screen (p<0.0001). Screen group: Differences persisted through years 2-4, but measures of behavior and dejection returned to baseline by 3 and 4 years. Control group: worse core scores than screen group for all 4 core scales at 1-4 years and 4 of 5 lung-cancer-specific scales for 1,2,4 year (p<0.036).
Byrne et al., 2008[24]	United States	PLuSS[1]	341	Pre-screen Post-screen 6 mo 12 mo	85	35	STAI PCQ Perceived risk of lung cancer (0–100%)	*Baseline:* No differences in outcome measures among NR, IR, or suspicious result groups. IR: perceived risk was higher than objective risk *Short-term (post-screen):* IR and suspicious results group: increased short term state anxiety (p<0.001), perceived risk and fear of cancer from baseline NR: temporary reduction in perceived risk of cancer All groups: perceived risk greater than objective risk *Long-term (6–12 months):* NR, IR: postscreen anxiety and perceived risk of cancer decreased while fear of

Study, year	Location	Trial Population	Sample Size	Follow-up Period	Response rate %	FP[1]/IR[2]%	Outcome Measures	Findings
								cancer was unchanged from short-term Suspicious results group: from postscreen, state anxiety was lower at 6 months while fear and perceived risk of cancer remained elevated at 12 months
Vierikko, et al., 2009[25]	Finland	Asbestos-exposed workers	633	Baseline 1 year	72.2	15.3	Questionnaire assessing Risk awareness Perceived lung cancer risk Health anxiety Lung cancer worry Screening necessity Trial adherence	*Baseline:* No differences in pre-screen perceived lung cancer risk or worry between NR and FP groups FP did not negatively affect trial adherence intention *Short term (postscreen):* Screening led to decrease in anxiety ($p<0.001$) in NR and FP groups compared to baseline No differences in post-screen perceived lung cancer risk or worry between NR and FP groups *Long term (1 year):* No significant differences in outcome measures between NR/TP and FP groups
Sinicrope, et al., 2010 [26]	United States	Individuals with 1 first degree relative and at least 3 other relatives with lung cancer (Mayo Clinic Lung Cancer Genetic Epidemiology Registry)	60	Pre-screen 1 month 6 month	NR	31	Questionnaireassessing Expectations of LCS accuracy Risk perception (likely/ unlikely/	*Baseline:* 64–76% of all respondents had higher perceived risk 94% reported concern for developing lung cancer

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Study, year	Location	Trial Population	Sample Size	Follow-up Period	Response rate %	FP[1]/IR[2]%	Outcome Measures	Findings
							neither) Lung cancer concern	*Short term (1 month):* Non-negative result group: increased perceived risk and lung cancer-related concern compared to baseline NR: comparable perceived risk but decreased lung cancer-related concerns compared to baseline *Long term (6 months):* Non-negative result group: cancer-related concerns decreased to baseline levels11 NR: decreased absolute perceived cancer risk and lung cancer- related concerns from baseline; increased perceived cancer risk in those who believe their risk comparable to those of same age sex, and race

[1] False positive

[2] Indeterminate result

[3] Dutch-Belgian Randomized Lung Cancer Screening Trial

[4] Negative result

[5] Mental Component score of SF-36 (see table 1)

[6] Health related quality of life

[1] National Lung Screening Trial

[2] Significant incidental finding

[3] True positive

[4] Danish Lung Cancer Screening Trial

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[5] Comparable population sample (control)

[6] Not reported

[7] Antidepressant

[8] Anxiolytic

[1] Pittsburg Lung Screening Study

Table 2

Measures of HRQOL[1] used in Reviewed Studies

Test	Measures	Description	Subcategories	Range
36-item short form questionnaire (SF- 36)[1–3]	Generic HRQoL	36-question survey used to derive 8 profiles of functional health	Physical component score (PCS): measures the absence of physical limitations, disability or decrease in well-being and energy level (physical functioning, role-physical, bodily pain, general health)	0-100 Higher score indicates better HRQoL
12-item short form questionnaire (SF- 12)[4, 5]	Generic HRQoL	Shorter version of SF-36	Mental component score (MCS) measures the absence of psychological distress and limitations in usual social/role activities because of emotional problems (Vitality, Social Functioning, Role-Emotional, and Mental Health)	
European quality of life (EQ-5D)[6, 7]	Generic HRQoL	5 questions that assess mobility, self care, usual activities, pain/discomfort, anxiety/ depression	Rate own health on visual analogue scale (VAS)	0–100 Higher score indicates better HRQoL
State-trait anxiety inventory (STAI- 20/6)[8, 9]	Generic anxiety	20 questions assessing state anxiety, 20 items in trait anxiety	State anxiety: unpleasant emotional arousal in face of threatening demands and dangers	20–80
		6 questions related to anxiety: calm, tense, upset, relaxed, content, worried	Trait anxiety: existence of stable individual differences in tendency to respond with anxiety when anticipating a threatening situation	Higher score indicates greater anxiety
Impact of event scale (IES) [10]	Lung cancer- specific distress	15 questions tailored assess lung cancer as a specific stressor.	Avoidance and intrusion	0–75 Higher score indicates more cancer specific distress
Consequences of screening (COS) and consequences of screening in Lung Cancer (COS-LC)[11]	Psychosocial consequences in screening and specifically lung cancer screening	4 core scales (anxiety, sense of dejection, negative impact on behavior, sleep), 2 single questions (busy to take mind of tings, less interest in sex) 5 LCS[2] specific scales (focus on airway symptoms, introvert, stigmatization, harm of smoking, self-blame)	Part I: psychosocial aspects relevant for potential screening participants Part II: applicable for participants after final diagnosis (screen group only)	Higher score indicates more negative psychosocial consequences
Psychological Consequences Questionnaire (PCQ)[12, 13]	Fear of lung cancer (nonvalidated)	Adapted from validated questionnaire to assess emotional, social, and physical consequences of breast screening	**1** Are you afraid that you may have cancer? **2** Does the thought of death from lung cancer scare you? **3** Are you afraid of dying soon from lung cancer?	Higher score indicates greater fear of lung cancer

[1] Health-related quality of life

[*] Based on validated questionnaire of psychological consequences of mammography screening in breast cancer.