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Research Article

Safety and Effectiveness of Lung Cancer Screening Using Low-dose Computed Tomography Scan in High-risk Individuals: A Comprehensive Review

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Abstract

Context: Lung cancer is the most important cause of cancer mortality. Given the incidence and mortality of this disease, the implementation of preventive interventions is necessary.

Objectives: The present study investigated the effectiveness of one of the most important interventions of lung cancer screening with low-dose computed tomography (LDCT) in high-risk individuals.

Evidence Acquisition: The present study was an applied study performed as a comprehensive review. For the assessment of safety, studies on the technical specifications of computed tomography scans and issues related to the safety of applying this device were searched using keywords in medical databases. For the evaluation of clinical effectiveness, a comprehensive review of health technology assessment studies, systematic review studies, and screening guidelines was performed.

Results: Based on 15 studies extracted for the safety issue, the diagnosis of harmless tumors, false positives cases and Unnecessary invasive complementary interventions, and possible negative effects of radiation exposure are discussable safety issues. Based on the synthesis of 16 studies on effectiveness, lung cancer screening intervention using LDCT was determined to reduce lung cancer mortality by 15 - 20% and mortality from other causes by 0 - 6%. Additionally, the incidence of this disease in its upper stages decreases significantly.

Conclusions: Lung cancer screening using LDCT does not threaten the health of individuals seriously and, in comparison to non-intervention is more clinically effective and will lead to a statistically significant reduction in lung cancer mortality and increase in the timely diagnosis of this disease.

Keywords: Lung Cancer Screening, Health Technology Assessment, Low-dose CT Scan, Smoking, Safety, Clinical Effectiveness

1. Context

Lung cancer is recognized as one of the most prevalent cancers and the most important cause of cancer mortality worldwide (1). According to Global Cancer Incidence, Mortality, and Prevalence, lung cancer (code: C33-34) had the second and first ranks in terms of incidence and mortality in 2020 in the world, respectively. The incidence of this cancer in 2020 was 10,465 individuals in Iran (http://gco.iarc.fr/today/home). The most important cause of lung cancer is heavy smoking (2). According to a study performed in South Korea in 2014, 80% of lung cancer patients smoked heavily (3). The incidence of lung cancer peaks within 55 - 65 years of age.

There are several treatments for lung cancer which, based on the diagnosis and progression of the disease, the treatment team decides on using them and generally have high costs for the patient and the community (4). Patients are referred for treatment when they are in the non-surgical stage. Therefore, the early diagnosis of lung cancer is of great importance. Based on the evidence, screening is one of the best methods to reduce

the incidence and the resulting mortality of this disease (5).

Lung cancer screening greatly reduces the risk of dying from this cancer. Screening for lung cancer aims to diagnose this disease at early stages (when the probability of treatment is high) (6). According to the recent recommendations of international organizations, including the American Cancer Society, the American College of Radiology, and the International Association for the Study of Lung Cancer in 2013, the annual screening of high-risk individuals using low-dose computed tomography scan (LDCT) is one of the most effective methods in preventing lung cancer mortality (7). Given limited health resources, using such methods requires ensuring their effectiveness for countries; therefore, performing studies on the evaluation of safety, effectiveness, and costs of using this method is among the requirements that should be considered to decide whether or not to use these methods as the main disease control interventions.

2. Objectives

Due to the lack of similar studies in the country, the present study was conducted aiming to evaluate the safety and clinical effectiveness of lung cancer screening using LDCT in Iran.

3. Evidence Acquisition

First, this study assessed the safety of lung cancer screening using LDCT in high-risk individuals compared to non-intervention. To this end, the issues that staff and individuals implementing the screening, individuals undergoing this intervention, and other individuals might encounter at the time of implementing the screening were assessed using the areas defined in the Health Technology Assessment Core Model® in the domain of safety via first searching in medical databases, such as Google Scholar, PubMed, and Scopus, using a combination of the general keywords, including "Safety", "Risk", "CT scan", "Computed Tomography", "LDCT", and "Screening". Then, the texts were reviewed, and the relevant cases were extracted and surveyed. In this section, an attempt was made to consider and examine any important issues. After search and review, the extracted studies were entered into EndNote software (version 8). Duplicate articles were removed, and finally, the results of 15 studies were used to review the safety issue. For the evaluation of clinical effectiveness, by the use of a comprehensive review of secondary studies (ie, health technology assessment studies, systematic review and meta-analysis studies, and lung cancer screening guidelines), the search strategy was defined as follows:

3.1. Population, Intervention, Comparison, and Outcome (PICO)

Population: Individuals at high risk of lung cancer, including those aged 50 - 75 years with at least 20 to 30 packs of cigarettes per year.

Index Test: Lung cancer screening using LDCT.

Comparison Group: Non-intervention.

Outcomes: The early diagnosis and timely treatment of lung cancer, increased incidence in the short run, change of diagnosis time from the final stages of the disease to the earlier stages, reduced lung cancer mortality, reduced overall mortality for any reason after screening, and increased quality of life.

According to the design of the current study, the search for related studies, which was a comprehensive review of secondary studies, was performed in two stages as follows:

1. A complete study of the International Network of Agencies for Health Technology Assessment (INAHTA) website to review all studies related to lung cancer screening: The INAHTA website, without any limitation in the type of intervention and population, was searched by the general keywords of "Screening" and "Lung Cancer", and all cases were reviewed.

2. A review of other medical databases to find systematic review studies and lung cancer screening guidelines of other countries: Other medical databases, including Cochrane, PubMed, and Google Scholar, were searched for systematic review studies and screening guidelines of other countries not listed on the INAHTA, both in English and in Persian, within 2010 - 2020 that were entered into the study. Regarding the related information, other relevant websites and dissertations were searched manually. Endnote software (version 8) was used to manage the extracted studies.

4. Results

As a result of searching and reviewing the above-mentioned medical databases regarding the safety issue of lung cancer screening using LDCT in high-risk individuals, 1982 articles were extracted. Finally, the results of 15 studies were used. Figure 1 shows the process of identifying Related studies, removing the duplicates, and screening based on the titles, abstracts, and full texts to evaluate clinical effectiveness. After searching, the studies were entered into EndNote software (version 8). A total of 17827 related articles were identified. After removing the duplicates, 16 articles remained, which were examined based on the titles, abstracts, and full texts. Subsequently, 16 studies were eligible for a full-text review.

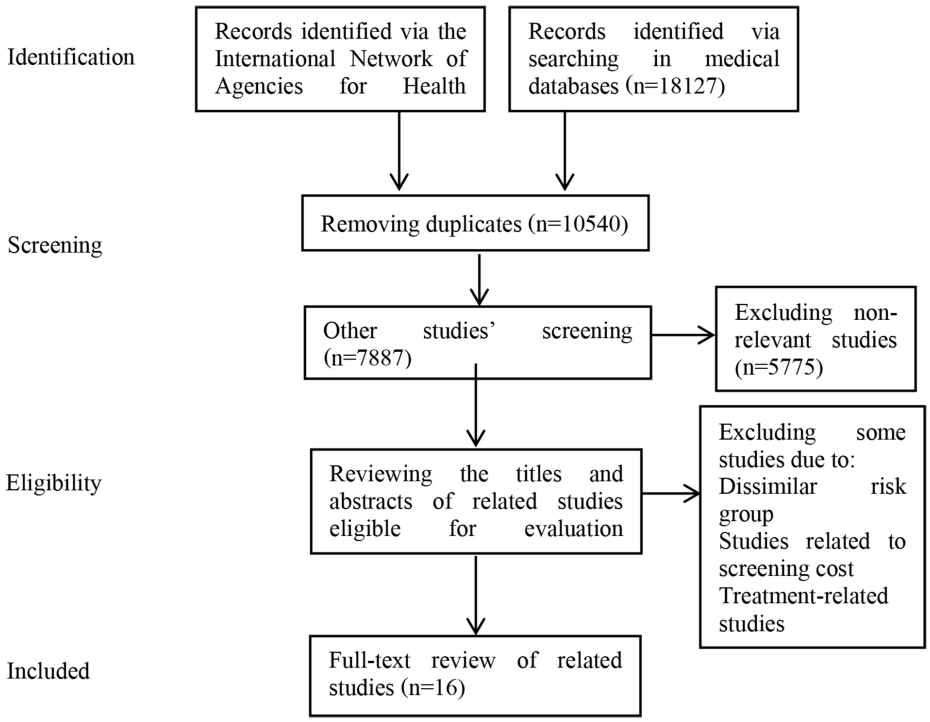

Figure 1. Flowchart of Screening Studies Based on the PRISMA Standard

The findings obtained from both safety and clinical effectiveness issues are reported separately as follows:

4.1. Safety

Regarding the advantages, disadvantages, and safety of LDCT screening, the obtained studies focused mainly on issues, such as the dose of used radiation and its related problems, the effects of this screening on individuals' mortality, false positives, and overdiagnosis which also leads to post-screening unnecessary interventions and side effects of radiation exposure. The results of each of the areas covering the safety issue are as follows:

4.1.1. Radiation Dose in LDCT

As a result of the obtained studies, there are different theories for determining radiation dose to perform a computed tomography (CT) scan on an individual. According to the research in this regard, some studies suggest a specific dose; however, others consider the dose of radiation based on factors, such as an individual's weight or the average dose recommended by other studies. The International Society for the Protection of Organs against Radiation promotes the use of LDCT to reduce radiation absorption by the individual being imaged. According to Van Sint Jan et al.'s study, the use of LDCT does not affect the reduction of image quality (8). Given the National Lung Screening Trial (NLST) and the International Early Lung Cancer Action Program, at least four multidetector computed tomography scanners are used for LDCT to ensure that a high-quality chest scan is performed with a single breath-holding. Additionally, due to the high-contrast resolution between air and lung masses, LDCT maintains quality and good detection and simultaneously provides low-dose radiation (6, 9).

The International Commission on Radiological Protection declared the radiation dose limits for 24-section and 12-section CT scans as 1.9 and 5.3 mSv, respectively. The effective dose of LDCT radiation in each examination is estimated to be 1.5 mSv; nevertheless, there is considerable variation in actual clinical trials. However, the dose used to evaluate the chest diagnostic CT identified lesions has been estimated to be 8 mSv and for positron emission tomography to be 14 mSv. According to Bach et al.'s study, during a three-year follow-up, each participant in the NLST project received approximately 8 mSv (on average, among all screened populations) (10). According to the NLST, the advantages of preventing lung cancer mortality outweigh the radiation risk, becoming apparent 10 - 20 years later. However, screening is less desirable for young individuals or those who are at a lower risk of developing lung cancer (10).

4.1.2. Reduced Lung Cancer Mortality

In 2011, the NLST reported that LDCT screening significantly reduced lung cancer mortality in the high-risk population (6). Accordingly, LDCT screening was observed to cause a 20% relative reduction in lung cancer mortality over a 5-to-6-year follow-up on average. Based on the evidence, for the prevention of an individual from lung cancer death, 310 individuals should be screened (10, 11).

4.1.3. Cases of Overdiagnosis, False Positives, and Unnecessary Interventions

In addition to cancerous tumors, benign masses are also detected by LDCT screening. Screening tests consider benign or noncancerous masses as "false positives". Most studies have reported that more than 90% of the masses are false positives.

Overdiagnosis also occurs by performing lung cancer screening, meaning that in addition to the diagnosis of malignant tumors, harmless tumors are also diagnosed, which, if not diagnosed, might never cause clinical symptoms. These cases of overdiagnosis indicate potentially significant harm in screening because the patient incurs extra costs, anxiety, and illness associated with cancer treatment and has to perform post-screening unnecessary interventions. The tumor size which requires an individual to refer for invasive tests, including sampling or subsequent imaging, varies. According to the NLST, 1.2% of patients who did not have lung cancer underwent invasive procedures, such as needle biopsy or bronchoscopy. In addition, 0.7% of patients who did not have lung cancer underwent thoracoscopy, mediastinoscopy, or thoracotomy (12). In the NELSON study, this value was 1.2% for the first phase of screening and 0.8% for the second phase of screening (13). Based on Gopal et al.'s study, lung cancer screening through LDCT leads to the increased diagnosis of benign masses (odds ratio [OR] = 3.1; 95% CI: 3.7 - 2.6) and increased unnecessary thoracotomies for benign lesions due to screening (14).

4.1.4. Negative Effects of Radiation

Regarding the effects of radiation exposure, based on Brenner's study, in general, the relative risks of radiation exposure of radiation significantly decrease with age; nonetheless, there is an incremental interaction effect between radiation effect and being a smoker in an individual exposed to radiation which, in the case of increasing the age of the population undergoing screening, this risk will reduce by 50%. The described estimates indicate that a CT screening initial examination for lung cancer leads to a relatively low risk (0.06%) for lung cancer and other cancers (15).

4.2. Clinical Effectiveness

The evaluation of the clinical effectiveness of lung cancer screening using LDCT in high-risk individuals in this study is a comprehensive review and aims to obtain the results of health technology assessments, systematic review studies, and screening guidelines regarding lung cancer. The clinical effectiveness of lung cancer screening has been evaluated in studies of different countries with generally similar goals and strategies but in different manners in terms of details. These differences mainly include items, such as the sample size of clinical trials under review, the type of main intervention and types of interventions in control groups, smoking rate, and the selection of a different age range to define the high-risk group. Table 1 shows the general specifications of the final reviewed studies.

Table 1. General Specifications of Studies Related to Clinical Effectiveness

Rank	Authors	Title	Research type	Country	Year
1	Snowsill et al. (16)	Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation	Health technology assessment	England	2018
2	Zhou et al. (17)	China national lung cancer screening guideline with low-dose computed tomography (2018 version)	Guideline as a result of global studies	China	2018
3	Zhou et al. (18)	China national lung cancer screening guideline with low-dose computed tomography (2015 version)	Guideline as a result of global studies	China	2015
4	Ellery et al. (19)	Horizon scanning technology Prioritizing summary update Screening for lung cancer utilizing computed tomography	Horizon scanning	Australia	2010
5	Black et al. (20)	Clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews	Health technology assessment	England	2006
6	Humphrey et al. (11)	Screening for lung cancer: systematic review to update the U.S. preventive services task force recommendation	Systematic review Recommendation of the Preventive Service Center	The United States	2013
7	Field et al. (21)	UK lung cancer RCT pilot screening trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer Screening	Lung cancer screening pilot	The United Kingdom	2015

8	Roberts et al. (22)	Screening high-risk populations for lung cancer guideline recommendations	Systematic review Guideline	Canada	2013
9	Lewin et al. (23)	Recommendations on screening for lung cancer	Systematic review Guideline	Canada	2016
10	Huang et al. (24)	Effects of low-dose computed tomography on lung cancer screening: a systematic review, meta-analysis, and trial sequential analysis	Systematic review and meta-analysis	Taiwan	2019
11	Manser et al. (25)	Screening for lung cancer (review)	Systematic review and meta-analysis	Cochrane lung cancer team	2013
12	Mazzone et al. (26)	Screening for lung cancer chest guideline and expert panel report	Systematic review and meta-analysis	The United States	2018
13	Gopal et al. (14)	Screening for lung cancer with low-dose computed tomography	Systematic review and meta-analysis	The United States	2010
14	Slatore et al. (27)	Patient-centered outcomes among lung cancer screening recipients with computed tomography	Systematic review	The United States	2014
15	Li et al. (28)	Lung cancer screening: a systematic review of clinical practice guidelines	Systematic review	China	2015
16	Sadate et al. (29)	Systematic review and meta-analysis on the impact of lung cancer screening by low-dose computed tomography	Systematic review	France	2020

As a result of the studies conducted to evaluate clinical effectiveness, 16 studies were entered into the analysis stage. Two of these studies were health technology assessment studies, and others included systematic review studies that examined the clinical effectiveness of lung cancer screening and were guidelines of lung cancer screening in some countries. All the under-review studies surveyed and evaluated lung cancer screening using LDCT. Their under-review population was the high-risk group, and the comparison group was mainly non-intervention and, in some cases, radiography or sputum cytology. The high-risk group was defined as older smokers. However, since the selected investigations were secondary studies, the smoking rate and age range of the under-review studies were different.

Numerous consequences are possible due to this screening. Based on the obtained studies, the main outcome variables of clinical effectiveness were reduced lung cancer mortality, early diagnosis of lung cancer, and its timely treatment. Furthermore, subsequent outcomes included parameters of reduced overall mortality due to other causes, increased incidence in the short run, and changing the diagnosis time from the final stages to the lower stages of the disease. Based on the results of the reviewed studies, lung cancer screening in high-risk individuals leads to reduced lung cancer mortality.

4.2.1. Mortality from Lung Cancer and Other Causes

The results of the systematic review and meta-analysis studies of the National Health Service (NHS) in 2018 showed that LDCT screening, compared to the control group (ie, non-screening and chest X-ray screening), caused a statistically significant reduction in lung cancer mortality (RR = 0.85; 0.98 - 0.74; CI = 0.95) (16).

According to Sadate et al.'s study that systematically evaluated and meta-analyzed the effect of lung cancer screening by LDCT, a statistically significant reduction in lung cancer mortality (17%) was observed, compared to that of the control group. The results of the aforementioned study showed that for the prevention of lung cancer in each individual, 294 individuals should be screened (29).

The results of a systematic review of lung cancer screening in high-risk individuals by Huang et al. in Taiwan showed a significant reduction in lung cancer mortality between LDCT and other control groups (RR = 0.83). In addition, the results of subgroup analysis showed that LDCT screening caused a significant reduction in mortality in high-quality trials; nevertheless, low-quality trials revealed no significant difference (24). Moreover, the results of the systematic review and meta-analysis conducted by the Cochrane lung cancer research team, including Manser et al.'s, showed that annual LDCT screening was associated with reduced lung cancer mortality in high-risk smokers (RR = 0.80; 0.92 - 0.70; CI = 0.95) (25).

4.2.2. Mortality from Other Causes

The results of the studies also show that if this screening is implemented in a large population and adheres to strict protocols in accordance with developed clinical guidelines for screening, it can lead to reduced mortality from other causes. The results of the NHS systematic review and meta-analysis in 2018 showed that LDCT screening, compared to the control group, caused a statistically significant reduction in mortality from all causes (RR = 0.95) (16). Moreover, the results of the systematic review and meta-analysis study by Sadate et al. showed a relative reduction in mortality

from other causes (4%), compared to that of the control group (29).

4.2.3. Changing Cancer Incidence and Disease Stage Distribution

According to the obtained results, screening in high-risk groups with the early diagnosis of cancer leads to increasing the incidence of this disease and changing the stage distribution. This finding means that the probability of increasing lung cancers diagnosed in the early stages (ie, stage I or II) will be significantly higher than cancers diagnosed in the late stages of the disease.

The results of the Pilot UK Lung Cancer Screening trial showed that more than 85% of detected lung cancers were in stage I or II, and more than 90% of these cases could be treated in a timely manner, 83% of which underwent surgery. The aforementioned study revealed that the malignancy rate in small masses is very low, and mass management is essential for proper and rational referral to a specialist physician (21).

In 2010, Gopal et al. carried out a systematic review and meta-analysis study on the existing studies. According to the aforementioned study, lung cancer screening using LDCT led to a significant increase in the number of first-stage lung cancers (OR = 3.9; CI = 95%), the higher total number of non-small cell lung cancers (OR = 5.5; CI = 95%), and an increase in the total number of lung cancers (OR = 4.1; CI = 95%) (14). The aforementioned study showed that lung cancer screening using LDCT resulted in the diagnosis of a significant number of patients in the early stages of lung cancer, compared to the lack of early diagnostic intervention (RR = 3.9; 7.4 - 2.0; CI = 0.95).

4.2.4. Health-related Quality of Life and Psychological Consequences

According to the evidence, there was no statistically significant difference in health-related quality of life (HRQoL) and psychological or mental consequences between the LDCT screening group and the control group at any time. According to the results of a systematic review by Slatore et al. on the studies related to patient-centered consequences of lung cancer screening, the limited and high-quality evidence showed that LDCT lung cancer screening in many individuals was associated with short-term mental illnesses; nevertheless, it did not affect distress, worry, or HRQoL. Moreover, false-positive results were associated with short-term increased distress that disappeared after performing subsequent tests and obtaining negative results (27).

5. Discussion

In this study, the results of 15 articles were used to evaluate the safety issue, and 16 studies were used to evaluate clinical effectiveness. Safety-related issues include cases of overdiagnosis of lung cancer, post-screening unnecessary interventions if the initial test is positive, mortality and other side effects in screened individuals, and effects of radiation exposure. Possible harms due to diagnosing abnormalities as a result of performing LDCT screening primarily include false positives that are benign tumors and, if left undiagnosed, they are harmless and will never have symptoms. False positives can also cause unnecessary interventions, including biopsy, bronchoscopy, thoracotomy, and other post-screening diagnostic interventions, which these invasive interventions are complementary. In this case, the proper and accurate classification of the size of diagnosed tumors in positive or negative cases and the implementation of screening retest in cases of uncertainty at a specific time after the first test are necessary.

Another issue regarding the discussion of technology safety is the effects of radiation exposure, which based on the research, the damage caused by performing LDCT is negligible. The effective dose of LDCT radiation in each examination is estimated to be 1.5 mSv. The evidence shows that reduced lung cancer mortality is also included in the safety issue, and performing this screening will lead to a statistically significant reduction in lung cancer (30).

In addition, studies performed on mortality and side effects due to this screening show that mortalities that occurred shortly after screening are not related to the screening test, and other observed side effects are related to patients with cancer and after performing the screening test, other diagnostic interventions, and surgery (16). The results of studies on the safety of LDCT lung cancer screening show that this technology is safe, and its advantages outweigh its probable disadvantages. While performing this screening, the radiation dose is low, and the quality of diagnosis is simultaneously maintained.

As a result of evaluating the clinical effectiveness of synthesizing 16 studies that entered into the final phase of analysis, lung cancer screening intervention using LDCT significantly reduced lung cancer mortality by 15 - 20% and mortality from other causes by 0 - 6%. Moreover, due to performing this screening, the incidence of lung cancer and its diagnosis in the early stages of the disease would increase, and its incidence in the upper stages of the disease would decrease significantly. A very important point in diseases that are diagnosed by screening is the determination of complementary diagnostic measures to ensure the type and stage of cancer and, therefore, to take action for the timely treatment of the disease.

The findings of the evaluation of clinical effectiveness show that this intervention is not significant in individuals' quality of life and causes no psychological consequences. It can be stated that the implementation of lung cancer screening and emphasis on the high-risk population, including smokers, can affect the smoking rate in the country in the long run.

For achieving the best results, maximizing the advantages of this screening, and obtaining the maximum clinical effectiveness, it is necessary to gain an accurate

understanding of the current at-risk population. Furthermore, it is essential to accurately define the specifications of the diagnosed masses (including their size and location) and determine the appropriate action at a given time for each of them. The determination of the type and timing of the next screening step is also necessary. For the development of a lung cancer screening program, it is required to gather a team of experts, including health policymakers, specialists in pulmonary diseases, oncologists, radiologists, and epidemiologists, to cover all aspects of this issue.

5.1. Conclusions

Lung cancer screening using LDCT in older individuals with a heavy-smoking history is safer than not performing the intervention and does not threaten the health of individuals undergoing screening. The disadvantages of this screening are negligible compared to its advantages. In comparison to non-intervention, this screening is more clinically effective and will lead to a statistically significant reduction in lung cancer mortality and an increase in the timely diagnosis of this disease.

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