Original Article

Lung cancers and pulmonary nodules detected by computed tomography scan: a population-level analysis of screening cohorts

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Background: An increasing number and proportion of younger lung cancer patients have been observed worldwide, raising concerns on the optimal age to begin screening. This study aimed to investigate the association between age and findings in initial CT scans.

Methods: We searched for low-dose CT screening cohorts from electronic databases. Single-arm syntheses weighted by sample size were performed to calculate the detection rates of pulmonary nodules, lung cancers (all stages and stage I), and the proportion of stage I diseases in lung cancers. In addition, we included patients who underwent chest CT in our center as a supplementary cohort. The correlation between the detection rates and age was evaluated by the Pearson Correlation Coefficient.

Results: A total of 37 studies involving 163,442 participants were included. We found the detection rates of pulmonary nodules and lung cancers increased with age. However, the proportion of stage I diseases in lung cancers declined with increased starting age and was significantly higher in the 40-year group than in other groups (40 *vs.* 45, 50, 55, $P<0.001$). In addition, the ratio of early-stage lung cancer to the number of nodules declined with age. Similarly, in our center, the detection rates of nodules ($R^2=0.86$, $P\leq0.001$), all lung cancer ($R^2=0.99$, $P\leq0.001$) and stage I diseases ($R^2=0.87$, $P=0.001$) increased with age, while the proportion of stage I diseases consistently declined with age ($R^2=0.97$, $P\leq0.001$).

Conclusions: Starting lung cancer screening at an earlier age is associated with a higher probability of identifying a curable disease, urging future research to determine the optimal starting age.

Keywords: Lung cancer; early stage; screening; age; cure

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Introduction

Lung cancer was the most commonly diagnosed cancer and the leading cause of cancer-related deaths worldwide, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018 (1). Over the past two decades, lung cancer death rates have declined due to tobacco control programs (2). But lung cancer mortality remains high as more than half of patients are diagnosed at a late stage (2,3). Lung cancer screening may be an effective strategy to detect early-stage cancers, enable timely treatments, and benefit patients significantly (4,5). In the 1980s, chest radiograph and sputum cytology become the most common screening methods for lung cancer but failed to bring benefits in the reduction of disease-specific mortality (6-12).

In the 1990s, low-dose computed tomography (LDCT) examination was considered as a potential screening tool due to its advantage of lower dosage levels than standard CT while still revealing pulmonary nodules and diagnosing lung cancers (13). In recent years, the results of the United States National Lung Screening Trial (NLST) indicated that individuals from 55 to 74 years of age with high-risk factors randomly assigned to screening with LDCT could reduce lung cancer mortality by 20% when compared with conventional chest radiography. Accordingly, the National Comprehensive Cancer Network (NCCN) (14), United States Preventative Services Task Force (USPSTF), and American Cancer Society (ACS) recommended that high-risk individuals should start lung cancer screening with LDCT (15,16). Thus, LDCT became the standard screening approach for lung cancer (17).

In the previous randomized clinical trials (RCTs) and single-arm prospective cohort studies, the initial screening age for lung cancer was mostly 50 or 55 in Europe and the United States (17-23), but was 40 or 45 in some Asian studies (24-27). In recent years, an increasing number and proportion of younger lung cancer patients have been observed worldwide (28-30). Such individuals are not covered by the current guidelines for screening candidates. Thus, they may be left out of ongoing screening projects. The target population for screening needs to be more accurate regarding the optimal starting age. To date, the relationship between an earlier age and the initial CT scan results is unclear, as few programs set the starting screening age before 40. Understanding the CT scan results (e.g., the association between age and lung cancer) will help develop a detailed screening strategy. In this study, we summarized the results of lung cancer screening trials with LDCT. In addition, we included patients who underwent a chest CT scan in our center as a supplementary cohort. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/atm-20-5210).

Methods

This study is registered with PROSPERO, number CRD42019128394.

Literature search and selection

A systematic and comprehensive literature search of electronic databases PubMed, Web of Science, Embase, and Cochrane Library was performed to identify the relevant studies published before October 2020, using a combination of keywords "lung cancer", "screening", and "low-dose computed tomography". RCTs and cohort studies of LDCT screening for lung cancer in populations of smokers (current and former) and non-smokers were included. Studies that focused on populations with some specific risk factors of lung cancer, such as exposure to asbestos or radiation or chronic obstructive pulmonary disease were excluded. Retrospective studies, studies that started screening after the age of 55, studies using risk models to screen populations, and studies without necessary data such as the number of baseline stage I diseases or nodules were excluded.

Data extraction

Data were extracted independently by two reviewers (Li C and Liao J) and were resolved by a third reviewer (Cheng B). The number of participants, pulmonary nodules, lung cancers (each stage and in total) in baseline and follow-up detection were extracted from eligible studies. The first author, country of origin, starting age for screening, smoking status of the population, and type of study design in each study were also extracted for further analysis. Subgroup analysis was performed according to smoking status.

Statistical analysis

The detection rates of all lung cancer cases, stage I–IV diseases, and the ratio of stage I diseases to all nodules and lung cancers were calculated using single-arm syntheses weighted by sample size, and Open Meta [Analyst] software (Accessed at http://www.cebm.brown.edu/openmeta/download.html) was used for quantitative data synthesis. The Chi-square test of independence was used to compare the detection rates between different age groups under Bonferroni adjustment (starting age of each group as the independent variable, total participants of each group as the denominator). The analysis was performed using SPSS version 23.0.

Patient selection and CT examination data in our center

Patients from age 18 to 69 who underwent a chest CT scan in our hospital for identifying the causes of disease (such as medical examination, screening) between April 2014 and May 2018 were eligible for analysis as a supplementary cohort. Of particular interest was the subgroup analysis of patients before the age of 40, as such data were rarely reported. Follow-up scans for positive findings were excluded. The detection rates of pulmonary nodules, lung cancer (in all stages and stage I), and the proportion of stage I diseases were analyzed. The correlation between detection rates and age was evaluated by the Pearson Correlation Coefficient. The analysis was performed using SPSS version 23.0.

Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The First Affiliated Hospital of Guangzhou Medical University (Registration number: kls2015-25). Considering that the study was a retrospective analysis, informed consent of all patients was waived by the ethics committee.

Results

Study selection

We identified 3,866 relevant records according to the aforementioned search strategy. Finally, a total of 37 studies involving 163,442 participants were included in our study, containing 10 RCTs and 27 cohort studies. One study started screening at 35 years of age (31), seven studies started screening at 40 years of age (4,24,25,32-35), three studies at 45 years of age (26,27,36), sixteen studies at 50 years of age (18-21,37-48), and ten studies at 55 years of age (17,22,23,49-55). The starting age for lung cancer screening varied from country to country. The flow chart and the main characteristics of each study were summarized in *Figure 1*, *Table 1*, and in total online: https://cdn.amegroups.cn/static/public/atm-20-5210-1.pdf, respectively.

Association between starting screening age and CT findings in prevalent round

A total of 31 screening programs reported the baseline results of 143,813 individuals in all lung cancer cases and stage I diseases. As expected, the detection rates of all lung cancer and stage I diseases increased with age. However, the proportion of stage I diseases declined with age and was significantly higher in the 40-year group than other age groups (40 *vs.* 45, 50, 55, $P<0.001$). Meanwhile, similar trends were observed in the ratio of early lung cancer to all nodules being detected (40 *vs.* 45, 50, 55, $P<0.001$). *Figure 2* summarized the pooled results.

Association between starting screening age and CT findings in follow-up scans

Subsequently, a total of 29 screening programs reported the follow-up scan results of 124,295 individuals in all lung cancer cases, and stage I diseases were analyzed. The detection rates of lung cancer and stage I diseases increased with age, while the proportion of stage I diseases declined with age; the differences were statistically significant among the various groups (40 *vs.* 45, $P=0.021$, 40 *vs.* 50, 55, $P<0.001$). However, since few nodule results were available in the follow-up study, we could not find the trend of the ratio of stage I diseases to all nodules. Figure S1 summarized the pooled results.

Subgroup analysis according to smoking status

In the smokers (current or former) subgroup, the proportion of stage I also declined with age in both baseline and follow-up results. The ratio of stage I to all nodules was the highest in the 40- and 45-year-old group in baseline and follow-up, respectively. However, no similar trend was found in the unfiltered population subgroup due to limited literature.

The findings of CT scans in different age groups in our center

A total of 12,405 CT scans were performed from April 2014 to May 2018 in our center, and 1,871 lung cancers were

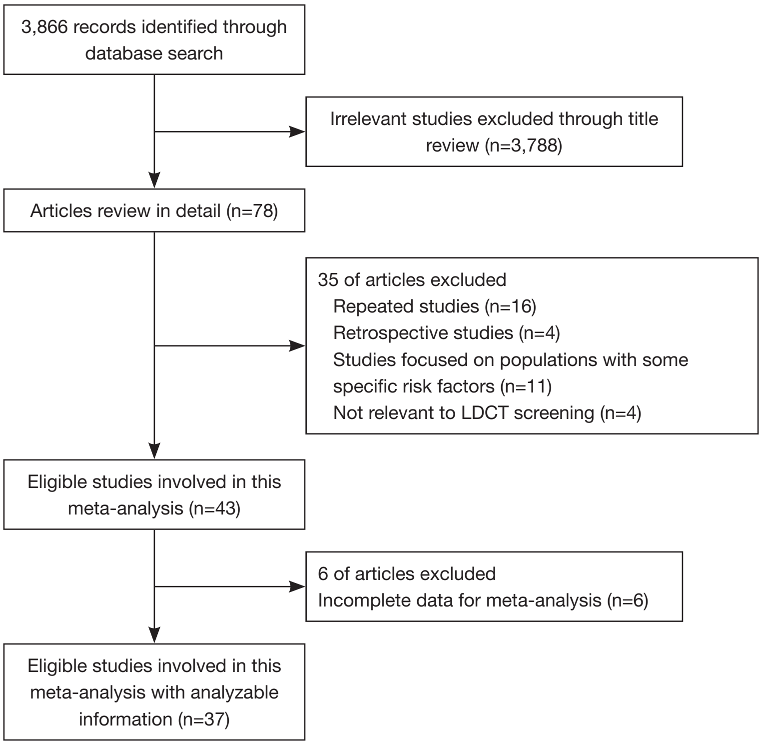

Figure 1 Flow chart of the studies included.

detected. The baseline characteristics of the population were described in *Table 2*. In our center, the detection rates of nodules (R^2=0.86, P≤0.001), all lung cancer (R^2=0.99, P≤0.001), and stage I diseases (R^2=0.87, P=0.001) increased with age (*Figure 3*). The detection rate of lung cancer was significantly lower in the 30–34 group compared to the 40–44 group (7.37% *vs.* 12.00%, P=0.002), but was comparable between the 35–39 and the 40–44 group (10.36% *vs.* 12.00%, P=0.284). Notably, the proportion of stage I diseases consistently declined with age (R^2=0.97, P≤0.001) (*Figure 3*).

Discussion

This is a population-level study to investigate the association between age and findings in initial CT scans. In this study, we found that the detection rates of all lung cancer and stage I diseases were highest in the 55-year starting group compared with other groups. However, the proportion of stage I diseases was highest in the age 40-year starting group in baseline screens and follow-up scans.

Because few RCTs or cohort studies carried out CT screening before the age of 40, we analyzed the baseline results with CTs in our hospital. And 135 individuals were diagnosed with lung cancer before age 40 after the CT examination. Furthermore, there was no statistically significant difference in the proportion of stage I diseases between the age 40–44 group and age 35–39 group, suggesting that a meaningful proportion of lung cancers might remain latent during this period and thus those with latent lung cancer at age 35–39 or age 40–44 may share similar outcomes under therapy. Therefore, the evidence is still insufficient to support initiating lung cancer screening before the age of 35, especially when considering the cost-effectiveness. It is noteworthy that our supplementary cohort mainly represented people who came to our hospital for a routine checkup or presented with mild symptoms. This could explain the different detection rates between the cohort of our center and screening cohort of population-level analysis.

The lung cancer screening aims to detect, diagnose and cure lung cancer in the early stage, which contributes to reducing lung cancer-related mortality with relatively limited harm, with the ultimate purpose of preventing death from lung cancer and prolonging life. Although NLST has achieved great success, some patients diagnosed through

Table 1 Characteristics of included studies

Study	Country	Number of screens	Starting age	Smoking status	Study design	Male (%)	Nodules in baseline	Cancer in baseline	Cancer in follow-up	Stage I cancer in baseline	Stage I cancer in follow-up
Fan (31)	China	14,506	35	Unfiltered population	Cohort	60	1,514	178	NA	140	NA
Miller (32)	America	1,267	40	Smokers (current or former)	Cohort	53	NA	NA	28	NA	18
Lei (33)	China	1,551	40	Unfiltered population	Cohort	68	NA	NA	8	NA	6
Henschke (4)	Multi-center	31,567	40	Smokers (current or former)	Cohort	NA	4,186	405	484	348	412
Bastarrika (34)	Spain	911	40	Smokers (current or former)	Cohort	74	131	14	16	11	13
Diederich (35,56)	Germany	817	40	Smokers (current or former)	Cohort	72	154	11	26	6	13
Sobue (24)	Japan	1,611	40	Unfiltered population	Cohort	88	185	13	36	10	29
Sone (25,57)	Japan	5,483	40	Unfiltered population	Cohort	NA	279	23	60	23	53
Yang (27)	China	3,512	45	Unfiltered population	RCT	46	479	51	NA	48	NA
Stephenson (26)	America	87	45	Smokers (current or former)	Cohort	52	12	4	NA	3	NA
Chong (36)	Korea	6,406	45	Unfiltered population	Cohort	86	NA	11	23	3	13
Luo (37)	China	11,332	50	Unfiltered population	Cohort	63	62	27	NA	22	NA
Rzyman (38)	Poland	8,649	50	Smokers (current or former)	Cohort	52	NA	NA	107	NA	65
Lam (39)	America	154	50	Smokers (current or former)	Cohort	42	85	0	0	0	0
Pastorino (40)	Italy	2,376	50	Smokers (current or former)	RCT	68	335	17	49	NA	32
Becker (19,58)	Germany	2,029	50	Smokers (current or former)	RCT	65	540	22	58	18	32
Menezes (41)	Canada	3,352	50	Smokers (current or former)	Cohort	54	600	56	62	NA	42
van Klaveren (42)	Europe	7,557	50	Smokers (current or former)	RCT	NA	1732	70	NA	46	NA

Table 1 (*continued*)

Table 1 (*continued*)

Study	Country	Number of screens	Starting age	Smoking status	Study design	Male (%)	Nodules in baseline	Cancer in baseline	Cancer in follow-up	Stage I cancer in baseline	Stage I cancer in follow-up
Pedersen (20,59)	Denmark	4,104	50	Smokers (current or former)	RCT	56	179	17	69	9	47
Wilson (21)	America	3,642	50	Smokers (current or former)	Cohort	51	1,477	53	80	31	40
Veronesi (43,60)	Italy	5,201	50	Smokers (current or former)	Cohort	66	560	55	210	36	NA
Callol (44)	Spain	482	50	Smokers (current or former)	Cohort	65	98	1	5	1	5
Blanchon (45)	France	385	50	Smokers (current or former)	RCT	71	81	8	NA	3	NA
MacRedmond (46,61)	Ireland	449	50	Smokers (current or former)	Cohort	50	75	2	6	1	2
Swensen (18,62)	America	1,520	50	Smokers (current or former)	Cohort	52	404	27	40	19	25
Pastorino (47)	Italy	1,035	50	Smokers (current or former)	Cohort	71	61	11	22	6	17
Nawa (48)	Japan	7,956	50	Unfiltered population	Cohort	79	1590	36	40	31	35
Lee (49)	Korea	256	55	Smokers (current or former)	Cohort	99	NA	NA	1	NA	1
Lanni (50)	America	1,065	55	Smokers (current or former)	Cohort	51	125	20	NA	9	NA
dos Santos (53)	Brazil	790	55	Smokers (current or former)	Cohort	50	312	11	NA	8	NA
Nahorecki (54)	Poland	332	55	Smokers (current or former)	Cohort	50	59	4	4	1	1
Crucitti (55)	Italy	1,500	55	Smokers (current or former)	Cohort	62	NA	NA	25	NA	22
Aberle (17)	America	26,722	55	Smokers (current or former)	RCT	59	7191	270	649	NA	400
Croswell (23)	America	1,610	55	Smokers (current or former)	RCT	58	338	0	0	0	0

Table 1 (*continued*)

Table 1 (*continued*)

Study	Country	Number of screens	Starting age	Smoking status	Study design	Male (%)	Nodules in baseline	Cancer in baseline	Cancer in follow-up	Stage I cancer in baseline	Stage I cancer in follow-up
Lopes Pegna (51,63)	Italy	1,046	55	Smokers (current or former)	RCT	65	426	20	35	11	23
Novello (52)	Italy	520	55	Smokers (current or former)	Cohort	73	114	5	11	2	8
Gohagan (22,64)	America	1,660	55	Smokers (current or former)	RCT	58	261	30	40	16	19

Note: "unfiltered population" included population of smokers (current or former) and non-smokers; [a], numbers of participants represented the numbers included in the screening arm.

LDCT cannot be cured because of advanced cancer. In fact, the starting age for screening used by the previous studies or guidelines was determined mainly by the point when the incidence of lung cancer significantly increased in the trend over age. There was a bias in the age of diagnosis. In the past, most cases of lung cancer were found by chest X-rays or by severe symptoms. At this time, it is too late for a large proportion of these patients to receive curative treatment. In addition, using a reliable lung-cancer risk-prediction model for individuals can identify one's cancer risk. The Pan-Canadian Early Detection of Lung Cancer [PanCan] model helped identify early and potentially curable lung cancer. However, the variable "age" did not show as an essential predictive factor in this model (65). Meanwhile, "age" was a continuous variable in the $PLCO_{2012}$ model, according to the data of age between 55 and 74 years to develop the predictors (66). Therefore, the predictive performance outside this age range was uncertain. It is warranted to develop and validate a modal using the screening data from general population before the age of 55.

In addition, we observed that the true positive rate (the ratio of early lung cancer to all nodules being detected) was the highest in the 40- and 45-year, followed by the 50- and 55-year subgroup populations. Benign nodule, a barrier for differential diagnosis, was more frequently found in CT scans as age increased. This observation suggests that screening at an earlier age might simplify the diagnosis and aid clinical decisions due to a clearer background in CT; even when the CT scan in the first round does not reveal any positive nodule associated with lung cancer, it can be used for comparison with a follow-up examination in the future (67). This study indicated that a considerable number of lung cancer, and early-stage in particular, already existed in individuals at earlier ages. Thus, to diagnose more patients at an early stage of lung cancer, the age threshold for screening may require modification based on the benefits, harm, and cost-effectiveness.

In this study, we summarized the results of lung cancer screening trials with LDCT in the past few years and analyzed patients who underwent chest CT scans in our center as a supplementary cohort to investigate the association between age and findings in initial CT scans. Still, there are some limitations. First, the study's design was based on data analysis reported in the literature, and we could not access individual-level data. Second, few trials began screening at 40 years of age in European and American countries, resulting in limited data for subgroup analysis. Third, we were not able to analyze the impact

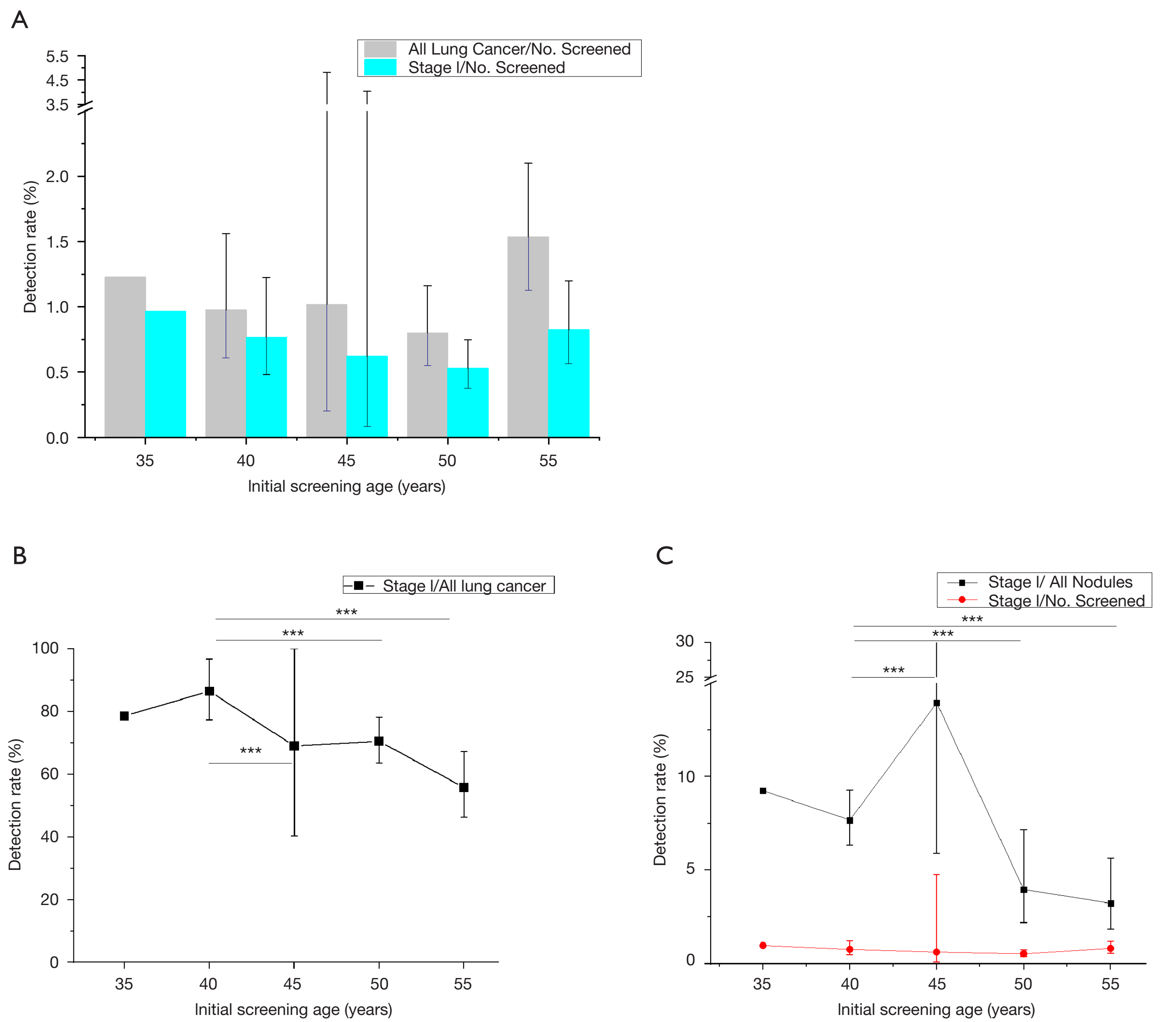

Figure 2 Baseline results in the prevalent round. The relationship between detection rates of all cancer cases and stage I diseases and initial starting age (A). The proportion of stage I diseases declined with starting age (***, P<0.001 versus 40–44 years old) (B). The ratio of early lung cancer to all nodules declined with starting age (***, P<0.001 versus 40–44 years old) (C). Vertical lines around each of the points were 95% confidence intervals.

of other high-risk factors, such as exposure to asbestos or radiation, or chronic obstructive pulmonary disease. As a result, we could not consider the possible role of covariates or logistic process regression or something similar way to analyze these data. Fourth, the LDCT settings and positivity criteria of each included study were not entirely consistent, which may affect the conclusion to some extent. In addition, showing a beneficial effect of screening is a challenge. This study did not address the impact of adverse effects by LDCT, such as the effect of overdiagnosis and radiation.

Conclusions

In summary, it is reasonable to start lung cancer screening at an earlier age than the currently recommended age for

Table 2 Baseline characteristics and findings of CT scans in our center

Characteristics	Total (N=12,405)	Nodule (N=4,568)	Detection rate of nodule (%)	Lung cancer(N=1,871)	Detection rate of lung cancer (%)	Stage I (N=854)	Detection rate of stage I (%)
Sex							
Male	7,012	2,497		1,003		355	
Female	5,393	2,071		868		499	
Mean age ± SD	51.6±11.2	53.4±11.1		55.5±10.0		53.6±10.6	
Age range							
18–24	353	56	15.86	6	1.70	5	1.42
25–29	463	100	21.60	18	3.89	13	2.81
30–34	624	186	29.81	46	7.37	36	5.77
35–39	695	217	31.22	72	10.36	42	6.04
40–44	1,125	414	36.80	135	12.00	75	6.67
45–49	1,395	501	35.91	187	13.41	99	7.10
50–54	1,814	717	39.53	297	16.37	145	7.99
55–59	1,896	728	38.40	309	16.30	130	6.86
60–64	2,269	902	39.75	424	18.69	168	7.40
65–69	1,771	747	42.18	377	21.29	141	7.96

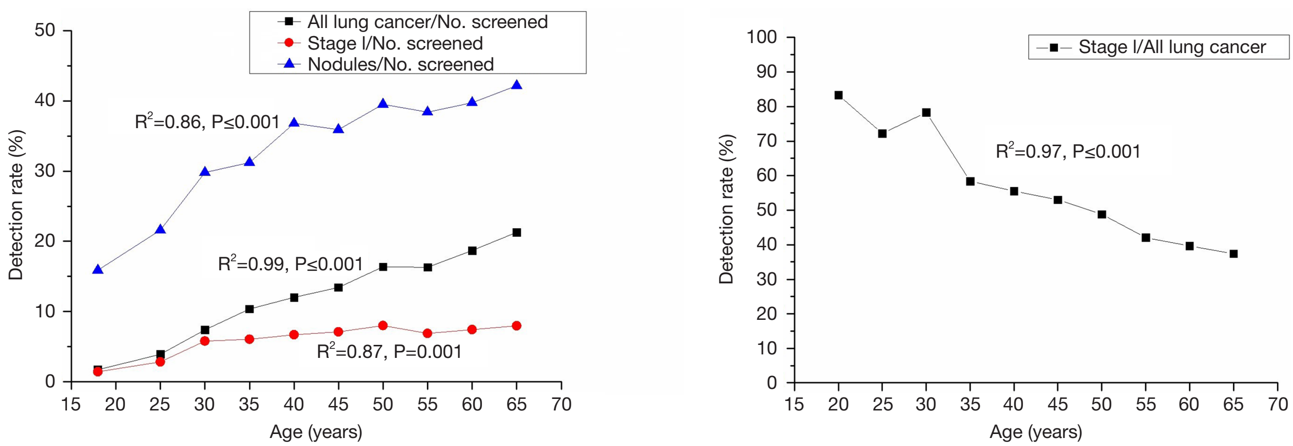

Figure 3 The findings of CT scans in different age groups in our center. The detection rates of nodules, all lung cancer, and stage I diseases increased with age, but the proportion of stage I diseases consistently declined with age.

timely detection to diagnose more patients at a curable stage of the disease. The optimal starting age requires further analyses based on original data in consideration of the survival benefits and costs and well-designed randomized controlled trials in the future.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-5210). Prof. JH serves as an unpaid Editor-in-Chief of *Annals of Translational Medicine* from Jun 2019 to May 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The First Affiliated Hospital of Guangzhou Medical University (Registration number: kls2015-25). Considering that the study was a retrospective analysis, informed consent of all patients was waived by the ethics committee.

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Supplementary

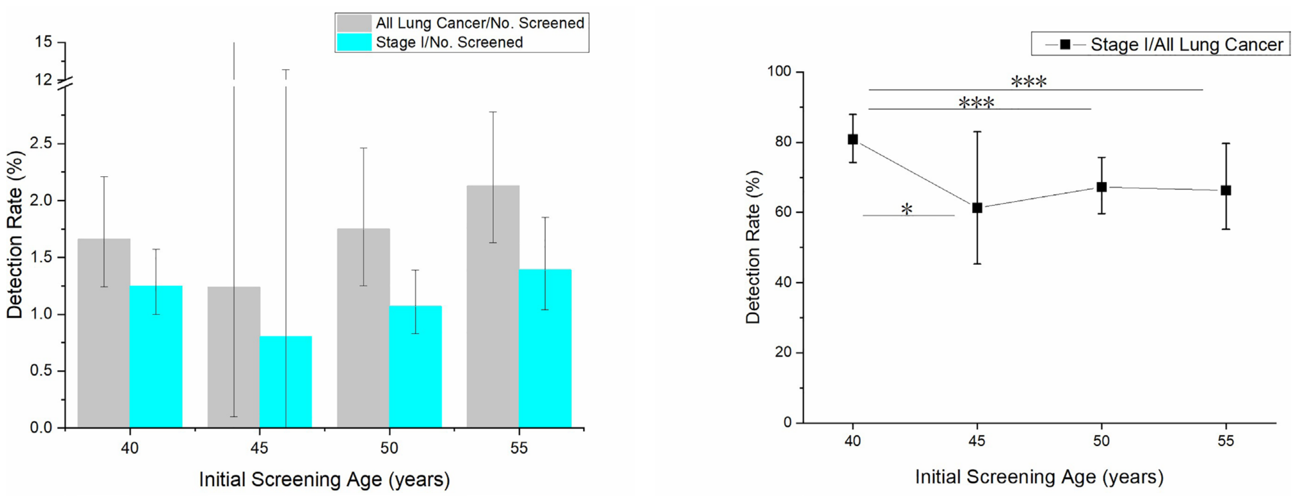

Figure S1 Follow-up scan results in incident screens. The relationship between detection rates of all cancer cases and stage I diseases and initial starting age (A). The proportion of stage I diseases declined with age (*, P=0.021 versus 40–44 years old, ***, P<0.001 versus 40–44 years old) (B). Vertical lines around each of the points were 95% confidence intervals.

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