

Lung cancer screening CT-based coronary artery calcification in predicting cardiovascular events

A systematic review and meta-analysis

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Abstract

Background: Coronary artery calcification (CAC) is a well-established predictor of cardiovascular events (CVEs). We aimed to evaluate whether lung cancer screening computed tomography (CT)-based CAC score has a good cost-effectiveness for predicting CVEs in heavy smokers.

Methods: A literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Pubmed, EMBASE, and Cochrane library databases were systematically searched for relevant studies that investigated the association between lung cancer screening CT-based CAC and CVEs up to December 31, 2017. We selected fixed-effect model for analysis of data heterogeneity. Statistical analyses were performed by using Review Manager Version 5.3 for Windows.

Results: Four randomized controlled trials with 5504 participants were included. Our results demonstrated that CVEs were significantly associated with the presence of CAC (relative risk [RR] 2.85, 95% confidence interval [CI] 2.02–4.02, $P < .00001$). Moreover, higher CAC score (defined as CAC score >400 or >1000) was associated with a significant increased CVE count (RR 3.47, 95% CI 2.65–4.53, $P < .00001$). However, the prevalence of CVEs was not different between male and female groups (RR 2.46, 95% CI 0.44–13.66, $P = .30$).

Conclusion: CAC Agatston score evaluated by lung cancer screening CT had potential in predicting the likelihood of CVEs in the early stage without sexual difference. Thus, it may guide clinicians to intervene those heavy smokers with increased risk of CVEs earlier by CAC score through lung cancer screening CT.

Abbreviations: BMI = body mass index, CAC = coronary artery calcification, CI = confidence interval, CT = computed tomography, CVEs = cardiovascular events, NLST = National Lung Cancer Screening Trial, RCTs = randomized controlled trials, RR = relative risk.

Keywords: cardiovascular events, coronary artery calcification, low-dose computed tomography, lung cancer

1. Introduction

Cigarette smoking is prevalent in economically developing regions of the world, which is associated with the development of coronary artery disease, chronic obstructive pulmonary disease, and lung cancer.^[1] Thus, US Preventive Services Task Force recommendations for low-dose computed tomography (CT) screening, which is done in people aged 55 to 80 years and having current or former smoking history of at least 30 pack-years, yields a population at risk not only for lung cancer, but also

for cardiovascular events (CVEs).^[2] In the National Lung Cancer Screening Trial (NLST), 50% deaths were due to CVEs, confirming observations in other cohorts.^[3] The NLST achievement is remarkable as it is the first cancer screening trial demonstrating an all-cause mortality reduction.^[4] This raises high expectations for chest CT-based lung cancer screening to guide clinically preventive therapies.

Coronary artery calcification (CAC) is an established predictor of CVEs and is strongly associated with advanced age and history of cigarette smoking.^[5] Interestingly, lung cancer screening CT is also used for quantification of CAC. Because CAC can be feasibly and reliably assessed by visual or software quantitative analysis methods based on low-dose CT for lung cancer screening.^[6–8] Although there are a series of randomized controlled trials (RCTs) in the lung cancer screening population,^[9–11] there is not yet a consensus within the lung cancer screening community on reporting of CAC. Some investigators do not consider CAC to be clinically relevant, but others consider CAC to be clinically significant only if it is extensive.^[12,13] Moreover, other studies suggest that CAC quantification could reduce cardiovascular morbidity and mortality, and enhance the cost effectiveness of CT-based screening in heavy smokers.^[14,15] Since the population of lung cancer screening rapidly increases, there may be an enormous primary prevention potential if lung cancer screening CT-based calcium scoring could stratify individuals in categories of cardiovascular risk and to identify those at high risks of CVEs.

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The authors declare that they have no conflicts of interest.

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The aim of this meta-analysis was to determine whether CT-based CAC can predict CVEs in the lung cancer screening population and further to determine the relationship in subgroup analysis for different degrees of CAC and CVEs.

2. Materials and methods

2.1. Search strategy

A literature search was conducted to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.^[16] We conducted a comprehensive search on studies about lung cancer and vascular calcification published from inception to December 31, 2016 in the PubMed, EMBASE, and Cochrane library databases. To identify the potential studies, we used the terms: “lung cancer,” “lung carcinoma,” “pulmonary carcinoma,” “calcification,” “vascular calcification,” “arterial calcification,” “aortic calcification.” We also searched the relevant reference lists of the selected literatures to find other potentially related studies.

2.2. Study selection

Studies were considered eligible for inclusion if they fulfilled the following inclusion criteria: type of study design was RCT; studies had the data of CVEs; vascular calcification was measured by low-dose CT; coronary calcium was evaluated by Agatston score; publications were written in English; full text was available in the peer-reviewed journals; each study must have written informed consent obtained from all participants. However, RCTs only reported calcification of valves or other aortic segments rather than coronary artery were not included in this study.

2.3. Data extraction

Two investigators independently extracted the data. Discrepancies were resolved by consensus or a third author adjudication. The following data were extracted: names of the authors, sample size, details of participant characteristics (age, sex, body mass index [BMI]), duration of smoking, number of participants with current smoking, hypertension, diabetes, CAC, or CVEs at baseline. Included CVEs were myocardial infarction, unstable angina pectoris, cardiovascular deaths congestive heart failure, coronary artery revascularization (including percutaneous or surgical procedures).

2.4. Assessment of study quality

Methodological quality was conducted using Cochrane Collaboration's tool for assessing risk of bias.^[17] The risk of bias tool covers 6 domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Within each domain, assessments are made for 1 or more items, which may cover different aspects of the domain, or different outcomes.

2.5. Data analysis

We explored the relationship between CAC and CVEs in the participants. Final results were presented as relative risk (RR) and 95% confidence interval (CI). We used I^2 statistic to evaluate the heterogeneity between studies, with significance being set at I^2 over 50%. Fixed-effect model or random-effect model was conducted in the absence or presence of heterogeneity among studies. Publication bias was evaluated using funnel plots and Begg test.

Statistical analyses were performed by using Review Manager Version 5.3 for Windows. Statistical significance was defined at $P < .05$.

3. Results

3.1. Eligible studies

The flow chart of the study selection was showed in Fig. 1. Briefly, we identified studies from the potentially relevant published literatures and retrieved 11 studies for further evaluation. At last, 4 RCT studies^[3,18–20] fulfilled our inclusion criteria and were recruited for final evaluation.

3.2. Baseline characteristics

The baseline characteristics of the 4 RCTs were summarized in Table 1. A total of 5504 participants with a mean age range of 57 to 62 years were identified, and, of them, 61.5% ($n=3384$) were men. In the identified studies, sample size was from 958 to 1945 participants, and mean follow-up interval was from 20 to 85.2 months. Also, the total number of participants with hypertension, diabetes, current smoking, and CVEs were 534, 1348, 3448, 812, respectively, in this meta-analysis.

3.3. The role of CAC in predicting CVEs in lung cancer screening population

Coronary artery calcification was estimated by Agatston score. CAC score of 0 indicates having no calcification. CAC score >0 indicates having calcification. Three RCTs were included for analysis. CVEs were significantly associated with the presence of CAC (RR 2.85, 95% CI 2.02–4.02, $P < .00001$) (Fig. 2). The fixed-effects model was used as statistical heterogeneity was not found ($I^2=0\%$, $P=.55$).

3.4. The prevalence of CVEs in different levels of CAC

Figure 3 showed the prevalence of CVEs according to different levels of CAC. We defined CAC score >400 or >1000 as higher CAC group. Since $I^2 >50\%$ in 1 group (CAC >400 vs CAC ≤ 400), we used random-effect model to analyze. It was shown that higher CAC was associated with a significant increased CVEs counts (RR 3.47, 95% CI 2.65–4.53, $P < .00001$).

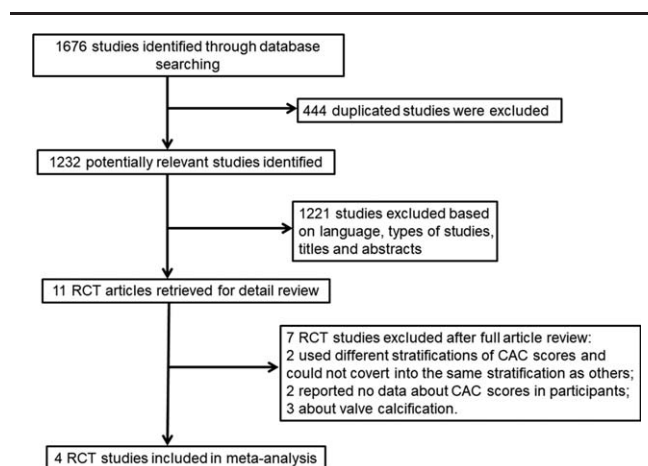


Figure 1. Flowchart of literature review and selection. RCT=randomized controlled trial.

Table 1
Baseline characteristics of 4 RCT studies in the meta-analysis.

Author, y	Name of the RCT	Number of participants	Mean duration of follow-up, mos	Mean age, y	Male sex, %	Mean BMI, kg/m ²	Hypertension, %	Diabetes, %	Current smoking, %	Mean pack-yr	CAC measurement, %	CAC reference, %	CVE ^a endpoints, %
Rasmussen et al, 2015 ^[18]	DLCST study	1945	85.2	57	55.3	25	13.9	1.8	75.5	34	CAC >400, 6.8	CAC=0, 53.2	6.4
Chiles et al, 2015 ^[3]	NLST study	1442	20	62	58.7	—	9.6	35.3	53.6	—	CAC >1000, 11.1	CAC=0, 27.7	32.3
Jacobs et al, 2012 ^[19]	NELSON study	958	21.5	59.5	70.0	—	6.0	54.0	47.2	—	CAC >1000, 16.4	CAC=0, 4.5	19.6
Sverzellati et al, 2012 ^[19]	MILD study	1159	36	57.5	68.4	26	6.0	24.9	65.1	38.4	CAC >400, 6.9	CAC ≤400, 93.1	2.8

BMI=body mass index, CAC=coronary artery calcium, CVE=cardiovascular events, DLCST=Danish Lung Cancer Screening Trial, MILD=Multicentric Italian Lung Detection, NELSON=Nederlands-Leuven Longkanker Screenings Onderzoek, NLST=National Lung Screening Trial, RCT=randomized controlled trial.

^aCVE includes myocardial infarction unstable angina pectoris, cardiovascular deaths, congestive heart failure, and coronary artery revascularization (including percutaneous or surgical procedures).

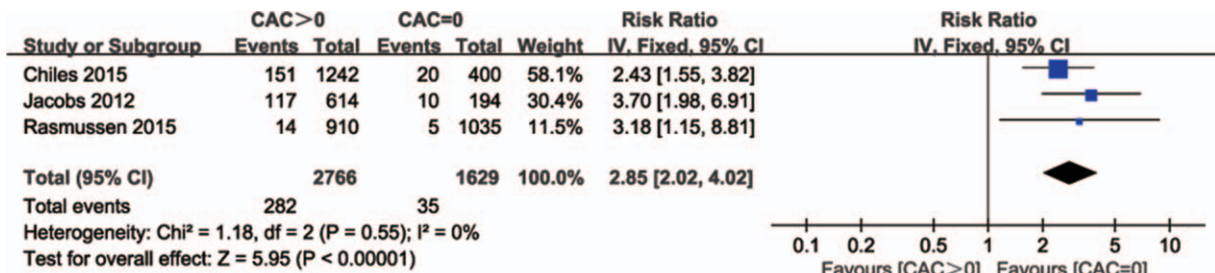


Figure 2. The relation between the presence of CAC and CVEs. CAC=coronary artery calcification, CI=confidence interval, CVEs=cardiovascular events.

According to different levels of CAC score, the prevalence of CVEs was significantly higher in CAC score >400 group compared with CAC score <400 group (RR 3.37, 95% CI 2.72–4.17, $P < .00001$). Moreover, this difference was even stronger in the comparison between CAC score >1000 group and CAC score ≤1000 group (RR 4.08, 95% CI 2.18–7.65, $P < .00001$).

3.5. The influence of sex on the prevalence of CVEs

To explore whether sex impacts on the results, we compared the prevalence of CVE subgroup analysis according to sex. As shown in Fig. 4, no significant difference of CVE prevalence was found between male and female groups (RR 2.46, 95% CI 0.44–13.66, $P = .30$).

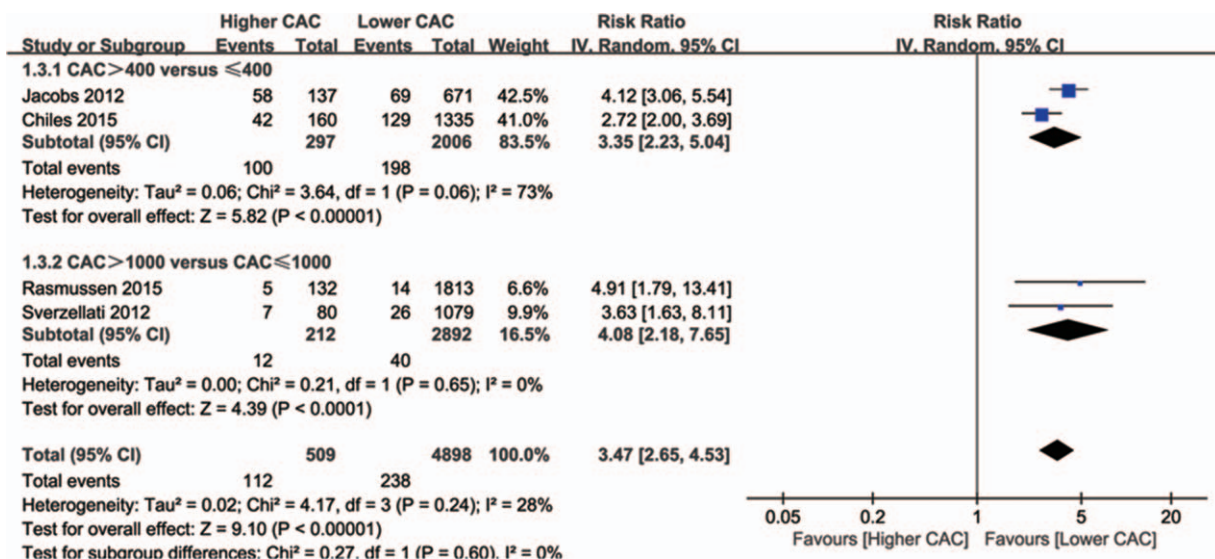


Figure 3. Association between different levels of CAC and the prevalence of CVEs. CAC=coronary artery calcification, CI=confidence interval, CVEs=cardiovascular events.

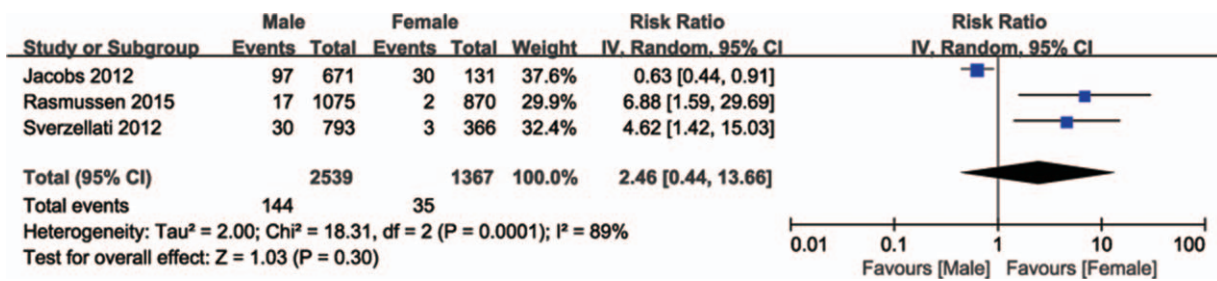


Figure 4. The prevalence of CVEs according to sex. CI=confidence interval, CVEs=cardiovascular events.

3.6. Publication bias

When we explored for potential publication bias, the funnel plot did not appear asymmetrical (Fig. 5), and Begg test was not significant ($t=0.74, P=.537$).

4. Discussion

This meta-analysis demonstrated that in lung cancer screening population, low-dose CT-based CAC measurement was useful for predicting CVEs. The different levels of CAC scores are strongly associated with the increased likelihood of CVEs. Furthermore, no significant difference of CVE prevalence was found between male and female groups.

With the increasing exposure to risk factors including environmental pollution and second-hand smoking, the population affecting lung cancer expands rapidly. Notably, cardiovascular diseases are the leading causes of lung cancer patients.^[21] It was demonstrated that the presence of CAC increased noncardiac and all-cause morbidity and mortality.^[22] There are several methods of measuring CAC through CT scans, including overall visual scoring, segmented vessel-specific scoring, and Agatston score, among which Agatston score is an widely used tool to quantify the severity of CAC. CAC Agatston score with electrocardiography-gated CT, which may include both atherosclerotic and nonatherosclerotic calcifications, has become an important prognostic imaging biomarker for CVEs in multiple settings.^[23] However, there is not yet a consensus on whether to include CAC as a significant incidental finding on low-dose CT performed for lung cancer screening or how to report CAC. Unlike cardiac CT screening, low-dose CT scans for lung cancer are ungated and have a lower signal-to-noise ration. Nevertheless, CAC is identifiable and measurable.^[24] Budoff et al^[25]

compared Agatston CAC scores on gated and ungated CT scans in 50 participants in the chronic obstructive pulmonary disease gene trial. Also, the result demonstrated that low-dose ungated CT was reliable for prediction of the presence of CAC and assessment of Agatston score. However, measurement of CAC was accurate from gated CT than that from ungated CT.^[25] A recent meta-analysis also showed that the prognostic value of nontriggered CT for lung cancer screening in coronary calcium assessment, but it could not replace electrocardiography-triggered CT, because absence of CAC in nontriggered CT may not reliably exclude the risk of CVEs.^[26] Thus, it needs more evidence to investigate the role of low-dose CT based CAC in predicting CVEs.

In the present meta-analysis of 4 RCTs involved in 5504 participants, we also observed a significantly stronger relationship between lung cancer screening-based CAC Agatston score with increased prevalence of CVEs, for its CAC scores ranked the highest. These findings confirm and extend similar findings on the basis of other lung cancer screening studies. Jacobs et al^[19] reported that CAC scoring with Agatston score from low-dose CT scans in the Netherlands-Leuven Longkanker Screenings Onderzoek study could be regarded as an independent predictor of CVEs and all-cause mortality. Similarly, in the Danish Lung Cancer Screening Trial, assessment of non-electrocardiogram-gated CAC in lung cancer screening programs was a robust prognostic measure of fatal or nonfatal CVEs in current and former smokers independent of traditional cardiovascular risk factors.^[18] This may eliminate the need for an additional, dedicated calcium scoring CT in this population with increased risk of CVEs. Moreover, it was found that male participants tended to have higher CAC scores than female participants in the Multicentric Italian Lung Detection study.^[20] However, the present meta-analysis did not confirm this result. There were possibly due to the baseline differences between 2 groups. For instance, the duration of smoking and diabetes mellitus prevalence were significantly higher in men than that in women.^[18,20] In addition, oestrogen is a key cardioprotective factor in women.^[27] However, most of included women have been postmenopausal (over 55 years old). With the levels of oestrogen decrease, its effects become less important.

It must be acknowledged that there are several limitations to this study. Firstly, our extracted data were not the original data. Although we analyzed the studies by CAC classifications, it was impossible to adjust potential confounders including inflammatory factors. Moreover, there were insufficient data on BMI and pack-years of smoking for a reliable analysis in this study. Second, it is noteworthy that the majority of subjects recruited in this study were heavy smoking. It should be cautious to generalize the findings to nonsmokers. Third, only 4 RCTs with 5504

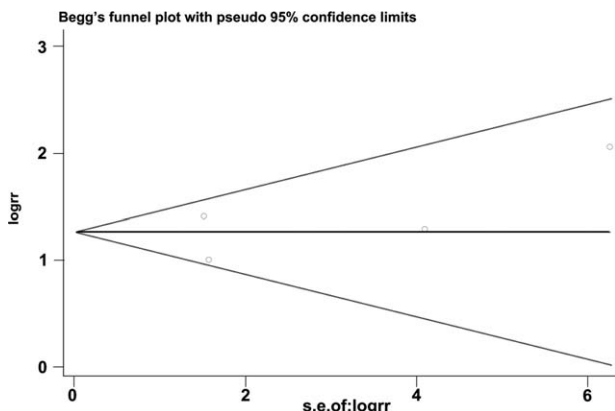


Figure 5. Begg funnel plot for publication bias.

participants were included in this analysis and none were double blind. Well-designed, large studies are still warranted.

In conclusion, lung cancer screening CT-based CAC Agatston score had potential in predicting the prevalence of CVEs in the early stage without sexual difference. Thus, it may guide clinicians to intervene those heavy smokers with increased risk of CVEs earlier by CAC scores through lung cancer screening CT.

Author contributions

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Writing – review & editing: lili Fan.

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