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Relationship between the number of new nodules and lung cancer probability in incidence screening rounds of CT lung cancer screening: The NELSON study

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ABSTRACT

Background: New nodules are regularly found after the baseline round of low-dose computed tomography (LDCT) lung cancer screening. The relationship between a participant's number of new nodules and lung cancer probability is unknown.

Methods: Participants of the ongoing Dutch-Belgian Randomized Lung Cancer Screening (NELSON) Trial with (sub)solid nodules detected after baseline and registered as new by the NELSON radiologists were included. The correlation between a participant's new nodule count and the largest new nodule size was assessed using Spearman's rank correlation. To evaluate the new nodule count as predictor for new nodule lung cancer together with largest new nodule size, a multivariable logistic regression analysis was performed.

Results: In total, 705 participants with 964 new nodules were included. In 48% (336/705) of participants no nodule had been found previously during baseline screening and in 22% (154/705) of participants > 1 new nodule was detected (range 1–12 new nodules). Eventually, 9% (65/705) of the participants had lung cancer in a new nodule. In 100% (65/65) of participants with new nodule lung cancer, the lung cancer was the largest or only new nodule at initial detection. The new nodule lung cancer probability did not differ significantly between participants with 1 (10% [56/551], 95%CI 8–13%) or > 1 new nodule (6% [9/154], 95%CI 3–11%, P = .116). An increased number of new nodules positively correlated with a participant's largest nodule size (P < 0.001, Spearman's rho 0.177). When adjusted for largest new nodule size, the new nodule count had a significant negative association with lung cancer (odds ratio 0.59, 0.37–0.95, P = .03).

Conclusion: A participant's new nodule count alone only has limited association with lung cancer. However, a higher new nodule count correlates with an increased largest new nodule size, while the lung cancer probability remains equivalent, and may improve lung cancer risk prediction by size only.

1. Introduction

Lung cancer screening using low-dose computed tomography (LDCT) is currently recommended by US guidelines for high-risk individuals [1–3], after the National Lung Screening Trial reported a 20% reduced lung cancer mortality for LDCT compared to chest radiography screening [4]. Lung nodules are common findings in LDCT lung cancer screening. European and American trials with no or very low detection limits reported a noncalcified lung nodule prevalence in 41–51% of participants at baseline screening [5–9]. Since most detected nodules are benign, the effective identification of potentially malignant nodules is central to current lung cancer screening programs. While nodule management is mainly based on size and growth [10,11], other nodule characteristics, such as nodule morphology or nodule location, have

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traditionally been associated with an increased probability for lung cancer [10–13]. Furthermore, patient characteristics such as age or smoking pack-years play a crucial role in identifying high-risk individuals eligible for screening [8,12,14].

However, within a lung cancer screening program, but also in regular clinical practice, individuals may be diagnosed with several nodules at baseline or at follow-up screening [5–9,12,13]. There are only limited data concerning the relationship of the number of nodules detected in a participant (or nodule count) and lung cancer probability. For nodules detected at baseline screening, a recent analysis of the largest European lung cancer screening trial indicated that the baseline nodule count alone does not predict lung cancer [15]. On nodule level, one large study indicated a negative association between the nodule count and a baseline nodule's lung cancer probability when assessed together with other known risk-factors, also reflecting the low incidence of double malignancies [12].

During a lung cancer screening program, annually in 3–13% of participants new nodules are detected that were not present at baseline screening [5,16–19]. Recently, it was shown that new nodules carry a higher lung cancer probability at smaller size than do baseline nodules [19]. However, an array of non-malignant diseases may be associated with the development of new lung nodules and some participants may tend to develop multiple benign lung nodules of varying size [9,20]. The appropriate risk-stratification of new nodules is important to a lung cancer screening program, as they account for a significant proportion of lung cancers found after the baseline round [19,21,22]. Till recently most research focused on nodules detected at baseline screening and there is only limited evidence on the management of new nodules [1,11,19]. In a current European position statement on lung cancer screening, it was stressed that the management of new nodules should be different from baseline nodules since they have a higher pretest probability which was also adopted in the British Thoracic Society Guidelines for the Investigation and Management of Pulmonary Nodules [22]. At present, there is no evidence regarding an association of the new nodule count after baseline lung cancer screening and the development of new nodule lung cancer. Aim of this study was to assess the relationship of a participant's number of new nodules and the new nodule lung cancer probability, using data from the largest European randomized controlled lung cancer screening trial.

2. Material and methods

2.1. Study population

The Dutch-Belgian Randomized Lung Cancer Screening (acronym NELSON, trial registration number: ISRCTN63545820) trial's study design and recruitment process have been published previously [7,23,24]. Briefly, (ex-) smokers aged 50–75, who had smoked at least 15 cigarettes daily for 25 years or 10 cigarettes daily for 30 years and were still smoking or stopped smoking less than 10 years ago were eligible. The Ethics committees of all participating centers approved the NELSON trial. All participants provided their written informed consent. Between April 2004 and December 2006, 7557 participants underwent baseline screening. The subsequent incidence screening rounds took place 1 year, 3 years, and 5.5 years after baseline screening. The current study included participants in whom the NELSON radiologists registered a new noncalcified nodule during the three incidence screening rounds.

2.2. CT scanning protocol and image reading

Low-dose CT scans were performed at one of four screening sites using 16-MDCT scanners or 64-MDCT scanners (Sensation-16, Siemens Medical Solutions, Forchheim, Germany; or Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Best, Netherlands). Depending on the participant's body weight (< 50 kg, 50–80 kg, or > 80 kg), low-dose settings (80–90 kVp, 120 kVp, and 140 kVp) were adapted to match a dose index volume of 0.8mGy, 1.6mGy, or 3.2 mGy respectively. Datasets were derived from images of the thorax with 1.0 mm slice width and a 0.7 mm reconstruction interval. The data acquisition and imagining protocols were standard across screening sites [7,23]. CT-image analysis occurred on digital workstations (Leonardo, Siemens Medical Solutions) which enabled semiautomated volume analysis using software (LungCare, version Somaris/5 VA70C-W, Siemens Medical Solutions). Image reading was performed by two independent radiologists in the first two rounds and by one radiologist in the third and fourth round, after it was demonstrated that reading consensus provides no benefit with the use of semiautomated software [25]. In case of high suspicion of malignancy (eg, enlarged mediastinal lymph nodes) or benignity (eg, benign calcification patterns), radiologist could overrule protocol-based screening results (as done for 195 [6%] of 3318 participants at the baseline screening round) and adjust the nodule volume in case of inappropriate segmentation [26]. Detected nodules were matched to previous scans by the software's algorithm and matching was visually confirmed by the radiologist. Data generated during CT evaluation were immediately uploaded to the NELSON management system (10). This study included data and measurements as uploaded to the NELSON management system and no new or repeat measurements were performed. Nodules were considered new if labeled as new and not present on previous scans by the NELSON radiologists.

2.3. Nodule management protocol

The detailed NELSON nodule management protocol was published previously [23]. At first detection, new nodules were classified into four categories according to their size and characteristics (NODCAT I–IV). Calcified nodules and nodules with other benign characteristics were considered benign (NODCAT I). New solid nodules measuring 15–50 mm^3 and new subsolid nodules with diameter 4–8 mm (NODCAT II, follow-up LDCT within one year) as well as new solid nodules 50–500 mm^3 and new subsolid nodules ≥ 8 mm (NODCAT III, follow up LDCT within six-eight weeks) were considered indeterminate, requiring nodule growth assessment. New solid nodules ≥ 500 mm^3 (NODCAT IV, immediate referral to pulmonologist) were considered positive.

2.4. Outcomes

A nodule was classified as lung cancer when it was diagnosed as lung cancer during diagnostic workup according to national and international guidelines including histologic examination [23]. Nodules were classified as benign when either: (a) the nodule was benign at histologic examination; (b) extensive workup by a pulmonologist, including contrast material–enhanced CT, PET, and bronchial washing, had a negative finding; (c) the nodule was ruled negative during the participant's last follow-up in the NELSON trial. As far as accessible in this ongoing trial, data was linked with the Dutch and Belgian national cancer registries and medical files reviewed concerning the occurrence of post-screening lung cancer (completed for the second and third incidence screening round) [21,23,27].

2.5. Nodule counts

For this study two nodule counts were calculated for each participant. First, the number of new noncalcified nodules detected simultaneously at a participant's first new nodule detection after baseline and second, the number of noncalcified nodules detected at baseline screening. The new nodule count may reflect the presence of non-malignant disease. The baseline nodule count might also reflect a participant's tendency to develop nodules.

2.6. Statistical analysis

Normality of continuous variables was evaluated through the Kolmogorov–Smirnov test and visual assessment. All included continuous variables were non-normally distributed and are presented as median and interquartile range (IQR). Categorical variables are shown as frequencies and respective percentages. The Agresti-Coull method was used to calculate 95% confidence intervals (95%CI) of proportions. The correlation of the participant's new nodule count and the participant's age at baseline, the smoking pack-years at baseline, the volume of the largest nodule and the volume of all new nodules was assessed using Spearman's rank correlation. Categorical variables stratified by the new nodule count (0, 1, 2, 3, 4, ≥5) were assessed using Fisher's exact test or the χ^2 test as appropriate. The Mann–Whitney *U* test was used for comparison of nodule volume between two groups. The discriminative performance of the nodule count with new nodule lung cancer as outcome was evaluated through construction of the area under the receiver-operating-characteristic curve (AUC). To evaluate new nodule count as predictor for new nodule lung cancer together with largest new nodule size (i.e. one case per participant), multivariable logistic regression analysis was performed including new nodule count and size (highest new nodule NODCAT classification and largest new solid nodule volume respectively). In participants where the largest new nodule could not be established based on the exact volume measurement (1% [10/705]), the nodule with the highest NODCAT classification was considered largest. The model calibration was assessed by a Hosmer-Lemeshow goodness-of-fit test and through comparison of observed and predicted probabilities. Statistical analyses were performed with SPSS version 24.0 (IBM, Armonk, NY, USA), Medcalc version 17.1 (Medcalc Software, Mariakerke, Belgium), and Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

3. Results

In total, 705 participants with 964 new nodules were included (Fig. 1). Participant characteristics are presented in Table 1. Median participant age at baseline was 59 years (IQR 55–63 years) and 79% (558/705) of participants were male. Subsolid new nodules were detected in 6% (49/705) of participants and 5% (3/65) of the new nodule lung cancers were found in subsolid lesions. In 48% (336/705) of participants no nodule had been found previously during baseline screening and in 22% (154/705) of participants > 1 new nodule was detected (range 1–12 new nodules). Eventually, 9% (65/705) of the participants were diagnosed with lung cancer in one of the detected new nodules. In all participants with new nodule lung cancer, the largest (14% [9/65]) or only (86% [56/65]) new nodule was diagnosed as lung cancer.

On participant level, receiver operating curve analysis demonstrated no significant predictive ability of the new nodule count for lung cancer (AUC 0.55, 95%CI 0.48–0.62). A participant's overall new nodule lung cancer probability did not significantly differ between participants with 1 new nodule (10% [56/551], 95%CI 8–13%) or > 1 new nodule (6% [9/154], 95%CI 3–11%, P = .116). Participants with multiple new nodules that clustered in one lung lobe had a lower but not statistically different lung cancer frequency when compared to participants with multiple new nodules but no clustering (2% [1/44] vs. 7% [8/110), P = .232. On nodule level, a lower number of simultaneously detected new nodules showed a moderate predictive ability for lung cancer (AUC 0.67, 95%CI 0.61–0.72) with no double cancers being detected. The participant's nodule count at baseline screening demonstrated no significant discriminative performance for new nodule lung cancer, neither participant level (AUC 0.52, 95%CI 0.45–0.59) nor nodule level (AUC 0.53, 95%CI 0.46–0.60).

The nodule size and lung cancer probability stratified by the participant's number of new nodules are shown in Table 2. While the median volume of the participant's largest nodule increased significantly with more new nodules detected (P < 0.001, Spearman's rho 0.177), the lung cancer probability remained equivalent (P = .63). The lung cancer probability of participants in whom the only detected new nodule was NODCAT III or IV was significantly higher compared to participants with NODCAT III or IV nodules but > 1 new nodule detected (15% [50/333], 95%CI 12–19% vs. 8% [9/119], 95%CI 4–14%, P = .04). When adjusted for the size of the largest new (solid) nodule (Table 3), the new nodule count was a significant predictor, having a negative association with new nodule lung cancer.

4. Discussion

This analysis focused on participants with new nodules detected during the three incidence rounds of the NELSON trial. We assessed the relationship between the number of new nodules detected in a participant and the probability of developing lung cancer in a new nodule.

There are five major findings. First, in 22% (154/705) of participants more than one new nodule was detected at initial new nodule detection. Second, the lung cancer probability, did not differ significantly between participants with one and more than one new nodule. Third, an increased number of new nodules was correlated with a greater largest new nodule size. Fourth, the new nodule count had a significant negative association with new nodule lung cancer when assessed together with nodule size. Fifth, the participant's overall nodule count at baseline screening was not significantly associated with new nodule lung cancer.

To our knowledge, this is the first study providing evidence concerning a possible impact of a participant's nodule count and the lung cancer probability in new solid nodules. Lung cancer screening participants only have one baseline screen, but potentially many incidence screenings and with increasing duration, a program's success depends on the management of new nodules. Contrary to baseline nodules, which may have been present for years, new nodules develop in a known timeframe and comprise a group of comparably young nodules [19]. A study focusing on the development of a lung cancer risk model for baseline nodules reported a reduced lung cancer probability with an increasing number of baseline nodules [12]. The findings of this study show similar results for new nodules on nodule level. Nevertheless, on participant level the new nodule count alone showed limited discriminative performance for new nodule lung cancer (AUC 0.55, 95%CI 0.48–0.62). This is comparable to a recent analysis of the NELSON baseline round, where baseline lung cancer probability did not differ significantly per baseline nodule count [15]. However, the here presented findings indicate that in combination with new nodule size the new nodule count has a significant negative association with new nodule lung cancer. This may be explained through the observation that an increased new nodule count is associated with a greater size of the largest nodule found in a participant, while the lung cancer probability remains at least equivalent.

At initial nodule detection and before growth assessment is feasible, nodule size is the most important predictor for lung cancer in both baseline and new nodules and is used for risk-stratification in present guidelines [10,11,19,22]. Currently, the management of detected nodules in lung cancer screening and clinical practice, focusses on the most suspicious or typically largest nodule detected [10,11,19,22]. This reflects a participant-based approach with a theoretical lung cancer probability of smaller nodules not taken into account. The findings of this study show that factoring in the new nodule count could adapt a participant's lung cancer risk stratification in a multivariate approach that includes the largest nodule size. However, additional data is needed to confirm these findings and assess new nodule count together with other risk factors.

This study has limitations. The NELSON trial's detection limit was 15 mm^3 and smaller new nodules could not be considered in this analysis. However, newly detected nodules above 15 mm^3 and visible below the studies detection limit on a previous scan were excluded.

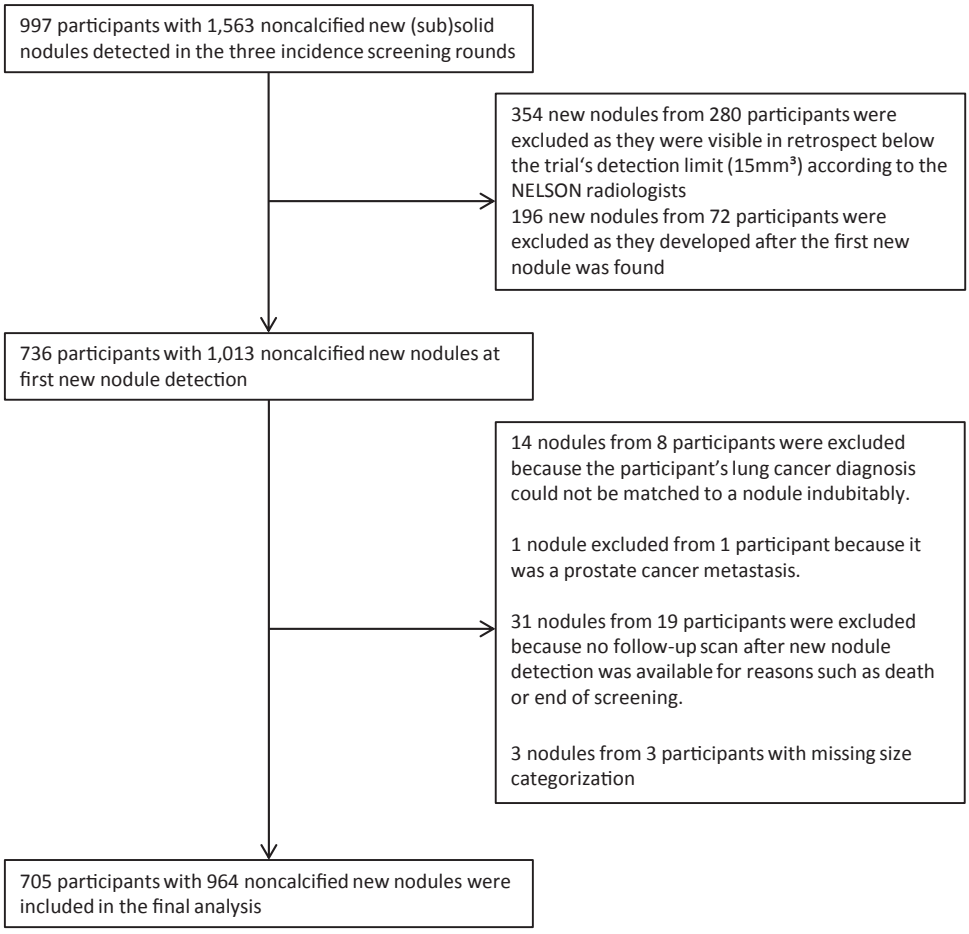

Fig. 1. Flowchart of participants and new nodules included in the analysis.

Further, the expertise of radiologist was shown to decrease false-positive screening results [26]. Radiologists potentially increased their expertise in distinguishing scars or infections from suspicious lesions during the trial and could have refrained from classifying them as suspicious nodules to avoid false-positive results. We cannot exclude the possibility that the actual number of new nodules is slightly higher than reported in the NELSON management system. Within the NELSON management protocol, larger nodules potentially received an additional follow-up LDCT or were referred for further diagnostic work-up. To minimize bias through the protocol, this analysis incorporated all follow-up data of a nodule within the NELSON trial including cancer diagnosis in later rounds and information from the national cancer registries concerning post-screening lung cancer.

5. Conclusion

In around one-fifth of participants with new nodules in incidence lung cancer screening rounds, more than one new nodule is present. A participant's number of new nodules alone only provides limited discriminatory information for new nodule lung cancer probability. However, with an increasing number of new nodules, the largest new nodule tends to be bigger, while the participant's overall new nodule lung cancer probability remains equivalent. Therefore, relating the largest new nodule size with the number of new nodules found could adjust a participant's lung cancer risk based on the largest nodule size only.

Table 1
Participant characteristics stratified by number of new nodules detected.

	All participants	Number of new nodules detected simultaneously in a participant					P-Value
		1	2	3	4	≥5	
Number of participants (%)	705 (100)	551 (78)	99 (14)	31 (4)	13 (2)	11 (2)	
Male sex (%)	558/705 (79)	442/551 (80)	72/99 (73)	23/31 (74)	12/13 (92)	9/11 (82)	0.334
Age at baseline							
Median	59	59	59	58	62	61	0.794
IQR	55–63	55–63	55–62	54–65	57–66	57–72	
Pack-years at baseline							
Median	39	39	39	44	49	34	0.455
IQR	30–53	30–53	30–49	38–56	27–58	31–38	
New subsolid nodule (%)	49/705 (6)	35/551 (6)	8/99 (8)	2/31 (6)	1/13 (8)	3/11 (27)	0.131

Abbreviations: IQR – Interquartile range.

Table 2
Nodule size and new nodule lung cancer probability stratified by number of new nodules detected.

	All participants	Number of new nodules detected simultaneously in a participant					P-Value
		1	2	3	4	≥5	
Size classification of largest new nodule[a]							
NODCAT II	253/705 (36)	218/551 (40)	26/99 (26)	7/31 (23)	2/13 (15)	0	0.002
NODCAT III	327/705 (46)	238/551 (43)	57/99 (58)	18/31 (58)	8/13 (62)	6/11 (55)	
NODCAT IV	125/705 (18)	95/551 (17)	16/99 (16)	6/31 (19)	3/13 (23)	5/11 (45)	
Median volume in mm^3							
All new nodules (IQR)	66 (32–188)	68 (33–204)	70 (32–166)	60 (28–206)	50 (27–129)	82 (35–298)	0.352
Largest new nodule (IQR)	84 (37–251)	68 (33–204)	125 (48–257)	165 (61–410)	124 (50–223)	380 (117–1021)	< 0.001[b]
Lung cancer							
n/N (%)	65/705 (9)	56/551 (10)	7/99 (7)	1/31 (3)	1/13 (8)	0/11 (0)	0.63
95% CI	7–12	8–13	3–14	0–18	0–35	0–30	

Abbreviations: CI – Confidence interval, IQR – Interquartile range.
[a] NODCAT II, Solid nodules measuring 15–50 mm^3 and subsolid nodules with diameter 4–8 mm; NODCAT III, solid nodules 50–500 mm^3 and subsolid nodules ≥8 mm; NODCAT IV, solid nodules ≥500 mm^3.
[b] Spearman's rho 0.177.

Table 3
Number of new nodules in the prediction of new nodule lung cancer.

Participants with a new (sub)solid nodule				
	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Number of new nodules	0.67 (0.42–1.07)	0.093	0.59 (0.37–0.95)	0.030
Size classification of largest new nodule				
NODCAT II			Reference	
NODCAT III			3.9 (1.58–9.65)	0.003
NODCAT IV			16.5 (6.67–40.93)	< 0.001
Participant with a new solid nodule				
	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Number of new nodules	0.60 (0.34–1.04)	0.07	0.37 (0.17–0.77)	0.008
Size of largest new solid nodule				
Ln-Volume			2.31 (1.86–2.91)	< 0.001

Abbreviations: CI – Confidence interval. [a]NODCAT II, Solid nodules measuring 15–50 mm^3 and subsolid nodules with diameter 4–8 mm; NODCAT III, solid nodules 50–500 mm^3 and subsolid nodules ≥8 mm; NODCAT IV, solid nodules ≥500 mm^3.

Summary conflicts of interest statements

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