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Surveillance of subsolid nodules avoids unnecessary resections in lung cancer screening: Long-term results of the prospective BioMILD trial

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Early View

Original research article

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TITLE

Surveillance of subsolid nodules avoids unnecessary resections in lung cancer screening: Long-term results of the prospective BioMILD trial

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Abstract

Background

The management of sub-solid nodules (SSNs) in lung cancer screening (LCS) is still a topic of debate, with no current uniform strategy to deal with these lesions at risk of overdiagnosis and overtreatment.

Objective

The BioMILD LCS trial has implemented a prospective conservative approach for SSNs, managing with annual low-dose CT nonsolid nodules (NSNs) and part-solid nodules (PSNs) with a solid component <5 mm, regardless of the size of the nonsolid component. The present study aims to determine the lung cancer (LC) detection and survival in BioMILD volunteers with SSNs.

Materials and methods

Eligible participants were 758 out of 4071 (18.6%) BioMILD volunteers without baseline LC and at least one SSN detected at the baseline or further LDCT rounds. The outcomes of the study were LC detection and long-term survival.

Results

A total of 844 NSNs and 241 PSNs were included. LC detection was 3.7% (31/844) in NSNs and 7.1% (17/241) in PSNs, being significantly greater in prevalent than incident nodules (8.4% vs. 1.3% in NSNs; 14.1% vs. 2.1% in PSNs; p-value for both nodule types < 0.01). Most LCs from SSNs were stage I (42/48, 87.5%), resectable (47/48, 97.9%), and caused no deaths. The 8-year cumulative survival of volunteers with LC derived from SSNs and not derived from SSNs was 93.8% and 74.9%, respectively.

Conclusion

Conservative management of SSNs in LCS enables timely diagnosis and treatment of LCs arising from SSNs while ensuring the resection of more aggressive LCs detected away from SSNs.

Introduction

Lung cancer screening (LCS) with low-dose computed tomography (LDCT) reduces mortality in heavy smokers by enabling early identification of lung cancers (LC) otherwise diagnosed as symptomatic advanced disease [1–6]. Nevertheless, LCS might lead to the diagnosis and treatment of lesions that would not affect prognosis, thus exposing volunteers to unnecessary risks of intervention, such as those related to biopsy procedures or excision [7–10].

Non-solid nodules (NSNs, also referred to as ground-glass nodules) and part-solid nodules (PSNs), collectively referred to as subsolid nodules (SSNs), may contribute to overdiagnosis and overtreatment in LCS [7, 11, 12]. Found in approximately 9% of LCS participants [13, 14], SSNs are associated with a higher rate of malignancy than solid nodules but, when malignant, tend to demonstrate a slower growth rate and lower risk for recurrence or metastatic disease than solid tumours [15–17]. This indolent behaviour challenges radiologists and clinicians in determining the risk of clinically significant malignancy of SSNs, whose prognostic weight may be overcome by competing causes of death, including non-neoplastic comorbidities and extrapulmonary cancer [18, 19].

Emerging data from LCS trials indicate that conservative management may be suitable for SSNs. In the NELSON trial (NELSON is a Dutch acronym for "Nederlands-Leuvens Longkanker Screenings Onderzoek"), only SSNs with a solid component > 500 mm^3 at baseline prompted immediate clinical referral, while all the other SSNs were followed and deemed worthy of further evaluation if increased in size or density [20]. Through this close follow-up strategy, no clinically relevant carcinomas were missed during a median follow-up of 95 months [20]. In the Multicentric Italian Lung Detection (MILD) trial, Silva et al. demonstrated the safety and efficacy of long-term active surveillance for SSNs [21]. The authors found that volunteers with SSNs showed a high risk of developing LC elsewhere in the lung, with only a minority of cases arising from SSNs and never representing the cause of death [21]. In keeping with these studies, a joint task force with members of the European Society of Radiology (ESR) and European Respiratory Society (ERS) recently stated that follow-up of persistent SSNs potentially reduces overdiagnosis in LCS [22]. That said, current strategies for SSNs are still mainly based on expert opinion, and the best approach for these nodules in LCS remains to be determined, pending prospective data.

The BioMILD trial, an ongoing prospective study evaluating the combined use of plasma miRNA and LDCT for improving the efficacy of LCS through individual risk profiling and personalized screening

intervals (clinicaltrials.gov ID: NCT02247453), has implemented a conservative approach to managing SSNs [23]. The present study aimed to detail the LC detection in BioMILD trial volunteers with SSNs over a 10-year follow-up period, stratifying SSNs by type, size, and time of appearance. The overall survival of the same group of participants was also explored.

Materials and methods

Study population

Data for the present analysis were extracted from the BioMILD trial, in which a total of 4119 volunteers were enrolled at the Istituto Nazionale dei Tumori of Milan from 2013 to 2016 [23]. Eligible participants were (i) aged 50-75 years and current heavy smokers of ≥ 30 pack-years or former smokers with the same smoking habits who stopped ≤ 10 years ago; (ii) aged 50-75 years and current or former smokers of ≥ 20 pack-years with a family history of LC or a prior diagnosis of chronic obstructive pulmonary disease (COPD) or pneumonia. The exclusion criteria were the presence of neoplasms within the previous 5 years and suspected lung nodules under investigation. The original Institutional Review Board approval and written informed consent allowed the use of the study data for future research.

Among the volunteers in the original BioMILD trial, those without baseline LC (i.e. LC cases detected within the planned 3/6 months recall from the baseline LDCT scan) and with at least one SSN, either NSN or PSN, detected at baseline or further LDCT rounds, were included in the present study.

LDCT evaluation and SSNs management

LDCTs underwent prospective double reading by one radiologist (first reading) using computer-aided detection (CAD) software (MM Oncology, *syngo*.via; Siemens Healthcare) and another radiologist (second reading) with the aid of the maximum intensity projection (MIP) images. In the case of discordant evaluations, consensus was reached through discussion.

The maximum diameter was recorded for NSNs measuring > 5 mm. All the NSNs were followed with annual LDCT. PSNs were managed according to the maximum diameter of the solid component. In particular, PSNs with a solid component < 5 mm were followed with annual LDCT, regardless of the size of the nonsolid component; PSNs with a solid component measuring ≥ 5 mm at baseline were sent to 3-month interval LDCT and, whenever persistent, assessed by the multidisciplinary team (MDT); PSNs with a new or growing solid component measuring ≥ 5 mm were assessed by the MDT as follows: calculation of the volume-doubling time of the solid component (threshold less than 400

days), ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET), and CT-guided transthoracic biopsy. The MDT was tasked with providing recommendations for treating suspicious PSNs. Given the low sensitivity and high positive predictive value of ^{18}F-FDG-PET in distinguishing malignant from benign SSNs, a negative ^{18}F-FDG-PET uptake did not necessarily rule out intervention, while a positive ^{18}F-FDG-PET outcome, as well as a positive biopsy, prompted surgery. Moreover, volunteers with PSNs showing a growing solid component were considered for direct surgical referral if a limited resection of the lesion was deemed feasible. A negative work-up led to continuous active surveillance by annual LDCT until evidence of solid component growth.

The time elapsed between the first LDCT that detected SSNs and surgical resection was prospectively recorded along with the histology and LC pathological stage. The vital status of the volunteers was obtained through the Istituto Nazionale di Statistica (ISTAT, SIATEL 2.0 platform), which provides the exact date of death within 3 months of occurrence. Person-years of follow-up were calculated for each participant from baseline until the date of death or the date of the last follow-up as of June 2023.

Study objectives

The primary outcome was the detection of LC, by means of biopsy or surgery, in SSNs (either NSNs or PSNs) detected at baseline (i.e., prevalent nodules) or further LDCT rounds (i.e., incident nodules). LC detection was further stratified by nodule size. The maximum diameter of the NSNs was retrospectively binarized into two categories, < 10 mm and ≥ 10 mm, in accordance with previous evidence suggesting this threshold to stratify NSNs based on malignancy risk [24]. The diameter of the solid component of the PSNs was classified as < 5 mm or ≥ 5 mm following the prospective LDCT reading. Characteristics of SSNs were referred to at the time of their detection. The secondary outcome was 8-year overall survival.

Statistical analysis

Categorical data were reported as numbers and percentages, whereas continuous data were reported as the median and interquartile range (IQR). The chi-square test or Fisher's exact test was used to compare categorical data, and the Mann–Whitney *U* test was used to compare continuous variables. The eight-year detection of LC derived from the SSNs was estimated by cumulative incidence curves, and the selected strata were compared by the log-rank test. Eight-year overall

survival was estimated by Kaplan–Meier curves and the selected strata were compared by using the log-rank test. A p-value < 0.05 was considered as the threshold for the statistical significance. The statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Study sample

A total of 1085 SSNs (844 NSNs and 241 PSNs) were detected in 758 out of 4071 (18.6%) BioMILD volunteers without baseline LC. Five hundred eighty-four (77.0%) volunteers had only NSNs, 130 (17.2%) had only PSNs, and 44 (5.8%) had both types of nodules; the demographic characteristics of these subgroups were similar **(Table 1)**. Overall, 52.6% (399/758) of the enrolled volunteers were male, the median age at baseline LDCT was 60 years [IQR 56-65], and 79.4% (602/758) were current smokers. A total of 4008 LDCT scans (mean number of LDCT scans per participant, 5.3) were performed during the study period. Volunteers with only NSNs, with only PSNs, and with both types of nodules underwent a mean of 5.2, 5.0, and 7.1 LDCT scans, respectively.

SSNs characteristics

SSNs were more likely to be incident (558/844, 66.1% NSNs; 142/241, 58.9% PSNs), but the differences in location and dimensions between incident and prevalent SSNs were not significant (**Table S1**). Most NSNs measured < 10 mm, while PSNs were almost equally likely to have a < 5 mm solid component and a ≥ 5 mm solid component (**Table S1**). Of the 718 NSNs and 219 PSNs that were subjected to at least one follow-up LDCT, 216 (30.1%) and 139 (63.5%) resolved over time, respectively (**Table 2**). Incident nodules resolved more frequently than prevalent nodules for both NSNs (34.8% vs. 22.3%, p-value < 0.001) and PSNs (69.8% vs. 54.8%, p-value = 0.0227). As expected, the median CT screening duration was longer for prevalent nodules (NSNs, 6.9 years [IQR 3.1-8.1]; PSNs, 5.3 years [IQR 2.2-7.5]) than for incident nodules (NSNs, 1.5 years [IQR 1.0-4.4]; PSNs, 3.6 years [IQR 0.4-5.6]) (p-value < 0.001 for both NSNs and PSNs).

Lung cancer derived from SSNs

The LC detection was 3.7% (31/844) for NSNs and 7.1% (17/241) for PSNs; in both groups, LC was significantly more common for prevalent than for incident nodules (8.4% vs. 1.3% for NSNs, p-value < 0.001; 14.4% vs. 2.1% for PSNs, p-value < 0.001). For both NSNs and PSNs, the median interval from nodule detection to LC diagnosis was greater for prevalent nodules than for incident nodules

(NSNs, 4.3 years [IQR 3.7-6.3] vs. 2.4 years [IQR 1.5-5.6], p-value = 0.0422; PSNs, 3.2 years [IQR 2.3-4.3] vs. 0.4 years [IQR 0.2-2.9], p-value = 0.0588). At the time of LC detection, all the SSNs showed a solid component, and the majority were found with a positive ^{18}F-FDG-PET uptake (35 out of 45 who underwent ^{18}F-FDG-PET, 78%); the LC diagnosis was made with CT-guided transthoracic biopsy (11/48, 23%) or surgery (37/48, 77%), the latter with (29/37, 78%) or without (8/37, 22%) intra-operative frozen section examination **(Table S2)**.

Most LCs derived from SSNs were diagnosed at stage I (42/48, 87.5%), irrespective of the nodule type (26/31, 83.9% in NSNs; 16/17, 94.1% in PSNs) or time of appearance (79.2% for prevalent vs. 100% for incident NSNs; p-value = 0.5622; 100% in prevalent vs. 66.7% in incident PSNs; p-value = 0.1765) **(Table 2)**. Most stage I LCs were diagnosed at stage IA in both NSNs (23/26, 88.5%) and PSNs (10/16, 62.5%) **(Table S3)**. No LC deaths were recorded in subjects with LC derived from SSNs, and no recurrence of LCs from SSNs was observed during follow-up.

The eight-year LC detection curves for SSNs stratified by nodule type and solid component size were significantly different; specifically, volunteers with prevalent NSNs ≥ 10 mm (**Figure 1A**) and prevalent PSNs with a solid component ≥ 5 mm **(Figure 1B)** had higher rates of LC (16.9% and 21.6%, respectively) than volunteers with other nodule subcategories (log-rank test p-value < 0.0001).

No LC was found within 1 year of NSN detection, and only 0.5% (4/844) of the NSNs were diagnosed as LC in the second year after detection (1 prevalent NSN ≥ 10 mm, 1 incident NSN < 10 mm, and 2 incident NSNs ≥ 10 mm) (**Figure S1A**). Of the 241 PSNs, 2 (0.8%) were diagnosed as cancer within 1 year after detection (both incident PSNs with a solid component ≥ 5 mm), and 4 (1.6%) within 2 years after detection (2 prevalent and 2 incident PSNs with a solid component ≥ 5 mm) (**Figure S1B**). LC cases arising from prevalent SSNs were essentially diagnosed over the entire screening period, while those derived from incident SSNs were diagnosed from the 4th year onwards (**Figure 2**).

Lung cancer not derived from SSNs

Thirty-two out of 80 (40.0%) LCs were not SSNs. These LCs, mostly located in a different lobe than SSNs (28/32, 87.5%), were deemed resectable in most cases. However, compared to those derived from SSNs, LCs not derived from SSNs were more frequently diagnosed at stages II-IV (50.0% of LCs not derived from SSNs vs. 10.4% of LCs derived from SSNs, p-value<0.0001) and were associated with relatively lower 5-year survival from LC diagnosis (71.9% vs. 93.8%, p-value = 0.01) **(Table 3)**.

Overall survival

Thirty-seven out of 758 (4.9%) participants died during a median follow-up period of 8.6 years. The 8-year cumulative survival in volunteers with LC derived from SSNs and not derived from SSNs was 93.8% and 74.9%, respectively, with the former being remarkably similar to that of volunteers with other cancers (95.7%) or free from malignancies (97.6%) (Log-rank test p-value < 0.01) **(Figure 3).**

Discussion

The management of SSNs remains an open question in LCS, and the most effective strategy to manage indolent lesions and reduce overdiagnosis and overtreatment has still to be defined. The findings of this study support the hypothesis that conservative management of SSNs in LCS is safe and effective because it prevents futile resections, enables timely diagnosis and treatment of the few invasive LCs arising from SSNs with excellent survival, and, in the meantime, ensures resection of the more aggressive LCs detected away from SSNs [20, 21]. Moreover, we provided information on the LC risk of SSNs detected in LCS, suggesting that small NSNs may be monitored with a prolonged LDCT interval and that an overcautious approach for incident SSNs, which did not exhibit more aggressive behaviour than prevalent SSNs, seems unjustified.

Retrospective analyses of the data from the National Lung Screening Trial (NLST) revealed that SSNs classified as Lung-RADS categories 2 and 3 had a malignancy risk of approximately 3% and 13%, respectively, according to baseline CT, exceeding those reported in the Lung-RADS 1.1 document (i.e., up to 2%) and approaching the rates found in the present cohort [24]. Consistent with our findings, the risk of malignancy was greater for PSNs and NSNs > 10 mm [24]. These results indicate the potential for safely managing smaller NSNs with an increased screening interval. In fact, in the BioMILD trial, only 1 out of 613 (0.2%) incident and prevalent NSNs < 10 mm was resected and proven to be cancer within 24 months of detection, suggesting that biennial scanning may be considered for these volunteers with no impact on survival while reducing costs and cumulative radiation burden. These results echo previous analyses encouraging biennial follow-up for negative LDCTs in LCS [25, 26] and provide evidence for further stratification of NSNs within the Lung-RADS 2 category based on a 10-year active surveillance strategy.

There are scarce data on the incidence and LC probability of new SSNs in LCS. In the I-ELCAP trial, nearly 70% of new SSNs resolved or decreased in size at follow-up, and 3.8% were ultimately diagnosed as LC versus 2.9% of those detected at baseline [13, 27]. The NELSON trial reported a similar likelihood of resolution yet a higher malignancy rate (i.e., 6%) for new SSNs [28]. According to a more recent analysis of SSNs detected via LDCT screening in Korea, 78.9% of new SSNs

disappeared or decreased in size, while 1.1% were diagnosed as cancer [29]. Of the 700 incident SSNs in the BioMILD trial, only 10 were malignant (1.4%), and 243 of the 571 incident SSNs that underwent follow-up (42%) resolved over time. Moreover, most incident SSNs that were revealed to be malignant led to a cancer diagnosis more than 12 months after detection (8/10, 80%), all of which were diagnosed with favourable staging. Our findings reveal that the malignancy risk of new SSNs is similar to or lower than that reported in previous studies and corroborate the hypothesis that a more aggressive follow-up for new than for baseline SSNs seems unwarranted.

The evidence from the BioMILD trial discourages early aggressive management of SSNs, an approach that led to the resection of benign lesions and a greater proportion of noninvasive LCs in the early era of LCS (e.g., 5-18% [7, 30–32]), but rather supports a more conservative strategy capable of ensuring timely intervention and the avoidance of unnecessary surgery [13, 20, 33]. Indeed, in the BioMILD cohort, no SSNs were diagnosed as benign disease or atypical adenomatous hyperplasia, and only one case of adenocarcinoma was found at stage 0. This result, along with the lack of increased mortality risk related to surveillance, arguably suggests that the early resection of SSNs should be considered overtreatment rather than timely diagnosis. Notably, 32 of the 80 LCs (40.0%) found in the BioMILD volunteers under surveillance for SSNs arose from lesions other than SSNs, most of which were located in the lung parenchyma far from concomitant SSNs. Volunteers with these LCs had lower survival than those diagnosed with SSNs, in accordance with previous data [21]. Therefore, in these cases, early SSN resection could have potentially hampered the surgical approach to treat more aggressive pulmonary lesions, which, instead, was ensured by SSN conservative management.

In the BioMILD trial, the median time interval from detection to LC diagnosis was up to 6 years, and LCs from SSNs were encountered over the entire 10-year follow-up period. New SSNs were detected up to 9 years after baseline, and there was no clear safety point at which to discontinue screening to avoid missing their detection. These findings suggest that SSNs should be followed up until the volunteers may benefit from intervention, in line with findings from the literature that favour long-term monitoring of SSNs to prevent misdiagnosis or missed diagnosis of clinically significant LC [34, 35]. Since a lower incidence of growth has been suggested for stable SSNs (e.g., after 2 or more years of stability [35–38]), further analyses may help optimize SSN management by evaluating individual nodule trajectories to personalize LDCT screening intervals [39].

The major strengths of the current analysis were the relatively large size of the study population, the prospective nodule management, and long-term follow-up.

The study also suffers from limitations. First, the conservative approach of the BioMILD protocol prevented histologic assessment of most SSNs because only suspicious lesions were considered for resection. Moreover, the dimensional evaluation of the SSNs was based on the maximal diameter rather than the volume or mean diameter, as now recommended by Lung-RADS [40], potentially affecting comparisons with the Lung-RADS categories.

In conclusion, a surveillance strategy has proven to be a safe option for monitoring SSNs in LCS, preventing unnecessary treatments without compromising the overall LC stage or survival, while ensuring the resection of more aggressive LCs detected away from SSNs. The results also reveal the potential for increasing LDCT intervals for volunteers with small NSNs and suggest that incident SSNs do not carry a greater risk of LC than prevalent SSNs, as otherwise indicated by current recommendations.

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FIGURE LEGENDS

Figure 1. Eight-year incidence of lung cancer derived from (A) nonsolid nodules and (B) part-solid nodules stratified by type, prevalence or incidence, and size.

Figure 2. Timeline of lung cancer diagnosis derived from subsolid nodules following the baseline screening round.

Figure 3. Kaplan–Meier survival curves of screened volunteers with subsolid nodules according to disease diagnosis.

Table 1. Characteristics of volunteers with subsolid nodules detected at baseline and further screening rounds

		Total 758	Only NSNs 584 (77.0%)	Only PSNs 130 (17.2%)	NSNs and PSNs 44 (5.8%)	P-value
Sex	**Female**	359 (47.4%)	281 (48.1%)	57 (43.9%)	21 (47.7%)	0.6770
	Male	399 (52.6%)	303 (51.9%)	73 (56.2%)	23 (52.3%)	
Age	**< 55 years**	152 (20.0%)	122 (20.9%)	23 (17.7%)	7 (15.9%)	0.5881
	55-64 years	388 (51.2%)	300 (51.4%)	63 (48.5%)	25 (56.8%)	
	≥ 65 years	218 (28.8%)	162 (27.7%)	44 (33.9%)	12 (27.3%)	
	Median (IQR)	60 (56-65)	60 (56-65)	61 (56-65)	61 (56-65)	0.5432
Pack-years	**< 30**	48 (6.3%)	37 (6.3%)	8 (6.2%)	3 (6.85)	0.9878
	≥ 30	710 (93.7%)	547 (93.7%)	122 (93.9%)	41 (93.2%)	
	Median (IQR)	41 (35-52)	41 (35-52)	42 (35-54)	41.5 (35.5-48.5)	0.6025
Smoking status	**Current smokers**	602 (79.4%)	462 (79.1%)	103 (79.2%)	37 (84.1%)	0.7318
	Former smokers	156 (20.6%)	122 (20.9%)	27 (20.8%)	7 (15.9%)	
BMI	**Median (IQR)**	24.6 (22.2-27.3)	24.6 (22.3-27.4)	24.8 (21.8-27.3)	24.4 (22.0-26.3)	0.5619
CRP	**Median (IQR)**	1.4 (0.7-2.7)	1.4 (0.7-2.7)	1.5 (0.8-3.3)	1.9 (0.9-3.1)	0.4468
Median person-years		8.6	8.6	8.7	9.2	
Total *n* of LDCT scans		4008	3051	645	312	
Mean LDCT scans per participant		5.3	5.2	5.0	7.1	

NSN, nonsolid nodule; PSN, part-solid nodule; IQR, interquartile range; BMI, body mass index; CRP, C-reactive protein; LDCT, low-dose computed tomography.

Table 2. Clinical course of subsolid nodules detected at baseline and further screening rounds

	Total	Prevalent	Incident	P value
NSN	**844**	**286 (33.9%)**	**558 (66.1%)**	
Incident lung cancer derived from NSNs	31 (3.7%)	24 (8.4%)	7 (1.3%)	<0.0001
% Stage I	26 (83.9%)	19 (79.2%)	7 (100%)	0.5622
Interval from NSN detection to incident LC (years), median, IQR	4.3 (3.1-5.8)	4.3 (3.7-6.3)	2.4 (1.5-5.6)	0.0422
LC deaths	0	0	0	
Resolution/NSNs with at least one follow-up LDCT	216/718 (30.1%)	61/273 (22.3%)	155/445 (34.8%)	0.0004
Duration from first detection of nodules to the last LDCT scan (years), median, IQR	3.4 (1.1-6.0)	6.9 (3.1-8.1)	1.5 (1.0-4.4)	<0.0001
PSN	**241**	**99 (41.1%)**	**142 (58.9%)**	
Incident lung cancer derived from PSNs	17 (7.1%)	14 (14.1%)	3 (2.1%)	0.0005
% Stage I	16 (94.1%)	14 (100%)	2 (66.7%)	0.1765
Interval from PSN detection to incident LC (years), median, IQR	2.9 (2.3-3.5)	3.2 (2.3-4.3)	0.4 (0.2-2.9)	0.0588
LC deaths	0	0	0	
Resolution/PSNs with at least one follow-up LDCT	139/219 (63.5%)	51/93 (54.8%)	88/126 (69.8%)	0.0227
Duration from first detection of nodules to the last LDCT scan (years), median, IQR	3.9 (1.2-6.5)	5.3 (2.2-7.5)	3.6 (0.4-5.6)	<0.0001
Incident lung cancer not derived from SSNs	32	18	14	
% Stage I	15 (46.9%)	7 (38.9%)	8 (57.1%)	
LC deaths	6	5	1	

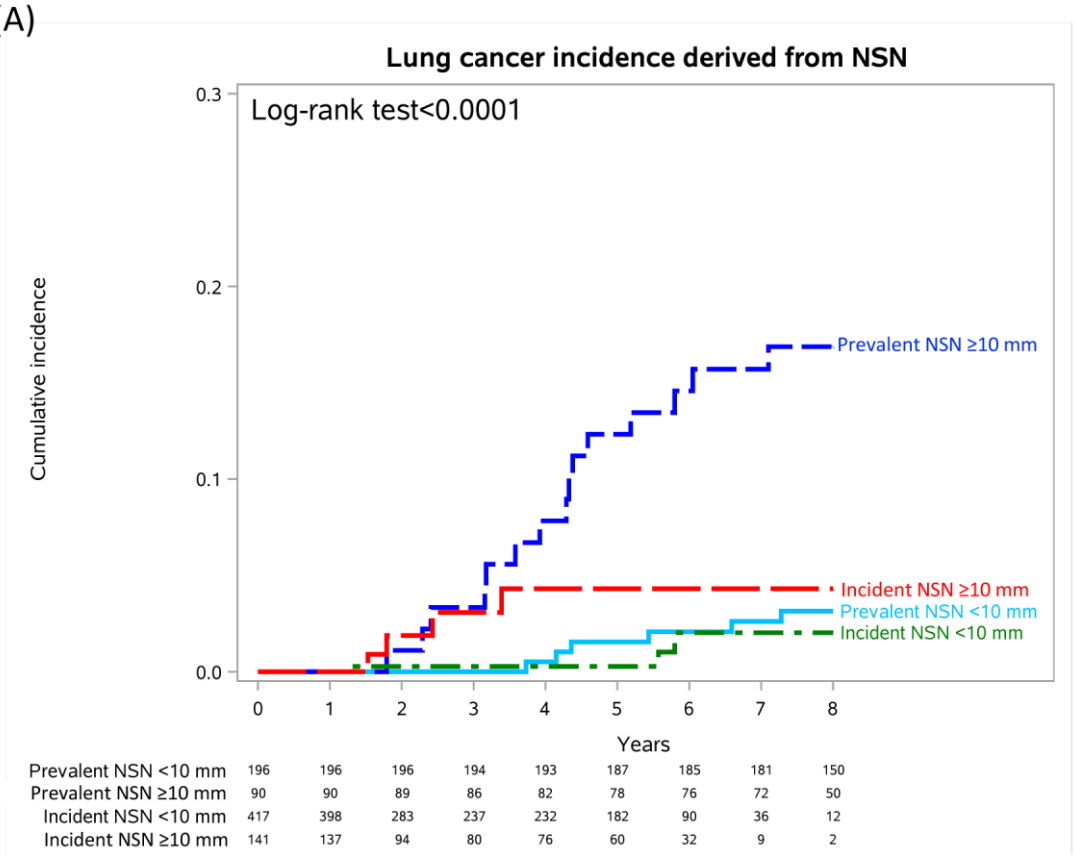
NSN, nonsolid nodule; LC, lung cancer; IQR, interquartile range; PSN, part-solid nodule; LDCT, low-dose computed tomography; SSN, subsolid nodule

Table 3. Clinical outcomes of volunteers diagnosed with incident lung cancer

	Total incident lung cancer	Incident lung cancer derived from SSNs	Incident lung cancer not derived from SSNs	P value
	80	48	32	
% resectability	72 (90.0%)	47 (97.9%)	25 (78.1%)	0.0059
Stage distribution				0.0003
Stage 0	2 (2.5%)	1 (2.1%)	1 (3.1%)	
Stage I	57 (71.3%)	42 (87.5%)	15 (46.9%)	
Stage II	9 (11.3%)	2 (4.2%)	7 (21.9%)	
Stage III	8 (10.0%)	3 (6.3%)	5 (15.6%)	
Stage IV	4 (5.0%)	0	4 (12.5%)	
% 5-year survival from LC diagnosis	68 (85.0%)	45 (93.8%)	23 (71.9%)	0.0105

SSN, subsolid nodule; LC lung cancer.

(A)


Lung cancer incidence derived from NSN
Log-rank test<0.0001
Cumulative incidence
0.3
0.2
0.1
0.0
Prevalent NSN ≥10 mm
Incident NSN ≥10 mm
Prevalent NSN <10 mm
Incident NSN <10 mm
0 1 2 3 4 5 6 7 8
Years
Prevalent NSN <10 mm 196 196 196 194 193 187 185 181 150
Prevalent NSN ≥10 mm 90 90 89 86 82 78 76 72 50
Incident NSN <10 mm 417 398 283 237 232 182 90 36 12
Incident NSN ≥10 mm 141 137 94 80 76 60 32 9 2

(B)

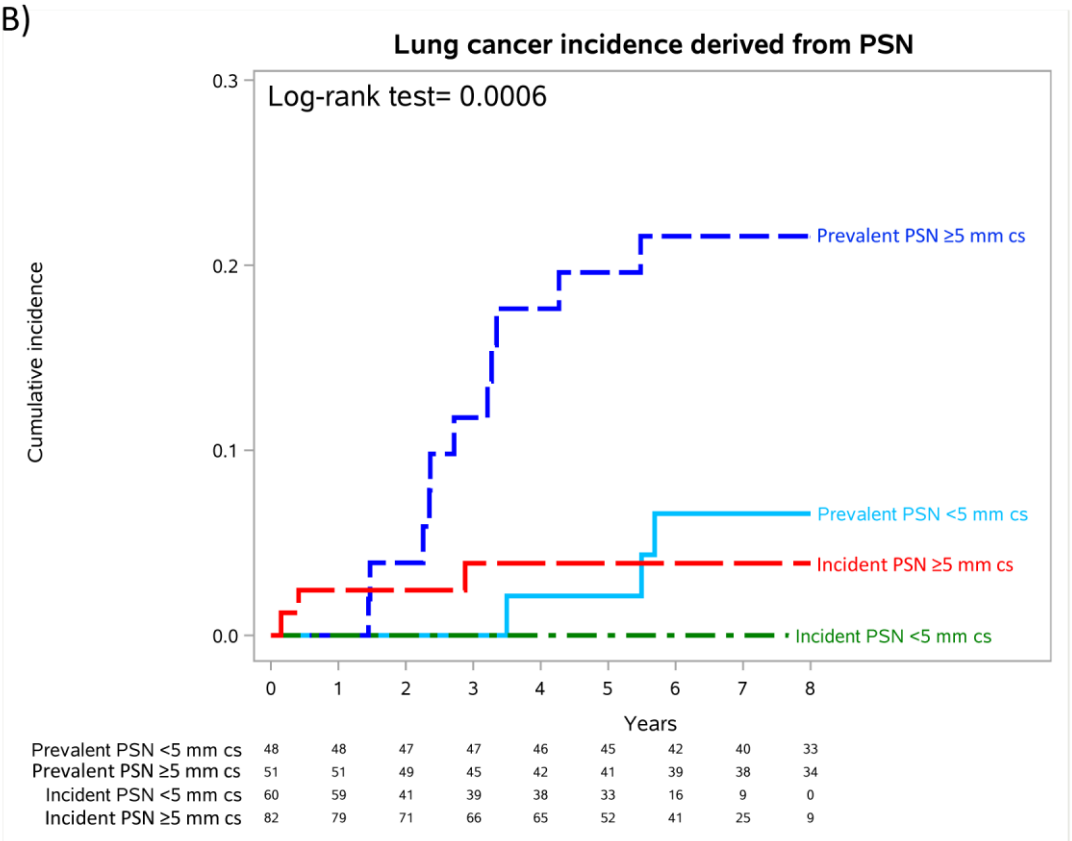

Lung cancer incidence derived from PSN
Log-rank test= 0.0006
Cumulative incidence
0.3
0.2
0.1
0.0
Prevalent PSN ≥5 mm cs
Prevalent PSN <5 mm cs
Incident PSN ≥5 mm cs
Incident PSN <5 mm cs
0 1 2 3 4 5 6 7 8
Years
Prevalent PSN <5 mm cs 48 48 47 47 46 45 42 40 33
Prevalent PSN ≥5 mm cs 51 51 49 45 42 41 39 38 34
Incident PSN <5 mm cs 60 59 41 39 38 33 16 9 0
Incident PSN ≥5 mm cs 82 79 71 66 65 52 41 25 9

Figure 1

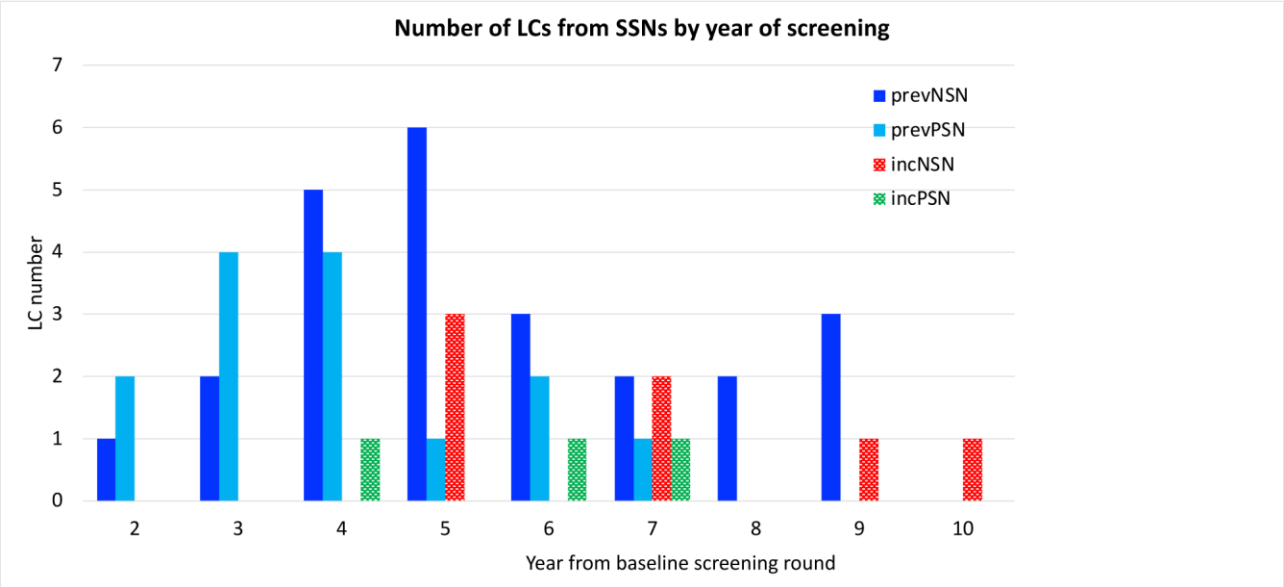

Number of LCs from SSNs by year of screening
LC number
0
1
2
3
4
5
6
7
2
3
4
5
6
7
8
9
10
Year from baseline screening round
prevNSN
prevPSN
incNSN
incPSN

Figure 2

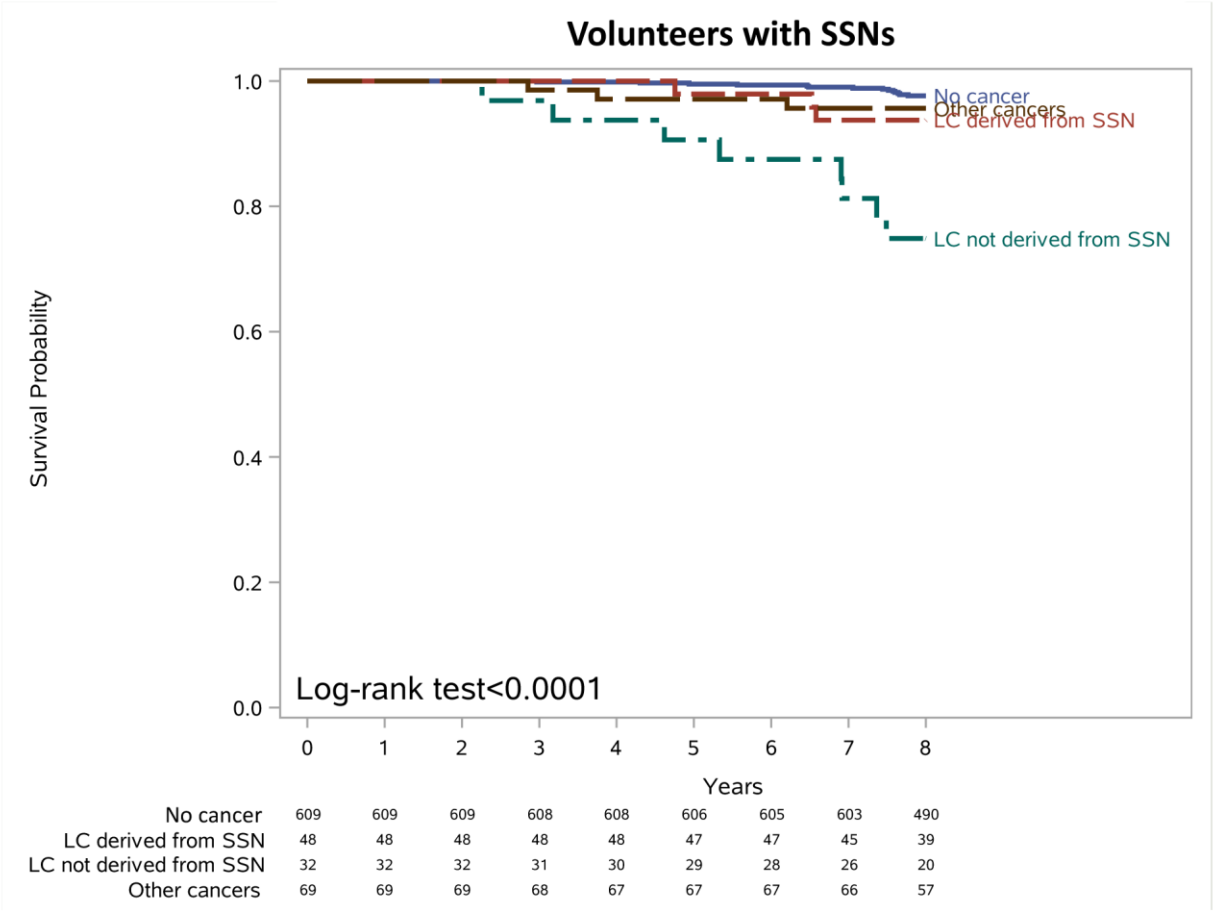

Volunteers with SSNs
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
No cancer
Other cancers
LC derived from SSN
LC not derived from SSN
Log-rank test<0.0001
0
1
2
3
4
5
6
7
8
Years
No cancer 609 609 609 608 608 606 605 603 490
LC derived from SSN 48 48 48 48 48 47 47 45 39
LC not derived from SSN 32 32 32 31 30 29 28 26 20
Other cancers 69 69 69 68 67 67 67 66 57

Figure 3

Supplementary Material

Surveillance of subsolid nodules avoids unnecessary resections in lung cancer screening: Long-term results of the prospective BioMILD trial.

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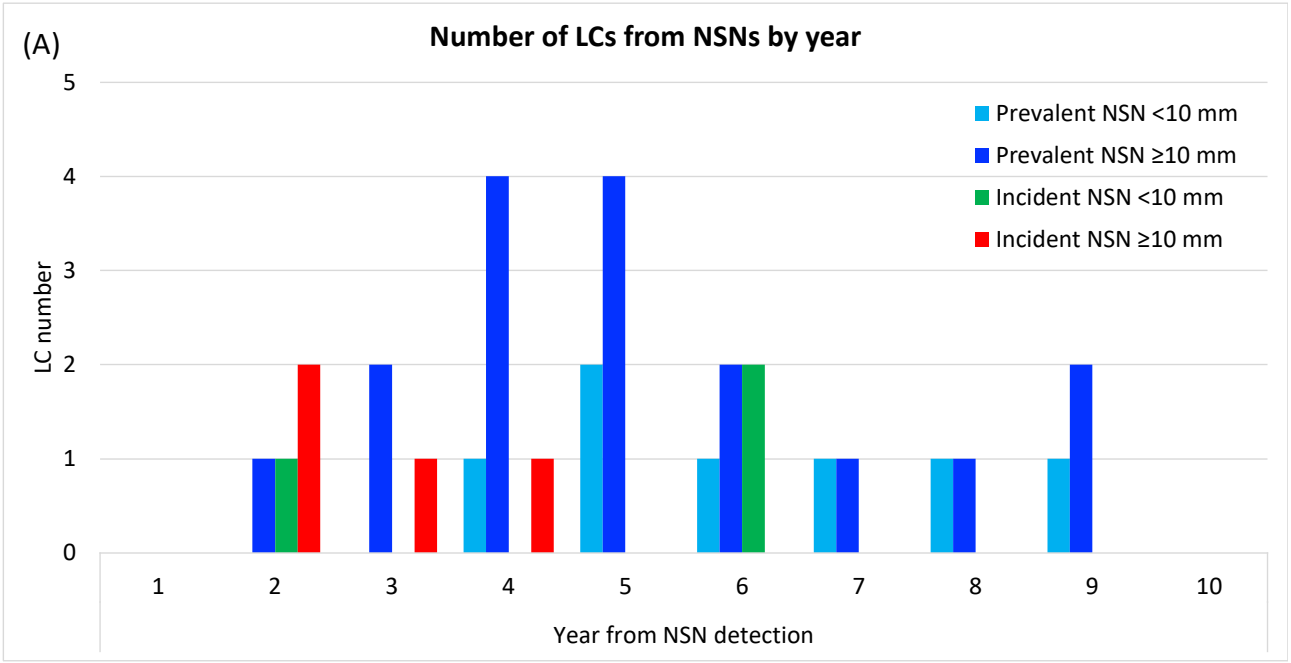
Figure S1. Timeline of detected lung cancers derived from subsolid lesions following the detection of (A) nonsolid nodules and (B) part-solid nodules.



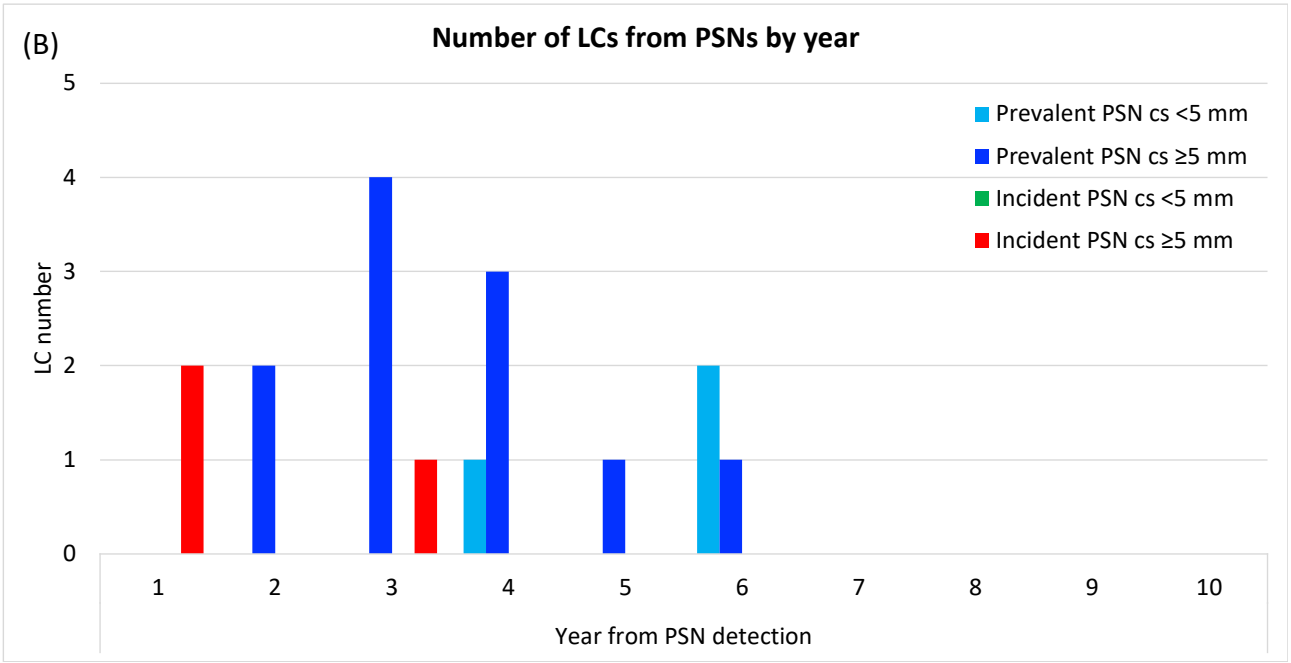


Table S1. Characteristics of SSNs detected at the baseline and further screening rounds.

	Total lesions 1085	**Prevalent 385 (35.5%)**	**Incident 700 (64.5%)**	**P value**
NSN	**844**	**286 (33.9%)**	**558 (66.1%)**	
Diameter < 10 mm	613 (72.6%)	196 (68.5%)	417 (74.7%)	0.0554
Diameter ≥ 10 mm	231 (27.4%)	90 (31.5%)	141 (25.3%)	
Upper/middle lobe	592 (70.1%)	211 (73.8%)	381 (68.3%)	0.0986
PSN	**241**	**99 (41.1%)**	**142 (58.9%)**	
Diameter sc < 5	108 (44.8%)	48 (48.5%)	60 (42.3%)	0.3386
Diameter sc ≥ 5	133 (55.2%)	51 (52.5%)	82 (57.8%)	
Upper/middle lobe	152 (63.1%)	59 (59.6%)	93 (65.5%)	0.3507

NSN, nonsolid nodule; PSN, part-solid nodule; sc, solid component.

Table S2. Diagnostic management of lung cancers derived from subsolid nodules.

	Total	Lung cancer from NSNs*	Lung cancer from PSNs*
Lung Cancer	**48**	**31**	**17**
Solid component at the time of lung cancer diagnosis	48 (100%)	31 (100%)	17 (100%)
^{18}F-FDG-PET	45 (94%)	28 (90%)	17 (100%)
^{18}F-FDG-PET positivity	35 (72.9%)	22 (71.0%)	13 (76.5%)
CT-guided transthoracic biopsy	11 (23%)	7 (23%)	4 (24%)

*Nodule type refers to the time of detection
18F-FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography
NSN, nonsolid nodule; PSN, part-solid nodule

Table S3. Stages distribution of stage I lung cancers derived from subsolid nodules.

	Total	**Prevalent**	**Incident**
Incident lung cancer derived from NSNs	31	24	7
% Stage I*	26 (83.9%)	19 (79.2%)	7 (100%)
IA	23	16	7
IB	3	3	0
IC	0	0	0
Incident lung cancer derived from PSNs	**17**	**14**	**3**
% Stage I*	16 (94.1%)	14 (100%)	2 (66.7%)
IA	10	9	1
IB	6	5	1
IC	0	0	0

*No cases of minimally invasive adenocarcinoma (MIA) were detected
NSN, nonsolid nodule; PSN, part-solid nodule