

Supplementary Table 1. Characteristics of participants who underwent low-dose chest computed tomography screening

	Total (n=50,132)	Never-smoker (n=22,631)	Ever-smoker (n=27,501)	p-value*
Age at first screening, n (%)				<0.001
<45 years	17,644 (35.2)	7,108 (31.4)	10,536 (38.3)	
45-49 years	8,453 (16.9)	3,681 (16.3)	4,772 (17.4)	
50-54 years	8,137 (16.2)	3,718 (16.4)	4,419 (16.1)	
55-59 years	6,368 (12.7)	3,059 (13.5)	3,309 (12.0)	
60-64 years	4,254 (8.5)	2,162 (9.6)	2,092 (7.6)	
65-69 years	2,867 (5.7)	1,515 (6.7)	1,352 (4.9)	
70-74 years	1,619 (3.2)	903 (4.0)	716 (2.6)	
≥75 years	790 (1.6)	485 (2.1)	305 (1.1)	
Mean ± SD	49.5±11.3	50.6±11.7	48.6±10.9	<0.001
Sex, male, n (%)	34,167 (68.2)	8,212 (36.3)	25,955 (94.4)	<0.001
Number of CT scans, including the first LDCT, mean ± SD	2.1 ± 2.1	2.0 ± 1.8	2.3 ± 2.3	<0.001
Participants with subsolid nodules detected, n (%)	4,545 (9.1)	2,426 (10.7)	2,119 (7.7)	<0.001
Subsolid nodule(s) detected at first screening, n (%)	3,608 (7.2)	2,040 (9.0)	1,568 (5.7)	<0.001
No subsolid nodule at first screening but new subsolid nodule(s) detected during follow-up screening, n (%)	937 (1.9)	386 (1.7)	551 (2.0)	0.014
Participants with single subsolid nodule, n (%)	3,380 (6.7)	1,860 (8.2)	1,520 (5.5)	<0.001
Participants with multiple subsolid nodules, n (%)	1,165 (2.3)	566 (2.5)	599 (2.2)	0.017
Underwent invasive biopsy for subsolid nodule, n (%) [†]	225 (0.4)	114 (0.5)	111 (0.4)	0.095
Diagnosed as lung cancer, n (%)	193 (0.4)	98 (0.4)	95 (0.3)	0.115
Diagnosed as other malignancy, n (%) [‡]	1 (0)	0 (0)	1 (0)	1.000
Diagnosed as benign (false-positive), n (%)	31 (0.1)	16 (0.1)	15 (0.1)	0.469

LDCT=low-dose chest computed tomography. SD=standard deviation.

*The p-value is based on the comparison between never-smokers and ever-smokers.

[†]Includes video-assisted thoracic surgery, percutaneous needle biopsy, and bronchoscopic biopsy.

[‡]One patient was diagnosed with malignant lymphoma, after the resection of a subsolid nodule.

Supplementary Table 2. Characteristics and clinical course of subsolid nodules detected at baseline screening and follow-up screening

	Total (n=6,725)	Baseline subsolid nodule (n=5,241)	New subsolid nodule (n=1,484)	p-value*
Nodule diameter at first detection (mm), mean \pm SD	6.9 \pm 3.4	6.9 \pm 3.5	6.9 \pm 3.1	0.895
Sex of participants with nodules, male, n (%)	4,132 (61.4)	3,000 (57.2)	1,132 (76.3)	<0.001
Smoking status of participants with nodules, n (%)				<0.001
Never-smoker	3,482 (51.8)	2,907 (55.5)	575 (38.7)	
Ever-smoker	3,243 (48.2)	2,334 (44.5)	909 (61.3)	
Nodule type, n (%)				<0.001
Pure GGN	5,116 (76.1)	4,088 (78.0)	1,028 (69.3)	
Part-solid	1,609 (23.9)	1,153 (22.0)	456 (30.7)	
Location, n (%)				<0.001
Right upper lobe	1,825 (27.1)	1,449 (27.6)	376 (25.3)	
Right middle lobe	646 (9.6)	491 (9.4)	155 (10.4)	
Right lower lobe	1,542 (22.9)	1,155 (22.0)	387 (26.1)	
Left upper lobe	1,444 (21.5)	1,178 (22.5)	266 (17.9)	
Left lower lobe	1,268 (18.9)	968 (18.5)	300 (20.2)	
Lung-RADS category at first detection of nodule, n (%)				<0.001
2	5,207 (77.4)	4,183 (79.8)	1,024 (69.0)	
3	923 (13.7)	815 (15.6)	108 (7.3)	
4A	405 (6.0)	164 (3.1)	241 (16.2)	
4B	182 (2.7)	71 (1.4)	111 (7.5)	
4X	8 (0.1)	8 (0.2)	0 (0)	
Subsolid nodules that received additional follow-up (including later screening), n (%)	4,918 (73.1)	3,607 (68.8)	1,311 (88.3)	<0.001
Number of CT scans, including the first LDCT, mean \pm SD	4.6 \pm 3.1	4.1 \pm 2.9	6.0 \pm 3.0	<0.001
Duration from first detection of a nodule to the last CT	43.4 \pm 39.5	46.3 \pm 41.4	35.5 \pm 32.5	<0.001

scan (months), mean \pm SD				
Outcome of subsolid nodules after follow-up, n/N (%)				
Resolution [†]	2,116/4,918 (43.0)	1,082/3,607 (30.0)	1,034/1,311 (78.9)	<0.001
Completely disappeared	2,029/4,918 (41.3)	1,037/3,607 (28.7)	992/1,311 (75.7)	<0.001
Decreased in size or solid portion	87/4,918 (1.8)	45/3,607 (1.2)	42/1,311 (3.2)	<0.001
Stable	2,512/4,918 (51.1)	2,268/3,607 (62.9)	244/1,311 (18.6)	<0.001
Growth [‡]	290/4,918 (5.9)	257/3,607 (7.1)	33/1,311 (2.5)	<0.001
Subsolid nodules that underwent invasive biopsy, n (%)	293 (4.4)	266 (5.1)	27 (1.8)	<0.001
Diagnosed as lung cancer, n (%)	227 (3.4)	210 (4.0)	17 (1.1)	<0.001
Diagnosed as other malignancy, n (%) [§]	1 (0)	1 (0)	0 (0)	1.000
Diagnosed as benign (false-positive), n (%)	65 (1.0)	55 (1.0)	10 (0.7)	0.192

GGN=ground-glass opacity nodule. SD=standard deviation. LDCT=low-dose chest computed tomography.

*The p-value is based on the comparison between baseline and new nodules.

[†]Nodules that disappeared, or exhibited a decrease of ≥ 2 mm in the total size or solid portion.

[‡]Nodules that exhibited an increase of ≥ 2 mm in the total size or solid portion, or emerging new solid portion.

[§]One subsolid nodule was diagnosed as malignant lymphoma.

Supplementary Table 3. Univariable and multivariable Cox proportional hazard analyses of the incidence of biopsy and lung cancer diagnosis (total n = 6,725)

Clinical outcome	Variable*	Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Incidence of invasive biopsy	Detected at follow-up screening	0.36 (0.24-0.54)	<0.001	0.39 (0.26-0.58)	<0.001
	Sex (male)	0.85 (0.67-1.08)	0.174	0.69 (0.50-0.95)	0.023
	Age at detection	1.05 (1.04-1.06)	<0.001	1.04 (1.03-1.05)	<0.001
	Smoking status (ever-smoker)	1.02 (0.81-1.21)	0.873	1.35 (0.99-1.85)	0.057
	Initial diameter	1.15 (1.14-1.16)	<0.001	1.13 (1.11-1.14)	<0.001
	Multiplicity	0.88 (0.70-1.11)	0.294	-	-
	Part-solid nodule (vs. pure GGN)	4.80 (3.80-6.07)	<0.001	2.99 (2.31-3.86)	<0.001
Incidence of lung cancer diagnosis	Detected at follow-up screening	0.29 (0.18-0.47)	<0.001	0.31 (0.19-0.51)	<0.001
	Sex (male)	0.82 (0.63-1.08)	0.160	0.66 (0.45-0.95)	0.025
	Age at detection	1.05 (1.03 -1.06)	<0.001	1.04 (1.03-1.05)	<0.001
	Smoking status (ever-smoker)	0.99 (0.76-1.29)	0.948	1.35 (0.94-1.92)	0.100
	Initial diameter	1.16 (1.15-1.17)	<0.001	1.13 (1.11-1.15)	<0.001
	Multiplicity	0.75 (0.58-0.97)	0.031	1.03 (0.79-1.35)	0.826
	Part-solid nodule (vs. pure GGN)	6.39 (4.84-8.43)	<0.001	3.93 (2.91-5.32)	<0.001

HR=hazard ratio. CI=confidence interval. GGN=ground-glass opacity nodule.

* Age and initial diameter (in mm) were included as continuous variables, and sex, smoking status, detection at follow up screening, multiplicity, and nodule type were included as categorical variables

Supplementary Table 4. International Classification of Disease for Oncology (ICD-O) morphologic code classification of diagnosed adenocarcinomas from screen-detected subsolid nodules

ICD-O classification of diagnosed adenocarcinomas	n=226
8140/2 (Adenocarcinoma in situ)	31 (13.7)
8250/2 (Minimally invasive adenocarcinoma)	59 (26.1)
8250/3 (Lepidic adenocarcinoma)	21 (9.3)
8253/3 (Invasive mucinous adenocarcinoma)	6 (2.7)
8254/3 (Mixed invasive mucinous and non-mucinous adenocarcinoma)	1 (0.4)
8260/3 (Papillary adenocarcinoma)	27 (11.9)
8265/3 (Micropapillary adenocarcinoma)	3 (1.3)
8551/3 (Acinar adenocarcinoma)	66 (29.2)
8230/3 (Solid adenocarcinoma)	2 (0.9)
8140/3 (Adenocarcinoma, not otherwise specified)	10 (4.4)