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CT characteristics of solid pulmonary nodules of never smokers versus smokers: A population-based study

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ABSTRACT

Purpose: Aim was to assess CT characteristics of lung nodules in never and former smokers compared to current smokers in a population-based setting.
Method: We included individuals aged 45–60 years taking part in the ImaLife (Imaging in Lifelines) study, with at least one solid lung nodule (≥30 mm^3) on low-dose chest CT. Qualitative (location, shape, margin, nodule type, attached structures) and quantitative (count, diameter, volume) nodule characteristics were evaluated. Based on Fleischner criteria, 'high risk' nodules were defined. To examine the association between smoking status and nodule CT characteristics of participants, multi-level multinomial logistic regression corrected for clustering of nodules within participants was performed, where all odds ratios (aORs) were adjusted for age and sex.
Results: Overall, 1,639 individuals (median age: 55.0, IQR:50.5–58.5, 50.5% men) were included, with 42.1% never smokers, 35.3% former smokers and 22.6% current smokers. A total of 3,222 solid nodules were identified; 39.7% of individuals had multiple nodules. Nodule size, location, type and attachment were similar for never compared to current smokers. The odds of nodules with an irregular shape and irregular margin was lower in never smokers (aOR:0.64, 95 %CI:0.44–0.93; aOR:0.60, 95 %CI:0.41–0.88, respectively) and former smokers (aOR:0.61, 95 %CI:0.41–0.90; aOR:0.57, 95 %CI:0.38–0.85, respectively) compared to current smokers. The odds of a detected nodule being 'high risk' was similar for never versus current smokers (never smokers: aOR = 0.90; 95% CI:0.73–1.11).
Conclusions: CT-based characteristics of solid lung nodules in never and former smokers differed only slightly from current smokers. Among individuals with solid nodules, 'high-risk' nodules were equally common in never smokers and current smokers.

1. Introduction

A pulmonary nodule is a frequent finding in chest computed tomography (CT) [1]. Etiology of lung nodules include infectious diseases, granulomatous diseases, benign tumors, fibrosis, round atelectasis, lymph nodes, autoimmune and vascular diseases, and malignancy [2]. Over 95% of incidentally detected nodules are benign [3]. Multiple population-based studies have shown that the prevalence of pulmonary nodules is strongly related to smoking [4–6].

Characteristics of solid nodules (such as larger nodule size, irregular

Abbreviations: CT, Computed tomography; VDT, Volume doubling time; COPD, Chronic obstructive pulmonary disease; CAD, Coronary artery disease; IQR, Interquartile range; GGN, Ground glass nodule.

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or spiculated margins, upper lobe location *etcetera*) on low-dose CT scans can be used to estimate the probability of the nodule being or becoming lung cancer[2,7–10]. According to the latest Fleischner society guidelines dated 2017 [10], the management and follow-up of pulmonary nodules should be based on risk-stratification based on both the individual's and nodule's characteristics. In contrast, in the previous Fleischner society guideline [11], to assess the nodule malignancy risk and follow-up management, subjects were stratified into low- or high-risk based on smoking, history of lung cancer in a first-degree relative or specific exposure. With the new Fleischner guidelines, stricter follow-up of lung nodules is also recommended for high-risk lesions in low-risk individuals. Thus, it is important to know more about nodule characteristics in low-risk, never smokers.

So far, the available CT evidence on lung nodule features, and their relationship to pathology, has primarily originated from lung cancer screening studies in heavy current and former smokers. Therefore, these observations are not fully representative for a general population, especially in view of the fact that never smokers comprise up to 75% of the global population [12]. Moreover, chest CT is increasingly applied in clinical practice, also in non-smoking individuals. Only few studies have focused on CT characteristics of lung nodules in never smokers, with the majority of those studies being based on Asian populations [5,13–15]. Although these studies elucidated important CT characteristics of lung nodules in Asian never smokers, they had several limitations that hinder the application of their findings to a broader setting. For instance, studies were retrospective, included few nodule characteristics, lacked comparisons between never and current smokers, or included a non-representative study population. There is a lack of knowledge about how CT characteristics of nodules in never smokers in Western populations differ from smokers, and which features are of potential clinical significance.

Therefore, the objective of this study was to assess CT characteristics of lung nodules in never and former smokers compared to current smokers in a population-based setting of Dutch middle-aged adults.

2. Materials and methods

2.1. Study population

The ImaLife study is an ongoing prospective population-based imaging study embedded in the Lifelines cohort, designed to assess reference distributions of early imaging biomarkers for lung cancer, COPD and coronary heart disease in the general population [16,17]. Lifelines is a multi-disciplinary prospective population-based cohort study with a unique three-generation design, on the health and health-related behaviors of 167,729 persons living in the North of the Netherlands. Using a broad range of study procedures, Lifelines evaluates the biomedical, physical, socio-demographic, psychological and behavioral factors contributing to disease and health in the general population. There is a special focus on multi-morbidity and complex genetics. Lifelines participants, who had completed lung function testing and were 45 years of age or older, were included in the ImaLife study and underwent a low-dose chest CT scan from August 2017 onwards. For the current analysis, participants aged 45 years at time of the CT scan were eligible, resulting in 8,760 participants. Next, participants were excluded if 1) older than 60 years, 2) missing smoking information, 3) they had no nodule or only a solid nodule < 30 mm^3 or sub-solid nodule. Participants with only sub-solid nodules were excluded because of the relatively low prevalence (149/8,760) and lack of guideline criteria for describing their morphological CT characteristics. In total, 1,639 participants were included in the current study. See Fig. 1 for the flow chart of the study population selection. All individuals provided written informed consent for participation in the ImaLife study. The ImaLife study obtained approval from the Medical Ethics Review Committee (METc 2016-436).

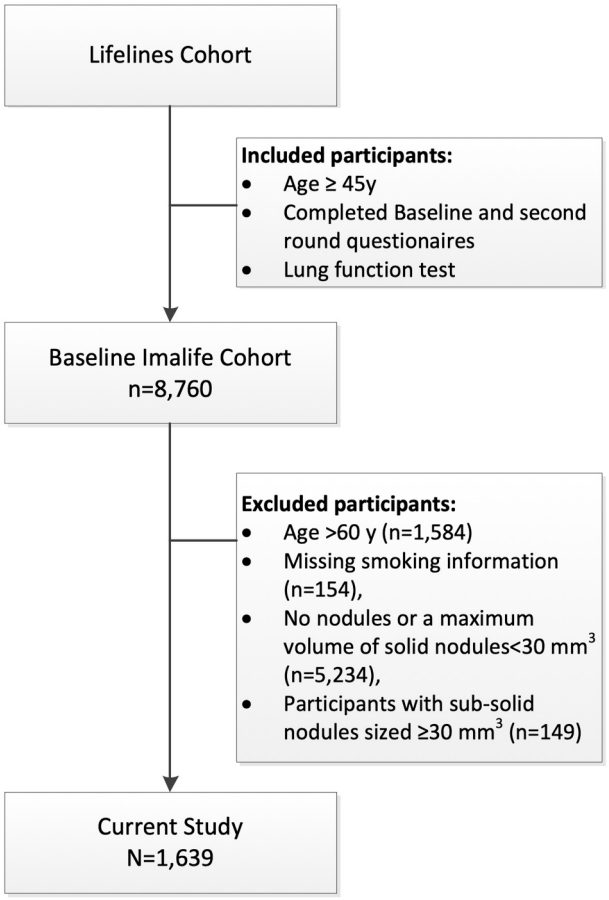

Fig. 1. Flow chart of the study population selection.

3. Data collection

3.1. Demographic and clinical data

For all participants, basic demographic and relevant clinical information was extracted from the baseline (2007–2013) and second round (2014–2017) questionnaires of Lifelines. The following information was used: age, sex, smoking history (smoking status [never, former, and current]), smoking intensity and years since quitting smoking. The smoking status was obtained from baseline questionnaires and supplemented by second round assessments, data on pack years and years since quitting were only used from the baseline examination due to a large number of missing values in the second-round assessment. Participants were considered to be smokers if they reported smoking in their lifetime and were further classified into current or former smokers by whether they "have stopped smoking at least for 4 weeks" [18]. Smoking intensity was calculated by the question: "How much do you smoke on average now?", where a threshold of 20 pack years was applied to distinguish between light to medium versus heavy smokers. Pack-years were calculated by multiplying intensity in packs/day by duration in years, with one pack containing 20 cigarettes [19]. Years since quitting smoking was calculated based on the question: "If you no longer smoke, how old were you when you stopped smoking?" and the age of starting smoking. Second-hand smoking was not considered in this study.

3.2. CT acquisition and image analysis

Study participants underwent a single-time-point low-dose chest CT examination with third-generation dual-source CT (SOMATOM Force, Siemens Healthineers, Germany) between August 2017 (inception of the

ImaLife study) and November 2020. CT scanning acquisition parameters were previously described in the design paper [16]. Radiological qualitative and quantitative characteristics of pulmonary nodules were analyzed with semi-automatic software (MM Oncology Syngo.via VB30, Siemens Healthineers, Germany).

3.3. Detection and description of the nodule's CT characteristics

Each CT scan as part of the ImaLife study was evaluated by one of the reading radiologists (MR, RV, JC, GK) or radiologists-in-training having over 4 years of experience in chest CT, or by a trained technical medicine graduate (GP) under supervision of a radiologist (GK/RV/MR). All scan readers received training for evaluation of lung nodules and characterization of nodules based on a predefined protocol. Hard to define nodule CT characteristics were reevaluated by an experienced EBCR-qualified cardiothoracic radiologist (RV, 13 years of experience at start of study) who gave a final judgment. Nodule size measurement was performed using semi-automatic software (MM Oncology, Syngo.via VB30, Siemens Healthineers). Readers were blinded for participant characteristics. Characteristics were collected for each solid nodule with a volume $\geq$ 30 mm^3. Readers described nodule characteristics on a predefined digital form, comprising: **1)** Number of nodules per participant. **2)** Size of each nodule: according to the Fleischner Guidelines [10]; the maximal long-axis and maximum orthogonal diameter expressed in millimeters, the average diameter on axial view and the volume, all semi-automatically measured. **3)** Nodule type: for the current analysis only solid nodules were included. Calcified nodules were defined by visual assessment in soft tissue kernel. Perifissural nodules (PFNs) were defined as solid nodules attached to the fissure, usually having a smooth margin, and triangular or polygonal shape, oval or flat [20]. **4)** Location of nodules based on lung lobes, central or peripheral in the lung: central location in the lung was defined as the inner one-third of the hilar costal diameter, the outer two-third was considered peripheral. **5)** Morphological features classified based on shape (regular or irregular) and margin (smooth or irregular). Regular shape contained round, oval, triangular or polygonal shape. A polygonal shape was determined in case the entire lesion surface was surrounded by concave margins [21]. An irregular shape was defined as an irregular shape, not belonging to one of the former shape categories [22]. A smooth margin was characterized by an even, gradually curving interface [2]. Irregular margin comprised lobulated and spiculated margin. Lobulated margin was defined as an abrupt bulging of the lesion contour, and spiculated margin was defined as the presence of thicker strands extending from the nodule margin into the lung parenchyma without reaching the pleural surface [23]. **6)** Attached structures: relation of nodule to other structures (vascular-, pleural-, and fissure-attached; or intraparenchymal). Examples of nodule morphological features and adjacent structures can be found in Supplementary Figs. 1 and 2.

For the current analysis, nodules were categorised into three groups based on the mean diameter rounded to nearest mm (<6 mm, 6–8 mm, >8 mm), and into one of three volume categories (<100 mm^3, 100–250 mm^3 and > 250 mm^3), in accordance with the Fleischner society categorization [10]. Next, nodules were classified into 'low' or 'high' risk. Apart from large nodule size (>8 mm), nodules were classified as 'high risk' based on irregular margin (lobulated or spiculated) and/or upper lobe location according to Fleischner criteria. Nodule were classified 'low risk' if none of the factors were present, or if the nodule was classified as (typical) PFN.

3.4. Statistical analysis

Variables were described and stratified by smoking status (never, former and current smokers). Continuous variables were presented as median and interquartile range (IQR) and categorical variables were presented as absolute number with percentages. The Pearson's chi-square test was applied to determine differences in categorical variables among the three smoking status groups. Mann-Whitney *U* test or Kruskal-Wallis H-test was applied for continuous variables. First, a descriptive analysis was performed for nodule CT characteristics on a nodule level.

A participant may have multiple nodules, which can be regarded as a clustered structure: the nodules within a participant may be more alike in CT characteristics than nodules from a random other participant, leading to overestimation of the relationship with smoking status. This was taken into account in the final evaluation of the relation between smoking status and CT nodule characteristics using multi-level analysis. The multi-level analysis was performed using a generalised linear mixed model (binary or multinomial logistic regression) adjusted for the participant's age and sex. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were estimated for all nodule CT characteristics, corrected for the multiple nodules within the same participant. Statistical significance was considered when $p < 0.05$ and all tests were 2-tailed. Statistical analysts (JC, GS) performed analysis with SPSS version 25.

4. Results

4.1. Characteristics of the study population

In total, 1,639 middle-aged participants with at least one solid nodule of $\geq$ 30 mm^3 were included in this study, see Fig. 1 for the flow chart. Median age was 55 years (IQR 50.5–58.5) and 50.5% were men. The population characteristics stratified by smoking status are shown in Table 1. Of the participants with a solid nodule, 42.1% were never smokers, 35.3% former smokers and 22.6% current smokers. The median age of quitting smoking was 23 (16.0–30.6) years for former smokers. The median number of pack-years was 7.6 (3.5–12.5) and 15.9 (8.7–23.0) years for former and current smokers, respectively. A larger proportion of heavy smokers (pack-years $\geq$ 20) was identified in current smokers (34.5%) compared to former smokers (10.6%) ($p < 0.001$).

4.2. Number of nodules per participant

A total of 3,222 solid pulmonary nodules of $\geq$ 30 mm^3 were identified. Of these, 39.9% (1,287/3,222) were detected in never smokers, 34.4% (1,107/3,222) in former smokers, and 25.7% (828/3,222) in current smokers. The distribution of nodule count is shown in Fig. 2. Overall, 988 (60.3%) participants had one nodule, 359 (21.9%) had two nodules, 148 (9.0%) had three nodules, 58 (3.5%) had four nodules, and 86 (5.3%) had five or more nodules. A higher percentage of never smokers had <4 nodules compared to former and current smokers. Current smokers (8.4%) tended to have more often $\geq$5 nodules compared to former (4.2%) and never smokers (4.5%) ($p < 0.05$) (see Fig. 2).

4.3. Nodule CT characteristics on a nodule level

The results of the descriptive analysis of the qualitative and quantitative CT characteristics of the 3,222 solid pulmonary nodules are shown in Table 2 per smoking group. Median nodule diameter was 5.0 mm (IQR, 4.5–5.8 mm), and median volume was 54.0 mm^3 (IQR, 40.0–82.0 mm^3). No differences in nodule location were found between smoking groups (distribution over the lobes and peripheral versus central location). Regularly shaped pulmonary nodules were slightly more frequent in never smokers (93.4%) compared to current smokers (90.2%). The same was observed for pulmonary nodules with smooth margin (never smokers (93.8%) compared to current smokers (90.4%)). The percentage of calcified nodules and PFNs in never smokers was 6.9% and 34.8%, respectively. The largest proportion of all detected nodules were intraparenchymal (42.8%), followed by vascular- (26.7%), fissural- (16.6%) and pleural-attached (13.9%). The percentage of high-risk nodules was similar in never smokers and current smokers (30.4% vs 31.6%).

Table 1
Characteristics for participants in a middle-aged general population with a solid nodule, by smoking status.

	Total (n = 1,639)	Never smoker (n = 690)	Former smoker (n = 578)	Current smoker (n = 371)	p value
Sex, Female, n (%)	812 (49.5)	349 (50.6)	306 (52.9)	214 (42.3)	**0.005** †
Age (yr), median (IQR)	55.0 (50.5–58.5)	53.8 (50.0–57.6)	56.3 (51.9–59.2)	55.1 (50.2–58.2)	**0.000** §
Years since quitting (yr), median (IQR)		NA	22.6 (16.0–30.6)	NA	–
Pack-years, median (IQR) *	9.8 (4.8–17.4)	NA	7.6 (3.5–12.5)	15.9 (8.7–23.0)	**0.000** ‡
Light-medium smoking, n (%)	720 (81.4)	NA	500 (89.4)	220 (65.5)	**0.000** †
Heavy smoking, n (%)	175 (19.6)	NA	59 (10.6)	116 (34.5)	

yr = year; IQR = interquartile range; † Pearson's chi-square test; § Kruskal-Wallis H test; ‡ Mann Whitney-*U* test; *For pack-years 56 cases were missing.

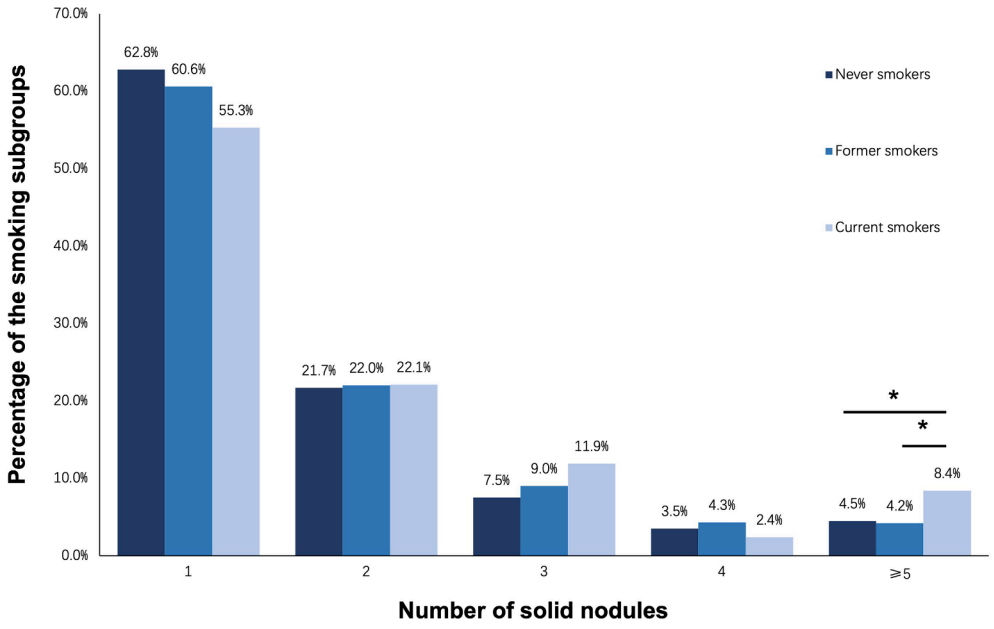

Fig. 2. Distribution of the number of solid pulmonary nodules stratified by smoking status. * P < 0.05 based on Pearson's chi-square test and Bonferroni method.

4.4. Nodule CT characteristics on a participant level

A multi-level analysis was performed to explore the CT characteristics of pulmonary nodules in association with smoking status (Table 3). No differences were found in nodule size and nodule location between never and current smokers (p > 0.328). The odds of a detected solid nodule having an irregular shape (aOR, 0.64; 95 %CI: 0.44–0.93) or irregular margin (aOR, 0.60; 95 %CI: 0.41–0.88) were lower in never smokers compared to smokers. Despite this lower odds for irregular margin (one of the criteria for 'high-risk' nodule) in never smokers, the odds of a detected nodule being high risk was similar for never and current smokers (aOR, 0.90; 95 %CI: 0.73–1.11, p = 0.316). In former smokers, nodules had lower odds to be 'high risk' (aOR, 0.74; 95 %CI: 0.59–0.92) compared to current smokers. Also, in former smokers nodules had lower odds to be intermediate sized (aOR, 0.69; 95% CI: 0.51–0.93), irregular-shaped (aOR, 0.61; 95 %CI: 0.41–0.90) or irregular-margin (aOR, 0.57; 95 %CI: 0.38–0.85) compared to current smokers.

5. Discussion

In one of the first studies focusing on pulmonary nodules in never smokers, we found minor differences in nodule CT characteristics between never and current smokers in a middle-aged general Dutch population. No difference in nodule size and location was found between never and current smokers. High-risk nodules were equally common in never and current smokers, which may impact nodule management.

In the current study, never smokers more often had only a single nodule compared to former and current smokers, whereas current smokers tended to have more often ≥ 5 nodules compared to former and never smokers. This finding may be related to the effect of long-term smoking which induces an inflammatory response in the lung parenchyma leading to infectious changes and/or granuloma formation [24]. In the NELSON study, an increased risk of lung cancer was found in subjects as the total nodule count increased from 1 to 4, while a reduced risk was found in subjects with 5 or more nodules [25]. Remarkably, although per participant never smokers had less nodules, the odds of a high-risk nodule in never smokers with solid lung nodules was similar to current smokers. Nonetheless, the probability of malignancy of a high-risk nodule in never smokers and smokers may differ and could be associated with the total number of nodules in a participant. Furthermore, the features of 'high-risk' nodules overlap with infectious nodules, which may complicate the issue [26]. Based on follow-up data, future research will have to shed more light on the actual risk of lung cancer in so-called high-risk nodules in never smokers.

Considering the increased likelihood of lung cancer in smokers, particularly in case of larger nodules, one might expect to find a higher percentage of small nodules in never smokers and a higher percentage of intermediate and large nodules in former and current smokers. However, in the current study we observed a similar distribution of nodule diameter and volume over the three size categories for never- and current smokers after correction for age and sex. This may be due to the fact

Table 2
CT characteristics of 3,222 solid nodules stratified by smoking status.

	Total (n = 3,222)	Never smokers (n = 1,287)	Former smokers (n = 1,107)	Current smokers (n = 828)
Nodule size				
Diameter (mm), median (IQR)	5.0 (4.5–5.8)	5.0 (4.5–5.9)	5.0 (4.4–5.8)	5.1 (4.5–5.9)
Volume (mm^3), median (IQR)	54.0 (40.0–82.0)	54.0 (39.0–81.0)	54.0 (39.0–81.0)	55.0 (41.0–86.0)
Diameter (mm), n (%)				
<6	2,495 (77.4)	986 (76.6)	873 (78.9)	636 (76.8)
6–8	585 (18.2)	247 (19.2)	187 (16.9)	151 (18.2)
>8	142 (4.4)	54 (4.2)	47 (4.2)	41 (5.0)
Volume (mm^3), n (%)				
<100	2,684 (83.3)	1,059 (82.3)	950 (85.8)	675 (81.5)
100–250	431 (13.4)	186 (14.5)	119 (10.7)	126 (15.2)
>250	107 (3.3)	42 (3.3)	38 (3.4)	18 (3.3)
Location in lung, n (%)				
Central	704 (21.9)	294 (22.9)	236 (21.4)	174 (21.0)
Peripheral	2511 (78.1)	991 (77.1)	867 (78.6)	653 (79.0)
Location-lobe, n (%)				
RUL	678 (21.0)	290 (22.5)	211 (19.1)	177 (21.4)
RML	446 (13.8)	170 (13.2)	160 (14.5)	119 (14.0)
RLL	770 (23.9)	302 (23.5)	277 (25.0)	191 (23.1)
LUL	447 (13.9)	180 (14.0)	144 (13.0)	123 (14.9)
LLL	881 (27.3)	345 (26.8)	315 (28.5)	221 (26.7)
Shape, n (%)				
Regular	2,971 (92.4)	1,199 (93.4)	1,025 (92.9)	747 (90.2)
Irregular	243 (7.6)	85 (6.6)	78 (7.1)	80 (9.7)
Margin, n (%)				
Smooth	2,982 (92.8)	1,205 (93.8)	1,029 (93.5)	748 (90.4)
Irregular	231 (7.2)	80 (6.2)	72 (6.5)	79 (9.6)
Calcified nodule, n (%)				
Yes	181 (5.7)	88 (6.9)	50 (4.6)	43 (5.3)
No	2,991 (94.3)	1181 (93.1)	1,037 (95.4)	773 (94.7)
PFN, n (%)				
Yes	1,148 (36.5)	437 (34.8)	406 (37.4)	305 (37.7)
No	2,001 (63.5)	818 (65.2)	679 (62.6)	504 (62.3)
Attached structures, n (%)				
Intraparenchymal	1,083 (43.3)	427 (42.8)	387 (44.3)	269 (42.6)
Pleural attached	310 (12.4)	139 (13.9)	110 (12.6)	61 (9.7)
Vascular attached	671 (26.8)	266 (26.7)	241 (27.6)	164 (26.0)
Fissural attached	439 (17.5)	166 (16.6)	136 (15.6)	137 (21.7)
Nodule risk, n (%)				
Low risk	2,275 (70.8)	894 (69.6)	815 (74.0)	566 (68.4)
High risk†	938 (29.2)	391 (30.4)	286 (26.0)	261 (31.6)

RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe; PFN: Perifissural nodule; † Large size(>8mm) and/or upper lobe location and/or irregular margin.

Table 3
Association between smoking status and nodule CT characteristics: a multilevel analysis.

	Never smokers compared to current smokers		Former smokers compared to current smokers	
	aOR (95% CI)	P value	aOR (95% CI)	P value
Diameter (mm)				
<6	Ref			
6–8	1.03 [0.80–1.32]	0.839	0.92 [0.71–1.19]	0.513
≥8	0.80 [0.51–1.25]	0.328	0.77 [0.48–1.23]	0.270
Volume (mm^3)				
<100	Ref			
100–250	0.90 [0.68–1.19]	0.458	**0.69 [0.51–0.93]**	**0.015**
≥250	0.87 [0.51–1.48]	0.606	0.83 [0.48–1.43]	0.496
Location in lung				
Central	Ref			
Peripheral	0.90 [0.71–1.16]	0.424	0.92 [0.71–1.19]	0.526
Location-Lobe				
RUL	Ref			
RML	0.91 [0.67–1.24]	0.541	1.14 [0.82–1.57]	0.436
RLL	0.98 [0.75–1.28]	0.867	1.18 [0.88–1.56]	0.267
LUL	0.91 [0.67–1.24]	0.542	0.95 [0.69–1.32]	0.778
LLL	0.95 [0.73–1.24]	0.713	1.16 [0.88–1.53]	0.281
Shape				
Regular	Ref			
Irregular	**0.64 [0.44–0.93]**	**0.019**	**0.61 [0.41–0.90]**	**0.013**
Margin				
Smooth	Ref			
Irregular	**0.60 [0.41–0.88]**	**0.009**	**0.57 [0.38–0.85]**	**0.006**
Calcified nodule				
No	Ref			
Yes	1.26 [0.89–1.79]	0.199	0.92 [0.62–1.35]	0.663
PFN				
No	Ref			
Yes	0.92 [0.74–1.15]	0.473	1.02 [0.81–1.28]	0.858
Attached structures				
Intraparenchymal	Ref			
Pleural based	1.37 [0.95–1.97]	0.093	1.17 [0.80–1.71]	0.414
Vascular attached	0.98 [0.74–1.29]	0.889	1.02 [0.77–1.35]	0.896
Fissural attached	0.75 [0.55–1.03]	0.078	**0.68 [0.49–0.94]**	**0.021**
Nodule risk				
Low risk	Ref			
High risk†	0.90 [0.73–1.11]	0.316	**0.74 [0.59–0.92]**	**0.007**

OR: odds ratio; 95 %C.I.: 95% confidence interval; aOR: odd ratio adjusted by age and sex;
† According to Fleischner 2017: Large size(>8mm) and/or upper lobe location and/or irregular margin.

that the current study included less severe former and current smokers when compared to other screening studies that focus on populations at high risk for lung cancer. The median number of pack-years at baseline round in our study was 7.6 and 15.9 in the former and current smokers respectively, which is remarkably lower than in a lung cancer screening setting such as in the NELSON study (median 38, IQR: 30–50) [8]. At the same time, the former smokers we included had quit smoking for a relatively long time (median 22.6 years), which could have resulted in relatively small impact of smoking in the former smokers. Consequently, any difference in nodule size distribution between smoking groups would have been less profound than expected in the context of lung cancer screening populations. A similar distribution was found in a South Korean study, showing no difference in the distribution of LUNG-RADS categories (version 1.0) and nodule size between never smokers and former smokers [27].

Nodules located in the (right) upper lobe have been identified as an independent risk factor for lung cancer, and were added in the definition of a 'high-risk' nodule in the recent Fleischer guidelines, even in low-risk individuals [10]. Reason for this particular location are that the airflow at the onset of breathing has the greatest effect on the right upper lobe bronchi [28], thus the deposition of particles from tobacco smoke and its carcinogenic effect is greatest at that location [29]. Nonetheless, the current study showed that nodules were equally frequent present at this location for never and current smokers with lung nodules. An explanation for this may be again related to the fact that in this population-based study the pack-years were lower than in the highly selected screening population like the NELSON study. In addition, with the relatively low proportion of current smokers (22.6%) and heavy smokers (10.7%)

included in the current study compared to lung cancer screening studies, the smoke-induced lung response may have been attenuated at the population level, resulting in a less profound relationship between nodule location and smoking status. However, it is important to realize that the Fleischner society guidelines are not aimed at lung cancer screening populations, but rather at incidentally detected lung nodules that can be detected in a broader cohort with indication for chest CT, derived from the general population. Also, Fleischner does not make distinction in management based on smoking pack-years (heavy or not), but merely between smokers and non-smokers.

In a systematic literature review by Wahidi et al., irregular, spiculated, and lobulated margin were found to be predictive of malignancy [30]. Similarly, in the Fleischner criteria an irregular margin is considered as 'suspicious' and therefore this was considered as one of the 'high risk' characteristics in our study. The odds for irregular margin (aOR:0.60) and shape (aOR:0.64) were lower in never smokers than in current smokers, but this did not result in an overall lower odds of high-risk nodules in never smokers. Potentially, margin and shape should be weighted differently in the definition of high-risk nodule when we consider low-risk individuals (e.g. never smokers). For instance, a large but smooth nodule in a never smoker could be regarded as 'intermediate-risk' nodule. However, to draw conclusions on this, longer-term follow-up and outcome results are needed.

6. Limitations

Our study did have some limitations. Firstly, for the current study no follow-up data and lung cancer diagnosis was yet available, but further studies will be conducted regarding outcomes of the 3–4 months follow-up CT scan within ImaLife, and lung cancer outcomes from Lifelines. Secondly, all of the included participants are living in the Northern parts of the Netherlands and are primarily Caucasian, which limits generalizability of our results to other ethnic populations. Thirdly, image annotations were performed in a single-blind manner, i.e. radiologists read scans independently and no consensus read was performed, therefore the intra- and inter-reader variability of nodule morphology evaluation could not be assessed. Nonetheless, in order to minimize variability, trained, experienced radiological readers using a standard evaluation protocol performed all nodule assessments. Fourthly, the ImaLife study was conducted as part of the Lifelines study during the period 2017–2020, while the baseline and second Lifelines round assessments were performed during 2007–2013 and 2014–2017, respectively. The individuals' smoking status may have changed during this period, but we were unable to assess this specific change and its impacts on the results.

6.1. Clinical implications

In this middle-aged general population with nodules, the odds of a 'high-risk' solid nodule were similar in never smokers versus current smokers. Since in the new Fleischner guidelines low-risk individuals with high-risk nodules are also considered for follow-up CT scan or referral, higher follow-up and referral rates may be expected in low-risk subjects under these recent guidelines. This increase of follow-up may be further enhanced with the increasing use of chest CT in clinical practice, and accordingly more and more nodules will be encountered in never smokers. Nonetheless, based on the results presented in the current study, one cannot determine whether a nodule with the same CT features carries an equal 'high risk' in never smokers as it would in current smokers. For instance, in a previous study, the mean size of malignant nodules in non-smokers was significantly smaller than in smokers [14]. Although we did not find any difference in nodule size between smoking groups, possibly different size cut-offs are warranted in low-risk individuals (never smokers) for risk categorization of nodules.

7. Conclusion

In conclusion, minor differences in the distribution of CT characteristics were found in never smokers when compared to smokers in a middle-aged general Dutch population. 'High-risk' nodules detected in never smokers with nodules were equally common when compared to current smokers. Research is needed to determine whether traditional high-risk nodule CT features carry the same risk of lung cancer in never smokers as in current smokers.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2022.110410.

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