[Thoracic Oncology Original Research]

CHEST

The Probability of Lung Cancer in Patients With Incidentally Detected Pulmonary Nodules

Clinical Characteristics and Accuracy of Prediction Models

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BACKGROUND: The frequency of cancer and accuracy of prediction models have not been studied in large, population-based samples of patients with incidental pulmonary nodules measuring > 8 mm in diameter.

RESEARCH QUESTIONS: How does the frequency of cancer vary by size and smoking history among patients with incidental nodules? How accurate are two widely used models for identifying cancer in these patients?

STUDY DESIGN AND METHODS: We assembled a retrospective cohort of individuals with incidental nodules measuring > 8 mm in diameter identified by chest CT imaging between 2006 and 2016. We used a validated natural language processing algorithm to identify nodules and their characteristics by scanning the text of dictated radiology reports. We reported patient and nodule characteristics stratified by the presence or absence of a lung cancer diagnosis within 27 months of nodule identification and estimated the area under the receiver operating characteristic curve (AUC) to compare the accuracy of the Mayo Clinic and Brock models for identifying cancer.

RESULTS: The sample included 23,780 individuals with a nodule measuring > 8 mm, including 2,356 patients (9.9%) with a lung cancer diagnosis within 27 months of nodule identification. Cancer was diagnosed in 5.4% of never smokers, 12.2% of former smokers, and 17.7% of current smokers. Cancer was diagnosed in 5.7% of patients with nodules measuring 9 to 15 mm, 12.1% of patients with nodules > 15 to 20 mm, and 18.4% of patients with nodules > 20 to 30 mm. In the full sample, the Mayo Clinic model (AUC, 0.747; 95% CI, 0.737-0.757) was more accurate than the Brock model (AUC, 0.713; 95% CI, 0.702-0.724; $P <$ .0001). When restricted to ever smokers, the Mayo Clinic model was still more accurate. Both models overestimated the probability of cancer.

INTERPRETATION: Almost 10% of patients with an incidental pulmonary nodule measuring > 8 mm in diameter will receive a lung cancer diagnosis. Existing prediction models have only fair accuracy and overestimate the probability of cancer. CHEST 2021; ■(■):■-■

KEY WORDS: clinical prediction models; lung cancer; non-small cell lung cancer; pulmonary nodule

ABBREVIATIONS: AUC = area under the receiver operating characteristic curve; KPSC = Kaiser Permanente Southern California; NLP = natural language processing

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Take-home Points

Study Questions: How does the frequency of cancer vary by size and smoking history among patients with incidental pulmonary nodules? How accurate are two widely used prediction models for identifying lung cancer in these patients?

Results: In a large, population-based sample of patients with pulmonary nodules measuring > 8 mm in diameter, cancer was diagnosed in 9.9% of patients, including 5.4% of never smokers, 12.2% of former smokers, and 17.7% of current smokers and including 5.7% of patients with nodules measuring 9 to 15 mm, 12.1% of patients with nodules measuring > 15 to 20 mm, and 18.4% of patients with nodules measuring > 20 to 30 mm. Accuracy of two widely used prediction models was only fair, and both models overestimated the probability of cancer. The Mayo Clinic model (area under the receiver operating characteristic curve [AUC], 0.747; 95% CI, 0.737-0.757) was more accurate than the Brock model (AUC, 0.713; 95% CI, 0.702-0.724; $P < .0001$).

Interpretation: Approximately 10% of pulmonary nodules measuring > 8 mm in diameter are lung cancers, with larger size and current smoking status as important predictors of cancer. Existing prediction models have acceptable accuracy, but seem to overestimate the probability of cancer.

Incidental pulmonary nodules are an increasingly common consequence of routine medical care, with an incidence that is much greater than recognized previously. Although nodule identification is increasing over time, the frequency of lung cancer diagnosis after incidental nodule detection is not well defined. A previous population-based study of incidental nodules suggested that substantial yearly increases in chest imaging and nodule detection produced more false-positive results and did not identify additional cases of lung cancer.[1]

Remarkably, large, population-based studies of the characteristics of incidental nodules and the corresponding likelihood of cancer are lacking. In one relatively small study of 300 patients with nodules from the Department of Veterans Affairs, the overall frequency of lung cancer was 9%, with cancer present in 20.2% of patients with nodules of > 8 mm in diameter.[2] It is not clear to what extent the results of studies of patients with screening-detected nodules can be generalized to the incidental nodule population.

According to clinical practice guidelines from *CHEST*,[3] a key step in the management of patients with nodules measuring > 8 mm in diameter is to estimate the probability of cancer, using either clinical intuition or a validated prediction model. Widely used models include the Mayo Clinic model for incidental nodules[4] and the Brock model for nodules detected by screening.[5] Despite being developed more than 20 years ago using data from patients with nodules identified on chest radiographs, the Mayo Clinic model has shown fair to excellent discrimination in diverse clinical settings.[6] The Brock model also has been validated widely, but was developed in a population of current or former smokers with screening-detected nodules, 75% of which were ≤ 5 mm in diameter.

Although one large prior study found that the Mayo and Brock models have similar accuracy for identifying cancer in patients with screening-detected nodules,[7] information on the comparative accuracy of these models in patients with incidental nodules is limited. *CHEST* guidelines do not provide specific recommendations on the choice of model. Guidelines from the British Thoracic Society recommend using the Brock model, although direct evidence of its superiority is lacking.[8] Finally, guidelines from the Fleischner Society provide surveillance recommendations for patients with nodules measuring ≤ 8 mm, but do not provide specific guidance for the management of larger nodules.[9]

To inform decision-making for patients with incidental nodules, it would be helpful to have data from a large, population-based cohort on how the frequency of lung cancer varies by patient and nodule characteristics. Furthermore, a need exists to identify the most accurate models to predict a lung cancer diagnosis. Therefore, we assembled a large population-based sample of patients with incidental pulmonary nodules of > 8 mm in diameter to describe patient and nodule characteristics associated with lung cancer and to compare the accuracy of the Mayo and Brock models for identifying cancer.

Methods

We performed a retrospective, observational study to identify patients with incidentally detected pulmonary nodules measuring > 8 mm in diameter and subsequent lung cancer diagnoses. We used electronic health records from Kaiser Permanente Southern California (KPSC) to identify adults who underwent chest CT imaging between January 1, 2006, and December 31, 2016. Subsequently, we used a natural

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language processing (NLP) algorithm to scan the free text of dictated radiology reports of chest CT scans obtained during this period and to identify reports that noted the presence of one or more pulmonary nodules.[1,10] Additional NLP programs were used to extract information about nodule characteristics, including size, lobe, attenuation, and edge.[11]

We described the frequencies of nodule identification and lung cancer diagnosis within 27 months after nodule detection to allow for standard 2-year follow-up with three additional months for diagnostic evaluation. We evaluated the accuracy and calibration of two existing lung cancer risk prediction models in this population. The institutional review board at KPSC approved the study.

Study Setting

KPSC is a large, integrated health-care system that currently insures and provides care for more than 4.7 million members. The KPSC population is sociodemographically diverse and largely representative of the general population of Southern California.[12] KPSC members receive care from primary care and specialty physicians at 15 hospitals and more than 200 medical offices throughout southern California.

Data Sources

Data were drawn from the KPSC Cancer Registry, the Radiology Information System and Services files, and the Research Data Warehouse, which merges clinical data from electronic health records with membership information and other administrative records. We collected sociodemographic and clinical variables including age, sex, race or ethnicity, geocoded information about education and income, smoking behavior, comorbid conditions, imaging findings, and nodule characteristics.

Study Population

We identified all adults (age ≥ 18 years) who at any time between January 1, 2006, and December 31, 2016, underwent at least one chest CT scan by searching the Radiology Information System and Services files for the following Current Procedural Terminology codes: 71250, 71260, 71270, and 71275. CT scans performed for lung cancer screening (code G0297) or nodule follow-up (code 73680) were not included. To identify chest CT scans in which one or more nodules measuring > 8 mm in diameter were identified, we refined an NLP algorithm that we developed and validated previously.[1,10] The revised NLP algorithm was expert rule-based and developed iteratively by using a combination of key words (eg, nodule, opacity), qualifiers (eg, nodule size), and excluding terms (eg, lymph, hepatic). In the most recent validation, the NLP algorithm showed a sensitivity of 98.6% and a specificity of 100%.[11] For this analysis, a qualifying (positive) result was defined as the recording of one or more nodules, the largest one of which was noted to measure 9 to 30 mm in diameter. The study population then was restricted to those without a prior history of cancer. The final study cohort consisted of the first CT scan per patient.

Clinical Prediction Models

For each patient with an identified nodule, we estimated the probability of cancer using the Mayo Clinic model and the Brock model. The Mayo Clinic model includes three patient characteristics (older age, ever smoking status, and remote [> 5 years] history of extrathoracic cancer) and three nodule characteristics (larger size, upper lobe location, and spiculation). The prevalence of cancer in the development set was 23%. We used the parsimonious version of the Brock model, which includes female sex, a nonlinear term for nodule size, upper lobe location, and spiculation. The prevalence of cancer in the development set was 5.5%.

Outcomes

The study outcome was a lung cancer diagnosis within 27 months of nodule identification, ascertained from either of two sources: (1) a new incident cancer in the KPSC Cancer Registry or (2) the presence of two identical International Classification of Diseases, Ninth or Tenth Revision, diagnosis codes for lung cancer within 60 days. For registry-identified cases, we also collected details of the American Joint Committee on Cancer collaborative stage and tumor histologic findings.

Statistical Analysis

We reported key demographic and nodule characteristics, overall and separately for patients with and without a lung cancer diagnosis within 27 months of initial nodule identification. Counts and percentages were provided when the variables were categorical; means were calculated when the variables were continuous. Nodule characteristics were categorized by size (9-15 mm, > 15-20 mm, and > 20-30 mm), attenuation (solid, part solid, nonsolid, and not specified), and edge (smooth, lobulated, irregular, spiculated, and not specified). We performed χ^2 tests to compare lung cancer prevalence between groups.

We compared the accuracy and discrimination of the Mayo Clinic model and the parsimonious Brock model to identify lung cancer among patients with nodules measuring > 8 mm in diameter. We estimated the probability of cancer by applying the published regression equations to each patient in the sample. To account for differences in patient characteristics, we compared the accuracy and discrimination of the models in the full sample and the subgroup of current and former smokers. To assess model accuracy and discrimination, we calculated the area under the receiver operating characteristic curve (AUC) for each model using SAS version 9.4 software (SAS Institute). Differences in AUCs were compared using the nonparametric approach of DeLong and colleagues.[13] To assess calibration, we plotted the predicted and observed frequencies of cancer by decile of predicted probability. All tests were two-sided with an α level of 0.05.

Results

We assembled a retrospective cohort of 23,789 KPSC members with no prior history of lung cancer or extrathoracic cancer and a nodule measuring ≥ 9 mm in largest diameter (Fig 1). Nodules of this size were identified in approximately 2,000 patients each year, drawn from a population that includes more than 2 million adult members ≥ 18 years of age, suggesting an incidence of approximately 1 per 1,000 adult member-years. The mean ± SD age was 65.0 ± 15.0 years, 53.1% were women, 55.8% were non-Hispanic White people, and 37.1% were never smokers. The mean ± SD Charlson Comorbidity Index was 1.7 ± 1.8, and 9.8% of patients had received diagnoses of COPD. Lung cancer seemed to be more frequent among older patients and those who were current or former smokers (Table 1). The median nodule size was 15.0 mm (interquartile range, 10.5-20.0 mm), with 56.2% measuring 9 to

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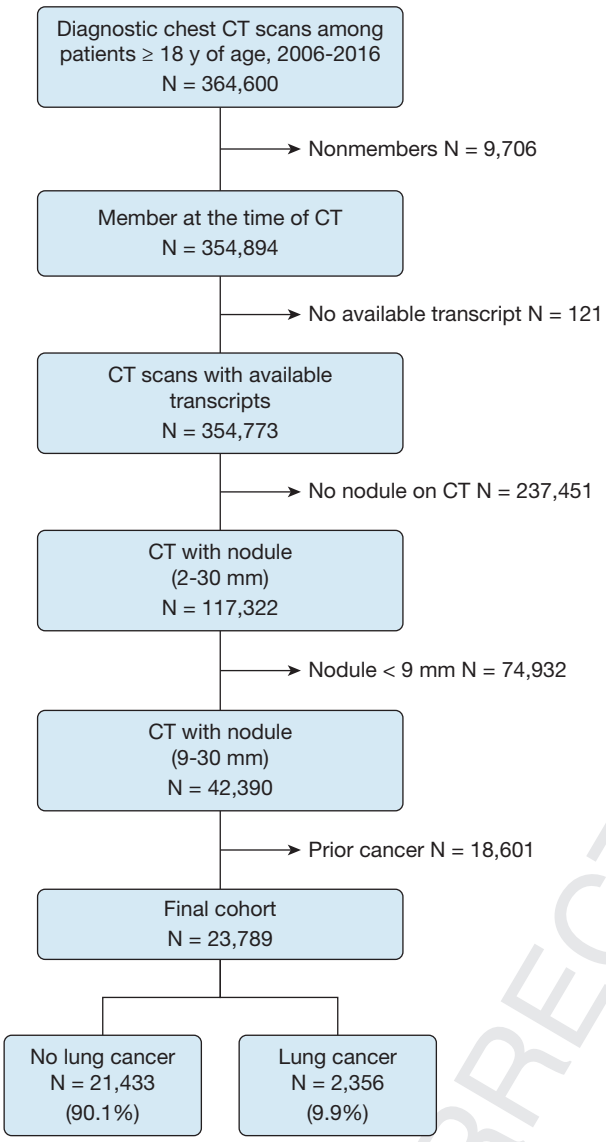

Figure 1 – *Flowchart showing cohort assembly.*

15 mm in diameter (Table 2). Edge characteristics and, especially, attenuation most commonly were not specified. Nodules were distributed roughly evenly between the upper and lower lobes, with a minority located in the middle lobe. Lung cancer seemed to be more common in nodules that were larger, were spiculated, and were located in the upper lobes (Table 2). Patient and nodule characteristics for the subgroup of current and former smokers are shown in e-Tables 1 and 2.

Among 23,789 patients with nodules, 2,356 (9.9%) received a diagnosis of lung cancer within 27 months of nodule identification. The frequency of lung cancer varied, depending on smoking status, nodule size, lobe, and edge characteristics (Table 3, e-Table 3). Lung cancer was diagnosed in 5.4% of never smokers, 12.2% of former smokers, and 17.7% of current smokers ($P < .001$). The relationship between nodule size and lung cancer was nonlinear (e-Fig 1), but the frequency of lung cancer increased monotonically from 5.7% for nodules measuring 9 to 15 mm in diameter, to 12.1% for nodules measuring > 15 to 20 mm in diameter, and to 18.4% for nodules measuring > 20 to 30 mm in size ($P < .0001$). Among never smokers, the frequency of lung cancer increased from 2.8% to 6.2% to 11.2% across the three size categories. Among current smokers, the frequency of lung cancer increased from 10.9% to 20.3% to 30.0% across size categories. Lung cancer was especially frequent among patients with upper lobe (12.8%), lobulated (16.3%), and spiculated (32.8%) nodules. Mean ± SD time to lung cancer diagnosis decreased from 5.8 ± 7.2 months in patients with cancerous nodules measuring 9 to 15 mm, to 3.9 ± 6.1 months in patients with cancers measuring > 15 to 20 mm, to 2.7 ± 4.5 months in patients with cancers measuring > 20 to 30 mm.

We constructed receiver operating characteristic curves (Fig 2) to compare the accuracy and discrimination of the Mayo and parsimonious Brock models for identifying a lung cancer diagnosis. For the full sample of individuals with a nodule of > 8 mm in diameter, the Mayo Clinic model (AUC, 0.747; 95% CI, 0.737-0.757) was more accurate than the parsimonious Brock model (AUC, 0.713; 95% CI, 0.702-0.724; $P < .0001$). When restricted to current or former smokers, the Mayo Clinic model (AUC, 0.728; 95% CI, 0.715-0.742) was still more accurate than the parsimonious Brock model (AUC, 0.716; 95% CI, 0.702-0.730; $P = .0012$), although the difference between the two was smaller.

To examine calibration, we compared expected vs observed frequencies of cancer across deciles of predicted probability (Fig 3). In the full sample, both models overestimated the risk of cancer; however, the excess of predicted cancers was less prominent for the parsimonious Brock model. Both models were calibrated better when applied to the subgroup of current and former smokers, with particularly good agreement between observed and expected lung cancers in the

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TABLE 1] Demographic Characteristics of Study Population

Characteristic	Total (N = 23,789)	No Lung Cancer (n = 21,433)	Lung Cancer (n = 2,356)[a]
Age	65.0 ± 15.0	64.5 ± 15.4	69.8 ± 10.5
Female sex	12,638 (53.1)	11,384 (52.9)	1,290 (54.8)
Race or ethnicity			
Asian/Pacific Islander	2,472 (10.4)	2,219 (10.4)	253 (10.7)
Black	2,616 (11.0)	2,322 (10.8)	294 (12.5)
Hispanic	4,983 (20.9)	4,673 (21.8)	310 (13.2)
White	13,276 (55.8)	11,804 (55.1)	1,472 (62.5)
Other/unknown	442 (1.9)	415 (1.9)	27 (1.1)
Marital status			
Partnered	12,817 (53.9%)	11,484 (53.6%)	1,333 (56.6%)
Nonpartnered	9,848 (41.4%)	8,886 (41.5%)	962 (40.8%)
Other/unknown	1,124 (4.7%)	1,063 (5%)	61 (2.6%)
Education			
College	13,707 (57.6%)	12,300 (57.4%)	1,407 (59.7%)
No college	8,620 (36.2%)	7,765 (36.2%)	855 (36.3%)
Missing	1,462 (6.1%)	1,368 (6.4%)	94 (4%)
Household median income			
No. (%)	22,322 (93.8)	20,061 (93.6)	2,261 (96.0)
Mean ± SD	65,834.7 ± 29,048.9	65,873.6 ± 29,165.5	65,489.3 ± 27,996.8
BMI, kg/m^2			
No. (%)	22,217 (93.4)	20,042 (93.5)	2,175 (92.3)
Mean ± SD	27.5 ± 6.8	27.6 ± 6.8	26.7 ± 6.0
Charlson comorbidity score			
No. (%)	23,722 (99.9)	21,417 (99.9)	2,355 (100.0)
Mean ± SD	1.7 ± 1.8	1.7 ± 1.8	1.7 ± 1.6
COPD	2,339 (9.8)	2,010 (9.4)	329 (14.0)
Smoking status			
Current	2,581 (10.8)	2,124 (9.9)	457 (19.4)
Former	8,376 (35.2)	7,351 (34.3)	1,025 (43.5)
Passive	120 (0.5)	112 (0.5)	8 (0.3)
Never	8,834 (37.1)	8,361 (39.0)	473 (20.1)
Unknown	3,878 (16.3)	3,485 (16.3)	393 (16.7)
Pack-years of smoking (among current or former smokers)			
No. (%)	6,123 (55.9)	5,207 (55.0)	916 (61.8)
Mean ± SD	30.2 ± 28.7	28.5 ± 26.8	39.7 ± 36.1
Quit years of smoking (among former smokers)			
No. (%)	6,883 (82.2)	6,034 (82.1)	849 (82.8)
Mean ± SD	21.3 ± 16.1	21.9 ± 16.3	17.1 ± 14.5

Data are presented as No. (%) or mean ± SD.
[a]Identified by cancer registry (International Classification of Diseases O-3 code C50) or ≥ 2 International Classification of Diseases, Ninth or Tenth Revision, codes for lung cancer within 27 months after the CT imaging.

lower deciles of probability. However, both models overestimated the probability of lung cancer in the higher-probability deciles.

We reparameterized both the Mayo and Brock models to fit the KPSC data using the full sample of ever smokers and never smokers (e-Tables 4 and 5) and

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TABLE 2] Nodule Characteristics on Chest CT Scan

	Total (N = 23,789)[a]	No Lung Cancer (n = 21,433)	Lung Cancer (n = 2,356)[b]
Year of nodule identification			
2006	1,939 (8.2)	1,726 (8.1)	213 (9.0)
2007	1,728 (7.3)	1,544 (7.2)	184 (7.8)
2008	1,901 (8.0)	1,696 (7.9)	205 (8.7)
2009	2,117 (8.9)	1,905 (8.9)	212 (9.0)
2010	2,223 (9.3)	1,999 (9.3)	224 (9.5)
2011	2,241 (9.4)	2,026 (9.5)	215 (9.1)
2012	2,235 (9.4)	2,018 (9.4)	217 (9.2)
2013	2,158 (9.1)	1,918 (8.9)	240 (10.2)
2014	2,151 (9.0)	1,937 (9.0)	214 (9.1)
2015	2,421 (10.2)	2,209 (10.3)	212 (9.0)
2016	2,675 (11.2)	2,455 (11.5)	220 (9.3)
Nodule size, mm	16.1 ± 6.2	15.7 ± 6.1	19.5 ± 6.3
Nodule size group, mm			
9-15	13,359 (56.2)	12,603 (58.8)	756 (32.1)
> 15-20	5,011 (21.1)	4,407 (20.6)	604 (25.6)
> 20-30	5,419 (22.8)	4,423 (20.6)	996 (42.3)
Attenuation			
Solid	351 (1.5)	290 (1.4)	61 (2.6)
Part solid	186 (0.8)	165 (0.8)	21 (0.9)
Nonsolid/pure ground glass	1,602 (6.7)	1,489 (6.9)	113 (4.8)
Not specified	21,650 (91.0)	19,489 (90.9)	2,161 (91.7)
Lobe			
Upper (including lingula)	9,016 (37.9)	7,858 (36.7)	1,158 (49.2)
Middle	2,018 (8.5)	1,832 (8.5)	186 (7.9)
Lower	8,203 (34.5)	7,532 (35.1)	671 (28.5)
More than 1 lobe	1,199 (5.0)	1,085 (5.1)	114 (4.8)
Not specified	3,353 (1.41)	3,126 (14.6)	227 (9.6)
Edge			
Smooth	1,254 (5.3)	1,165 (5.4)	89 (3.8)
Lobulated	724 (3.0)	606 (2.8)	118 (5.0)
Irregular	3,571 (15.0)	3,213 (15.0)	358 (15.2)
Spiculated	1,915 (8.0)	1,287 (6.0)	628 (26.7)
Not specified	16,325 (68.6)	15,162 (70.7)	1,163 (49.4)

Data are presented as No. (%) or mean ± SD.
[a]Data are based on the first scan per patient.
[b]Identified by cancer registry (International Classification of Diseases O-3 code C50) or ≥ 2 International Classification of Diseases, Ninth or Tenth Revision, codes for lung cancer within 27 months after the CT imaging.

found that these models had only slightly better discrimination than the original models, with AUCs of 0.755 (95% CI, 0.744-0.765) for the Mayo Clinic model and 0.725 (95% CI, 0.714-0.736) for the Brock model. However, the refitted models seemed to have much better calibration (e-Fig 2).

Discussion

In this retrospective cohort study, we found that pulmonary nodules measuring > 8 mm were relatively common in a large population-based sample from an integrated health-care system in Southern California, with an incidence of approximately 1 per 1,000 adult

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TABLE 3] Frequency of Lung Cancer Within Subgroups Defined by Smoking Status and Nodule Size

Subgroup			Lung Cancer	
Smoking Status	Nodule Size, mm	Total No.	No. (%)[a]	95% CI
Any	Any	23,789	2356 (9.9)	9.5-10.3
Never/passive	Any	8,954	481 (5.4)	4.9-5.9
Former	Any	8,376	1025 (12.2)	11.5-13.0
Current	Any	2,581	457 (17.7)	16.3-19.2
Unknown	Any	3,878	393 (10.1)	9.2-11.1
Any	9-15	13,359	756 (5.7)	5.3-6.1
Any	> 15-20	5,011	604 (12.1)	11.2-13.0
Any	> 20-30	5,419	996 (18.4)	17.4-19.4
Never/passive	9-15	5,127	144 (2.8)	2.4-3.3
	> 15-20	1,824	113 (6.2)	5.1-7.4
	> 20-30	2,003	224 (11.2)	9.8-12.7
Former	9-15	4,616	321 (7.0)	6.2-7.7
	> 15-20	1,795	271 (15.1)	13.5-16.8
	> 20-30	1,965	433 (22.0)	20.2-23.9
Current	9-15	1,381	151 (10.9)	9.3-12.7
	> 15-20	557	113 (20.3)	17.0-23.9
	> 20-30	643	193 (30.0)	26.5-33.7
Unknown	9-15	2,235	140 (6.3)	5.3-7.4
	> 15-20	835	107 (12.8)	10.6-15.3
	> 20-30	808	146 (18.1)	15.5-20.9

[a]Row percentages.

member-years. Lung cancer was diagnosed within 27 months in almost 10% of these individuals. More than one-third of the nodules were detected in never smokers. Of concern, the frequency of cancer was nontrivial in never smokers with a nodule of this size (5.4%), although cancer was much more common

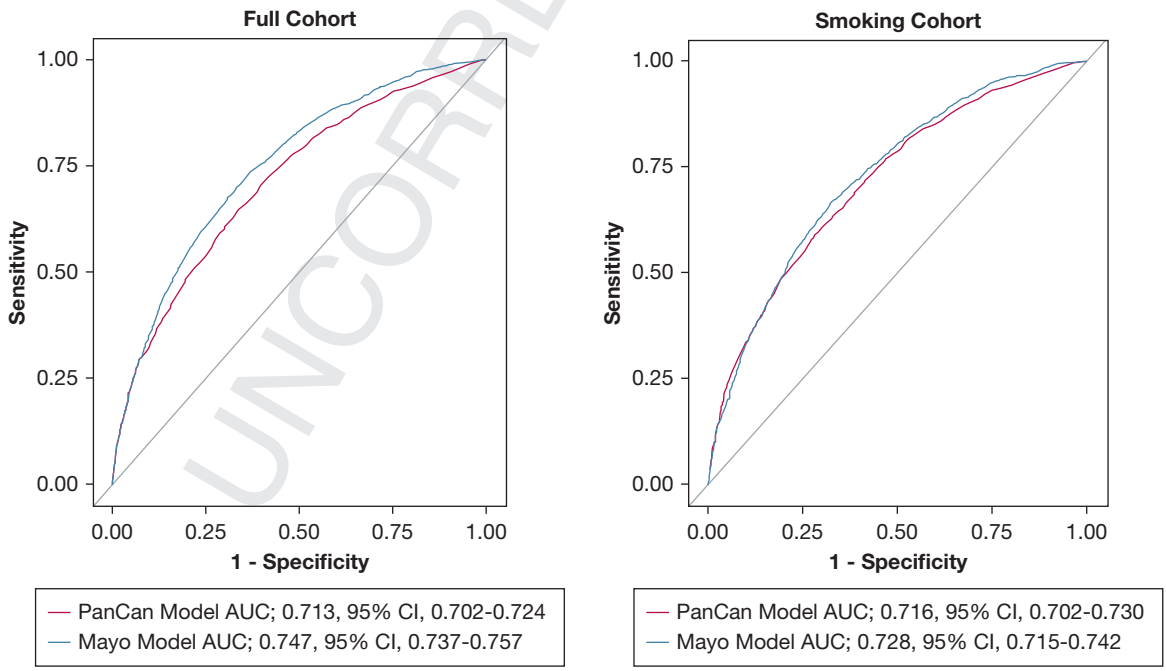

Figure 2 – *A, B, Accuracy and discrimination of models for identifying lung cancer in the full sample (A) and in the subgroup of current and former smokers (B). AUC = area under the receiver operating characteristic curve.*

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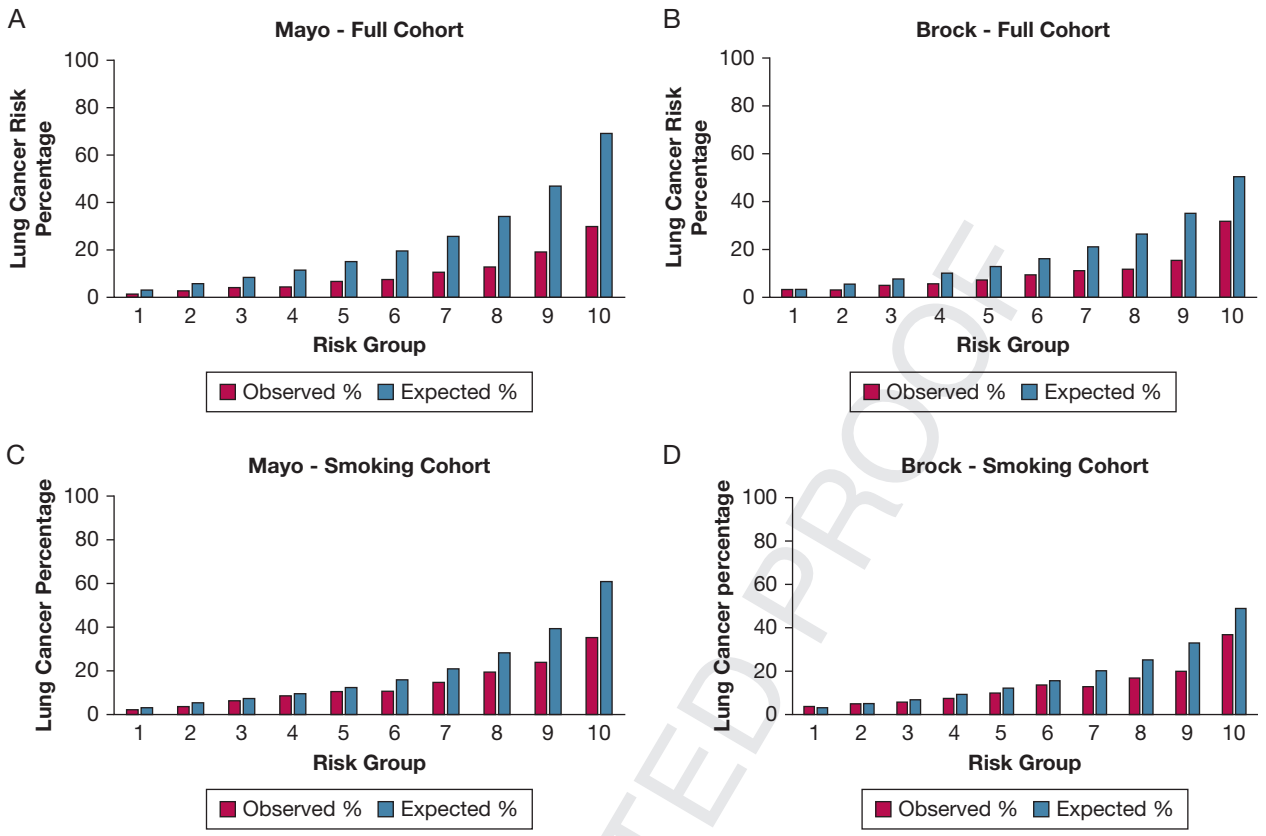

Figure 3 – *A-D, Bar graphs showing observed and expected frequencies of lung cancer for the Mayo Clinic model in the full sample (A) and in the subgroup of current and former smokers (B) and for the Brock model in the full sample (C) and in the subgroup of current and former smokers (D).*

among former (12.2%) and current (17.7%) smokers. The probability of cancer also increased with nodule size, ranging from 5.7% in nodules measuring 9 to 15 mm in diameter to 18.4% in nodules measuring > 20 to 30 mm.

We also found that two commonly used models to estimate the probability of cancer showed acceptable, although far from perfect, discrimination in both the full sample of patients with a large nodule and the subgroup of ever smokers. The Mayo Clinic model showed somewhat better discrimination than the Brock model. Perhaps this is not surprising because the Mayo Clinic model was developed in a sample of ever and never smokers with nodules detected incidentally on chest radiography, whereas the Brock model was developed in a population of current and former smokers with nodules identified on a screening low-dose CT scan. Importantly, both models overestimated the probability of lung cancer. In the case of the Mayo Clinic model, this can be explained easily by the higher prevalence of cancer in the development set. In the case of the Brock model, although the overall prevalence of cancer was only 5.5%, the prevalence of cancer in the subgroup of patients with larger nodules measuring > 8 mm in diameter was probably much higher, perhaps explaining the poor calibration in the sample. Overestimation of the probability of cancer has profound implications for clinical practice and suggests that clinicians may need to apply an intuitive so-called correction factor when making this determination, especially in never smokers and at the higher end of predicted probability among ever smokers. Prior research findings suggest that clinicians may apply such a correction factor to improve prediction when they use intuition to estimate the probability of cancer.[14]

Although the Fleischner Society recommendations for the evaluation of patients with incidental nodules do not specify an estimate for the probability of cancer for nodules measuring > 8 mm in diameter, the observed size-specific values for the prevalence of cancer in the current sample correspond roughly to the lower limits of cancer prevalence ranges cited by the Lung Imaging Reporting and Data System for nodules detected by screening, including estimates of 5% to 15% for solid

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nodules measuring ≥ 8 to < 15 mm (compared with 7.0%-10.9% in the current subgroups of former and current smokers) and > 15% for solid nodules measuring ≥ 15 mm in diameter (compared with 15.1%-30.0% in the current subgroup of current and former smokers). Thus, our findings provide additional support for the Lung Imaging Reporting and Data System classification scheme and its potential applicability to nodules detected incidentally.

To guide clinical practice, we propose a so-called rule of 10s for current smokers as a reminder that the expected frequency of cancer is approximately 10%, 20%, and 30% for smokers with nodules measuring > 8 to 15 mm, > 15 to 20 mm, and > 20 to 30 mm, respectively. A corresponding rule of 3s can be used to remember the estimated frequency of lung cancer in never smokers with nodules measuring > 8 to 15 mm (3%), > 15 to 20 mm (6%), and > 20 to 30 mm (12%).

The prevalence of cancer in our sample was lower than that reported in two smaller prior studies, in which the prevalence of cancer among those with nodules measuring > 8 mm in diameter was much higher (20%-25%), possibly related to a higher prevalence of smoking in one case[2] and to referral bias in the other.[15] Our results may be more consistent with those from a more recent and larger study of 5,057 unselected patients with incidental nodules from two health-care systems in which the overall prevalence of cancer was much lower (3.8%).[16] This study did not report the frequency of cancer as a function of nodule size.

Prior studies have validated the Mayo Clinic, Brock, and other models to estimate the probability of cancer among patients with both incidental and screening-detected nodules. In eight previous studies of patients with incidental nodules summarized by Choi and colleagues,[6] the median AUC of the Mayo Clinic model was 0.79 (range, 0.6-0.89).[17-24] In these studies, the prevalence of cancer was much higher (range, 40.6%-93%) than it was in our study, in large part because of the selective inclusion of patients who were referred for surgery or PET imaging. In contrast, we included unselected patients from a population-based sample, which explains the lower prevalence of cancer, but not necessarily the somewhat lower accuracy of the Mayo Clinic model in our population. However, the inclusion of patients with nodules measuring ≤ 8 mm in some of the prior studies may have resulted in easier predictions and better accuracy.

Several studies have validated the Brock model in patients with screening-detected nodules.[7,25-27] In these studies, the prevalence of cancer in screening-detected nodules was similar to that in our sample of incidental nodules, but the Brock model was substantially more accurate than what we observed, with AUCs ranging from 0.83 to 0.96. One of these studies examined the accuracy of the Mayo Clinic model in patients with nodules measuring > 8 mm in diameter and reported an AUC of 0.82 in this subgroup, higher than the AUC of 0.74 in our study. Thus, the lower AUC in our study does not seem to be related to disease prevalence, and subsequent studies should attempt to unravel sources of heterogeneity in model accuracy. By fitting the models to the KPSC data, we found that although calibration seemed to be better, discrimination improved only marginally, suggesting that the variables used for prediction have limited discrimination in this population.

This study has limitations. Our results should not necessarily be extended to patients with incidental nodules measuring ≤ 8 mm in diameter, because these patients were not included in the sample. We limited inclusion to patients with nodules measuring > 8 mm because one of the first steps in managing these patients is to estimate the probability of cancer to guide subsequent decisions about the use of particular diagnostic tests. Smaller nodules are almost always managed by surveillance imaging and do not necessarily require an estimation of cancer probability.

Another limitation of our study is the large number of cases in which the radiologist did not specify the attenuation or edge characteristics of the nodule. We assumed that spiculation was not present when edge characteristics were not mentioned, an assumption that we validated in a separate report.[12] Future studies of the prevalence of cancer in incidental nodules according to edge and attenuation would be welcome. Strengths of our study include the large population-based sample, the inclusion of large numbers of both never smokers and ever smokers with incidental pulmonary nodules, and the use of a highly accurate NLP algorithm to identify nodules and their characteristics from the free text of dictated radiology reports.

Interpretation

We found that pulmonary nodules measuring > 8 mm in diameter are relatively common in clinical practice and that approximately 10% of these nodules are lung

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cancers, with larger size and current smoking as important predictors of cancer. Existing prediction models have acceptable accuracy, but seem to overestimate the probability of cancer, especially in never smokers and in the higher deciles of predicted probability.

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Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

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