5-year overall survival in patients with lung cancer eligible or ineligible for screening according to US Preventive Services Task Force criteria: a prospective, observational cohort study

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Summary

Background The US Preventive Services Task Force (USPSTF) recommends lung cancer screening among individuals aged 55–80 years with a 30 pack-year cigarette smoking history and, if they are former smokers, those who quit within the past 15 years. Our previous report found that two-thirds of newly diagnosed patients with lung cancer do not meet these criteria; they are reported to be either long-term quitters (≥15 years since quitting) or from a younger age group (age 50–54 years). We aimed to assess survival outcomes in these two subgroups.

Methods For this prospective, observational cohort study we identified and followed up patients aged 50–80 years with lung cancer, with a smoking history of 30 pack-years or more, and included both current smokers and former smokers who quit within the past 30 years. We identified patients from two cohorts in the USA: a hospital cohort (Mayo Clinic, Rochester, MN) and a community cohort (Olmsted County, MN). Patients were divided into those meeting USPSTF criteria (USPSTF group) versus those not meeting USPSTF criteria (long-term quitters or the younger age group). The main outcome was overall survival at 5 years after diagnosis. 5-year overall survival was analysed with and without matching age and pack-years smoked for long-term quitters. The USPSTF group was subdivided into two age subgroups (55–69 years and 70–80 years) for multivariable regression analysis.

Findings Between Jan 1, 1997, and Dec 31, 2017, 8739 patients with lung cancer were identified and followed up. Median follow-up was 6·5 (IQR 3·8–10·0) years, and median overall survival was 16·9 months (95% CI 16·2–17·5). 5-year overall survival was 27% (95% CI 25–30) in long-term quitters, 22% (19–25) in the younger age group, and 23% (22–24) in the USPSTF group. In both cohorts, 5-year overall survival did not differ significantly between long-term quitters and the USPSTF group (hospital cohort: hazard ratio [HR] 1·02 [95% CI 0·94–1·10]; p=0·72; community cohort: 0·97 [0·75–1·26]; p=0·82); matched analysis showed similar results in both cohorts. 5-year overall survival also did not differ significantly between the younger age group and the USPSTF group in both cohorts (hospital cohort: HR 1·16 [95% CI 0·98–1·38], p=0·08; community cohort: 1·16 [0·74–1·82]; p=0·52); multivariable regression analyses stratified by age group yielded similar findings.

Interpretation Patients with lung cancer who quit 15 or more years before diagnosis and those who are up to 5 years younger than the age cutoff recommended for screening, but otherwise meet USPSTF criteria, have a similar risk of death to those individuals who meet all USPSTF criteria. Individuals in both subgroups could benefit from screening, as expansion of USPSTF screening criteria to include these subgroups could enable earlier detection of lung cancer and improved survival outcomes.

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Introduction

Lung cancer continues to be the leading cause of deaths from malignancy worldwide.[1,2] Survival remains poor because most patients are diagnosed at an advanced stage.[3] Therefore, there have been widespread efforts to develop safe and effective screening methods to detect lung cancer at an earlier stage. Based on the results of the National Lung Screening Trial (NLST), which showed a 20% reduction in lung cancer mortality from screening of high-risk individuals by use of low-dose CT,[4] the US Preventive Services Task Force (USPSTF) recommends screening for lung cancer in individuals aged 55–80 years, who have a smoking history of 30 pack-years or more, and who either currently smoke or quit within the past 15 years.[5] A comparative modelling study based on the USPSTF criteria predicted that an estimated 18 000 lives per year could be saved in the USA if low-dose CT is widely used in the eligible population.[6] However, the Surveillance Epidemiology and End Results Program (SEER) database as well as data from two other independent cohorts have shown that only a third of patients diagnosed with lung cancer in the USA meet the USPSTF screening criteria,[7–9] suggesting that many potentially high-risk individuals are not eligible for low-dose CT screening. Among patients outside of the

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Research in context

Evidence before this study

We searched PubMed for articles published up to Oct 31, 2018, using the terms "lung cancer", "screening", "low-dose CT", "smoking cessation", "former smoker", and "younger age", without any language restrictions. This search showed that screening of high-risk individuals by use of low-dose CT in the National Lung Screening Trial was associated with a 20% reduction in lung cancer mortality. The US Preventive Services Task Force (USPSTF) recommends screening for lung cancer in individuals aged 55–80 years, who have a smoking history of 30 or more pack-years, and who currently smoke or quit within the past 15 years. The results of the NELSON randomised controlled screening trial have shown a 26% reduction in the risk of death from lung cancer with low-dose CT screening of individuals aged 50–74 years, who have a history of smoking more than ten cigarettes daily for more than 30 years or more than 15 cigarettes daily for more than 25 years, and who currently smoke or quit within the past 10 years. However, the Surveillance Epidemiology and End Results Program database as well as data from two other independent cohorts have shown that only a third of patients with lung cancer would have met the USPSTF screening criteria, suggesting that many potentially high-risk individuals are not eligible for low-dose CT screening. Among patients outside of the high-risk population defined by the USPSTF, the three largest subgroups at potentially high risk for developing lung cancer are patients who quit smoking 15–30 years before diagnosis (termed long-term quitters), those aged 50–54 years at the time of lung cancer diagnosis (termed the younger age group), and those with a smoking history of around 20–30 pack-years.

Added value of this study

To the best of our knowledge, no previous study has directly compared overall survival between patients with lung cancer who meet USPSTF screening criteria and those who are ineligible because they are long-term quitters (those who quit smoking ≥15 years before diagnosis) or aged 50–54 years at the time of lung cancer diagnosis. We estimated overall survival at 5 years after diagnosis in two cohorts (a hospital cohort and a community cohort) and stratified our analysis by age group. In both cohorts, long-term quitters had the same risk of death at 5 years as the USPSTF group; matched analysis showed similar results. The younger age group also had similar 5-year overall survival to the USPSTF group; age-group stratified analysis yielded similar findings.

Implications of all the available evidence

Our findings suggest that patients with lung cancer who quit smoking more than 15 years before diagnosis or those who are 5 years younger than those who are eligible for screening but otherwise meet the USPSTF screening criteria have similar lung cancer survival to those who meet all the USPSTF screening criteria. Careful consideration of the optimal screening criteria is needed to guide the decision to screen individuals at high risk of developing lung cancer. Our findings highlight the need to update the USPSTF screening criteria and the conventional risk assessment model based on smoking history. In future, more sophisticated screening programmes combining low-dose CT and biomarkers could be developed to identify high-risk individuals who would benefit most from screening.

high-risk population defined by the USPSTF, the three largest subgroups at potentially high risk for developing lung cancer are patients who quit smoking 15–30 years before lung cancer diagnosis (termed long-term quitters), those aged 50–54 years at the time of lung cancer diagnosis (termed the younger age group), and those with a smoking history of around 20–30 pack-years.[8,9] The risk of developing lung cancer in individuals in these groups remains high.[10,11] Our previous reports revealed that nearly two-thirds of patients (4162 [61%] of 6838) with newly diagnosed lung cancer did not meet the USPSTF criteria and that almost a fifth (1285 [19%] of 6838) were either long-term quitters or in the younger age group.[8,9] By contrast with the high-risk population defined by the USPSTF, multiple organisations including the International Association for the Study of Lung Cancer, the American Association of Thoracic Surgery, the American College of Chest Physicians, and the National Comprehensive Cancer Network have recommended low-dose CT screening of patients according to NLST smoking history criteria or of patients aged 50–54 years, along with one additional lung cancer risk factor, which could include occupational exposure or a history of pulmonary disease.[12–14] The results of the NELSON randomised controlled screening trial showed a 26% reduction in the risk of death from lung cancer in individuals aged 50–74 years, who have a history of smoking more than ten cigarettes daily for more than 30 years or more than 15 cigarettes daily for more than 25 years, and who either currently smoke or quit within the past 10 years. The NELSON trial thus included individuals younger than 55 years and those with a shorter smoking history than the patients enrolled in the NLST.[15]

Screening has been an essential component of efforts to decrease the burden from lung cancer in high-risk populations.[16] The ultimate measure of an effective screening tool is mortality reduction, and it remains unclear whether any additional randomised trials have been planned to investigate and justify any adjustments to current criteria. We explored whether the potentially high-risk subgroups that are not eligible for USPSTF screening have similar overall survival to those who are eligible. To our knowledge, no study has directly compared overall survival between patients with lung cancer meeting USPSTF screening criteria and those who are ineligible

	Hospital cohort (n=7168)		p value	Community cohort (n=863)		p value
	Long-term quitters* (n=1299)	USPSTF criteria† (n=5869)		Long-term quitters* (n=105)	USPSTF criteria† (n=758)	
Age at diagnosis, years	71·7 (5·7)	66·7 (6·5)	<0·0001	72·7 (5·6)	67·8 (6·7)	<0·0001
Sex						
Female	394 (30%)	2477 (42%)	<0·0001	27 (26%)	317 (42%)	0·002
Male	905 (70%)	3392 (58%)	..	78 (74%)	441 (58%)	..
Race or ethnicity						
White	1192 (92%)	5210 (89%)	0·002	103 (98%)	731 (96%)	0·38
Other	107 (8%)	659 (11%)	..	2 (2%)	27 (4%)	..
Cigarette smoking status at diagnosis						
Former	1299 (100%)	2262 (39%)	NA	105 (100%)	296 (39%)	NA
Current	NA	3607 (61%)	..	NA	462 (61%)	..
Pack-years‡	47 (36·0–65·0)	56 (44·0–80·0)	<0·0001	52 (40·0–75·0)	60 (46·0–80·0)	0·004
Tumour stage§						
Non-small-cell lung cancer	1143 (88%)	4864 (83%)	..	95 (91%)	625 (83%)	..
I	357 (31%)	1300 (27%)	0·001	32 (34%)	199 (32%)	0·89
II	139 (12%)	538 (11%)	..	9 (10%)	48 (8%)	..
III	271 (24%)	1388 (29%)	..	25 (26%)	170 (27%)	..
IV	376 (33%)	1638 (34%)	..	29 (31%)	208 (33%)	..
Small-cell lung cancer	126 (10%)	901 (15%)	..	10 (10%)	133 (18%)	..
Limited	53 (42%)	399 (44%)	0·64	3 (30%)	51 (38%)	0·60
Extensive	73 (58%)	502 (56%)	..	7 (70%)	82 (62%)	..
Histology						
Adenocarcinoma	647 (50%)	2367 (40%)	<0·0001	57 (54%)	266 (35%)	0·003
Squamous-cell carcinoma	341 (26%)	1612 (28%)	..	27 (26%)	239 (32%)	..
Small-cell carcinoma	128 (10%)	915 (16%)	..	10 (10%)	135 (18%)	..
Other non-small-cell lung cancer¶	34 (3%)	178 (3%)	..	3 (3%)	48 (6%)	..
Unspecified non-small-cell lung cancer	149 (12%)	797 (14%)	..	8 (8%)	70 (9%)	..
Treatment‖						
Surgery only	389 (30%)	1359 (23%)	<0·0001	34 (32%)	193 (26%)	0·60
Chemotherapy only	216 (17%)	975 (17%)	..	18 (17%)	116 (15%)	..
Chemotherapy and radiation	189 (15%)	1150 (20%)	..	17 (16%)	170 (22%)	..
Radiation only	94 (7%)	385 (7%)	..	13 (12%)	80 (11%)	..
Surgery and chemotherapy	83 (6%)	300 (5%)	..	2 (2%)	28 (4%)	..
Surgery and radiation	28 (2%)	128 (2%)	..	4 (4%)	21 (3%)	..
Surgery, chemotherapy, and radiation	59 (5%)	355 (6%)	..	3 (3%)	31 (4%)	..
Other treatment	39 (3%)	230 (4%)	..	4 (4%)	22 (3%)	..
No treatment	145 (11%)	741 (13%)	..	10 (10%)	97 (13%)	..

Data are n (%), mean (SD), or median (IQR). USPSTF=US Preventive Services Task Force. NA=not applicable. *Long-term quitters: individuals aged 55–80 years, who have a smoking history of 30 or more pack-years and quit smoking within the past 15–30 years. †USPSTF criteria: individuals aged 55–80 years, who have a current or past smoking history of 30 or more pack-years; if former smokers, those who had quit within the past 15 years. ‡Pack-years: packs smoked daily multiplied by years. §Unknown stage: 30 (2%) of the 1299 long-term quitters and 104 (2%) of 5869 patients among the USPSTF group in the hospital cohort. ¶Large-cell neuroendocrine and adenosquamous carcinoma. ‖Unknown treatment: 57 (4%) of 1299 long-term quitters and 246 (4%) of 5869 patients among the USPSTF group in the hospital cohort.

Table 1: **Characteristics of 8031 patients aged 55–80 years in the hospital cohort and community cohort, including long-term quitters, diagnosed 1997–2015**

because they are classified as long-term quitters or in a younger age group at the time of lung cancer diagnosis. We estimated 5-year overall survival after diagnosis in both of these subgroups, assessed 5-year overall survival after matching age and pack-years smoked for long-term quitters, and did a regression analysis stratified by age group for the younger age group.

Methods

Study population

For this prospective, observational cohort study, patients with pathologically diagnosed primary lung cancer, aged 50–80 years, with 30 or more pack-years of smoking history, who were either current smokers or former smokers who quit within the past 30 years, were identified

and enrolled from a hospital cohort (Mayo Clinic, Rochester, MN, USA) and a community cohort (Olmsted County, MN, USA). All patients aged 55–80 years were divided into those meeting USPSTF screening criteria (USPSTF group) and long-term quitters in both cohorts. Based on age at the time of lung cancer diagnosis, all enrolled patients who quit smoking within the past 15 years were divided into the USPSTF group (age 55–80 years) and the younger age group (age 50–54 years) in both cohorts. The long-term quitters and the younger age group were selected on the basis of our previous studies,[8,9] where we evaluated the top seven potential high-risk subgroups by frequency that missed USPSTF criteria for low-dose CT screening; long-term quitters and younger age group were ranked the highest. The community cohort comprised patients in the Rochester Epidemiology Project database with medical records of all people residing in Olmsted County, and the hospital cohort comprised patients diagnosed at the Mayo Clinic in Minnesota between Jan 1, 1997, and Dec 31, 2015 (excluding Olmsted County residents). Both cohorts were followed up through Dec 31, 2017. The community cohort was matched to the same 19 years of diagnosis as the hospital cohort.[9] The community cohort consisted of approximately 140 000 people, 83% of whom are non-Hispanic white; the population is socioeconomically similar to the white population of the USA and is representative of the population of the midwestern USA.[8,9,17] The Institutional Review Boards of Mayo Foundation and Olmsted County Medical Center approved this study. No written consent from patients was needed for this study.

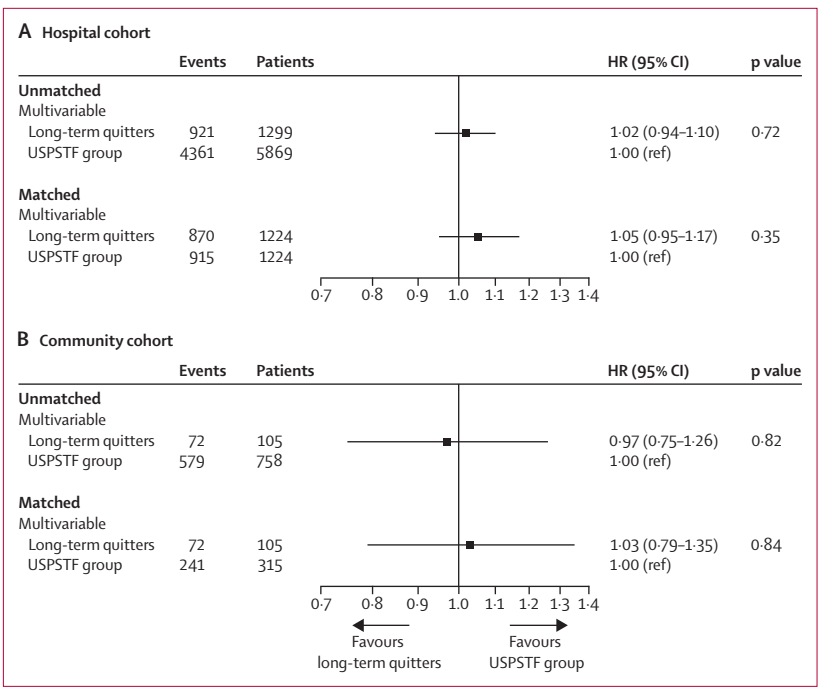

Figure 1: **Multivariable Cox proportional hazard models of overall survival in patients meeting USPSTF screening criteria versus long-term quitters**
(A) Hospital cohort. (B) Community cohort. Results are presented for unmatched and matched analyses for age at diagnosis and pack-years. Multivariable Cox proportional hazards models were used to adjust for age, sex, race, smoking status, pack-years smoked, tumour histology and stage, and treatment modalities. USPSTF=US Preventive Services Task Force.

Data collection

Detailed procedures of patient enrolment, data collection, and routine follow-up have been reported in previous studies[8,9,17] and in the appendix (p 2), including the definition of pack-years and years since quitting.[8,9,18] A never-smoker was defined as an individual who had smoked fewer than 100 cigarettes during their lifetime. A former smoker was defined as an individual who quit at least 1 year before lung cancer diagnosis. Current smokers were defined as individuals who were actively smoking, and who had stopped smoking within 1 year before lung cancer diagnosis.

Outcomes

The main outcome was overall survival, defined as the time from the date of diagnosis to death from any cause in the hospital and community cohorts; patients who were alive or lost to follow-up were censored. 5-year overall survival after diagnosis was also analysed for long-term quitters, the younger age group, and the USPSTF group.

Statistical analysis

Patient characteristics are presented as means (SD) and medians (IQR) for continuous variables and as frequency (%) for categorical variables. Demographic and clinical characteristics were assessed with the Wilcoxon rank-sum test for continuous variables and with the χ^2 test for categorical variables. Overall survival was evaluated with the Kaplan-Meier method and log-rank test. Models were developed from the hospital cohort and validated in the community cohort. Univariable Cox proportional hazards models were used to assess the association of known prognostic factors (ie, age at diagnosis, sex, cigarette smoking history, tumour histology, stage, and treatment modalities) with estimated 5-year survival. Multivariable Cox models were developed with significant variables (defined as $p<0\cdot10$) in the univariable analysis, and hazard ratios (HR) with 95% CI were calculated. Cox model assumption was verified by rejecting non-proportional hazards with Kaplan-Meier curves on key variables that show neither crossing nor levelling off or sharply dropping to zero and rejecting collinearity or absence of independence after checking pairwise correlations among key covariates.

See Online for appendix

A matching study was used to balance the distributions of age at diagnosis and pack-years smoked for long-term quitters and those meeting USPSTF screening criteria, by use of pair matching without replacement.[19] The maximum allowable difference of 3 years in age and 10 pack-years smoked was calculated to produce well-balanced matched groups on baseline characteristics

	Hospital cohort (n=2448)		p value	Community cohort (n=420)		p value
	Long-term quitters* (n=1224)	USPSTF criteria† (n=1224)		Long-term quitters* (n=105)	USPSTF criteria† (n=315)	
Age at diagnosis, years	71·6 (5·7)	71·4 (5·6)	0·35	72·7 (5·6)	72·0 (5·4)	0·17
Mean pack-years‡	54·1 (23·5)	54·8 (23·0)	0·17	59·9 (25·8)	60·8 (24·8)	0·55
Median pack-years	47 (36·0–65·0)	50 (38·0–65·0)	0·17	52 (40·0–75·0)	53 (40·0–75·0)	0·55
Sex						
Female	372 (30%)	476 (39%)	<0·0001	27 (26%)	151 (48%)	<0·0001
Male	852 (70%)	748 (61%)	..	78 (74%)	164 (52%)	..
Race or ethnicity						
White	1133 (93%)	1116 (91%)	0·21	103 (98%)	308 (98%)	0·85
Other	91 (7%)	108 (9%)	..	2 (2%)	7 (2%)	..
Cigarette smoking status at diagnosis						
Former	1224 (100%)	640 (52%)	NA	105 (100%)	159 (50%)	NA
Current	NA	584 (48%)	..	NA	156 (50%)	..
Tumour stage						
Non-small-cell lung cancer	1100 (90%)	1102 (90%)	..	96 (91%)	270 (86%)	..
I	354 (32%)	351 (32%)	0·20	32 (33%)	90 (33%)	0·94
II	136 (12%)	135 (12%)	..	9 (9%)	20 (7%)	..
III	258 (24%)	298 (27%)	..	25 (26%)	74 (27%)	..
IV	352 (32%)	318 (29%)	..	30 (31%)	86 (32%)	..
Small-cell lung cancer	124 (10%)	122 (10%)	..	9 (9%)	45 (14%)	..
Limited	51 (41%)	48 (39%)	0·78	3 (33%)	21 (47%)	0·46
Extensive	73 (59%)	74 (61%)	..	6 (67%)	24 (53%)	..
Histology						
Adenocarcinoma	613 (50%)	548 (45%)	0·03	57 (54%)	118 (38%)	0·04
Squamous cell carcinoma	321 (26%)	389 (32%)	..	27 (26%)	100 (32%)	..
Small cell carcinoma	125 (10%)	125 (10%)	..	10 (10%)	45 (14%)	..
Other non-small-cell lung cancer§	33 (3%)	28 (2%)	..	3 (3%)	19 (6%)	..
Unspecified non-small-cell lung cancer	132 (11%)	134 (11%)	..	8 (8%)	33 (11%)	..
Treatment						
Surgery only	388 (32%)	370 (30%)	0·39	34 (32%)	87 (28%)	0·76
Chemotherapy only	213 (17%)	204 (17%)	..	18 (17%)	40 (13%)	..
Chemotherapy and radiation	184 (15%)	203 (17%)	..	17 (16%)	67 (21%)	..
Radiation only	91 (7%)	100 (8%)	..	13 (12%)	39 (12%)	..
Surgery and chemotherapy	82 (7%)	58 (5%)	..	2 (2%)	11 (4%)	..
Surgery and radiation	26 (2%)	37 (3%)	..	4 (4%)	10 (3%)	..
Surgery, chemotherapy, and radiation	61 (5%)	60 (5%)	..	3 (3%)	7 (2%)	..
Other treatment	39 (3%)	43 (4%)	..	4 (4%)	10 (3%)	..
No treatment	140 (11%)	149 (12%)	..	10 (10%)	44 (14%)	..

Data are n (%), mean (SD), or median (IQR). USPSTF=US Preventive Services Task Force. NA=not applicable. *Long-term quitters: individuals aged 55–80 years, who have a smoking history of 30 or more pack-years and quit smoking within the past 15–30 years. †USPSTF criteria: individuals aged 55–80 years, who have a current or past smoking history of 30 or more pack-years; if former smokers, those who quit within the past 15 years. ‡Pack-years: packs smoked daily multiplied by years. §Large-cell neuroendocrine and adenosquamous carcinoma.

Table 2: **Characteristics of matched sets in the hospital and community cohorts (long-term quitters and those meeting USPSTF criteria), diagnosed 1997–2015**

while including optimal case numbers. Kernel density plots were used for visual comparisons of matching results. Additionally, bootstrapping was used as a form of internal cross-validation, where 1000 replicate samples were drawn with replacements from the original sample, each with the same sample size.

Considering age and competing causes of death, we did a multivariable regression analysis stratified by age group, and compared 5-year overall survival in the USPSTF age subgroups (five consecutive 5-year age groups: 55–59 years, 60–64 years, 65–69 years, 70–74 years, and 75–80 years) with that in the younger

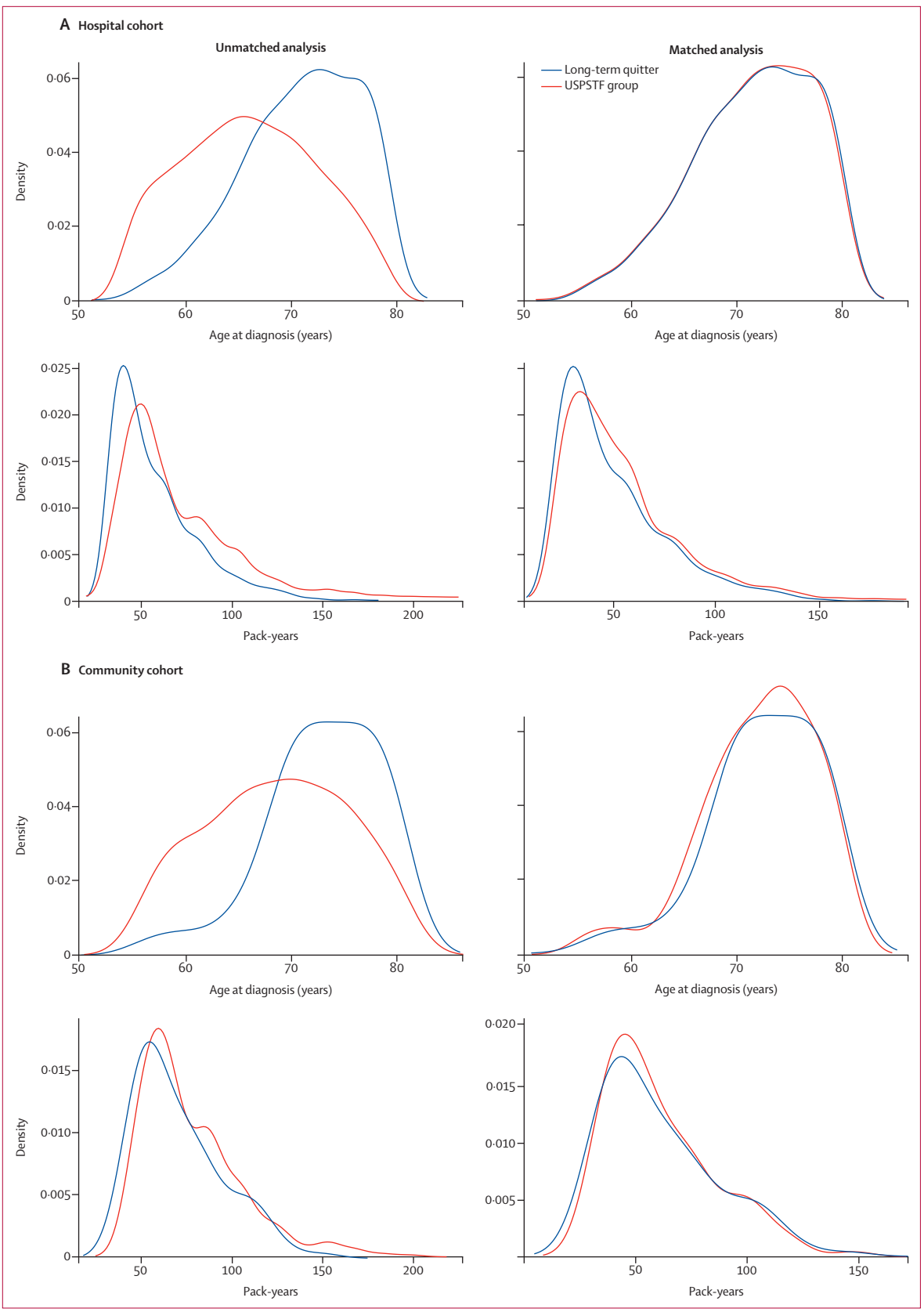

Figure 2: **Kernel density plots showing the balance improvement for age at diagnosis and pack-years smoked between patients meeting USPSTF screening criteria and long-term quitters**

(A) Hospital cohort. (B) Community cohort. The density of the kernel density plot represents the kernel density estimate of the probability function of a variable from patients (eg, age or pack-year), which is interpreted as a probability differential. Results are presented for unmatched and matched analyses. USPSTF=US Preventive Services Task Force.

	Hospital cohort (n=6499)		p value	Community cohort (n=836)		p value
	Younger age group* (n=630)	USPSTF criteria† (n=5869)		Younger age group* (n=78)	USPSTF criteria† (n=758)	
Age at diagnosis, years	52·1 (1·4)	66·7 (6·5)	<0·0001	52·3 (1·4)	67·8 (6·7)	<0·0001
Sex						
Female	285 (45%)	2477 (42%)	<0·0001	39 (50%)	317 (42%)	0·16
Male	345 (55%)	3392 (58%)	..	39 (50%)	441 (58%)	..
Race or ethnicity						
White	534 (85%)	5210 (89%)	0·003	76 (97%)	731 (96%)	0·65
Other	96 (15%)	659 (11%)	..	2 (3%)	27 (4%)	..
Cigarette smoking status at diagnosis						
Former	114 (18%)	2262 (39%)	<0·0001	17 (22%)	296 (39%)	0·003
Current	516 (82%)	3607 (61%)	..	61 (78%)	462 (61%)	..
Pack-years‡	48 (35·0–65·0)	56 (44·0–80·0)	<0·0001	45 (36·0–64·0)	60 (46·0–80·0)	<0·0001
Tumour stage§						
Non-small-cell lung cancer	527 (84%)	4864 (83%)	..	66 (85%)	625 (83%)	..
I	69 (13%)	1300 (27%)	<0·0001	16 (24%)	199 (32%)	0·50
II	61 (12%)	538 (11%)	..	4 (6%)	48 (8%)	..
III	172 (33%)	1388 (29%)	..	19 (29%)	170 (27%)	..
IV	225 (43%)	1638 (34%)	..	27 (41%)	208 (33%)	..
Small-cell lung cancer	89 (14%)	901 (15%)	..	12 (15%)	133 (18%)	..
Limited	38 (43%)	399 (44%)	0·77	3 (25%)	51 (38%)	0·36
Extensive	51 (57%)	502 (56%)	..	9 (75%)	82 (62%)	..
Histology						
Adenocarcinoma	298 (47%)	2367 (40%)	<0·0001	41 (53%)	266 (35%)	0·02
Squamous cell carcinoma	104 (17%)	1612 (28%)	..	15 (19%)	239 (32%)	..
Small cell carcinoma	91 (14%)	915 (16%)	..	12 (15%)	135 (18%)	..
Other non-small-cell lung cancer ¶	23 (4%)	178 (3%)	..	2 (3%)	48 (6%)	..
Unspecified non-small-cell lung cancer	114 (18%)	797 (14%)	..	8 (10%)	70 (9%)	..
Treatment‖						
Surgery only	91 (14%)	1359 (23%)	<0·0001	19 (24%)	193 (26%)	0·75
Chemotherapy only	131 (21%)	975 (17%)	..	12 (15%)	116 (15%)	..
Chemotherapy and radiation	163 (26%)	1150 (20%)	..	24 (31%)	170 (22%)	..
Radiation only	32 (5%)	385 (7%)	..	5 (6%)	80 (11%)	..
Surgery and chemotherapy	35 (6%)	300 (5%)	..	4 (5%)	28 (4%)	..
Surgery and radiation	12 (2%)	128 (2%)	..	1 (1%)	21 (3%)	..
Surgery, chemotherapy, and radiation	57 (9%)	355 (6%)	..	3 (4%)	31 (4%)	..
Other treatment	33 (5%)	230 (4%)	..	3 (4%)	22 (3%)	..
No treatment	57 (9%)	741 (13%)	..	7 (9%)	97 (13%)	..

Data are n (%), mean (SD), or median (IQR). USPSTF=US Preventive Services Task Force. NA=not applicable. *Younger age group: individuals aged 50–54 years, with a smoking history of 30 or more pack-years, and currently smoke or quit within the past 15 years. †USPSTF criteria: individuals aged 55–80 years, with a smoking history of 30 or more pack-years, and who currently smoke or quit within the past 15 years. ‡Pack-years: packs smoked daily multiplied by years. §Unknown stage: 14 (2%) of 630 patients among the younger age group and 104 (2%) of 5869 patients among the USPSTF group in the hospital cohort. ¶Large-cell neuroendocrine and adenosquamous carcinoma. ‖Unknown treatment: 19 (3%) of 630 patients among the younger age group and 246 (4%) of 5869 patients among the USPSTF group in the hospital cohort.

Table 3: **Characteristics of 7335 patients aged 50–80 years in the hospital cohort and community cohort, including the younger age group, diagnosed 1997–2015**

age group. All statistical tests were done as two-tailed tests and p values less than 0·05 were deemed significant. Analyses were done with SAS (version 9.4). Missing data were not included in our analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 1997, and Dec 31, 2017, 8739 patients with lung cancer were identified and followed up, with a median follow-up of 6·5 (IQR 3·8–10·0) years. Of

8739 patients, 7846 (90%) were white. The community cohort comprised 941 patients, and the hospital cohort comprised 7798 patients. Among all patients in the hospital cohort, lung cancer stage was unknown for 30 (2%) of 1299 patients termed long-term quitters, for 104 (2%) of 5869 patients in USPSTF group, and for 14 (2%) of 630 patients in the younger age group. Treatment was unknown for 57 (4%) of 1299 long-term quitters, 246 (4%) of 5869 patients in USPSTF group, and 19 (3%) of 630 patients in the younger age group. The characteristics of 8031 patients aged 55–80 years who quit within the past 30 years from the hospital cohorts and community cohorts, stratified by USPSTF criteria, are shown in table 1. Long-term quitters were significantly older, and more frequently men, more likely to have smoked fewer pack-years, and to have adenocarcinoma histology than were those who met USPSTF screening criteria.

Median overall survival was 16·9 months (95% CI 16·2–17·5) in the study population. 5-year overall survival was 27% (95% CI 25–30) in long-term quitters, 22% (19–25) in the younger age group, and 23% (22–24) in the USPSTF group.

In univariable Cox models, known prognostic factors including age, sex, race, smoking status, pack-years smoked, tumour histology, stage, and treatment modality were significant variables, which were then analysed in multivariable Cox models. In multivariable analyses, 5-year overall survival was not significantly different in long-term quitters in the hospital cohort versus in those who met USPSTF criteria (HR 1·02; 95% CI 0·94–1·10; p=0·72) after adjustment of significant variables in univariable analysis (figure 1A). In the community cohort, long-term quitters also had the same mortality risk at 5 years as did those who met the USPSTF criteria (HR 0·97; 95% CI 0·75–1·26; p=0·82; figure 1B). A bootstrap validation did not alter the results in the fitness of both models (data not shown).

Matching based on age at diagnosis and pack-years smoked yielded 1224 patient pairs in the hospital cohort, and 315 individuals meeting USPSTF criteria versus 105 long-term quitters in the community cohort (table 2). Figure 2 shows the balanced comparison groups, and table 2 presents well-balanced characteristics except for sex. In the multivariable analysis, 5-year overall survival did not differ significantly between long-term quitters and patients meeting USPSTF criteria in the hospital cohort (figure 1A) or in the community cohort (figure 1B).

The characteristics of 7335 patients aged 50–80 years who quit within the past 15 years from the hospital cohort and community cohort, stratified by USPSTF criteria, are shown in table 3. 5869 patients in the hospital cohort and 758 patients in the community cohort met the USPSTF screening criteria. In both cohorts, patients were predominantly male and white, and age at diagnosis was significantly different between the USPSTF group and younger age group. Most patients were current smokers.

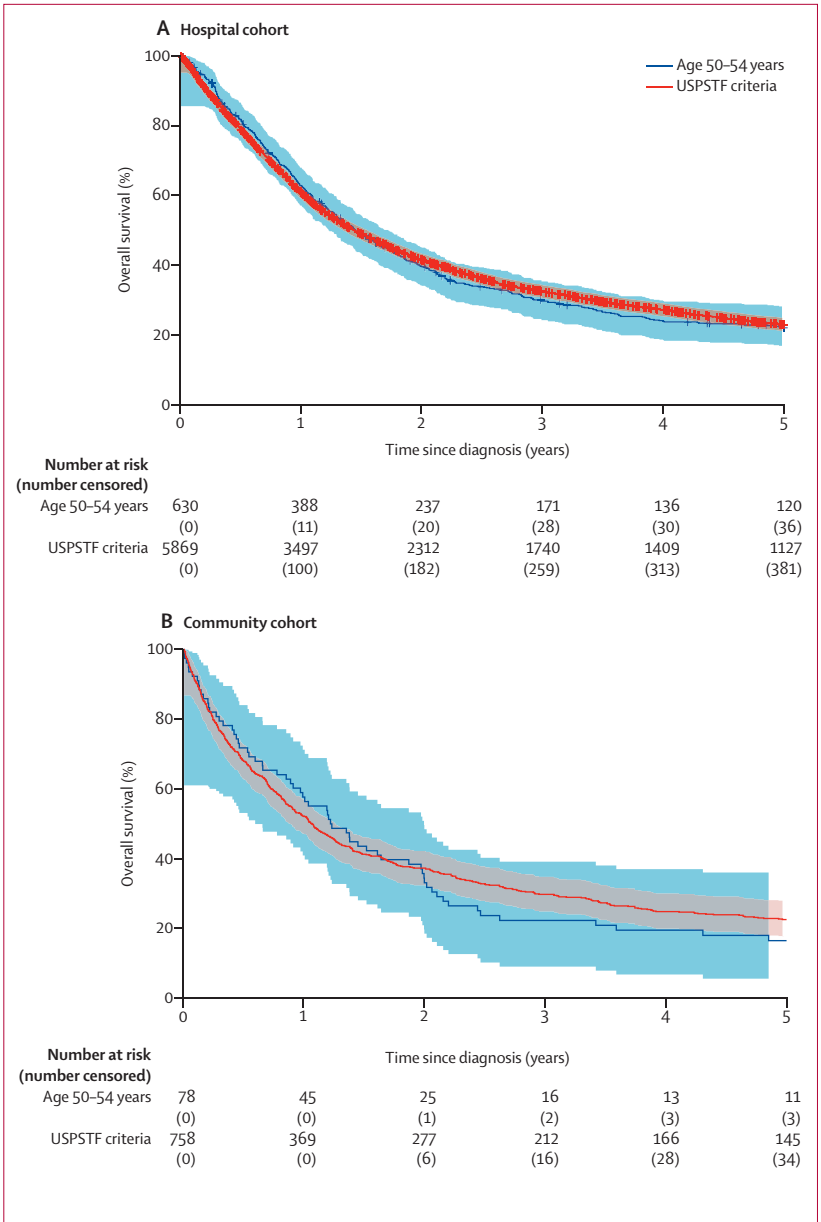

***Figure 3*: Kaplan-Meier curves of overall survival of the younger age group and USPSTF group**
(A) 5-year overall survival in the hospital cohort. (B) 5-year overall survival in the community cohort. USPSTF=US Preventive Services Task Force. The shading represents 95% CIs for the survival curves.

Most patients had stage III–IV lung cancer and the most prevalent histology was adenocarcinoma. Compared with the USPSTF group, the younger age group comprised mostly current smokers, and most patients were female, with stage III/IV lung cancer and adenocarcinoma.

For patients in the hospital cohort, median overall survival was 17·4 months (95% CI 15·5–19·7) in the younger age group and 17·2 months (16·5–18·2) in the USPSTF group. 5-year overall survival was 22% (95% CI 17–27) in the younger age group and 23% (21–25) in the USPSTF group (p=0·78; figure 3A). In the community

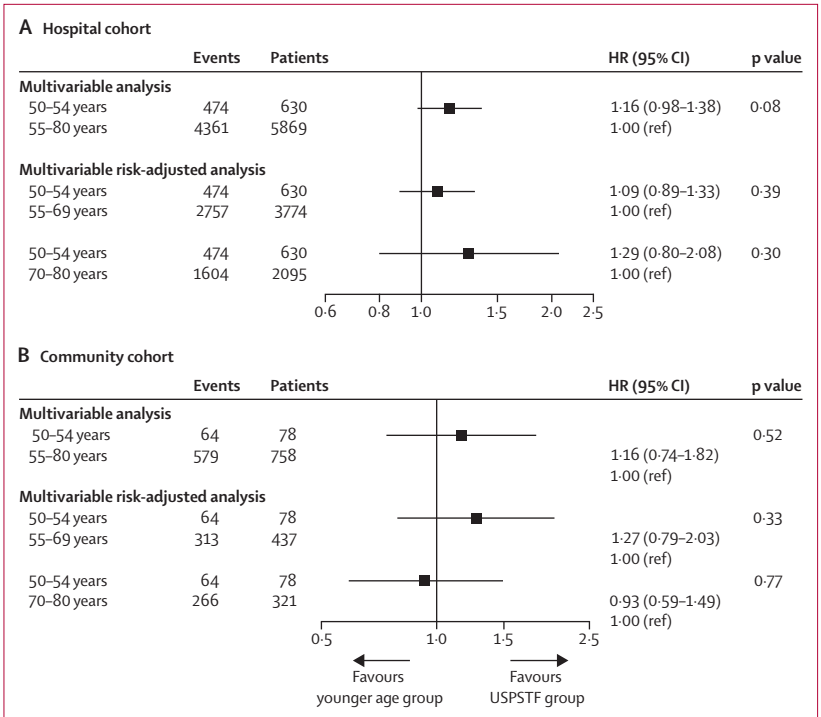

Figure 4: **Multivariable Cox proportional hazard models of patients meeting USPSTF screening criteria versus the younger age group**
(A) Hospital cohort. (B) Community cohort. USPSTF=US Preventive Services Task Force.

cohort, median overall survival was 14·7 months (95% CI 10·7–22·4) in the younger age group and 12·8 months (11·1–14·4) in the USPSTF group. 5-year overall survival was 16% (95% CI 5–33) in the younger age group and 23% (18–28) in the USPSTF group (p=0·57; figure 3B). In univariable Cox models, sex, cigarette smoking status, pack-years smoked, years since quitting, tumour histology, stage, and treatment modality were significant variables, which were then analysed in multiple Cox models. In multivariable analyses, 5-year overall survival was not significantly different between the younger age group in the hospital cohort and the USPSTF group (HR 1·16; 95% CI 0·98–1·38; p=0·08; figure 4A). In the community cohort, 5-year overall survival was not significantly different between the younger age group and the USPSTF group (HR 1·16; 95% CI 0·74–1·82; p=0·52; figure 4B).

The USPSTF group (patients aged 55–80 years) was subdivided into five consecutive 5-year age groups. Results of the age-group stratified analysis are in the appendix (pp 3–4). Three USPSTF subgroups with similar risks (55–59 years, 60–64 years, and 65–69 years) were combined into the younger USPSTF subgroup (age 55–69 years), and the other two subgroups with similar risks (70–74 years and 75–80 years) were combined into the older USPSTF subgroup (age 70–80 years; appendix pp 3–4).

In multivariable risk-adjusted analysis, 5-year overall survival was not significantly different between the younger age group and the two USPSTF subgroups in the hospital cohort (figure 4A). Similarly, 5-year overall survival did not differ significantly between the younger age group and the younger USPSTF subgroup in the community cohort (figure 4B). The younger age group had the same risk of death at 5 years as the older USPSTF subgroup in the community cohort.

Discussion

The results of this prospective, observational cohort study suggest that 5-year overall survival after lung cancer diagnosis in patients who do not meet certain USPSTF criteria (long-term quitters and younger age groups) is similar to that of patients who meet USPSTF criteria. Most patients were white; the effect of racial or ethnic background was analysed, but was not significant as an independent covariate, which might reflect the small sample size of patients who were not white. Our previous study showed that expanding the USPSTF screening criteria to include long-term quitters might save more lives without significantly increasing the number of cases of overdiagnosis.[9] Findings from this study indicate that long-term quitters have similar overall survival to patients meeting USPSTF criteria. Additionally, our results show a higher frequency of early-stage lung cancer among long-term quitters than among the USPSTF group in the hospital and community cohorts. Therefore, in terms of tumour stage, long-term quitters might have a higher survival benefit from screening than those who quit within the past 15 years, as a result of greater detection of early-stage lung cancer.

Patients aged 50–54 years with lung cancer (ie, the younger age group) who otherwise meet the USPSTF screening criteria are one of the three largest subgroups at potentially high risk of developing lung cancer outside of the high-risk population defined by the USPSTF.[8,9] Our data suggest that overall survival in individuals in the younger age group was similar to that of those in the USPSTF group, suggesting that the risk of death in the younger age group might be underestimated by the USPSTF criteria. Therefore, the use of 55 years as the lower age limit in the USPSTF criteria might exclude younger patients who could benefit from earlier detection of their lung cancer at a potentially curable stage. Furthermore, the incidence and mortality of most malignancies, including lung cancer, usually increases with age until the age of about 80 years.[3,20] However, the older USPSTF subgroup in this study did not have worse overall survival than the younger age group, which is consistent with previous reports suggesting that lung cancer occurring in younger individuals might represent a biologically distinct subgroup associated with higher mortality,[21] so identification and screening of high-risk younger individuals is essential. A recent study indicated that 50 years of age was as a useful cutoff for prognosis and genomic alterations in non-small-cell lung cancer,[22] which is supported by our study in which patients aged

50–54 years had the same overall survival as those aged 70–80 years (ie, the older USPSTF subgroup). Collectively, patients with lung cancer who are 50 years or older represent a subgroup with a similar risk of death after lung cancer diagnosis, and therefore patients aged 50–54 years should also be included in the screening criteria.

Previous studies have shown that the risk of lung cancer exponentially decreases within 15 years of quitting;[10,11] however, our results suggest that patients with lung cancer aged 55–80 years, with 30 or more pack-years smoked and who quit smoking within the past 15–30 years (long-term quitters) had the same survival 5 years after diagnosis as patients who quit smoking less than 15 years since diagnosis. Additionally, our study showed that the younger age group had more current smokers in both cohorts than the USPSTF group. These findings are compatible with data from the NLST and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.[4,23] Previous research has reported that abnormalities detected at screening are significantly associated with subsequent smoking behaviour and could be used as a learning point for smoking cessation interventions.[24] Accordingly, lung cancer screening in the younger age group could, by uncovering abnormalities, help to increase smoking cessation in this group relative to that in patients who meet USPSTF screening criteria. From the viewpoint of smoking cessation, patients aged 50–54 years might benefit more from screening than those aged 55 years and older, which could also affect other smoking-related diseases, such as stroke and cardiovascular and pulmonary disease. Screening of the younger age group could, therefore, substantially reduce morbidity and mortality and extend life expectancy.

Substantial progress in lung cancer screening, diagnosis, and treatment has led to improved survival over the past decades. However, older patients are reported to be more likely to be ineligible for novel therapies because of comorbidities.[25,26] Therefore, the younger age group might benefit more than the USPSTF group from continuous advances in lung cancer care.

Cost-effectiveness is especially important for lung cancer screening programmes, and the selection of age groups for screening has a large impact on cost-effectiveness.[6] A previous investigation showed that screening of individuals aged 50 years or older was the most cost-effective option, whereas screening of those aged 60 years or older was the least cost-effective.[27] Additionally, screening for long-term quitters might identify 16% more lung cancers with an acceptable cost and minimal harm.[9] Collectively, these studies imply that patients who can be classified as long-term quitters and who are 50–54 years of age should be included in screening criteria for lung cancer; future studies about the overall cost-effectiveness of expanding efficacious screening to long-term quitters and the younger age group are warranted.

Although this study enrolled the next largest subgroups at high risk for lung cancer (ie, long-term quitters and the younger age group) outside of the high-risk population defined by the USPSTF, other potentially high-risk groups might also exist that are ineligible for screening. Therefore, improvement of the screening criteria and the conventional risk assessment model based on smoking history is needed. Additional large randomised trials that only focus on differing cutoffs of age and smoking history might not be cost-effective; instead, promising biological and physiological markers should be tested on a regular basis. Molecular biomarkers in the biological fluid, such as blood, urine, saliva, and sputum, have been intensively investigated and shown the potential ability to improve selection of patients for lung cancer screening, and to assess the likelihood of malignancy in lung nodules detected at screening.[28] Combination of low-dose CT and biomarkers with optimal discriminating power in high-risk individuals before or after screening has the potential to optimise the efficacy of screening.[29]

A limitation of this study is that all patients were diagnosed with lung cancer, which makes it difficult to accurately examine trade-offs between the benefits and potential harms of screening. Another concern is that approximately 1% of patients were initially identified via low-dose CT screening with a relatively earlier stage;[30] however, the effect of staging has been carefully adjusted in our analyses. Additionally, several unmeasured confounders could have affected the survival outcome, such as other comorbidities, personal cancer history, and family history of lung cancer. Furthermore, missing data for stage and treatment were not included in our analyses, although the magnitude of missing data is minimal, and the proportions of missing data were similar between patients who met all USPSTF criteria and those who did not. Despite these limitations, our study has several strengths. First, we carefully chose two independent cohorts: the hospital cohort represents the natural setting of an observational patient population at a tertiary medical centre, whereas the community cohort represents the midwest region of the USA. Data were collected from these two prospectively observed cohorts with a long-term follow-up; therefore, longitudinal and comprehensive data could be obtained, which enabled us to adjust for major known prognostic factors. Second, survival models were developed in the hospital cohort and validated in the community cohort, and all patients were diagnosed or treated at the same medical institution. Our results can be considered robust since the data from both cohorts are reasonably consistent. Third, smoking history was obtained from medical records and further confirmed with a follow-up questionnaire or an interview.

In conclusion, our findings suggest that patients with lung cancer who quit smoking more than 15 years before a diagnosis or were up to 5 years younger than the age cutoff outlined in the USPSTF screening criteria but who otherwise met the USPSTF screening criteria were not

only at substantially high risk of developing the disease but also had similar survival to patients meeting the USPSTF screening criteria. Screening of the younger age group might lead to increased smoking cessation. Individuals in these two subgroups might benefit from screening as expanding the USPSTF criteria to include these subgroups could enable earlier detection of lung cancer.

Contributors

PY and DEM contributed to the concept and design of this report. PY, DL, YW, LL, and Y-HL were responsible for collection and assembly of data. PY, JAW, DEM, AAA, DL, YW, LL, and Y-HL were responsible for analysis and interpretation of the data. PY, LL, and Y-HL were responsible for drafting of the manuscript. PY, DEM, AAA, and Y-MC were responsible for essential revisions of the manuscript and for incorporation of important intellectual content. PY, AAA, and DEM provided final approval of the article. PY, LL, Y-HL, and JAW were responsible for provision of study materials or identification of patients. PY, JAW, DL, YW, LL, and Y-HL were responsible for statistical analysis. PY, JAW, DL, YW, LL, and Y-HL provided administrative, technical, or logistic support. PY and AAA supervised the study.

Declaration of interests

We declare no competing interests.

Acknowledgments

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