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Incidence, Correlates, and Chest Radiographic Yield of New Lung Cancer Diagnosis in 3398 Patients With Pneumonia

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Background: One reason chest radiographs are recommended after pneumonia is to exclude underlying lung cancer. Our aims were to determine the incidence and correlates of new lung cancer and the diagnostic yield of new lung cancer by chest radiography in patients with pneumonia.

Methods: We conducted a population-based cohort study of patients with chest radiography–confirmed pneumonia, who were discharged alive from hospitals and emergency departments in Edmonton, Alberta, Canada. Patients were enrolled from 2000 through 2002 and followed up for 5 years. We determined incidence of new lung cancer and receipt of chest radiographs within 90 days, 1 year, and 5 years. Multivariable proportional hazards analyses were used to determine independent correlates of lung cancer.

Results: There were 3398 patients; 59% were 50 years or older, 52% were male, and 17% were smokers. Half (49%) were admitted to hospital. At 90 days, 36 patients (1.1%) had new lung cancer; at 1 year, 57 patients (1.7%); and over 5 years, 79 patients (2.3%). The median time to diagnosis was 109 days (interquartile range, 27-423 days). Characteristics independently associated with lung cancer included age 50 years or older (adjusted hazard ratio [aHR], 19.0; 95% confidence interval [CI], 5.7-63.6), male sex (aHR, 1.8; 95% CI, 1.1-2.9), and smoking (aHR, 1.7; 95% CI, 1.0-3.0). Of the patients, 1354 (40%) had follow-up chest radiographs within 90 days, and the diagnostic yield of lung cancer was 2.5%; if radiographs were restricted to patients 50 years or older, the yield would have been 2.8%.

Conclusions: The incidence of new lung cancer after pneumonia is low: approximately 1% within 90 days and 2% over 5 years. Routine chest radiographs after pneumonia for detecting lung cancer are not warranted, although our study suggests that patients 50 years or older should be targeted for radiographic follow-up.

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COMMUNITY-ACQUIRED pneumonia is common, with an approximate annual incidence of 12 episodes per 1000 persons.[1-3] Since 2000, several evidence-based guidelines from the United States, Canada, and Europe have been published with regard to diagnosis, treatment, and follow-up of pneumonia.[4-8] A follow-up chest radiograph is recommended 4 to 8 weeks after the treatment of pneumonia in all of these guidelines,[4,6-8] although the most recent Infectious Disease Society of America–American Thoracic Society consensus guidelines are (for the first time) silent on the topic.[5] Other than for ongoing symptoms related to nonresolution, the main reason for these follow-up chest radiographs seems to be to exclude underlying malignant neoplasms that may have predisposed to postobstructive pneumonia.[4,6-8] This recommendation may be important for groups at higher risk for lung cancer, such as older patients and smokers.[4,8]

There is, however, very little evidence to support any recommendations for chest radiographic follow-up.[9-12] A recent study by Mortensen et al[9] showed a 9.2% inci-

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Associate Editor's Note

For the last 2 decades, guidelines have suggested repeating chest radiography a couple of months after treatment for pneumonia to make sure that a lung mass was not the cause of the pneumonia. This study suggests that the incidence of lung cancer after pneumonia is low and that routine posttreatment chest radiographs are not warranted in patients at low risk of lung cancer, whose symptoms resolve with treatment.

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dence of new lung cancer after pneumonia over 5 years of follow-up, which would support the need for routine follow-up chest radiographs. Nevertheless, all other studies have previously indicated the incidence of new lung cancer was much lower, on the order of 2% or less,[10-12] and this lower estimate would not provide a strong rationale for routine follow-up radiographs.

Therefore, we undertook the present study. Our aims were 3-fold: (1) to determine the short- and longer-term incidence of new lung cancer after treatment for pneumonia, (2) to clarify the independent correlates associated with a new lung cancer diagnosis, and (3) to determine the lung cancer diagnostic yield of routine chest radiography within 90 days of pneumonia.

METHODS

SETTING AND SUBJECTS

From 2000 to 2002, all 6874 patients with pneumonia evaluated in any of the 7 emergency departments (EDs) and 6 hospitals serving Edmonton, Alberta, Canada, were enrolled in a population-based clinical registry and followed up for up to 5 years. The metropolitan Edmonton region has a population of more than 1 million people with universal health care coverage cared for by more than 1000 family physicians and an annual health care budget of almost $2 billion.

Details and analyses related to the subgroups of patients admitted to hospital,[13,14] transferred to the intensive care unit,[15] or discharged home from the ED and treated as outpatients[16] have been previously published. All patients were cared for according to a validated clinical pathway that had triage and site-of-care suggestions based on the Pneumonia Severity Index (PSI) as well as recommendations for investigations and antibiotics.[13-16] For the present study, we included all 4261 adults with symptoms and signs of pneumonia (defined as ≥2 of the following: cough, pleurisy, shortness of breath; temperature >38°C, crackles, or bronchial breathing, on auscultation), who also had a chest radiography-confirmed diagnosis. The registry did not capture patients with tuberculosis, cystic fibrosis, or immunocompromised status or who were pregnant. The only patients who we excluded from the present analyses were those who died in hospital, those with any documented cancer at the time of presentation, and those who could not be linked to provincial databases to identify longer-term outcomes. The study was approved by the institutional ethics review board of the University of Alberta, Edmonton.

DATA COLLECTION AND MEASUREMENTS

Research nurses prospectively collected sociodemographic, clinical, and laboratory data. For pragmatic reasons, data collection was more limited for outpatients than inpatients.[16] For example, for outpatients we did not collect all data for long-term medications, and most laboratory values were dichotomized and collected as abnormal vs normal, based on PSI criteria. The PSI is a validated tool designed to predict 30-day all-cause mortality in patients with pneumonia, but it has also been used for purposes of risk adjustment.[13]

OUTCOMES

The primary study outcome was a new diagnosis of lung cancer at any time over the entire duration of follow-up. We did not make any distinctions between "primary" and "secondary (metastatic)" lung cancers because either could lead to a post-obstructive pneumonia. Because we excluded all extant (prevalent) cancers, these new lung cancers were considered incident. We used *International Classification of Diseases, Ninth Revision (ICD-9)* and *International Statistical Classification of Diseases, 10th Revision (ICD-10)* codes to identify primary and secondary cancers of the bronchus and lung. Specifically, we used *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 162.x, 209.61, and 209.21 before 2002 and *ICD-10* codes C34.0-3, C34.8, C34.9, 39.0, 39.8, and 39.9 after 2002. The use of these *ICD* codes to identify lung cancer has been previously validated.[17-21] To ascertain outcomes, we linked registry patients to provincial administrative databases that included vital statistics and all health care resource utilization. The rate of successful linkage between population-based clinical registries, and our provincial administrative databases generally exceeds 95%.[13-16]

ANALYSIS

Patient characteristics were stratified according to the presence or absence of a new lung cancer over follow-up. Cumulative incidence of new lung cancer at 90 days, 1 year, and the entire duration of follow-up across different age strata (<40 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years, or ≥80 years) were determined.

Time-to-event data were plotted and calculated using Kaplan-Meier curves and survival analysis techniques. Censoring occurred at the time of new lung cancer diagnosis, death, departure from Alberta (mandating disenrollment from provincial health insurance coverage), or the end of study follow-up in March 2006. Multivariable (adjusted) hazard ratios were estimated using Cox proportional hazards models. We forced age, sex, and severity of initial pneumonia according to the PSI into all models. Additional candidate variables were considered for inclusion in our models based on concurrent availability in both inpatient and outpatient data sets, clinical relevance, literature review, univariable association with lung cancer of $P < .10$, or demonstrable confounding (ie, a 10% or greater change in β coefficient). All first-order interaction terms were considered; none achieved statistical significance ($P < .10$) and none were included in final models. The final model included age, sex, smoking status (current vs former vs the reference group of never smoker), chronic obstructive pulmonary disease, and the initial severity of pneumonia; unless specified otherwise, whenever the term *adjusted* is used it refers to this model. Assessment of the proportional hazards assumptions was undertaken using log-log survivor plots and time interaction terms, and no violations were present.

We undertook several secondary analyses. First, to provide some plausible ranges for incidence, we recalculated the incidence of lung cancer using a more "specific" approach (ie, diagnoses restricted to only fatal lung cancer) and a more "sensitive" approach (ie, diagnoses expanded to a far broader but not so well-validated range of codes used by Mortensen et al[9]). Second, we repeated all analyses using new diagnosis of lung cancer within 90 days and within 1 year of pneumonia because these are the most plausible timeframes within which any new lung cancer would have been associated with pneumonia and discovered using routine follow-up chest radiographs. Third, we repeated analyses after excluding all patients 40 years or younger on the assumption that these younger adults would have virtually no risk whatsoever of lung cancer. Fourth, we examined the rates and potential predictors of receiving a follow-up chest radiograph within 90 days of pneumonia and undertook some simple utility analyses to determine how best to

Table 1. Characteristics of 3398 Patients Diagnosed as Having Pneumonia According to the Presence or Absence of a New Diagnosis of Lung Cancer[a]

Characteristics	No Lung Cancer (n = 3319)	Lung Cancer (n = 79)	*P* Value
Age, mean (SD), y	57.2 (20.9)	72.2 (10.6)	<.001
Age ≥50 y	1934 (58)	76 (96)	<.001
Male sex	1710 (52)	52 (66)	.01
Inpatient	1634 (49)	42 (53)	.49
Nursing home	350 (11)	4 (5)	.11
Current smoker	553 (17)	22 (28)	.002
COPD	583 (18)	24 (30)	.003
Diabetes	338 (10)	14 (18)	.03
CKD	252 (8)	5 (6)	.67
PSI class			
I/II	1683 (51)	20 (25)	<.001
III	563 (17)	21 (27)	
IV	778 (23)	33 (42)	
V	295 (9)	5 (6)	

Abbreviations: COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; PSI, pneumonia severity index.
[a]Data are given as number (percentage) of patients unless otherwise specified.

maximize the diagnostic yield of follow-up chest radiographs. All analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS

There were 4261 patients potentially eligible for inclusion in this study. After excluding those with a documented history of any cancer at presentation (n=472), who died in hospital (n=189), or who could not be linked to provincial databases for outcomes ascertainment (n=202), our final study cohort consisted of 3398 patients. Their mean (SD) age was 58 (21) years, 2010 (59%) were 50 years or older, 1762 (52%) were male, 575 (17%) were current smokers, 607 (18%) had chronic obstructive pulmonary disease, and 1676 (49%) were treated as inpatients (**Table 1**).

LUNG CANCER INCIDENCE

Within 90 days of presenting with pneumonia, 36 of 3398 patients were diagnosed as having a new lung cancer, for an incidence of 1.1%; within 1 year, incidence was 1.7% (57 patients); by 2 years, 2.1% (70 patients); by 3 years, 2.2% (75 patients), and over the entire duration of follow-up, 2.3% (79 patients). The median time to diagnosis was 109 days (interquartile range, 27-423 days; **Figure 1**). At 1 year, 55 of 57 patients (96%) with lung cancer had died and 47 (82%) had it listed as their cause of death; over 5 years of follow-up, 73 of 79 patients (92%) had died and 60 (76%) had it listed as cause of death. Over the duration of follow-up, the incidence of fatal lung cancer (specific estimate) was 1.8%, while the incidence using a broader range of diagnostic codes (sensitive estimate) was 2.6%—the range of plausible estimates using these

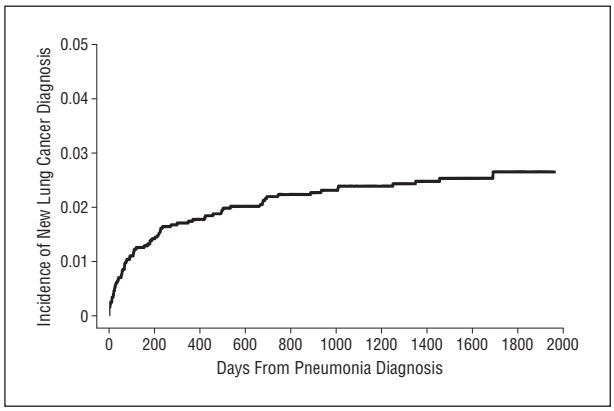

Figure 1. Cumulative incidence of new lung cancer diagnosis after an episode of pneumonia over 5 years of follow-up.

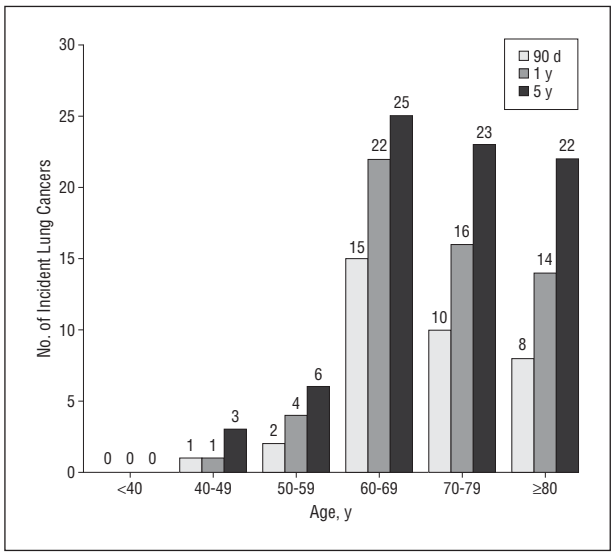

Figure 2. Distribution of new lung cancers after an episode of pneumonia according to age and time of diagnosis.

2 different approaches was almost identical to the directly calculated 95% confidence intervals (CIs) around the estimate of 2.3% (95% CI, 1.8%-2.8%).

CORRELATES OF LUNG CANCER

Compared with those without lung cancer, the patients who had a new lung cancer diagnosis were more likely to be older, male, and smokers; they also tended to have more severe pneumonia (Table 1). The findings in Table 1 were almost identical when examining patients with cancer diagnoses at 90 days and 1 year (data not shown). There were no lung cancers diagnosed in patients 40 years or younger, but the incidence started to climb after the age of 50 years (**Figure 2**). There was more than a 20-fold difference in new lung cancer diagnoses when comparing the subgroup of men 50 years or older (51 of 79 cancers [65%]) with the subgroup of women younger than 50 years (2 cancers [3%]). After multivariable adjustment, the only characteristics independently associated with a postpneumonia lung cancer diagnosis within 1 year or over the duration of follow-up were age 50 years or older and male sex (**Table 2**). These 2 characteristics

Table 2. Independent Correlates of Lung Cancer at 1 Year and 5 Years in Patients With Pneumonia: Multivariable Proportional Hazards Analysis[a]

Variable	Adjusted Hazard Ratios (95% CI)	*P* Value
At 1 y		
Age ≥50 y	43.3 (5.7-326)	<.001
Male sex	2.3 (1.3-4.0)	.006
Over entire follow-up		
Age ≥50 y	19.0 (5.7-63.6)	<.001
Male sex	1.8 (1.1-2.9)	.01
After excluding those aged <40 y		
Age ≥50 y	7.8 (2.4-25.6)	<.001
Male sex	1.8 (1.1-2.9)	.01

Abbreviation: CI, confidence interval.
[a]Model adjusted for variables presented in the Table as well as smoking status, presence of chronic obstructive pulmonary disease, and the severity of the initial pneumonia.

Table 3. Patient Characteristics According to Receipt of a Routine 90-Day Follow-up Chest Radiograph[a]

Characteristics	No Chest Radiograph (n = 2044)	Chest Radiograph (n = 1354)	*P* Value
Age, mean (SD), y	57.2 (21.1)	57.9 (20.3)	.36
Age ≥50 y	1180 (58)	830 (61)	.04
Male sex	1039 (51)	723 (53)	.14
Inpatient	1011 (49)	665 (49)	.84
Nursing home	223 (11)	131 (10)	.25
Current smoker	317 (16)	258 (19)	.05
COPD	335 (16)	272 (20)	.006
Diabetes	198 (10)	154 (11)	.11
CKD	133 (7)	124 (9)	.004
PSI class			
I/II	1064 (52)	639 (47)	.04
III	346 (17)	238 (18)	
IV	461 (23)	350 (26)	
V	173 (8)	127 (9)	

Abbreviations: COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; PSI, pneumonia severity index.
[a]Data are given as number (percentage) of patients unless otherwise specified.

were also the only variables independently associated with lung cancer diagnosis in analyses that excluded all patients younger than 40 years (Table 2). In addition, over the entire duration of follow-up, current smoking was also associated with new lung cancer diagnosis (adjusted hazard ratio [aHR], 1.7; 95% CI, 1.0-3.0).

POTENTIAL YIELD OF CHEST RADIOGRAPHS

In total, 1354 of all patients (40%) received a chest radiograph within 90 days of pneumonia diagnosis. Patients who had chest radiographs were somewhat older and had more severe pneumonia (**Table 3**). However, in adjusted analyses only 2 characteristics were statistically associated with receipt of a follow-up chest radiograph within 90 days: age 50 years or older (aHR, 1.2; 95% CI, 1.0-1.4) and smoking (aHR, 1.2; 95% CI, 1.0-1.4). Since 34 new lung cancers were diagnosed in 1354 patients who had a chest radiograph within 90 days, the yield of follow-up radiographs when ordered at the discretion of the treating physicians in our region was 2.5%.

In terms of a diagnostic utility analysis, we assume that the only reason follow-up radiographs were ordered was to detect lung cancer and that all 57 cancers diagnosed within 1 year could have been detected by chest radiographs taken within 90 days. All 57 lung cancers would have been captured with universal follow-up requiring 3398 chest radiographs, for a yield of 1.7%. To maximize yield, our findings suggest restricting follow-up radiographs to patients 50 years or older. This strategy would have identified 56 of 57 (98%, 1 missed) lung cancers and required just 2010 chest radiographs for an estimated yield of 2.8%.

COMMENT

In a population-based cohort of 3398 patients with chest radiography–confirmed pneumonia, the incidence of new lung cancer was 1.1% at 90 days, 1.7% at 1 year, and 2.3% over 5 years of follow-up. The only characteristics independently associated with a new lung cancer diagnosis were 50 years or older, male sex, and smoking. In fact, there were no lung cancers in patients younger than 40 years, and the incidence only started rising after age 50 to 60 years. Fewer than half (40%) of patients received follow-up chest radiographs, and 90-day incidence of a new lung cancer diagnosis was 2.5% in this subgroup, similar to the incidence over the entire duration of follow-up.

Several previous articles have examined the incidence of lung cancer diagnosed by chest radiography after pneumonia.[9-12] The most recent of these, and most comparable to ours, is the study by Mortensen et al[9] in which the incidence over 5 years of follow-up was 9.2%—almost 4 times the incidence we found. The reason for the large discrepancy between their work and ours is most likely due to the populations examined: their study essentially only considered male veterans 65 years or older, a group already at very high risk of lung cancer owing to heavy smoking and military-related (and other occupational) exposures.[9] Indeed, using different methods at different times in different countries, the studies of Marrie,[10] Holmberg et al,[11] and Søyseth et al[12] report incidences of lung cancer after pneumonia ranging from 1.2% to 2.5%, which is very similar to what we observed.

As important as an estimate of the true incidence of lung cancer after pneumonia is, it has to be interpreted within the context of the background rate of lung cancer in the population. Determining this background rate is not straightforward. The annual incidence of lung cancer in the general population in Canada and the United States is approximately 0.06%,[22,23] and when restricted to those 65 years or older it is approximately 10-fold greater (0.3%-0.4%).[24,25] Conversely, the incidence of lung cancer in men and women 50 years or older who smoke 1 or more packs per day ranges from 0.7% to 1.3%.[26] Thus, compared with the population as a whole, the incidence

of lung cancer after pneumonia seems somewhat higher but it is still within the range of incidences reported for elderly smokers without pneumonia.

Though most (but not all[5]) guidelines recommend a follow-up chest radiograph after pneumonia,[6-8] including the multinational guidelines in force at the time of our study,[4] we found that only 40% of patients received a chest radiograph within 90 days. The diagnostic yield of new lung cancer by follow-up chest radiography 90 days after pneumonia was 2.5% in our study. This may represent a maximal yield, since some of these radiographs were certainly undertaken for those with ongoing or nonresolving symptoms—a group expected to have a higher incidence of postobstructive pneumonia. The diagnostic yield of routine follow-up chest radiography could be increased by selecting patients at higher risk for lung cancer. For example, no patients younger than 40 years and only 3 patients younger than 50 years were diagnosed as having new lung cancer. To maximize potential yield in asymptomatic patients, our utility analysis suggests restricting routine follow-up chest radiography to patients 50 years or older. This would triple current rates of lung cancer diagnosis within 90 days (from 1.1% observed to 2.8% predicted) and miss only 1 of 57 lung cancers detected within 1 year. This strategy would reduce the total number of chest radiographs recommended by 40%, while sparing the many patients with pneumonia younger than 50 years unnecessary tests and radiation exposure. In our jurisdiction, a chest radiograph with interpretation costs $35; thus the cost per lung cancer detected using an age-restricted followup strategy is approximately $1250 vs $2125 if all 3398 patients received a follow-up chest radiograph. While $1250 per lung cancer detected may seem inexpensive, given the 96% 1-year case fatality rate in our study and the fact that there is good randomized trial evidence that chest radiographic screening of asymptomatic patients does not reduce all-cause or lung cancer-specific mortality,[27] whether this is a worthwhile expenditure could (and should) be debated.

Despite its strengths, this study has several limitations. First, we did not require histopathologic confirmation of lung cancer diagnosis. However, of the 79 patients with lung cancer, 73 died during the course of follow-up, and 60 (76%) had lung cancer listed as the cause of death. This high case fatality rate is very consistent with lung cancer[28-30] and confirms our belief that our patients most likely had the disease in question.

Second, we chose as our primary outcome the incidence of lung cancer over the course of follow-up over 5 years rather than within 90 days or 1 year of pneumonia. Our rationale was that even if patients did not receive a 90-day follow-up chest radiograph, they may have eventually developed symptoms that warranted a later chest radiograph. That is, patients diagnosed as having lung cancer after 90 days may have received an earlier diagnosis if a routine follow-up radiograph had been done as guidelines suggested. Our assumptions would tend to falsely elevate incidence estimates, since patients may have developed a de novo lung cancer not present at the time of the original pneumonia.

Third, we did not rereview baseline chest radiographs specifically looking for lung cancer, and we did not look back at the chest radiographs of those who were diagnosed as having lung cancer to determine if the original radiographs might have been suggestive for lung cancer at the time of pneumonia. Furthermore, although we know patients received a radiograph during follow-up, we do not know the exact reason it was undertaken (eg, routine follow-up vs ongoing pneumonia-related symptoms vs new symptoms).

In conclusion, we found that the incidence of a new lung cancer diagnosis after an episode of pneumonia was relatively low: only about 1% at 90 days and 2% over 5 years of follow-up. Since 98% to 99% of patients will not have lung cancer, we believe routine follow-up chest radiographs (other than those indicated for ongoing pneumonia-related symptoms) are not warranted. Instead, our study suggests that the greatest potential diagnostic yield for lung cancer could be realized by restricting routine chest radiographic follow-up to patients 50 years or older, particularly those who are male or smoke.

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