Lung Cancer Risk Following Detection of Pulmonary Scarring by Chest Radiography in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

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**Background:** Fibrotic scars are frequently found in proximity to lung cancer at the time of cancer diagnosis. However, the nature of the relationship between pulmonary scarring and lung cancer remains uncertain. Our objective was to test whether localized pulmonary scarring is associated with increased lung cancer risk.

**Methods:** Cohort analysis of data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. We included 66,863 cancer-free trial participants aged 55 to 74 years, who received a baseline chest radiographic examination and were followed up subsequently for up to 12 years. We used proportional hazards models to estimate hazard ratios (HRs) for lung cancer associated with scarring, adjusting for age, sex, race, and cigarette smoking, and in relation to laterality of scarring. The main outcome measure was incident lung cancer.

**Results:** Scarring was present on the baseline chest radiograph for 5041 subjects (7.5%). Scarring was associated with elevated lung cancer risk (809 lung cancer cases [HR, 1.5; 95% confidence interval (CI), 1.2-1.8]). This association was specific for cancer in the lung ipsilateral to the scar (HR, 1.8; 95% CI, 1.4-2.4) and absent for contralateral cancer (HR, 0.9; 95% CI, 0.7-1.2). Ipsilateral lung cancer risk was elevated throughout the follow-up period (interval-specific HRs, 1.6, 2.0, 2.1, and 1.7 during 0.01-2.00, 2.01-4.00, 4.01-6.00, and 6.01-12.00 years after baseline chest radiography, respectively).

**Conclusions:** The relationship between pulmonary scarring and lung cancer was specific to the same lung and extended over time. These findings are consistent with the hypothesis that localized inflammatory processes associated with scarring promote the subsequent development of lung cancer.

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**See Invited Commentary at end of article**

Lung cancer accounts for more deaths than any other cancer in the United States. While tobacco use is the major risk factor for lung cancer, epidemiologic evidence has also demonstrated an elevated risk of lung cancer in people with certain nonmalignant lung diseases. Some of these conditions (eg, chronic obstructive pulmonary disease [COPD], tuberculosis) are thought to promote carcinogenesis by creating an inflammatory environment that induces genetic damage in lung epithelial cells, although the mechanistic pathways are not well understood.

A feature shared by several chronic pulmonary conditions is pulmonary fibrosis (ie, scarring), which is a lasting process of cellular inflammation and wound repair characterized by deposition of connective tissue. Pulmonary scarring can result from lung diseases caused by a variety of occupational exposures, such as to asbestos and silica, and inflammatory or infectious lung conditions, such as tuberculosis and some other forms of pneumonia; it also occurs for unknown reasons (ie, idiopathic pulmonary fibrosis). Since the 1930s, scars have been postulated to play an etiologic role in lung cancer, based on the observation that lung cancers frequently arise in proximity to scar tissue. Nonetheless, limited inference can be drawn from autopsy or pathologic evaluation. Indeed, laboratory studies have challenged the concept of scar carcinoma by suggesting that the scarring around lung cancers is an ongoing reactive process. As a result, it is unclear whether lung cancer can develop from pulmonary fibrosis or may itself cause scarring as a fibrotic reaction.

The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial
is a 2-arm randomized trial with ongoing follow-up that was initiated by the National Cancer Institute in 1992 to examine the effectiveness of screening in reducing cancer mortality. Screening modalities include, for lung cancer, baseline single-view posteroanterior chest radiography (ie, “chest x-ray,” abbreviated herein as CXR) followed by repeated CXRs at study years 1, 2, and 3. In a 2006 study, PLCO investigators reported on the prevalence of a range of abnormalities identified by radiologists on the baseline CXR and the association between these abnormalities and incidence of lung cancer as well as non-lung cancer mortality. Of interest, scarring and/or pulmonary fibrosis on CXR was associated with a 2-fold increased risk of lung cancer, which suggested that pulmonary scarring and/or fibrosis could be related to development of lung cancer.

In the present study, we aimed to build on the prior findings of the PLCO investigators to better assess the evidence that pulmonary scarring and/or fibrosis might play a role in the etiology of lung cancer. Specifically, we focused on the physical and temporal relationships between scarring and lung cancer. We reasoned that an increased risk of lung cancer largely limited to the same lung in which scarring was detected would suggest a causal explanation. In contrast, if scarring is merely a marker for a systemic exposure to an unmeasured lung cancer risk factor or for an illness linked to lung cancer (both of which would affect both lungs), then the increased risk of cancer would be present in both lungs. Likewise, we reasoned that a causal relationship between scarring and cancer would be manifested in elevated lung cancer risk over an extended period after the baseline CXR, whereas if the lung cancer caused the scar, this association would be manifested only in the period immediately following the CXR because the cancer would already have been present at baseline.

**METHODS**

**STUDY POPULATION AND STUDY DESIGN**

As described previously, 154,942 trial participants, aged 55 to 74 years and in general good health, were randomized to receive either annual cancer screening or regular care. Of the 77,464 PLCO participants in the screening arm, 10,338 (13.6%) either did not complete a baseline study questionnaire or did not receive a baseline CXR, and 63 (0.1%) had CXRs that were inadequate for radiological interpretation. We included in this study the remaining 66,863 participants in the screening arm who had a completed questionnaire and an interpretable baseline CXR. All PLCO participants provided written informed consent. The study was approved by the institutional review board of the National Cancer Institute.

Chest radiographic screening was conducted at 10 US centers by more than 100 PLCO Trial radiologists. Radiologists interpreted the CXRs blinded to participants’ medical history and to prior and subsequent radiological data. Chest radiographs were characterized by radiologists according to whether the findings were suggestive of lung cancer (eg, presence of a nodule or mass), and persons with positive reports were referred to their primary health care provider for management and tracked for diagnostic outcomes. Radiologists from the PLCO Trial also documented other abnormal CXR findings, including scarring, which was specifically mentioned as “scarring/pulmonary fibrosis/honeycombing” on the CXR evaluation form used for the trial. Scarring is a common thoracic radiologic diagnosis and would typically be noted on a CXR if characteristic linear opacities were present. However, because the focus of the trial was on detection of cancer, no detailed instruction regarding how to diagnose scarring was provided to radiologists. Location of scarring was characterized according to the posteroanterior view of the CXR, sectioned into the upper, middle, and lower one-third of the left or right hemithorax. Alternatively, if scarring was widespread in the lung, scarring was noted as (left and/or right) diffuse.

We included lung cancers diagnosed during the PLCO follow-up period through June 30, 2005. Annual study surveys were mailed to trial participants inquiring about any cancer diagnosis. A final diagnosis of lung cancer was confirmed by a review of medical records, which included histologic subtype and lobar position of the cancer in the left and/or right hemithorax.

**STATISTICAL ANALYSIS**

We first evaluated associations between participant characteristics and scarring detected on baseline CXR using logistic regression, both with and without adjustment for cumulative cigarette smoking. Cumulative cigarette smoking was measured using the variable “logcig-year,” defined as log(number of cigarettes smoked per day + 1) x years of smoking, which is log-linearly related to lung cancer risk. We then used multivariate proportional hazards models to estimate lung cancer risk associated with scarring, adjusting for sex, age at baseline, race/ethnicity, and cumulative cigarette smoking reported at baseline. Subjects were censored in the analyses at the earliest of death, loss to follow-up, or June 30, 2005. Race/ethnicity was classified as non-Hispanic black vs other groups to account for elevated lung cancer risk observed among non-Hispanic blacks even after adjustment for cigarette smoking.

We evaluated the relationship between the location of scarring in relation to that of subsequent cancers, using the lung as the unit of analysis to estimate lung cancer risk with respect to laterality (ie, a “lung-specific model”). In this approach, we recreated the data set by entering each person twice, each time with information regarding one of the lungs. We then estimated hazard ratios (HRs) for ipsilateral lung cancer (ie, occurring in the same lung in which scarring was detected) and for contralateral lung cancer (ie, opposite of the lung in which scarring was detected). This model does not differentiate the left lung from the right lung in deriving the HRs for ipsilateral and contralateral cancer. Because the observations on the paired lungs for each subject were not independent, we used a robust estimator to derive variances of HRs that incorporated within-subject correlations.

We conducted additional analyses to further characterize the association between scarring and lung cancer risk. First, by incorporating interaction terms into the proportional hazards model, we examined whether the association of lung cancer risk with scarring varied by smoking status or history of COPD. Second, to examine whether the association with scarring varied by lung cancer histologic subtype, we estimated HRs for adenocarcinoma, squamous cell carcinoma, and small cell carcinoma. Third, we assessed the temporality of the association between scarring and lung cancer by estimating separate HRs in 4 successive follow-up intervals. We reasoned that if the HR was strongest immediately after the baseline CXR, this association would indicate that lung cancer may already have been present at baseline, whereas an association extended over time would suggest that the scarring preceded the development of cancer. In addition, lack
of variation in the HR over time supports the proportional hazards assumption underlying estimation of a single HR. Finally, we also evaluated cancer risk related to the extent of scarring, ie, diffuse vs discrete scarring.

**RESULTS**

**PARTICIPANT CHARACTERISTICS**

Baseline characteristics of the 66,863 participants in the study cohort are given in Table 1. At baseline, the median age was 62 years, 50.9% were men, and 70.3% had at least some post–high school education. The majority (89.1%) of the cohort were non-Hispanic whites, 4.8% were non-Hispanic blacks, and 4.1% were Asian/Pacific Islanders. History of lung cancer in a first-degree relative was reported by 10.5% and personal history of COPD by 6.4% of the cohort. Of the cohort, 10.1% were current cigarette smokers, 43.2% were former smokers, and 46.6% had never smoked.

A CXR diagnosis of pulmonary scarring was reported at baseline for 5041 subjects (7.5%). As given in Table 1, scarring was most common among men, older persons, Asian/Pacific Islanders, those with less education, smokers (especially heavy smokers), and those with a history of COPD. The associations between these factors and baseline scarring remained significant after adjustment for smoking (Table 1). Also, 8.7% of the cohort had CXRs noted to be suggestive of lung cancer at baseline, but this was not associated with the presence of scarring on the same radiograph ($P = .63$).

Table 2 describes the scarring lesions detected on the baseline CXR and shows that considerably more scars were noted in the left lung than in the right lung (prevalence 3.3% vs 1.4%), which mostly resulted from an excess of scarring in the left lower lung compared with the right lower lung (prevalence 2.7% vs 0.7%). Only 0.7% of subjects had scars that were characterized as diffuse, most of which were bilateral ($n=444$). Location data for scarring were missing for 37 subjects.
A total of 809 participants developed lung cancer, of which 455 (56.2%) involved the right lung and 308 (38.1%) involved the left lung. These included 7 bilateral cancers. The remaining lung cancers occurred in other locations (ie, main stem bronchus or carina, n=15) or had missing data on location (n=38). According to histologic subtype, 349 lung cancers (43.1%) were adenocarcinoma, 152 (18.8%) squamous cell carcinoma, and 107 (13.2%) small cell carcinoma. Other non–small cell subtypes accounted for 19.4% of lung cancers, while the remainder (5.4%) had no specified subtype.

Among those who were diagnosed as having lung cancer, 15% had evidence of pulmonary scarring at baseline (Table 3). Thus, a baseline diagnosis of pulmonary scarring was associated with an increased risk of lung cancer during subsequent follow-up (HR, 2.2; 95% confidence interval [CI], 1.8-2.7). This association was attenuated but remained significant with adjustment for age, sex, race, and cumulative cigarette smoking (adjusted HR, 1.5; 95% CI, 1.2-1.8) (Table 3). Individuals with bilateral scarring had a greater risk of lung cancer than those with unilateral scarring (adjusted HRs, 1.8 [95% CI, 1.4-2.4] and 1.3 [95% CI, 1.0-1.7], respectively). Similarly, diffuse scarring (most of which was bilateral) was associated with a higher risk of lung cancer (adjusted HR, 2.6; 95% CI, 1.8-3.8) than the risk associated with discrete scarring (adjusted HR, 1.3; 95% CI, 1.1-1.6). Additional adjustments for family history of lung cancer, educational attainment, or history of COPD did not change the estimates (data not shown). Therefore, all HRs presented in the remainder of this section are adjusted only for age, sex, race/ethnicity, and smoking. The association between scarring and lung cancer did not vary across strata defined by smoking status (P = .84 for interaction) or history of COPD (P = .18 for interaction).

We next examined cancer risk for each lung in relation to scarring in that lung, using the lung as the unit of analysis. Scarring in the right lung was strongly associated with an increased risk of right lung cancer (HR, 2.2; 95% CI, 1.7-3.0), whereas the association of left lung cancer with left lung scarring was weaker and nonsignificant (HR, 1.2; 95% CI, 0.8-1.9). As given in Table 3, when we considered the left and right lungs together, we found an increased risk of ipsilateral lung cancer associated with scarring (HR, 1.8; 95% CI, 1.4-2.4) but not for contralateral lung cancer (HR, 0.9; 95% CI, 0.7-1.2). Also given in Table 3, scarring was associated with a sig-

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**Table 2. Prevalence of Pulmonary Scarring Detected by Baseline Chest Radiography, by Type and Location of Scar**

<table>
<thead>
<tr>
<th>Extent and Location of Scarring on Chest Radiograph</th>
<th>Laterality, No. of Subjects With Scar (% of Cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unilateral Left</td>
</tr>
<tr>
<td>Any scarring</td>
<td>2226 (3.3)</td>
</tr>
<tr>
<td>Discrete scarring</td>
<td>2194 (3.3)</td>
</tr>
<tr>
<td>Upper one-third of lung only</td>
<td>138 (0.2)</td>
</tr>
<tr>
<td>Middle one-third of lung only</td>
<td>175 (0.3)</td>
</tr>
<tr>
<td>Lower one-third of lung only</td>
<td>1836 (2.7)</td>
</tr>
<tr>
<td>Multiple locations</td>
<td>45 (0.1)</td>
</tr>
<tr>
<td>Diffuse scarring</td>
<td>32 (0.0)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

*The table does not include 37 subjects with scarring at baseline who had missing data on location of scars.*

**Table 3. Association Between Pulmonary Scarring Detected by Baseline Chest Radiography and Subsequent Risk of Lung Cancer**

<table>
<thead>
<tr>
<th>Category</th>
<th>Lung Cancer Cases, No.</th>
<th>Lung Cancers With Scarring, %</th>
<th>Lung Cancer With Scarring in the Same/Opposite Lung, No./No.*</th>
<th>Risk of Lung Cancer Associated With Scarring, HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ipsilateral Lung Cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contralateral Lung Cancer</td>
</tr>
<tr>
<td>All lung cancer</td>
<td>809</td>
<td>122 (15.1)</td>
<td>91/75</td>
<td>1.5 (1.2-1.8)</td>
</tr>
<tr>
<td>Histologic subtype of lung cancer</td>
<td>349</td>
<td>54 (15.5)</td>
<td>40/30</td>
<td>1.6 (1.2-2.2)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>152</td>
<td>24 (15.8)</td>
<td>21/20</td>
<td>1.3 (0.8-2.0)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>97</td>
<td>13 (12.1)</td>
<td>9/7</td>
<td>1.2 (0.6-2.1)</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>268</td>
<td>37 (13.8)</td>
<td>28/24</td>
<td>1.3 (0.9-1.8)</td>
</tr>
<tr>
<td>Follow-up interval after baseline, y</td>
<td>2.01-4.00</td>
<td>34 (15.5)</td>
<td>27/21</td>
<td>1.5 (1.0-2.2)</td>
</tr>
<tr>
<td>4.01-6.00</td>
<td>143</td>
<td>24 (16.8)</td>
<td>17/13</td>
<td>1.8 (1.0-3.0)</td>
</tr>
<tr>
<td>6.01-12.00</td>
<td>178</td>
<td>27 (15.2)</td>
<td>19/17</td>
<td>1.6 (1.0-2.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

*Persons with bilateral scarring or bilateral cancer were counted as having scarring both in the same and in the opposite lung as the cancer. Persons with missing location data on scarring or cancer were not counted in these categories.*

**LUNG CANCER RISK IN RELATION TO PULMONARY SCARRING**

A total of 809 participants developed lung cancer, of which 455 (56.2%) involved the right lung and 308 (38.1%) involved the left lung. These included 7 bilateral cancers. The remaining lung cancers occurred in other locations (ie, main stem bronchus or carina, n=15) or had missing data on location (n=38). According to histologic subtype, 349 lung cancers (43.1%) were adenocarcinoma, 152 (18.8%) squamous cell carcinoma, and 107 (13.2%) small cell carcinoma. Other non–small cell subtypes accounted for 19.4% of lung cancers, while the remainder (5.4%) had no specified subtype.

Among those who were diagnosed as having lung cancer, 15% had evidence of pulmonary scarring at baseline (Table 3). Thus, a baseline diagnosis of pulmonary scarring was associated with an increased risk of lung cancer during subsequent follow-up (HR, 2.2; 95% confidence interval [CI], 1.8-2.7). This association was attenuated but remained significant with adjustment for age, sex, race, and cumulative cigarette smoking (adjusted HR, 1.5; 95% CI, 1.2-1.8) (Table 3). Individuals with bilateral scarring had a greater risk of lung cancer than those with unilateral scarring (adjusted HRs, 1.8 [95% CI, 1.4-2.4] and 1.3 [95% CI, 1.0-1.7], respectively). Similarly, diffuse scarring (most of which was bilateral) was associated with a higher risk of lung cancer (adjusted HR, 2.6; 95% CI, 1.8-3.8) than the risk associated with discrete scarring (adjusted HR, 1.3; 95% CI, 1.1-1.6). Additional adjustments for family history of lung cancer, educational attainment, or history of COPD did not change the estimates (data not shown). Therefore, all HRs presented in the remainder of this section are adjusted only for age, sex, race, and smoking. The association between scarring and lung cancer did not vary across strata defined by smoking status (P = .84 for interaction) or history of COPD (P = .18 for interaction).

We next examined cancer risk for each lung in relation to scarring in that lung, using the lung as the unit of analysis. Scarring in the right lung was strongly associated with an increased risk of right lung cancer (HR, 2.2; 95% CI, 1.7-3.0), whereas the association of left lung cancer with left lung scarring was weaker and nonsignificant (HR, 1.2; 95% CI, 0.8-1.9). As given in Table 3, when we considered the left and right lungs together, we found an increased risk of ipsilateral lung cancer associated with scarring (HR, 1.8; 95% CI, 1.4-2.4) but not for contralateral lung cancer (HR, 0.9; 95% CI, 0.7-1.2). Also given in Table 3, scarring was associated with a sig-

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nificantly increased risk of ipsilateral adenocarcinoma (HR, 2.1; 95% CI, 1.4-3.2), and the associations were similar in magnitude, although not significant, for ipsilateral squamous cell carcinoma (HR, 1.5; 95% CI, 1.0-2.4) and ipsilateral small cell carcinoma (HR, 1.7; 95% CI, 0.8-3.6). Scarring was not associated with risk of contralateral lung cancer of any subtype.

Table 3 further describes the association with baseline scarring according to follow-up interval. An association between baseline scarring and ipsilateral lung cancer appeared to be present within each interval of follow-up after baseline CXR (HRs, 1.6-2.1, extending out to 12 years of follow-up). Also, risk of ipsilateral lung cancer was similarly elevated with diffuse scarring (HR, 2.0; 95% CI, 0.6-6.2) and discrete scarring (HR, 1.7; 95% CI, 1.3-2.3). In contrast, no association between scarring and contralateral cancer was seen regardless of follow-up interval or extent of the scarring (diffuse vs nondiffuse). Finally, after we excluded subjects with baseline CXRs suggestive of cancer, the association between scarring and ipsilateral cancer still persisted (HR, 2.0; 95% CI, 1.4-2.7).

Because of the frequent clinical observation of pulmonary scars in the proximity of lung cancers, it has been speculated that scars may induce lung cancer. The PLCO Trial, a large prospective study of the effectiveness of CXRs in screening for lung cancer, provided a framework for us to evaluate this hypothesis. We observed increased risks of lung cancer following a CXR diagnosis of pulmonary scarring, confirming findings of a previous analysis of PLCO data that explored associations between a range of pulmonary abnormalities and several outcomes.13 To our knowledge, our study is the first to use CXRs to relate the laterality of pulmonary scarring to the risk of lung cancer and to characterize the temporal sequence between scarring and the subsequent development of cancer.

It is notable that the elevated risk was found for cancers that were ipsilateral, but not contralateral, to the scarring and/or fibrotic lesions. This finding supports the hypothesis that scarring is associated with a localized process of tissue damage and repair that may contribute to development of cancer. The absence of an increased risk of contralateral cancer argues against the alternative explanation that scarring is a marker for a systemic disease process that increases cancer risk more broadly. Indeed, the greater risk of lung cancer in persons with bilateral scarring (compared with those who had only unilateral scarring) can be explained by the fact that the former group has 2 lungs at increased risk of cancer (instead of only 1), rather than by a difference in the disease process between the 2 groups. Likewise, lung cancer risk was especially high in persons with diffuse scarring, but this elevation arose because diffuse scarring was largely bilateral, while the magnitude of lung cancer risk ipsilateral to the scarring was actually similar for diffuse and discrete scarring.

Another important finding of our study regards the temporal pattern of lung cancer in relation to scarring. Previous evidence has been inconclusive on whether scarring causes or results from the cancer (ie, reverse causality). We found that lung cancer risk in relation to pulmonary scarring remained elevated for 12 years following CXR detection of scarring and was similar in magnitude in each time interval. Although reverse causality could still play a role, we saw no association between detection of the 2 conditions (scarring and lung cancer) on the same baseline film, and an elevated risk of lung cancer related to scarring was observed even when we excluded subjects who had baseline CXRs suggestive of lung cancer. Indeed, reverse causality becomes less likely as an explanation for the associations seen during extended follow-up (Table 3) because it seems improbable that a lung cancer that had caused a scar would have remained otherwise silent for many years subsequently.

After considering alternative explanations, we suggest that our observations are consistent with a possible pathway connecting pulmonary scarring (or closely associated lung processes, such as inflammation) and the subsequent development of lung cancer. To put our findings into context, there are other lines of evidence that support a role for pulmonary inflammation and scarring in the development of lung cancer.22 Fibrotic processes may induce or promote lung cancer by causing excessive or persistent localized inflammation at sites of wounding and repair.23 Inflammatory processes have been shown to contribute to damage of the lung epithelium.24 Cytokines such as tumor necrosis factor and interleukin 1, secreted by infiltrating macrophages and lymphocytes, stimulate the production of other cytokines as well as proliferation of lung epithelial cells.9 Inflammatory cells also produce reactive oxygen species that can induce chromosomal strand breaks, leading to DNA mutations when inaccurate repairs accumulate.22 Consistent with these findings, inflammatory injury due to pulmonary scarring is characteristic of inflammatory lung diseases, such as COPD and pneumonia, which are themselves associated with an increased risk of lung cancer independent of smoking.26 High serum levels of C-reactive protein, which is a marker of inflammation, have been shown to be associated with an elevated risk of lung cancer.24 Finally, recent evidence links polymorphisms in inflammation-related genes, such as interleukin 1α and interleukin 1β, to altered susceptibility to lung cancer.25

A limitation of our study was the reliance on CXRs to diagnose the presence of scarring. Investigators from the PLCO Trial previously reported only fair agreement in scarring diagnoses across successive CXRs, which were interpreted independently of one another (ie, κ=0.40 for paired CXRs obtained at different times and interpreted by different radiologists).13 This level of agreement is similar to that for other CXR diagnoses, such as COPD and emphysema (κ=0.38) and bone and soft tissue lesions (κ=0.45).13 Without a reference test, we could not estimate the sensitivity and specificity of CXRs for detecting true pulmonary scarring lesions. Another limitation of our study was that we were not able to fully characterize the relationship between locations of the scars and subsequent cancers owing to different descriptive classifications because scarring was reported according to the region of the lungs on a single-view posteroanterior CXR, whereas cancers were localized according to the lobe of the lungs.
The association of scarring and lung cancer appeared stronger for lesions in the right lung than in the left lung. We believe that this difference could be due to misclassification of noncancer lesions as scars in the left lung. There were many more scars reported in the left lung, particularly in the lower part, than in the right lung. The position of the heart in the left lung partly obscures the left lower lobe on the CXR, which may cause difficulty in distinguishing scarring from other lesions, such as linear atelectasis. Also, pleural scarring (eg, due to asbestosis) can be mistaken for scarring within the lung itself, and this error may occur more commonly in the left hemithorax than in the right because of the unique anatomy of the left lung. Alternatively, one could hypothesize that some types of scarring common in the left lower lobe may not be related to cancer risk. For example, in patients with cardiac disease or following abdominal surgery, the left lower lung often becomes atelectatic, which may lead to scarring over time. Because we did not have strong evidence that the biological effects of scarring would differ for the 2 lungs, we considered the 2 lungs together in our analyses. To the extent that the results for the left lung may have reflected a stronger likelihood of misclassification of scars and perhaps less deleterious scarring processes, combining the analyses for the 2 lungs would have underestimated the HRs for ipsilateral cancer. More generally, we note that the difficulties with CXR diagnosis of scarring that we discuss herein together serve to attenuate the apparent association between scarring and cancer and that future detailed evaluations with a better imaging modality (eg, computed tomography) would be expected to provide more definitive evidence regarding this association.

As the major risk factor for lung cancer, cigarette smoking contributed to some of the excess of lung cancer risk associated with scarring. Scarring was more common among current and former smokers and was related to the cumulative amount of tobacco use. However, an association between scarring and lung cancer persisted even after adjustment for smoking. Likewise, we observed a similarly elevated HR associated with scarring across strata of smoking status or previous diagnosis of COPD, which is more prevalent among smokers. We therefore believe that the increased lung cancer risk among individuals with pulmonary scarring is not entirely explained by smoking habits. We were unable to examine other medical conditions or exposures, such as work-related exposures, as the source of scarring because such data were not collected in the trial.

Our conclusions were supported by a number of strengths of the study, which included prospective collection of CXR and lung cancer data and a large sample size. Although diffuse fibrosis frequently manifests clinically with respiratory symptoms, less extensive pulmonary fibrosis is usually clinically silent. This situation has complicated the systematic study of scarring and its potential adverse outcomes. Thus, a strength of our study was that it incorporated CXR diagnoses of scarring and/or fibrosis from mostly asymptomatic subjects, who received a CXR examination for screening purposes rather than evaluation of scar-related symptoms. Also, detection bias was minimized because lung cancer in subjects with and without scarring would be equally likely to be detected by CXR screening and subsequent evaluation.

In conclusion, our findings provide support for a model whereby pulmonary scarring and localized inflammation promote subsequent development of lung cancer. Lung scarring can result from a variety of infections, environmental exposures, and pulmonary diseases. Further research is needed to elucidate the biological mechanisms underlying the associations between pulmonary scarring, inflammation, and lung cancer. Additional research is also necessary to determine whether asymptomatic persons with CXR-detected pulmonary scarring would benefit from clinical monitoring for the development of lung cancer.

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REFERENCES

A n association between cancer and chronic inflammation has been recognized for centuries. Hermann Boerhaave of Leiden (1668-1738) wrote that inflammation might lead to “scirrhus” (scar formation), and that scirrhous “may change to cancer under unfavorable circumstances.” Many of the cancers related to inflammation are associated with specific viral, parasitic, or bacterial infections (eg, hepatitis C, papillomavirus, chistosomes, Helicobacter), others to chronic nonspecific infections (eg, chronic urinary catheters with recurrent infections, chronic cholecystitis, draining cutaneous ulcers from osteomyelitis), and still others to noninfectious chronic inflammatory processes, such as ulcerative colitis, reflux esophagitis, chronic pancreatitis, and atrophic gastritis.

With this large body of data in mind, the historical, mostly anecdotal, reports that lung cancers occasionally arose in pulmonary scars (so-called scar carcinomas) were consonant with these observations in other organs. Detailed statistical estimates of the incidence and risk of these cancers, however, awaited more recent studies of larger groups, such as the 2007 British study of lung cancer incidence in patients with idiopathic pulmonary fibrosis. These patients showed a significant increase in lung cancer risk.

In this issue of the Archives, Yu et al have performed a systematic study of the risk for lung cancer associated with pulmonary scarring, presumably related to prior or ongoing inflammation. They included more than 66,000 cancer-free participants, aged 55 to 74 years, who received baseline chest radiography as part of their participation in the PLCO Screening Trial. Subjects were followed up for up to 12 years. The data were adjusted for variables such as age, sex, race, and smoking.

Over the course of the study, subjects with evidence of pulmonary scarring on their screening examination had a risk for lung cancer in the ipsilateral lung almost twice that of the subjects without scarring.

What are the common threads linking the causes of inflammation-associated cancers? In addition to clinical observations, the inflammatory milieu has been proven experimentally to be conducive to cancer development. The primary effector cells of inflammation, phagocytes such as neutrophils and macrophages, produce a wide variety of toxic substances and metabolites that are proven carcinogens and can cause genetic damage and genetic instability in the adjacent “innocent bystander” tissues. Furthermore, the inflammatory microenvironment can contain high concentrations of mediators such as growth factors, cytokines, and chemokines, that can trigger proliferation, activate antiapoptotic signaling pathways, promote loss of adherence and invasion, and promote angiogenesis.

Finally, can these cancers be prevented? While there is an increased risk of lung cancer in the presence of pulmonary scarring, the overall risk appears relatively low. In the study by Yu et al, 91 cancers arose in the ipsilateral scarred lungs of 5041 subjects with pulmonary scarring, and the incidence did not appear to be increasing over time. Chemoprevention trials in otherwise healthy people require effective agents that are extremely safe—so safe that they can be taken for long periods with negligible risk. There are no agents proven useful for this purpose in lung cancer. Studies of genetic susceptibility may in the future suggest why certain individuals with chronic inflammation get cancer and others do not. Recent studies on screening individuals at higher risk of lung cancer show the promise of reducing mortality. Perhaps individuals with pulmonary scarring may ultimately benefit from screening for cancer.

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