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Asbestos, Pleural Plaques, and Lung Cancer: Untangling the Relationships

Asbestos exposure remains an important public health and clinical problem; industrial use has been significantly reduced but not eliminated (1). Significant risks of asbestosis, lung cancer, malignant mesothelioma, and other effects continue for many former exposed workers and family members with prior paraoccupational exposure. Pleural plaques, or localized thickening of the parietal pleura, are the most common consequence of asbestos exposure (2). Assessing the relationship between pleural plaques and lung cancer risk is particularly timely now that low-dose computed tomography (LDCT) screening of high-risk tobacco smoking–exposed populations has been demonstrated to reduce mortality. High-resolution computed tomographic screening policy largely focuses on tobacco smokers and inadequately addresses persons with significant risk from asbestos or other occupational carcinogens.

Brims and colleagues (3) in this issue of the *Journal* (pp. 57–62) provide very important data on the relationship of pleural plaques to lung cancer risk. Asbestos exposure causes lung cancer and produces pleural plaques. The paper by Brims and colleagues addresses the important question, "Among persons with known moderate-heavy asbestos exposure, do those with pleural plaques have increased lung cancer risk relative to similarly exposed persons without plaques?" All participants were known to have significant asbestos exposure. The investigators used Cox regression analyses to assess whether pleural plaques were associated with an elevated hazard ratio (HR) for lung cancer. The analyses were adjusted for asbestos exposure, sex, tobacco smoking, and the presence of asbestosis. Pleural plaque status was determined from the most recent radiographic imaging (either CT or chest radiography) or the most recent imaging at least 1 year before cancer diagnosis.

The authors conclude that plaques *per se*, when adjusted for the extent of asbestos exposure and other risk factors, do not enhance the risk of lung cancer. This has important implications for patient counseling and selecting participants to optimize the benefit–risk relationship for individuals and programmatic cost-effectiveness of LDCT screening.

This study has unique strengths. The results were consistent in two distinct, well-defined cohorts. Western Australian crocidolite asbestos miners and community members with extensive residential exposure comprise the first cohort. The second cohort is a nationwide collection of workers in occupations well known to have extensive exposure. The Australian surveillance program is particularly effective at accurately assessing each participant's individual cumulative exposure (4–7). The long latency between initial asbestos exposure and development of malignancy requires long-term studies; the Australian program includes annual

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follow-up since 1990 and well-standardized radiographic methods. Specificity of plaques for asbestos exposure was increased by limiting the definition to bilateral plaques to reduce the likelihood of observed thickening due to chest trauma or a prior infection.

Several technical limitations do not seriously reduce the impact of the data. Asbestos fiber–type exposures were heterogeneous; the Western Australian cohort was exposed largely to crocidolite, whereas the national worker group had mixed fiber types, including multiple amphiboles and chrysotile types. In the national worker group, the association of cumulative exposure with lung cancer risk did not reach traditional statistical significance (HR, 1.81; 95% confidence interval, 0.94–3.50). The optimal exposure covariate metric may not be log-linear or dichotomous as used in the regression analyses. The potentially complex causal interactions among exposure, pulmonary fibrosis/asbestosis, plaque, cancer, age, and smoking constrain drawing mechanistic conclusions (8), but they have less impact on the practical implications for counseling and screening.

Pairon and colleagues previously reported results for 5,400 participants in a 6-year follow-up study of asbestos-exposed workers in a CT screening program in France (9). In contrast to the study by Brims and colleagues, they found a significantly elevated HR (HR, 2.41; 95% confidence interval, 1.21–4.85) for pleural plaques and lung cancer when adjusting for smoking and asbestos cumulative exposure. The difference might be due to lower overall cumulative exposure in the French study or to not adjusting for asbestosis. Both the Pairon and Brims studies are much more powerful than earlier approaches to this important topic (10).

The strengths of the study by Brims and colleagues limit its policy implications for screening groups with less–well-characterized exposure. Their finding that plaques do not in themselves confer risk of lung cancer depends on accurate and precise estimates of cumulative exposure (4–7). Both the Western Australian crocidolite miners/residents and the cohort of workers in occupations with well-known asbestos exposure had clear *a priori* indication of significant exposure and reasonably good estimates of cumulative exposure. Therefore, finding bilateral plaques did not add significant new information about each subject's exposure. However, more general populations have less precise information about asbestos exposure. Many workers may be unaware of prior exposure or may have forgotten owing to the long latency. In a study of male LDCT participants selected for smoking rather than asbestos exposure, most with plaques were unaware of prior exposure (11).

Hence, when exposure misclassification or inaccurate quantification is likely, the presence of bilateral pleural plaques is likely to confer useful exposure information. Plaques are a biomarker of exposure, albeit imperfect; plaques increase the likelihood of sufficient exposure to seriously consider preventive interventions such as LDCT screening or tobacco control program enrollment.

Several reports show that LDCT screening of exposed workers detects lung cancers with yields similar to those of high-risk smokers (12–14). A meta-analysis (12) showed that the baseline prevalence of cancers was similar in asbestos workers and in heavy smokers (about 1%). Many of the malignancies were in an early stage and therefore potentially curable. The studies are relatively small and generally limited to initial tests, and they have not examined impact on population mortality.

LDCT screening of high-risk individuals appears advisable even if not yet empirically proved by large prospective trials. The study by Brims and colleagues (3) shows that exposure rather than plaque determines risk, and therefore persons with known moderate to heavy exposure should not be denied screening if they do not have plaques. Conversely, for a general population in which exposure classification and quantification are more ambiguous, detecting bilateral plaques should prompt the clinician to assess exposure history in detail, consulting industrial hygienists or occupational medicine specialists as appropriate. Although the study by Brims and colleagues focuses on plaques *per se*, additional analyses may develop integrated individual risk–benefit profiles considering multiple personal factors such as smoking, asbestosis, age, and comorbidities. ■

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ILC2 the Rescue?

In this issue of the *Journal*, Monticelli and colleagues (pp. 63–72) are the first to describe innate lymphoid cell (ILC) subsets in donor lungs before and after reperfusion in allograft transplantation, and they correlate the ILC subsets with primary graft dysfunction (PGD) (1). In a cohort of patients who underwent lung transplant for chronic obstructive pulmonary disease or interstitial lung disease at the University of Pennsylvania, there was a selective decrease in the percentage of group 2 ILC (ILC2s) in patients who developed PGD. Those patients who did not have PGD had an increased frequency of ILC2s after allograft perfusion, suggesting that these cells may protect against PGD.

ILC2s comprise one subset of the five major groups of ILC, which also include natural killer (NK) cells, lymphoid tissue inducer cells, ILC1s, and ILC3s (2). These subsets are defined by the transcription factors that regulate their differentiation and the cytokines that they secrete. Although NK cells were discovered more than 40 years ago (3, 4) and lymphoid tissue inducer cells were identified over 20 years ago (5), the other ILC subsets were first described within this decade. ILC1s produce IFN-γ as their signature cytokine and have Tbet as their master transcription factor. ILC3s produce IL-17A and IL-22 while using RORc as the key transcription factor (6).

The increased number of ILC2s in the lungs of patients who did not have PGD is particularly interesting and may be relevant to protection against PGD. ILC2s express the transcription factor GATA-3 while secreting IL-5, IL-9, IL-13, and amphiregulin, in addition to IL-4 under certain circumstances (6). It is tempting to consider the possibility that the increased number of ILC2s in patients who did not experience PGD may have provided protection against disease as a result of the cytokines they produce. Several cytokines produced by ILC2s may promote tissue repair in the lung. For instance, amphiregulin is a member of the EGF (epidermal growth factor) family and is related to TGF-α (transforming growth factor α) (7). Amphiregulin promotes the restoration of tissue integrity after damage from either acute or chronic inflammatory processes. Amphiregulin is produced not only by ILC2s but also by epithelial cells and immune cells that are predominantly, but not exclusively, associated with type 2 responses, such as mast cells, basophils, and eosinophils. IL-4 and IL-13 promote macrophage differentiation toward alternatively activated macrophages that produce TGF-β, and these cells are also important in tissue repair (8). A previous study demonstrated that IL-9 produced by ILC2 acts in an autocrine manner to amplify ILC2 survival and function, and in a mouse model of *Nippostrongylus brasiliensis* infection showed that IL-9 was crucial for restoring pulmonary tissue integrity and lung function (9). Although amphiregulin and IL-13 are involved in tissue repair, they also contribute to fibrosis by depositing connective tissue proteins such as collagen and fibronectin in sites of injury. The balance of the restoration/fibrosis response in the lung and the fine-tuning mechanisms that control repair versus an overexuberant fibrotic response are still being defined.

Although the data in the work by Monticelli and colleagues are very interesting, there are several caveats that must be recognized in interpreting their data (1). First, the number of subjects studied was very low. For example, the authors began with 18 subjects but were variably able to obtain meaningful pre- and postperfusion ILC data from as few as 3 subjects per endpoint. Data were obtainable from 3 to 5 subjects in the PGD group and from 3 to 11 subjects in the non-PGD group. This weakens some of the conclusions that were made regarding the significance of the associations with reperfusion injury and the development of PGD. Therefore, it is difficult to know the generalizability of the data. Another possible important confounding factor is that there was on average a sizable 94-minute difference in ischemia time between patients with and without PGD, which despite the low number of patients almost reached statistical significance. This could also be likely a critical reason for graft failure, perhaps even more so than the difference in ILC populations between patients with and without PGD.

Despite these limitations, this work makes some important contributions. For the first time, the authors demonstrate the feasibility of live-cell isolation and high-resolution flow-cytometric phenotyping of immune cell populations (CD4 T cells, NK cells, ILC1s, ILC2s, and ILC3s) from small biopsy specimens for up to 18 patients. Furthermore, the unique design of this cohort study gave the investigators an opportunity to track dynamic changes in the ILC family subset composition by examining donor grafts before and immediately after reperfusion, and is highly innovative. Lastly, although the sample size was small for patients who developed PGD, the investigators were still able to observe statistically significant changes among both ILC1s and ILC2s that provide preliminary support for an association between ILC population changes and PGD development. Thankfully, the authors do not overstate the strength of their findings and acknowledge that further analysis in a larger cohort will be necessary to examine whether these cells play a mechanistic role in lung injury or repair during graft rejection.

The data from this study complement previous publications in which the numbers of neutrophils, macrophages, and lymphocytes

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