

## WHAT'S NEW IN LUNG CANCER?

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### Asbestos or Asbestosis?

There are three primary hypotheses regarding the relationship between asbestos exposure and lung cancer. [H1] proposes that an increased risk of lung cancer only occurs among individuals with asbestosis. [H2] proposes that lung cancer and pulmonary fibrosis are independent manifestations of asbestos exposure, both of which exhibit a dose response relationship with asbestos exposure. [H3] proposes that there is a dose response relationship between asbestos exposure and lung cancer risk, but that there is no threshold for an increase in risk. Henderson et al. reviewed nearly 400 references from the literature on the issue of lung cancer and asbestos exposure. The data are most consistent with a linear dose response relationship with a threshold (see below).

### Fiber Burden Studies

Karjalainen et al. (1994) demonstrated that fiber burden is a predictor of lung cancer risk, independent of cigarette smoking and asbestosis. These researchers showed that a fiber burden of one million amphibole fibers per gram of dry lung (as determined by SEM) is associated with an increased risk of lung cancer, and the findings were statistically significant for adenocarcinoma and for lower lobe tumors. Fiber burdens in this range are associated with exposures that lead to asbestosis in some individuals. Roggli and Sanders (2000) studies 234 cases of lung cancer, including 70 with asbestosis and 44 with pleural plaques (but without asbestosis). A fiber burden equivalent to that seen in individuals with asbestosis (i.e., one million amphibole fibers per gram of dry lung or 50,000 amphibole fibers 5  $\mu$ m or greater in length per gram of wet lung as determined by SEM) was observed in 82% of patients with histologic asbestosis but in only 10% of patients with plaques and only 5% of those with neither asbestosis nor plaques. Most of the patients with asbestosis and fewer than 50,000 fibers per gram had grade 1 disease.

Our database includes 273 patients with carcinoma of the lung for whom fiber analyses of lung tissue samples have been performed (Table 1). Asbestosis was also present in 74 of these cases and pleural plaques in 54. The median asbestos body counts for patients with asbestosis was about 40 times greater than those with pleural plaques, and the median uncoated fiber count by SEM was about 10 times higher. Similarly, the median asbestos body counts for patients with plaques was about 10 times higher than those with neither asbestosis nor plaques, and the uncoated fiber count by SEM was

about 1.5 times higher. Although all patients had some history of asbestos exposure, the fiber burden for the 145 patients with neither plaques nor asbestosis was within our normal range in nearly one third of the cases. The predominant fiber type was amosite. Smoking history was available in 180 cases, and 164 were current or ex-smokers.

It is the author's opinion that lung cancer can be related to asbestos if the patient has asbestosis or a lung amphibole fiber burden equivalent to that seen in patients with asbestosis. In patients with an adequate sampling of lung parenchyma and an absence of asbestos bodies in histologic sections, the odds are approximately 100:1 that the fiber burden in such a case will not satisfy the Karjalainen criteria for an increased lung cancer risk. If asbestos bodies are present but there is no appreciable peribronchiolar fibrosis (i.e., no asbestosis), then a fiber burden analysis should be performed in such cases.

The study by Roggli and Sanders showed a very close correlation between histologic asbestosis and an amphibole fiber burden of greater than or equal to 50,000 fibers per gram of wet lung tissue by SEM. Therefore, it is unlikely that epidemiologic studies alone will be able to distinguish between H1 and H2.

### **Fiber Type**

All fiber types are associated with an increased risk of lung cancer. Criteria for relating amphibole exposure to lung cancer risk are discussed in the previous section. Chrysotile poses special problems in this regard. Studies examining the relationship between chrysotile asbestos exposure and lung cancer risk show a wide range of findings. Textile workers have a high risk and a very steep dose response curve, whereas friction product exposures show a risk that is not significantly different from that of the general population. Chrysotile miners and millers fall somewhere in between. It is the author's view that most of these discrepancies may be related to fiber dimensions and dose. Chrysotile does not accumulate within the lungs to the extent that the amphiboles do, so fiber burden analysis is not an accurate determinant of prior chrysotile exposure. The best indicator in such cases is the work history, with an exposure of greater than or equal to 25 fibers/cc-yrs associated with an increased lung cancer risk.

### **Synergism**

Numerous studies have indicated that there is a synergistic effect between cigarette smoking and asbestos exposure in the production of carcinoma of the lung. This means that the two risks are multiplied together to obtain the combined risk. Thus in an individual who did not smoke, the relative risk from smoking is 1 and the combined risk is 1 x the risk from asbestos exposure alone. Similarly, in an individual who smokes, if the risk from asbestos exposure is not significantly different from that of the background

population, the combined risk is 1 x the risk from smoking alone. Hence, *synergism only results in an increased lung cancer risk if the risk from both asbestos and smoking are significantly greater than 1.*

Hillerdal (1994) demonstrated a very modest increased risk of lung cancer (RR 1.43) for patients with parietal pleural plaques but without asbestosis. This small risk could be accounted for by the 10% of plaque cases in our study with a fiber burden exceeding 50,000 fibers per gram of wet lung. Plaque cases had on average a higher asbestos body and uncoated fiber count than cases with neither asbestosis nor plaques. Consequently, the latter group would have a lesser lung cancer risk than that observed for patients with plaques alone. Indeed, there is no evidence that the lung cancer risk for asbestos-exposed individuals with neither plaques nor asbestosis is significantly different from 1.0. Therefore, synergism plays no role in such cases, and the risk is the same as that for an equivalent cigarette smoker (unless the patient falls within the 5% who have a sufficiently elevated amphibole fiber burden by SEM).

### **Tumor Type and Location**

Carcinoma of the lung includes four basic histologic types: adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma. The distribution of histologic types in 895 cases of lung cancer studied in the author's laboratory is shown in Table 2. There is no significant difference in the histologic types of lung cancer between asbestos-exposed and non-exposed groups. Some studies have reported that lung cancers in asbestos workers are more common in the lower lobes, whereas others have reported them to be more common in the upper lobes. In the author's series, upper lobe cancers outnumbered lower lobe cancers by about 3:1 in patients with asbestosis, plaques only, and cases with neither plaques nor asbestosis.

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**TABLE 1. Asbestos Content of Lung Tissue in 273 Cases of Lung Cancer<sup>a</sup>**

	<u>N</u>	<u>AB/gm (LM)</u>	<u>N</u>	<u>UF/gm (SEM)</u>
Lung cancer plus asbestosis	74	28,600	71	180,000
Lung cancer plus PPP	54	710	54	19,200
Lung cancer (Other) <sup>b</sup>	145	68	137	12,400

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- a. Asbestos bodies per gram of wet lung tissue as determined by light microscopy (LM) and uncoated fibers 5  $\mu$ m or greater in length per gram of wet lung tissue as determined by scanning electron microscopy (SEM). Values reported as median.
- b. Cases of lung cancer with neither asbestosis nor PPP, or uninformative cases with respect to asbestosis or plaques. PPP = parietal pleural plaques.

**Table 2. Distribution of Histological Types in 895 Lung Cancer Cases With and Without Asbestosis\***

	<b>ASBESTOSIS</b>	<b>PPP<sup>a</sup></b>	<b>OTHER<sup>b</sup></b>	<b>REF. POP.<sup>c</sup></b>
Squamous cell carcinoma	56 (29%)	10 (24%)	182 (33%)	31 (31%)
Small cell carcinoma	30 (15)	9 (21)	69 (12)	11 (11)
Adenocarcinoma	79 (41)	16 (38)	226 (41)	39 (39)
Large cell carcinoma	22 (11)	7 (17)	70 (13)	19 (19)
Adenosquamous carcinoma	8 (4)	0 (0)	11 (2)	-
<b>TOTAL</b>	<b>195</b>	<b>42</b>	<b>558</b>	<b>100</b>

**a** PPP = parietal pleural plaques, no evidence of asbestosis

**b** No histologic evidence of asbestosis or biopsy of tumor only (no lung tissue sampled)

**c** 100 consecutive lung cancer cases collected at Baylor Affiliated Hospitals, 1979-1980.