



Are lung and pleural benign asbestos induced diseases a preliminary step in the pathogenic process of mesothelioma and lung cancer development?

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Occup. Environ. Med. 2005;62:663-664
doi:10.1136/oem.2005.021865

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the common cause without interaction hypothesis for peritoneal mesothelioma. On the other hand, benign chest diseases may also have been underestimated, either because they appeared only after the initial radiographic examination at the inclusion of the subjects in the cohort, or because they were too small to be apparent using conventional radiographic techniques.

The question of the mechanisms of asbestos induced cancers still remains open. It is of great importance to clarify further this question for scientific reasons, but also because the single sequential pathogenic process hypothesis is taken for granted in countries that compensate asbestos induced diseases only in cancer patients that exhibit chest abnormalities.

Occup Environ Med 2005;**62**:663–664.
doi: 10.1136/oem.2005.021865

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Competing interests: none declared

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Epidemiology

Are lung and pleural benign asbestos induced diseases a preliminary step in the pathogenic process of mesothelioma and lung cancer development?

M Goldberg

Commentary on the paper by Reid *et al* (see page 665)

Asbestos is and will remain for decades a major public health problem in many countries: it has been estimated that in Western Europe alone, about 500 000 cancer deaths due to asbestos exposure will occur up to 2029.¹ Apart from being of public health concern, there are some major scientific questions about the health effects of asbestos exposure: What are the specific chemical and morphological characteristics of asbestos fibres involved in carcinogenesis? Is fibre persistency in the lung parenchyma an important determinant of the risk of developing a malignant mesothelioma? Is the potency for lung cancer induction the same regardless the type of asbestos fibres (chrysotile, amosite, crocidolite, tremolite, anthophyllite)? Is lung or pleural fibrosis a preliminary step in the process of mesothelioma and lung cancer development?

Research done by pathologists, biologists, and epidemiologists, provides findings that may be crucial to answer these questions.² It would be of utmost importance to better understand the relations between benign pleural diseases (plaques and pleural calcification, pleural thickening), pulmonary fibrosis (asbestosis), and the risks of lung cancer and malignant mesothelioma. Most studies that looked at asbestos induced benign pleural and/or lung diseases among patients suffering from cancer found that these diseases were also present.³

Both benign and malignant diseases have been associated with asbestos exposure. To understand the mechanisms of asbestos induced cancers, we should understand whether the strong association between benign and malignant asbestos related diseases only reflects the common cause—asbestos—without being involved in the same pathological process, or whether benign diseases are a preliminary step towards

cancer. If benign pleural and lung diseases are on the pathways towards cancer, an additional specific question is whether this is a necessary step, or if benign pleural and lung diseases only increase the risk of developing a cancer by interacting with other factors, such as tobacco smoke.

Animal data give some indications that fibrosis of the mesothelial sera may precede malignant mesothelioma development.⁴ Animal experimentation also showed that lung cancer develops more frequently among rats that developed alveolar inflammation and fibrosis than among those who did not.⁵ However, these studies in favour of a carcinogenic mechanism involving inflammation and fibrosis as a preliminary stage of cancer had some limitations,⁶ and do not provide sufficient support for the hypothesis of a single pathogenic process for benign and malignant asbestos induced disease.

Epidemiological studies considering the association between asbestos exposure and cancer of the lung or malignant mesothelioma tested whether, when adjusting for asbestos exposure, the excess cancer risk disappeared for those with no history of chest radiographic abnormalities (single sequential pathogenic process hypothesis), or remained at the same level (common cause without interaction hypothesis), or was still raised but at a lower level (common cause with interaction hypothesis).

In cohort studies of asbestos workers, where chest radiographs and estimates of cumulative exposure were available, findings were not consistent: some found that, when adjusting for cumulative exposure to asbestos, the lung cancer risk was not increased among those having pleural plaques or radiological symptoms of asbestosis compared to those without radiological abnormalities, whereas some found

such an increased risk.^{6,7} Contradictory results were also published about pleural plaques or asbestosis and malignant mesothelioma.⁸⁻¹⁰ In a case-control study of lung cancer of hospital patients, Wilkinson and colleagues¹¹ showed that the increase of the odds ratios associated with asbestos exposure was of the same order among subjects with fibrosis radiographic symptoms and among subjects without abnormalities.

In this context, the study of Reid *et al*, published in this issue,¹² brings new important findings about the relations between exposure to crocidolite asbestos, benign lung and pleural diseases, and the risk of malignant mesothelioma. Unique features of this cohort study are the long follow up, the availability of good quantitative estimates of asbestos exposure for every subject included in the cohort, as well as standardised chest radiographs. The investigators could thus show that for the same level of asbestos exposure, the risk of pleural mesothelioma was not different for subjects with and without radiological signs of lung and pleural fibrosis, whereas the risk of peritoneal mesothelioma was higher for those showing radiological signs. However, the risk of peritoneal mesothelioma associated with benign pleural diseases was lower when adjustments were made for asbestos exposure, indicating that there was some excess risk due to benign chest diseases.

These results are in favour of the common cause without interaction hypothesis for pleural cancer, pleural abnormalities and asbestosis being proxies of asbestos exposure without bearing a specific contribution to the increase in the risk of mesothelioma. For peritoneal cancer, the findings give some strength to the common cause with interaction hypothesis. There are however several questions that remain open. First, the cohort was exposed to crocidolite asbestos, while other types of asbestos—especially less biopersistent forms—may act differently during the carcinogenic process. Another concern is exposure assessment: as the authors acknowledge, the higher exposures may have been underestimated. In such a case, as mesothelioma of the peritoneum is associated with higher cumulative exposure than pleural mesothelioma, even if benign chest diseases were not involved in the carcinogenic process, one would expect that some relation between radiographic abnormalities due to heavy asbestos exposure would still be apparent after adjusting for asbestos exposure.

Thus, the findings from the study by Reid *et al* do not totally discard