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The Attribution of Lung Cancer to Asbestos

To the Editor:

In the January 1992 issue of *Chest*, Dr Takumi Kishimoto[1] reported a study of the association between asbestos body concentrations in lung tissue and autopsy evidence of various cancers. He observed that concentrations of 500 or more asbestos bodies per 5 g of lung tissue (wet) were found in 89 percent of 19 cases of mesothelioma, 38 percent of 104 cases of lung cancer, 37 percent of 62 cases of gastric cancer, and 28 percent of 45 cases of colon cancer, but in only 10.5 percent of 200 control autopsies performed during the period from 1984 to 1989. These results were obtained in the city of Kure, a major Japanese shipbuilding center for warships since the 1920s.

He uses the figures for mesothelioma and lung cancer to state in his discussion that almost all mesotheliomas were induced by asbestos and that about 40 percent of the lung cancers were related to asbestos exposure. His conclusion about mesothelioma is probably correct in a shipbuilding area, since no specific cause for this disease other than asbestos or asbestiform fibers has been established by epidemiologic methods, and there are consequently no well-known confounding agents to be adjusted for.

For lung cancer, however, his conclusion is in error for the following reasons. First, his study is based on autopsy data from a case-control investigation at one hospital. There is no information on sources of potential bias that could be engendered by failure to establish whether the cancer cases were representative of cases in a defined population at risk and whether the controls were representative of the population that gave rise to the cancer cases. These two criteria must be satisfied to obtain a valid set of data. Selection bias may occur if the hospital is not the only one to serve the city of Kure and its suburbs and does not admit all cancer cases in the population at risk. There is also no information that the cancer series and the controls were matched by age and sex or that these factors were adjusted for in the analysis. Also unknown is what proportion of deaths were actually investigated at autopsy in the two groups.

Second, the primary confounding agent for lung cancer is smoking. There is no information on how the groups compared in this respect and whether adjustments were made if necessary. There is experimental evidence that smoke inhibits asbestos clearance.[2]

Third, there is no information on the frequency of asbestosis in the groups. This is important because there is evidence that asbestosis is a precursor of lung cancer attributable to asbestos.[3,4]

Fourth, and most important, is Kishimoto's failure to recognize that association alone does not establish a causal relationship.[5] If it did, we would have to conclude that the declining stork population is the cause of the associated declining human birth rate in Europe in 1965 to 1975.

Since most lung cancer cases are due to smoking, it is necessary to establish an elevated relative risk (RR) for asbestos exposure after controlling for smoking. When this is done, the proportion of cases due to asbestos, the attributable risk (AR), can be estimated by a simple formula,

$$AR = \frac{RR - 1}{RR}.$$

The RR for lung cancer among people in shipyard counties in the United States was estimated by Blot et al[6] (Kishimoto's reference 11) to be 1.11 in the period from 1950 to 1969. This means that only 9.9 percent of the lung cancer deaths were attributable to asbestos, at least in part. The AR may be even lower in the later period studied by Kishimoto, 1984 to 1989, if asbestos exposure was better controlled in Japan during the last two decades, as it was in the United States.

It should be kept in mind that elevated concentrations of asbestos bodies in lung tissue are only estimates of exposure. They cannot be used to establish a causal relationship with a disease like lung cancer, which is so common in the general population.

Finally, Kishimoto distorts the findings of Kannerstein and Churg[7] (his reference 25) when he says that "the type of lung cancer induced by exposure to asbestos has been mainly peripheral adenocarcinoma in the inferior lobes." While these authors did find that lung cancer was more common in the lower lobes among exposed cases than among unexposed control cases of lung cancer, they found no difference in the distribution of lung cancers by cell type or position in the lung (peripheral versus central), and they did not stratify their data in such a way that they would support Kishimoto's statement.

William Weiss, M.D.,
Emeritus Professor of Medicine,
Hahnemann University,
Philadelphia

Reprint requests: Dr. Weiss, 3912 Netherfield Road, Philadelphia, PA 19129

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To the Editor:

I would like to reply to Dr Weiss's comments on my article.[1]

1. Autopsied cases of lung cancer represent about 40 percent of the cases of lung cancer that were treated in Kure Kyosai Hospital in the period of our study. About 80 percent of the cases of lung cancer in our hospital occurred in men, and the incidence of lung cancer in men was significantly higher than in other districts in Japan. We published these data in *Chest* in 1988,[2] and the complete data from these lung cancer cases is now in press in another journal.[3] I hope that Dr Weiss will take a look at that article.

2. The relationship between smoking and lung cancer is an important point. We have already submitted our data on this relationship to a Japanese journal. Almost all asbestos-exposed patients with squamous cell and small-cell-type cancers were heavy smokers, but about 40 percent of adenocarcinomas of the lung occurred in patients who were nonsmokers or not heavy smokers.

3. Eighteen cases of lung cancer in our article were asbestosis, and five cases had evidence of pleural plaques. Other cases had no typical pathologic changes of asbestosis.

4. The volume of asbestos used in Japan in the period from 1920 to 1990 is higher than that used in the United States in the period from 1950 to 1969. Since the volume of asbestos imported into Japan in the five years of our study was the largest in the world, the

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incidence of lung cancer induced by asbestos exposure would be expected to be higher than that based on the data of Blot et al.[4]

5. We have previously reported the histologic types of lung cancer induced by asbestos exposure in our study group: there were 26 cases of adenocarcinoma, 13 cases of squamous cell carcinoma, and one case of small cell carcinoma of peripheral origin.[2] We are currently preparing these data in detail for submission.

Takumi Kishimoto, M.D., F.C.C.P.,
Chief of Clinical Investigation,
Kure Kyosai Hospital,
Kure, Japan

Reprint requests: Dr. Kishimoto, 231-37 Higashiune, Okayama 701-02, Japan

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Small-Volume Nebulizers versus Metered-Dose Inhalers

To the Editor:

Several recent articles in *Chest* have suggested that economy and quality assurance demand switching from small-volume nebulizers (SVNs) to metered-dose inhalers (MDIs). We believe that, when viewed critically, these studies do not support that conclusion.

In the February 1992 issue of *Chest*, Alvine et al[1] made much about the mechanical unreliability of SVNs. No comparison data were presented regarding the mechanical reliability of MDIs, nor were there data reported about the clinical reliability. We have performed weighing and puff-counting on six each of professional-sample MDIs from four prominent manufacturers. The results are shown in Table 1. Using radioaerosol techniques, we compared the lung deposition of these devices (expressed as a percentage of medication placed in the SVN or as a percentage of medication in five puffs from the MDI) in six trained subjects. Radioaerosol results are shown in Table 2. It is apparent that MDIs are mechanically reliable, but in terms of lung deposition, the SVN reliability is superior. The coefficient of variation for SVN is 20 percent, compared to 45 percent for MDI, presumably because the latter is more difficult to use. Possibly the use of a spacer with MDIs would lessen this difference.

The articles by Bowton et al[2] and Tenholder et al,[3] in the February and March 1992 issues, respectively, purport to show cost savings.

Table 1—*Characteristics of MDI Samples**

MDI	Weight of Contents, g	No. of Puffs
Ventolin	8.3±0.4	101±8
Alupent	8.8±0.3	119±3
Proventil	8.7±0.2	110±7
Maxair	8.6±0.2	129±3

*Values are expressed as mean ± SD.

Table 2—*Lung Deposition of Aerosol*

Subject	SVN, %	MDI, %
1	8	13
2	14	23
3	10	13
4	8	13
5	10	5
6	9	13
Mean ± SD	10±2	13±6

Both fail to use equivalent dosing, giving only three or four puffs from the MDI. In addition to the data presented above, there is abundant evidence that the equivalent of one SVN treatment is about ten puffs from an MDI whether studied with radioactive aerosol particles,[4] bronchoprovocation,[5] or relief of bronchospasm.[6] Since the claimed cost savings are largely in technician time, recalculation using ten puffs at 1-min intervals actually makes supervised MDI therapy relatively expensive. Moreover, the practical realities are ignored. For most patients, technicians really do have to supervise MDI therapy, whereas commonly the SVN is set up and the patient is left on his own. Switching from an SVN to three or four puffs from an MDI is the equivalent of the hospital pharmacy reducing by mandate the prescribed dose of any medication by 60 to 70 percent simply to save money. Few patients or physicians would tolerate such intrusion.

Modern aerosol therapy is actually relatively simple. About 10 percent of aerosol inhaled is deposited in the lungs. For example, albuterol delivered by MDI at 0.09 mg per puff × 10 puffs × 0.1 lung deposition equals a 0.09-mg lung dose and a 0.9-mg total-body dose. In a typical SVN there is a "dead volume" of retained droplets of about 0.8 ml. Albuterol, 2.5 mg in 3-ml volume, produces about 2.2 ml of aerosol, half of which is lost to the environment during exhalation (inspiratory-expiratory ratio = 1:1), producing a 1.1-ml, or 0.9-mg, inhaled total-body dose and a similar 0.09-mg lung dose. The 90 percent of the inhaled dose that is extrapulmonary and may promote toxicity may be lessened by the use of a spacer or baffle to reduce the larger "*nonrespirable*" particles.

The message is clear that we are probably vastly underdosing the lungs. There is preliminary information that higher doses of aerosol are safe and effective.[7] Our clinical experience supports this, especially if the devices used are configured to maximize pulmonary deposition and minimize pharyngeal deposition.

Warren C. Miller, M.D., F.C.C.P., and
John W. Mason, R.R.T.,
Humana Pulmonary Center,
Webster, Texas

Reprint requests: Dr. Miller, 450 Blossom Street, Suite B, Webster, TX 77598

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