Lung Asbestos Content in Lungs Resected for Primary Lung Cancer

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Introduction: The majority of Australia’s burden of lung cancer occurs in current or former tobacco smokers. To determine the possible contribution of asbestos exposure in Australians presenting with primary lung cancer, we measured lung asbestos content in cases resected consecutively at a single cardio-thoracic hospital.

Methods: Asbestos bodies were quantified by lung tissue digestion, filtration, and light microscopy, and were correlated with exposure questionnaires and clinicopathological features.

Results: We demonstrate high intrarater reproducibility and interrater reliability using these methods. In 463 patients with resected primary lung cancers, asbestos content ranged from 0 to 749 asbestos bodies per gram wet weight (AB/gww). Forty-eight percent of patients had no asbestos bodies identified. One-third had less than or equal to 20 AB/gww (a level previously found to be consistent with urban dwelling). Nineteen percent had lung content in excess of this level. Only 20 cases had AB >100/gww, approximately equivalent to the Helsinki threshold for attribution of lung cancer to asbestos. Median asbestos body counts were higher in patients who reported previous asbestos exposure than in those who reported no exposure. A subgroup of cases gave detailed exposure histories that did not predict presence or absence of asbestos bodies in men or women. In cases with cumulative tobacco exposure less than 20 pack-years, asbestos body counts exceeding 20 AB/gww were overrepresented.

Conclusions: We found that the majority of patients with primary lung cancer at a single Australian center have detectable asbestos in resected lung tissue, but fiber burdens are generally low. The contributory role of this low-level asbestos exposure in causing lung cancer remains uncertain.

Key Words: Asbestos, Lung cancer, Asbestos bodies.

Lung cancer is a major global health problem. It is the leading cause of cancer death in Australia, responsible for 22% of male cancer deaths and 15% of female cancer deaths in 2004 and 5.3% of all deaths. Smoking is the largest single cause of lung cancer, responsible for 85 to 90% of lung cancers. The strength of this association and the prevalence of smoking have contributed to difficulties with quantifying the contribution of occupational carcinogen and atmospheric pollutant exposures to an individual’s risk of lung cancer. The precise contribution of asbestos exposure to the burden of lung cancer in modern times is uncertain. Global estimates are that 4 to 11% of lung cancers in industrialized nations are attributable in part to occupational exposure to asbestos.2,3 In the United States, an estimated 9 to 10,000 men and 9 to 1900 women develop lung cancer annually because of past exposure to occupational carcinogens, and more than half of these lung cancers are related to asbestos.4 In Australia, asbestos was mined in Western Australia (Wittenoom 1938–1966) and NSW (Baryulgil 1940–1979) and was imported from South Africa and Canada. Perhaps the most extensive use of asbestos product as housing stock in the world occurred in Australia. It has been suggested approximately one in three Australian homes built before 1987 and most public buildings contain some form of asbestos.

Asbestos-related lung cancer has no unique clinical or pathologic features that distinguish it from other lung cancers. Lower lobe predilection has been suggested, but is controversial. The apparent adenocarcinoma subtype predominance mirrors that of lung cancers in general.5,6 In addition to occupational histories, coexisting asbestos-related pleural disease or asbestosis help to identify individuals with significant past asbestos exposure. There is debate as to whether lung cancer can be attributed to asbestos exposure in the absence of asbestosis,7 with evidence both supporting8,9 and refuting10,11 this contention.
Many asbestos-related lung cancers may result from the combined effects of asbestos and carcinogens in tobacco smoke. The causal interaction between asbestos and tobacco smoke has been reported to vary from additive to multiplicative.12–14 Recent reviews support a cumulative exposure model for lung cancer risk as a consequence of asbestos exposure.7,15–18 To investigate the potential contribution of past asbestos exposure to the current burden of lung cancer, we measured lung asbestos body counts in a large series of patients undergoing resection for primary lung cancer.

Subjects

Patients gave informed written consent to participate in this study, which was approved by The Prince Charles Hospital Research Ethics Committee. The subjects were unsolicited consecutive cases of primary lung cancer resected at The Prince Charles Hospital. Preoperatively, patients were asked whether they had ever been exposed to asbestos and responses were recorded as “Yes,” “No,” or “I don’t know.” A subset of patients completed a more-detailed questionnaire including job matrices. The demographics, smoking, and clinical characteristics of these subjects are summarized in Table 1.

### METHODS

#### Tissue Digestion and Filter Preparation

Lung fiber burdens were assessed using a sodium hypochlorite digestion and filtration technique.19 Fresh lung tissue was collected from each patient’s resected lung at a macroscopically normal site remote from the tumor. Lung tissue was snap frozen in liquid nitrogen, and stored at −80°C. Cryopreserved lung (~0.3 g) was weighed, cut into 1 to 2 mm pieces, and then digested in 10 mL of commercial bleach (4.0–4.2% sodium hypochlorite) overnight on a shaker until no visible particles remained in suspension, then filtered through a 0.4 μm, 25 mm Nucleopore polycarbonate membrane (Crown Scientific, NSW, Australia) under nega-

### TABLE 1. Demographics, Clinical, and Pathologic Characteristics of Primary Lung Cancer Cohort

<table>
<thead>
<tr>
<th>Lung Asbestos Burden (AB/gww)</th>
<th>0</th>
<th>0–20</th>
<th>20–100</th>
<th>&gt;100</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort</td>
<td>223</td>
<td>152</td>
<td>68</td>
<td>20</td>
<td>463</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>147 (66)</td>
<td>102 (67)</td>
<td>51 (75)</td>
<td>17 (85)</td>
<td>317 (68)</td>
</tr>
<tr>
<td>Females</td>
<td>76 (34)</td>
<td>50 (33)</td>
<td>17 (25)</td>
<td>3 (15)</td>
<td>146 (32)</td>
</tr>
<tr>
<td>Age (yrs), median (range)</td>
<td>66 (33–82)</td>
<td>70 (37–85)</td>
<td>69 (40–84)</td>
<td>71 (52–82)</td>
<td>67 (33–85)</td>
</tr>
<tr>
<td>Smoking status (Total pack-years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ever, n, median (range)</td>
<td>214, 46 (5–240)</td>
<td>144, 47 (3–225)</td>
<td>60, 45 (1–243)</td>
<td>18, 43 (15–94)</td>
<td>436, 45 (1–243)</td>
</tr>
<tr>
<td>Never, n</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>Reported asbestos exposure, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (10)</td>
<td>26 (17)</td>
<td>15 (23)</td>
<td>11 (55)</td>
<td>74 (16)</td>
</tr>
<tr>
<td>No</td>
<td>137 (61)</td>
<td>82 (54)</td>
<td>18 (26)</td>
<td>6 (30)</td>
<td>243 (52)</td>
</tr>
<tr>
<td>Unsure</td>
<td>15 (7)</td>
<td>7 (5)</td>
<td>9 (13)</td>
<td>0 (0)</td>
<td>31 (7)</td>
</tr>
<tr>
<td>No data</td>
<td>49 (22)</td>
<td>37 (24)</td>
<td>26 (38)</td>
<td>3 (15)</td>
<td>115 (25)</td>
</tr>
<tr>
<td>Resected lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RLL</td>
<td>22</td>
<td>23</td>
<td>8</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td>RML</td>
<td>12</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>RUL</td>
<td>62</td>
<td>41</td>
<td>18</td>
<td>4</td>
<td>125</td>
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<tr>
<td>LLL</td>
<td>28</td>
<td>15</td>
<td>10</td>
<td>2</td>
<td>55</td>
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<tr>
<td>LUL</td>
<td>53</td>
<td>42</td>
<td>14</td>
<td>5</td>
<td>114</td>
</tr>
<tr>
<td>R Bi-lobe</td>
<td>11</td>
<td>70</td>
<td>50</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>R Lung</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>L Lung</td>
<td>25</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td>45</td>
</tr>
<tr>
<td>Other (Lingula, Other Bi-lobe)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Tumour histology, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>103 (46.2)</td>
<td>68 (44.7)</td>
<td>30 (44.1)</td>
<td>14 (70)</td>
<td>215 (46.4)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>76 (34.1)</td>
<td>57 (37.5)</td>
<td>26 (38.2)</td>
<td>4 (20)</td>
<td>163 (35.2)</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>15 (6.7)</td>
<td>4 (2.6)</td>
<td>3 (4.4)</td>
<td>0 (0)</td>
<td>22 (4.8)</td>
</tr>
<tr>
<td>Large cell undifferentiated</td>
<td>16 (7.2)</td>
<td>12 (7.9)</td>
<td>6 (8.8)</td>
<td>1 (5)</td>
<td>35 (7.6)</td>
</tr>
<tr>
<td>Bronchioloalveolar cell carcinoma</td>
<td>4 (2.0)</td>
<td>4 (2.6)</td>
<td>2 (3.0)</td>
<td>0 (0)</td>
<td>10 (2.1)</td>
</tr>
<tr>
<td>Other primary lung cancer</td>
<td>9 (4.0)</td>
<td>7 (4.6)</td>
<td>1 (1.5)</td>
<td>1 (5)</td>
<td>18 (3.9)</td>
</tr>
</tbody>
</table>

Cases were defined as “ever smokers” if there was a cumulative total of at least one pack-year. Cases were defined as “never smokers” if the cumulative total tobacco consumed was less than one pack-year.

AB/gww, asbestos bodies counted by light microscopy per gram wet weight of lung tissue (see Methods section); total pack-years, number of years smoked × number of cigarettes per day/20; L, left; R, right; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RLL, right lower lobe; RML, right middle lobe; R Bi-lobe, right middle and upper lobectomy OR right middle and lower lobectomy.
ative pressure, using Millipore filtration apparatus. Aliquots of digested tissue in suspension were treated with equal volumes of 8% oxalic acid (Sigma, NSW, Australia), 100% ethanol and bleach sequentially to remove organic residues, followed by distilled water to prevent crystal deposition on the filter surface. The filter was then rinsed with a final aliquot of 100% ethanol. Filters containing captured asbestos bodies were affixed to coated glass slides, dried, dissolved with chloroform, cover-slipped, and mounted.

Asbestos Body Counting

Slide mounted filter preparations were systematically examined by light microscopy using a Nikon Eclipse E200 light microscope. The whole slide was scanned at 100× magnification to identify putative asbestos bodies then morphology was confirmed at 400× magnification. Asbestos bodies were identified by morphologic criteria: beaded appearance, thin translucent cores, bulbous ends, roughly parallel sides, and length greater than 20 to 50 μm. Representative examples are shown in Figure 1.

Reliability and Reproducibility

To assess the interrater reliability of the asbestos body counting procedure, 15% of tissue preparations (n = 60) were counted by three independent readers blind to the patient’s self-reported exposure response and to the counts of the other readers. Intrarater reproducibility was assessed by analysis of asbestos body counts recorded for lung tissue preparations by the same reader on two separate occasions without reference to previous results. The mean intervals between repeat counts were 66 days (reader 1), 58 days (reader 2), and 64 days (reader 3).

Statistical Procedures

All statistical procedures were performed with SPSS 13.0 (SPSS Inc., Chicago, IL). Asbestos body counts were not normally distributed and results are reported as median and range. Nonparametric methods were used for analysis. Reliability and reproducibility were analyzed using the SPSS Reliability procedure to compute intraclass correlation coefficients (ICC) for absolute agreement between counts. In both analyses a two-way mixed effects model was used to interpret the ICC for a single reader (as opposed to average measures) as it was intended to indicate the suitability of relying on a single rater’s count for the majority of samples. The ICC has been interpreted by Fleiss as more than 0.75 excellent agreement, 0.4 to 0.75 fair-to-good agreement, and less than 0.4 poor agreement. The null hypothesis was rejected if the computed ICC was greater than 0.4 at a significance level of p < 0.05.

RESULTS

Interrater Reliability

The ICC for absolute interrater agreement between three readers’ counts on 60 lung tissue samples was 0.93 (95% CI, 0.89–0.95; p < 0.0001). Figure 2A shows the asbestos body counts per gram wet weight of lung reported by three readers on 60 lung samples.

Intrarater Reliability

The data for intrarater reproducibility consisted of two separate counts of asbestos bodies per gram wet weight of lung tissue on each of 23, 32, and 31 lung samples (readers 1, 2, and 3, respectively). The ICCs (95% CI) for absolute agreement between repeated measurements were 0.933 (0.869–0.967) for reader 1, 0.987 (0.969–0.994) for reader 2, and 0.995 (0.990–0.998) for reader 3, p < 0.0001 for all (Figure 2B).

Asbestos Body Content in Lungs Resected for Primary Cancer

Lung asbestos fiber burden was measured by light microscopy in 463 consecutive cases (146 women and 317
men) of primary lung cancer resected at The Prince Charles Hospital between 2000 and 2006. From analysis of the correlation between lung fiber burden measured by light microscopy with detailed exposure histories in US residents during the 1970s and 1980s, it was concluded that an asbestos body count of 20 AB/gww was the upper limit associated with urban dwelling without occupational or significant environmental asbestos exposure.24 We found lung asbestos content equal to or greater than 20 AB/gww in 88 cases (19%), up to 20 AB/gww in 152 cases (33%), and 0 AB/gww in 223 (48%) of cases (Table 1). The age of patients with lung burdens in excess of 20 AB/gww did not differ from that in cases with low asbestos content (<20 AB/gww) or those with no asbestos detectable by the filter and light microscopy method used here. In this cohort, women and men with primary lung cancer had a similar distribution of lung asbestos body counts (Figure 3).

Responses to the question whether they had asbestos exposure were available for 348 of 463 cases of primary lung cancer (75%). Most respondents reported no exposure (n = 243, 70% of respondents), 74 reported previous exposure (21%), and 31 were uncertain (9%) (Table 1). Asbestos body counts were significantly lower in individuals reporting no prior exposure (median, 0 AB/gww; range, 0–749), than in those who were able to recall past asbestos exposure (median, 8.4 AB/gww; range, 0–524; p < 0.0001, Mann-Whitney test); however, there was considerable overlap in lung fiber content between these two groups. Detailed occupational and environmental exposure questionnaire data were available for 77 primary lung cancer cases (17 women and 60 men). Occupational exposure to asbestos was reported by almost half of the men (29/60) but none of the women (0/17). Among the 17 women with negative occupational history questionnaires seven had asbestos bodies detected in lung

**FIGURE 2.** A, Intraclass correlation coefficient (ICC) was computed for absolute agreement using SPSS Reliability procedure using a two-way mixed effects model. The null hypothesis tested was that that ICC = 0.4 (i.e., that interreader reliability is low to moderate). ICC = 0.93 (0.89–0.95) indicated a high level of agreement between these three readers, p < 0.0001. B, The mean interval between readings was 66 days for reader 1, 64 days for reader 2, and 58 days for reader 3. ICC was computed using a two-way mixed model for absolute agreement in SPSS Reliability procedure. p values tested the null hypothesis that ICC = 0.4 (i.e., that intrarater consistency is low to moderate). Reader 1: ICC = 0.933 (0.869–0.967), p < 0.0001, n = 23; Reader 2: ICC = 0.987 (0.969–0.994), p < 0.0001, n = 32; Reader 3: ICC = 0.995 (0.990–0.998), p < 0.0001, n = 31.

**FIGURE 3.** Y axes show asbestos body counts on Log 10 scale. Reference line is positioned at 20 asbestos bodies per gram wet weight of lung. (Values of 0 AB/gww for which log10 transformation could not be done were imputed as zero, for the purpose of graphically displaying the complete distribution of values on a log scale.) X-axis shows age in years.
tissue, and in four the fiber burden was greater than 20 AB/gww. Eighty-three percent of men reporting occupational exposure on the detailed questionnaire had asbestos bodies in their resected lung (24/29). However, 39% of men (12/31) returning negative exposure questionnaires also had detectable lung asbestos.

Lung fiber content did not differ significantly in relation to the lobe resected (upper versus lower, \( p = 0.455 \)) nor to laterality of the resection, (left versus right, \( p = 0.806 \), Mann-Whitney).

The spectrum of histologic subtypes of primary lung cancer was similar between patients with lung asbestos content more than or equal to 20 AB/gww and those with less than 20 or 0 AB/gww (Table 1).

Among cases of lung cancer with relatively low cumulative tobacco exposure, asbestos body counts in excess of 20 AB/gww were over-represented (Pearson \( \chi^2 = 8.875, df = 1, p = 0.003 \), Table 2).

**DISCUSSION**

For the years 1987–2020, 30,000 to 79,000 cases of lung cancer related to asbestos are predicted in Australia. Asbestos-related lung cancer is also an important compensable disease in Australia with payments made for dust-related lung cancer in 2004–2005 (DDB NSW) in excess of \( $A79m \). The NSW compensation body recorded that deaths from mesothelioma outnumbered deaths due to asbestos-related lung cancer by 16.6:1. Given the overall prevalence of the two diseases, lung cancer may be underrepresented among compensated asbestos-related diseases in Australia.

We report results of lung asbestos burden in a contemporary and unselected cohort of patients undergoing resection for primary lung cancer within the past 6 years. Within our laboratory, quantification of asbestos bodies in resected lung tissue is highly reproducible. Nineteen percent of an unselected cohort from this single Australian center have fiber burdens greater than expected for urban dwellers who have not been occupationally or otherwise exposed to significant respirable asbestos.

**Methodological Considerations**

We counted only ferruginous bodies (“asbestos bodies”), i.e., coated fibers with defined dimensions and morphology. Although ferruginous bodies may form on amphibole or chrysotile and mainly on longer fibers (\( \geq 8 \mu m \)), the limited resolution of light microscopy means that this technique cannot reliably detect short fibers (\( \leq 5 \mu m \)) that are usually uncoated or thin fibers (\( <0.2 \mu m \)). Therefore, our light microscopic methods of counting asbestos bodies are very likely to underestimate total lung asbestos fiber content. Also, it cannot reliably identify the mineralogy of the core fibers, and therefore retained chrysotile is not accurately assessed by this method. A variable relationship between uncoated fiber burden and ferruginous body counts among individuals has been found in other studies.

For these reasons, and also because of the higher biopersistence of amphibole in relation to serpentine asbestos in human lung, our counts predominantly reflect amphibole exposure. We recognize that an unknown and interindividually variable proportion of “asbestos bodies” counted in this study may have serpentine asbestos cores or nonasbestos fiber cores, and that the proportion of amphibole fibers retained in lung that are coated differs between individuals.

The quantification of lung asbestos burden by bleach extraction and filtration may also not be directly comparable with that obtained with hot “ashing,” although at least one study has shown that fiber counts were not significantly different between the two methods. Wet/dry lung weight ratios were not measured for each sample. Instead, we relied on previously reported estimates of these relationships to extrapolate the Helsinki thresholds to an estimated equivalent per gram wet weight of lung tissue. As the exact relationship between wet and dry lung weight might be expected to differ between individual samples, this extrapolation is an approximation. However, considerable experimental consistency in wet to dry lung weight ratios (approximately 7.5–10 fold) has been demonstrated previously making it less probable that sample to sample variation in wet/dry lung weight represents a major source of unaccounted error.

Despite the advantages of simplicity, low cost, and reproducibility the method we used is not comparable with electron microscopic methods of quantifying lung asbestos content. The latter can both quantify the burden of uncoated fibers and identify the composition of the fiber core but may be subject to greater sampling error. Finally, we are currently in the process of determining fiber burden in other cohorts such as those with pleural plaques or asbestosis to establish validated reference ranges for these various conditions, as well as measuring the consistency of fiber content in different anatomic regions of lung. Lung fiber content varies considerably between different regions of the same lung (up to 10-fold), but data are based on studies of relatively few individuals.

**Contemporary Significance of Lung Asbestos Content in Primary Lung Cancer Patients**

We noted a weak association between asbestos body counts and self-reported asbestos exposure. It is likely that responses were affected by numerous factors. Positive responses in cases with low lung fiber burden would be expected in cases of predominantly chrysotile exposure for which lung fiber burden is a less accurate index than exposure history, or in circumstances of long latency between exposure.

<table>
<thead>
<tr>
<th>Exposure Category</th>
<th>0 or &lt;20 pack-yrs</th>
<th>≥20 pack-yrs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–20 AB/gww</td>
<td>53 (62.4)</td>
<td>332 (312.6)</td>
<td>375</td>
</tr>
<tr>
<td>&gt;20 AB/gww</td>
<td>24 (14.6)</td>
<td>64 (73.4)</td>
<td>88</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>386</td>
<td>463</td>
</tr>
</tbody>
</table>

Pearson \( \chi^2 = 8.875, df = 1, p = 0.003 \). Expected values for each cell are shown in brackets.

AB/gww, asbestos bodies per gram wet weight. Pack-years, number of years smoked multiplied by number of cigarettes per day divided by 20.
and fiber burden determination. However, some individuals may be referring to trivial exposure or exposure to asbestos in nonrespirable forms. On the other hand, negative responses may be returned when distant past exposure is not recalled, or where the patient is unaware of exposure, e.g., childhood exposure. For the cohort reported here, we have no systematic corroborative evidence of past asbestos exposure such as detailed occupational histories or presence or absence of pleural plaques on CT scans. Because these correlations provide important verification of exposure levels, we are now prospectively collecting this data. A study from Germany reported a highly variable relationship between work-place exposure expressed in “fiber-years” and lung asbestos fiber concentration where almost half of patients considered to have asbestosis had cumulative work-place exposure of less than 25 fiber-years.

Asbestos fibers are durable in lung tissue for many years, but as a consequence of legislation prohibiting the mining and milling of asbestos and the manufacture of new asbestos products since the late 1960s, we expected younger Australian patients to have significantly less exposure and therefore lower lung fiber content. The age distribution of the cohort indicates that the majority of patients were of working age during the late 1960s. Of the 30 patients who were aged less than 16 years in 1966, 14 had asbestos bodies detected in resected lung, mostly with counts of less than 20 AB/gww. These individuals were unlikely to have been exposed to asbestos mining or manufacturing of new asbestos product, but may have been exposed in building or construction, demolitions, automotive, or other occupations where respirable asbestos is generated from existing product. Childhood exposure, such as in households with an occupationally exposed parent, could explain the presence of asbestos at this level in the lungs of these younger patients, but other types of exposure associated with a low lung burden are not excluded. It is worth noting that Australia differs from many European countries in its extensive use of asbestos building products in housing stock. The extent to which Australian householders, including children, have been exposed to asbestos during housing renovations is unknown.

We expected few women to have evidence of significant past exposure to asbestos and surprisingly there was a similar distribution of asbestos load in lung resected from women and men. Lung fiber content in women was not associated with self-reported exposure status. Of the 21 women with greater than 20 AB/gww lung, only four had given detailed occupational exposure information, but none reported either personal occupational exposure or an occupationally exposed spouse. The lung fiber content in these women is not explained by recalled asbestos exposure. Asbestos product manufacture was conducted in Brisbane suburbs within 5 km of the center from which this cohort was drawn until the mid 1960s. Urban dwelling in such a vicinity is a possible explanation for this observation but residential information on these cases is not available to us. Mesothelioma rates associated with environmental exposure to crocidolite in Wittenoom, Western Australia, recently described by Reid et al., indicated steeper dose response curves for women than for men. An association between lung cancer and environmental asbestos exposure has never been described, and would be difficult to recognize in individuals with concurrent active or passive tobacco exposure.

The Helsinki criteria for lung cancer estimate that cumulative exposure of 25 fiber-years (1 fiber/cm² for 1 year = 1 fiber-year) increases the risk of lung cancer 2-fold, and relates this risk to retention of 2 million amphibole fibers more than 5 μm or 5 million amphibole fibers more than 1 μm per gram dry lung tissue as assessed by electron microscopy. This is approximately equivalent to 5000 to 15,000 asbestos bodies per gram dry tissue, and to 500 to 1500 asbestos bodies per gram wet weight lung. Only two lung cancer patients in this cohort had fiber burdens in this range. Extrapolation of the Helsinki criteria indicates that more than 100 asbestos bodies per gram wet tissue identifies persons with a high probability of exposure to asbestos dust at work. Twenty lung cancer patients in this cohort (17 men and 3 women) had lung asbestos content in this range, representing only 4.3% of the total. Women with lung asbestos content in the “occupational exposure” range did not report previous asbestos exposure and may have been unaware of it. The finding of greater than 20 asbestos bodies per gram wet weight in a disproportionately high number of lung cancer cases in this cohort with less than 20 pack years of cumulative tobacco exposure, raises the issue of whether asbestos contributed materially to lung cancer risk in these individuals.

The Helsinki criteria have recently been criticized on the basis that (1) they are derived from studies in which exposure levels derived from years of employment in particular occupations or general environmental levels are crude estimates of actual exposure in individuals, (2) they fail to take account of differing risk due to different fiber types, and (3) they do not provide for variation in assessment of lung fiber burden due to different measurement methodologies between laboratories. Notwithstanding this, we considered direct measurement of fiber burden in lung tissue to have advantages over the more indirect approach of estimating exposure from occupational histories for investigating the relationship between asbestos exposure and lung cancer, particularly in Australia where most exposure included a significant component of amphibole.

Animal models have not provided strong evidence that fiber mineralogical independence of fiber dimensions is responsible for differential fiber carcinogenicity. Rodent animal models have the disadvantage of short animal life-span in relation to fiber retention and durability in tissue and therefore do not faithfully represent human fiber carcinogenesis. On the other hand human epidemiological studies provide consistent evidence that chrysotile is less potent than amphiboles for induction of mesothelioma and also (to a lesser extent) lung cancer. The disadvantage of the human epidemiological studies is that the exact fiber composition of exposure is often not precisely known. Nevertheless from published epidemiology studies crude aggregate percentages of mesothelioma cases among cohorts of workers exposed to amphiboles, mixed fiber types, and chrysotile were recently reported as 1.23%, 0.67%, and 0.04%, respectively.
fact that the diagnoses in the cases among chrysotile workers were unconfirmed is relevant to the contentious issue of whether exposure to chrysotile with its 40 times lower biopersistence than crocidolite in animal studies is carcinogenic in humans, except under conditions of intense repeated exposures. Exposure specific excess lung cancer mortality estimates in cohorts exposed to amphiboles, mixed asbestos, and chrysotile of 2 to 10%, 0.32%, and <0.5% per f/ml yr, respectively indicated a clear fiber type risk gradient for lung cancer in occupational cohort studies analyzed by Hodgson and Darnton.  

In summary, we have demonstrated reproducible lung asbestos fiber counts in a large cohort of Australian patients undergoing resection for lung cancer since the year 2000. We found that approximately half of these patients had no lung asbestos detectable by light microscopy, one-third had body counts below 20 AB/gww, one-fifth had body counts exceeding 20 AB/gww, and only two patients had body content above 500 AB/gww (approximated Helsinki threshold for causal attribution of lung cancer). We found no significant differences in distribution of demographic variables, lung cancer lobar location, or histologic subtypes based on lung asbestos fiber content in this cohort. The retained asbestos fiber burden in the lungs of this contemporary series of patients undergoing resection for lung cancer is very low in comparison with the lung burden epidemiologically associated with increased lung cancer risk, indicating that asbestos is not likely to be a major causal contributor to lung cancer in the majority of the cases. However, the true extent to which even low level asbestos exposure interacts with tobacco exposure in human lung carcinogenesis remains unknown.

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