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# Association Between Laryngeal Cancer and Asbestos Exposure

## A Systematic Review

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**IMPORTANCE** It has been debated whether a link exists between laryngeal cancer and asbestos exposure. Prior systematic reviews have been conducted on this topic, but no updates have been performed on the most recent literature since 2000.

**OBJECTIVE** To provide an updated systematic review of the association between laryngeal cancer and asbestos exposure.

**EVIDENCE ACQUISITION** A search of electronic databases, including PubMed and the Cochrane Library, was performed for articles published between January 1, 2000, and April 30, 2016. Search terms, including *laryngeal cancer* and *asbestos*, were used to identify publications reviewing the risk of laryngeal cancer in association with asbestos exposure. Studies analyzing this association that were published in any language and translated reliably were included. Two independent reviewers assessed articles based on predetermined eligibility criteria. Each study was reviewed for quality using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence and assessed for their findings of support for or against a correlation between asbestos exposure and laryngeal cancer.

**FINDINGS** A total of 160 studies were retrieved from all databases, and 2 additional articles were identified by cross-references. Of the 162 articles screened, 15 articles comprising 438 376 study participants were included in this review. Of these 15 studies, 10 showed no correlation between asbestos exposure and laryngeal cancer. The remaining 5 studies claimed a correlation between asbestos exposure and incidence of laryngeal cancer, although only 1 accounted for smoking or alcohol exposure while 3 others did not, and 1 study included only 2 patients.

**CONCLUSIONS AND RELEVANCE** Although asbestos is considered hazardous and carcinogenic, current evidence is lacking to support a correlation between asbestos exposure and laryngeal cancer. Few studies have been able to definitively conclude a causal association between asbestos exposure and laryngeal cancer, and those that found an association often did not account for the confounding factors of tobacco and alcohol exposure.

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**A**sbestos has long been used in the construction, vehicle, and textile industries. Most commonly, chrysotile asbestos is used because of its abundance compared with other types of asbestos, including amosite and crocidolite. Since the 1950s, there has been a causal association between asbestos exposure and a variety of malignant tumors, especially lung cancer. The carcinogenic effect of asbestos has resulted in a sharp decline in its use around the world.

Asbestos exposure continues to be associated with malignant tumors. Owing to a latency period (mean, 40 years; range, 15-60 years) between exposure and presentation of disease, asbestos-associated disease may be difficult to diagnose.<sup>1</sup> Peak use of asbestos was between the 1930s and 1970s. Therefore, it is estimated that the number of cases of asbestos-associated disease will peak between 2015 and 2020.<sup>2</sup> Suggested causes for such a lag time have been linked to the ability of asbestos fibers to avoid mucociliary clearance and reside longer in the aerodigestive system,<sup>2</sup> although an explanation for delayed presentation of disease has yet to be proven. To our knowledge, this latency period has not been specifically addressed regarding the development of laryngeal cancer. Nevertheless, asbestos was ultimately deemed a group 1 definite carcinogen according to the International Agency for Research on Cancer classification,<sup>2</sup> and several cancers have been identified as directly associated with asbestos exposure. Lung cancers, including mesothelioma, have been the primary malignant neoplasms associated with asbestos exposure. Increased risk of such malignant neoplasms based on asbestos exposure has been suggested for other sites of the aerodigestive system, including the stomach, lung, and larynx.<sup>3-5</sup>

In general, laryngeal cancer is considered to be a relatively rare malignant neoplasm, representing 0.8% of all new cancer cases annually in the United States.<sup>6</sup> It is estimated that there will have been 13 560 new cases of laryngeal cancer and 3640 deaths from laryngeal cancer in 2015.<sup>6</sup> Laryngeal cancer becomes more common with increased age and is more common in men than in women. The most important risk factors cited for developing laryngeal cancer have been smoking and alcohol exposures, especially when these exposures occur in conjunction with one another.<sup>7</sup> The association between asbestos exposure and laryngeal cancer, however, continues to be debated. Most of the reports that suggest this association are based on older studies. The most recent systematic review on this topic was conducted in 2000 by Browne and Gee,<sup>5</sup> who concluded that current evidence does not indicate that asbestos exposure increases the relative risk (RR) of laryngeal cancer. This report compiled data from nearly 2 decades ago. As the lag time between asbestos exposure and presentation of disease progresses, continued review of the literature is essential to obtain a better understanding of any association between asbestos exposure and laryngeal cancer. In this systematic review, we conducted an update on the literature from 2000 to 2016 to assess the potential association between asbestos and laryngeal cancer.

## Methods

A search strategy containing the terms *laryngeal cancer*, *asbestos*, *larynx*, *cancer of larynx*, *laryngeal cancer and asbestos*, and *larynx cancer and asbestos* was used. The electronic databases PubMed and

## Key Points

**Question** Is there a causal association between asbestos exposure and laryngeal cancer?

**Findings** In this systematic review that included 15 articles published between 2000 and 2016, there was no evidence of a correlation between asbestos exposure and laryngeal cancer.

**Meaning** Further studies are needed to definitively establish whether asbestos exposure increases the risk of developing laryngeal cancer.

the Cochrane Library were used to identify studies regarding laryngeal cancer and asbestos exposure published from January 1, 2000, until April 30, 2016, including only literature reported since the systematic review by Browne and Gee.<sup>5</sup> After removal of duplicates, this search identified 160 articles. Two additional articles were identified by cross-references. Full-text articles were retrieved if the topic was potentially relevant. Abstracts and titles were screened based on predefined inclusion and exclusion criteria. Articles were included if they were published in 2000 or later, involved a diagnosis of laryngeal cancer, and included only human participants who were adults who had been exposed to asbestos. Articles were excluded if they were published before 2000, did not involve a diagnosis of laryngeal cancer, did not assess laryngeal cancer outcomes (ie, mortality), and did not differentiate between laryngeal cancer and head and neck cancer in the reported data. A total of 147 articles were excluded: 102 were published before 2000, 41 did not include a diagnosis of laryngeal cancer, 3 did not involve asbestos exposure, and 1 was a published poster rather than an article.

Studies written in all languages were included and, if the primary language was not English, the article was included if it could be translated validly, meaning that access to online translation services were necessary for that specific language. Translated articles included those written by Sartor et al<sup>8</sup> and Brusis et al,<sup>9</sup> which were translated and validated using 3 online translation programs: Google Translate (Google Inc), Microsoft Translate (Microsoft Inc), and PROMT Free Online Translator (PROMT Service LLC). Each article was read and evaluated to determine whether it was a primary research study specific to laryngeal cancer and occupational asbestos exposure. A total of 15 articles met this criterion and were included in the review (Table).

## Data Extraction

The study was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement.<sup>10</sup> Data included the type of study, population, sample size, asbestos exposure, type of asbestos fibers, smoking and alcohol exposure, and outcomes.

## Assessment of Quality

The level of evidence for each study was assessed with the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence on a scale of 1 to 5 for harm. Level 1 evidence is derived from systematic reviews; level 2 from randomized trials; level 3 from nonrandomized controlled cohort or follow-up studies with a sufficient duration of follow-up; level 4 from case series, case-control studies, or

Table. Findings Regarding Asbestos Exposure and Laryngeal Cancer

Source	Study Components	Details
Elci et al, <sup>13</sup> 2002	Methods	Design: Case-control Time period: 1979-1984
	Participants	250 controls, 150 patients; Turkish men Geographical region: Turkey
	Outcomes	Measures: OR, 1.0 (95% CI, 0.8-1.3) Does account for smoking or alcohol exposure
	Conclusion	Asbestos exposure does not correlate with incidence of laryngeal cancer
	Level of evidence	4/5
Marchand et al, <sup>16</sup> 2000	Methods	Design: Case-control Time period: 1989-1991
	Participants	185 controls, 216 patients; French men Geographical region: France
	Outcomes	Measures: OR, 1.24 (95% CI, 0.83-1.90) Calculates cumulative risk of asbestos exposure and smoking but does not calculate to exclude smoking and alcohol exposure
	Conclusion	Asbestos exposure does not correlate with incidence of laryngeal cancer
	Level of evidence	4/5
Finkelstein and Verma, <sup>18</sup> 2004	Methods	Design: Cohort Time period: 1967-1999
	Participants	25 285 piping and plumbing workers Geographical region: United States and Canada
	Outcomes	Measures: Observed to expected ratio, 1.63 (95% CI, 0.34-4.76) Does not account for smoking or alcohol exposure
	Conclusion	Asbestos exposure correlates with incidence of laryngeal cancer
	Level of evidence	4/5
Smalyte et al, <sup>19</sup> 2004	Methods	Design: Cohort Time period: 1978-2000
	Participants	1887 Lithuanian asbestos-cement workers Geographical region: Lithuania
	Outcomes	Measures: SIR, 1.4 (95% CI, 0.7-2.9) Does not account for smoking or alcohol exposure
	Conclusion	No increased risk of laryngeal cancer with asbestos exposure; noted increased risk of colorectal cancers
	Level of evidence	4/5
Reid et al, <sup>20</sup> 2004	Methods	Design: Cohort Time Period: 1979-1999
	Participants	19 Australian male asbestos workers Geographic region: Western Australia
	Outcomes	Measures: SIR, 182 (95% CI, 116-285) Does not account for smoking or alcohol exposure
	Conclusion	No increased risk of laryngeal cancer with asbestos exposure alone; increased risk in those with asbestos exposure and smoking history combined
	Level of evidence	4/5
Pira et al, <sup>22</sup> 2005	Methods	Design: Cohort Time period: 1946-1984
	Participants	1966 Italian asbestos workers Geographical region: Italy
	Outcomes	Measures: SMR, 238 (95% CI, 95-490) Does not account for smoking or alcohol exposure
	Conclusion	No significant increase in laryngeal cancer for patient exposed to asbestos
	Level of evidence	4/5
Shangina et al, <sup>14</sup> 2006	Methods	Design: Case-control Time period: 1999-2002
	Participants	728 controls, 350 patients; European study centers Geographical region: Europe
	Outcomes	Measures: OR, 0.86 (95% CI, 0.51-1.45) Does account for smoking and alcohol exposure
	Conclusion	No correlation between asbestos exposure and laryngeal cancer
	Level of evidence	4/5

(continued)

Table. Findings Regarding Asbestos Exposure and Laryngeal Cancer (continued)

Source	Study Components	Details
Purdue et al, <sup>25</sup> 2006	Methods	Design: Cohort Time period: 1971-2001
	Participants	307 799 Swedish construction workers Geographical region: Sweden
	Outcomes	Measures: RR, 1.8 (95% CI, 0.8-4.3) Does account for smoking but not alcohol exposure
	Conclusion	Only 2 patients with laryngeal cancer; therefore, low study power. Authors state evidence for association between asbestos and laryngeal cancer
	Level of evidence	4/5
Lehman et al, <sup>27</sup> 2008	Methods	Design: Cohort Time period: 1971, 1979, 1987, 1995
	Participants	5416 US unionized pipe or steam fitters Geographical region: United States
	Outcomes	Measures: PMR, 1.28 (95% CI, 0.97-1.66) Does not account for smoking or alcohol exposure
	Conclusion	No significant increase of laryngeal cancer incidence with exposure to industrial materials, including asbestos; asbestos exposure was not an isolated exposure in this population
	Level of evidence	4/5
Magnani et al, <sup>24</sup> 2008	Methods	Design: Cohort Time period: 1950-1986.
	Participants	3434 Italian asbestos cement workers Geographical region: Italy
	Outcomes	Measures: SMR, 124.9 (95% CI, 69.9-206.1) Does not account for smoking or alcohol exposure
	Conclusion	No association between asbestos exposure and incidence of laryngeal cancer
	Level of evidence	4/5
Pira et al, <sup>23</sup> 2009	Methods	Design: Cohort Time period: 1987-2003.
	Participants	1056 Asbestos miners Geographical region: Balangero, Italy
	Outcomes	Measures: SMR, 1.82 (95% CI, 0.78-3.59) Does not account for smoking or alcohol exposure
	Conclusion	Significant association between asbestos exposure and laryngeal cancer
	Level of evidence	4/5
Strand et al, <sup>21</sup> 2010	Methods	Design: Cohort Time period: 1950-1987.
	Participants	28 345 Royal Norwegian Navy servicemen Geographical region: Norway
	Outcomes	Measures: SIR, 0.85 (95% CI, 0.56-1.22) Does not account for smoking or alcohol exposure
	Conclusion	No increased incidence of laryngeal cancer with asbestos exposure
	Level of evidence	4/5
Ramroth et al, <sup>15</sup> 2011	Methods	Design: Case-control Time period: 1998-2000.
	Participants	158 controls, 73 patients; German nationals Geographical region: Germany
	Outcomes	Measures: OR, 0.95 (95% CI, 0.51-1.8) Does account for smoking and alcohol exposure
	Conclusion	Moderately elevated risk of laryngeal cancer with asbestos exposure
	Level of evidence	4/5
Offermans et al, <sup>26</sup> 2014	Methods	Design: Cohort Time period: 1986-2003.
	Participants	58 279 Netherlands males Geographical region: the Netherlands
	Outcomes	Measures: HR, 6.36 (95% CI, 2.18-18.53) Does account for smoking and alcohol exposure
	Conclusion	No association between asbestos exposure and laryngeal cancer
	Level of evidence	4/5

(continued)

Table. Findings Regarding Asbestos Exposure and Laryngeal Cancer (continued)

Source	Study Components	Details
Menvielle et al, <sup>17</sup> 2016	Methods	Design: Case-control Time period: 2001-2007
	Participants	2780 controls, 473 patients; French males Geographical region: France
	Outcomes	Measures: OR, 1.81 (95% CI, 1.32-2.48) for highest level of asbestos exposure Separate calculated levels for combined effects of asbestos exposure with alcohol or smoking; no calculation reported to exclude alcohol or smoking exposure
	Conclusion	Statistically significantly increased risk of laryngeal carcinoma with asbestos exposure, regardless of extent of tobacco or alcohol exposure
	Level of evidence	4/5

Abbreviations: HR, hazard ratio; OR, odds ratio; PMR, proportionate mortality ratio; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

historically controlled studies; and level 5 from mechanism-based reasoning. Each included study was classified according to this schema.<sup>11,12</sup>

### Statistical Analysis

Each of the included studies was categorized based on the type of study, including cohort and case-control. Data from these studies were documented, including each study's calculated outcomes. These outcomes included standardized mortality ratio (SMR), standardized incidence ratio, proportionate mortality ratio, hazard ratio, RR, observed to expected ratio, and odds ratio (Table).

## Results

Fifteen studies comprising 438 376 study participants met the inclusion criteria for the systematic review (Table). The studies included were those published after the latest systematic review published in 2000.<sup>5</sup> Study sample sizes ranged from 19 to 58 279. Twelve of the 15 the studies were conducted in Europe, 2 of which were conducted in France and 3 in Italy. Five of the studies were case-control design, and 10 were cohort studies.

### Case-Control Studies

All 5 case-control studies included in this review reported odds ratios for their statistical analysis. All studies included individuals of European origin. The time periods for data inclusion ranged from 1979 to 1984 and from 2001 to 2007.

Among the case-control studies, 3 accounted for exposure to smoking and alcohol when determining the odds ratios in patients with laryngeal cancer and asbestos exposure.<sup>13-15</sup> Odds ratios from these studies ranged from 0.86 (95% CI, 0.51-1.45) to 1.0 (95% CI, 0.8-1.3). Two of the 3 studies did not find a correlation between asbestos exposure and laryngeal cancer after accounting for smoking and alcohol use.<sup>13,14</sup> Ramroth et al<sup>15</sup> conducted a study of German nationals, including 158 controls and 73 patients, with a calculated odds ratio of 0.95 for laryngeal cancer in light of asbestos exposure, showing a moderately elevated risk of laryngeal cancer with significant asbestos exposure. However, this study population was the smallest of the 3 case-control studies that accounted for exposure to smoking and alcohol.

Studies that did not account for alcohol and smoking exposure showed varying results.<sup>16,17</sup> Menvielle et al<sup>17</sup> report a correlation between asbestos exposure and laryngeal cancer occurrence, while Marchand et al<sup>16</sup> do not report such a correlation. Interestingly, both of these studies attempted to quantify the risk of laryngeal cancer with concurrent exposure to tobacco and alcohol.

### Cohort Studies

Statistical analysis methods varied among the 10 cohort studies included in this review, with 1 study reporting the observed to expected ratio,<sup>18</sup> 3 reporting standardized incidence ratio,<sup>19-21</sup> 3 reporting SMR,<sup>22-24</sup> 1 reporting RR,<sup>25</sup> 1 reporting proportionate mortality ratio,<sup>2</sup> and 1 reporting hazard ratio.<sup>26</sup> Seven studies included participants from Europe, 2 included participants from the United States, and 1 included participants from Australia. The time periods for data inclusion ranged from 1946 to 1984 and from 1986 to 2003.

Among the cohort studies, 2 accounted for exposure to smoking and alcohol when determining the RR and hazard ratio in their patient populations.<sup>25,27</sup> Relative risk in the study by Purdue et al<sup>25</sup> was 1.8 (95% CI, 0.8-4.3) and the hazard ratio in the study by Offermans et al<sup>26</sup> was 6.36 (95% CI, 2.18-18.53). Purdue et al<sup>25</sup> described only 2 patients with laryngeal cancer as a result of asbestos exposure, but concluded that there is an association between asbestos exposure and laryngeal cancer, while the study by Offermans et al<sup>26</sup> did not find any correlation.

The remaining 8 studies did not account for smoking and alcohol when determining the risk of laryngeal cancer with asbestos exposure. Two studies<sup>18,23</sup> reported an increased risk of developing laryngeal cancer with asbestos exposure, while the remaining cohort studies did not.<sup>19-22,24,27</sup>

## Discussion

The mechanism of asbestos-associated cancers, especially mesothelioma, has been studied extensively. Regarding the combined effects of smoking and asbestos exposure, direct and indirect causes for carcinogenicity, specifically within the respiratory tract, have been described. Direct mechanisms include genotoxic and nongenotoxic pathways elicited by exposure of respiratory tissues to

asbestos fibers. The fibers are phagocytosed by macrophages, which results in the production of reactive oxygen species, leading to higher levels of oxygen free radicals and inducing DNA damage and subsequent mutations.<sup>28,29</sup> Other direct mechanisms include increased cell proliferation caused by asbestos fibers activating growth factor receptors.<sup>30</sup>

Indirect mechanisms caused by asbestos fibers have been more frequently correlated with synergistic interaction between smoking and asbestos.<sup>31</sup> Decreased mucociliary clearance occurs with smoking, allowing for inhaled asbestos fibers to remain within the airway.<sup>32</sup> Asbestos fibers are also thought to have increased epithelial penetration in the presence of cigarette smoke.<sup>33</sup> In addition, alcohol and asbestos are known to have multiplicative effects in causing cancers of the respiratory tract. Alcohol use alone is a minor risk factor for the development of laryngeal cancer, and the mechanism behind the synergy with alcohol and asbestos remains unknown.

Although mechanisms for pulmonary malignant neoplasms with asbestos exposure are better understood, their application to laryngeal cancer has come into question based on differences in histologic structure, with the larynx being lined by squamous epithelium whereas the pulmonary tree is lined by ciliated columnar epithelium.<sup>34</sup> The pathophysiologic findings of an effect of asbestos on laryngeal cancer have yet to be determined.

The effect of different types of asbestos fibers on the larynx also has been studied. A recent meta-analysis found that overall risks of laryngeal cancer were increased with exposure to all types of asbestos fibers.<sup>3</sup> The highest risk was found in those exposed to crocidolite asbestos fibers, with a calculated SMR of 1.99, which was significantly higher than the SMRs of other asbestos subtypes, including chrysotile (1.73) and amosite (1.60).<sup>3</sup> Other studies have shown higher rates of laryngeal cancer with exposure to amphibole asbestos fibers, while some studies have not found any correlation of laryngeal cancer with exposure to chrysotile fibers.<sup>35,36</sup>

Prior studies have attempted to determine the biological effects of these types of asbestos fibers. In a study by Parnes,<sup>37</sup> patients exposed to asbestos were found to have laryngeal irritation, indicating that asbestos is an irritant; however, no evidence was found to conclude that it causes carcinoma. Kambic et al<sup>38</sup> also noted laryngitis as a result of asbestos exposure and that, on pathologic findings, asbestos fibers were found to sit on the laryngeal epithelium without penetrating through the epithelium. Therefore, although recent meta-analyses show increased SMRs with all types of asbestos fiber exposure, to our knowledge, the biological mechanism for this effect has yet to be determined.

Many studies have been conducted to estimate the effect of asbestos exposure on RRs of several cancers. Data from the French Institute of Public Health Surveillance have been collected to estimate the incidence of cancers possibly associated with asbestos exposure, estimating that, for laryngeal cancer, 2821 men had potentially developed laryngeal cancer as a result of their asbestos exposure.<sup>39</sup> This number was estimated by calculating the RR of developing laryngeal cancer after asbestos exposure, but no adjustment for alcohol or smoking history was performed. Although such data have been collected, true causation for these estimated incidences has yet to be concluded.

A recent meta-analysis by Peng et al<sup>3</sup> reviewed 21 published articles regarding an association between asbestos exposure and la-

ryngeal cancer. Through combining results of these studies, Peng et al<sup>3</sup> calculated an SMR of 1.69 (95% CI, 1.45-1.97). When compared with SMRs reported in previous meta-analyses, as calculated by Li et al<sup>40</sup> (SMR, 1.42; 95% CI, 0.72-2.80) and Goodman et al<sup>41</sup> (SMR, 1.57; 95% CI, 0.95-2.45), Peng et al<sup>3</sup> report a significantly increased likelihood of laryngeal cancer in patients with asbestos exposure. These meta-analyses, however, do not control for smoking or alcohol when calculating SMRs, and they include studies with flawed designs that fail to account for these critical confounding factors.

One recent study by Menvielle et al<sup>17</sup> explores the joint effect of both smoking and alcohol with asbestos exposure in the development of laryngeal cancer. The authors state that their study aimed to examine the combined association between smoking, alcohol, and asbestos exposure. It was found that, regardless of extent of exposure to both alcohol and tobacco, patients with occupational asbestos exposure had a significantly increased risk of laryngeal cancer. As smoking and alcohol are frequently used in conjunction with one another, this study heightens concern for a synergistic association of asbestos, tobacco, and alcohol exposure. This combined risk is important even if, ultimately, asbestos exposure alone is not found to be a cause of laryngeal cancer.

Asbestos has been called into question as a cause of laryngeal cancer for decades. Among leaders in the field of otolaryngology, there has been debate regarding potential causality of asbestos exposure in patients with laryngeal cancer. In 2009, an editorial by Ahmad and Sataloff<sup>42</sup> described an absence of correlation between asbestos exposure and laryngeal cancer and said that current evidence does not account for confounders, including alcohol and tobacco exposure. Review articles, including those by Browne and Gee<sup>5</sup> and Griffiths and Molony,<sup>34</sup> were used to show that significant confounding by alcohol and smoking does not allow for a causal link or a strong association between asbestos and laryngeal cancer to be concluded.

Sturgis<sup>43</sup> published a response, criticizing the lack of citation of the National Academy of Sciences' monograph<sup>7</sup> in the editorial by Ahmad and Sataloff.<sup>42</sup> In this monograph, the National Academy of Sciences' committee claims a "lack of confirmatory evidence from animal studies or documentation of fibers in the larynx."<sup>7(pg7)</sup> Evidence was sufficient to infer a causal relationship "between asbestos exposure and laryngeal cancer."<sup>7(p18)</sup> Ahmad and Sataloff<sup>42</sup> responded to this criticism that, although an association and causal link seem likely, they interpreted the wording in the monograph as having been very intentionally selected to avoid definitively stating that asbestos causes laryngeal cancer. This published debate underscores the controversy and urged investigators to study this topic further.

The known causality between mesothelioma and asbestos brings the potential risk of laryngeal cancer with asbestos exposure to the forefront in the minds of patients, clinicians, and lawyers, as the potential for successful litigation is present. Because litigation is often pursued by patients with mesothelioma, asbestos exposure has become one of the most highly discussed medicolegal topics. Studies regarding a multidisciplinary approach to legal discussions have been conducted. One recent report by Benavides et al<sup>44</sup> reviewed a lawsuit of an individual with mesothelioma and the utility of scientific proof of causation in litigation. The knowledge of asbestos-associated disease and the source of exposure were

discussed extensively in this lawsuit, resulting in an emphasis on occupational precautions to prevent disease.

For laryngeal cancer, asbestos exposure is still greatly debated. In our review, 10 of the 15 studies published since the systematic review by Browne and Gee<sup>5</sup> in 2000 show no correlation between laryngeal cancer and asbestos exposure. Although many studies did not account for confounding variables, these studies do not support a causal link between asbestos exposure and laryngeal cancer. Several studies, including the study by Purdue et al<sup>25</sup> and the recent report by the French Institute of Public Health Surveillance<sup>39</sup> claim a significant correlation between asbestos exposure and laryngeal cancer. With this claimed correlation, Purdue et al<sup>25</sup> did account for smoking in their data but failed to account for alcohol exposure, thereby weakening their argument. In addition, there were only 2 participants in this study, making its power low. The French Institute of Public Health Surveillance<sup>39</sup> also recently claimed a similar correlation, but their data are only a calculation of RR based on known asbestos exposure in males with laryngeal cancer. In that study, there is no account for any confounding factors of alcohol and tobacco exposure, also weakening their conclusions.

A lack of support for causation may be linked to the multiple facets of confounding within these studies. In addition, many of the studies were performed to analyze multiple types of cancer and their possible association with asbestos exposure. Other industrial exposures were also examined in many of the included studies, also acting as potential confounders, as individuals may have had multiple types of occupational exposures. Overall, many of these studies contained low sample sizes for laryngeal cancer.

Each of the included studies also has risk for confounding secondary to recall bias, with patients potentially underestimating or

overestimating asbestos exposure, various industrial exposures, or use of alcohol or tobacco. This bias also could confound the data presented, adding more uncertainty about the true correlation between asbestos exposure and laryngeal cancer. Sex and geographical region could be considered confounders as well, with most patients included being men and most countries being European. It is likely that the higher number of such patients is owing to the fact that mostly men are employed in industries with higher rates of asbestos exposure, and that European nations have older infrastructure and a higher likelihood of asbestos in buildings. Only with further knowledge of the pathophysiologic findings of asbestos in the larynx, as well as studies accounting adequately for confounders and recall bias, will a valid conclusion be reached on this topic.

## Conclusions

The current literature brings forth conflicting conclusions regarding the effect of asbestos exposure on the incidence of laryngeal cancer. Assessment of the literature published since 2000 continues to be complicated by confounding effects of smoking and alcohol. Lack of knowledge about the presence or absence of a causal association, as well as of exact mechanisms of possible asbestos effects in laryngeal cancer, continues to encourage litigation, especially in light of the known causal link between asbestos exposure and pulmonary malignant neoplasms. A causal link between asbestos exposure and laryngeal cancer has not been established definitively, and analysis of asbestos exposure while accounting effectively for other confounding exposures is needed to clarify this complex question.

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**Study concept and design:** Ferster, Schubart, Goldenberg.

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