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Review Article

Mesothelioma in patients with nonoccupational asbestos exposure An evidence-based approach to causation assessment

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Abstract The specific parameters of nonoccupational asbestos exposures (NOAE) that can distinguish an idiopathic from an asbestos-caused malignant mesothelioma (MM) are controversial. A systematic literature review yielded 1028 cases with this putative association. Only 287 of those reports had a defined single exposure to a household, building occupant, or neighborhood/community asbestos source. The available "evidence" was used to develop semiarbitrary evidence-based causation guideline rules for the assessment of putative associations between MM and NOAE. The rules are classified into class A (tissue burden analysis shows asbestos body counts or fiber counts in lung tissues comparable to MM caused by occupational exposure to asbestos) and classes B to D based on whether certain combinations of NOAE features and MM (evidence) have been described in over 15% (class B), 5% to 15% (class C), and less than 5% (class D) of the patients reviewed. The proposed 4 classes of evidence-based causation guidelines provide a semiarbitrary framework to evaluate the causation of individual MM patients by NOAE based on decreasing levels of currently available evidence. The neoplasms in classes A to C patients are probably caused by NOAE, with decreasing weight of evidence in the 3 groups. There is minimal evidence to support the causation of MM by NOAE in class D patients. There is no evidence or only anecdotal evidence to support a causal association between MM and NOAE in individuals who cannot be classified into any of the 4 classes. Future studies are needed to provide more comprehensive data regarding the association between MM and NOAE.

Keywords: Mesothelioma; Asbestos; Causes of neoplasms; Evidence-based medicine

1. Introduction

Malignant mesothelioma (MM) is an uncommon neoplasm involving the serosal surfaces of the pleura, peritoneum, and other serosal cavities [1,2]. Cumulative occupational exposure to amphibole asbestos fibers, such as crocidolite, amosite, and tremolite, has been recognized as a cause of MM in a substantial number of cases, more so in men than in women [3,4]. Specific details that are important to assess the role of objectively proven above-background asbestos exposure in MM causation include fiber type, fiber size, fiber burden, length of the operative latency period, anatomic tumor location, and other factors [5]. The mesotheliomagenic role of occupational-level exposure to chrysotile asbestos remains controversial, and 3 principal theories of possible attribution have been formulated. These are mutually exclusive, holding that all chrysotile exposures may contribute to MM causation, or only very high fiber burdens do so, or exposure to pure chrysotile does not cause MM at all [3,6-16]. In the last of those constructs, carcinogenesis is explained by concomitant exposure to tremolite or other amphiboles, which have contaminated chrysotile products in the past [3,4,12].

Malignant mesothelioma can also be caused by exposure to therapeutic-level irradiation or erionite, a fibrous but nonasbestiform mineral found naturally in Anatolia, Turkey [17-19]. Other potential etiologic factors of MM include chronic serosal inflammation and fibrosis and exposure to Thorotrast, a radiological imaging agent that was used in the

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past [1,2]. Idiopathic MM occurs in adult patients with no objectively documented exposure to asbestos or other above-cited causes or in children. Obviously, pediatric MM patients have not lived long enough for accrual of the latency period that pertains to asbestos-related tumors [18,20]. The role of SV40 infection in the causation of MM is unsettled; however, it is generally believed that, at a minimum, that agent probably requires cocarcinogens to contribute pathogenically in this context [1,2,18].

Nonoccupational asbestos exposure (NOAE) has been claimed in past publications to cause MM. The premise is that paraoccupational exposure to such minerals has occurred in the homes of "asbestos workers," in neighborhoods or communities with increased ambient levels of asbestos fibers in the air (eg, in proximity to a mine, factory, or asbestos processing facility), or in individuals who have resided or worked in buildings constructed with asbestos-containing materials [21-26]. A few communities in California have also been shown to have increased air levels of asbestos fibers derived from natural rock formations [27]. The specific parameters of NOAE, if any, that may cause MM are not known; most of the examples with this putative association have been reported as individual case reports or very small case series.

Evidence-based medicine (EBM) promotes the use of a systematic approach for the evaluation of scientific information [28,29]. Proponents of this discipline suggest that one perform a systematic review of pertinent scientific evidence, evaluate its quality, and use the available "best evidence" to answer specific questions. This approach has also been proposed for the evaluation of the extensive scientific literature that is available on the association between asbestos exposure and various diseases [5]. The goal of this process is to objectify our understanding of specific factors such as fiber types, asbestos tissue burdens, cocarcinogens, and other considerations that impact the causation of MM. The authors performed a systematic review of the English literature on purportedly NOAE-related MM. Our goals were to learn what data regarding this association are available and evaluate their quality in an EBM context. Information extracted from these queries was used to propose evidence-based causation guidelines

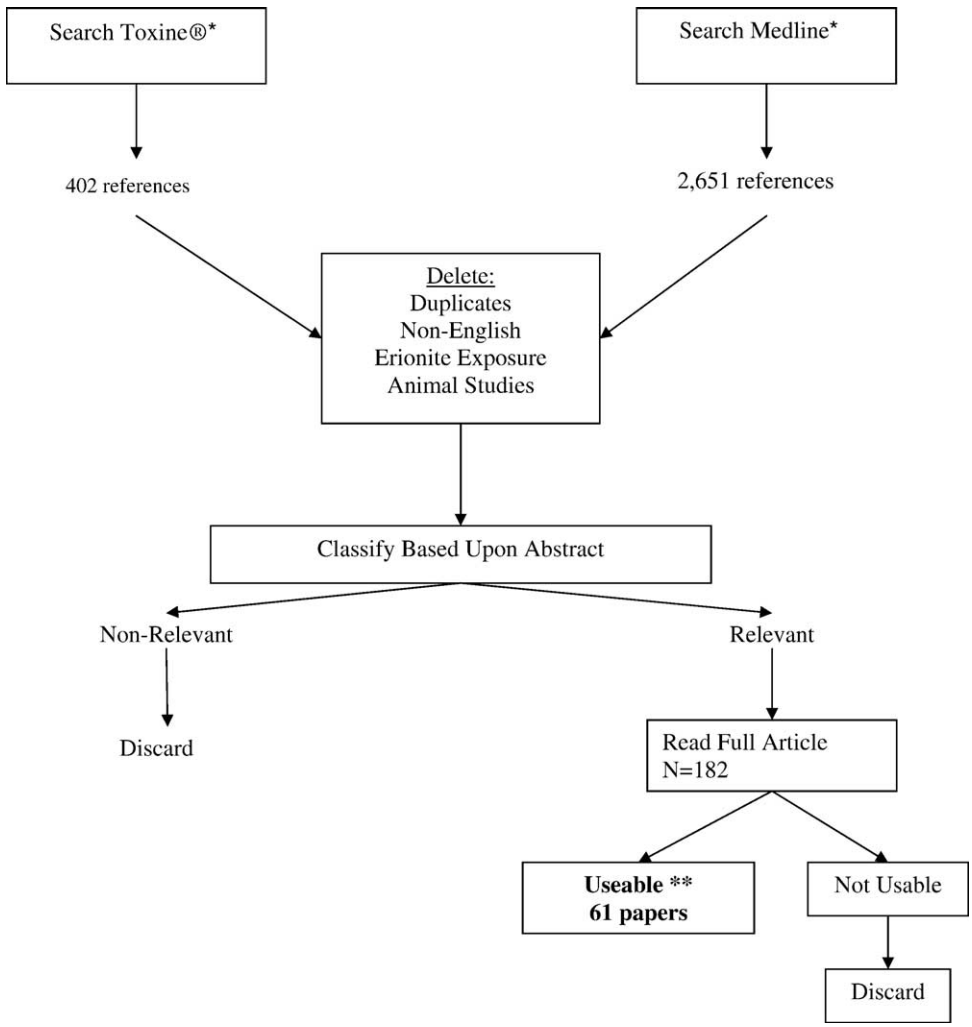

Fig. 1. Flow chart showing the procedure followed to review the literature about MM in persons nonoccupationally exposed to asbestos.

Table 1
Specific features extracted from the literature

Type of study
Year published
First author
Journal
No. of cases
Age
Sex
Type of nonoccupational exposure
Tumor location
Cell type
Asbestos worker occupation
Relationship of patient to asbestos worker
Duration of exposure
Latency period
Type of asbestos fiber
Source of asbestos fiber information
Type of fiber analysis performed
Smoking history

(EBCG) as supported by the best currently available evidence on attribution in this setting.

2. Materials and methods

2.1. Search strategy for the systematic review

The English literature regarding NOAE and MM was reviewed using PubMed and TOXLINE as search engines and the search strategy outlined in Fig. 1. PubMed is an online search service of the National Library of Medicine that includes over 14 million citations for biomedical articles with coverage from 1957 to the present [30]. TOXLINE is another online service of the National Library of Medicine that includes articles specifically related to toxicology dating back to 1965 [31]. The systematic literature search was conducted in March 2004. A follow-up search in February 2006 using the search terms "Mesothelioma and non-occupational," "Nonoccupational and Mesothelioma," "Para-occupational and Mesothelioma," or "Building and Mesothelioma" yielded no additional studies of interest. To capture as many relevant articles as possible, the search was initially very broad and queried for all the search terms shown in Fig. 1 in any field of the article. For example, the terms Mesothelioma and Environmental were queried to yield 712 articles in PubMed and 155 articles in TOXLINE, the largest number of published studies for any of the search terms used in our systematic review. The number of articles was subsequently narrowed by removal of duplicates. Articles reporting the following conditions were excluded from our systematic review: erionite exposure, MM not associated with asbestos exposure, MM associated with mixed occupational and NOAE, review articles that did not report new cases, animal studies, and articles written in a foreign language. The remaining articles, including the title, abstract, and all available keywords, were exported to Word software (Microsoft, Redmond, Wash). The software was used to automatically identify potential articles of interest by highlighting the search terms of interest within the title and abstract to facilitate the detection of articles that would provide data for review. Articles that appeared to report at least one original MM case with a clearly defined source of NOAE were selected, identifiying 182 candidate articles with a high likelihood of including cases of MM associated with NOAE. The full texts of these articles were read in an attempt to determine if the MM cases being reported included sufficient information to provide evidence about the various qualitative and quantitative features listed in Table 1.

Nonoccupational asbestos exposures were classified using the categories listed in Table 2. Patients with Malignant mesothelioma with multiple sources of well-described NOAE were included in the review as shown in Table 3 but not in later development of EBCG guidelines. Cases of MM associated with "not otherwise specified" (NOS) NOAE were excluded from the review because they did not provide the detailed information needed to learn

Table 2
Sources of NOAEs

Exposure source	Code	Description	Example(s)
Paraoccupational exposure			
Household/Domestic	HOE	Household contacts of exposed workers	Wives that launder clothes of their husbands who work with asbestos
Work[a]	WE	Indirectly exposed to asbestos activities occurring at their work site	Office worker in a shipyard
Nonoccupational exposure			
Exposure in a particular neighborhood due to a source that is not well described	AMBIENT AIR	Asbestos found in polluted ambient air	Industrial pollution
Neighborhood/Community	NCE	Living near asbestos mine or factory processing asbestos	Live or attend school in vicinity of a textile factory
Building occupant	BOE	Asbestos containing materials	Asbestos tiles, asbestos roofing
Hobby/Home improvement	INCIDENTAL	Use asbestos in course of a hobby or home improvements	Working with insulation, pottery, jewelry, ironing boards
Multiple exposure sources	MULTIPLE	Multiple different nonoccupational exposures	
NOS	NOS	Listed as nonoccupational without additional details	

[a] This category was not included in the analysis because few well-documented cases were available for review.

about the exposure categories listed in Table 2. Of the 182 articles, 61 were selected for inclusion in the final data set for analysis [14,20-26,32-84].

The sources of NOAE were categorized into paraoccupational and other categories shown in Table 2. For purposes of the meta-analysis, data were limited to the 3 nonoccupational exposure groups with the largest number of cases, the household group (HOE), the "Neighborhood/Community" (NCE) group, and the building occupant (BOE) group.

2.2. Extraction of features of interest and categorization of the available evidence regarding the association between MM and NOAE

The data from the 61 publications that provided the core data set for this study were entered into an Access (Microsoft) database, including all available information about the features listed in Table 1. The types of studies and number of MM cases reported in the 61 publications selected for the review were classified into observational, epidemiological, and review studies, as shown in Table 3.

Malignant mesothelioma cases that were published in more than one article were included in our data set as single entries summarizing all available information from each case. The few well-documented cases of paraoccupational asbestos exposure in the workplace (WE) were omitted from later analyses because they might be considered more closely related to occupational than nonoccupation exposures. The data were summarized according to the main sources of exposure: HOE, BOE, and NCE, respectively, as shown in Tables 4-6.

2.3. Assessment of the quality of the available information

The 61 publications used for this systematic review were queried as to whether they included information about the type of asbestos fiber in tissues or other samples, the method, if any, used for fiber burden analysis, whether the source of the NOAE was described, and specific information about MM cell type, smoking history, sex, and other details listed in Tables 5–7. These features were arbitrarily selected as "markers" of the comprehensiveness

Table 3
Malignant mesothelioma associated with nonoccupational exposure to asbestos

Primary type of study	No. of publications reviewed	Total number of MM cases
Observational		
Case report	10	12
Case series	25	606
Epidemiological		
Epidemiology, NOS	3	104
Cohort	10	136
Case control	12	162
Review		
Literature review	1	8
	61	1028[a]

[a] May include duplicate cases, data shown in Tables 4-6 are based on unique cases.

Table 4
Malignant Mesothelioma associated with HOE

	n			
Total number of cases:	150			
Source of data				
No. of papers	23[a]			
Primary type of paper				
Observational	12			
Epidemiological	10			
Review	1			
Sex				
Male	2			
Female	94			
Unspecified	54			
Average age (y)	58.1			
Tumor site				
Pleura	97			
Peritoneum	5			
Other	0			
Unspecified	48			
Tumor cell type				
Unspecified	95			
Epithelioid	23			
Sarcomatoid/Desmoplastic	10			
Biphasic/Mixed	22			
Occupation of asbestos worker				
NOS asbestos worker	61			
Asbestos product manufacturing	26			
Shipyard	27			
Insulator	10			
Cement worker	7			
Pipe fitter	6			
Multiple	4			
Automotive	3			
Refinery	1			
Paper	1			
Merchant marine	1			
Maintenance	1			
Machinist	1			
Construction	1			
Relationship to asbestos worker				
NOS Household contact	88			
Wife	29			
Daughter/Son	17			
Spouse	3			
Mother	3			
Other	2			
Multiple[a]	8			
	No. of cases	Min	Max	Average
Length of exposure (y)				
Pleural	21	2	41	16.1
Peritoneal	4	6	37	22.8
Latency (s)				
Pleural	9	17	46	33
Peritoneal	0			
Type of asbestos				
Crocidolite only	16			
Amosite only	2			
Chrysotile only	1			
Mixed fiber types	23			
Unspecified	108			

[a] Multiple exposure sources, for example, daughter and wife or wife and mother.

Table 5
Malignant mesothelioma in BOEs to asbestos containing materials

Total number of cases	31			
Source of data				
No. of papers	9			
Primary type of paper				
Observational	7			
Epidemiological	2			
Review	0			
Sex				
Male	11			
Female	20			
Unspecified	0			
Average age (y)	64			
Tumor site				
Pleura	25			
Peritoneum	6			
Tumor cell type				
Unspecified	24			
Epithelioid	4			
Biphasic/Mixed	2			
Sarcomatoid/Connective/ Desmoplastic	1			
Source of exposure				
Home	10			
School	18			
Other public building	3			
Profession of exposed patients				
School teacher/ Teacher's aides/ School administrators	16			
Home occupant	10			
Student	2			
Office workers	3			
	No. of cases	Min	Max	Average
Duration of exposure (y)				
Pleural	21	18	20	19
Peritoneal	4	6	12	9
Latency (y)				
Pleural	9	14	60	29
Peritoneal	5	15	60	36.4
No. of cases by type of asbestos				
Unspecified	18			
Mixed fiber types	6			
Chrysotile only	4			
Crocidolite only	1			
Amosite only	1			
Tremolite only	1			

and quality of the 61 studies based on the hypothesis that "ideal reports" would include full diagnostic information using the latest MM pathologic classification schema and modern immunostains, dose of asbestos exposure including concentration of inhaled fibers and length of exposure, fiber type obtained with transmission and/or scanning electron microscopy with x-ray diffractive analysis (EDXA) or comparable methods, and other details.

2.4. Attempt to analyze the data with meta-analysis and develop arbitrary EBCG to assess attribution of causation in individual patients with MM and a history of NOAE

The information collected from the systematic review of the literature was reviewed to determine if there were enough data to perform quantitative meta-analysis; there were not. As there are no widely accepted causation models that help translate data from populations described in observational or epidemiological studies into probabilities of a causal association for individual patients, we developed semiarbitrary rules based on available data regarding the following parameters summarized in Tables 4-6: type of NOAE, tumor location, occupation of the asbestos worker in HOE cases, length of exposure, and length of the latency period. Initially we attempted to develop EBCG that would provide probability statements of causation [85]. This approach requires detailed information about patients in study groups and control groups. The EBCG that would

Table 6
Summary data about patients with MM with NCE

Total number of cases	106			
Source of data				
No. of papers	16			
Type of paper				
Observational	8			
Epidemiological	8			
Review	0			
Sex				
Male	43			
Female	45			
Unspecified	18			
Average age (y)	56.3			
Tumor site				
Pleura	87			
Peritoneum	2			
Other	0			
Unspecified	17			
Tumor cell type (eg, mixed, epithelial)				
Unspecified	100			
Mixed	3			
NOS	2			
Epithelioid	1			
Sarcomatous	1			
Lived in proximity to				
Asbestos mine or mill	13			
Asbestos products factory	12			
Asbestos cement factory	68			
Navy shipyard	2			
Mine or factory	6			
Jute bag recycling business	3			
Dockyard	1			
Iron foundry	1			
	No. of cases	Min	Max	Average
Duration of exposure (y)				
Pleural	2	2	20	10
Peritoneal	2	10	10	10
Latency (y)				
Pleural	10	13	78	43.4
Peritoneal	5	45	47	46
No. of cases by type of asbestos				
Crocidolite only	77			
Unspecified	19			
Mixed fiber types	6			
Chrysotile only	2			
Amosite only	1			
Anthophyllite only	1			

Table 7
Information provided by the study selected to provide best available evidence

	n	%
Asbestos type determined by		
From fiber analysis	20	32.8
Unspecified	19	31.1
Historical/Records	10	16.4
Air sampling/Material analysis	9	14.8
Anecdotal	3	4.9
Type of fiber burden analysis		
None	29	47.5
TEM/EDXA[a]	9	14.8
AB by LM[b]	8	13.1
AB by LM and SEM/EDXA[c]	6	9.8
AB by LM and TEM/EDXA	4	6.6
Unspecified	3	4.9
SEM/EDXA	2	3.3
Smoking history obtained		
Unspecified	43	70.5
Yes	18	29.5
Paraoccupational source job[a]		
Poor	18	50.0
Unspecified	11	30.6
Very good	6	16.7
Good	1	2.8
Paraoccupational source industry[a]		
Very good	17	47.2
Unspecified	12	33.3
Poor	4	11.1
Good	3	8.3
Tumor cell type (eg, mixed, epithelial)		
Unspecified	37	60.7
Yes	24	39.3
Tumor site		
Unspecified	619	60.2
Pleural	393	38.2
Peritoneal	15	1.5
Other	1	0.1
Sex		
Unspecified	573	55.7
Females	314	30.5
Males	141	13.7

[a] TEM indicates transmission electron microscopy.
[b] AB indicates asbestos bodies by light microscopy.
[c] SEM indicates scanning electron microscopy.

provide probability statements of causation could not be developed from our data, as control group information was not available in most of the MM cases reviewed. However, it was noted that certain combinations of specific parameters of MM and NOAE have been described mainly in selected subsets of patients. Based on this simple information, we developed 4 "classes" of association. Class A includes individual MM patients where tissue burden studies of lung tissues show increased levels of ferruginous bodies or asbestos fibers comparable to those of MM caused by occupational exposures. The remainder 3 semiarbitrary classes of individuals, for the assessment of individual MM patients where tissue burden studies are not available, are based on the type of NOAE and the frequency of certain features in the patients selected for review: class B, the association between these features of NOAE and MM has been described in over 15% of the patients reviewed; class C, the association between these features of NOAE and MM has been described in 5% to 15% of the patients reviewed; and class D, the association between these features of NOAE and MM has been described in fewer than 5% of the patients reviewed. The 15% cutoff was arbitrarily selected to include the 3 most frequent occupations of the workers in the HOE group, the 2 most frequent professions of BOE, and the 3 most frequent sources of asbestos in NCE cases. The 5% cutoff was arbitrarily selected to include most reports of single patients or very few individuals with MM.

3. Results

A total of 1028 MM associated with NOAE were described in the 61 articles selected for review (Table 3), but 763 of these cases had to be deleted from further analysis because the reports did not provide information about the source of nonoccupational exposures, the cases had multiple sources of NOAE, or there were only a handful of cases in the nonoccupational exposure group. For example, some cases were described as having NOAE but the type was not determined, or the type of nonoccupational

Table 8
Proposed EBCG for assessing the possible causation of a MM by NOAE[a]

Class A
Tissue burden analysis performed by a qualified laboratory demonstrates significantly increased concentrations in lung tissues of asbestos bodies or longer than 5 μm in length asbestos fibers equivalent to those of patients with MMs caused by occasional asbestos exposure
Class B[b]
Pleural MM and household exposure for a minimum of 2 y as a result of contact with an asbestos product manufacturing, insulator, or shipyard worker
Pleural MM and occupants of asbestos containing building for a minimum of 18 y exposure
Pleural MM and neighborhood/community exposure resulting from living in proximity to an asbestos cement factory
Class C[c]
Pleural MM and household exposure for a minimum of 2 y as a result of contact with cement workers or pipe fitters
Pleural MM and living in proximity to an asbestos mine, mill, or product factory for a minimum of 2 y
Class D[d]
Peritoneal MMs and household or neighborhood/community exposures other than those included in classes B to C
Pleural MM and household exposure for less than 2 y
Pleural MM and household exposure for a minimum of 2 y as a result of contact with cement workers or pipe fitters
Pleural MM and building occupants of asbestos containing building for less than 18 y

[a] The guidelines do not include proposed criteria to assess the differential exposure to amphibole asbestos, chrysotile or mixed exposures as the reviewed cases do not provide sufficient data to evaluate this important characteristic of asbestos exposure.
[b] Class B—the association between these features of NOAE and MM has been described in over 15% of the patients reviewed.
[c] Class C—the association between these features of NOAE and MM has been described in 5% to 15% of the patients reviewed.
[d] Class D—the association between these features of NOAE and MM has been described in less than 5% of the patients reviewed.

exposure was specified but the number of cases was not clearly specified. Tables 4-6 describe the information available in the remaining 287 MM cases reviewed in greater detail, including the NOAE type (HOE, BOE, or NCE), number of MM cases described, number and type of publications, basic patient demographics (age, sex), tumor location, cell type, occupation of the asbestos worker and relationship to the worker in HOE, length of exposure, latency, and number of cases by asbestos type (crocidolite, amosite, chrysotile, mixed fiber exposure, unspecified).

A review of the comprehensiveness and quality of the data reported in the 61 articles selected for review indicates that the quality of the literature regarding the association between MM and NOAE is not up to the standards of best evidence being proposed in the EBM literature [86]. As shown in Table 3, approximately a third of the cases of MM associated with NOAE were described in epidemiological studies. Most of the cases of HOE reported in this type of study lacked sufficient details to distinguish between the specific industry that occupied the asbestos worker and their job title. The epidemiological studies also frequently lacked sufficient information regarding whether the diagnosis of MM was confirmed pathologically by the use of appropriate immunostains and/or electron microscopy. The remainder of the cases of MM associated with NOAE was described in observational studies, mostly case series. As shown in Table 7, these studies frequently lacked controls, specific information about type of asbestos exposure, latency period, and other details. Indeed, Table 7 shows that considerably less than 50% of the 61 articles included in this systematic review included information regarding the asbestos fiber type, fiber burden analysis, histologic type, and even patient sex. In 60% of the cases, the tumor location was not specified. Detailed information regarding the source job and source industry of the asbestos workers related to the patients with MM associated with HOE NOAE was available in less than 50% of the cases. Most of the MM cases resulting from HOE and BOE lacked sufficient information regarding asbestos fiber type. In contrast, all reviewed MM associated with NCE included information about fiber type.

The reports summarized in Tables 4-6 have too many missing data elements to perform quantitative meta-analysis. Table 8 lists the rules proposed to classify the association between MM and NOAE into 4 classes, according to the relative "weight" of the available evidence, as determined by the proportion of reported cases that included various combinations of features. For example, all patients with pleural MM and HOE with a minimum of 2 years contact with an asbestos product manufacturing or shipyard worker are classified as class B. For the HOE cases, where information was available (21/150), 2 years was reported as the minimum duration of exposure to asbestos. Workers occupied in asbestos product manufacturing or shipyards are the only occupational sources for cases of household exposure with greater than 15% of the 150 described. Patients with peritoneal MM associated with HOE or NCE and no fiber burden analysis data are classified as class D, as only 9 cases of the 256 cases were described in association with these categories of NOAE.

Peritoneal MM in NCE was classified as class D, as only 2 of 106 cases has been described in the data set reviewed. As shown in Table 6, the significance of the association between MM and BOE is difficult to determine based on the description, mostly in observational studies of only 31 patients; the type of tumors in 24 of those cases was unspecified.

4. Discussion

This review shows that the literature supplies only limited and incomplete information on the possible association between MM and NOAE. As indicated in Table 3, most of the MMs reported in this context have been encompassed in small case series that frequently lacked control groups, details on asbestos exposure, asbestos fiber type(s), and other data needed to distinguish NOAE-related MM and idiopathic mesothelial neoplasms. Moreover, NOAE-associated MMs in epidemiological reports often were vaguely defined with regard to modes of pathologic diagnosis [21,33,34]. Indeed, the histologic category of MM was not specified in 219 of the 287 cases represented in Tables 4-6; they were nonetheless retained in our review because they did include "best available evidence" regarding other features of interest [14,20-26,32-84]. Information on the duration of exposure, tumor latency, and fiber type(s) was represented in a minority of HOE and BOE MM patients, but fiber type information was available in most of the NCE cases. Approximately 70% of the latter appeared to be associated with exposure to crocidolite. Chrysotile-only asbestos exposure was reported in only 2 of 106 NCE patients. Only 13 cases of peritoneal MM were present among all of the citations in this review; those neoplasms are generally believed to be either idiopathic, or they are associated with extremely high tissue burdens of amphiboles [87,88].

It is difficult to develop EBCG supported by best evidence in the presence of such incomplete and inconsistent information on the characteristics of the association between MM and NOAE. Epidemiological analyses have suggested that NOAE may be associated with the causation of MM, but there is no evidence that can be used to provide reliable probability statements on causation in that context. Information about characteristics of the populations studied, nature of exposure, and pathology are crucial to estimation of likelihood of causation in regard to an individual case of MM [85,89,90].

Table 8 lists the proposed semiarbitrary EGCG for the classification of NOAE-associated MM cases according to the relative weights of available evidence. The EBCG rule in class A is based on the availability of tissue burden analysis data, a method that can provide objective information about

past exposures to amphiboles and chrysotile. The EBCG in classes B to D are based on the proportion of cases having particular combinations of features in the 61 publications under discussion here, using arbitrary 5%, 5% to 15%, and greater than 15% cutoffs. These arbitrary selection criteria do not take into consideration the prevalence of various groups of NOAE; information would provide a denominator to the various proportions of findings used in the EBCG. However, information about the prevalence of various groups of people with NOAE, for example, what proportion of building occupants are teachers or what percentage of housewives married to mechanics had past HOE exposures, is not available in the literature reviewed. Although the use of these semiarbitrary selection criteria may not be the ideal methodology for forming opinions on whether individual MMs were, in fact, caused by NOAE, the EBCG are based on the best approach that we could design to summarize currently available best evidence and do provide a frame of reference to approach that task. The proposed 4 classes of EBCG provide a framework to evaluate the possible causation of individual MM patients by NOAE based on decreasing levels of currently available best evidence. The neoplasms in classes A to C patients are probably caused by NOAE, with decreasing weight of evidence in the 3 classes. There is minimal evidence to support the causation of MM by NOAE in class D patients. There is no evidence or only anecdotal evidence to support a causal association between MM and NOAE in individuals that cannot be classified into any of the 4 classes.

Tort litigation regarding claims of asbestos-related diseases has reached epidemic proportions [91,92]. It is overwhelming the legal system, with over 60,000 cases still to be resolved in US Courts [91,92]. No generally accepted and validated methods currently exist to determine causation in individual MM cases [85,89]. One attempt at providing such guidelines was undertaken several years ago by a group of people interested in this topic; they convened in Helsinki and produced a document concerning attribution guidelines [93]. However, those criteria are much too general for use in assigning attribution of causation in individual cases of MM [5]. Fundamentally speaking, there are no generally accepted and validated methods to translate medical and exposure data from individual patients into legal opinions that are reasonably certain or probable [85,89,90]. Medical information is, by its very nature, “continuous.” In contrast, legal opinion is “Boolean,” requiring arbitrary yes-no decisions. The scientific method is designed to test various theories or hypothesis with experiments, yielding continuous data that are distributed along a spectrum. Thus, the evaluation of such data with statistical methods designed for the study on population groups is difficult to extrapolate to individuals [94]. Various heuristics on medical causation have been proposed in the literature on worker’s compensation to evaluate similar problems [94].

In summary, a systematic review of the available evidence on the possible association between MM and NOAE illustrates that the information in the literature is limited. A 4-tiered system for classification of causation is proposed herein in an attempt to address this issue. It can summarize available evidence and provide a preliminary framework for categorizing individual cases with variable strengths of evidence, concerning possible associations between MM and NOAE. Further reports should investigate this topic further, with efforts to provide complete data regarding diagnostic criteria, fiber type, fiber size, fiber burdens, tumor latency, and other pertinent observations that would allow for development of more precise EBCG.

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