

Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis

Environmental exposure to asbestos and mesothelioma

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Abstract. A number of epidemiological studies have addressed the risk of pleural mesothelioma from environmental (household and neighborhood) exposure to asbestos, but no overall risk estimate is available. We reviewed the epidemiological studies on risk of pleural mesothelioma and household or neighborhood exposure to asbestos. We identified eight relevant studies; most were conducted in populations with relatively high exposure levels. We combined the risk estimates in a meta-analysis based on the random-effects model. The relative risks (RRs) of pleural mesothelioma for household expo-

sure ranged between 4.0 and 23.7, and the summary risk estimate was 8.1 (95% confidence interval [CI]: 5.3–12). For neighborhood exposure, RRs ranged between 5.1 and 9.3 (with a single RR of 0.2) and the summary estimate was 7.0 (95% CI: 4.7–11). This review suggests a substantial increase in risk of pleural mesothelioma following high environmental exposure to asbestos; however, the available data are insufficient to estimate the magnitude of the excess risk at the levels of environmental exposure commonly encountered by the general population in industrial countries.

Key words: Asbestos, Meta-analysis, Non-occupational exposure, Pleural mesothelioma

Introduction

Asbestos and asbestiform fibers are naturally occurring fibrous silicates with important commercial use mainly in acoustical and thermal insulation. They can be divided into chrysotile and the group of amphiboles, including amosite, crocidolite, anthophyllite, actinolite and tremolite fibers. Chrysotile is the most widely used type of asbestos. While all types of asbestos are carcinogenic to the lung and the mesothelium, the biological effects of amphiboles on the pleura and the peritoneum seem stronger than those of chrysotile [1]. The use of asbestos has been restricted or banned in many countries.

In contrast to the large amount of epidemiological studies of asbestos exposure at the workplace, the evidence concerning the health effects of environmental exposure is rather limited. Two main types of environmental asbestos exposure are distinguished: domestic or household and residential or neighborhood exposure. The most common source of household exposure is the installation, degradation, removal or repair of asbestos-containing products. An additional source of household exposure, concerning family members of asbestos workers, is the asbestos dust brought home from the workplace on the clothes.

Neighborhood exposure, which results from outdoor air pollution, is mainly due to asbestos mining

and manufacturing close to the place of residence. It may also result from release of fibers from buildings or other sources, like vehicle brake linings, and from re-aerosolization of fibers following indoor or outdoor sedimentation. In addition, a natural source is the erosion of asbestos or asbestiform rocks.

The assessment of environmental asbestos exposure is difficult since levels are generally low and the duration and frequency of exposure and the type of fiber are seldom known with precision. Table 1 summarizes the results of selected studies on non-occupational exposure to asbestos. In general, levels of indoor exposure show a greater variability than outdoor levels. In some cases, values above 10 fibers/ml have been reported.

While there is a general acceptance that environmental exposure to asbestos may cause pleural mesothelioma, the magnitude of such an effect is not known with precision. We conducted a review of epidemiological studies of pleural mesothelioma and environmental (household and neighborhood) exposure to asbestos; our review also included a quantitative meta-analysis.

Methods

We carried out a literature search on articles included in Medline and Current Contents that appeared

Table 1. Results of selected measurements of non-occupational exposure to asbestos

Source of exposure	Country	Level (fibers/l) (range, mean)	Reference
Mining and industrial sources			
Asbestos cement plant	USA	0.6-2.2	[2]
Asbestos cement plant, mines	Canada	7.8	[3]
Residence of miners	South Africa	2-11	[3]
Near asbestos cement plant	Austria	0-2.2	[3]
Near asbestos deposits	Austria	0-0.5	[3]
Near asbestos cement plant	Italy	48.4	[4]
Geological sites			
Near chrysotile mine	Italy	2.5	[4]
Near tremolite mine	New Caledonia	59-670	[1]
Near erionite sources	Turkey	6	[5]
Near chrysotile mines	France	1-17	[1]
Mining area: 1974	Canada	46	[6]
Mining area: 1984	Canada	10	[6]
Rural and urban pollution			
Large city: Heavy traffic	USA	0.9	[2]
Large city: Expressway	USA	3.3	[2]
Sacramento and San Francisco	USA	1	[7]
Los Angeles	USA	9	[7]
San Jose	USA	150	[7]
Important urban traffic	Austria	4.6	[3]
Urban areas	Canada	2-4	[3]
Urban areas	Germany	0.2-5	[3]
Residence outside mining area	South Africa	0.2-0.8	[3]
Urban area	Italy	5.6	[4]
Rural areas	Japan	4-91	[8]
Urban areas	Japan	4-111	[8]
Urban areas	France	0.47	[9]
Household			
Sweeping houses	New Caledonia	78000	[1]
Colour washing (tremolite)	New Caledonia	558	[1]
Residential	UK	0.4	[10]
Residential	UK	0.28	[11]
Residential	USA	0.1	[12]
Sprayed buildings			
Schools	USA	1-40	[2]
Offices and plant buildings	Austria	< 22	[13]
Schools	UK	0.5	[10]
Schools: Chrysotile	USA	8.3	[14]
Schools: Amphiboles	USA	0.65	[14]
Schools	USA	0.24	[15]
Buildings	Canada	0.42	[16]

between 1966 and 1988. In order to identify additional studies we systematically searched the contents of key journals and the lists of references of all identified studies.

We analysed those studies which provided results on pleural or peritoneal mesothelioma from household or neighborhood exposure by inhalation. We retained only studies comparing clearly defined exposed and unexposed groups, including those using an ecological approach. The interpretation of ecological studies is, however, limited by the lack of individual information on asbestos exposure and potential confounders. We excluded a small number of case reports

and case series because of the lack of a definition of the population at risk and of a comparison group. Finally, only studies were included for which a risk estimate and its variance or confidence interval (CI) either were reported or could be obtained from the raw data. When the same population had been studied several times, we used only the most recent report.

We included studies presenting results on either mortality or incidence since the average survival from mesothelioma is low. We focused on adult neoplasms, since mesothelioma is very rare in children [17].

We extracted from each study the main characteristics of the design, the definition of asbestos

exposure, the predominant type of asbestos fiber, the risk estimate (rate ratio, odds ratio, standardized mortality ratio, thereafter denoted as relative risk [RR]) and its variance, back calculated from the CI if not available. In addition to a narrative review of the studies, we performed a meta-analysis on a random-effects model [18], which takes into account additional inter-study variability into the calculation of combined risk estimate and its variance.

We considered separately household and neighborhood exposure to asbestos. Since results in women are less likely to be confounded by concomitant occupational exposure to asbestos, we focussed on results specific to women. If a study provided separate results for men and women, we combined them and considered also the combined estimate.

We also stratified the studies according to the design of the study (cohort, case-control and ecological) and to the predominant type of asbestos (chrysotile, amphiboles, and mixed or unspecified), as defined by the authors of the original reports.

Results

Only two studies [19, 20] presented results on peritoneal mesothelioma following environmental asbestos exposure. Newhouse and Thompson [20] reported two cases of peritoneal mesothelioma in women with household exposure, none with neighborhood exposure and seven cases, including three in men, without evidence of occupational or environmental exposure to asbestos. Vianna and Polan [19] reported eight cases of peritoneal mesothelioma among women without occupational exposure: household exposure was reported for seven of them, and residential exposure for three, including the case without the household exposure.

We retained eight studies providing results on pleural mesothelioma [20-25] (Table 2). Two studies were from USA or Canada, two from UK, two from Italy, and one each from South Africa and Turkey. Four studies had an ecological design, one was a cohort study and three were case-control studies. Two studies investigated populations predominantly exposed to amphibole asbestos, while the main exposure was chrysotile in two studies and in the remaining four studies there was no clear indication of a predominant type of asbestos. Three studies presented separate analyses on neighborhood and household asbestos exposure for a total of six studies reporting risk estimates for neighborhood exposure and five studies reporting risk estimates for household exposure.

Four studies reported estimates of standardized mortality ratios of mesothelioma based on ecological assessment of asbestos exposure. Residents of three crocidolite mining districts in South Africa had a ninefold increased mortality as compared to the population of the region [21]. Residents in three

villages in South-eastern Turkey used whitewash and stucco contaminated with tremolite fibres: the standardized mortality ratio of mesothelioma was 21, as compared to non-contaminated villages [5]. Other studies reported an excess of mesothelioma following similar exposure circumstances to reunite in Central Turkey [26]. Finally, a study from Quebec, Canada, reported seven deaths (0.92 expected) among women resident in villages with chrysotile mines, with an estimated prevalence of occupational exposure of 5% [6]. The incidence of pleural mesothelioma was 5.8-fold higher among residents of an Italian city with an asbestos cement factory, after exclusion of occupationally related cases, as compared to the region [24]. An additional study reported three deaths from mesothelioma among women in New Caledonia during 1978-1987, which represents a fivefold excess when compared to rates in New South Wales, Australia [27].

In a cohort study of non-occupationally exposed wives of asbestos workers from Italy, three deaths from pleural mesothelioma were reported, which represented a 8-fold excess risk [23]. Three case-control studies analyzed the risk of pleural mesothelioma from household or neighborhood exposure to asbestos. Risk estimates were elevated in one early case-control study from the UK [20]. In the other two studies, the RR from household exposure was in the order of 5; the risk from residential exposure, on the other hand, was not increased in one of these studies, from the USA and Canada (exposure defined as living within 20 miles of chrysotile mines) [22], while it was increased in the other study, from London (exposure defined as residence within 0.5 km of industrial sources) [25].

Table 3 presents the results of the meta-analysis. The combined RR for neighborhood exposure was 7.0 (95% CI: 1.8-7.0). There was a non-significant increased risk in the two studies considering mainly chrysotile exposure. The design of the study did not seem to influence the combined risk estimate; similarly, the results did not change depending on whether the studies considered mortality or incidence of cancer or according to gender (results not shown in detail).

The combined RR of pleural mesothelioma from household exposure was 8.1 (95% CI: 5.3-12). All but one study were conducted in areas at either predominant or concomitant amphibole exposure, a fact that limited the analysis according to fiber type.

Discussion

The main result of this analysis is a strong relationship between pleural mesothelioma and high environmental exposure to asbestos, whether the source of exposure is domestic or neighborhood. The results also suggest a higher risk from exposure to

Table 2. Studies on environmental exposure to asbestos and pleural mesothelioma included in the meta-analysis

Country	SD	O	TF	Study design	E	Sex	Occ	Ca	RR	95% CI	Ref.
South Africa*	Ec	M	A	Non-Blacks residents in three crocidolite districts in Northern Cape region, 1968-1977, compared to region	N	F	<1	30	9.3	6.3-13	[21]
Canada**	Ec	M	C	Women residing in two chrysotile mining areas in Quebec, Canada, during 1970-1989, compared to province	N	F	5	7	7.6	3.1-16	[6]
Canada, USA	CC	I	C	307 pleural mesotheliomas and matched controls, 1967-1975, interviews to relatives. Exposures were contact with dusty clothing of asbestos workers and residence within 20 miles of asbestos mines	H	M + F	0	8	4.0	0.8-19	[22]
					N	M + F	0	1	0.2	0.01-1.7	
Italy	Co	M	UM	1740 wives of asbestos cement workers, follow-up 1965-1988, compared to region	H	F	0	3	7.8	4.3-12	[23]
Italy	Ec	I	UM	Residents in a city with asbestos cement plant (1-11 fb/l), 1980-1989, compared to national rates	N	F	0	16	8.2	5.0-13	[24]
					M	M	0	20	5.1	2.4-7.8	
Turkey	Ec	I	A	Residents in three rural districts using tremolite-rich withewash or stucco, 1977-1978, compared to neighboring districts	H	M + F	0	22	21.0	2.8-156	[5]
UK	CC	M	UM	Cases (mostly deceased) from one hospital, living hospital controls, use of interviews and workplace and medical records. Exposures were relative of an asbestos worker and living within 0.5 miles of an asbestos factory	H	M + F	0	7	23.7	4.7-120	[20]
					N	M + F	0	11	7.5	2.5-22	
UK	CC	M	UM	185 deceased cases from one district, 159 necropsy controls, questionnaire to relatives. Exposures were likely or possible domestic exposure and living within 0.5 km of one industrial asbestos source	H	M + F	0	17	5.8	1.7-19	[25]
					N	M + F	0	5	6.6	0.9-50	

SD, study design: Ec, ecological study; Co, cohort study; CC, case-control study; O, outcome; M, mortality; I, incidence; F, predominant type of fiber: A, amphiboles; C, chrysotile; UM, unspecified and mixed; E, type of exposure: N, neighborhood; H, household; Sex: F, female; M, male; Occ, percentage of subjects with occupational exposure to asbestos; Ca, number of exposed cases; RR, relative risk; CI, confidence interval; Ref., reference.

* Including cases of asbestosis.

** Pleural tumors.

Table 3. Results of the meta-analysis of studies on environmental exposure to asbestos and pleural mesothelioma

	Neighborhood exposure			Household exposure		
	N	RR	95% CI	N	RR	95% CI
All studies	6	7.0	4.7-11	5	8.1	5.3-12
Type of fiber						
Chrysotile	2	1.5	0.04-53	1	4.0	0.8-20
Amphiboles	1	8.7	6.7-11	1	21	2.8-157
Mixed/unspecified	3	6.7	4.4-10	3	8.2	5.2-13

N = Number of studies; RR = relative risk; CI = confidence interval.

amphiboles than from exposure to chrysotile. Most of the available studies addressed the effect of long-term environmental exposure.

A problem in the interpretation of our results depends from the fact that the studies investigated different sources of environmental asbestos exposure. Natural sources were included in the study from Turkey, while mining represented the main source of environmental exposure in studies from Canada, South Africa and the USA, and asbestos cement plants were the main source of exposure in Italy and the UK.

However, the studies included in the meta-analysis addressed circumstances of exposure to relatively high levels of asbestos. No epidemiological studies are available on more common situations such as exposure in buildings, in schools, or in the general urban environment. The results of our meta-analysis are therefore likely to overestimate the risk of environmental asbestos exposure experienced by residents of industrialized countries without a specific source of exposure; they are, however, useful to indicate a plausible upper range of the risk from environmental asbestos exposure.

One possible limitation of our review and meta-analysis is publication bias. Publication bias may occur when studies are performed but not published, a reason not to publish a study being the fact that it did not show a strong association. Ignoring these results may lead to overestimate the effect of exposure. A second case of publication bias occurs when studies are published but not identified in the literature review. We tried to minimize this potential bias by using various source of references. A third source of publication bias depends on the inclusion criteria of our meta-analysis. We excluded one study that did not provide the number of exposed cases [28] and a few studies which did not provide a comparison with a reference population (e.g., the studies by Goldberg et al. [27 and Anderson [29]). The size of a study has an impact on the precision of the resulting risk estimate, thus affecting the level of statistical significance of any increase or decrease in risk. It is therefore plausible that results of small studies that did not

show a significant result, are less likely published than results of larger studies. In order to assess publication bias, the risk estimates from individual studies can be plotted against the inverse of their variance [30]. The plot for pleural mesothelioma (Figure 1) did not suggest that small negative studies were missing for the set of results we used, speaking against publication bias.

Heterogeneity across studies may result from chance, from different strategies of adjustment for potential confounding factors, and from differences in definition and assessment of exposure, in level and duration of exposure, and in ascertainment of diagnosis. A meta-analysis can help to elucidate the impact of such factors.

A potential confounding factor in this study is represented by concomitant occupational exposure to asbestos, particular in studies collecting information on asbestos exposure from proxies. In some studies, household exposure of women was assessed based on questionnaires on the occupational history of patients and their relatives [19, 20]. In some cases the authors excluded subjects with occupational exposure [23, 24]. Respondents in a study from Canada and the USA were asked whether any member of the household had brought home some dusty clothing and, if so, the nature of the work [22]. The proportion of subjects included in the meta-analysis who might have been exposed to asbestos in the workplace is very small (Table 2).

Another possible source of bias deals with outcome misclassification and is relevant in particular when the diagnosis of mesothelioma is derived from death certificates [31]. However, only one of the studies on mesothelioma included in the present meta-analysis was based on death certificates [23], and its exclusion would not affect the overall results. Underdiagnosis will not lead to bias as long as both the exposed and the unexposed populations are concerned in the same proportion. In contrast, bias may arise when diagnosis is related to exposure, as in the case of a higher probability of diagnosis among subjects exposed to asbestos. As an example, in a mining area of Quebec

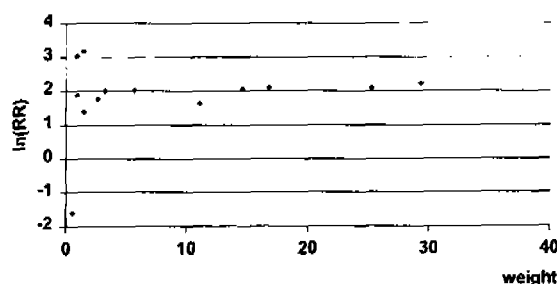


Figure 1. Plot of logarithm of relative risks [$\ln(RR)$] and weights used in the meta-analysis (inverse of variance of relative risk) of studies on mesothelioma risk from environmental exposure to asbestos.

with high rates of mesothelioma, overdiagnosis was suggested after review by a pathology panel [32].

Comparison of RRs between different study populations is feasible if the populations experienced similar levels of exposure, as is probably the case in our meta-analysis. However, even if there were a common underlying dose-response curve of risk from asbestos exposure, the RRs reported in each study would be modified by the mean cumulative exposure in each population. Unfortunately the required information (e.g., average lifetime cumulative asbestos exposure) was not available from most studies.

A higher risk of mesothelioma from exposure to amphiboles than to chrysotile has been suggested from studies of occupational cohorts: [33] our meta-analysis indicates that this pattern may also hold for environmentally exposed populations, although the difference is not statistically significant and it should be interpreted with caution.

The excess risk of mesothelioma is lower than that reported among workers occupationally exposed to asbestos: most cohort studies, however, refer to exposure circumstances in the order of 1000–100,000 fibers/l [1], that is, two or three orders of magnitude higher than the exposures encountered in most non-occupational circumstances (Table 1).

In conclusion, our meta-analysis showed an increase of several folds in mesothelioma risk among subjects at high levels of environmental exposure to asbestos. The available data are insufficient to estimate the magnitude of the risk at the levels of environmental exposure encountered by the majority of the population in industrial countries. It is plausible, however, that such low levels are responsible for a sizable number of mesothelioma cases, although a precise quantitative estimate of the risk cannot be based only on the results of this meta-analysis.

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