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ORIGINAL ARTICLE

Risk of mesothelioma after cessation of asbestos exposure: a systematic review and meta-regression

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Abstract

Purpose A 'risk reversal' has been observed for several human carcinogens following cessation of exposure, but it is unclear whether it also exists for asbestos-related mesothelioma.

Methods We conducted a systematic review of the literature and identified nine studies that reported information on risk of mesothelioma after cessation of asbestos exposure, and performed a meta-regression based on random effects models. As comparison we analyzed results on lung cancer risk from four of these studies.

Results A total of six risk estimates from five studies were included in the meta-analysis. The summary relative risk (RR) of mesothelioma for 10-year interval since cessation of exposure was 1.02 [95% confidence interval (CI) 0.87–1.19; *p*-heterogeneity 0.01]. The corresponding RR of lung cancer was 0.91 (95% CI 0.84–0.98).

Conclusions This analysis provides evidence that the risk of mesothelioma does not decrease after cessation of asbestos exposure, while lung cancer risk does.

Keywords Asbestos · Mesothelioma · Time since last exposure

Introduction

The fact that quitting exposure to most carcinogens, including tobacco smoking, reduces the relative risk of cancer has been known for several decades (IARC 2007). The effect of discontinuing an exposure and the accompanying "risk reversal" follows different patterns for various smoking-related cancers. For example, in the case of lung cancer, it is well established that (1) the relative risk diminishes within few years of cessation, (2) the pattern of risk reversal is similar no matter the age at quitting, and (3) even after long-term quitting, an excess risk persists: for example, the risk at 75 years for smokers who quit at age 30 is about twice that of never smokers of comparable age (Brennan et al. 2006).

The possible effect of quitting exposure to asbestos on the risk of mesothelioma has been studied less extensively, since in the early analyses of cohort studies, characterized by high risk of the disease, there was a relatively small proportion of workers with sufficient time since cessation of exposure to produce stable risk estimates. A few studies from the 1980s and 1990s reported results according to time since elimination of the source of exposure (e.g., closure of the plant in which workers from the cohort had been employed). These results pointed toward the persistence of an increased risk; however, they were not based on estimates of time since cessation of exposure and onset of disease for individual subjects. For example, in a study of German workers enrolled in a surveillance program, mortality from mesothelioma remained elevated 10 years after cessation of exposure (Woitowitz et al. 1986), and in a study of Swedish

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shipyard workers, a standardized incidence ratio (SIR) of 7.3 was reported 7–15 years after banning asbestos use in the industry (Sandén et al. 1992).

In recent years, a growing number of studies have analyzed the risk of mesothelioma after cessation of asbestos exposure, based on individual-level data. Some of these studies were included in a review of the effects of recent versus older exposure we published a few years ago (La Vecchia and Boffetta 2012). We have now conducted a systematic review of cohort and case–control studies that reported results on risk of mesothelioma after quitting asbestos exposure, aiming at performing a meta-regression analysis.

Methods

The systematic review and meta-analysis was conducted in April 2018 according to the MOOSE guidelines (Stroup et al. 2000). All steps were conducted independently by two authors (PB, FD), and differences were resolved by consensus.

Selection of studies

We conducted a search in PubMed using the keywords (*quit* or cessation or stop**) *and asbestos and* (*pleura or peritoneum or mesothelioma*). We also reviewed the lists of references included in recent reviews of asbestos exposure and mesothelioma risk (e.g., Boffetta 2014), as well as the lists of references of studies identified in the search. When a study has been reported in multiple publications (e.g., subsequent follow-up of the same cohort), we used only the most informative report (e.g., that including the largest number of deaths). The primary outcome of interest was mesothelioma, but in several studies results were reported for pleural or peritoneal cancers.

Abstraction of data

We reviewed the original publications and abstracted information on (1) total number of subjects and person-years in the cohort, of cases or deaths of mesothelioma or pleural/peritoneal cancer, and of controls, as appropriate; (2) type of asbestos to which the study population was exposed, if available; (3) average duration of exposure of the study population; (4) risk estimates of the outcome of interest, together with 95% confidence intervals (CI), separately for categories of time since last exposure. Risk estimates included standardized mortality ratios (SMRs), rate ratios, or relative risks (RRs) and odds ratios (ORs). If results based on external comparisons (e.g., SMRs) as well as internal comparisons (e.g., ORs or RRs) were reported for the same study, we considered both types of results, but we gave priority to those based on internal comparisons. If multiple sets of results of internal comparisons were reported (e.g., results of regression models including different variables), we gave priority to those based on a larger number of variables. Results based on mortality or incidence of mesothelioma or pleural/peritoneal cancer were included. In the study by Lacourt et al. (2012), RRs and CIs were calculated by combining through a fixed-effects meta-analysis the results for two categories of duration of exposure. We also abstracted comparable results on risk of lung cancer from the studies that reported them.

Meta-regression

We conducted dose–response meta-analyses (meta-regressions) of the available results, using a two-stage approach (Greenland and Longnecker 1992), in which we first estimated the RR for an interval of 10 years since last exposure for each outcome within each study, based on a linear model, and then combined the study-specific RRs according to a random-effect meta-analytic model (DerSimonian and Laird 1986). This approach is based on the assumptions that (1) the change in risk, if any, is linear and constant across the whole interval of time since last exposure analyzed by the different studies, and (2) the relationship between time since last exposure and risk is the same for pleural and peritoneal mesothelioma. Only studies providing details on numbers used to calculate risk estimates (number of cases and number of controls or person-years) in each category of time since cessation of exposure were included in the meta-regression, which was based on the program *glst* of STATA (Orsini et al. 2006).

Results

A total of eight studies were identified, that provided results on risk of pleural mesothelioma according to time since cessation of asbestos exposure (Fig. 1). The key characteristics of their design are summarized in Table 1. Seven were industry-based studies, of either cohort or nested case–control design, and one was a community-based case–control study. Six studies were based on death certificates (five investigated pleural or peritoneal cancer, one mesothelioma), the remaining two studies were based on mesothelioma incidence data.

Industry-based studies

Magnani et al. (2008) studied a cohort of 3434 asbestos cement workers (2657 men, 777 women) from northern Italy, active in 1950 or hired between 1950 and 1986 and followed up for mortality between 1965 and 2003. Regional mortality rates were used as reference. The average duration of exposure was 16.2 years. The SMR analysis was based on

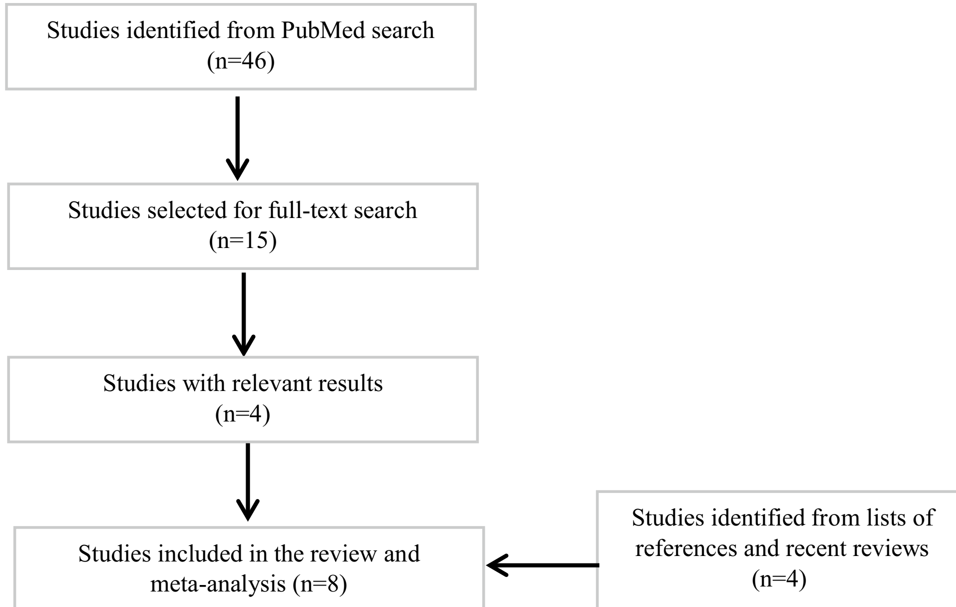

Fig. 1 Flow-chart of selection of studies that provided results on risk of pleural mesothelioma according to time since cessation of asbestos exposure

135 observed and 3.6 expected deaths from pleural cancer (SMR based on data reported in the article 37.5; 95% CI 31.4–44.4). The authors conducted a regression analysis, based on 139 cases of pleural cancer that included terms for time since first exposure, duration of exposure and time since last exposure, as well as age, sex, and period of follow-up. No trend was suggested in the analysis by time since last exposure, in which the reference category was set at 3–15 years since last exposure (Table 2). The risk among workers with more than 30 years since last exposure was similar to that of workers with less than 3 years since last exposure.

Harding and Darnton (2010) analyzed the data of the Great Britain Asbestos Workers Survey that included over 98,000 asbestos workers recruited since 1971, and followed up for mortality during 1988–2005. The survey recruited asbestos-exposed workers on a voluntary basis during 1971–1983, when statutory medical examinations were required for all exposed to asbestos above a certain level. The average duration of exposure, estimated from the categories reported in the article, was 21.0 years. During the follow-up a total of 649 deaths from mesothelioma were observed (48 expected; SMR 13.5; 95% CI 12.5–14.6). In a multivariate model, including age and sex, the RR of mesothelioma did not decrease with time since last exposure (Table 2).

Pesch et al. (2010) studied a cohort of 576 male former asbestos workers enrolled in a screening program from Germany between 1993 and 1997, and followed up to 2007. Median duration of exposure was 20 years. A total of 15 deaths from pleural cancer were observed, compared to 0.53 expected based on national rates (SMR 28.1; 95% CI 15.7–46.4). In a multivariate analysis, the RR was 0.1 (95% CI 0.0–0.6) for 30 years or more versus less than 30 years since last exposure (Table 2). However, in the same multivariate model, there was also a significant inverse relation with duration (RR 0.1; 95% CI 0.0–0.7, for 20 or more versus less than 20 years of exposure). The number of variables in the model was not specified, but was probably too large, given the small number of deaths, and there was a large difference between that adjusted results and those based on the univariate model (RR for 30 or more years since last exposure 0.5; 95% CI 0.2–1.5). The results of the multivariate model should, therefore, be interpreted with caution.

Pira et al. (2016) updated the follow-up of a cohort that had been studied in two previous occasions (Pira et al. 2005, 2007). The cohort included 1977 workers (894 men, 1083 women) employed by an Italian asbestos textile company between 1946 and 1984, and followed up to death, loss to follow-up, age 85, or 30 November 2013, for a total of 74,126 person-years of observation. Workers were exposed to amphibole asbestos, mainly crocidolite, and a large proportion of them were employed for a short period (691 workers (35.0%) were employed for less than 1 year, and 28,363 person-years (38.3%) were enumerated in this category). The average duration of exposure, estimated from the categories reported in the article, was 4.4 years. Regional and national rates were used as reference. The number of observed pleural cancer deaths was 60, resulting in a SMR of 33.7 (95% CI 25.7–43.4). The SMR of pleural cancer increased during the first 2 decades after cessation of exposure and remained elevated thereafter, although a decline in the excess risk was suggested 35 or more years after last exposure. The results of an internal analysis based on multivariable Poisson regression and adjusted for age and sex confirmed this pattern (Table 2;

Table 1 Selected characteristics of studies included in the review

References	Study design	Industry	Asbestos type	Country	Period of employment	Period of follow-up	Outcome	Sex	Number of workers	Pleura mesothelioma cases/deaths	Peritoneal mesothelioma cases/deaths	Adjustment
Magnani et al. (2008)	Co	Cement workers	PC	Italy	1950–1986	1965–2003	Mo–PC	M	3434	139	–	A, S, P, TSF, D
Harding and Darnton (2010)	Co	Mixed	Mix	UK	1971–1983	1988–2005	Mo–Me	PM	98,117	649	–	A, S
Pesch et al. (2010)	Co	Workers enrolled in screening program	Mix	Germany	1993–1997[a]	1993–2007	Mo–PC	M	576	15	–	NAv
Pira et al. (2016)	Co	Textile product manft	Mix	Italy	1946–1984	1946–2013	Mo–PC	MF	1977	60	48	A, S, TSF
Levin et al. (1998)	Co	Asbestos insulation material manft	A	USA	1954–1972	1954–2011	Mo–PC	PM	1130	16	7	A, S, P
Swiatkowska and Szeszenia-Dabrowska (2017)	NCC	Workers in surveillance program	Mix	Poland	NAv	2000–2014[b]	Inc–Me	PM	NAp	131	–	A, S, Av, D, Cr
Pira et al. (2017)	Co	Miners	C	Italy	1930–1990	1946–2014	Mo–PC	M	1056	7	1	A,S
Lacourt et al. (2012)	CCC	NAv	Mix	France	NAp	1987–1993; 1998–2006[b]	Inc–Me	M	NAp	1041	–	A, Av

Study design: *Co* cohort study, *NCC* case–control study nested in cohort, *CCC* community-based case–control study. Asbestos type: *A* amosite, *C* chrysotile, *Mix* mixed, unknown, *PC* predominantly chrysotile, *Mo* mortality, *Inc* incidence, *PC* pleural/peritoneal cancer, *Me* mesothelioma, *M* male, *PM* predominantly male, *MF* male and female. Adjustment (variables adjusted for in the analysis of time since last exposure): *A* age, *S* sex, *P* calendar period, *TSF* time since first exposure, *D* duration of exposure, *Av* average exposure, *Cr* crocidolite exposure

[a]Period of enrolment in the program

[b]Period of ascertainment of cases. *NAp* not applicable, *NAv* not available

Table 2 Relative risk of mesothelioma and lung cancer after cessation of asbestos exposure

References	YSLE	Pleural mesothelioma			Peritoneal mesothelioma			Lung cancer		
		N	RR	95% CI	*N*	RR	95% CI	*N*	RR	95% CI
Magnani et al. (2008)	< 3	13	0.67	0.32–1.40				21	0.38	0.22–0.65
	3–15	55	1	Ref.				125	1	Ref.
	15–30	55	0.9	0.53–1.43				89	0.70	0.52–0.95
	> 30	16	0.65	0.26–1.63				23	0.56	0.35–0.92
Harding and Darnton (2010)[a]	< 10	334	1	Ref.						
	10–20	225	0.90	0.76–1.08						
	20–30	89	0.99	0.78–1.26						
	> 30	1	0.99	0.14–7.02						
Pesch et al. (2010)	< 30	8	1	Ref.				4	1	Ref.
	30 +	7	0.1	0.01–0.6				4	0.1	0.01–2.0
Pira et al. (2016)	< 15	7	1	Ref.	5	1	Ref.	41	1	Ref.
	15–29	27	3.56	1.53–8.31	24	3.58	1.34–9.54	58	1.10	0.72–1.67
	30+	26	3.10	1.26–7.67	19	2.08	0.73–5.89	44	0.67	0.42–1.06
Levin et al. (1998)[bc]	0–5	1	481.9	12.20–2685	0	0	NA			
	5–10	0	0	NA	0	0	NA			
	10–15	0	0	NA	0	0	NA			
	15–20	0	0	NA	1	35.09	0.89–195.5			
	20–25	0	0	NA	1	28.53	0.72–159.0			
	25–30	3	241.2	19.47–580.7	0	0	NA			
	30+	12	416.3	215.1–727.2	5	31.31	10.17–73.07			
Swiatkowska and Szeszenia-Dabrowska (2017)[c]	5	NA	1	Ref.						
	10	NA	1.27	0.90–1.80						
	20	NA	1.96	0.81–4.78						
	30	NA	2.70	0.84–8.65						
	40	NA	3.46	0.76–15.1						
Pira et al. (2017)[e]	< 1	4[d]	1	Ref.				2	1	Ref.
	1–9							12	2.97	0.60–14.7
	10–29							22	1.63	0.32–8.24
	30 +	3	0.75	0.15–3.84				17	2.12	0.38–11.8
Lacourt et al. (2012)[c]	0	NA	*1*	*Ref.*						
	10	NA	*1.4*	*0.8–2.0*						
	20	NA	*2.2*	*0.9–3.5*						
	30	NA	*2.5*	*0.7–4.2*						
	40	NA	2.3	1.1–4.8						
	50	NA	1.9	0.7–5.0						

Results in italics were derived from data reported in the original papers

YSLE years since last exposure, *N* number of deaths, *RR* relative risk, *CI* confidence interval, *NA* not available, *Ref.* reference category

[a] Results refer to pleural and peritoneal mesothelioma combined

[b] Results are expressed as SMR

[c] Results not included in the meta-regression because of lack of number of exposed cases, controls or person-years

[d] < 30 years since last exposure

[e] Results obtained from the original investigators

p value of test for linear trend, 0.03). The SMR for peritoneal cancer was 29.1 (21.5–38.6), based on 48 observed deaths. The SMR of peritoneal mesothelioma increased until 25 years after cessation of exposure, and decreased for longer time since quitting exposure. A similar pattern was suggested by the Poisson regression analysis (*p* value of test for linear trend, 0.5).

Levin et al. (1998) extended the follow-up of a cohort of 1130 workers employed in the manufacturing of asbestos pipe insulation from 1954 to 1972, who were exposed to amosite (Levin et al. 1998). Follow-up to mortality was conducted to 2011, national rates were used as reference. More than half of cohort members were employed less than 3 months; the average duration of exposure, estimated from the categories reported in the article, was 1.1 years. The SMR for pleural cancer was 222.5 (95% CI 12.71–361.4, based on 16 deaths), that of peritoneal cancer was 21.45 (95% CI 8.62–44.19, based on 7 deaths). The authors reported an analysis according to time since last exposure: although results were unstable in most categories because of the small number of events, there was no evidence of a decreased risk 30 or more years after last exposure.

Swiatkowska and Szeszenia-Dabrowska (2017) conducted a case–control study nested in the Polish national surveillance program of asbestos workers, the majority of whom were employed in the asbestos cement industry. Among workers examined during 2000–2014, 131 cases of pleural mesothelioma were identified, and were individually matched on sex and year of birth to 5 controls selected from alive participants in the program, for a total of 655 controls. Average duration of exposure was 13.9 years for cases and 13.7 years for controls. Most subjects were exposed to crocidolite in addition to chrysotile. Multivariate logistic regression models were used to estimate odds ratios (ORs), adjusted for birth year, sex, estimated average exposure, duration of exposure and crocidolite exposure. For continuous variables, including time since last exposure, restricted cubic spline functions were used to estimate dose–response. Results for time since last exposure were reported for 5 years (reference category), 10 years, 20 years, 30 years, and 40 years, and are summarized in Table 2. An increased risk of mesothelioma was suggested according to time since last exposure, although the risk estimates did not reach the formal level of statistical significance. In particular, the OR for 30 years since last exposure was 2.70 (95% CI 0.84–8.65) and that for 40 years since last exposure was 3.46 (95% CI 0.76–15.1). However, when cumulative exposure to asbestos was entered in the regression model, the OR for the latter group became statistically significant (RR 2.68; 95% CI 1.16–6.21).

Pira et al. (2017) updated a cohort of 1056 men employed for at least 1 year during 1930–1989 in an asbestos mine in northern Italy, which was studied by Rubino et al. (1979), Piolatto et al. (1990) and Pira et al. (2009). The cohort was followed up from 1946 to 2014 for a total of 37,471 person-years of observation. The average duration of exposure, estimated from the categories reported in the article, was 13.1 years. Seven deaths from pleural cancer were observed, yielding a SMR of 5.54 (95% CI 2.22–11.41). No trend was observed according to time since last exposure (p value of test for linear trend, 0.32; Table 2).

Community-based studies

Lacourt et al. (2012) compared cases of mesothelioma either diagnosed between 1987 and 1993 in hospitals located in five regions of France or included in a national surveillance program conducted during 1998–2006 in 22 districts; controls were healthy individuals who either participated in a national survey conducted in 2007 or were included in one of 15 population-based case–control studies conducted in various regions of France during 1984–2000. Information on occupational asbestos exposure was collected with different instruments in the original studies. The methodological limitations of the approach chosen study, and the potential resulting bias have been discussed (Boffetta et al. 2018a). The analysis was restricted to 1041 male cases of mesothelioma and 1425 non-cases who were exposed to asbestos. Table 2 summarizes the results by time since quitting asbestos exposure. These results suggest that the risk of pleural mesothelioma increases after cessation of exposure, and may remain elevated even 50 years of cessation; in addition, the effect might be stronger after cessation of longer exposure than after cessation of shorter exposure. However, given the methodological limitations of this study, which was based on series of cases and non-cases enrolled in different geographic areas and time periods, and based on different instruments, special care should be applied in the interpretation of these results.

Meta-regression

The meta-regression included six sets of results from five studies, listed in Table 2. The study-specific RRs for an increase in 10 years since last exposure ranged from 0.60 to 1.36 (Fig. 2); the summary RR was 1.02 (95% CI 0.87–1.19; p value of test for heterogeneity 0.01). The data were too sparse to explain the heterogeneity of result across studies based on characteristics of exposure (e.g., duration, type of asbestos) or outcome. A comparable meta-regression of results on risk of lung cancer after cessation of exposure included four studies (Table 2) and resulted in a summary RR of 0.91 (95% CI 0.84–0.98; p-heterogeneity 0.42).

Discussion

Our meta-analysis of studies reporting individual-based results on risk of mesothelioma by time since cessation of asbestos exposure supports the hypothesis that a decrease in risk does not occur following cessation of exposure. The summary RR per 10-year increase in time since last exposure was 1.02, with 95% CI 0.87–1.19. Although some studies were excluded from the meta-analysis because of lack of number of exposed cases, controls or person-years, (Levin

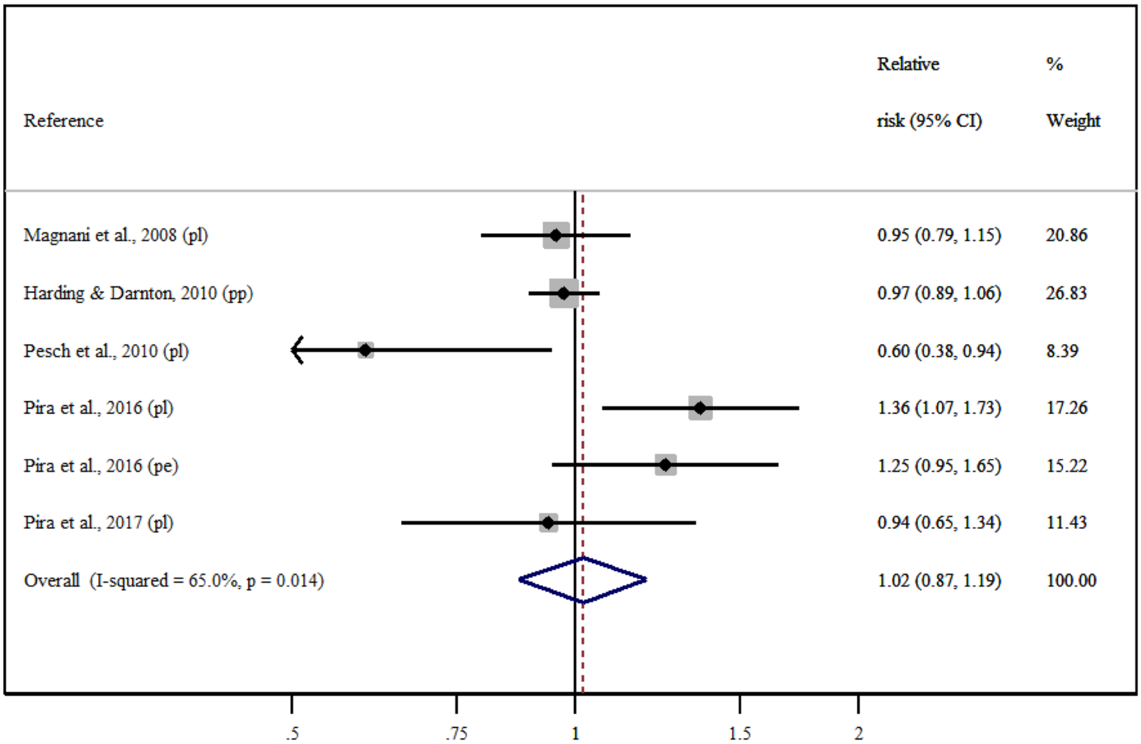

Fig. 2 Meta-analysis of study-specific RRs for an increase in 10 years since last asbestos exposure. *pe* peritoneal mesothelioma, *pl* pleural mesothelioma, *pp* peritoneal and pleural mesothelioma

et al. 1998; Swiatkowska and Szeszenia-Dabrowska 2017; Lacourt et al. 2012), their results are consistent with this conclusion.

The meta-analysis confirms the conclusion of an earlier review, conducted by some of us on a smaller number of studies (La Vecchia and Boffetta 2012). This result is also consistent with a theoretical model of mesotheliomagenesis in which the risk mainly increases with time since beginning of exposure (latency) and is not modified by duration of exposure or time since cessation of exposure. Despite providing the strong evidence on the lack of a decrease in risk of mesothelioma following cessation of asbestos exposure, our results suffer from limitations which may complicate their interpretation. First, the number of cohort and case–control studies that provided individual results on time since cessation of exposure is rather small; in particular, results on mesothelioma arising three of more decades after cessation of exposure are sparse.

Second, our results rest on the assumptions that cessation of employment in the industry or occupation under study translated into cessation of asbestos exposure. This assumption has several ramifications: on the one hand, workers were considered exposed until the last date of employment, despite the fact that in many 'asbestos' industries the proportion of workers who were actually exposed to the agent decreased over time, e.g., in the years before the closure of the factory under study. Conversely, the assumption implies that cohort members did not move to another asbestos-exposed job after cessation of employment in the industry under study. This is a reasonable assumption for workers last employed in the 1990s, when asbestos exposure was being phased out, but may result in overestimation of time since cessation of exposure in workers who left the cohorts in earlier decades, and might have been exposed to asbestos in subsequent jobs. Both sources of exposure misclassification would have likely biased the results of our analysis toward the null. Other possible forms of exposure misclassification comprise those affecting occupational cohort studies in general, e.g., the fact that not all workers employed in a given cohort experienced the same probability and level of exposure: they would also have biased our results toward the null.

Third, we combined results for mesothelioma with results for pleural and peritoneal cancer, the categories in which mesothelioma was classified in the 8th and 9th versions of the International Classification of Diseases (ICD). However, the majority of the neoplasms in these categories are likely to be mesothelioma (Boffetta et al. 2018b), and in our analysis there was no indication of a systematic difference in results according to the version of ICD.

Fourth, our meta-analysis revealed a substantial heterogeneity of results among studies. It is difficult to formally investigate potential sources of heterogeneity because of the small number of studies, but possible reasons include duration of employment (as discussed above), type of asbestos, and exposure level. In addition, the risk estimates were adjusted for different sets of potential confounders across the different studies. Age at cessation of exposure might have also differed among cohort, possibly contributing to heterogeneity of results. Fifth, the data on the risk function 30 or more years since cessation of exposure are sparse, and no conclusions can be drawn before more person-time accumulates in the available cohorts.

The fact that the risk of mesothelioma remains fairly stable after cessation of exposure (at least for the first three decades) is compatible with the hypothesis of a key role of persistence of fibers in the pleura in the genesis of mesothelioma (Mossman and Churg 1998). It is also compatible with the hypothesis of a limited role of asbestos in the later stages of the carcinogenic process. In this respect it is of note that a comparable meta-analysis of results on risk of lung cancer, which was restricted to the studies selected for the mesothelioma review and was not based on a systematic review of the literature, showed a decrease in risk with time since cessation of exposure.

It would have been of interest to explore whether the risk of mesothelioma differed according to the type of asbestos fibers study subjects were exposed to. Such effect can be hypothesized because of differences in biopersistence (Lippmann 1994). However, most studies were conducted on workers exposed to mixed or unspecified fibers (see Table 1), which prevented us from assessing whether there was a difference by fiber type on the effect of cessation of exposure.

The fact that risk of mesothelioma remains elevated several decades after cessation of occupational exposure to asbestos bears significance for the medical surveillance of former exposed workers. While no early detection methods have been established for mesothelioma (Carbone et al. 2016), medical examination might detect early symptoms of the disease, possibly resulting in better prognosis; this is particularly important to groups of workers with elevated risk of mesothelioma, such as crocidolite textile workers (Pira et al. 2016) or Australian crocidolite miners and millers (Berry et al. 2004).

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Compliance with ethical standards

Conflict of interest PB, EP and CLV acted as experts for the defense (PB, EP, CLCV) and the court (EP, CLV) in asbestos-related litigation.

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