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Stomach cancer and occupational exposure to asbestos: a meta-analysis of occupational cohort studies

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Background: A recent Monographs Working Group of the International Agency for Research on Cancer concluded that there is limited evidence for a causal association between exposure to asbestos and stomach cancer.

Methods: We performed a meta-analysis to quantitatively evaluate this association. Random effects models were used to summarise the relative risks across studies. Sources of heterogeneity were explored through subgroup analyses and meta-regression.

Results: We identified 40 mortality cohort studies from 37 separate papers, and cancer incidence data were extracted for 15 separate cohorts from 14 papers. The overall meta-SMR for stomach cancer for total cohort was 1.15 (95% confidence interval 1.03–1.27), with heterogeneous results across studies. Statistically significant excesses were observed in North America and Australia but not in Europe, and for generic asbestos workers and insulators. Meta-SMRs were larger for cohorts reporting a SMR for lung cancer above 2 and cohort sizes below 1000.

Conclusions: Our results support the conclusion by IARC that exposure to asbestos is associated with a moderate increased risk of stomach cancer.

The most recent IARC monograph on asbestos (Straif *et al*, 2009; IARC, 2011) concluded that all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite) are carcinogenic to humans (Group 1). They concluded that asbestos causes mesothelioma and cancer of the lung, larynx and ovary (Group1), and note that positive associations have been observed between asbestos and cancer of the pharynx, stomach and colorectum (group 2A). However, no quantitative estimates of these associations were carried out, except for ovarian cancer (Camargo *et al*, 2011).

We conducted a meta-analysis of the results on stomach cancer of cohort studies of workers exposed to asbestos, as part of our work estimating the burden of occupational cancer in the United Kingdom (Rushton *et al*, 2010). The present analysis was built on the US IOM report published in 2006 (IOM, 2006); we have updated their results and extended the analyses by gender and subcategory (geography, industry and type of asbestos).

MATERIALS AND METHODS

Literature search. A search of the literature was performed to find all published reports of asbestos-exposed cohorts according to the MOOSE guideline (Stroup *et al*, 2000). As stomach cancer was not generally the primary disease of concern in those studies, each paper was read and those reporting mortality from or incidence of cancer of the stomach were selected. Searches of Medline and Embase were conducted for papers published worldwide in English between 1964 and 2010. Only cohorts of workers with predominant exposure to asbestos were included. For example, although

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workers in the rubber industry are exposed to asbestos, the causal role of this specific carcinogen cannot be established (IARC, 1998). When several publications relating to the same cohort were available, we used the most recent report. References of identified papers were examined for additional relevant publications, and a check was made with previous reviews to ensure all cohorts were identified.

For each study, we extracted the following data (when the information was available): observed and expected numbers of cases due to stomach cancer and/or the SMR/SIR and its associated confidence interval (CI), the total number of cases, the lung cancer SMR/SIR, the dates when the study was carried out, inclusion and exclusion criteria, the comparison population, the percentage of men, the average duration of employment, the geographical area, the industry sector, the type of asbestos. For the studies that reported results based on latency period, latency periods were defined as the time since the first exposure or employment. We extracted both sets of results with and without latency.

Methods for quantitative syntheses. Overall pooled estimates of the SMR/SIR (meta-SMR/SIR) with associated 95% CI were obtained using random- and fixed-effects methods (Sutton *et al*, 2000). When not provided, 95% CI of SMR/SIR were obtained via Byar's approximation (Breslow and Day, 1987). For studies in which there were zero observed cases, 1 was added to both observed and expected cases. Sensitivity analyses to this approach were undertaken in which either studies with zero observed case were excluded from the analysis or the observed number of cases was set to equal to the expected number of cases (Alder *et al*, 2006).

A test for heterogeneity between study results was performed as a χ^2-test with degrees of freedom equal to the number of studies minus one and associated *P-value* was reported. As this test is susceptible to the number of studies included in the meta-analysis, Higgins and Thompson (2002) developed an alternative approach that quantifies the effect of heterogeneity, providing a measure of the degree of inconsistency in the studies' results. This quantity I^2 describes the proportion of total variation in study estimates that is due to heterogeneity. Negative values of I^2 are put equal to zero so that I^2 lies between 0 and 100%. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity. This quantity was also reported with its associated 95% CI; a value $>50\%$ was considered to indicate substantial heterogeneity (Higgins *et al*, 2003).

The influence of individual studies on the overall meta-SMR was assessed visually via radial plots, by re-estimating the overall effect omitting each study in turn. In addition, we used common influence diagnostics to highlight outlying influential studies (Viechtbauer and Cheung, 2010). Meta-regression techniques and stratified analyses were used to explore the influence of cohort and study characteristics. Publication bias was also assessed graphically with a funnel plot and by using Egger's test (Egger *et al*, 1997).

Analyses were performed separately for men and women, and for both genders combined. We also analysed the data according to the latency, that is, the time since the first exposure: studies were categorised as to whether they had carried out a lagged analysis or not, with the definition of a lagged category being an exposure lag of at least 10 years after the first exposure/employment. Separate subgroup analyses were carried out by geography (Europe, North America and Australia, China and Russia together) and by occupation/industry. The latter contained six categories as defined in the IOM reports (IOM, 2006): insulators, generic asbestos workers (where no occupation or industry was specified), textile asbestos workers, cement asbestos workers, miners and other occupations with substantial exposure to asbestos (such as shipyard workers). We also provided a pooled estimated by type of asbestos, sample size and publication year.

To analyse the dose–response effect of asbestos exposure, we used two different methods. The first one was based on the RR for the highest category of exposure, as the categories for the dose–response relationships were not comparable. In the second approach, studies were divided according to the magnitude of the lung cancer SMR (below or above 2), corresponding to low and high occupational exposure to asbestos. Lung cancer mortality/incidence was used as a substitute for the exposure measurements, because of the clear relationship between asbestos exposure and lung cancer (IARC, 2011).

All the analyses described above were carried out using the Metafor package (Viechtbauer, 2010) for R software.

RESULTS

Characteristics of the studies. The literature search identified 70 references that contained potentially relevant information for the meta-analysis. Mortality was the outcome in most of the cohort studies reviewed. Data on mortality were extracted for 40 cohorts from 37 separate papers, and data on cancer incidence were extracted for 15 separate cohorts from 14 papers. Table 1 summarises the study characteristics. Unique cohorts are numbered 1–55.

Mortality cohort studies have been carried out mainly in Europe (23 studies, 58%) and North America (12 studies, 30%). Three mortality cohorts were Chinese, one was Russian and one was Australian. Study mortality cohorts ranged in size between 145 and 52 387 workers. Thirteen (33%) of the mortality cohorts included women, although in most women were a small proportion of the total. Four studies involved only women (Acheson *et al*, 1982; Peto *et al*, 1985; Germani *et al*, 1999), and four reported results for the total cohort (Gardner *et al*, 1986; Zhu and Wang, 1993; Frost *et al*, 2008; Harding *et al*, 2009). The most common occupations were insulators (20%), generic asbestos workers (20%), textile asbestos workers (15%), cement asbestos workers (13%) and miners (10%). The latency (exposure lag) ranged between 10 and 20 years. The earliest follow-up period started in 1941 and the latest ended in 2007. The average length of follow-up was 29.9 years (range = 9–49). The largest overall cohort RRs were among the earliest insulation workers (Selikoff *et al*, 1979) with a RR of 3.52 (Figure 1), and among two sets of workers in Chinese asbestos factories (Zhu and Wang, 1993; Pang *et al*, 1997): RRs were 4.4 and 2.2, respectively. Two studies carried out in Canada (Liddell *et al*, 1997) and the United Kingdom (Harding *et al*, 2009), involving 183 and 322 deaths from stomach cancer, showed consistent RR estimates with narrow 95% CI (1.24 and 1.66, respectively).

Incidence studies have been carried out in Northern Europe (11 studies, 73%), in France (2 studies), in Lithuania (1 study) and in Australia (1 study) and included fewer than 900 subjects to over 24 200. Half of the studies included women, in a small proportion of the total cohort. The largest overall cohort RR was among Danish asbestos cement workers (Raffn *et al*, 1989) with a RR of 1.43 (95% CI 1.03–1.93). All the other studies reported RRs close to one.

Quantitative synthesis. Table 2 summarises all the meta-SMRs and meta-SIRs obtained for men and women separately, and by consideration of an exposure lag or not. The meta-SIR for stomach cancer incidence was 1.09 (95% CI 0.94–1.26; 14 studies) and 1.10 (95% CI 0.52–2.33; 6 studies) for men and women, respectively, with homogenous results ($P = 0.16$ and 0.99, respectively).

The pooled analysis for stomach cancer mortality yielded a meta-SMR of 1.16 (95% CI 1.00–1.34; 30 studies) for men, with large heterogeneity of results ($P < 0.001$, $I^2 = 63.5\%$); a meta-SMR of 0.93 (95% CI 0.67–1.30, 13 studies) was found for women, with homogeneous results across studies ($P = 0.90$). For the total cohort,

Table 1. Study characteristics–mortality and incidence studies

ID	Reference (related papers)	O	Year	Country	Industry	Asbestos type	Gender	Employment	End of follow-up	No of subjects
1	Selikoff 1979 (Selikoff *et al*, 1979) (Selikoff *et al*, 1964; Selikoff and Seidman, 1991; Selikoff *et al*, 1980)	M	1979	USA	Insulation workers (union)	Ch, Am	Men	Union before 1943	1976	632
2	Acheson 1982. I (Acheson *et al*, 1982)	M	1982	UK	Manufacture of gas masks	Ch	Women	From 1939	1980	570
3	Acheson 1982.I (Acheson *et al*, 1982)	M	1982	UK	Manufacture of gas masks	Cr	Women	From 1939	1980	757
4	Acheson 1984 (Acheson *et al*, 1984)	M	1984	UK	Manufacture of insulation board	Am	Men	1947–1978	1980	5969
5	Olshon 1984 (Ohlson *et al*, 1984)	M	1984	Sweden	Railroad shop	Mixed	Men	1939–1980	1980	3442
6	Peto 1985.I (Peto *et al*, 1985)	M	1985	UK	Asbestos textile workers	Ch, Cr	Men	1916–1983	1983	145
7	Peto 1985.II (Peto *et al*, 1985)	M	1985	UK	Asbestos textile workers	Ch, Cr	Women	1916–1983	1983	283
8	Peto 1985.III (Peto *et al*, 1985)	M	1985	UK	Asbestos textile workers	Ch, Cr	Men	1916–1983	1983	3211
9	Gardner 1986 (Gardner *et al*, 1986)	M	1986	UK	asbestos cement factory	Ch	Men and women	1941–1983	1984	2167
10	Seidman 1986 (Seidman *et al*, 1986)	M	1986	USA	Insulation workers	Am	Men	1941–1945	1985	820
11	Amandus 1987 (Amandus and Wheeler, 1987)	M	1987	USA	Vermiculite miners and millers	Tr-Ac	Men	Until 1970	1981	575
12	Enterline 1987 (Enterline *et al*, 1987)	M	1987	USA	Asbestos products company	Ch, Cr, Am	Men	1941–1967	1980	1074
13	Hughes 1987 (Hughes *et al*, 1987)	M	1987	USA	Asbestos cement factory	Ch, Cr, Am	Men	Until 1970	1982	6931
14	Sanden 1987 (Sandén and Järvholm, 1987)	I	1987	Sweden	Shipyard workers	Ch	Men	1977–1979	1983	3787
15	Tola 1988 (Tola *et al*, 1988)	I	1988	Finland	Shipyard workers	Mixed	Men	1945–1960	1981	7775
16	Melkild 1989 (Melkild *et al*, 1989)	I	1989	Norway	Shipyard workers	Ch	Men	1946–1977	1986	4778
17	Raffn 1989 (Raffn *et al*, 1989)	I	1989	Denmark	Asbestos cement factory	Mixed	Men	1928–1984	1984	7996
18	Neuberger 1990 (Neuberger and Kundi, 1990)	M	1990	Austria	Asbestos cement factory	Ch, Cr	Men and women	1950–1981	1987	2816
19	Botta 1991 (Botta *et al*, 1991)	M	1991	Italy	Asbestos cement factory	Ch, Cr	Men and women	1950–1980	1986	3367
20	Selikoff 1991 (Selikoff and Seidman, 1991) (Selikoff *et al*, 1964; Selikoff *et al*, 1979; Selikoff *et al*, 1980)	M	1991	USA/ Canada	Insulation workers (union)	Ch, Am	Men	In union 1967	1987	17 800
21	Cheng 1992 (Cheng and Kong, 1992)	M	1992	China	Chrysolite asbestos products workers	Ch	Men and women	Present in 1972	1987	1172
22	Sanden 1992 (Sandén *et al*, 1992)	M	1992	Sweden	Shipyard workers	Ch	Men	1977–1979	1987	3893
23	Danielsen 1993 (Danielsen *et al*, 1993)	I	1993	Norway	Shipyard production workers	Ch	Men	1940–1979	–	4571
24	Kogan 1993 (Kogan *et al*, 1993)	M	1993	Russia	Friction products	Ch	Men and women	–	1988	2834
25	Zhu 1993 (Zhu and Wang, 1993)	M	1993	China	Asbestos factory	Ch	Men and women	–	1986	5893
26	Meurman 1994 (Meurman *et al*, 1994)	I	1994	Finland	Asbestos miners	An	Men and women	1953–1967	1991	903
27	Liddell 1997 (Liddell *et al*, 1997) (McDonald *et al*, 1993; McDonald *et al*, 1980)	M	1997	Canada	Miners and millers	Ch	Men	–	1992	9780
28	Pang 1997 (Pang *et al*, 1997)	M	1997	China	Asbestos factory	Ch	Men and women	Until 1972	1994	530

Table 1. (Continued)

ID	Reference (related papers)	O	Year	Country	Industry	Asbestos type	Gender	Employment	End of follow-up	No of subjects
29	Levin 1998 (Levin *et al*, 1998)	M	1998	USA	Manufacture of asbestos pipe insulation	Am	Men	Alive in 1964	1993	1121
30	Battista 1999 (Battista *et al*, 1999)	M	1999	Italy	Rail carriage construction and repair	Ch, Cr	Men	1945–1969	1997	734
31	Germani 1999 (Germani *et al*, 1999)	M	1999	Italy	Women compensated for asbestosis	Ch, Cr	Women	Alive in 1979	1997	631
32	Karjalainen 1999.I (Karjalainen *et al*, 1999)	I	1999	Finland	Patients with asbestos-related pulmonary	Mixed	Men and women	1964–1995	1995	1376
33	Karjalainen 1999.II (Karjalainen *et al*, 1999)	I	1999	Finland	Patients with pleural fibrosis	Mixed	Men and women	1964–1995	1995	4887
34	Berry 2000 (Newhouse *et al*, 1985; Berry *et al*, 2000)	M	2000	UK	Asbestos factory	Ch, Cr, Am	Men and women	1933–1964 1936–1942	1980	5100
35	Szeszenia 2000 (Szeszenia-Dabrowska *et al*, 2000)	M	2000	Poland	Asbestos cement factory	Ch, Cr	Men	Until 1980	1991	2525
36	Puntoni 2001 (Puntoni *et al*, 2001)	M	2001	Italy	Shipyard workers	Mixed	Men	1960–1981	1996	3984
37	LaProvote 2002 (de La Provôté *et al*, 2002)	I	2002	France	Manufacture fireproof textiles and friction materials	Mixed	Men and women	Until 1978	1995	1820
38	Ulvestad 2002 (Ulvestad *et al*, 2002)	I	2002	Norway	Asbestos cement factory	Mixed	Men	1942–1976	1999	541
39	Szeszenia 2002 (Szeszenia-Dabrowska *et al*, 2002)	M	2002	Poland	Workers compensated for asbestosis	Mixed	Men	1970–1997	1999	907
40	Koskinen 2003 (Koskinen *et al*, 2003)	I	2003	Finland	Asbestos workers (screening campaign)	Mixed	Men and women	–	1992	24 215
41	Finkelstein 2004 (Finkelstein and Verma, 2004)	M	2004	Canada	Pipe trades workers (union)	Mixed	Men	From 1949	1999	25 285
42	Reid 2004 (Armstrong *et al*, 1988; Reid *et al*, 2004)	I	2004	Australia	Crocidolite miners and millers	Cr	Men	1943–1966	1999	5685
43	Smailyte 2004 (Smailyte *et al*, 2004)	I	2004	Lithuania	Asbestos cement factory	Ch	Men and women	Until 1978	2000	1887
44	Ulvestad 2004 (Ulvestad *et al*, 2004)	I	2004	Norway	insulation workers (union)	Ch, Am	Men	1930–1975	1999	1116
45	Wilczynska 2005 (Wilczynska *et al*, 2005) (Szeszenia-Dabrowska *et al*, 1991; Szeszenia-Dabrowska *et al*, 1988a; Szeszenia-Dabrowska *et al*, 1988b)	M	2005	Poland	Asbestos processing plant	Mixed	Men and women	1945–1980	1999	4187
46	Hein 2007 (Hein *et al*, 2007) (Brown *et al*, 1994; Dement *et al*, 1994; Dement *et al*, 1983)	M	2007	USA	Asbestos textile workers	Ch	Men and women	1940–1965	2001	3072
47	Krstev 2007 (Krstev *et al*, 2007)	M	2007	USA	Shipyard production workers	Mixed	Men and women	1950–1964	2001	4702
48	Pira 2007 (Pira *et al*, 2005, 2007)	M	2007	Italy	Asbestos textile workers	Mixed	Men and women	1946–1984	2004	1966
49	Frost 2008 (Frost *et al*, 2008)	M	2008	GB	Asbestos removal workers (campaign)	Mixed	Men and women	From 1971	2005	52 387
50	Musk2008 (Musk *et al*, 2008) (Armstrong *et al*, 1988; Reid *et al*, 2004)	M	2008	Australia	crocidolite miners and millers	Cr	Men	1943–1966	2000	6943
51	Clin 2009 (Clin *et al*, 2009)	I	2009	France	Asbestos reprocessing plant (textile, friction)	Mixed	Men and women	Before 1978	2004	2024

Table 1. (Continued)

ID	Reference (related papers)	O	Year	Country	Industry	Asbestos type	Gender	Employment	End of follow-up	No of subjects
52	Harding 2009 (Hutchings *et al*, 1995; Harding *et al*, 2009)	M	2009	UK	Asbestos survey	Mixed	Men and women		2005	9811
53	Loomis 2009 (Loomis *et al*, 2009)	M	2009	USA	Asbestos textile workers	Ch	Men and women	1950–1973	2003	5770
54	Pira 2009 (Pira *et al*, 2009) (Piolatto *et al*, 1990; Rubino *et al*, 1979)	M	2009	Italy	Chrysotile asbestos miners	Ch	Men	1930–1975	1946	2003
55	Pesch 2010 (Pesch *et al*, 2010)	M	2010	Germany	Asbestos survey	Mixed	Men	1993–1995	2007	576

Abbreviations: - = not applicable; Am = Amosite; An = Anthophyllite; Ch = Chrysotile; Cr = Crocidolite; I = Incidence; M = Mortality; O = Outcome.

the meta-SMR was similar to that found for men only (meta-SMR = 1.17, 95% CI 1.03–1.33, 40 studies).

Because mortality is a relatively accurate measure of disease incidence as stomach cancer has a low survival rate, and because of the very limited numbers of primary studies in which incidence data were reported, pooled analyses are also reported using mortality and incidence combined. In this situation, the meta-SMRs were similar to those found using only mortality data, with a slight reduction in heterogeneity ($I^2 = 54.7\%$). Figure 1 presents the individual study results and the overall meta-SMR for total cohort.

As the meta-SMRs from studies reporting results with exposure lag did not differ substantially from the overall results, the meta-SMRs below are reported for all exposure lag group and for mortality and incidence combined, unless specified otherwise.

Between study heterogeneity and influence of individual studies. Table 2 also shows the heterogeneity (*P-value*) for each analysis. There was no evidence of heterogeneity in women but some in men. A few specific studies contributed to this heterogeneity, as illustrated by outlying points in the radial plot for stomach cancer for men (Figure 2): cohort 1 (Selikoff *et al*, 1979) was conducted in the earliest period, cohort 5 (Ohlson *et al*, 1984) was the only study to find a significant decrease in risk, cohort 28 (Pang *et al*, 1997) was carried out in China. For the total cohort, another cohort in China, cohort 25 (Zhu and Wang, 1993) also contributed to the heterogeneity.

The covariates listed in the Methods section were explored as potential sources of heterogeneity using meta-regression methods. Table 3 gives the meta-SMR by subgroup for men and women. No significant predictor of the meta-SMR for women was found. Apart for type of asbestos and publication year, all the variables were a significant predicator for men, with some heterogeneity. The meta-SMRs for men showed elevated risks in the United States and Australia (meta-SMR = 1.30, 95% CI 1.10–1.55), and China and Russia (meta-SMR = 1.91, 95% CI 1.03–3.56). The pooled analysis within occupational strata demonstrated the highest meta-SMR for stomach cancer among generic asbestos workers (meta-SMR = 1.41, 95% CI 1.10–1.82), followed by insulators (meta-SMR = 1.27, 95% CI 1.05–1.53). Meta-regression also showed positive associations for stomach cancer for the cohort sizes below 1000 compared with cohort size above 1000. Similar results were found for the total cohort (Supplementary Table 1).

Figure 3 shows, for men, the investigation of the influence of individual studies via systematic 'leave one out' exclusion. The studies appearing to contribute to heterogeneity also influence the meta-SMR. Using the other diagnostics, only Selikoff *et al* (1979) and Ohlson *et al* (1984) were influential (Supplementary Figure 1). The meta-SMR for stomach cancer excluding these 2 studies were 1.13 (95% CI 1.05–1.22), relatively similar to the one found with all the studies for men. The exclusion of the 3 influential studies (Selikoff *et al*,1979; Ohlson *et al*, 1984; Pang *et al*, 1997) led to a meta-SMR of 1.12 (95% CI 1.04–1.20) and eliminated completely the heterogeneity ($P = 0.59$, $I^2 = 7.3\%$) as well as the residual heterogeneity in the meta-regressions ($P > 0.44$). The associations were generally attenuated (Supplementary Table 2), except for the miners (meta-SMR = 1.21, 95% CI 1.07–1.36) compared with the other occupations.

Dose–response associations. Estimates of cumulative or duration of exposure among asbestos-exposed workers were reported for only 11 studies (Supplementary Table 3). The pooled SMR estimate of stomach cancer for men was 1.40 (95% CI 0.81–2.40), with a large degree of heterogeneity ($I^2 = 67.7\%$).

Using a low/high exposure categorisation based on the lung cancer SMR, cohorts that reported a lung cancer SMR above 2.0 had higher meta-SMRs (SMR = 1.46; 95% CI 1.22–1.77) compared with other cohorts (SMR = 1.02; 95% CI 0.91–1.15).

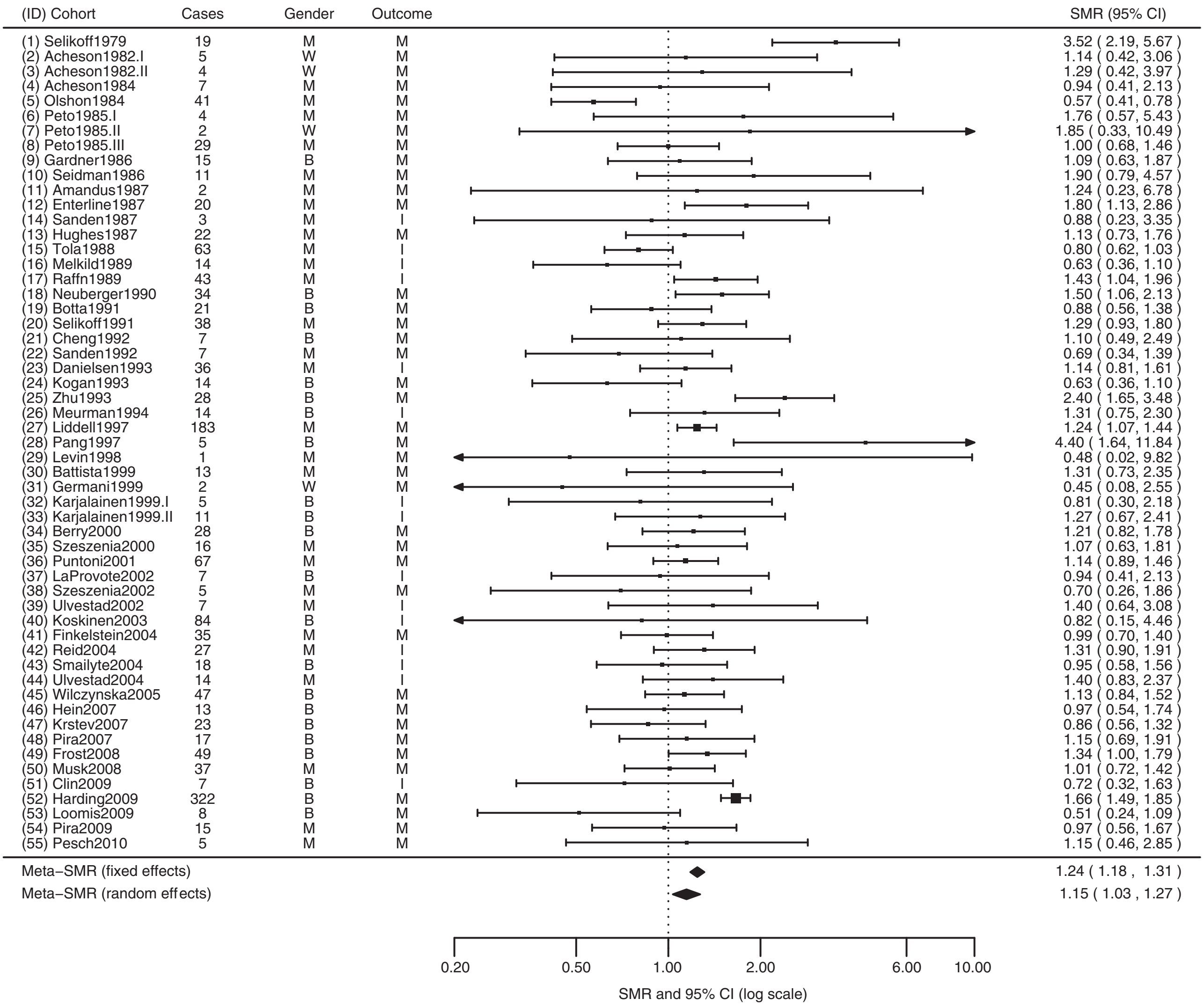

Figure 1. Meta-analysis of stomach cancer mortality and incidence for total cohort, all exposure lags.

Assessment of publication bias. For men and women, there was no evidence of publication bias from plots and statistical tests. However, for the total cohort, there is an evidence of publication bias (funnel plot in Supplementary Figure 2), with a suggestive lack of studies in the top right-hand corner of the plot, that is, large cohorts with large associations.

Zero cases. Four studies reported no deaths from stomach cancer for women; (Cheng and Kong, 1992; Pang *et al*, 1997; Hein *et al*, 2007; Krstev *et al*, 2007); only one study with men was concerned with this issue (Levin *et al*, 1998) Therefore, the investigation of the influence of approaches to handling zero cases was carried out only for women. Both excluding studies for which observed cases are zero and setting observed equal to expected values resulted in an increase in meta-SMRs and a slight widening of the confidence intervals compared with the default method of adding 1 to both observed and expected values. Whatever the latency, the meta-SMRs were 1.00 (95% CI 0.73–1.36) and 1.03 (95% CI 0.77–1.39) with the exclusion approach and imputation approach, respectively, compared with a meta-SMR of 0.96 (95% CI 0.71–1.30) with the default method.

DISCUSSION

The association between asbestos and stomach cancer has been estimated in a meta-analysis of studies of workers in which a major portion of the cohort is presumed to have been exposed to asbestos. Our results demonstrated an increase in the pooled estimate in men (meta-SMR = 1.13, 95% CI 1.02–1.26) for stomach cancer in relation to exposure to asbestos. Our meta-analysis provided an update of studies, compared with previous reviews and quantitative estimates and also thoroughly explored heterogeneity and publication bias.

The magnitude of the association in our meta-analysis was similar to that reported in the IOM report that included 42 cohorts (meta-SMR = 1.17, 95% CI 1.07–1.28). More recently, Gamble (2008) reported that point estimates for cancer of the stomach mortality tended towards 1, with an overall RR estimate of 1.01 (95% CI 0.94–1.08), results more similar to those obtained by Goodman *et al* (1999).

Our analysis addressed heterogeneity and was based on studies included in the published meta-analyses and more recent publications. The observed overall heterogeneity among studies seemed to be explained by four cohorts. The cohort by Selikoff *et al* (1979) considered an early exposure period (up to 1962). Ohlson *et al* (1984) were the only ones to find a significant decrease in risk (SMR = 0.57, 95% CI 0.42–0.79). Two studies (Zhu and Wang, 1993; Pang *et al*, 1997) were conducted in China, where asbestos production and exposure can be very high (LaDou, 2004).

We carried out meta-regression to investigate the influence of several variables. Positive and statistically significant associations were observed for non-European cohorts, generic asbestos workers, cohorts reporting a SMR for lung cancer above 2, and cohort size below 1000.

Table 2. Pooled analysis for stomach cancer mortality and incidence by exposure lag (latency) and type of outcome using random effects model

	Outcome	n^a	SMR	95% CI	$\tau^{2\,b}$	$P_Q^{\,c}$	I^2 (%)[d]
Men							
All exposure lags	I	14	1.09	(0.94–1.26)	0.019	0.16	28.0
	M	30	1.16	(1.00–1.34)	0.085	<0.001	63.5
	M+I	44	1.13	(1.02–1.26)	0.057	<0.001	54.7
At least 10 yr exposure lag	I	2	–	–	–	–	–
	M	9	1.16	(0.79–1.69)	0.213	<0.001	75.3
	M+I	11	1.09	(0.77–1.53)	0.197	<0.001	71.8
No exposure lag	I	14	1.09	(0.94–1.26)	0.019	0.16	28.0
	M	26	1.18	(0.99–1.40)	0.111	<0.001	69.6
	M+I	40	1.14	(1.01–1.28)	0.069	<0.001	59.7
Women							
All exposure lags	I	6	1.1	(0.52–2.33)	0	0.99	–
	M	13	0.93	(0.67–1.30)	0	0.90	0
	M+I	19	0.96	(0.71–1.30)	0	0.99	–
No exposure lag	I	6	1.1	(0.52–2.33)	0	0.99	–
	M	12	0.89	(0.62–1.26)	0	0.90	0
	M+I	18	0.92	(0.67–1.27)	0	0.99	–
Total cohort							
All exposure lags	I	15	1.07	(0.91–1.25)	0.022	0.26	25.5
	M	40	1.17	(1.03–1.33)	0.087	<0.001	69.1
	M+I	55	1.15	(1.03–1.27)	0.069	<0.001	61.9
At least 10 yr exposure lag	I	0	–	–	–	–	–
	M	10	1.12	(0.80–1.56)	0.182	<0.001	81.6
	M+I	12	1.07	(0.79–1.44)	0.169	<0.001	78.5
No exposure lag	I	15	1.07	(0.91–1.25)	0.022	0.26	25.5
	M	36	1.18	(1.03–1.36)	0.102	<0.001	72.7
	M+I	51	1.15	(1.03–1.28)	0.078	<0.001	64.8

Abbreviations: – = not applicable; CI = confidence interval; I = incidence, M = mortality. No results for women for at least 10 year exposure lag as only one mortality study reported a SMR.
[a]Number of cohorts included.
[b]Variance (amount of heterogeneity).
[c]*P*-value for the heterogeneity test.
[d]Percentage of total variability due to heterogeneity.

Our meta-analysis mainly represented studies conducted in developed geographical areas, particularly among European populations. It is possible that studies conducted in other geographic regions (e.g., developing countries) may be available through other biomedical literature databases. The meta-analysis (da Sun *et al*, 2008) published in Chinese with an abstract in English, which searched Chinese literature as well, found a meta-SMR of 1.20 ($P<0.01$) among workers exposed to chrysotile alone or mixed asbestos. The stomach cancer SMR was significantly increased in the asbestos cement workers, the screening mine workers and the insulators, (1.27, 1.21 and 2.13, respectively, $P<0.05$). These results seem consistent with the ones we observed. Another source of publication bias can arise from the lack of publications in parts of Asia, South America and the former Soviet Union where asbestos use is increasing (LaDou, 2004).

Some studies may have failed to take account of co-exposures that have been to be associated with excess risk of stomach cancer. The reported SMRs were not adjusted for known risk factors such as chronic infection with *Helicobacter pylori*, smoking and diet habits. Liddell *et al* (1997), for example, report that their finding of no trend of lung cancer with exposure up to 300 mpcf.y suggests that the 21% excess was due to some other factor, probably smoking, and that the effect of smoking on stomach cancer was twice as high as the effect of >300 mpcf.y. A recent study found statistically significant increased hazard ratios for gastric cancer and several asbestos exposure variables, adjusted for age and family history of gastric cancer, although, with the exception of long duration at high exposure, these associations tended to disappear after adjusting for smoking (Offermans *et al*, 2014).

Increases in stomach cancer have also been associated with work in a variety of dusty industries and from exposure to fumes and metal particles, for example, in foundry, steel and mining work (Cocco *et al*, 1996; Ji and Hemminki, 2006). A study in Swedish construction workers found exposure to silica exposure, but not asbestos, was significantly related to stomach cancer (Sjodhal *et al*, 2007). However, in our meta-analysis we restricted our studies to only those where the dominant exposure was asbestos.

We found a suggestive but nonsignificant association between asbestos type and the stomach cancer meta-SMR. Cohorts exposed to mixed asbestos showed larger SMRs than those exposed only to chrysotile asbestos. A meta-analysis by Li *et al* (2004) of 15 studies published before 2003 of workers exposed only to chrysotile found also a nonsignificant association (meta-SMR = 1.24; 95% CI 0.95–1.62). Our risk estimate was slightly smaller as we did not include four cohorts, as they were published in Chinese. There has been a considerable controversy over the potency of asbestos fibre types with the risks of lung cancer and mesothelioma. As discussed in the review by Hodgson and Darnton (2000) some studies showed no difference in risk between these cancers and asbestos fibre types, while others have claimed a reduced potency for chrysotile, leading to a substantial heterogeneity in the findings. Our results tend to support a reduced risk for chrysotile and stomach cancer compared with the risk associated with other asbestos types.

In summary our results support the conclusion by IARC that exposure to asbestos is associated with a moderate increased risk of stomach cancer. Given the large number of workers exposed to asbestos worldwide, this may contribute to a substantial burden of mortality and morbidity.

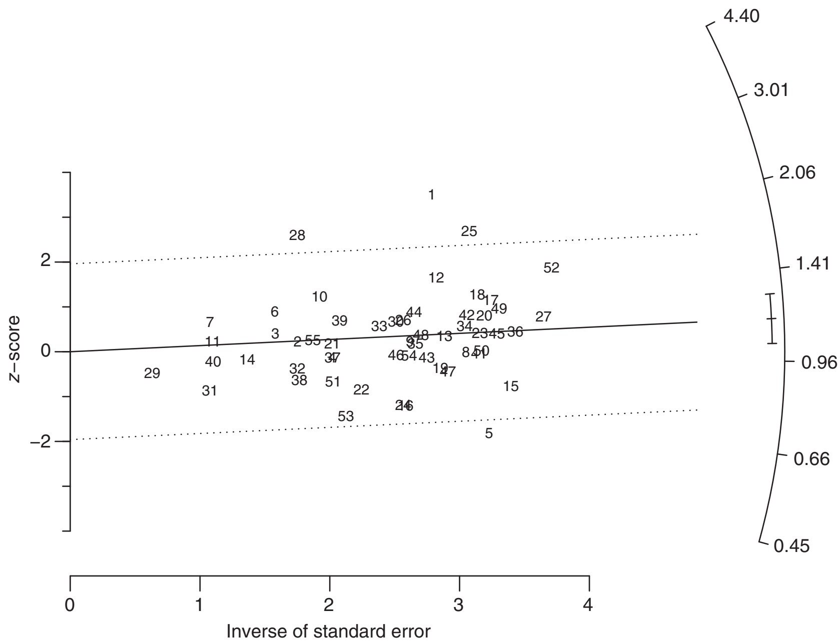

Figure 2. Radial plot for SMRs in a meta- analysis of stomach cancer mortality and incidence for total cohort, all exposure lags.

Table 3. Stratification of cohort studies by subgroups, for men and women, mortality and incidence combined, all exposure lags (random effects model)

	Men						Women					
	n[a]	SMR	95% CI	τ^2 [b]	P_{QE} [c]	P_{QM} [d]	n[a]	SMR	95% CI	τ^2 [b]	P_{QE} [c]	P_{QM} [d]
Geography												
Europe	28	1.03	(0.91–1.16)	0.042	<0.001	<0.001	14	1.1	(0.77–1.57)	0	1	0.48
North America + Australia	13	1.3	(1.10–1.55)				2	0.37	(0.04–3.13)			
China + Russia	3	1.91	(1.03–3.56)				3	0.69	(0.38–1.28)			
Occupation												
Cement asbestos workers	6	1.12	(0.88–1.42)	0.028	<0.001	<0.001	2	1.27	(0.59–2.72)	0	0.95	0.97
Generic asbestos workers	7	1.41	(1.10–1.82)				5	0.87	(0.44–1.73)			
Insulators	10	1.27	(1.05–1.53)				1	0.63	(0.03–12.89)			
Miners	6	1.18	(0.95–1.47)				1	0.67	(0.05–9.13)			
Textile asbestos workers	4	1.15	(0.83–1.61)				3	1.22	(0.53–2.79)			
Other occupation	11	0.87	(0.73–1.04)				7	0.87	(0.56–1.34)			
SMR for lung cancer												
⩽2	25	1.02	(0.91–1.15)	0.039	<0.001	<0.001	5	0.88	(0.54–1.42)	0	0.98	0.86
>2	17	1.46	(1.22–1.77)				13	1.02	(0.69–1.52)			
Type of asbestos												
Amosite	3	1.25	(0.64–2.44)	0.058	<0.001	0.32	–	–	–	0	0.97	0.95
Chrysotile	11	1.09	(0.87–1.37)				6	0.84	(0.52–1.35)			
Crocidolite	2	1.14	(0.75–1.74)				1	1.14	(0.42–3.06)			
Mixed	27	1.13	(0.99–1.29)				11	1.05	(0.68–1.64)			
Sample size												
<1000	12	1.68	(1.32–2.15)	0.034	0.001	<0.001	15	1.15	(0.77–1.71)	0	1	0.56
1000–1500	6	1.19	(0.88–1.61)				3	0.79	(0.38–1.62)			
>1500	26	1.04	(0.93–1.16)				1	0.7	(0.37–1.33)			
Publication year												
Before 1999	26	1.16	(1.00–1.34)	0.057	<0.001	0.07	11	0.94	(0.63–1.40)	0	0.98	0.95
After 1999	18	1.1	(0.94–1.29)				8	0.99	(0.62–1.59)			

Abbreviations: – = not applicable; CI = confidence interval.
[a]Number of cohorts included.
[b]residual variance (residual amount of heterogeneity).
[c]*P*-value for the residual heterogeneity test.
[d]*P*-value for the test of moderators (if the SMRs are different or not within the subgroup).

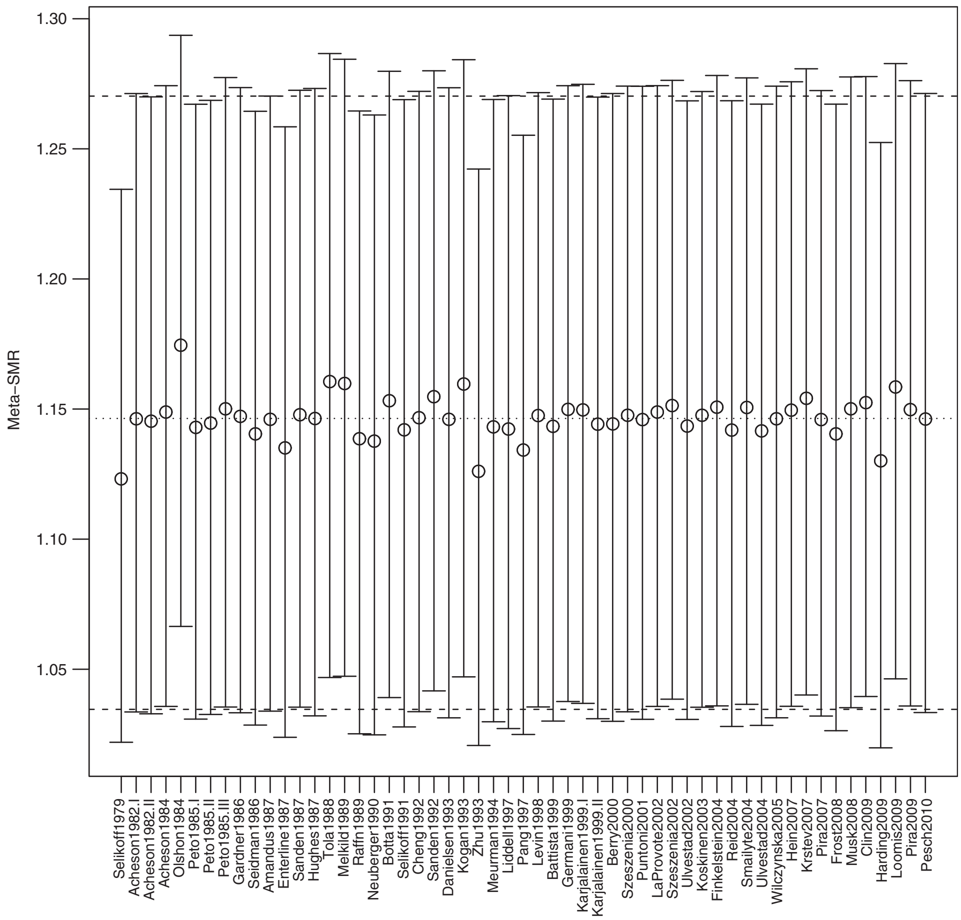

Figure 3. Influence of excluding each individual cohort for men, mortality and incidence combined, all exposure lags. Meta-SMRs and associated 95% CI (random-effects model). Dotted and dash lines represent the overall meta-SMR and its 95% CI.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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