Stomach cancer mortality among workers exposed to asbestos: a meta-analysis

Wen-jia Peng · Xian-jie Jia · Bing-gan Wei ·
Lin-sheng Yang · Ying Yu · Lei Zhang

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Abstract

Background The relationship between asbestos and stomach cancer is not well understood because of small number of cases. This study aimed to determine the incidence and mortality of stomach cancer among workers exposed to asbestos based on a systematic review and meta-analysis approach.

Methods Relevant English electronic databases were systematically searched for published studies characterizing the risk of developing stomach cancer as a result of asbestos exposure. Standardized mortality rate (SMR) for stomach cancer with its 95 % confidence interval (CI) was pooled using a fixed-/random-effect model in STATA.

Results A total of 32 independent studies were included for the analysis. The overall SMR for stomach cancer was 1.19 (95 % CI 1.06–1.34), with a moderate degree of heterogeneity across the studies ($I^2 = 37.6\%$, $P = 0.011$). Being

male, exposure to crocidolite, miners, studies conducted in Europe and Oceania, and long study follow-up (≥ 25 years) all contribute to significantly higher SMR. Significant publication bias was observed.

Conclusion Elevated risk of stomach cancer mortality was evidenced among workers exposed to crocidolite, especially male miners.

Keywords Asbestos · Stomach cancer · Standardized mortality rate · Meta-analysis

Introduction

As the rapid development of industrialization, the humanity while pollution causing own health and safety. Asbestos is an important non-metallic mineral raw material and is generally divided into two specific structures: serpentine and amphibole. The most common types of asbestos fiber used are chrysotile (white) asbestos, which is a serpentine mineral, amosite (brown), and crocidolite (blue) asbestos, which is an amphibole mineral (IARC 1977). The colors are seen in clean fibers and may not be clearly visible when the fibers are mixed with other material. Asbestos is widely used in buildings, vehicles and industries because of its chemical and physical properties of high tensile strength, flexibility, heat resistance and good thermal and electrical insulation properties.

It is estimated that there were 125 million people worldwide working in environments exposed to asbestos (WHO 2006). Asbestos exposure has caused a series of health problems. Three main diseases are currently related to asbestos exposure: asbestosis, lung cancer, and mesothelioma. Around 43,000 people died from malignant mesothelioma, and a much larger number of lung cancer died due to occupational exposure to asbestos (Driscoll et al. 2005).

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W. Peng · X. Jia (✉)
Department of Epidemiology and Health Statistics, Bengbu
Medical College, Bengbu, Anhui, China
e-mail: xjjia@139.com

B. Wei · L. Yang
Institute of Geographic Sciences and Natural Resources
Research, Chinese Academy of Sciences, Beijing, China

Y. Yu
Department of Physiology, Bengbu Medical College, Bengbu,
Anhui, China

L. Zhang (✉)
Kirby Institute, The University of New South Wales, Sydney,
Australia
e-mail: lzhang@kirby.unsw.edu.au

A large volume of studies have discussed the relationship between asbestos exposure and malignant tumors. Several meta-analyses have suggested an increased risk of cancers, including ovarian cancer, colorectal cancer, and laryngeal cancer.

Stomach cancer is the fourth common cancer worldwide, followed by lung, breast, colon and rectum, and the second most frequent cause of cancer death. Stomach cancer is observed predominantly in males, with a ratio of 2:1 (Jemal et al. 2011). Up to now, the precise pathogenesis of stomach cancer is not yet fully understood. A growing body of evidence suggests genetic factors, and environmental triggers are contributed to the development of stomach cancer. Occupational exposure to asbestos has been intensely addressed as a possible risk factor for stomach cancer. However, the conclusions did not reach a consensus.

Considering the limitations of a single research, the aim of this study was to review the epidemiology studies that have reported the association of asbestos exposure with stomach cancer incidence or mortality and perform a meta-analysis of those studies to quantitatively evaluate whether exposure to asbestos could cause stomach cancer.

Materials and methods

Selection of studies

Studies were identified by searching PubMed, Elsevier, and Web of Science databases using the following keywords: “cancer,” “stomach cancer,” “gastric cancer,” “asbestos,” “crocidolite,” “chrysotile,” “amosite,” “mortality,” “standardized mortality ratio (SMR),” and “cohort.” Language was restricted to English and Chinese. The reference lists of relevant publications were also reviewed manually to identify additional studies. As some papers on the same cohort study were published several times, only the newest or most informative single article was included. When one article reported different industry types in one cohort, we treated them independently.

Inclusion criteria

To be eligible for inclusion, studies had to meet the following criteria:

1. they must have a cohort design with fully published;
2. they must have a unequivocal evidence of asbestos exposure;
3. they must provide SMR or standardized incidence rate. We accepted the standardized mortality rate as a surrogate of incidence, because of the relatively short survival time and the high case fatality rate of stomach cancer.

Exclusion criteria

The following studies were excluded: (1) overlapping articles or duplicate data; (2) articles conducted on animal; (3) review article without original data; (4) insufficient information; and (5) occupational exposure to a variety of factors, not just asbestos.

Data extraction

To minimize the bias and to improve the reliability, two reviewers checked all potentially relevant studies independently. Potential disagreements were resolved by consensus. The following information was extracted from each study: name of first author, publication year, original country, industry type, asbestos type, cohort size, period of employment, follow-up period, total person-years of observation and total observed numbers of cancers, and fixed-/random-effect model.

Statistical analysis

A SMR with its corresponding 95 % confidence interval (CI) extracted from each study was combined based on a fixed-effect (Mantel–Haenszel method) or a random-effect (DerSimonian–Laird method) model (Mantel and Haenszel 1959; DerSimonian and Laird 1986). Given the significant amount of heterogeneity, only the random-effect estimates are presented. The heterogeneity among studies was assessed Cochran’s Q test and I^2 metric. For the Q statistic, a P value <0.10 was considered statistically significant for heterogeneity; for I^2 , a value ranged from 0 to 100 %, and value >25 % represented the possibility for substantial heterogeneity (Higgins and Thompson 2002). Meta-regression was performed to assess the potentially important variables exerting substantial impact on between-study heterogeneity. The leave-one-out sensitivity analysis was conducted to determine whether our assumptions or decisions had a major effect on the results of the review by omitting each study (Tobias 1999). Evaluation of publication bias was first assessed by the Begg’s funnel plot (Begg and Mazumdar 1994) and then performed for each of the pooled study groups using Egger’s bias indicator test (Egger et al. 1997).

Results

Characteristics of eligible studies

The flow chart of literatures selection was provided in Fig. 1. Based on the predetermined search strategies, a total of 1,327 papers were identified. We carefully reviewed the abstracts or full texts of these papers. Totally, forty cohorts from 32 independent studies (Harding et al. 2009; Musk

Fig. 1 Flow diagram of articles selection process

et al. 2008; Wang et al. 2013; Du et al. 2012; Menegozzo et al. 2011; Tomioka et al. 2011; Pesch et al. 2010; Clin et al. 2009; Loomis et al. 2009; Pira et al. 2009; Frost et al. 2008; Reid et al. 2008; Hein et al. 2007; Kjaerheim et al. 2005; Pira et al. 2005; Wilczyńska et al. 2005; Reid et al. 2004; Smailyte et al. 2004; Sun et al. 2003; de La Provôté et al. 2002; Szeszenia-Dabrowska et al. 2002; Berry et al. 2000; Battista et al. 1999; Germani et al. 1999; Kurumatani et al. 1999; Tsai et al. 1996; Dement et al. 1994; Tarchi et al. 1994; Magnani et al. 2008; Raffn et al. 1989; Armstrong et al. 1988; Acheson et al. 1982) met the criteria for inclusion in the meta-analysis. Table 1 summarized all the available cohort studies with acknowledged asbestos exposure, which we have been able to identify. The study from Acheson et al. (1982) reported two different cohorts, which were treated independently. Studies conducted by Dement et al. (1994) and Brown et al. (1994) were based on the same cohort, and the former one was subjected to the final analysis. Two studies (Kang et al. 1997 and Sun et al. 1997) were excluded because of reporting proportionate mortality ratios for stomach cancer.

Five studies (Clin et al. 2009; Kjaerheim et al. 2005; Reid et al. 2004; Smailyte et al. 2004; and de La Provôté et al. 2002) reported findings on stomach cancer incidence, and the remaining studies were based on mortality. Most studies were performed in Europe, five in Asia (Wang et al. 2013; Du et al. 2012; Tomioka et al. 2011; Sun et al. 2003; Kurumatani et al. 1999), three in America (Loomis et al. 2009; Hein et al. 2007; and Tsai et al. 1996),

and four in Oceania (Musk et al. 2008; Reid et al. 2008, 2004; and Armstrong et al. 1988). Thirteen studies (Musk et al. 2008; Menegozzo et al. 2011; Tomioka et al. 2011; Pesch et al. 2010; Pira et al. 2009; Kjaerheim et al. 2005; Reid et al. 2004; Szeszenia-Dabrowska et al. 2002; Battista et al. 1999; Kurumatani et al. 1999; Kurumatani et al. 1999; Raffn et al. 1989; and Armstrong et al. 1988) were conducted only in male cohort, and five cohorts (Reid et al. 2004; Sun et al. 2003; Germani et al. 1999; Magnani et al. 2008; and Acheson et al. 1982) included only female. The main type of industries included refitting shipyard, mining, textile, and cement. Only six studies (Harding et al. 2009; Musk et al. 2008; Frost et al. 2008; Kjaerheim et al. 2005; Raffn et al. 1989; and Armstrong et al. 1988) reported a significant association of excess asbestos exposure with stomach cancer risk.

Quantitative data synthesis

As shown in Fig. 2, summarizing the evidence from these 32 studies, the combined SMR based on a random-effect model for stomach cancer among asbestos-exposed workers was 1.19 (95 % CI 1.06–1.34), with a moderate degree of heterogeneity among the studies ($Q = 60.85$, $P = 0.011$, $I^2 = 37.6$ %).

Subgroup analysis by basic characteristics

Pooled SMR for stomach cancer among asbestos-exposed men was 1.30 (95 % CI 1.16–1.45) with no significant heterogeneity (Figure S1). A significantly increased risk of stomach cancer for cohorts exposed to only crocidolite (SMR = 1.55, 95 % CI 1.27–1.89) and mixed asbestos (OR 1.22 95 % CI 1.06–1.41) was observed. Moderate heterogeneity was detected for subgroup of mixed asbestos (Figure S2). Pooled estimates were significant for the outcome of mortality (SMR = 1.19, 95 % CI 1.04–1.35) (Figure S3). Pooled SMRs were increased for European (SMR = 1.21, 95 % CI 1.05–1.40) and Oceanian cohorts (SMR = 1.53, 95 % CI 1.26–1.86) compared with cohorts from Asian and American, for which there appeared to be no increase in stomach cancer mortality (Figure S4). Worker from mining appeared an elevated risk of stomach cancer reported exposure to asbestos (SMR = 1.43, 95 % CI 1.20–1.70) (Figure S5). The long study follow-up (≥ 25 years) reported a significantly excess risk of stomach cancer (SMR = 1.26, 95 % CI 1.11–1.42) (Figure S6). The detail results are presented in Table 2.

Meta-regression

Since there was moderate heterogeneity among included studies, a univariate meta-regression analysis was

Table 1 Characteristics of studies included in the meta-analysis

First author	Year	Country	Industry type	Asbestos type	Cohort size	Period of employment	Follow-up period	Person-years	Total cancers
Harding AH	2013	Great Britain	Mixed	Mixed	98,117	NA	1971–2005	1,779,580	5,529
Musk AW	2013	Australia	Miners and millers	Crocidolite	6,943	1943–1966	1943–2000	NA	830
Wang XR	2013	China	Textile	Chrysotile	865	NA	1972–2008	27,475	106
Du LL	2012	China	Miners	Chrysotile	1,932	NA	1981–2010	50,362	106
Menegozzo S	2011	Italy	Cement	Mixed	1,247	1950–1986	1965–2005	NA	195
Tomiko K	2011	Japan	Refitting shipyard	Mixed	249	1947–1979	1947–2007	8,467	20
Pesch B	2010	Germany	NA	Mixed	576	NA	1993–2007	NA	58
Clin B	2009	France	Reprocessing plant	Mixed (mainly chrysotile)	420	NA	1978–2004	NA	11
Loomis D	2009	United States	Textile	Chrysotile	5,770	1950–1973	Up to Dec. 31, 2003	181,640	642
Pira E	2009	Italy	Miners	Chrysotile	1,056	1930–1975	1946–2003	34,432	142
Frost G	2008	Great Britain	Stripping/removal work.	Mixed	31,302	NA	1971–2005	NA	384
Reid A	2008	Australia	Mining and milling	Blue asbestos	2,552	1943–1992	1950–2004	NA	149
Hein MJ	2007	South Carolina	Textile	Chrysotile	3,072	1916–1977	1991–2001	NA	463
Kjærheim K	2005	Norway	Lighthouse keepers	Mixed	726	NA	1960–2002	NA	200
Pira E	2005	Italy	Textile workers	Mixed	1,966	1946–1984	Up to 1996	53,024	222
Wilczynska U	2005	Poland	Plant manufacturing	Mixed	4,497	1945–1980	1945–1999	NA	396
Reid A	2004	Australia	Mining and milling	Crocidolite	535	1943–1966	NA	NA	196
Smalyte G	2004	Lithuania	Cement	Mixed	1,887	NA	1978–2000	37,000	118
Sun TD	2003	China	Manual spinning	Chrysotile	5,681	1960–1980	1990–2000	NA	213
de La Provôté S	2002	France	Fireproof textiles and friction materials	Mixed	1,820	NA	1978–1995	27,734	56
Szesczenia-Dabrowska N	2002	Poland	Mixed	Mixed	1,397	NA	1970–1999	NA	91
Berry G	2000	United Kingdom	Textile and prefabricated cement pipes	Mixed	700	1936–1942	Up to June, 1980	17,146	129
Battista G	1999	Italy	Railway carriage construction workers	Mixed	734	1945–1969	1970–1997	NA	99
Germani D	1999	Italy	Textile (compensated for asbestosis)	Chrysotile	276	NA	1980–1997	3,761	40
Kurumatani N	1999	Japan	Refitting shipyard	Mixed	249	1947–1979	1947–1996	NA	15
Tsai SP	1996	Texas	Refinery and petrochemical plant	Mixed	2,504	NA	1948–1989	68,632	185
Dement JM	1994	South Carolina	Textile	Chrysotile	3,022	1940–1965	1975–1990	NA	283
Tarchi M	1994	Italy	Mining	Chrysotile	487	NA	1965–1989	NA	41
Magnani C	1993	Italy	Cement	Mixed	1,740	1950–1986	1965–1988	33,925	64
Raffin E	1989	Denmark	Cement	Mixed	8,580	1944–1972	1928–1984	NA	580
Armstrong BK	1988	Western Australia	Mining and milling	Crocidolite	6,916	1943–1966	1943–1980	100,178	216
Acheson ED	1982	United Kingdom	Gas mask assemblers (in Leyland and Preston)	Mixed	1,327	1927–1939	1951–1980	18,781	66

Fig. 2 Forest plot of stomach cancer risk associated with the asbestos exposure. The *squares* and *horizontal lines* correspond to SMR and 95 % CI of each included study. The area of *squares* represents weight of individual study. The *diamond* represents the summary SMR and 95 % CI

performed to explore the potential source of heterogeneity (Table 3). The results suggested that follow-up period was the significant source of heterogeneity ($P = 0.039$, $\tau = 0.01664$, $I^2_{\text{res}} = 22.08\%$, $\text{Adj } R^2 = 43.78\%$). Including gender in the regression model virtually eliminated any degree of heterogeneity ($P = 0.035$, $\tau = 0$, $I^2_{\text{res}} = 0.00\%$, $\text{Adj } R^2 = 100.00\%$). Other covariates (type of asbestos, type of outcome, region, type of industry, sample size) could not explain the heterogeneity.

Sensitivity analysis

As shown in Fig. 3, the corresponding pooled SMRs were not significantly altered by exclusion of any one study, which suggested stability of our results.

Evaluation of publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias. As a result, the funnel plot was not symmetrical, suggesting potential publication bias. By using the trim and fill method, the adjusted estimation was attenuated but remained significant (data not shown).

Discussion

Asbestos has been classified as the confirmed carcinogen by International Agency for Research on Cancer (IARC). There are strong epidemiological and other evidences supporting that occupational asbestos exposure results in an increased risk of lung cancer and mesothelioma. Whether asbestos fibers are associated with the development of other cancers is still investigation. The majority of cohort studies and literature reviews attempted to answer the question on an association between asbestos exposure and gastrointestinal cancer, but the results are inconclusive. IARC suggested that the association of asbestos exposure with cancers of digestive system is "sufficient" in 1987 (IARC 1987); however, in 2006, US Institute of Medicine Committee indicated that the evidence is "suggestive but not sufficient" (2006).

In current study, we quantitatively assessed the relationship of excessive exposure to asbestos with stomach cancer risk by applying a meta-analysis technique based on 32 independent literatures. Our results revealed an increased stomach cancer risk among workers exposed to asbestos. In other words, workers exposed to asbestos have 1.19 times

Table 2 Pooled results of stomach cancer with asbestos exposure by study characteristics

Study characteristics	No. of studies	SMR (95 % CI), <i>P</i>	Heterogeneity test (<i>Q</i> , <i>I</i> ² , <i>P</i>)
All	32	1.19 (1.06–1.34), 0.003	60.85, 37.6 %, 0.011
<i>Gender</i>			
Male	25	1.30 (1.16–1.45), <0.001	27.16, 11.6 %, 0.297
Female	11	0.97 (0.76–1.24), 0.788	4.65, 0.0 %, 0.913
<i>Type of asbestos</i>			
Chrysotile	9	0.97 (0.80–1.17), 0.721	7.47, 0.0 %, 0.588
Crocidolite	4	1.55 (1.27–1.89), <0.001	2.04, 0.0 %, 0.565
Mix	19	1.22 (1.06–1.41), 0.002	34.30, 32.9 %, 0.061
<i>Type of outcome</i>			
Incidence	5	1.21 (0.97–1.52), 0.094	4.94, 0.0 %, 0.423
Mortality	27	1.19 (1.04–1.35), 0.009	54.59, 43.2 %, 0.006
<i>Region</i>			
Europe	20	1.21 (1.05–1.40), 0.009	34.63, 36.5 %, 0.042
Asia	5	1.04 (0.84–1.30), 0.711	5.11, 0.0 %, 0.646
America	3	0.74 (0.48–1.13), 0.161	1.90, 0.0 %, 0.387
Oceania	4	1.53 (1.26–1.86), <0.001	3.14, 0.0 %, 0.535
<i>Type of industry</i>			
Refitting shipyard	2	1.14 (0.73–1.79), 0.556	0.84, 0.0 %, 0.839
Mining	6	1.43 (1.20–1.70), <0.001	5.72, 0.0 %, 0.455
Textile	8	0.94 (0.77–1.15), 0.545	6.64, 0.0 %, 0.576
Cement	5	1.15 (0.91–1.46), 0.232	7.84, 36.3 %, 0.165
Mix	3	1.36 (0.95–1.94), 0.095	5.18, 61.4 %, 0.075
<i>Follow-up period (years)</i>			
<25	7	0.97 (0.79–1.19), 0.778	0.43, 0.0 %, 1.000
≥25	25	1.26 (1.11–1.42), <0.001	48.33, 35.9 %, 0.024

Table 3 Meta-regression analysis to explore potential source of heterogeneity

Variable	Coefficient	<i>P</i> value	τ	<i>I</i> ² _{res} (%)	Adj <i>R</i> ² (%)
Gender (1 = male, 2 = female)	−0.3086	0.035	0	0.00	100.00
Type of asbestos (1 = chrysotile, 2 = crocidolite, 3 = mix)	0.0971	0.137	0.02135	24.40	27.85
Type of outcome (1 = incidence, 2 = mortality)	0.0344	0.825	0.03137	36.22	−6.03
Region (1 = Europe, 2 = Asia, 3 = America, 4 = Oceania)	0.0363	0.460	0.03243	37.32	−9.59
Type of industry (1 = refitting shipyard, 2 = mining, 3 = textile, 4 = cement, 5 = mix, 6 = other)	0.0106	0.752	0.03053	33.73	−3.16
Sample size (1 = <500, 2 = 500–1,000, 3 = >1,000)	0.0037	0.966	0.03118	35.18	−5.37
Follow-up period (1 = <25, 2 = ≥25)	0.2870	0.039	0.01809	23.93	43.61

of suffering from stomach cancer compared with the general population.

Higher risk of stomach cancer was observed in male workers. It was not surprising that male may have more chances to exposure to other risk factors, such as smoking or alcohol habit. Lifestyle exposure to alcohol and smoking were associated with increased stomach cancer risks. Studies have showed that cigarette smoking may play the most harmful role in the initial development of stomach cancer and that drinking alcohol may promote the process (Li et al. 2012).

We found an excess mortality of stomach cancer in miners group, which is consistent with the majority of the miner cohorts. Musk et al. (2008) identified a slightly increased risk of mortality from stomach cancer in miners and millers cohort at Wittenoom. Wang et al. (2012) also found excess mortality of gastrointestinal cancers in the miner group. A substantial excess in mortality from gastrointestinal cancers was reported in the Quebec miner cohort (McDonald et al. 1980). A case–control study showed a significantly elevated risk of GI cancers in the miners who had a prolong exposure to coal mine dust (Ames 1983).

Fig. 3 Sensitivity analysis by removing each study in each turn. Rows represent the results of meta-analysis of all studies except the omitted study named in that row. Omission of any study did not affect the whole estimate results significantly

Results from subgroup analysis by follow-up period found that higher risk of stomach cancer was observed in follow-up period above 25 years, which seems to indirectly suggest a dose–response relation.

The exact mechanisms of asbestos exposure leading to stomach cancer are not fully understood. They may be due to the chronic inflammation in stomach tissue caused by persistent presence of asbestos fibers. Kogan et al. (1987) performed an experiment by continuous contact of the stomach wall with asbestos in rats to understand the role of asbestos in the etiology of stomach cancer. Experiment suggested that the tumors in the stomach and the adjacent part of the abdominal cavity were induced by asbestos.

Considering moderate heterogeneity among studies, a meta-regression approach was conducted by adjusting for the covariates to explore the potential important sources. We found gender and follow-up period as the important contributors to the between-study heterogeneity.

Inherent properties of asbestos may affect its carcinogenicity, including fiber diameter and length, surface properties of the fiber, and the fiber durability. The diameter of crocidolite fibers is the finest followed by chrysotile, amosite, and anthophyllite, and was considered the most harmful to human health. In subgroup analysis by asbestos type, workers exposed only to crocidolite found a significant association.

Consistency of evaluation indicators is important for a meta-analysis as different outcomes may introduce potential heterogeneity. The outcome of five studies is a

standardized incidence rate. Considering higher death rate and lower survival of stomach cancer, we included the five studies to the final analysis. However, a subgroup analysis by outcome was performed, and positive conclusion was only observed in SMR outcomes.

There are some limitations to this study that should be acknowledged. Firstly, available data in our study could not make us further perform interaction and subgroup analysis by confounding factors, such as alcohol and smoking habit or concomitant occupational exposure to other substances or the diameter of fibers. Second, a further dose–response relationship of stomach cancer with asbestos was not able to be performed due to limited data from original cohorts. Third, significant publication bias was observed. The reason may arise from many aspects, such as positive findings tend to be accepted by journals, while negative results are often rejected or not even submitted. Therefore, the results should be interpreted with caution.

In conclusion, this present meta-analysis found that exposure to asbestos is associated with an increased risk of stomach cancer, especially male miners, and crocidolite is more harmful to human beings. Few studies focus on the elucidation of the mechanisms of asbestos leading to stomach cancer, and constant efforts should be made to clarify the association of asbestos exposure with stomach cancer.

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Conflict of interest The authors have declared that no conflict of interest exists.

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