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Cohort Studies on Cancer Mortality Among Workers Exposed Only to Chrysotile Asbestos: a Meta-analysis[1]

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Objective To determine whether there was excessive risk of cancer among workers exposed to chrysotile fiber alone by applying a meta-analysis technique. **Methods** All data meeting the criteria of cohort studies on cancer mortality among workers exposed only to chrysotile were incorporated into meta-analysis. Pooled standardized mortality ratios (SMRs) and their corresponding 95% confidence intervals (CIs) for main cancer sites were calculated using two approaches of unweighted ratio and random effect model. The heterogeneity and its sources of the results were examined with a Q-statistic and Z-score test. The dose-response effect as reflected in the percentage of all deaths due to mesothelioma served as a proxy measure of chrysotile exposure. **Results** A cohort of twenty six workers exposed to chrysotile alone was summarized. The significantly elevated meta-SMRs for all deaths (1.27), all cancers (1.28), cancers of respiratory organs (2.51), cancers of lung (2.35) and cancers of stomach (1.24) were observed. The significantly elevated meta-SMRs for lung cancer within occupational strata were observed among textile workers (3.55), asbestos product manufacturers (3.30), miners and millers (2.24), cement product workers (1.22), and for stomach cancer among asbestos product manufacturers (1.49). Meta-SMRs for cancers at other sites were not significant. Meta-SMR for lung cancer showed an increasing trend with an elevated percentage of all deaths from mesothelioma, but no such trend for stomach cancer. **Conclusion** There are excessive risks of lung cancer and mesothelioma among workers exposed to chrysotile fiber alone, and likely no convincing indication of an etiological association between chrysotile exposure and cancers at other sites.

Key words: Chrysotile asbestos; Cancer; Mortality; Cohort study; Meta-analysis

INTRODUCTION

Asbestos is one of the most versatile and useful industrial materials, known for its multiple important applications. Inhalation of asbestos dust may not only result in fibrosis of the lung, but also induce lung cancer and malignant mesothelioma. However, there are

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conflicting opinions on the carcinogenic effects of exposure to chrysotile fibesr alone[1-4]. The mineral oil hypothesis, the amphiobole hypothesis, or the disproportionate distribution of dimension and biopersistence of asbestos fibers have been put forward[5]. Since there were some limitations such as consistency and representation in individual cohort studies, the relationship between asbestos exposure and cancer was explored by applying a meta-analysis[6,7]. But those workers who exposed exclusively and predominantly to chrysotile usually constituted 5% or less of amphibole asbestos and were classified into the same category, i.e. the predominantly chrysotile-exposed workers. So it was difficult to explain the carcinogenic effects of exposure only to chrysotile. To provide a summary measure of risk for malignant tumors associated with exclusively chrysotile exposure, we conducted a meta-analysis of cohort studies on cancer mortality among workers exposed only to chrysotile.

MATERIALS AND METHODS

Inclusion Criteria

Only cohort studies on cancer mortality among workers exposed to chrysotile alone were incorporated into the meta-analysis.

Exclusion Criteria

Workers who were exposed to other types of asbestos fibers except for chrysotile fiber, or predominately to chrysotile but to mixed other asbestos fibers simultaneously, with unknown and non-occupational exposure were excluded. Descriptive epidemiological study, case-control study, experimental epidemiological study, and cohort study of incidence were also excluded.

Search Strategy

We conducted searches of MEDLINE database from 1966 to January 2003, and Chinese BioMedical disc (CBMdisc) from 1978 to February 2003, using Mesh headings including “asbestos or chrysotile” and “cancer or tumor or neoplasm”, and “mortality” without restriction on language, supplemented by manual searching the relevant articles listed in medical key journals in China during recent 10 years and references of all identified studies. The authors of all identified articles were contacted in order to obtain or check the relevant information.

Data Extraction

The data were independently extracted by two investigators with blinding method using a standardized data-abstraction form. The following information was sought from each identified study: author’s name, title, year of publication, occupation, location; follow-up size, person-year and period, observed and expected number of deaths for all causes, all cancers and cancers at major sites, latency of lung cancer, number of mesothelioma deaths. Standardized mortality ratios (SMRs) for cancers and their corresponding 95% confidence intervals (CIs) of the identified study were calculated. As some papers on the same cohort study were published several times, only independent studies and the most recent publications were included. When a study consisted of several groups exposed to different types of asbestos, only the subgroup in which workers were exposed to chrysotile alone was included

in the meta-analysis.

As direct measurements of airborne asbestos dust were not obtained in most cohort studies, we analyzed the dose-response effect as reflected in the percentage of all deaths due to mesothelioma that served as a proxy measure of chrysotile exposure. Since the dose-response relationship between asbestos exposure and mesothelioma has been proven[7], studies were stratified by the percentage of deaths due to mesothelioma into three groups: 0%-0.49%, 0.50%-0.99%, and over 1.00%.

Statistical Analysis

The pooled estimates of SMRs and their corresponding 95% CIs were calculated according to the following two approaches:

(1). Unweighted ratio of the sum of observed and exposed deaths[7]:

meta-SMR = $\sum O_i / \sum E_i$, meta-SMR$_{U,L}$ = exp[ln(meta-SMR) $\pm$ 1.96/$\sqrt{\sum Oi}$].

(2). Random effect model (REM)[6]:

meta-SMR = exp[$\sum W_i^* \theta_i / W_i^*$],

meta-SMR$_{U,L}$ = exp[ln(meta-SMR) $\pm$ 1.96/$\sqrt{Wi^*}$],

$W_i^* = (s_i^2 + \tau^2)^{-1}$, $s_i^2 = O_i^{-1}$, $\tau^2 = \max\{0, [Q-(K-1)]/(\sum W_i^2 / \sum W_i)\}$,

$\theta_i = \ln(SMR_i)$, $W_i = s_i^{-2}$, $s_i^2 = O_i^{-1}$,

The heterogeneity and its sources of the results for each study were examined with a Q-statistics[6] and Z-score[7] test:

$Q = \sum W_i (\theta_i - \overline{\theta}_w)^2$, $\overline{\theta}_w = \sum W_i \theta_i / \sum W_i$,

$Z = [\log(SMR_i) - \log(\text{meta-SMR})]/SE$, $SE = 1/\sqrt{Oi}$.

Where O_i, E_i, SMR_i denote the number of observed and expected deaths and SMR in the cohort, respectively, K is the number of cohort. Meta-SMR$_{U,L}$ denotes the upper limit and lower limit of 95% CI of meta-SMR.

Sensitivity analysis was performed by calculating again the meta-SMRs for cancers at main sites after exclusion of those cohorts of principal sources of heterogeneities in all cohorts[8].

All data were assumed as a Poisson distribution and calculations were performed by using SAS system for Window, release 6.03 Edition[9]. Statistical significance of SMR and Q-statistics were evaluated by using the score-test and Chi-square test, respectively.

RESULTS

Initially, a total of 453 articles were searched. Two hundred and fifty three articles were excluded due to non-cohort study after reviewing the abstracts. One hundred fifty seven articles were excluded because types of exposed asbestos and study outcomes could not meet the inclusion criteria after reviewing the full texts and contacting the authors of the identified studies. Eighteen repeated publications were rejected. Our final literature search identified 25 articles reporting 26 cohorts that met the inclusion criteria. Table 1 summarizes the study characteristics[10-34]. Ten (38.46%) of the 26 identified cohorts were in China, 6 (23.08%) in USA, 4 (15.38%) in UK, 2 (7.69%) in Canada and Italy, 1 (3.85%) in Sweden and Denmark, respectively. The earliest cohort study was published in USA in 1977[34] and the most recent one in China in 2003[13]. By occupation, the major was among asbestos product manufacturers (38.46%), followed by textile workers and asbestos cement workers (19.23%, respectively), miners and millers and friction material workers (11.54%, respectively).

TABLE 1

Study Characteristics of All Identified Cohorts

First Author	Occupation	Location	Size	Total Cancers	Cases of Lung Cancer	Cases of Stomach Cancer	% of All Deaths Due to Mesothelioma
Peto, J.[9]	Textile[b]	UK	145	34	20	4	5.69
McDonald, A. D.[10]	Textile	USA	2543	120	NA[a]	NA	0.12
Dement, J. M.[11]	Textile	USA	3022	283	126	9	0.16
Sun, T. D.[12]	Textile	China	5681	213	87	42	0
Germani, D.[13]	Textile	Italy	276	43	9	2	5.00
Liddell, F. D. K.[14]	Miner[c]	Canada	10 918	1900	646	183	0.47
Piolatto, G.[15]	Miner	Italy	1058	82	22	12	0.47
Wang, Z. M.[16]	Miner	China	7668	116	36	NA	0.88
Hughes, J. M.[17]	Cement[d]	USA	3594	226	107	15	0.34
Raffn, E.[18]	Cement	Denmark	163	NA	12	NA	NA
Gardner, M. J.[19]	Cement	UK	2167	121	41	15	0.21
Thomas, H. F.[20]	Cement	UK	1540	74	30	NA	0.57
Ohlson, C. G.[21]	Cement	Sweden	1176	44	11	1	0
McDonald, A. D.[22]	Friction[e]	USA	3515	202	73	NA	0
Newhouse, M. L.[23]	Friction	UK	12 571	735	254	NA	0.07
Finkelstein, M. M.[24]	Friction	Canada	701	35	12	NA	1.55 (double)
Acheson, E. D.[25]	Product[f]	USA	570	44	7	4	0.56
Cheng, W. N.[26]	Product	China	1172	44	21	7	NA
Zhang, Z. Q.[27]	Product	China	370	10	6	2	0
Wang, Z. M.[28]	Product	China	515	50	22	NA	1.43
Wang, Z. H.[29]	Product	China	551	75	32	16	1.33
Pang, Z. C.[30]	Product	China	530	22	9	NA	NA
Zhou, K. H.[31]	Product	China	669	50	24	5	0
Zhu, H.[32]	Product	China	5893	183	67	28	0.40
Wang, Z. M.[16]	Product	China	9950	106	42	NA	0.31
Weiss, W.[33]	Product	USA	264	13	4	NA	NA

Note. [a]NA, data not available; [b]Textile, asbestos textile workers; [c]Miner, asbestos miners and millers; [d]Cement, asbestos cement workers; [e]Friction, friction material workers; [f]Product, asbestos product manufacturers.

Follow-up study ranged in size between 145[10] and 12 571[24] subjects, in length of the follow-up period ranging from 5 years[33] to 51 years[12], and in person-years from 3761[14] to 14 122 000[15], however person-years could not be obtained in 8 cohorts. The earliest follow-up period started in 1933[10] and the latest follow-up ended in 2000[13]. The percentage of all deaths due to mesothelioma was 0.41% on average ranging from 0%[13,22,23,28,32] to 5.69%[10]. The proportion of deaths due to mesothelioma could not be calculated in 4 cohorts[19,27,31,34].

Table 2 shows the pooled analysis results of SMRs for cause-specific cancers. Meta-SMRs (REM, similarly hereinafter) for all causes (1.27) and all cancers (1.28) were significantly elevated ($P<0.01$), significant heterogeneities were both present, and their principal sources were from the cohort of Newhouse *et al*.[24] (Z=-5.93) and Zhang *et al*.[28] (Z=4.58), the cohort of Wang *et al*.[30] (Z=4.90) and Newhouse *et al*.[24] (Z=-3.42), respectively.

Meta-SMRs for cancers of respiratory organs (2.51) and cancer of lung (2.35) were both significantly elevated ($P<0.01$), but not for cancer of laryngeal (1.42, $P>0.05$). The highest SMR for lung cancer of the single cohort study was reported among miners and millers of the cohort of Wang *et al*.[17] (SMR 7.63), the lowest among asbestos product manufacturers of the cohort of Thomas *et al.*[21] and Weiss[34] (SMR 0.93, respectively). The percentage of excessive lung cancer cases was 52.97% on average from -9.09%[21] to

TABLE 2

Meta-SMRs for Site-specific Cancers Among Workers Exposed Only to Chrysotile

Cancer Sites	No. of Cohorts	Unweighted Ratio		Random Effects Model		Q
		Meta-SMR[a]	95% CI[b]	Meta-SMR[a]	95% CI[b]	
All Causes	20	1.10**	1.08-1.12	1.27**	1.09-1.48	447.59**
All Cancers	25	1.22**	1.18-1.26	1.28**	1.24-1.33	425.06**
Cancers of Digestive Organs	17	1.03	0.97-1.09	1.12	0.96-1.31	37.64**
Oesophagus	5	0.79	0.54-1.17	0.85	0.59-1.22	1.94
Stomach	15	1.19**	1.07-1.32	1.24**	0.95-1.62	31.79**
Intestine	9	0.90	0.76-1.07	1.09	0.74-1.61	18.09*
Liver	5	1.06	0.84-1.33	1.11	0.82-1.51	4.85
Cancers of Respiratory Organs	7	1.57**	1.48-1.67	2.51**	1.67-3.76	135.50**
Larynx	8	1.13	0.87-1.45	1.42	0.72-2.80	21.28**
Lung	25	1.53**	1.46-1.60	2.35**	1.43-3.86	505.00**
Breast Cancer	4	0.97	0.76-1.25	0.97	0.75-1.26	0.46
Cancers of Genitourinary Organs	6	1.13	0.96-1.32	1.25	0.90-1.75	11.74*
Ovary	3	1.33	0.84-2.11	1.81	0.61-5.36	7.74*
Cancers of Lymphatic and Hematopoietic Tissues	4	1.02	0.83-1.25	0.99	0.73-1.33	4.28

Note. [a]SMR, standardized mortality ratio; [b]CI, confidence interval; *$P<0.05$; **$P<0.01$.

662.71%[17]. Meta-SMR for lung cancer demonstrated extreme heterogeneity (Q=505.00, P<0.01), its principal sources were the cohort of Liddell *et al*.[15] (Z=-5.96) and Wang *et al*.[17] (Z=3.07). The calculated results of Z-scores for all cancer of lung studies are presented in Fig. 1. Eight (30.77%) cohorts with latency of lung cancer were available, ranging from 12 years[30] to 48 years[30].

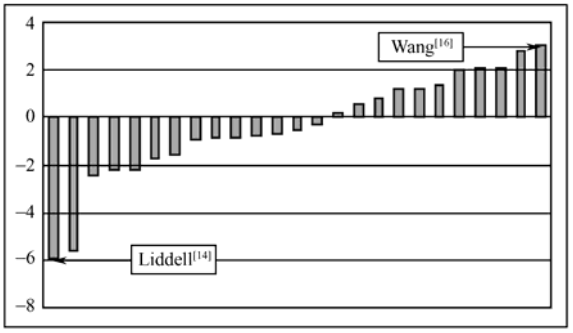

FIG. 1. Z-scores of meta-SMR for all cancer of lung studies.

Table 3 shows the re-calculated results of summary SMRs for all deaths, all cancers and cancer of lung after exclusion of those cohorts of principal sources of heterogeneities in all cohorts. The results were similar to those of all their corresponding cohorts (Table 2).

When studies were stratified according to occupation categories (Table 4), the pooled analysis results showed a significant elevation except for friction material workers (meta-SMR 1.25, P>0.05). The highest meta-SMR for lung cancer was among textile workers (3.55), followed by asbestos product manufacturers (3.30), miners and millers (2.24) and asbestos cement workers (1.22). When studies were stratified according to the percentage of all deaths due to mesothelioma (Table 4), the data showed an increasing trend in the meta-SMR for lung cancer with percentages of all deaths due to mesothelioma, but no such trend was seen for cancer of stomach.

TABLE 3

Sensitivity Analysis Results of Meta-SMRs for Main Cancers Among Workers Exposed Only to Chrysotile

Cancer Sites	No. of Cohorts[a]	Unweighted Ratio		Random Effects Model		Q
		Meta-SMR[b]	95% CI[c]	Meta-SMR[b]	95% CI[c]	
All Causes	18	1.12**	1.10-1.14	1.18**	1.05-1.33	267.74**
All Cancers	23	1.28**	1.23-1.33	1.34**	1.29-1.39	232.93**
Cancer of Lung	23	1.60**	1.51-1.70	2.28**	1.09-4.78	383.83**

Note. [a]No. of cohorts, after exclusion of those cohorts of principal sources of heterogeneities in all cohorts; [b]SMR, standardized mortality ratio; [c]CI, confidence interval; **P<0.01.

The pooled analysis results for other cancers of digestive organs, cancer of larynx, cancer of breast, cancers of genitourinary organs, cancers of lymphatic and hematopoietic tissues were all not significantly elevated except for cancer of stomach (meta-SMR 1.24, P<0.01). The significantly elevated meta-SMR for stomach cancer was among asbestos product manufacturers (1.49, P<0.05), not for other occupations.

TABLE 4

Stratification Analyses of Major Site-specific Cancers Rates Among Workers Exposed Only to Chrysotile

	All Cancers			Cancer of Lung			Cancer of Stomach		
	No. of Cohorts	Meta-SMR[a] (95% CI[b])	Q	No. of Cohorts	Meta-SMR (95% CI)	Q	No. of Cohorts	Meta-SMR (95% CI)	Q
By Occupation:									
Textile Workers	5	1.66** (1.20-2.30)	29.65**	4	3.55** (2.00-6.32)	33.20**	4	1.06 (0.80-1.40)	1.40
Miners and Millers	3	1.26** (1.05-1.52)	15.06**	3	2.24** (1.37-3.69)	102.61**	2	1.21 (1.04-1.41)	1.16
Cement Workers	4	0.98 (0.83-1.15)	5.83	5	1.22* (0.90-1.65)	9.51	3	1.01 (0.57-1.79)	3.73
Friction Materials Workers	3	1.12 (0.93-1.35)	13.70**	3	1.25 (0.98-1.58)	7.48		NA[c]	NA NA
Asbestos Products Workers	10	1.70** (0.84-3.45)	153.66**	10	3.30** (1.59-6.85)	58.88**	6	1.49* (0.77-2.89)	17.03**
By % of All Deaths Due to Mesothelioma:									
0-	14	1.21** (1.17-1.26)	234.28**	15	2.11** (1.23-3.43)	330.75**	10	1.28* (0.93-1.76)	28.93*
0.50-	4	1.75** (1.56-1.96)	114.61**	4	2.08** (0.44-9.86)	79.55**	2	0.92 (0.59-1.43)	0.53
1.00-	3	1.92** (1.61-2.28)	6.80	3	5.33** (3.23-8.80)	4.49	2	1.50 (0.67-3.34)	0.31

Note. [a]SMR, standardized mortality ratio; [b]CI, confidence interval; [c]NA, data not available; *$P<0.05$; **$P<0.01$.

DISCUSSION

The primary focus of the study was to determine whether there was excessive risk of malignant tumors among workers exposed only to chrysotile asbestos by applying a meta-analysis technique.

There has been a heated debate on carcinogenic effects of exposure only to chrysotile during the recent 20 years. It was not only for scientific interest, but also had legal, public policy, and public health importance[1-3,5]. The amphibole hypothesis[1] postulated that amphiboles are the major cause of mesotheliomas in asbestos workers, the lung burden of chrysotile and non-asbestos fibers bear no relation to the occurrence of mesotheliomas and lung cancer, and amphiboles are more potent than chrysotile in the induction of fibrotic lung disease and associated lung cancers. Chrysotile asbestos mining companies in Canada stated that chrysotile was harmless and indispensable[35]. However, some investigators demonstrated that the fiber counts found in the lung might not accurately reflect the concentrations found at the sites for mesothelioma induction, and raised serious questions about the validity of using lung burden studies to assess mesothelioma risk[2,3]. All types of asbestos had the potential to induce cancer of lung and mesothelioma in experimental animal models[2,3]. Meanwhile, the significantly elevated mortality of lung cancer and mesothelioma among workers exposed to chrysotile alone was found in some cohort studies. Thus, a controversy apparently existed between those who supported the amphibole hypothesis (the 'chrysophiles') and those who opposed it (the 'chrysophobes'), and remains unsolved until now[5].

According to our study, meta-SMRs for all cancers (1.28) and lung cancer (2.35) were significantly elevated ($P<0.01$). The sensitivity analysis showed that the results from this meta-analysis were robust. The proportionate mesothelioma mortality was 0.41% on average. As the incidence of mesothelioma was extremely low in general population, its expected number was nearly close to null[7]. Goodman *et al*.[7] demonstrated that meta-SMR for lung cancer among workers exposed to mixed asbestos was 163 and 148 with and without years of latency, respectively. This was similar to our results. It was suggested that chrysotile asbestos was similar potent in carcinogenic risks as other types of asbestos. There were excessive risks of lung cancer and mesothelioma among workers exposed to chrysotile fibers alone. In fact, chrysotile constitutes 95% of all asbestos used worldwide, and it has been the main cause of pleural mesothelioma in humans[3]. No threshold has been identified for carcinogenic risk. Some asbestos-containing products have posed particular concern and chrysotile use in these circumstances should not be recommended[36].

We found that meta-SMRs for other cancers of digestive organs, cancer of larynx, cancer of breast, cancers of genitourinary organs, cancers of lymphatic and hematopoietic tissues were all not significantly elevated except for cancer of stomach (meta-SMR 1.24, $P<0.01$). But we did not find an increasing trend in meta-SMR for stomach cancer with the percentage of mesothelioma deaths. This was consistent with that in other literatures[6,7]. It was suggested that there was likely no convincing indication of an etiological association between chrysotile exposure and cancers at other sites[36].

The quality of the data and some limitations of the study, however, should be discussed. Firstly, measurements of airborne asbestos dust concentration were not reported in most cohort studies. So it was difficult to establish the direct quantitative exposure-response relationship between chrysotile exposure and cancers. When using the percentage of all deaths due to mesothelioma as a proxy estimate of asbestos exposure, we found an increasing trend in meta-SMR for cancer of lung with the percentage of all deaths due to mesothelioma, but we did not find any support evidence of a dose-response relationship by a statistically significant positive correlation coefficient ($r=0.319$, $P>0.05$). This finding was difficult to interpret. Misclassification rate of mesothelioma was possibly significant because it was often quite difficult to diagnose. The diagnosis of a rare cancer needed pathological examinations, especially postmortem, which was not so well practiced in some areas. Pleural mesothelioma that was misdiagnosed as lung cancer and peritoneal mesothelioma as gastrointestinal cancer might affect the risk of estimates of individual studies[7]. Secondly, specific pooled-analysis cohorts were less. There were some inherent limitations including publication bias, overrepresentation and oversimplification in the meta-analytical approach[7]. They may affect the pooled-analysis results.

In conclusion, the findings in the present meta-analysis study suggest that there are excessive risks of lung cancer and mesothelioma among workers exposed to chrysotile fibers alone, and that no convincing indication of an etiological association between chrysotile exposure and cancers at other sites is likely present.

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