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# Additive Synergism between Asbestos and Smoking in Lung Cancer Risk: A Systematic Review and Meta-Analysis

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## Abstract

Smoking and asbestos exposure are important risks for lung cancer. Several epidemiological studies have linked asbestos exposure and smoking to lung cancer. To reconcile and unify these results, we conducted a systematic review and meta-analysis to provide a quantitative estimate of the increased risk of lung cancer associated with asbestos exposure and cigarette smoking and to classify their interaction. Five electronic databases were searched from inception to May, 2015 for observational studies on lung cancer. All case-control (N = 10) and cohort (N = 7) studies were included in the analysis. We calculated pooled odds ratios (ORs), relative risks (RRs) and 95% confidence intervals (CIs) using a random-effects model for the association of asbestos exposure and smoking with lung cancer. Lung cancer patients who were not exposed to asbestos and non-smoking (A-S-) were compared with; (i) asbestos-exposed and non-smoking (A+S-), (ii) non-exposure to asbestos and smoking (A-S+), and (iii) asbestos-exposed and smoking (A+S+). Our meta-analysis showed a significant difference in risk of developing lung cancer among asbestos exposed and/or smoking workers compared to controls (A-S-), **odds ratios** for the disease (*95% CI*) were (i) **1.70** (A+S-, *1.31–2.21*), (ii) **5.65;** (A-S+, *3.38–9.42*), (iii) **8.70** (A+S+, *5.8–13.10*). The additive interaction index of synergy was 1.44 (95% CI = *1.26–1.77*) and the multiplicative index = 0.91 (95% CI = *0.63–1.30*). Corresponding values for cohort studies were 1.11 (95% CI = *1.00–1.28*) and 0.51 (95% CI = *0.31–0.85*). Our results point to an additive synergism for lung cancer with co-exposure of asbestos and cigarette smoking. Assessments of industrial health risks should take smoking and other airborne health risks when setting occupational asbestos exposure limits.

## Introduction

Lung cancer is responsible for 20% of all global cancer deaths. Its latency period is long (~20 yr) and survival rate poor (10%) [1]. Meta-analyses of epidemiological studies demonstrated that smoking had a strong relationship with lung cancer [2,3] and 70–90% of lung cancer patients are directly attributed to cigarette smoking [4]. Several compounds in tobacco smoke are classified as human carcinogens (Group 1) by the IARC including tobacco specific nitrosamines and benzo(a)pyrene, a carcinogenic polycyclic aromatic hydrocarbon [4,5]. Second-hand smoke also increases the risk of developing lung cancer by an estimated 25% in by-standers [6]. Besides smoking, other risk factors for lung cancer are arsenic, particulates from diesel engine exhausts, radon, and exposure to asbestos and other mineral fibers, [7,8].

Asbestos is a group of naturally occurring silicate mineral fibers widely used in building materials, vehicle brakes and thermal insulators since the 1900s. Asbestos types are classified according to their structures, chemical composition and thermal stability. Chrysotile or white asbestos (mainly $Mg_3(Si_2O_5)(OH)_4$) [9,10] accounts for most current use where asbestos is permitted while amosite (brown) and crocidolite (blue asbestos), belonging to the amphibole class, are stronger, more durable, and more heat resistant than chrysotile. There are many well documented lung disease cases in asbestos factory workers and miners from 1900 onwards [11–15]. The most common asbestos-associated diseases are benign pleural disease, asbestosis, lung carcinoma (small cell, squamous, and adenocarcinoma) and mesothelioma [16]. Mesothelioma has a very high association with asbestos exposure but otherwise uncommon [17]. It has high incidences among males of western countries and Japan where it is projected to peak between 2012 and 2030, a latency of 40–50 years after the peak use of asbestos during the 1930s-1970s [18].

Numerous studies have shown a clear association between carcinogenesis and either smoking or asbestos. However, associations may result from independent and unrelated mechanisms and therefore show additive effects while effects greater than summed individual actions implies biological interactions [19,20]. This is commonly referred to as synergism [21] but additive synergism is more appropriate. Conversely, a smaller effect than the sum of effects may be due to antagonistic interactions. Synergism might, less commonly, be multiplicative due to different types of interaction, for example where an effect requires the activation of two or more serial processes. Such distinctions are important for both possible treatment considerations and public health such as identifying those at greatest risk of disease. Some authors have sought to assess interactions between asbestos and smoking on lung cancer [22,23], and found the effects to be additive [24], more than additive [25] and multiplicative [26,27]. In animal experiments, co-exposure to asbestos and cigarette smoke also found contradictory interaction models [28–30]. Two previous meta-analyses [31,32] found associations between asbestos exposure and smoking for increased lung cancer risk and that the two carcinogenic effects were greater than the sum of their separate actions but again failed to agree on the type of interaction (multiplicative or additive). These reviews had some weakness (assessing individual interactive effects in each study and could not explain the dose-response for asbestos exposure). Also, they have been superseded by additional studies which relate asbestos exposure with smoking and lung cancer [22–27]. Besides increasing the power and weight of the data, these later studies were better designed and controlled, especially the Markowitz et al. study [24], and therefore better able to resolve these issues. Thus, we incorporated this data into a new systematic review and meta-analysis. We anticipate that such a study will better inform the risk assessment process in developing nations where most male semi-skilled workers are smokers, and occupational asbestos exposure continues to pose a health risk in populations where lung disease is a leading cause of mortality [33].

## Methods

The study was conducted and reported using the PRISMA (S1 PRISMA Checklist) [34] and MOOSE [35] guidelines.

### Search Strategy and study selection

We searched titles and abstracts PubMed, Embase, Scopus, ISI Web of Knowledge, and TOXLINE databases from their inception to May 2015. Combinations of the following key words were used: asbestos, crocidolite, amosite, chrysotile, tremolite, actinolite, anthophyllite, cigarette, cigarette smoke, cigarette smoking, pipe, cigar, tobacco, tobacco smoking, lung cancer, mesothelioma, lung carcinoma, and lung adenocarcinoma. There was no language restriction. Additional studies were also hand-searched from bibliographies of the selected studies.

### Inclusion and exclusion criteria

Studies were included if they met all of the following criteria: (1) original articles published in peer-reviewed journals; (2) human studies; (3) observational studies; (4) studies investigating associations between asbestos exposure and smoking with lung cancer, and; (5) studies reporting sufficient data for calculating odds ratios and relative risks. The studies not meeting the inclusion criteria described above were excluded. If there were duplicate populations, only the studies providing the most details, grater number of participants, followed populations for longer follow-up periods, or the most recently published were selected for meta-analysis. Two reviewers (YN, WT) independently appraised titles and abstracts retrieved from the comprehensive searches. The controversial reviews were discussed and resolved by a third reviewer (OL). If further details were required, the reviewers contacted the authors for more information.

### Data Abstraction and Quality Assessment

Information extracted from each study included first author, publication year, geographic area, study type (hospital-based case-control, population-based case-control, nested case-control, retrospective cohort, prospective cohort, and cross-sectional), total number of cases, and controls, fiber type (chrysotile, crocidolite, tremolite), industry type, measurement of asbestos and/or smoking exposure, asbestos exposure assessment method, definition of asbestos exposure and/or smoking, period of employment/exposure, measurement method (asbestos exposure, smoking), and classification of outcome. The Newcastle-Ottawa quality assessment scale (NOS) was used to assess the quality of the selected observational studies. The categories of NOS was based on selection of participants, comparability of study groups, and the exposure of interest (case-control studies) or outcome of interest (cohort studies) [36]. When each category is satisfied it attracts one or sometimes two 'star(s)' and a maximum of 9 stars for either case-control or cohort study, indicates the highest quality study [37].

### Statistical Analysis

Asbestos exposure was arbitrarily taken as more than 100 air-borne fiber-yr/ml of environmental air for >5% of their work time and cigarette smoking was categorized as smokers who smoked >15 cigarettes/day. Those subjects having lower and shorter fiber exposures and lower cigarette consumption were deemed as non-exposed or non-smokers, respectively.

Using the above cut-offs, subjects were placed into four groups: (1) those people not exposed to asbestos and non-smokers were classified as not exposed to asbestos and non-smoking (A-S-), (2) workers exposed asbestos and non-smokers were classified as asbestos-exposed and non-

smoking (A+S-), (3) those not exposed to asbestos but smoked were grouped as non-exposed to asbestos and were smokers (A-S+), and (4) workers exposed to asbestos and smoked were classified as asbestos-exposed and smokers (A+S+). The primary outcome of the pooled analysis focused on comparing the summary effect of lung cancer risk in people without asbestos exposure and non-smoking versus co-exposure to asbestos and/or smoking as follows: (i) A+S- compared with A-S- (ii) A-S+ compared with A-S-, and (iii) A+S+ compared with A-S- and interaction between asbestos and smoking were evaluated using the Rothman Synergy Index [38]. Summary effect estimates were assessed discretely by averaging the natural logarithmic OR and/or RR weighted by their inverse variances. The pooled effect estimates were calculated using a random effects model by the method of DerSimonian and Laird [39]. Heterogeneity among selected studies was determined using the Q-statistic and *I*-squared tests [40]. *I*-squared ($I^2$) values of 25%, 50%, and 75% represented low, moderate, and high degrees of heterogeneity, respectively [41]. The meta-analysis of case-control and cohort studies were conducted separately due to differences in the nature of study design [42].

Subgroup analyses were performed according to the geographic area (Europe, America, others), asbestos type, study design (hospital or population, retrospective, prospective), and stratification of smoking level were used to assess the impacts of study characteristics on outcomes. Publication bias was quantified using funnel plot, Begg's test and Egger's test, where $p>0.05$ for both tests was considered to have no significant publication bias [43,44]. All analyses were performed using STATA software V.10.1 (Stata Corp, College Station, TX, USA).

## Determination of interactive effect

For measurement of interaction, there are 2 models to calculate this: the additive and the multiplicative scales. If these yield more than additive and multiplicative, there is a positive interaction. If less than additive/multiplicative, it is referred to as a negative interaction. The word "synergistic" means the effect two exposures is greater than the combined effect of each exposure. Thus, the value of interaction is more than either the additive or the multiplicative scales as appropriate, i.e., either additive or multiplicative synergism.

The joint effect of exposure to asbestos and smoking was first examined by estimating odds ratio (ORs) and relative risk (RRs). To determine whether co-exposure to asbestos and smoking is an additive and multiplicative scale, the synergy (*S*) and multiplicative (*V*) indices were calculated as follow [38,45].

Synergy index (*S*)

$$S = \frac{X_{AS} - X_0}{X_A + X_S - 2X_0}$$

Multiplicative index (*V*)

$$V = \frac{X_0 \times X_{AS}}{X_A \times X_S}$$

Where $X_0$ is the odds ratio and/or relative risk for lung cancer among non-exposed to asbestos and non-smokers; $X_A$ is the corresponding value for lung cancer among asbestos exposure in non-smokers; $X_S$ is for lung cancer and smoking in those without asbestos-exposure; and $X_{AS}$ is for lung cancer and co-exposure to asbestos and smoking. The synergy index (*S*) is an interaction on an additive scale. The interpretation is $S = 1$ suggests no interaction between asbestos exposure and smoking on lung cancer; $S > 1$ suggests a positive interaction (synergism); and $S < 1$ suggests a negative interaction (i.e., antagonism). For the multiplicative index (*V*), it can

be interpreted as either: when $V = 1$, there is no interaction on the multiplicative scale; when $V > 1$, the multiplicative interaction is positive; or when $V < 1$, it is negative. Confidence intervals (CIs) were calculated using the method of Rothman, and Andersson et al. [38,45,46].

## Results

### Study Selection

We identified 2,499 records of which 2,479 were duplicated, irrelevant, review articles, case reports, non-human or experimental studies, or lacked lung cancer outcomes or lacking control groups, and were excluded. Five additional publications meeting the inclusion criteria were added from the bibliographies of the retrieved articles (Fig 1). In the final review of 25 studies, we excluded 5 studies [47–51] due to duplicate populations, and 3 studies [52–54] had insufficient data. Only one by Kjuus et al [55] was selected of three articles [47,48,55] which analyzed the same data. Case-control studies by Bovenzi (1992 and 1993) [49,56], the cohort studies of McDonald 1980 and Liddell 1984 [51,57]; and cohort studies of Klerk 1991 and Reid 2006 [26,50] also described the same populations of which the most recent [26,56,57] was selected. The Blot et al. study 1982 [52] did not report smoking status in asbestos-exposed populations. Finally, the studies of Hilt et al. 1986, and Markowitz et al. 1992 [53,54] were excluded because numbers of controls were missing. Therefore, a total of 17 studies (10 case-control and 7 cohort studies) were included for meta-analysis. The 13 included studies were identified using the search terms, and another 4 studies derived from their bibliographies.

### Study Characteristics

The characteristics and information of the included studies are shown in Table 1. The 10 case-control studies [22,25,27,55,56,58–62], contained 10,223 participants in all of which 4,768 were population-based controls, and 1,128 hospital-based controls. Seven cohort studies [23,24,26,57,63–65] had an aggregate of 64,924 participants, comprising of the 3,316 cases and 61,608 controls. In all the included studies asbestos exposure was occupational. Where

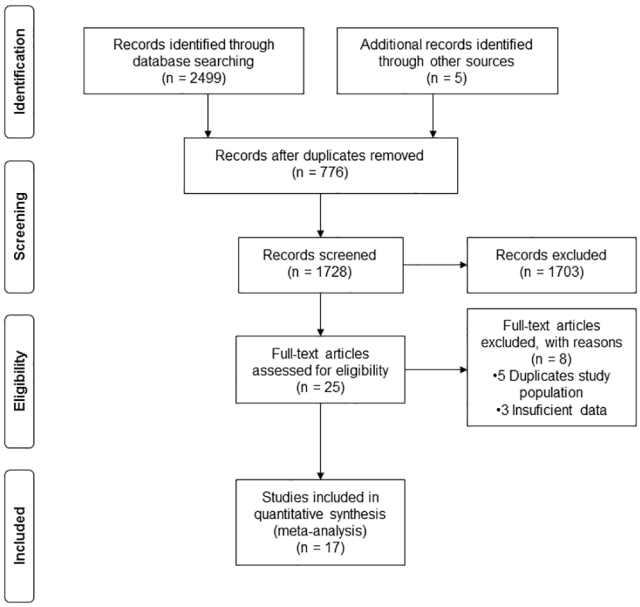


**Fig 1. Summary of study search and selection.**

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**Table 1. Characteristics of studies included in the meta-analysis.**

| First author(year) | Location | Industrial type* | Asbestos type | Study design | Total population Case (n) | Total population Control (n) | NOS** |
|---|---|---|---|---|---|---|---|
| **Case-control studies (n = 10)** | | | | | | | |
| Martischnig(1977) | United Kingdom | Not specified | Not reported | Hospital-Based | 201 | 201 | 6 |
| Blot(1978) | Coastal Georgia, USA | Shipbuilding | Not reported | Hospital-Based | 458 | 553 | 5 |
| Blot(1980) | Coastal Virginia, USA | Shipyard | Not reported | Population-Based | 319 | 341 | 6 |
| Pastorino(1984) | Lombardy Northern, Italy | Manufacturing, textiles | Mixed | Population-Based | 106 | 226 | 6 |
| Kjuus(1986) | Southern Norway | Not specified | Not reported | Hospital-Based | 176 | 176 | 7 |
| Dave(1988) | Southeast Sweden | Not specified | Not reported | Hospital-Based | 62 | 198 | 5 |
| Bovenzi(1993) | Northeast Italy | Not specified | Not reported | Population-Based | 516 | 561 | 6 |
| Luce(2000) | New Caledonia, France | Mining & refining | Tremolite | Population-Based | 103 | 110 | 6 |
| Gustavsson(2002) | Stockholm, Sweden | Not specified | Not reported | Population-Based | 768 | 1519 | 6 |
| Villeneuve(2012) | 8 locations, Canada | Not specified | Not reported | Population-Based | 1618 | 2011 | 7 |
| **Cohort studies (n = 7)** | | | | | | | |
| Berry(1972) | London, England | Asbestos factory | Not reported | Prospective | 61 | 1678 | 6 |
| Rubino(1979) | Balangero mine, Italy | Mining | Chrysotile | Prospective | 12 | 54 | 7 |
| Liddell(1984) | Quebec, Canada | Mining & milling | Chrysotile | Prospective | 223 | 715 | 6 |
| Berry(1985) | London, England | Asbestos factory | Not reported | Prospective | 66 | 1268 | 6 |
| Reid (2006) | Western Australia | Mining & milling | Crocidolite | Prospective | 138 | 2595 | 7 |
| Markowitz(2013) | USA | Insulator | Not reported | Prospective | 2760 | 55161 | 8 |
| Wang (2013) | China | Mining | Chrysotile | Prospective | 56 | 137 | 7 |

*All studies are occupational exposures

**NOS = Newcastle Ottawa-Scale

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reported, the average participant age was approximately 60 (range 40–80 y) for case control studies. Some [22,60] reported the type of asbestos used (tremolite or mixed asbestos), while the remaining eight [25,27,55,56,58,59,61,62] did not categorize the asbestos (Table 1). The settings for the exposure was occupational, either asbestos mines (one study [22]), ship building/repair (two studies [59,62]), textile production (one study [60]), and the remaining six [25,27,55,56,58,61] studies failed to specify. Environmental monitoring was measured by using the membrane filter method and were analyzed by phase contrast microscopy [25] but most studies relied on personal/telephone interview and/or questionnaire. Smoking habits of participants were quantified by personal/telephone interview and/or questionnaire. If the subject had already died, the appropriate information was sought from their next-of-kin or spouse (Table 2).

There were seven cohort studies, and all of these collected asbestos exposure data prospectively and also prospectively for smoking data in six studies and retrospectively in one [64].

**Table 2. Descriptions of Asbestos Exposure and Smoking of Included Studies.**

| First author (year) | Measurement of exposure | Definition of asbestos exposure<br>Exposed | Definition of asbestos exposure<br>Non-exposed | Measurement of exposure | Definition of smoking<br>Exposed | Definition of smoking<br>Non-exposed |
|---|---|---|---|---|---|---|
| **Case-control studies (n = 10)** | | | | | | |
| Martischnig (1977) | Questionnaire | Occupational history (work in asbestos manufacturing or used asbestos) | No occupational history | Questionnaire | 14 cigarettes/ day or more | 0–14 cigarettes/day |
| Blot(1978) | Personal interview | Occupational history (work in shipbuilding or used asbestos) | No occupational history (never work in shipbuilding) | Personal interview | 10 cigarettes/ day or more | <1/2 pack/day and stopped smoking at least 10 years |
| Blot(1980) | Personal interview | Occupational history (shipyard) | No occupational history (never work in shipyard) | Personal interview | 10 cigarettes/ day or more | <1/2 pack/day and stopped smoking at least 10 years |
| Pastorino (1984) | Personal interview | Exposed to asbestos only | Exposed other carcinogenic chemicals | Personal interview | 10 cigarettes/ day or more | 0–9 cigarettes/day |
| Kjuus(1986) | Personal interview and questionnaire | Asbestos exposure at least 1 year or more and job title information | No exposure and no job title | Personal interview and questionnaire | 10 cigarettes/ day or more | 0–9 cigarettes/day |
| Dave(1988) | Self-administered questionnaire and telephone interview | Occupational history (works related to asbestos) | Occupational history (other works) | Self-administered questionnaire and telephone interview | >80 cigarette-years | 0 cigarette-years |
| Bovenzi(1993) | Personal interview | Occupational history (classified by job titles and asbestos exposure information) | No occupational history | Personal interview | >1 cigarette/day | No smoked |
| Luce(2000) | Personal interview | Occupational history (classified by expert assessment) | No occupational history | Personal interview | >20 pack-years | < 20 pack-years |
| Gustavsson (2002) | Questionnaire, telephone interview and environmental measurement | Occupational history and asbestos exposure > 0 fiber-years | No occupational history and asbestos exposure 0 fiber-years | Questionnaire and telephone interview | >1 cigarette/day | No smoked |
| Villeneuve (2012) | Questionnaire | Occupational history (classified by concentration, frequency and reliability) | No occupational history | Questionnaire | 10 pack-years or more | < 10 pack-years |
| **Cohort studies (n = 7)** | | | | | | |
| Berry(1972) | Questionnaire | Occupational history | No occupational history | Questionnaire | smoked | No smoked |
| Rubino(1979) | Environmental measurement | Occupational history (mining) | No occupational history | Personal interview | smoked | No smoked |
| Liddell(1984) | Environmental measurement | Cumulative exposure >100 fiber/year | Cumulative exposure 0–100 fiber/year | Questionnaire | >1 pack-years | 0 pack-years |
| Berry(1985) | Questionnaire | Occupational history | No occupational history | Questionnaire/ interview | smoked | No smoked |
| Reid(2006) | Questionnaire and environmental measurement | Occupational history | No occupational history | Questionnaire | Smoked and ex-smoked < 20 years | No smoked and ex-smokers > 20 years |

(*Continued*)

**Table 2.** (*Continued*)

| First author (year) | Measurement of exposure | Definition of asbestos exposure Exposed | Definition of asbestos exposure Non-exposed | Measurement of exposure | Definition of smoking Exposed | Definition of smoking Non-exposed |
|---|---|---|---|---|---|---|
| Markowitz (2013) | Clinical method (x-ray and spirometry) | Occupational history (insulation) | No occupational history | Not reported | smoked | No smoked |
| Wang(2013) | Environmental measurement | Cumulative exposure >20 fiber-year/ml | Cumulative exposure <20 fiber-year/ml | Questionnaire/ interview | smoked | No smoked |

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The mean follow-up period of cohort studies was 19.3 yr. Exposure was to chrysotile in three studies [23,57,65], one study to crocidolite [26], and the asbestos type was unspecified in remaining three studies [24,63,64] (Table 1). Four studies [23,26,57,65] were from mining and three studies [24,63,64] originated from factories making asbestos products. Workplace asbestos exposure was assessed by lung histology, counting fibers trapped by midget impingers or membrane filters [23,57,65], a long-duration personal konimeter [26], or postal questionnaires [63,64]. Only one study assessed exposure by chest X-ray radiographs and a low FEV1 by spirometry [24]. Smoking was assessed by interviewing or questionnairing the workers or their next-of-kin (Table 2). Diagnosis of lung cancer was confirmed by histological examination of lung biopsies, chest X-ray, CT scan, MRI, bronchoscopy, or thoracoscopy. Most studies classified lung cancer using the International Classification of Diseases (ICD), published by the World Health Organization (Table 3).

## Quality Assessment

The methodological quality of case-control studies was summarized as a mean NOS of 6 (range 5–7) and a score of 6.7 (range 6–8) for cohort studies (Table 1).

## Quantitative Synthesis

(i) **Case-control studies:** A random-effects meta-analysis of 10 studies [22,25,27,55,56,58–62] revealed associations between asbestos exposure and/or smoking, and developing lung cancer. The summary odds ratio of (A+S-) workers compared with (A-S-) workers was 1.70 (95% CI = 1.31–2.21). The summary odds ratio of (A-S+) workers compared with (A-S-) was 5.65 (95% CI = 3.38–9.42). Additionally, the summary odds ratio of (A+S+) workers compared with (A-S-) workers was 8.70 (95% CI = 5.78–13.10). Evidence of heterogeneity was found in A-S+/A-S- and A+S+/A-S- groups ($I^2$ = 90.6%, $p$ = 0.000 and $I^2$ = 78.7%, $p$ = 0.000) (Fig 2A–2C). As shown in Table 4, the results of subgroup analyses according to different characteristics are in close agreement with our major findings. Such heterogeneity probably arises from the differing interaction effects across varying levels of smoking exposure. We stratified studies with similar smoking classification by subdivision into 3 levels: non-smokers (non-smoking or light smoking), moderate smokers (1–19 cigarettes/day) and heavy smokers (>20 cigarettes/day) (Table 5). There were no differences between non-smokers 2.63 (95% 1.43–4.83) and light smokers 2.63 (95% 1.57–4.42) for exposed-asbestos group. But for both subgroups, the moderate and heavy smoking categories showed elevated odds ratios with asbestos exposure.

**Table 3. Descriptions of Outcome of Included Studies.**

| Author (Year) | Case confirmation method | Diagnosis period | Lung cancer classification | Control matching | Period of exposure or employment |
|---|---|---|---|---|---|
| **Case-control studies (n = 10)** | | | | | |
| Martischnig (1977) | Radiography, bronchoscopy or thoracotomy | 1972–1973 | Not reported | Age (±2 years) | 1–5 years and 6 years and over |
| Blot(1978) | By physician | 1970–1976 | ICD 8 162.1 | Sex, race, age (±2 years) | 6 months or more |
| Blot(1980) | By physician | 1976 | ICD 162.1 | Race, age, death year, city of residence | 6 months or more |
| Pastorino (1984) | By physician | 1976–1979 | Not reported | Age (±2 years) | 6 months or more |
| Kjuus(1986) | By examination of histology | | ICD 162–163 | Age (±5 years) | 1979–1983 |
| Dave(1988) | Not reported | 1980–1982 | ICD 162–163 | Age, sex | Not reported |
| Bovenzi (1993) | Histology, autopsy reports | | ICD 9$^{th}$ 162 | Age (±2 years) | Not reported |
| Luce(2000) | Clinical, radiological & endoscopic | 1993–1995 | ICD for oncology topography code 160–162,148 | Sex, age (±5 year) | Not reported |
| Gustavsson (2002) | Not reported | 1985–1990 | ICD 7$^{th}$ 162.1 | Age (±5 year) and year of inclusion study (1985–1990) | 1969–1973 |
| Villeneuve/ 2012 | By examination of histology | 1994–1997 | ICD 9$^{th}$ 162 | Age, sex | At least 12 months |
| **Cohort studies (n = 7)** | | | | | |
| Berry(1972) | By examination of histology | Not reported | ICD 162,163 | Not reported | Men 1933–1955 Women 1936–1942 |
| Rubino(1979) | By physician | 1957 | ICD 7 162/163 | Age (±1 year) | 1930–1965 |
| Liddell(1984) | Not reported | Not reported | ICD 7$^{th}$ | Not reported | 1966–1975 |
| Berry(1985) | By examination of histology | Not reported | The Office of Population Censuses and Surveys | Not reported | Men 1933–1955 Women 1936–1942 |
| Reid(2006) | By physician | 2000 and 2002 | ICD-0 2$^{nd}$ edition categories c33.9-c34.9 | Sex, age (±5 years) | 1979–2002 |
| Markowitz (2013) | By chest radiographs | 1981 and 1983 | ICD-9 code 162 (1981–1998) and ICD-10 codes C-33 and C-34 (1999–2008) | Not reported | 1982–2008 |
| Wang(2013) | By pathology or biopsy | The first two decades | The Chinese Radiographic Diagnosis Criteria of Pneumoconiosis | Not reported | 1981–2006 |

ICD stands for International Classification of Diseases

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*Publication bias*: Begg's funnel plot and Egger's test were performed to assess publication bias of the literature. Publication bias for (i) A+S- was $p = 0.437$ (Begg's test), and 0.659 (Egger's), (ii) A-S+ was $p = 0.252$ (Begg's test), and 0.362 (Egger's), and (iii) A+S+, $p = 0.154$ (Begg's test) and 0.294 (Egger's test) suggesting no bias. Funnel plots suggested evidence of publication bias. There was asymmetry of funnel plots accordant with high heterogeneity studies (A-S+ and A+S+). However, trim and fill analysis showed that the overall odds ratios were unchanged (data shown in supplement, S1 Fig).

(ii) **Cohort studies:** Seven studies [23,24,26,57,63–65] were included in our primary analysis (Fig 3A–3C). The summary relative risks for lung cancer in the cohort studies of (A+S-)

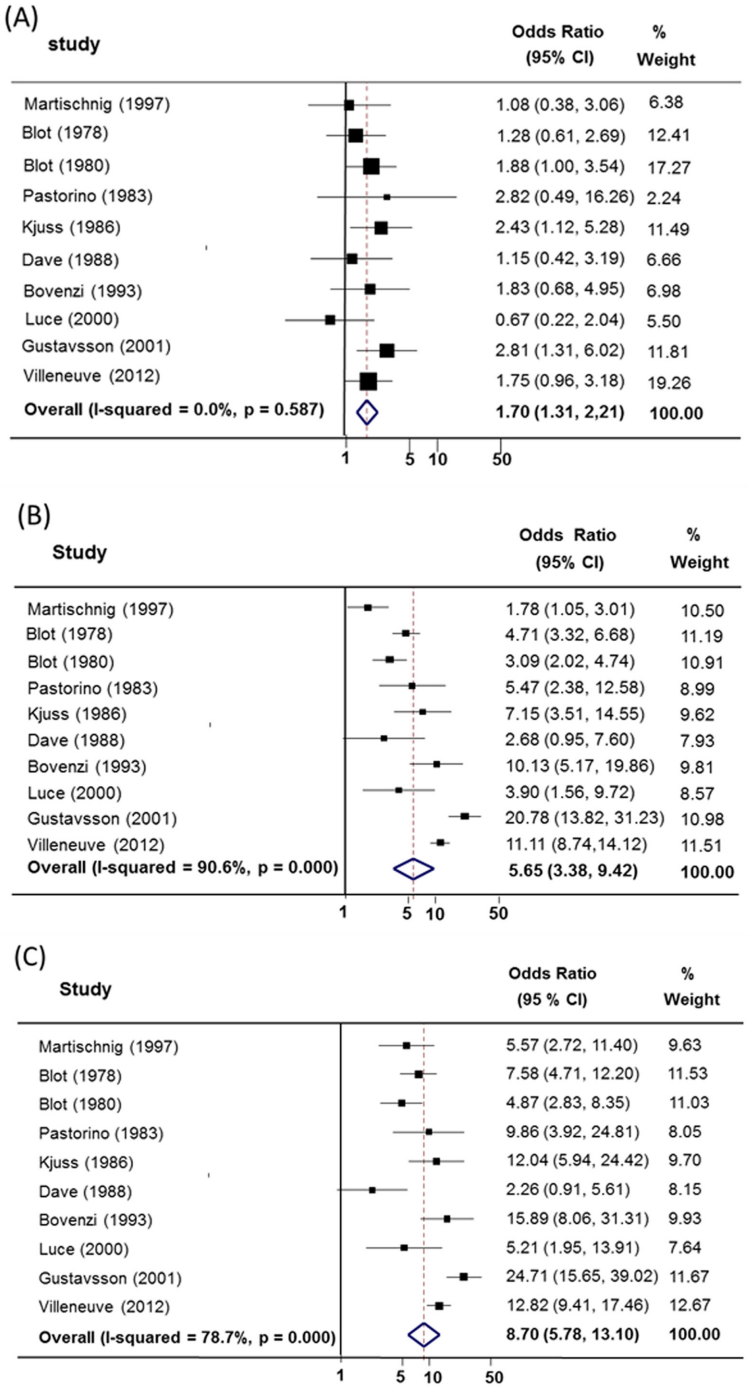


**Fig 2. Random-effects meta-analysis of the synergistic effect between asbestos exposure and smoking cause lung cancer- Case control studies.** (A) Summary odds ratio of asbestos-exposed and non-smoking (A+S-) compared with not asbestos-exposed and non-smoking (A-S-). (B) Summary odds ratio of non-exposure to asbestos and smoking (A-S+) compared with not asbestos-exposed and non-smoking (A-S-). (C) Summary odds ratio of asbestos-exposed and smoking (A+S+) compared with not asbestos-exposed and non-smoking (A-S-).

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**Table 4. Effect of the Exposure to Asbestos (A) and/or Cigarette Smoking (S) on Lung Cancer Risk.**

| Groups | No. of studies | Reference** | ORs and RRs* (95% CI) A | ORs and RRs* (95% CI) S | ORs and RRs* (95% CI) A and S | *P* for heterogeneity A | *P* for heterogeneity S | *P* for heterogeneity A and S | $I^2$ (%) A | $I^2$ (%) S | $I^2$ (%) A and S |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Case-control studies** | | | | | | | | | | | |
| ***Geographic area*** | | | | | | | | | | | |
| USA | 2 | 1.00 | 1.60 (0.99–2.59) | 3.89 (2.58–5.86) | 6.19 (4.01–9.54) | 0.435 | 0.136 | 0.228 | 0.0 | 55.0 | 31.3 |
| Europe | 7 | 1.00 | 1.71 (1.15–2.54) | 5.63 (2.49–12.71) | 8.89 (4.77–16.56) | 0.339 | 0.000 | 0.000 | 11.9 | 90.4 | 80.3 |
| ***Study design*** | | | | | | | | | | | |
| Population Based | 6 | 1.00 | 1.83 (1.32–2.55) | 7.60 (4.09–14.11) | 10.92 (6.54–18.22) | 0.464 | 0.000 | 0.000 | 0.0 | 89.7 | 79.2 |
| Hospital Based | 4 | 1.00 | 1.49 (0.97–2.29) | 3.60 (1.94–6.69) | 6.19 (3.47–11.06) | 0.501 | 0.005 | 0.034 | 0.0 | 76.8 | 65.3 |
| **Cohort studies** | | | | | | | | | | | |
| ***Asbestos type*** | | | | | | | | | | | |
| Chrysotile | 3 | 1.00 | 2.58 (1.13–5.89) | 3.58 (1.75–7.33) | 5.04 (2.50–10.18) | 0.807 | 0.798 | 0.685 | 0.0 | 0.0 | 0.0 |
| Not reported | 3 | 1.00 | 3.05 (1.53–6.08) | 7.33 (4.18–12.85) | 10.47 (7.90–13.88) | 0.736 | 0.326 | 0.501 | 0.0 | 10.8 | 0.0 |

*Odds ratios is for case-control, relative risk is for cohort study

** Reference is equal one as control group

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workers was 2.72 (95% CI = 1.67–4.40), (A-S+) workers was 6.42 (95% CI = 4.23–9.75), and for (A+S+) workers was 8.90 (95% CI = 6.01–13.18) compared with (A-S-) workers. The results of the cohort studies are consistent with the analysis of the case-control studies. Evidence of heterogeneity was not found in cohort studies ($I^2$ = 0.0%, $p$ = 0.968, $I^2$ = 25.1%, $p$ = 0.237 and $I^2$ = 17.3%, $p$ = 0.298). In addition, case-control studies estimates of the combined effect of asbestos and smoking on lung cancer risk were in concordance with those from cohort studies.

*Publication bias*: Evaluation of publication bias for A+S-, A-S+ and A+S+ are Begg's test ($p$ = 0.063) Egger's test ($p$ = 0.079), Begg's test ($p$ = 0.026) Egger's test ($p$ = 0.065) and Begg's test ($p$ = 0.118) Egger's test ($p$ = 0.254), respectively. These results did not indicate a potential for publication bias when using funnel plots (data shown in supplement, S2 Fig).

**Table 5. Effect of the Exposure to Asbestos (A) and/or Cigarette Smoking (S) on Lung Cancer Risk in Case-Control Studies, Stratified by smoking levels.**

| Smoking level | No. of studies | ORs (95% CI) A | ORs (95% CI) S | ORs (95% CI) A and S | *P* for heterogeneity A | *P* for heterogeneity S | *P* for heterogeneity A and S | $I^2$ (%) A | $I^2$ (%) S | $I^2$ (%) A and S |
|---|---|---|---|---|---|---|---|---|---|---|
| Non smokers | 2[25,55,56] | 2.63 (1.43–4.83) | - | - | 0.785 | - | - | 0.0 | - | - |
| 1–19 cigarettes/day | 2 | - | 9.98 (3.44–28.96) | 15.38 (7.34–32.24) | - | 0.010 | 0.083 | - | 85.1 | 66.8 |
| >20 cigarettes/day | 2 | - | 25.41 (8.96–72.00) | 30.31 (15.77–58.25) | - | 0.011 | 0.168 | - | 84.4 | 47.5 |
| 0–9 cigarettes/day | 3[25,55,60] | 2.63 (1.57–4.42) | - | - | 0.964 | - | - | 0.0 | - | - |
| 10–19 cigarettes/day | 3 | - | 8.54 (2.76–14.76) | 13.13 (7.34–32.24) | - | 0.000 | 0.019 | - | 87.6 | 74.9 |
| >20 cigarettes/day | 3 | - | 15.76 (4.36–56.94) | 25.94 (11.94–56.39) | - | 0.000 | 0.119 | - | 87.7 | 53.0 |

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### Interaction between asbestos exposure and cigarette smoking

Evaluation of interaction is summarized in Table 6. All 17 studies provided data which enabled evaluation of the joint effects of co-exposure of both asbestos and cigarette smoking on the risk of lung cancer. For case-control studies, the interaction index of synergy (*S*) and multiplicative index (*V*) were 1.44 (95% CI = 1.26–1.77) and 0.91 (95% CI = 0.63–1.30), respectively, with corresponding values for the cohort studies of 1.11 (95% CI = 1.00–1.28) and 0.51 (95% = 0.31–0.85). These results suggest that the interaction between asbestos exposure and smoking can be a positive interaction on the additive scale (an additive synergistic effect). There was a suggestion of a negative multiplicative interaction for both case-control and cohort studies. Notably our results do not show a multiplicative effect between the two known human carcinogens.

## Discussion

Our results demonstrate a positive synergistic interaction on an additive scale between asbestos exposure and cigarette smoking in workers developing lung cancer (Table 6). Employees exposed to asbestos and having a history of smoking have a higher risk of developing lung cancer than those only exposed to one risk (either smoking or asbestos alone). In contrast, the multiplicative index for case-control studies was close to 1.0, although for cohort studies, a negative multiplication interaction is suggested ($V = 0.51$, 95%CI = 0.31–0.85).

Some data suggests that smoking does not enhance mesothelioma [66], which implies that the synergistic lung cancer risk arises from the two carcinogens interacting in the same lung tissue. There are several mediators contributing to cigarette smoke and asbestos-induced lung diseases. Both smoking [67] and asbestos [68] elicit chronic inflammation, which is central to tumorigenesis and is augmented through reduced active immunity, increased infections, and compromised tumor surveillance [69,70]. Tobacco smoke causes inflammation through a vast

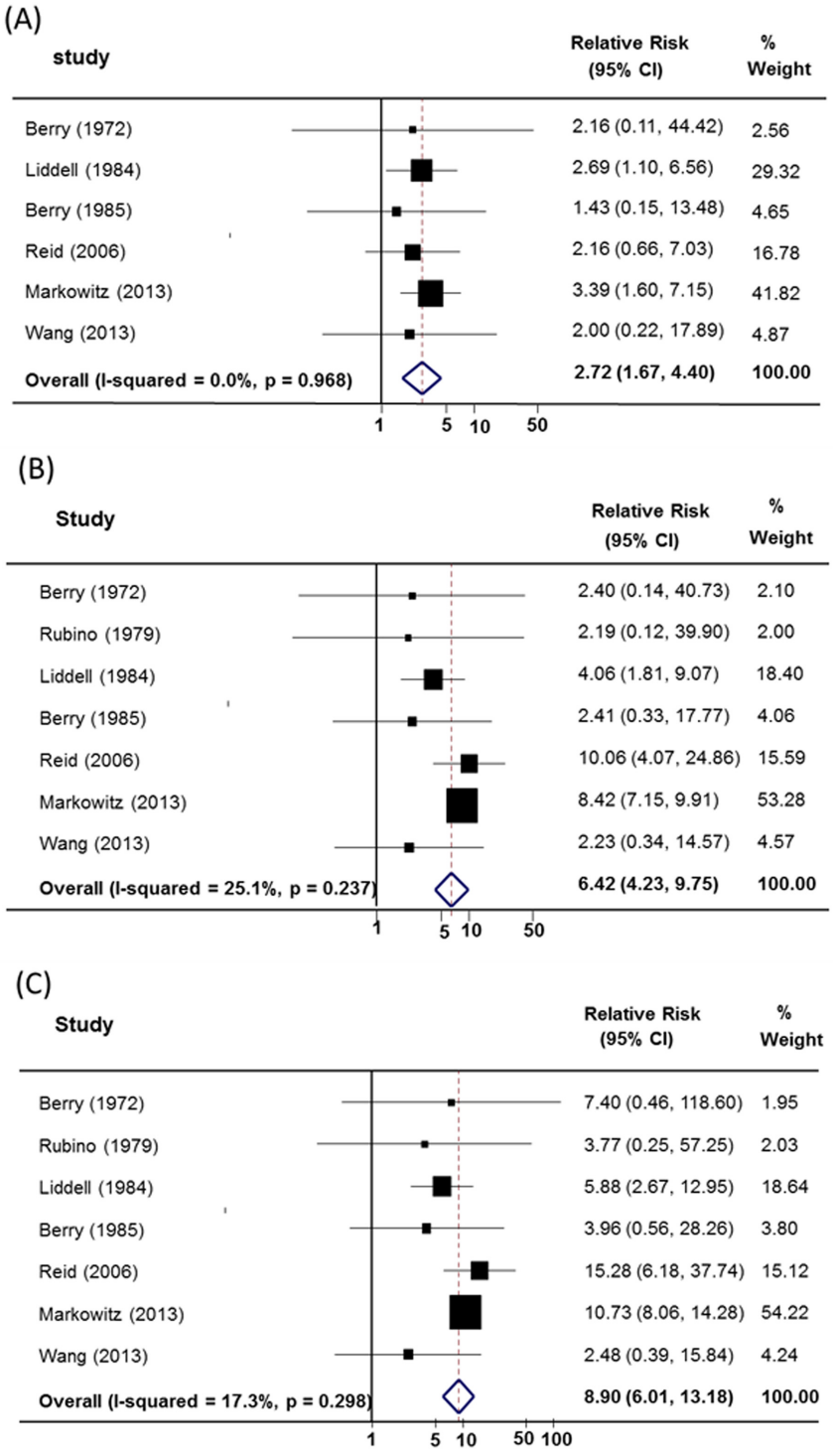


**Fig 3. Random-effects meta-analysis of the synergistic effect between asbestos exposure and smoking cause lung cancer- Cohort study.** (A) Summary relative risk of asbestos-exposed and non-smoking (A+S-) compared with not asbestos-exposed and non-smoking (A-S-). (B) Summary relative risk of non-exposure to asbestos and smoking (A-S+) compared with not asbestos-exposed and non-smoking (A-S-). (C) Summary relative risk of asbestos-exposed and smoking (A+S+) compared with not asbestos-exposed and non-smoking (A-S-).

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**Table 6. Synergy and Multiplicative Indices between Asbestos Exposure and Cigarette Smoking.**

| Overall risk estimates | Reference | Asbestos | Smoking | Asbestos and smoking | Interaction index* synergy | Interaction index* multiplicative |
|---|---|---|---|---|---|---|
| Odds Ratio | 1.00 | 1.70(1.31–2.21) | 5.65(3.38–9.42) | 8.70(5.78–13.10) | 1.44 (1.26–1.77) | 0.91(0.63–1.30) |
| Relative Risk | 1.00 | 2.72(1.67–4.40) | 6.42(4.23–9.75 | 8.90(6.01–13.18) | 1.11 (1.00–1.28) | 0.51(0.31–0.85) |

* Rothman synergy index

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array of chemical and particulate irritants. Mineral fibers are inflammatory primarily through activation of Nod-like receptor-family protein 3 (NLRP3) of inflammasomes in tissue macrophages. Asbestos fibers evoke vain attacks by macrophages ensuring their continual activation while also adversely affecting function of other immune cells [71,72]. Symptoms of inflammation include oxidative stress, which is worse in blue asbestos (amosite, crocidolite, tremolite) containing Fe ions which generate additional reactive species through Fenton catalysis [73]. The prolonged bio-persistence of these amphiboles further contributes to their greater carcinogenicity than chrysotile and other mineral fibers. Tobacco smoke also contains multiple carcinogens (e.g., 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone or NNK, 1,3-butadiene, ethylene oxide, chromium, polonium-210, arsenic, ethyl carbamate, and hydrazine) that directly interact with DNA [74]. Thus, the common localized inflammatory actions of tobacco smoke and asbestos readily explains additive effects, while the additional actions (direct carcinogenesis and Fenton catalysis) of each insult could account for the additive synergistic interaction.

The present study has some limitations which are mostly inherent in this type of study.

Odds ratios were roughly estimated from the included studies where the measurement methods used and exposure classification varied between studies. For example there were several studies claiming that the duration of asbestos exposure was the same as the period of employment in the workplace. Therefore, short duration jobs reduce the validity and reliability of questionnaires about occupational history. Some studies [58,60,61] did not provide estimates of adjusted risks (age, sex, etc.). The methods used to quantitate exposures to asbestos and cigarette smoke were arbitrary and varied across studies. The type of asbestos used was usually not stated. The diagnosis for lung cancer used different criteria (by physician, chest x-ray, radiography, or information taken from the death certificate). In contrast, other studies have objective exposure and clinical criteria (e.g., Markowitz et al. [24]). The type of lung cancer was rarely stated or even whether mesothelioma was excluded but mesothelioma was never explicitly included. Some case-control studies [55,59] used control populations who had other diseases (e.g., myocardial infarction, bladder cancer, other malignant neoplasms or other lung disease). Most of these diseases are also smoking-related. Nevertheless, all case-control studies endeavored to match controls for confounders. Some studies have data derived from recalling events that took place 10 years or more before the interview/questionnaire, which raises the issue of recall bias and misclassification. Subgroup analysis by smoking level retained high heterogeneity (Table 5) probably due to different methods of data collection and measurement, uncertain duration of smoking (only daily number of cigarettes smoked quoted).

Nevertheless, our study has some strength. It includes new data and the selection criteria complied with the PRISMA and MOOSE guidelines to perform the first systematic review and meta-analysis. Our analysis differed from previous analyses because (i), the strict selection criteria and heterogeneity testing, (ii) testing for statistical interaction (additive and multiplicative). Most studies randomly enrolled greater numbers of control subjects from hospital registers or health authority databases thus reducing selection bias. One study [59] excluded participants who provided incomplete questionnaire data, were non-responders, or who had

emigrated from the area. These unavoidable variations in the study population and diverse methods utilized readily explain the substantial heterogeneity we detected.

While the most dangerous asbestos types are no longer used, other siliceous fibers and chrysotile (in developing nations) are still incorporated into many building products without clear long-term health assessments in humans. Workers exposed to chrysotile showed increased risk of lung cancer (Table 4) [75]. The scientific rigor of cohort studies has improved since the early asbestos work. However, the long latencies for asbestos-induced neoplasms [76] make retrospective study the only practical protocol. Cigarette smoke inhalation and hence airway exposure can be accurately assessed (cigarette numbers, inhalation, filters). However, our study reiterates the difficulty in accurately assessing actual airway exposure to asbestos and was best assessed in the Markowitz et al. study [24]. Personal monitors provided the best indication of exposure but ultimately, only random sputum fiber counts by public health agencies can provide unbiased and accurate measures of exposure. Another problem highlighted by Markowitz et al. [24] and our study is accurately diagnosing the end-stage pathology. Again, monitoring by independent public health authorities is the mechanism most likely to yield accurate reporting. In addition, potential confounders including life-style and especially local air quality data need collecting for the same cohorts.

## Conclusion

The present meta-analysis collected and synthesized data currently available and revealed a positive interaction on an additive scale between asbestos exposure and smoking, while showing little evidence of an interaction on a multiplicative scale. The combined effect of asbestos exposure with moderate and heavy smoking in lung cancer suggested a strong positive interaction on an additive scale, i.e., an additive synergism.

## Supporting Information

**S1 Fig. Funnel plot for 10 case-control studies of relationship between asbestos and cigarette smoking on lung cancer with subjects whom are exposed to asbestos and non-smokers (A), subjects whom are not exposed to asbestos and smokers (B) and subjects whom are exposed to asbestos and smokers (C).**
(DOCX)

**S2 Fig. Funnel plot for 7 cohort studies of relationship between asbestos and cigarette smoking on lung cancer with subjects whom are exposed to asbestos and non-smokers (A), subjects whom are not exposed to asbestos and smokers (Be) and subjects whom are exposed to asbestos and smokers (C).**
(DOCX)

**S1 PRISMA Checklist. PRISMA 2009 Checklist.**
(DOC)

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## Author Contributions

Conceived and designed the experiments: ML YN. Performed the experiments: YN OL WT NC. Analyzed the data: YN OL WT. Contributed reagents/materials/analysis tools: ML OL YN WT CNS BR NC. Wrote the paper: ML OL YN WT CNS BR NC.

## References


1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA: A Cancer Journal for Clinicians. 2012; 62: 10–29. doi: 10.3322/caac.20138
2. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: A meta-analysis. International Journal of Cancer. 2008; 122: 155–164. doi: 10.1002/ijc.23033
3. Lee PN, Forey BA, Coombs KJ. Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer. BMC Cancer. 2012; 12. doi: 10.1186/1471-2407-12-385
4. IARC. Tobacco Smoke and Involuntary Smoking. IARC momographs on the evaluation of carcinogenic risks to humans. 2004; 83: 1–1438.
5. IARC. Tobacco smoking. IARC momographs on the evaluation of carcinogenic risks to humans. 1986; 38: 1–421.
6. (US) Office on Smoking and Health. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US), 2006. Available from: http://www.ncbi.nlm.nih.gov/books/NBK44324/.
7. Hubaux R, Becker-Santos DD, Enfield KS, Lam S, Lam WL, Martinez VD. Arsenic, asbestos and radon: emerging players in lung tumorigenesis. Environmental Health. 2012; 11. doi: 10.1186/1476-069X-11-89
8. Yang M. A current global view of environmental and occupational cancers. Journal of environmental science and health Part C, Environmental carcinogenesis & ecotoxicology reviews. 2011; 29: 223–249. doi: 10.1080/10590501.2011.601848
9. IARC. Asbestos (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite and Anthophyllite). IARC Monographs on the evaluation of carcinogenic risks to humans. 2012; 100 C.
10. IARC. Asbestos IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. 1977; 14: 1–106. PMID: 863456
11. Ferguson DA, Berry G, Jelihovsky T, Andreas SB, Rogers AJ, Fung SC, et al. The Australian Mesothelioma Surveillance Program 1979–1985. Medical Journal of Australia. 1987; 147: 166–172. PMID: 3657627
12. Rake C, Gilham C, Hatch J, Darnton A, Hodgson J, Peto J. Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study. British Journal of Cancer 2009; 100: 1175–1183. doi: 10.1038/sj.bjc.6604879 PMID: 19259084
13. Olsen NJ, Franklin PJ, Reid A, de Klerk NH, Threlfall TJ, Shilkin K, et al. Increasing incidence of malignant mesothelioma after exposure to asbestos during home maintenance and renovation. Medical Journal of Australia. 2011; 195: 271–274. doi: 10.5694/mja11.10125 PMID: 21895596
14. Yano E, Wang X, Wang M, Qiu H, Wang Z. Lung cancer mortality from exposure to chrysotile asbestos and smoking: a case-control study within a cohort in China. Occupational and Environmental Medicine. 2010; 67: 867–871. doi: 10.1136/oem.2009.051615 PMID: 20833758
15. Liddell FD, McDonald AD, McDonald JC. Dust exposure and lung cancer in Quebec chrysotile miners and millers. The Annals of Occupational Hygiene. 1998 42: 7–20. doi: 10.1093/annhyg/42.1.7 PMID: 9566111
16. Niklinski J, Niklinska W, Chyczewska E, Laudanski J, Naumnik W, Chyczewski L, et al. The epidemiology of asbestos-related diseases. Lung Cancer 2004; 45: S7–S15. PMID: 15261426
17. Law MR, Ward FG, Hodson ME, Heard BE. Evidence for longer survival of patients with pleural mesothelioma without asbestos exposure. Thorax 1983; 38: 744–746. pmcid: pmc459649. PMID: 6648853
18. Neumann V, Löseke S, Nowak D, Herth FJ, Tannapfel A. Malignant pleural mesothelioma: incidence, etiology, diagnosis, treatment, and occupational health. Deutsches Ärzteblatt international. 2013 110: 319–326. doi: 10.3238/arztebl.2013.0319 PMID: 23720698
19. Nelson HH, Kelsey KT. The molecular epidemiology of asbestos and tobacco in lung cancer. Oncogene 2002; 21: 7284–7288. doi: 10.1038/sj.onc.1205804 PMID: 12379872
20. Vainio H, Boffetta P. Mechanisms of the combined effect of asbestos and smoking in the etiology of lung cancer. Scandinavian Journal of Work, Environment & Health. 1994; 20: 235–242. doi: 10.5271/sjweh.1402

21. Nielsen Elsa, Ostergaard Grete, John Christian Larsen. Toxicological Risk Assessment of Chemicals: A Practical Guide. New York: Informa Healthcare: CRC Press, 2008.
22. Luce D, Bugel I, Goldberg P, Goldberg M, Salomon C, Billon-Galland MA, et al. Environmental exposure to tremolite and respiratory cancer in New Caledonia: a case-control study. American Journal of Epidemiology. 2000; 151: 259–265. PMID: 10670550
23. Wang X, Yano E, Lin S, Yu IT, Lan Y, Tse LA, et al. Cancer mortality in Chinese chrysotile asbestos miners: exposure-response relationships. PLoS One. 2013; 8. doi: 10.1371/journal.pone.0071899
24. Markowitz SB, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer. New findings from the North American insulator cohort. American Journal of Respiratory and Critical Care Medicine. 2013; 188: 90–96. doi: 10.1164/rccm.201302-0257OC PMID: 23590275
25. Gustavsson P, Nyberg F, Pershagen G, Schéele P, Jakobsson R, Plato N. Low-dose exposure to asbestos and lung cancer: dose-response relations and interaction with smoking in a population-based case-referent study in Stockholm, Sweden. American Journal of Epidemiology. 2002; 155: 1016–1022. doi: 10.1093/aje/155.11.1016 PMID: 12034580
26. Reid A, de Klerk NH, Ambrosini GL, Berry G, Musk AW. The risk of lung cancer with increasing time since ceasing exposure to asbestos and quitting smoking. Occupational and Environmental Medicine. 2006; 63: 509–512. doi: 10.1136/oem.2005.025379 PMID: 16849527
27. Villeneuve PJ, Parent MÉ, Harris SA, Johnson KC, The Canadian Cancer Registries Epidemiology Research Group. Occupational exposure to asbestos and lung cancer in men: evidence from a population-based case-control study in eight Canadian provinces. BMC Cancer. 2012; 12. doi: 10.1186/1471-2407-12-595
28. Sekhon H, Wright J, Churg A. Effects of cigarette smoke and asbestos on airway, vascular and mesothelial cell proliferation. International Journal of Experimental Pathology. 1995; 76: 411–418. pmcid: pmc1997213. PMID: 8652361
29. Jung M, Davis WP, Taatjes DJ, Churg A, Mossman BT. Asbestos and cigarette smoke cause increased DNA strand breaks and necrosis in bronchiolar epithelial cells in vivo. Free Radical Biology and Medicine. 2000; 28: 1295–1299. doi: 10.1016/S0891-5849(00)00211-2 PMID: 10889460
30. Eastman A, Mossman BT, Bresnick E. Influence of asbestos on the uptake of benzo(a)pyrene and DNA alkylation in hamster tracheal epithelial cells. Cancer Research. 1983; 43: 1251–1255. PMID: 6297722
31. Erren TC, Jacobsen M, Piekarski C. Synergy between asbestos and smoking on lung cancer risks. Epidemiology. 1999; 10: 405–411. PMID: 10401875
32. Lee PN. Relation between exposure to asbestos and smoking jointly and the risk of lung cancer. Occup Environ Med. 2001; 58: 145–153. doi: 10.1136/oem.58.3.145 PMID: 11171926
33. Hashim D, Boffetta P. Occupational and environmental exposures and cancers in developing countries. Ann Glob Health. 2014; 80: 393–411. PMID: 25512155
34. Liberati Alessandro, Altman Douglas G, Tetzlaff Jennifer, Mulrow Cynthia, Gøtzsche Peter C, Ioannidis John P A, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLOS Medicine. 2009; 6. doi: 10.1136/bmj.b2700
35. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283: 2008–2012. doi: 10.1001/jama.283.15.2008
36. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. International Journal of Epidemiology. 2007; 36: 666–676. doi: 10.1093/ije/dym018 PMID: 17470488
37. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
38. Rothman KJ. The estimation of synergy or antagonism. American Journal of Epidemiology. 1976; 103: 506–511. PMID: 1274952
39. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986; 7: 177–188. doi: 10.1016/0197-2456(86)90046-2 PMID: 3802833
40. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine. 2002; 21: 1539–1558. doi: 10.1002/sim.1186 PMID: 12111919
41. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327: 557–560. doi: 10.1136/bmj.327.7414.557. pmcid: pmc192859. PMID: 12958120
42. Wong O, Raabe GK. Application of meta-analysis in reviewing occupational cohort studies. Occupational and Environmental Medicine 1996; 53: 793–800. pmcid: pmc1128611. PMID: 8994397

43. Begg CB, Berlin JA. Publication bias and dissemination of clinical research. Journal of the National Cancer Institute. 1989; 81: 107–115. doi: 10.1093/jnci/81.2.107 PMID: 2642556

44. Egger M, Smith GD. Bias in location and selection of studies. BMJ. 1998; 316: 61–66. pmcid: pmc2665334. PMID: 9451274

45. Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. European Journal of Epidemiology. 2005; 20: 575–579. PMID: 16119429

46. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. Epidemiology. 1992; 3: 452–456. PMID: 1391139

47. Kjuus H, Skjaerven R, Langård S, Lien JT, Aamodt T. A case-referent study of lung cancer, occupational exposures and smoking. I. Comparison of title-based and exposure-based occupational information. Scandinavian Journal of Work, Environment & Health. 1986; 12: 193–202. doi: 10.5271/sjweh.2158

48. Kjuus H, Skjaerven R, Langård S, Lien JT, Aamodt T. A case-referent study of lung cancer, occupational exposures and smoking. II. Role of asbestos exposure. Scandinavian Journal of Work, Environment & Health. 1986; 12: 203–209. doi: 10.5271/sjweh.2157

49. Bovenzi M, Stanta G, Antiga GL, Peruzzo P, Cavallieri F. Occupation and lung cancer risk in the province of Trieste: a case-control study. Medicina del Lavoro. 1992; 83: 338–348. PMID: 1334212

50. de Klerk NH, Musk AW, Armstrong BK, Hobbs MS. Smoking, exposure to crocidolite, and the incidence of lung cancer and asbestosis. British Journal of Industrial Medicine. 1991; 48: 412–417. pmcid: pmc1035388. PMID: 1648376

51. McDonald JC, Liddell FD, Gibbs GW, Eyssen GE, McDonald AD. Dust exposure and mortality in chrysotile mining, 1910–75. British Journal of Industrial Medicine. 1980; 37: 11–24. pmcid: pmc1061328. PMID: 7370189

52. Blot WJ, Davies JE, Brown LM, Nordwall CW, Buiatti E, Ng A, et al. Occupation and the high risk of lung cancer in Northeast Florida. Cancer Research. 1982; 50: 364–371. doi: 10.1002/1097-0142(19820715)50:2<364::AID-CNCR2820500234>3.0.CO;2-Q

53. Morabia A, Markowitz S, Garibaldi K, Wynder EL. Lung cancer and occupation: results of a multicentre case-control study. British Journal of Industrial Medicine. 1992; 49: 721–727. pmcid: pmc1012148. PMID: 1419861

54. Hilt B, Langård S, Lund-Larsen PG, Lien JT. Previous asbestos exposure and smoking habits in the county of Telemark, Norway—a cross-sectional population study. Scandinavian Journal of Work, Environment & Health. 1986; 12: 561–566. doi: 10.5271/sjweh.2106

55. Kjuus H, Langård S, Skjaerven R. A case-referent study of lung cancer, occupational exposures and smoking. III. Etiologic fraction of occupational exposures. Scandinavian Journal of Work, Environment & Health. 1986; 12: 210–215. doi: 10.5271/sjweh.2156

56. Bovenzi M, Stanta G, Antiga G, Peruzzo P, Cavallieri F. Occupational exposure and lung cancer risk in a coastal area of northeastern Italy. International Archives of Occupational and Environmental Health. 1993; 65: 35–41. doi: 10.1007/BF00586056 PMID: 8354573

57. Liddell FD, Thomas DC, Gibbs GW, McDonald JC. Fibre exposure and mortality from pneumoconiosis, respiratory and abdominal malignancies in chrysotile production in Quebec, 1926–75. Annals of the Academy of Medicine, Singapore. 1984; 13: 340–344. PMID: 6497336

58. Martischnig KM, Newell DJ, Barnsley WC, Cowan WK, Feinmann EL, Oliver E. Unsuspected exposure to asbestos and bronchogenic carcinoma. British Medical Journal. 1977; 1: 746–749. pmcid: pmc1605619. PMID: 856382

59. Blot WJ, Morris LE, Stroube R, Tagnon I, Fraumeni JF Jr. Lung and laryngeal cancers in relation to shipyard employment in coastal Virginia. The Journal of the National Cancer Institute. 1980; 65: 571–575. PMID: 6931936

60. Pastorino U, Berrino F, Gervasio A, Pesenti V, Riboli E, Crosignani P. Proportion of lung cancers due to occupational exposure. International Journal of Cancer. 1984; 33: 231–237. doi: 10.1002/ijc.2910330211

61. Dave S K, Edling C, Jacobsson P, Axelson O. Occupation, smoking, and lung cancer. British Journal of Industrial Medicine. 1988; 45: 790–792. pmcid: pmc1009698. PMID: 3203084

62. Blot WJ, Harrington JM, Toledo A, Hoover R, Heath CW Jr, Fraumeni JF Jr. Lung cancer after employment in shipyards during World War II. New England Journal of Medicine. 1978; 299: 620–624. doi: 10.1056/NEJM197809212991202 PMID: 683235

63. Berry G, Newhouse ML, Antonis P. Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. British Journal of Industrial Medicine. 1985; 42: 12–18. pmcid: pmc1007410. PMID: 3965010

64. Berry G, Newhouse ML, Turok M. Combined effect of asbestos exposure and smoking on mortality from lung cancer in factory workers. Lancet. 1972; 2: 476–478. PMID: 4115357

65. Rubino GF, Piolatto G, Newhouse ML, Scansetti G, Aresini GA, Murray R. Mortality of chrysotile asbestos workers at the Balangero Mine, Northern Italy. British Journal of Industrial Medicine. 1979; 36: 187–194. pmcid: pmc1008562. PMID: 500777

66. Muscat JE, Wynder EL. Cigarette smoking, asbestos exposure, and malignant mesothelioma. Cancer Research. 1991; 51: 2263–2267. PMID: 2015590

67. Valavanidis Athanasios, Vlachogianni Thomais, Fiotakis Konstantinos, Loridas Spyridon. Pulmonary oxidative stress, inflammation and cancer: respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms. International Journal of Environmental Research and Public Health. 2013; 10: 3886–3907. doi: 10.3390/ijerph10093886. pmcid: pmc3799517. PMID: 23985773

68. Matsuzaki Hidenori, Maeda Megumi, Lee Suni, Nishimura Yasumitsu, Kumagai-Takei Naoko, Hayashi Hiroaki, et al. Asbestos-induced cellular and molecular alteration of immunocompetent cells and their relationship with chronic inflammation and carcinogenesis. Journal of Biomedicine and Biotechnology. 2012; 2012. doi: 10.1155/2012/492608. pmcid: pmc3304550.

69. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144: 646–674. PMID: 21376230

70. Lee J, Taneja V, Vassallo R. Cigarette smoking and inflammation cellular and molecular mechanisms. Journal of Dental Research. 2012; 91: 142–149. doi: 10.1177/0022034511421200 PMID: 21876032

71. Donaldson K, Murphy FA, Duffin R, Poland CA. Asbestos, carbon nanotubes and the pleural mesothelium: a review of the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma. Particle and Fibre Toxicology. 2010; 7. doi: 10.1186/1743-8977-7-5. pmcid: pmc2857820.

72. Nishimura Y, Maeda M, Kumagai-Takei N, Lee S, Matsuzaki H, Wada Y, et al. Altered functions of alveolar macrophages and NK cells involved in asbestos-related diseases. Environmental Health and Preventive Medicine. 2013; 18: 198–204. doi: 10.1007/s12199-013-0333-y. pmcid: pmc3650181. PMID: 23463177

73. Liu G, Cheresh P, Kamp DW. Molecular basis of asbestos-induced lung disease. Annual Review of Pathology: Mechanisms of Disease. 2013; 8: 161–187. doi: 10.1146/annurev-pathol-020712-163942. pmcid: pmc3900296.

74. Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. Nature Reviews Cancer. 2003; 3: 733–744. doi: 10.1038/nrc1190 PMID: 14570033

75. Bernstein D, Dunnigan J, Hesterberg T, Brown R, Velasco JA, Barrera R, et al. Health risk of chrysotile revisited. Critical Reviews in Toxicology. 2013; 43: 154–183. doi: 10.3109/10408444.2012.756454 PMID: 23346982

76. Kamp DW. Asbestos-induced lung diseases: an update. Translational Research. 2009; 153: 143–152. PMID: 19304273