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Occupational Asbestos Exposure and Lung Cancer—A Systematic Review of the Literature

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ABSTRACT. The objective of this study was to evaluate the scientific literature concerning asbestos and lung cancer, emphasizing low-level exposure. A literature search in PubMed and Embase resulted in 5,864 citations. Information from included studies was extracted using SIGN. Twenty-one statements were evidence graded. The results show that histology and location are not helpful in differentiating asbestos-related lung cancer. Pleural plaques, asbestos bodies, or asbestos fibers are useful as markers of asbestos exposure. The interaction between asbestos and smoking regarding lung cancer risk is between additive and multiplicative. The findings indicate that the association between asbestos exposure and lung cancer risk is basically linear, but may level off at very high exposures. The relative risk for lung cancer increases between 1% and 4% per fiber-year (f-y)/mL, corresponding to a doubling of risk at 25–100 f-y/mL. However, one high-quality case-control study showed a doubling at 4 f-y/mL.

KEYWORDS: asbestos, interaction between exposures, lung cancer, lung neoplasms, occupational exposure, smoking and asbestos

In 2012 the Danish National Board of Industrial Injuries requested a scientific reference document concerning low-dose asbestos exposure and lung cancer. The Department of Occupational and Environmental Medicine received the grant to write the document. This paper is a slightly revised version of the reference document that has been submitted to the Danish National Board of Industrial Injuries. The document is available at their Web site (www.ask.dk/~/media/ASK/pdf/Rapporter/Udredningsrapport%20asbestos%20lung%20cancer%202013pdf.ashx).

Lung cancer is the most commonly diagnosed male cancer worldwide[1] and in Denmark, accounts for 13.3% of all new cancers in males and 12.3% in females.[2,3] Since the 1950s, lung cancer incidence has steadily increased among females, whereas morbidity and mortality in males has declined after the 1980s.[3]

Asbestos is an important occupational risk factor for lung cancer. Asbestos is a generic term that represents 6 naturally occurring fibrous minerals that can be generally grouped into 2 distinct classes. The serpentine class includes chrysotile (white), whereas the amphibole class includes amosite (brown), crocidolite (blue), tremolite, actinolite, and anthophyllite asbestos.[4] The 2 main classes differ significantly in terms of their physical and chemical properties.[5,6]

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Chrysotile fibers are cleared more readily by mucociliary action and more easily broken down.[7] Amphibole fibers are far more resistant with a longer residence time.[8–10]

In 1997, the Helsinki criteria for identifying individuals with a high probability of asbestos exposure at work were adopted.[11] Until now, there has been general international consensus on the use of the criteria that include quantifying asbestos fiber or bodies in lung tissue or bronchoalveolar lavage. Histology and location of lung cancer have no significant value in deciding whether or not lung cancer can be attributable to asbestos. In addition, 1 year of heavy asbestos exposure (eg, manufacturing of asbestos products, asbestos spraying, insulation work with asbestos, demolition of old buildings) and 5–10 years of moderate exposure (eg, construction, shipbuilding) were judged adequate to increase the risk of lung cancer by 2-fold or more. In Denmark as well as in many other countries (eg, Germany and The Netherlands), asbestos exposure of 25 fiber-years (f-y)/mL or more is considered to be associated with a 2-fold increased lung cancer risk, which is compensable.

The overall objective was to produce a stringent and critical review of the scientific literature concerning asbestos exposure and its causation of lung cancer. Particular emphasis was placed on the exposure-response relationship at low-level exposure. In addition, the possibility for a threshold and the interaction between asbestos and smoking were taken into account.

METHODS

A writing group and an internal expert group with specific knowledge on asbestos and/or lung cancer were established. At a seminar the groups agreed on the wording of 21 statements and reached consensus about the classification of each statement. See Appendix 1 for members of the 2 groups.

Nineteen research questions were formulated directly from the grant announcement and divided into 4 main groups: lung cancer (LC), asbestos exposure (AE), exposure-response (ER), and competing and predisposing conditions (CPC) (see Appendix 2). On the basis of these search questions, 21 key statements were composed (see Appendix 3).

Literature search

The literature search consisted of a series of top-down and bottom-up searches. The top-down searches were performed in PubMed MEDLINE and Embase using the terms asbestos and lung cancer (July 2–3, 2012). Hits from the 2 databases were merged and duplicates removed. The bottom-up searches consisted of 19 specific searches for each of the 19 predefined search questions and were restricted to PubMed MEDLINE (July 23–27, 2012). Moreover, the electronic searches were supplemented with additional relevant citations achieved by manual review from the bibliographies of retrieved papers as well as inputs from members of the working groups. Finally, a few citations were identified through PubMed alerts that appeared after July 3, 2012.

Selection of articles

The selection of publications to be included was a multistep, iterative process. Studies were included if (i) the main focus was on associations between lung cancer and asbestos exposure; (ii) they describe results from an original study; (iii) they were in English, Scandinavian, German, or French language.

First based on title and second based on reading of the abstract, one researcher (D.S.) selected the citations from the top-down and bottom-up literature searches eligible for further consideration. In addition, the citations were grouped according to the 19 search questions, with the possibility for a citation to appear in more than one group. In order to exclude papers that lacked sufficient data or analytic structure to warrant in-depth review, a final screening of the publications was completed. Exclusion criteria were (i) case reports, case series, or expert opinions; (ii) very old publications and/or small study populations; (iii) high risk of bias; and (iv) older studies that were followed up with a more recent updated publication.

Figure 1 illustrates the literature search. The top-down yielded 4,088 discrete citations; 3,633 were excluded based on title and 289 were excluded based on abstract. The bottom-up literature search for all 19 search questions revealed 907 citations, of which 430 were excluded based on title or abstract. A total of 643 citations were pooled from the 2 literature searches; 471 of these citations were excluded based on exclusion criteria, which resulted in a total of 172 included citations. During the writing process, this pool of citations was increased, with 123 citations emerging from manual reading of reference lists, inputs from coauthors, and PubMed alerts, resulting in a total of 295 included citations.

Data extraction and quality appraisal

Each original publication concerning exposure-response associations between asbestos exposure and lung cancer was double reviewed and quality graded by 2 researchers. A data extraction sheet based on the Scottish Intercollegiate Guidelines Network (SIGN) and adjusted to the present review was used.[12] Reviews and meta-analysis were double reviewed and quality graded with the R-AMSTAR checklist quality assessment sheet.[13] For the original studies, quality appraisals were compared and discrepancies between the 2 researchers reconciled by mutual agreement resulting in a grade of 2++ (very low risk of confounding, bias, chance), 2+ (low risk of confounding, bias, chance), or 2− (high risk of confounding, bias, chance). For meta-analysis and reviews, the final R-AMSTAR score was a mean of the 2 independent scores.

Assessment of causal association or to substantiate the statement

The evidence model recommended by the Danish Working Environmental Authority was slightly adapted as all statements did not include a causal relationship:

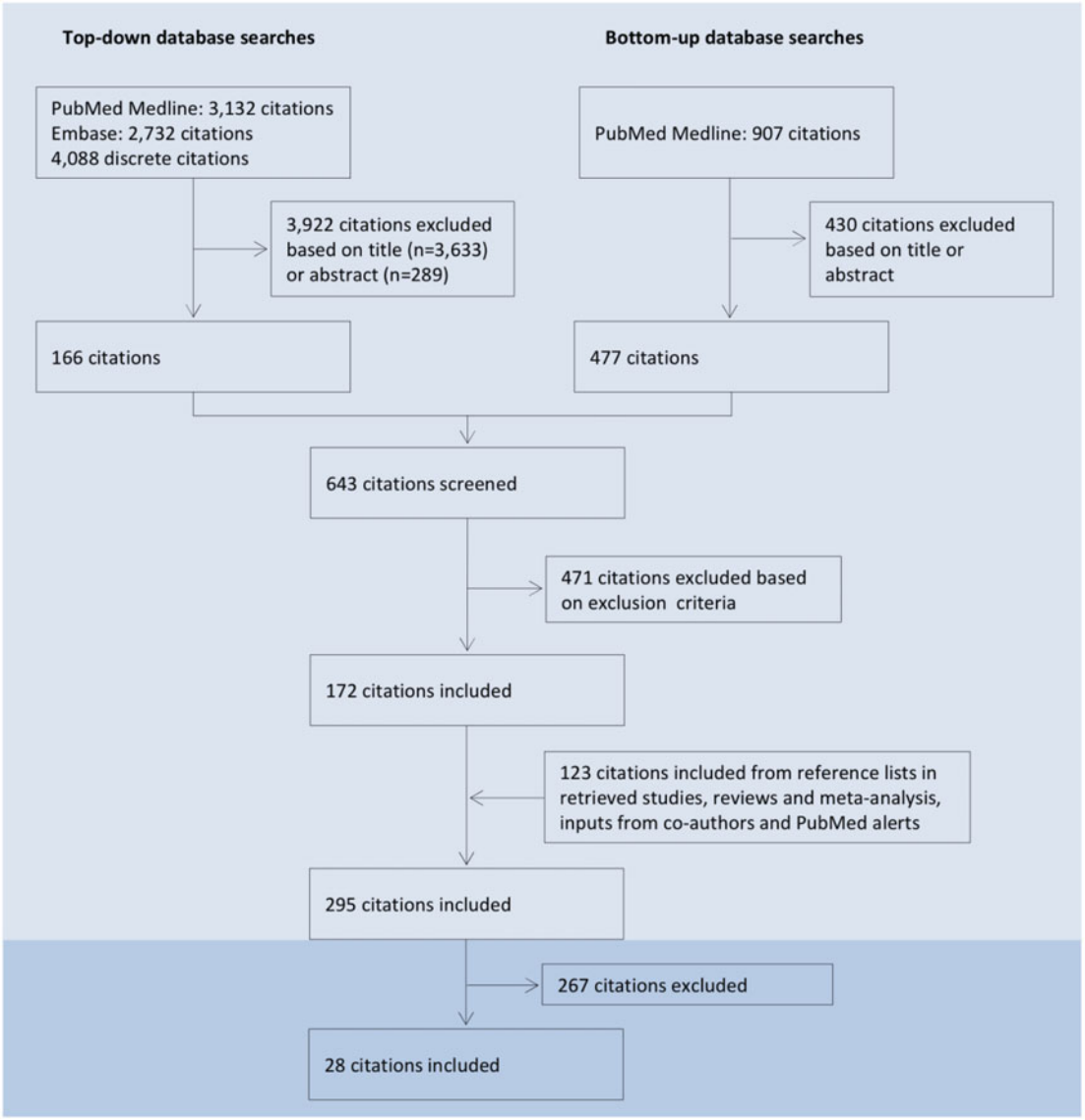

Fig. 1. Flowchart on stages of identification, screening, and selection of original studies (color figure available online).

+++ Strong evidence (to substantiate the statement)
++ Moderate evidence (to substantiate the statement)
+ Limited evidence (to substantiate the statement)
0 Insufficient evidence (to substantiate the statement)
− Evidence suggesting lack of knowledge to substantiate the statement

Article review

Each of the double-reviewed original articles on exposure-response association (ER) between asbestos exposure and lung cancer was tabulated in a standardized form. Information on study design, study population, exposure measurement, outcome measurement, key findings, and the final grading was included. Information from the other 3 areas, AE, LC, and CPC, were presented in a narrative form.

RESULTS

The review is structured around the 21 statements (see Appendix 3).

Lung cancer

Asbestos-Related Lung Cancer (ARLC): Histology, Location, Prognosis, and Screening

Older studies (>20 years) were poorly controlled and showed inconsistent results concerning lobe of origin and

histology of ARLC. Some studies described a lower lobe association with asbestos exposure,[14–17] whereas other studies showed upper lobe location similar to tobacco-related lung cancers.[18–21] As in the case of tumor location, results concerning ARLC histology were conflicting. Excess adenocarcinomas were shown in some studies.[19,22–24] However, other studies have failed to show this increased risk.[25] The more recent, well-controlled studies that we reviewed with the SIGN also have failed to show any significant differences between ARLC and non-ARLC regarding cell type or location.[26–30] Based on these findings, we conclude that:

Statement 1: When evaluating ARLC location and cell type, do not differentiate asbestos-related and non–asbestos-related lung cancer (+++).

Our literature search did not find any references that specifically dealt with ARLC prognosis. The only available data were obtained from reviewing 422 consecutive lung cancer cases diagnosed at the Department of Respiratory Medicine, Odense University Hospital, between 2007 and 2010. Of these 25% reported asbestos exposure. No survival differences were observed after 1 and 2 years. Kaplan-Meier estimates updated June 2013 suggest a 5-year survival rate of about 9% for both ARLC and non-ARLC.[31]

Statement 12: The prognosis of ARLC does not differ from that of other lung cancers (+).

The US National Lung Cancer Screening Trial (NLST) has recently demonstrated that annual low-dose computed tomographic (CT) screening can reduce the relative mortality by 20%.[32] On this background, the National Comprehensive Cancer Network (NCCN) published recommendations in 2012 concerning low-dose CT screening for well-defined high-risk groups such as heavy smokers, including those with previous asbestos exposure.[25] However, a review of annual screening recommendations has stated that there are 2 key problems in relation to the procedure: it is costly and complicated by numerous false positives.[33] To further complicate the question, a recent randomized controlled trial in Denmark did not show mortality reduction so far.[34] Results from the ongoing European prospective screening trials are not yet available. But the coming results may help clarify the dilemma.

Asbestos exposure

Exposure Assessment

Case-by-case expert assessment and job exposure matrices (JEMs) are commonly used instruments to assess occupational exposures. Case-by-case expert assessment is generally considered the best method for assessing occupational exposures in population-based studies.[35] However, it requires considerable resources.[36–38] JEMs have proven to be similar when compared with the expert assessment and are therefore useful in asbestos exposure assessment. However, exposure duration estimations in JEMs may result in misclassification.

Statement 2: Job exposure matrices (JEMs) are useful in estimating previous asbestos exposure in addition to individual exposure evaluation (+).

Biological Markers of Asbestos Exposure: Pleural Plaques, Asbestos Bodies, and Asbestos Fibers

Numerous studies have verified that pleural plaques (PPs) are associated with previous asbestos exposure.[39] Even though most authors state that PPs are rarely seen until 20 years after the initial exposure, a reevaluation of previous chest x-rays in exposed workers indicated that they may occur as early as 10 years after exposure.[40] PPs do not reflect the degree of exposure. However, a positive association between the degree and duration of asbestos exposure and the likelihood of finding PPs on a chest x-ray has recently been confirmed.[25] Asbestos fibers (AFs) and asbestos bodies (ABs) in bronchoalveolar lavage (BAL) and lung tissue reflect some degree of asbestos exposure.[11,41–44] However, the absence of PPs, ABs, or AFs does not preclude considerable previous asbestos exposure. The presence of asbestosis is associated with considerable asbestos exposure sufficient to cause ARLC.[45]

Statement 3: The existence of uni- or bilateral pleural plaques increases the likelihood of previously asbestos exposure (++).

Statement 4: The presence of pleural plaques cannot be used to estimate the degree of previous asbestos exposure (+++).

Statement 5: The presence of asbestosis is a marker of previously high asbestos exposure and is associated with an increased risk of lung cancer (+++).

Exposure-response

Exposure-Response Relationship

Of the 28 original studies with information on lung cancer risk in relation to occupational asbestos exposure, 24 were cohort[46–69] and 4 were case-control studies.[70–73] Twenty-two studies included only men[47,50–52,54–57,59–67,69–73] and 6 studies included around 60–80% men.[46,48,49,53,58,68] Exposure to asbestos in 8 studies was restricted to chrysotile,[50,51,53,57,58,60,63,68] 7 studies indicated that the asbestos exposure was mainly to chrysotile,[46–49,55,59,62] 1 study was mainly based on exposure to amosite and very little chrysotile,[64] 1 study was on amosite alone,[56] and 4 studies were on amphibole.[65–67,69] Four studies with mixed exposures did not indicate the distribution of asbestos types,[52,54,71,72] and 3 studies did not describe the asbestos type.[61,70,73] The following industries were presented: textile production,[46,49,50,53,58,59,61,62,68] mining and/or milling,[57,63,66,67,69]

Table 1.—Tabular Presentation of Cohort Studies With Exposure Measurements <50 f-/mL

Study (reference no.); country	Population	Exposure*	Outcome	Measure of risk, SMR, Kα, 95% CI, or p value	SIGN grading
Elliott et al. 2012 (46); USA	$N = 6{,}136$, men and women	CHR, small amount of CRO and AMO, textile production	Lung cancer death, death certificates	**RR increased with 2% per f-y/mL exposure**. SMR = 1.90 (95% CI 1.70–2.11), for South Carolina workers.	2++
Albin et al. 1990 (47); Sweden	$N = 1{,}465$, men only	CHR (95%), smaller amounts of CRO and AMO, cement workers	Lung cancer death, death certificates, and cancer register	No significant relations. Lung cancer RR (f-y/mL): <15 = 1.8 (95% CI 0.8–3.9), 15–39 = 1.9 (95% CI 0.7–5.3), >40 = 1.9 (95% CI 0.5–7.1).	2+
Clin et al. 2011 (48); France	$N = 2{,}004$, men and women	CHR (80%), AMO (20%), textile and friction materials production	Lung cancer, cancer register	No significant relations between cumulative exposure and lung cancer: HR = 1.05 (95% CI 0.42–2.62) and 1.89 (95% CI 0.74–4.84) for ≥40 to <140 and ≥140 to <853 f-y/mL, respectively, with <40 f-y/mL as reference.	2+
Dement et al. 1994 (49); USA	$N = 3{,}022$, white men and women and black men	CHR, a little AMO, textile production	Lung cancer death, death certificates	**RR increased with 2–3% per f/cc-year exposure** for the entire cohort. Significant relations with SMR = 2.30 (1.88–2.79) and 2.75 (2.06–3.61) for white men and women, respectively.	2++
Dement et al. 1982 (50); USA	$N = 768$, white men	CHR, textile production	Lung cancer death, death certificates	Linear exposure-response relation with no threshold. SMR = 223, 357, 978, 1553 for <10,000, 10,000–40,000, 40,000–100,000, and 100,000–200,000 fiber cm^{-3}/days, respectively.	2+
Deng et al. 2012 (51); China	$N = 586$, men only	CHR (very high), textile, brake, and cement production	Lung cancer death, death certificates	Significant relations ($p < .001$) in which clear exposure-response relationships were seen. No threshold observed.	2+
Hein et al. 2007 (53); USA	$N = 3{,}072$, mainly white men and women	CHR, textile production	Lung cancer death, death certificates	**RR = 0.0198 per f-y/mL** (SE 0.000496) with 10-year lag time. Exposure-response associations found.	2+
Hughes et al. 1987 (54); USA	$N = 6{,}931$, black and white men	CHR, CRO, AMO, cement manufacturing plants	Lung cancer death, death certificates	**RR = 1 + 0.0076 per f-y/mL** (significant).	2−
Lacquet et al. 1980 (55); Belgium	29,366 man-years of observation, men only	CHR (mainly), CRO, AMO, asbestos cement industry	Lung cancer death, personnel records, and interviews with family doctors and social workers	No significant relations ($p = .11$) found between lung cancer and asbestos exposure.	2−
Liddell et al. 1997 (57); Canada	$N = 10{,}918$, men only	CHR, Quebec mining and milling	Lung cancer death, death certificates	A negligible excess lung cancer risk below 300 mppcf-years with average SMR = 1.21.	2−
Loomis et al. 2009 (58); USA	$N = 5{,}770$ men and women	CHR, textile industry	Lung cancer death, death certificates	**RR = 1.102 per 100 f-y/mL** (95% CI 1.044–1.164), which amounts to about 10% increase per 100 f-y/mL. Also, significant relation found with SMR = 1.96 (95% CI 1.73–2.20).	2+
McDonald et al. 1984 (60); USA	$N = 3{,}641$, men only	CHR, friction products and packing manufacturing facility	Death from lung cancer and mesothelioma, death certificates	SMR = 148.7. However, lack of any clear or systematic exposure-effect pattern. No exposure-effect relation with cumulative exposure.	2−
Peto et al. 1985 (62); United Kingdom	$N = 3{,}211$, men, non-Asian	CHR (95%), CRO (5%), textile industry	Lung cancer death, death certificates	**SMR = 1+0.01x per f-y/mL** was a suggested prediction. SMR = 1.53×10^{-4} per particle-y/mL, approximated for SMR = 0.005 and 0–015 per f-y/mL for the entire cohort and those employed 1951 or later, respectively.	2+
Sluis-Cremer 1991 (66); South Africa	$N = 7{,}317$, white men	CRO, AMO, mining and milling	Lung cancer death, death certificates	**RR = 1.01 per f-y/mL** exposure (95% CI 1–1.01) and **RR = 1.12 per year of exposure** (95% CI 1.04–1.20).	2+

(Continued on next page)

Table 1.—Tabular Presentation of Cohort Studies With Exposure Measurements <50 f-/mL *(continued)*

Study (reference no.); country	Population	Exposure*	Outcome	Measure of risk, SMR, Kα, 95% CI, or p value	SIGN grading
Sluis-Cremer 1992 (67); South Africa	$N = 7{,}317$, white men	CRO, AMO, mining and milling	Lung cancer death, death certificates	SMR = 1.7 (95% CI 1.32–2.21). SMR = 1.38 (95% CI 0.97–1.91) and 2.03 (95% CI 1.43–2.80) for AMO and CRO, respectively.	2+
Stayner et al. 1997 (68); USA	$N = 3{,}041$, women and men, predominately white	CHR, textile industry	Lung cancer death, death certificates	**RR = 0.021 per fiber-y/mL** (95% CI 0.008–0.036). No evidence for a threshold.	2++
Sullivan et al. 2007 (69); USA	$N = 1{,}672$, white men	AMP, vermiculite mining and milling, and process workers	Lung cancer death, death certificates	Dose-related increases in lung cancer mortality. SMR = 1.7 (95% CI 1.4–2.1) with 15 years lag time, SMR = 1.5 (95% CI 0.9–2.3) for low exposures (<4.5 f-y/mL), SMR = 1.6 (95% CI 1.1–2.1) for short-term employment (<1 year).	2++

*CHR = chrysotile; CRO = crocidolite; AMO = amosite; AMP = amphibole.
Bold font indicates which articles include a specific dose-exposure result.

cement production,[47,54,55] and insulation.[56,64,65] Four studies' cohorts comprised combined industries.[51,52,60,74] Twenty-four studies focused on lung cancer deaths[46,47,49–69,72] and 4 studies on lung cancer cases.[48,70,71,73] Among the 24 studies with lung cancer death as outcome, only 1 study was not based on death certificates but on personnel records combined with interviews with family doctors.[55] Six studies adjusted for smoking as a potential confounder[51,66,67,70,71,73] and

Table 2.—Tabular Presentation of Cohort Studies With Exposure Measurements >50 f-y/mL

Study (reference no.); country	Population	Exposure*	Outcome	Measure of risk, SMR, Kα, 95% CI, or p value	SIGN grading
Enterline et al 1987 (52); USA	$N = 1{,}074$, white men	CHR, CRO, AMO, production of insulation, roof, and engineered products	Lung cancer death, death certificates	Significant relation. SMR = 182, 203, 322, 405, and 699 for dust exposure <125, 125–249, 250–499, 500–749, and ≥750 mppcf-y, respectively.	2−
Levin et al 1998 (56); USA	$N = 1{,}121$, men only	AMO, pipe insulation	Lung cancer death, death certificates	Significant relation found. SMR = 277 (95% CI 193–385).	2−
McDonald et al 1983 (59); USA	$N = 4{,}137$, men only	CHR (mainly), some AMO, less CRO, textile industry	Death from lung cancer and mesothelioma, death certificates	**RR = 1 + 0.051 mppcf-year** in a linear model. SMR = 4.16.	2−
Peto et al 1980 (61); United Kingdom	$N = 679$, men only	Unknown asbestos type, textile industry	Lung cancer death, death certificates	No formal exposure-response analysis was undertaken. But an overall excess of lung cancer death claimed to be compatible with **RR = 2–3 for 200–300 f-y/mL of exposure.**	2−
Pira et al 2009 (63); Italy	$N = 1{,}056$, men only	CHR, mining	Lung cancer death, death certificates	No significant risk for lung cancer death in spite of high exposures over 400 f-y/mL. SMR = 1.27 (0.93–1.70).	2−
Seidman et al 1986 (64); USA	$N = 820$, white men	AMO, very little CHR, ship insulators of pipes, boilers, and turbines	Lung cancer death, death certificates + best evidence from additional information	A linear zero threshold exposure-response relation was found. SMR = 541 from 5 to 40 years after onset of work.	2−
Selikoff et al 1991 (65); USA and Canada	$N = 17{,}800$, men only	AMP, insulation workers	Lung cancer death, death certificates	RR increased from 2.32 at <15 years from start of exposure to 4.90 after 30–40 years since onset of exposure.	2+

*CHR = chrysotile; CRO = crocidolite; AMO = amosite; AMP = amphibole.
Bold font indicates which articles include a specific dose-exposure result.

Table 3.—Tabular Presentation of Case-Control Studies With Exposure Measurements <50 f-y/mL

Study (reference no.); country	Population	Exposure*	Outcome	Measure of risk, SMR, Kα, 95% CI, or p value	SIGN grading
Gustavsson et al. 2002 (70); Sweden	Cases: all lung cancer male cases 1985–1990, Stockholm, age 40–75 years ($N = 1{,}038$). Controls: 2,359. Random selection from the general population frequency-matched with regard to age and inclusion year.	Unknown asbestos type	Lung cancer, Cancer register	Excess risk of lung cancer at low exposure levels was seen and an exposure-response relation of 4 f-y/mL associated with a RR of 1.9 (95% CI 1.32–2.74).	2+
Pohlabeln et al. 2002 (71); Germany	Cases: $N = 839$, male patients with lung cancer in Bremen and a small group in Frankfurt, 1988–1993. Controls: $N = 839$, males individually matched on age and region, from all hospitals in Bremen (1988–1993) and Frankfurt/Main (1989–March 1990).	Mixed exposure	Lung cancer	Log transformed (ln(f-y/mL + 1)) gave the best fit. The estimate was ln(f-y/mL + 1): OR = 1.18 (95% CI 1.05–1.32), corresponding to a doubled risk from exposure to 25 f-y/mL.	2++
Berry et al. 1983 (72); United Kingdom	Cases: $N = 106$, men working with production of friction materials, dead of lung cancer. Controls: $N = 318$ workers (same factory), matched for started in the factory, date of birth, survival up to time of death from lung cancer.	CHR, CRO	Lung cancer death, death certificates	**RR = 0.00058 per f-y/mL**. No indication of an increased risk of lung cancer with duration of exposure or cumulative exposure in the categorical analysis.	2−
Gustavsson et al. 2000 (73); Sweden	Cases: all lung cancer male cases 1985–1990, Stockholm, age 40–75 years ($N = 1{,}038$). Controls: 2,364. Random selection from the general population frequency-matched with regard to age and inclusion year.	Unknown asbestos type	Lung cancer, Cancer register	**RR increased about 14% per f-y/mL**. Exposure-response relation for mean exposure and poor correlation with length of exposure.	2+

*CHR = chrysotile; CRO = crocidolite; AMO = amosite; AMP = amphibole.
Bold font indicates which articles include a specific dose-exposure result.

1 study compared smoking habits between the study population and the US population and concluded that smoking was not a confounder.[54] A tabular presentation of the studies including their main characteristics and a SIGN grading are given in Table 1 (cohort studies with exposure measurements <50 f-y/mL), Table 2 (cohort studies with exposure measurements >50 f-y/mL), and Table 3 (case-control studies with exposure measurements <50 f-y/mL). A tabular presentation of reviews and meta-analyses[75–83] are given in Table 4.

Statement 6: The exposure-response relationship is approximately linear, but levels off at very high exposures (>150 f-y/mL) (+++).

Statement 7: An increase in risk ratio (RR) of 0.01–0.04 per f-y/mL (corresponding to a doubling of risk at 25–100 f-y/mL) has been observed, with the highest estimates obtained in the few high-quality epidemiological studies. One high-quality population-based case-control study in the low-exposure range found a higher risk estimate (a doubling around 4 f-y/mL) (++).

No Observed Effect Level

The possible existence of a threshold for lung cancer risk due to asbestos has been widely discussed. Data from a series of cohorts on risk rates at various exposure levels have shown that no increased lung cancer risk was seen below an exposure of about 25 f-y/mL.[84] On the other hand, 6 meta-analyses[78–83] have all been based on linear models, which imply no threshold. In a population-based study by Gustavsson et al,[73] an elevated risk was seen at an estimated exposure of 4 f-y/mL. The recent meta-analysis by van der Bij et al[85] has analyzed the exposure-response at low exposures and calculated relative risks of 1.01–1.03 at 4 f-y/mL and 1.12–1.32 at 40 f-y/mL, suggesting no threshold.

Statement 8: There is no evidence for a no observed effect level (NOEL) concerning ARLC (++).

Statement 9: The lowest documented increased ARLC risk is seen at about 4 f-y/mL (+).

Table 4.—Tabular Presentation of Meta-analysis and Reviews

Study (reference no.), Study type*	No of studies included	Result	R-AMSTAR score
Hendersen et al. 2004 (75), R		Evidence supports a cumulative exposure model. Insufficient evidence to draw meaningful conclusions concerning variation in asbestos-mediated lung cancer risk relative to individual resistance and susceptibility factors. Different attribution criteria (eg, grater cumulative exposures) are appropriate for chrysotile-only exposures. No significant differences in the phenotypic repertoire or the anatomical distribution of lung cancers related to asbestos versus those that are not. All 4 major lung cell types occur among asbestos-exposed subjects with no differences when compared with controls.	16 of 44
Pierce et al. 2008 (76), R	14	The preponderance of cumulative "no-effect" exposures (ie, no statistical significance) for lung cancer were about 25–1000 f-y/mL. However, many studies were too small and thus lacked statistical power to assess possible increased risk at the reported "no-effect" level.	20.5 of 44
Steenland et al. 1997 (77), R	24	15 studies showed an exposure response. The lowest lung cancer risk among workers was found in cement and friction products industries. Highest risks were among mining and textile workers. Smoking differences could not explain the variable industry risks. Smoking-asbestos interaction is between additive and multiplicative.	15 of 44
Goodman et al. 1999 (78), MA	69	Very large heterogeneity of the studies with SMRs ranging from unity (= 100) to 1,700 in Finnish asbestos sprayers. Including latency increased the common SMR from 148 (144–152) to 163 (158–169), but it was not shown whether this increase was due to exclusion of 18 studies or inherited within the single study. Some variation between different occupations was seen with asbestos product manufacturing and cement workers having the highest SMRs, 196 (95% CI: 176–209) and 170 (95% CI: 156–185), respectively. Railroad workers and friction material workers had the lowest. 13 studies with more than 2.4% mesothelioma deaths showed a common SMR of 285 (271–299), whereas those below 0.6% and between 0.6% and 2.4% had values of 127 (121–134) and 138 (126–151), respectively.	16 of 44
Lash et al. 1997 (79), MA	22	Estimates of the study specific exposure-response coefficient (k_L) ranged from 0 to 42 $\times$ 10^{-3} f-y/mL. Smoking habits and type of asbestos industry, but also standardization to different populations between the cohorts, and possible conversion between different measures of asbestos exposure (ie, between mppcf and f/mL) were identified as sources of heterogeneity. Under the random effect model, implemented due to the heterogeneity between the studies: the maximum likelihood estimate of k_L was found to be 2.6 $\times$ 10^{-3} (95% CI: 0.65 to 7.4 $\times$ 10^{-3}) (f-y/mL)$^{-1}$ and the estimate for the intercept (a_i) to be 1.36 (95% CI: 1.05 to 1.76).	19 of 44
Hodgson et al. 2000 (80), MA	18	Excess lung cancer risk for amphibole exposures was about 5% per f-y/mL. For mixed fibers and chrysotile large heterogeneities were seen. Chrysotile risk was less consistent, around 0.1–0.5% per f-y/mL with very large variation, especially between the Quebec miners and the South Carolina textiles. Interstudy exposure-response for amphibole suggests a nonlinear relationship, between linear and square. However, due to statistical uncertainties a linear relationship remains arguable for lung cancer.	21 of 44
Lenters et al. 2011 (81), MA	19	Stratified by quality in the exposure assessment, the authors found that studies with better exposure assessment generally had higher k_L values. This was most pronounced for studies with better exposure data and better completeness of job histories. Under the random effect model, the unrestricted meta-k_L was 1.3 $\times$ 10^{-3} (95% CI: 0.4 to 2.2 $\times$ 10^{-3}) (f-y/mL), increasing by stepwise exclusion to k_L 5.5 $\times$ 10^{-3} (f-y/mL)$^{-1}$.	34 of 44
Van der Bij et al. 2012 (82), MA	19	The best fit was obtained with a natural spline model. This model suggested a nearly linear increase in the relative lung cancer risk at low levels of exposure, and a slight decrease in the slope at exposures >150 (f*y/mL)$^{-1}$. For a cumulative exposure level of 4 f-y/mL, the RR for lung cancer was estimated to be between 1.013 and 1.027 and for 40 f-y/mL to be between 1.13 and 1.30. A nonsignificant difference (3–4-folds) in the RR was observed between exposure to amphibole and mixed fibers versus chrysotile fibers for exposures below 40 f-y/mL.	26 of 44
Berman and Crump 2008 (83), MA	18	In the analysis of raw data, the authors found that k_L values were 1/3 to 1/10 in models assuming α being estimated than when α was set to 1. The association with industry seems to be at least as strong as for fiber type, mining being the least and textile production by far the highest. For mining, however, exposure to mixed or amphibole fibers showed higher k_L values than chrysotile. Sharp discrepancy between Quebec mining and South Carolina textile factory handling the same chrysotile asbestos stands out (values with the uncertainty intervals 0.29 [0.085–1.1] vs 1.8 [7.5–5.6] $\times$ 10^{-3} (f-y/mL)$^{-1}$).	23 of 44

*R = review; MA = meta-analysis.

Latency

Latency has been defined assuming that it takes at least 10 years to develop a solid tumor as lung cancer. In epidemiological studies, 2 approaches have been taken: one is to only include subjects who were observed 10 years or more after first exposure (latency time), the other approach has been to exclude the last 10 years of exposure (lag time). Berman and Crump[86] looked at the possible decrease in lung cancer risk after exposure cessation. They reanalyzed data from 2 cohorts (Wittenoom miners and South Carolina textiles) and found a striking difference. The Wittenoom cohort exposed to crocidolite had only a marginal decline in lung cancer risk, even after 40 years,[87–89] whereas a decline in RR was seen after 20–30 years in the South Caroline cohort exposed predominantly to chrysotile.[50] Limited evidence suggests that lung cancer risk may be reduced or absent 7–15 years after the cessation of asbestos exposure.[90] Due to limited evidence, we concluded that it is likely that lung cancer risk decreases decades after exposure cessation.

Statement 10: Lung cancer risk decreases decades after the cessation of exposure (+).

Statement 11: No minimal latency time for ARLC has been established. For practical purposes, it can be assumed to be 10 years after exposure onset (+).

Carcinogenicity of Fiber Types

The different types of asbestos have been thoroughly studied. All fiber types have been shown to be carcinogenic in laboratory animals.[91] Epidemiological studies of amphibole as well as chrysotile exposed workers have shown varying degrees of increased lung cancer risk.[75,80] In spite of some areas of controversy,[6] we concluded that all types of asbestos fibers should be considered carcinogenic.

Statement 13: All types of asbestos fibers are associated with lung cancer risk (+++).

Statement 14: Different exposure-response estimates for lung cancer have been reported according to fiber type (amphibole vs chrysotile), size, distribution, and industry. However, these patterns are not clear, when study quality is taken into account. Thus, there is not sufficient evidence to derive different risk estimates for different fiber types (++).

Competing and predisposing conditions

Diseases and Conditions Influencing the Development of ARLC

Lung cancer develops in a minority of individuals exposed to carcinogens such as asbestos or tobacco smoke. This suggests that individual susceptibility is important. Family history of lung cancer predicts lung cancer risk.[92,93] The genetics and molecular epidemiology of lung cancer are actively being investigated. However, present knowledge is insufficient to calculate susceptibility when evaluating most cases of potential ARLC.

Pulmonary fibrosis is associated with an increased lung cancer risk.[94,95] The presence of asbestosis is associated with considerable asbestos exposure, sufficient to cause ARLC.[45] Pulmonary tuberculosis has also been associated with increased lung cancer risk.[25] Those with a primary cancer have an increased risk of developing a second primary cancer, including lung cancer.[96–101] Numerous studies have demonstrated associations between lung cancer risk and chronic obstructive pulmonary disease (COPD).[95a] As smoking is the main cause of both, it is difficult to completely control for.

Statement 15: There is insufficient evidence to include predisposing factors (age, sex, and genetics) in the individual apportionment of ARLC (++).

Statement 16: It is rarely relevant to account for other diseases or disorders in individual apportionment assessments in Denmark. However, this does not apply to lung fibrosis of any origin (+++).

Occupational Risk Factors

Asbestos workers have frequently been exposed to other occupational exposures, which should be considered when evaluating ARLC. Welding and polycyclic aromatic hydrocarbons (PAHs) are often encountered. Two epidemiological studies describe a synergistic effect between PAH and asbestos exposure. Gustavsson et al.[102] analyzed 1,042 lung cancer cases. The RR for asbestos exposure was 1.61, for combustion products 1.67, and for both exposures 2.24, suggesting an additive effect. In a case-control study of 204 lung cancer cases Pastorino et al.[103] found a RR for PAH exposure of 1.6, for asbestos exposure 1.9, and for both exposures 3.3 when adjusted for smoking, consistent with a multiplicative effect. However, for compensation purposes, it is preferable to use attributable fraction for the occupational carcinogens one has been exposed to and not only rely on RR.

Statement 17: Assessment of work-related risk for lung cancer needs to consider all established occupational lung carcinogens in the individual case (+++).

Environmental Risk Factors

Radon and air pollution have been associated to increased lung cancer risks. The excess risk of lung cancer from exposure to radon is dose-dependent and ranges between 2% and 25% per 100 Bq/m^3.[104] About 25% of houses in Denmark are estimated to have a radon concentration >100 Bq/m^3 and 5% above 200 Bq/m^3.[105] Using estimates of radon deaths from a British study,[106] the number of annual deaths in the Danish population attributable to radon is estimated to be about 240, the majority of this being the joint effect of radon and smoking. With regard to air pollution, it has been estimated that 1–2% of lung cancer cases in Denmark may be related to

air pollution, which corresponds to 35–70 cases annually in Denmark.[92,94,107–109] As exposure ranges are generally low in Denmark, they can usually be discounted when considered ARLC apportionment.

Statement 18: In Denmark, there is no need to include environmental radon and air pollution exposures in individual apportionment assessments of ARLC (++).

Nonoccupational/Environmental Asbestos Exposure and Lung Cancer

Nonoccupational/environmental asbestos exposure is not significantly related to lung cancer except in special circumstances, eg, household exposure from asbestos workers, areas with very high exposures (residence near mines or processing plants), and areas where asbestos occurs naturally in the soil. The level of environmental asbestos exposure in Denmark is not known, but based on Dutch and English studies the background level in outdoor city air is about 0.0001–0.0005 f/mL.[110] This is in orders of magnitude below the levels measured in occupational settings on which risk is assessed and extrapolated. The World Health Organization (WHO) estimates that based on a life time exposure of 1,000 f/mL^3 (0.001 f/mL), the excess lung cancer risk would be in order of 10^{-6} to 10^{-5}.[111] In Denmark, this would account for 10 out of 3,600 lung cancer deaths, assuming exposure levels about 10 times higher than expected based on exposure measurements from comparable countries.

Statement 19: In Denmark, there is no evidence that nonoccupational asbestos exposure is associated with lung cancer (+++).

Interaction Between Asbestos and Smoking

Data on the interaction between asbestos exposure and smoking and their joint impact on lung cancer risk are inconsistent. Some studies have suggested a multiplicative effect,[112–114] others an additive model.[115] Studies from the 1970s or earlier based on populations with very high asbestos exposures tended to support the multiplicative model. Later studies with low or moderate exposures tend to conclude that the effect is "more than additive and less than multiplicative."[116,117] This rather imprecise statement seems to represent the present state of knowledge. Risk expressed as attributable proportion due to asbestos among never-smokers has been estimated at approximately 30–40%. Recent data from Great Britain with exposure levels and regulations comparable to Denmark are in accordance with that, and showed that risk attributable to the combined effect of asbestos and smoking was 96% among smoking asbestos workers.[25] Thus, about 96% of lung cancer deaths could have been avoided by avoiding both asbestos and smoking.

Statement 20: Asbestos-exposed smokers are at higher risk of lung cancer compared with asbestos-exposed nonsmokers (+++).

Statement 21: 20 years after smoking cessation, the relative risk of lung cancer due to smoking is reduced by about 90% (+++).

COMMENT

Asbestos is one of the most carefully characterized and researched occupational hazards. Numerous risk assessment models have been developed in an attempt to provide reliable information about workplace lung cancer risks. In spite of these efforts, important knowledge gaps exist, generating both scientific interest and difficulties in establishing regulations. Some of the key issues concern the validity of exposure assessments, the validity of outcome measures, as well as study bias, confounding, and effect modification.

In our systematic review, we have attempted to be thorough and critical. However, our review has some limitations. The existing literature is massive. Only one experienced physician did all the rough reference sorting. A team of sorters may have produced a more systematic process. It would have been desirable to have had additional articles read and graded by 2 reviewers, but was not possible due to time and financial limitations. However, we feel that our results are robust, as both internal and external highly qualified reviewers were part of the process. In addition, 3 standard grade systems were used.

Asbestos exposure

Methods for both sampling and analyzing of asbestos have changed dramatically through the years. Unfortunately, these developments have introduced substantial uncertainties that still are difficult to overcome. Exposure misclassifications may make it difficult or impossible to demonstrate true associations between exposures and effects. Systematic misclassification may lead to risk estimates that are either too low or too high. True associations may be masked by random misclassifications. Some of the key reasons for uncertainty are discussed below.

Thin fibers, width less than 0.25 μm, are more carcinogenic than thicker ones.[118,119] Unfortunately, early airborne concentration measurements using phase-contrast microscopy (PCM) did not account for these thin fibers, potentially underestimating asbestos exposures to the thinnest fibers. As PCM cannot identify thin fibers, incorrect risk attributions may be attributed to the countable thicker fibers. Including these less biologically relevant exposures in most cases leads to an overestimation of the exposure, and thereby to a less steep exposure-response curve.

There are more than 30 "standard" methods of analyzing asbestos fibers. The same sample analyzed by different methods can vary 2 or 3 orders of magnitude.[120] A US program for standardizing the testing and measurements of asbestos samples (The National Voluntary Laboratory Accreditation Program) was first introduced in 1976. Many of the measurements in epidemiological studies were obtained before 1976.

In many studies, the asbestos fiber measurements methods have been unclear. In earlier studies, stationary or area samples have predominated, whereas personal samplers have been the standard during the last decades. Area samples are less connected to individual exposures, and may either under- or overestimate. Besides, it has often been unclear if the measurement was taken to evaluate worst cases or aimed at being representative for a typical working day. Worst-case measurements tend to overestimate exposures. Lack of data concerning local ventilation and respiratory protection adds additional uncertainties when using area sampling to estimate personal exposures. Measurements from one job may be used to estimate exposures at other jobs, other shifts, or time periods, which may add uncertainties that cannot be adequately evaluated. In addition, work histories are often incomplete, with possible job misclassifications. Relative air concentrations of amphibole and chrysotile are often unknown. The relative amounts of purchased amphibole and chrysotile have been used as a proxy.

There have been numerous attempts to convert historical air measurements to newer units. There have been 2 types of conversion attempts. Midget impinger dust counts have been converted to PCM fiber counts. Based on paired analyses, conversion multipliers are generated. A number of studies have used 1 mppcf = 3 f/mL. However, generated conversion factors from parallel sampling have actually ranged between 0.1 and 52.[121]

The other conversion area has been from total fiber counts to specific fiber counts with fiber type, length, and diameter. These specific fiber counts were made with transmission electron microscopy (TEM) starting around 1980, but this technique is still not a routine method for monitoring occupational asbestos exposures. These measurements were applied to earlier epidemiological studies where exposures were judged to be similar. Thus, measurements from one time and place are applied to another time and place. Additional uncertainties arise when PCM fiber data are converted to TEM exposures. There is only a reasonable correlation for fibers >5 μm in length. TEM measurements have shown substantial variation in the ratio of total fibers to fibers over 5 μm, which can vary from 2 to >130.[122] Thus there is generally poor correlation between PCM and TEM measurements.

Reliability and validity of outcome measurements

The reliability and validity of outcome measurements are associated with uncertainties. In the cohort studies, standardized mortality ratio (SMR) has mainly been used to estimate RR. Using SMR induces variation, as the comparison is made with a hypothetical population with the same age distribution as the exposed cohort, and not that of the background population. In elderly cohorts,[52,57] this will automatically tend to give SMRs close to 100 due to high background mortality.[123] Very high exposure levels give rise to high absolute rates of cancer as well as competing risks (ie, for asbestosis). As you can only die once, this may tend to underestimate the risk, when interpolating to lower levels.

Smoking is the main risk factor for lung cancer and the interaction with asbestos is still not totally clear. Very few studies have sufficient information on smoking habits. Others looking especially at this interaction have come to various results. However, the initial pure multiplicative effect claimed by Hammond et al in 1979[112] has never been reproduced. A model somewhere between additive and multiplicative is the most likely. This has some effect on the estimated relative etiological fractions due to smoking and asbestos but not least on the common estimated risk in the epidemiological studies.

Exposure-response analyses

Analysis of exposure-response relationships implies a hypothesis in the form of a curve. A linear model has been the primary model where the RR increases steadily with the exposure (in f-y/mL). In a formula, this can be shown as $RR_{exp\,i} = 1 + k_L \times exp_i$. This model suggests that RR is 1 when exposure is 0, and k_L denotes the increase in RR per unit of exposure measure, ie, the potency of carcinogenity. However, as the investigated population is not always compatible with the reference population a constant link is inserted: $RR_{exp\,i} = a_i\,(1 + k_L \times exp_i)$ where a_i is the RR of population i with no exposure. In the case of lung cancer, a_i >1 is often assumed to be due to more smoking in the exposed population than in the reference population. However, it may also be due to misclassification of exposure. Various ways of expressing k_L have been shown in different articles. In the present paper, all these have been expressed as the number $\times\ 10^{-3}$ $(\text{f-y/mL})^{-1}$ (ie, n excess cases in 1,000 persons for each increase in f-y/mL).

A very large variation in the exposure-response calculated increase per f-y/mL has been shown ranging from almost zero in Quebec miners,[57] over high values in the textile factories,[53] to very high values in a Swedish case-control study.[70,73] Therefore, the estimated exposures tend to be much lower, and more in agreement with the exposure of the more recent lung cancer cases. The very high k_L (140×10^{-3} $(\text{f*y/mL})^{-1}$) of Gustavsson is mainly based on exposures below 5 f-y/mL, whereas most studies in the meta-analyses have much higher exposures.[79,81,82] The other case-control study[71] showed an intermediary k_L (40×10^{-3} $(\text{f-y/mL})^{-1}$) and suggested a curve linear exposure-response in accordance with the Swedish study. A joint ongoing analysis of several case-control studies (SYNERGY) will be anticipated to get a better estimate of k_L in these low exposures in various jobs.[124] Preliminary results from the SYN-JEM exposure matrix based on 14 case-control studies showed increased lung cancer risk among nonsmoking asbestos-exposed workers. Both smoking and other occupational exposures exerted only minor confounding effects.[125]

Based on the reviews and meta-analyses, it seems that k_L increases with increasing study quality. The best estimate may be taken from Lenters et al.[81] and the Dutch position pa-

per,[126] k_L being 4–6 × 10^{-3} (f-y/mL)$^{-1}$ calculated to double lung cancer risk at 150–250 f-y/mL, a k_L considerably lower than estimated from the more recent case-control studies. Therefore, weighing the evidence between a series of mainly older studies based on high asbestos concentrations in selected trades and a few newer studies with lower exposures with various tasks in different jobs is still an enigma.

Conclusion

There is not enough evidence to include age, sex, or family lung cancer history when evaluating cases of potential asbestos-related lung cancer. Nor should most other diseases be taken into consideration except for lung fibrosis. Exposure to radon and air pollution in Denmark is generally low and thus should not be considered when evaluating individual cases of possible asbestos-related lung cancer. The association between asbestos exposure and lung cancer risk is basically linear, but may level off at very high exposures. Many studies demonstrate that the relative risk for lung cancer increases between 1% and 4% per f-y/mL, corresponding to a doubling of risk at 25–100 f-y/mL. However, one high-quality study has shown a doubling of lung cancer risk at about 4 f-y/mL.

Cell type and location of lung cancer are not helpful in differentiating asbestos-related lung cancer from other lung cancers. The presence of pleural plaques, asbestos bodies, or asbestos fibers is useful as markers of asbestos exposure and as such is helpful in supporting previous asbestos exposure. All asbestos types are associated with lung cancer. The interaction between asbestos and smoking regarding lung cancer risk is between additive and multiplicative.

The results of this systematic review are generally in accordance with the Helsinki criteria.

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References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61:69–90.
2. International Agency for Research on Cancer. *World Cancer Report*. Lyon, France: International Agency for Research on Cancer; 2003.
3. NordCan. *The Association of the Nordic Cancer Registries (Denmark)*. Available at: http://www-dep.iarc.fr/NORDCAN/English/frame.asp. Accessed June 2013. 2012.
4. International Agency for Research on Cancer (IARC). *Asbestos (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite, and Anthophyllite). IARC Monographs on Evaluation of Carcinogenic Risks to Humans*. Vol. 100c. Lyon, France: IARC; 2012.
5. Shukla A, Gulumian M, Hei TK, Kamp D, Rahman Q, Mossman BT. Multiple roles of oxidants in the pathogenesis of asbestos-induced diseases. *Free Radic Biol Med*. 2003;34:1117–1129.
6. Bernstein DM, Hoskins JA. The health effects of chrysotile: current perspective based upon recent data. *Regul Toxicol Pharmacol*. 2006;45:252–264.
7. Churg A. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. *N Engl J Med*. 1998;339:999; author reply 1001–1002.
8. Jaurand MC, Bignon J, Sebastien P, Goni J. Leaching of chrysotile asbestos in human lungs. Correlation with in vitro studies using rabbit alveolar macrophages. *Environ Res*. 1977;14:245–254.
9. Roggli VL, Brody AR. Changes in numbers and dimensions of chrysotile asbestos fibers in lungs of rats following short-term exposure. *Exp Lung Res*. 1984;7:133–147
10. Hesterberg TW, Chase G, Axten C, et al. Biopersistence of synthetic vitreous fibers and amosite asbestos in the rat lung following inhalation. *Toxicol Applied Pharmacol*. 1998;151:262–275.
11. Tossavainen A. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. *Scand J Work Environ Health*. 1997;23:311–316.
12. Scottish Intercollegiate Guideline Network. *SIGN 50: A Guideline Developer's Handbook. Revised edition*. Available at: http://www.sign.ac.uk/pdf/sign50.pdf. Accessed August 2012. 2011.
13. PEROSH. OSH Evidence. Clearinghouse of Systematic Reviews. *Methods*. (Updated). 2012. Available at: http://www.perosh.eu/wp-content/uploads/2013/06/PEROSH-OSH-Evidence-Methods_Last-update-sep-12.pdf. Accessed August 2012.
14. Anttila S, Karjalainen A, Taikina-aho O, Kyyronen P, Vainio H. Lung cancer in the lower lobe is associated with pulmonary asbestos fiber count and fiber size. *Environ Health Perspect*. 1993;101:166–170.
15. Hillerdal G, Karlen E, Aberg T. Tobacco consumption and asbestos exposure in patients with lung cancer: a three year prospective study. *Br J Ind Med*. 1983;40:380–383.
16. Sluis-Cremer GK. The relationship between asbestosis and bronchial cancer. *Chest*. 1980;78(2 Suppl):380–381.
17. Weiss W. Lung cancer and occupational lung disease. *Clin Chest Med*. 1981;2:289–300.
18. Hiraoka K, Horie A, Kido M. Study of asbestos bodies in Japanese urban patients. *Am J Ind Med*. 1990;18:547–554.
19. Johansson L, Albin M, Jakobsson K, Mikoczy Z. Histological type of lung carcinoma in asbestos cement workers and matched controls. *Br J Ind Med*. 1992;49:626–630.
20. Warnock ML, Isenberg W. Asbestos burden and the pathology of lung cancer. *Chest*. 1986;89:20–26.
21. Auerbach O, Garfinkel L, Parks VR. Histologic type of lung cancer and asbestos exposure. *Cancer*. 1984;54:3017–3021.
22. Whitwell F, Newhouse ML, Bennett DR. A study of the histological cell types of lung cancer in workers suffering from asbestosis in the United Kingdom. *Br J Ind Med*. 1974;31:298–303.
23. Hourihane DO, McCaughey WT. Pathological aspects of asbestosis. *Postgrad Med J*. 1966;42:613–622.
24. Raffn E, Lynge E, Korsgaard B. Incidence of lung cancer by histological type among asbestos cement workers in Denmark. *Br J Ind Med*. 1993;50:85–89.
25. Weill D, Dhillon G, Freyder L, Lefante J, Glindmeyer H. Lung function, radiological changes and exposure: analysis of ATSDR data from Libby, MT, USA. *Eur Respir J*. 2011;38:376–383.
26. Brodkin CA, McCullough J, Stover B, et al. Lobe of origin and histologic type of lung cancer associated with asbestos exposure in the Carotene and Retinol Efficacy Trial (CARET). *Am J Ind Med*. 1997;32:582–591.
27. Gonzalez M, Vignaud JM, Clement-Duchene C, et al. Smoking, occupational risk factors, and bronchial tumor location: a possible impact for lung cancer computed tomography scan screening. *J Thoracic Oncol*. 2012;7:128–136.
28. Karjalainen A, Pukkala E, Kauppinen T, Partanen T. Incidence of cancer among Finnish patients with asbestos-related pulmonary or pleural fibrosis. *Cancer Causes Control*. 1999;10:51–57.
29. Lee BW, Wain JC, Kelsey KT, Wiencke JK, Christiani DC. Association of cigarette smoking and asbestos exposure with location and histology of lung cancer. *Am J Respir Crit Care Med*. 1998;157(3 Pt 1):748–755.
30. Paris C, Benichou J, Saunier F, et al. Smoking status, occupational asbestos exposure and bronchial location of lung cancer. *Lung Cancer (Amsterdam, Netherlands)*. 2003;40:17–24.

31. Hansen NC. *Personal communication*. 2013.
32. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395–409.
33. Midthun DE. Screening for lung cancer. *Clin Chest Med*. 2011;32:659–668.
34. Saghir Z, Dirksen A, Ashraf H, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax*. 2012;67:296–301.
35. Nieuwenhuijsen MJ. *Exposure Assessment in Occupational and Environmental Epidemiology*. New York: Oxford University Press; 2003.
36. Peters S, Vermeulen R, Cassidy A, et al. Comparison of exposure assessment methods for occupational carcinogens in a multi-centre lung cancer case-control study. *Occup Environ Med*. 2011;68:148–153.
37. Teschke K, Olshan AF, Daniels JL, et al. Occupational exposure assessment in case-control studies: opportunities for improvement. *Occup Environ Med*. 2002;59:575–593; discussion 594.
38. McGuire V, Nelson LM, Koepsell TD, Checkoway H, Longstreth WT Jr. Assessment of occupational exposures in community-based case-control studies. *Annu Rev Public Health*. 1998;19:35–53.
39. Hillerdal G, Henderson DW. Asbestos, asbestosis, pleural plaques and lung cancer. *Scand J Work Environ Health*. 1997;23:93–103.
40. Larson TC, Meyer CA, Kapil V, et al. Workers with Libby amphibole exposure: retrospective identification and progression of radiographic changes. *Radiology*. 2010;255:924–933.
41. De Vuyst P, Dumortier P, Moulin E, Yourassowsky N, Yernault JC. Diagnostic value of asbestos bodies in bronchoalveolar lavage fluid. *Am Rev Respir Dis*. 1987;136:1219–1224.
42. Finnish Institute of Occupational Health. *Proceedings of an International Expert Meeting on Asbetsos, Asbestosis and Lung Cancer. People and Work Research Report 14*. Helsinki: Finnish Institute of Occupational Health; 1997.
43. Sebastien P, Armstrong B, Monchaux G, Bignon J. Asbestos bodies in bronchoalveolar lavage fluid and in lung parenchyma. *Am Rev Respir Dis*. 1988;137:75–78.
44. American Thoracic Society. Diagnosis and initial management of nonmalignant diseases related to asbestos. *Am J Respir Crit Care Med*. 2004;170:691–715.
45. Hessel PA, Gamble JF, McDonald JC. Asbestos, asbestosis, and lung cancer: a critical assessment of the epidemiological evidence. *Thorax*. 2005;60:433–436.
46. Elliott L, Loomis D, Dement J, Hein MJ, Richardson D, Stayner L. Lung cancer mortality in North Carolina and South Carolina chrysotile asbestos textile workers. *Occup Environ Med*. 2012;69:385–390.
47. Albin M, Jakobsson K, Attewell R, Johansson L, Welinder H. Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. *Br J Ind Med*. 1990;47:602–610.
48. Clin B, Morlais F, Launoy G, et al. Cancer incidence within a cohort occupationally exposed to asbestos: a study of dose-response relationships. *Occup Environ Med*. 2011;68:832–836.
49. Dement JM, Brown DP, Okun A. Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses. *Am J Ind Med*. 1994;26:431–447.
50. Dement JM, Harris Jr RL, Symons MJ, Shy C. Estimates of dose-response for respiratory cancer among chrysotile asbestos textile workers. *Ann Occup Hyg*. 1982;26:869–887.
51. Deng Q, Wang X, Wang M, Lan Y. Exposure-response relationship between chrysotile exposure and mortality from lung cancer and asbestosis. *Occup Environ Med*. 2012;69:81–86.
52. Enterline PE, Hartley J, Henderson V. Asbestos and cancer: a cohort followed up to death. *Br J Ind Med*. 1987;44:396–401.
53. Hein MJ, Stayner LT, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. *Occup Environ Med*. 2007;64:616–625.
54. Hughes JM, Weill H, Hammad YY. Mortality of workers employed in two asbestos cement manufacturing plants. *Br J Ind Med*. 1987;44:161–174.
55. Lacquet LM, van der Linden L, Lepoutre J. Roentgenographic lung changes, asbestosis and mortality in a Belgian asbestos-cement factory. *IARC Sci Publ*. 1980(30):783–793.
56. Levin JL, McLarty JW, Hurst GA, Smith AN, Frank AL. Tyler asbestos workers: mortality experience in a cohort exposed to amosite. *Occup Environ Med*. 1998;55:155–160.
57. Liddell FD, McDonald AD, McDonald JC. The 1891–1920 birth cohort of Quebec chrysotile miners and millers: development from 1904 and mortality to 1992. *Ann Occup Hyg*. 1997;41:13–36.
58. Loomis D, Dement JM, Wolf SH, Richardson DB. Lung cancer mortality and fibre exposures among North Carolina asbestos textile workers. *Occup Environ Med*. 2009;66:535–542.
59. McDonald AD, Fry JS, Woolley AJ, McDonald JC. Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. *Br J Ind Med*. 1983;40:368–374.
60. McDonald AD, Fry JS, Woolley AJ, McDonald JC. Dust exposure and mortality in an American chrysotile asbestos friction products plant. *Br J Ind Med*. 1984;41:151–157.
61. Peto J. Lung cancer mortality in relation to measured dust levels in an asbestos textile factory. *IARC Sci Publ*. 1980(30):829–836.
62. Peto J, Doll R, Hermon C, Binns W, Clayton R, Goffe T. Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. *Ann Occup Hyg*. 1985;29:305–355.
63. Pira E, Pelucchi C, Piolatto PG, Negri E, Bilei T, La Vecchia C. Mortality from cancer and other causes in the Balangero cohort of chrysotile asbestos miners. *Occup Environ Med*. 2009;66:805–809.
64. Seidman H, Selikoff IJ, Gelb SK. Mortality experience of amosite asbestos factory workers: dose-response relationships 5 to 40 years after onset of short-term work exposure. *Am J Ind Med*. 1986;10:479–514.
65. Selikoff IJ, Seidman H. Asbestos-associated deaths among insulation workers in the United States and Canada, 1967–1987. *Ann N Y Acad Sci*. 1991;643:1–14.
66. Sluis-Cremer GK. Asbestos disease at low exposures after long residence times. *Ann N Y Acad Sci*. 1991;643:182–193.
67. Sluis-Cremer GK, Liddell FD, Logan WP, Bezuidenhout BN. The mortality of amphibole miners in South Africa, 1946–80. *Br J Ind Med*. 1992;49:566–575.
68. Stayner L, Smith R, Bailer J, et al. Exposure-response analysis of risk of respiratory disease associated with occupational exposure to chrysotile asbestos. *Occup Environ Med*. 1997;54:646–652.
69. Sullivan PA. Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: update of a cohort mortality study. *Environ Health Perspect*. 2007;115:579–585.
70. Gustavsson P, Nyberg F, Pershagen G, Scheele 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. *Am J Epidemiol*. 2002;155:1016–1022.
71. Pohlabeln H, Wild P, Schill W, et al. Asbestos fibre years and lung cancer: a two phase case-control study with expert exposure assessment. *Occup Environ Med*. 2002;59:410–414.
72. Berry G, Newhouse ML. Mortality of workers manufacturing friction materials using asbestos. *Br J Ind Med*. 1983;40:1–7.
73. Gustavsson P, Jakobsson R, Nyberg F, Pershagen G, Jarup L, Scheele P. Occupational exposure and lung cancer risk: a population-based case-referent study in Sweden. *Am J Epidemiol*. 2000;152:32–40.
74. Clin B, Morlais F, Launoy G, et al. Cancer incidence within a cohort occupationally exposed to asbestos: a study of dose–response relationships. *Occup Environ Med*. 2011;68:832–836.
75. Henderson DW, Rodelsperger K, Woitowitz HJ, Leigh J. After Helsinki: a multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997–2004. *Pathology*. 2004;36:517–550.
76. Pierce JS, McKinley MA, Paustenbach DJ, Finley BL. An evaluation of reported no-effect chrysotile asbestos exposures for lung cancer and mesothelioma. *Crit Rev Toxicol*. 2008;38:191–214.
77. Steenland K, Stayner L. Silica, asbestos, man-made mineral fibers, and cancer. *Cancer Causes Control*. 1997;8:491–503.
78. Goodman M, Morgan RW, Ray R, Malloy CD, Zhao K. Cancer in asbestos-exposed occupational cohorts: a meta-analysis. *Cancer Causes Control*. 1999;10:453–465.
79. Lash TL, Crouch EA, Green LC. A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. *Occup Environ Med*. 1997;54:254–263.
80. Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg*. 2000;44:565–601.
81. Lenters V, Vermeulen R, Dogger S, et al. A meta-analysis of asbestos and lung cancer: is better quality exposure assessment associated with steeper slopes of the exposure-response relationships? *Environ Health Perspect*. 2011;119:1547–1555.

82. van der Bij S, Koffijberg H, Lenters V, et al. Lung cancer risk at low cumulative asbestos exposure: meta-regression of the exposure-response relationship. *Cancer Causes Control*. 2013;24(1):1–12. doi: 10.1007/s10552-012-0107-7. Epub 2012 Nov 28.
83. Berman DW, Crump KS. A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. *Crit Rev Toxicol*. 2008;38(Suppl 1):49–73.
84. Browne K. A threshold for asbestos related lung cancer. *Br J Ind Med*. 1986;43:556–558.
85. van der Bij S, Koffijberg H, Lenters V, et al. Lung cancer risk at low asbestos exposure: meta-regression of the exposure-response relationship. *Occup Environ Med*. 2011;68:A21.
86. Berman DW, Crump KS. Update of potency factors for asbestos-related lung cancer and mesothelioma. *Crit Rev Toxicol*. 2008;38(Suppl 1):1–47.
87. Armstrong BK, de Klerk NH, Musk AW, Hobbs MS. Mortality in miners and millers of crocidolite in Western Australia. *Br J Ind Med*. 1988;45:5–13.
88. de Klerk NH, Armstrong BK, Musk AW, Hobbs MS. Cancer mortality in relation to measures of occupational exposure to crocidolite at Wittenoom Gorge in Western Australia. *Br J Ind Med*. 1989;46:529–536.
89. Musk AW, de Klerk NH, Reid A, et al. Mortality of former crocidolite (blue asbestos) miners and millers at Wittenoom. *Occup Environ Med*. 2008;65:541–543.
90. Sanden A, Jarvholm B, Larsson S, Thiringer G. The risk of lung cancer and mesothelioma after cessation of asbestos exposure: a prospective cohort study of shipyard workers. *Eur Respir J*. 1992;5:281–285.
91. Stayner LT, Dankovic DA, Lemen RA. Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. *Am J Public Health*. 1996;86:179–186.
92. Fucic A, Gamulin M, Ferencic Z, et al. Lung cancer and environmental chemical exposure: a review of our current state of knowledge with reference to the role of hormones and hormone receptors as an increased risk factor for developing lung cancer in man. *Toxicol Pathol*. 2010;38:849–855.
93. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. *Br J Cancer*. 2005;93:825–833.
94. Alberg AJ, Ford JG, Samet JM. Epidemiology of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl):29S–55S.
95. Archontogeorgis K, Steiropoulos P, Tzouvelekis A, Nena E, Bouros D. Lung cancer and interstitial lung diseases: a systematic review. *Pulm Med*. 2012;2012:315918.
96. Kaufman EL, Jacobson JS, Hershman DL, Desai M, Neugut AI. Effect of breast cancer radiotherapy and cigarette smoking on risk of second primary lung cancer. *J Clin Oncol*. 2008;26:392–398.
97. Richardson GE, Tucker MA, Venzon DJ, et al. Smoking cessation after successful treatment of small-cell lung cancer is associated with fewer smoking-related second primary cancers. *Ann Intern Med*. 1993;119:383–390.
98. Tucker MA, Murray N, Shaw EG, et al. Second primary cancers related to smoking and treatment of small-cell lung cancer. Lung Cancer Working Cadre. *J Natl Cancer Inst*. 1997;89:1782–1788.
99. Chen MC, Chen PT, Chan CH, et al. Second primary esophageal or lung cancer in patients with head and neck carcinoma in Taiwan: incidence and risk in relation to primary index tumor site. *J Cancer Res Clin Oncol*. 2011;137:115–123.
100. Chuang SC, Hashibe M, Scelo G, et al. Risk of second primary cancer among esophageal cancer patients: a pooled analysis of 13 cancer registries. *Cancer Epidemiol Biomarkers Prev*. 2008;17:1543–1549.
101. Youlden DR, Baade PD. The relative risk of second primary cancers in Queensland, Australia: a retrospective cohort study. *BMC Cancer*. 2011;11:83.
102. Gustavsson P, Ahlbom A, Andersson T, Scheele P. Calculation of fractions of lung cancer incidence attributable to occupational exposure to asbestos and combustion products in Stockholm, Sweden. *Eur J Epidemiol*. 2003;18:937–940.
103. Pastorino U, Berrino F, Gervasio A, Pesenti V, Riboli E, Crosignani P. Proportion of lung cancers due to occupational exposure. *Int J Cancer*. 1984;33:231–237.
104. Krewski D, Lubin JH, Zielinski JM, et al. A combined analysis of North American case-control studies of residential radon and lung cancer. *J Toxicol Environ Health A*. 2006;69:533–597.
105. Andersen CE, Ulbak K, Damkjaer A, Gravesen P. *Radon in Danish houses: A Survey of National, Regional and Municipal Measurements*. Copenhagen: National Board of Health, Institute for Radiation Protection; January 2012. (In Danish)
106. Darby S. Residential radon, smoking and lung cancer. *Radiat Res*. 2005;163:696.
107. Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, et al. Lung cancer incidence and long-term exposure to air pollution from traffic. *Environ Health Perspect*. 2011;119:860–855.
108. Raaschou-Nielsen O, Bak H, Sorensen M, et al. Air pollution from traffic and risk for lung cancer in three Danish cohorts. *Cancer Epidemiol Biomarkers Prev*. 2010;19:1284–1291.
109. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst*. 1981;66:1191–1308.
110. Environmental Protection Agency. *Asbestos Fibers in the Ground: An Assessment of Their Destiny and Health Risk*. Copenhagen: Environmental Protection Agency; 2008. (In Danish)
111. World Health Organization. *Air Quality Guidelines for Europe. 2nd ed.* World Health Organization Regional Publications, European Series, No. 91. Geneva: World Health Organization; 2000.
112. Hammond EC, Selikoff IJ, Seidman H. Asbestos exposure, cigarette smoking and death rates. *Ann N Y Acad Sci*. 1979;330:473–490.
113. Lee PN. Relation between exposure to asbestos and smoking jointly and the risk of lung cancer. *Occup Environ Med*. 2001;58:145–153.
114. Erren TC, Jacobsen M, Piekarski C. Synergy between asbestos and smoking on lung cancer risks. *Epidemiology*. 1999;10:405–411.
115. Samet JM, Epler GR, Gaensler EA, Rosner B. Absence of synergism between exposure to asbestos and cigarette smoking in asbestosis. *Am Rev Respir Dis*. 1979;120:75–82.
116. 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. *Occup Environ Med*. 2006;63:509–512.
117. Wraith D, Mengersen K. Assessing the combined effect of asbestos exposure and smoking on lung cancer: a Bayesian approach. *Stat Med*. 2007;26:1150–1169.
118. Stanton MF, Layard M, Tegeris A, et al. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. *J Natl Cancer Inst*. 1981;67:965–975.
119. Stayner L, Kuempel E, Gilbert S, Hein M, Dement J. An epidemiological study of the role of chrysotile asbestos fibre dimensions in determining respiratory disease risk in exposed workers. *Occup Environ Med*. 2008;65:613–619.
120. Brattin WJ. *Proposed Approach for Estimation of Bin-Specific Cancer Potency Factors for Inhalation Exposure to Asbestos*. Washington, DC: US Environmental Protection Agency Office of Solid Waste and Emergency Response; 2008. Contract GS-00F-0019L.
121. Berman DW, Crump KS. Technical support document for a protocol to assess asbestos-related risk. Prepared for US Environmental Protection Agency Office of Solid Waste and Emergency Response. *EPA* 93454–06. 2003.
122. Dement J, Wallingford K. Comparison of phase contrast and electron microscopis methods for evaluation of asbestos exposure. *Appl Occup Environ Hyg*. 1990;5:242–247.
123. Langard S, Lee LJ. Methods to recognize work-related cancer in workplaces, the general population, and by experts in the clinic, a Norwegian experience. *J Occup Med Toxicol*. 2011;6:24. doi: 10.1186/1745-6673-6-24.
124. Peters S, Vermeulen R, Olsson A, et al. Development of an exposure measurement database on five lung carcinogens (ExpoSYN) for quantitative retrospective occupational exposure assessment. *Ann Occup Hyg*. 2012;56:70–79.
125. Olsson A. Improved risk estimation through advanced exposure modelling in community-based studies: the example of occupational asbestos exposure in the SYNERGY project. Presented at the 7th International Conference on the Science of Exposure Assessment; Edinburgh, Scotland; July 2–5, 2012.
126. Health Council of the Netherlands. *Asbestos. Risks of Environmental and Occupational Exposure*. The Hague: Health Council of the Netherlands, 2010; publication no. 2010/10E.u.

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Appendix 2.—Research questions

Lung cancer

1. How valid is the diagnosis of lung cancer? (LC1)
2. How has the distribution of lung cancer cell types changed over time? (LC2)
3. Does the distribution of cell type of asbestos-related lung cancer differ from that of other lung cancers? (LC3)
4. Does the location of asbestos-related lung cancer differ from other lung cancers? (LC4)

Asbestos exposure

1. Which jobs and industries can be associated with asbestos exposure? (AE1)
2. Can the presence of bilateral pleural plaques be used to estimate previous asbestos exposure? (AE2)
   a. Can the presence of diffuse pleural thickening be used to estimate previous asbestos exposure? (AE2a)
3. Can the presence of asbestos bodies be used to estimate previous asbestos exposure (AE3)
4. How can the degree of exposure (intensity) been evaluated? (AE3)
5. How can the length of exposure be evaluated? (AE4)

Exposure-response

1. What is the exposure-response and exposure-effect response between asbestos and lung cancer? (ER1).
2. Has a no effect level for asbestos and lung cancer been described in humans or laboratory animals? (ER2)
3. What is the latency between asbestos exposure the development of lung cancer? (ER3)
   a. How does lung cancer risk develop after the cessation of asbestos exposure? (ER3a)
4. What is the prognosis for asbestos-related lung cancer? (ER4)
5. How does the degree of asbestos exposure effect prognosis? (ER5)

Competing and predisposing conditions

1. Which other diseases or conditions can influence the development of asbestos-related lung cancer? (CPC1)
   a. What is the risk of developing lung cancer among those with asbestosis? (CPC1a)
2. What are the nonoccupationally related causes of lung cancer? (CPC2)
3. Is nonoccupational asbestos exposure related to lung cancer? (CPC3)
4. How do other nonoccupationally related factors influence the development of lung cancer (eg, sex, age, genetics)? (CPC4)
5. How can the effect of occupationally related asbestos exposure compared with nonoccupational factors be measured? (CPC5)

Appendix 3.—List of statements including the SIGN grades

Lung cancer (LC)

Statement 1: When evaluating ARLC, location and cell types do not differentiate asbestos-related and non–asbestos-related lung cancer (+++).

Statement 12: The prognosis of ARLC does not differ from that of other lung cancers (+).

Asbestos exposure (AE)

Statement 2: Job exposure matrices (JEMs) are useful in estimating previous asbestos exposure in addition to individual exposure evaluations (+).

Statement 3: The existence of pleural plaques increases the likelihood of previously asbestos exposure (++).

Statement 4: The presence of pleura plaques cannot be used to estimate the degree of previous asbestos exposure (+++).

Statement 5: The presence of asbestosis is a marker of previously high asbestos exposure and is associated with an increased risk of lung cancer (+++).

Exposure-response (ER)

Statement 6: The exposure-response relationship is approximately linear, but levels off at very high exposure levels (>150 f-y/mL) (+++).

Statement 7: An increase in RR of 14% per f-y (corresponding to a doubling of risk at 25–100 f-y/mL) has been observed with the higher estimates obtained in the few high-quality epidemiological studies. One high-quality population-based case-control study in the low-exposure range found a higher risk estimate (a doubling of risk around 4 f-y/mL) (++).

Statement 8: There is no evidence for a no observed effect level (NOEL) concerning ARCL (++).

Statement 9: The lowest documented increased ARLC risk is seen at about 4 f-y (+).

Statement 10: Lung cancer risk decreases decades after the cessation of exposure (+).

Statement 11: No minimal latency time for ARLC has been established. For practical purposes, it can be assumed to be 10 years after exposure onset (+).

Statement 13: All types of asbestos fibers are associated with lung cancer risk (+++).

Statement 14: Different exposure-response estimates for lung cancer have been reported according to fiber type (amphibole vs chrysotile), size, distribution, and industry. However, these patterns are not clear, when study quality is taken into account. Thus, there is not sufficient evidence to derive different risk estimates for different fiber types (++).

Competing and predisposing factors (CPC)

Statement 15: There is insufficient evidence to include predisposing factors (age, sex, and genetics) in the individual apportionment of ARLC (++).

Statement 16: It is rarely relevant to account for other diseases or disorders in individual apportionment assessments in Denmark. However, this does not apply to lung fibrosis of any origin (+++).

Statement 17: Assessment of work-related risk for lung cancer needs to consider all established occupational lung carcinogens in the individual case (+++).

Statement 18: In Denmark, there is no need to include environmental radon and air pollution exposures in individual apportionment assessments (++).

Statement 19: In Denmark, there is no evidence that nonoccupational asbestos exposure is associated with lung cancer (+++).

Statement 20: Asbestos-exposed smokers are at higher risk of lung cancer compared with asbestos-exposed nonsmokers (+++).

Statement 21: 20 years after smoking cessation, the relative risk of lung cancer due to smoking is reduced by about 90% (+++).