Estimating the asbestos-related lung cancer burden from mesothelioma mortality

V McCiomreck1, J Peto2, G Byrnes3, K Straif4 and P Boffetta5,6
1Section of Environment and Radiation, International Agency for Research on Cancer, 150 cours Albert Thomas, Lyon 69008, France; 2Faculty of Epidemiology and Population Health, Department of Epidemiology, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK; 3Biostatistics Group, Section of Genetics, International Agency for Research on Cancer, 150 cours Albert Thomas, Lyon 69008, France; 4Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, Lyon 69008, France; 5Institute for Translational Epidemiology and Tisch Cancer Institute, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029-6574, USA; 6International Prevention Research Institute, Lyon, France

**BACKGROUND:** Quantifying the asbestos-related lung cancer burden is difficult in the presence of this disease’s multiple causes. We explore two methods to estimate this burden using mesothelioma deaths as a proxy for asbestos exposure.

**METHODS:** From the follow-up of 55 asbestos cohorts, we estimated ratios of (i) absolute number of asbestos-related lung cancers to mesothelioma deaths; (ii) excess lung cancer relative risk (%) to mesothelioma mortality per 1000 non-asbestos-related deaths.

**RESULTS:** Ratios varied by asbestos type; there were a mean 0.7 (95% confidence interval 0.5, 1.0) asbestos-related lung cancers per mesothelioma death in crocidolite cohorts (n = 6 estimates), 6.1 (3.6, 10.5) in chrysotile (n = 16), 4.0 (2.8, 5.9) in amosite (n = 4) and 1.9 (1.4, 2.6) in mixed asbestos fibre cohorts (n = 31). In a population with 2 mesothelioma deaths per 1000 deaths at ages 40–84 years (e.g., US men), the estimated lung cancer population attributable fraction due to mixed asbestos was estimated to be 4.0%.

**CONCLUSION:** All types of asbestos fibres kill at least twice as many people through lung cancer than through mesothelioma, except for crocidolite. For chrysotile, widely consumed today, asbestos-related lung cancers cannot be robustly estimated from few mesothelioma deaths and the latter cannot be used to infer no excess risk of lung or other cancers.

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Asbestos is an established human carcinogen, the major effects being on cancers of the lung and mesothelioma of the pleura and peritoneum (IARC, 1987). Inhalation of asbestos fibres predominantly occurs during occupational exposure including in mines, construction, shipyards, railway and textile industries. Restrictions or bans on the use of certain asbestos fibres were introduced in the United States and Europe from the 1980s onwards, but latency periods of several decades mean that the mesothelioma epidemic is yet to peak. In 2000, an estimated 43 000 malignant mesotheliomas worldwide were due to occupational exposures (Driscoll *et al*, 2005), the largest absolute burdens being in the United States, Australia, Japan, New Zealand and Western Europe (Peto *et al*, 1999). Global asbestos (chrysotile) consumption was 2.3 million tonnes in 2003, predominantly in the lower income countries (Virta, 2006). The asbestos-related lung cancer (ARLC) burden is more difficult to quantify as most lung cancers are not attributable to asbestos, unlike for mesothelioma (Bianchi and Bianchi, 2007). ARLCs occur on top of varying lung cancer incidence rates and they are not clinically distinguishable from those not caused by asbestos. Furthermore, reliable population-based data on asbestos exposure (by fibre type, length, age at exposure, intensity) and associated relative risks are not known precisely, preventing the calculation of population attributable fractions (PAFs).

We present two methods to estimate the relationship between ARLC deaths and mesothelioma deaths, using the latter as a proxy for asbestos exposure. The first is the ratio of absolute excess lung cancer deaths to mesothelioma deaths. However with a synergistic interaction between asbestos and smoking on lung cancer, the ARLC burden will be particularly large in settings where smoking rates are high, thus a more appropriate ratio may be a relative effect on lung cancer to the absolute effect on mesothelioma. Using published cohorts of asbestos-exposed workers, we summarise these two ratios by asbestos type to gauge the magnitude of the population-level ARLC burden in different countries.

**MATERIALS AND METHODS**

**Ratio estimates**

We estimated the ratio of asbestos-related lung cancers to mesothelioma deaths from asbestos cohorts. Two ratios were calculated for each cohort. Method 1: the absolute ratio (R1), of the absolute number of ARLC deaths to mesothelioma deaths is estimated by $R_1 = (O_{L+L}/E_{L+L})/O_{M}$, where $O$ and $E$ refer to the observed deaths and expected deaths in the absence of asbestos, with subscripts LC and M referring to lung cancer and...
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RESULTS

Statistical methods

Extracted data were used to calculate \( R_1 \) and \( R_2 \) as defined. Estimates of \( R_1 \) were plotted by asbestos type, with the variance of \( \log(R_1) \) estimated as \((1/E_{\text{LC}} + 1/E_{\text{M}})\) and for \( R_2 \) as \((1/E_{\text{LC}} + 1/O_{\text{M}} + 1/O_{\text{all}})\). Summary values of \( R_1 \) and \( R_2 \) and of SMRs for lung cancers were obtained from a random-effects meta-analysis implemented in STATA version 11. Meta-regression models were used to examine whether the ratio estimates systematically differed between studies, where smoking was controlled for or not. To evaluate which of the ratios \( R_1 \) and \( R_2 \) was most appropriate, we assessed which one explained a greater proportion of the variation when regressing the numerators on the denominators of the respective ratios, weighted by the inverse of the appropriate variances given above.

To apply the ratio estimates to external larger populations, ARLCs were calculated using method 1, as \( R_1 \) times the number of mesothelioma deaths (\( R_1 \times O_{\text{M}}) \), or using method 2, PAFs for lung cancer due to asbestos were calculated as \((1 + 0.1 \times O_{\text{all}}(R_2 \times O_{\text{M}}))^{-1}\). Using these results, we calculated PAF ranges for men aged 40–84 years during years 2001–2005, using the WHO mortality database for selected countries with mortality data coded to ICD-10 (WHOSIS Mortality Database ICD-10, 2009).

Population attributable fraction estimates were based firstly on ratio estimates as provided in Tables 1 and 2, and thereafter on ratio estimates corrected for smoking if smoking had not been accounted for. The correction applied was to reduce ratio estimates by 25% if smoking had not been taken into account, which corresponds to the degree of positive confounding in the lung cancer SMR, resulting from a smoking prevalence of 70% in the asbestos cohort compared with 50% in the general population and a smoking relative risk of 10. This is likely to be an exaggerated correction and thus possibly underestimates ratio and PAF estimates.

RATIO ESTIMATES

Fifty five publications were included, from which 68 risk estimates were reported, 6 for crocidolite, 8 for crocidolite and chrysotile, 14 for predominantly chrysotile, 4 for amosite and 32 to mixed or unspecified asbestos fibres (Table 1, with an extended version in online Supplementary Table 1). In total, follow-up included over 67194 deaths, of which 1963 were from lung cancer and 1962 from mesothelioma. Most studies were conducted in North America or Europe, with only seven in other regions (Japan, Australia, China and South Africa). The two largest cohorts were the insulation workers’ union of the United States and Canada (n = 17 000), and the Great Britain Asbestos Survey of over 98 000 registered asbestos workers (Selikoff and Seidman, 1991; Harding, 2010). Lung cancer SMRs for 78% of cohorts were not adjusted for smoking, other than in a few studies where internal analyses using lung exposed to unexposed subjects adjusted for smoking and in certain cohorts smoking prevalence of workers was noted to be comparable (or not) to that of the general population. We used the proportional mortality ratio in the British Asbestos survey in an attempt to get closer to a smoking-adjusted SMR (estimates 66 and 67).

Figure 1 plots absolute and relative lung cancer excess vs mesotheliomas, that is, the numerator and denominators of ratios \( R_1 \) and \( R_2 \) by asbestos type. Note that axes for each subplot are on different scales, particularly for mesothelioma because of greatly varying mesothelioma-producing potential of the different fibres. The line on each plot corresponds to two excess lung cancer deaths per mesothelioma death, that is, the same ratio across graphs to aid comparison.
Table 1 Crocidolite, chrysotile and amosite asbestos cohorts providing estimates of lung cancer and mesothelioma mortality, by asbestos type

| No. | Cohort description (reference) | N | % Male | Smoking adjustment | Total deaths | Lung cancer deaths (Olc) | Lung cancer SMR | Mesothelioma deaths (Omr) | Ratio R1 | Ratio R2 |
|-----|-------------------------------|---|--------|-------------------|-------------|------------------------|----------------|--------------------------|---------|---------|
| 1   | Canadian gas mask canisters (McDonald and McDonald, 1978) | 199 | NK | N | 55 | 2.92 | 9 | 0.5 | 0.9 |
| 2   | Nottingham gas masks, UK (Jones et al, 1980) | 951 | 0 | N | 166 | 1.90 | 17 | 0.3 | 0.8 |
| 3   | Leyland gas masks UK. Crocidolite, some chrysotile (Acheson et al, 1982) | 757 | 0 | N | 219 | 2.10 | 5 | 1.4 | 4.6 |
| 4   | South African crocidolite mines (Sluis-Cremer et al, 1992) | 3430 | 100 | N | 423 | 2.03 | 20 | 0.7 | 2.0 |
| 5   | Tuscany rail construction Italy (Battista et al, 1999) | 734 | 100 | N | 199 | 1.24 | 5 | 1.0 | 0.9 |
| 6   | Wittenoom mine/mill, Australia (Musk et al, 2008) | 6943 | 100 | C | 2408 | 2.60 | 222 | 0.8 | 1.5 |

Chrysotile and crocidolite

7 Rochdale textile workers, UK. Chrysotile, 5% crocidolite during 1932–1968 (Peto et al, 1985); men, 20+ years employment starting <1933 | 145 | 100 | N | 123 | 20 | 3.61 | 7 | 2.1 | 3.7 |
8 As for 7. Rochdale women, 10+ years employment after 1933 | 283 | 0 | N | 49 | 4 | 2.11 | 0 | No meso. |
9 As for 7. Rochdale principal cohort, men first employed >1933 | 3211 | 100 | N | 1113 | 132 | 1.31 | 11 | 2.9 | 3.1 |
10 New Orleans cement Plant 2, USA (Hughes et al, 1987) | 3594 | 100 | C | 874 | 107 | 1.44 | 4 | 8.2 | 9.2 |
11 Voelkabruck cement workers, Austria (Neuberger and Kundi, 1990) | 2816 | Both | A | 540 | 49 | 1.04 | 4 | 0.5 | 0.6 |
12 Ferodo friction factory, UK. Predominantly chrysotile, crocidolite use for a short period (Berry, 1994) | 13 | 450 | 68 | N | 2577 | 241 | 0.99 | 13 | –0.2 | –0.2 |
13 North Israel cement workers, 90% chrysotile, 10% crocidolite (Tuchinsky et al, 1999) | 3057 | 100 | N | — | 34 | 1.26 | 21 | 0.3 |
14 Norwegian asbestos cement factory. Chrysotile, 8% amphiboles (Ulvestad et al, 2002) | 545 | 100 | N | — | 33 | 3.1 | 18* | 1.2 | — |

Chrysotile (pure or predominantly)

15 Blackburn gas masks, UK. Pure chrysotile (Acheson et al, 1982) | 570 | 0 | N | 177 | 6 | 1.25 | 1 | 1.2 | 4.4 |
16 Wales cement workers. After 1936, chrysotile only. Before 1936, some crocidolite used (Thomas et al, 1982) | 1970 | 100 | N | 351 | 22 | 0.85 | 2* | –1.9 | –2.6 |
17 Connecticut friction industry, USA. Pure chrysotile (McDonald et al, 1984) | 3531 | 100 | N | 803 | 73 | 1.49 | 0 | No meso. |
18 Swedish cement workers. Chrysotile predominantly, <1% amosite/ crocidolite during short periods (Ohlson and Hogstedt, 1985) | 1176 | 100 | C | 220 | 11 | 1.22 | 0 | No meso. |
19 Tamworth cement workers, UK. Chrysotile, with amosite used during 4 months out of 42 years (Gardner et al, 1986) | 2167 | 70 | N | 486 | 41 | 0.97 | 1 | –1.4 | –1.6 |
20 Balanergo mine, Italy. Pure chrysotile (Piolatto et al, 1990) | 1058 | 100 | N | 427 | 22 | 1.11 | 2* | 1.1 | 2.2 |
21 Quebec. Canada: Quebec asbestos factory, chrysotile (Liddell et al, 1997) | 792 | 100 | N | 508 | 49 | 1.34 | 5 | 2.5 | 3.6 |
22 As for 21: Thetford company 3, chrysotile and tremolite | 4732 | 100 | N | 3080 | 280 | 1.45 | 21 | 4.1 | 7.2 |
23 As for 21: Thetford company 4, chrysotile+tremolite | 368 | 100 | N | 267 | 25 | 1.65 | 2 | 4.9 | 9.5 |
24 As for 21: Quebec asbestos mine/mill, chrysotile | 4503 | 100 | N | 2924 | 253 | 1.29 | 8 | 7.1 | 11.8 |
25 Chongjin asbestos workers, China. Pure crocidolite, tremolite | 515 | 100 | A | 132 | 22 | 6.64 | 2 | 9.3 | 31.4 |
26 South Carolina textile workers, USA. Chrysotile, <0.01% crocidolite (Hein et al, 2007) | 3072 | 59 | C | 1961 | 198 | 1.95 | 3 | 32.2 | 58.9 |
27 North Carolina textile plants, USA. Predominantly chrysotile, with some amosite in plant 3 (Loonis et al, 2009) | 5770 | 69 | N | 2583 | 277 | 1.96 | 8* | 16.9 | 29.1 |
28 Greece asbestos cement factory. Chrysotile with 0.5% amphibole contamination (Schleiditsis et al, 2009) | 317 | 100 | N | 52 | 16 | 1.71 | 0 | No meso. |
29 Chrysotile miners, China (Wang X et al, 2011) | 1080 | 100 | A | 343 | 50 | 4.61 | 0 | No meso. |
30 Chrysotile textile workers, China (Wang XR et al, 2011). Medium- and high-exposed groups compared with low-exposed group | 461 | 100 | N | 207 | 46 | 1.83 | 2 | 10.4 | 7.6 |

Asbestos

31 Uxbridge amosite insulation, UK (Acheson et al, 1984) | 4820 | 100 | N | 422 | 57 | 1.96 | 5 | 5.6 | 7.5 |
32 Paterson amosite asbestos factory, NJ, USA (Seidman et al, 1986) | 820 | 100 | N | 593 | 98 | 4.78 | 17 | 4.6 | 11.1 |
33 South African amosite mines (Sluis-Cremer et al, 1992) | 3212 | 100 | N | 648 | 26 | 1.38 | 4 | 1.8 | 6.1 |
34 Tyler pipe insulation, amosite, TX, USA (Levin et al, 1998) | 1130 | 100 | N | 222 | 35 | 2.78 | 6 | 3.7 | 5.7 |

Anthophyllite and vermiculite

35 Finnish anthophyllite mines, Paakkila, Majasalmi (Meurman et al, 1994) | 903 | 82 | N | — | 77 | 2.86 | 4 | 12.5 |
36 Vermiculite mine, Libby Montana, USA (contains tremolite) (Sullivan, 2007) | 1672 | 96 | N | 711 | 89 | 1.69 | 6 | 6.1 | 7.7 |

Abbreviations: A = adjusted; C = smoking prevalence in cohort comparable to the general population; N = none or not mentioned. SMR = standardised mortality ratio. * Pleural mesothelioma only. The two mesotheliomas were in men who were employed before 1936 when exposure to crocidolite was likely. bDeaths 20 years after first employment. cFour cancers of pleura and four mesothelioma (the latter only available from 1999 with ICD10). The four mesotheliomas were in workers who had been employed in plant 4, where there was no record of amphibole use. Three pleural cancers were in plant 3, but these workers had not worked in the insulation section of plant 3, where amosite was used.
In the six crocidolite-exposed cohorts, workers experienced increased lung cancer mortality, of the order of a two-to-three-fold increase (pooled SMR 2.0, Table 3), and increased mesothelioma risk, with mesothelioma deaths contributing to a median of 93.2 per thousand deaths (range 23 – 217). In all but two smaller cohorts, there were less or equivalent numbers of excess lung cancers compared with mesothelioma deaths, giving a combined R₁ estimate of 0.71 ARLC deaths per mesothelioma death (Table 3, Figure 2). The combined estimate of ratio R₂ suggests a 1.2% increase in lung cancer deaths (PAF = 1.2%) associated with crocidolite for every mesothelioma death in 1000 deaths.

For cohorts with a mixture of chrysotile and some crocidolite, mesothelioma risk was also raised but to a lesser extent than for pure crocidolite (7.6 mesothelioma deaths per 1000 non-asbestos-related deaths). Lung cancer risk was increased (SMR 1.58), varying from no lung cancer excess in the Ferodo friction factory (estimate 12) to increases of over three-fold (Table 1 and Figure 2). These combined to give an overall R₁ estimate of 1.44 excess lung cancers per mesothelioma death (Table 3).

**Chrysotile** Chrysotile cohorts had a wider range of estimates, resulting from little correlation between excess lung cancers and mesotheliomas (Figures 1 and 2). Almost all SMRs for lung cancer were between 1 and 2, with two notable exceptions of two Chinese cohorts (estimates 17, 18, 28 and 29, Table 1).
The small denominator and wide range makes ratio estimates of excess lung cancers to mesotheliomas large, but imprecise for chrysotile.

**Amphiboles** In the follow-up of four amosite cohorts, there was a marked correlation between lung cancer SMR and mesothelioma. The combined SMR for lung cancer was 2.5, slightly stronger than that for crocidolite and thus, with a mesothelioma risk approximately one-fifth of that for crocidolite (18 vs 93 mesotheliomas per 1000 deaths in amosite and crocidolite, respectively, Table 3), ratio \( R_1 \) was much higher at 4 excess lung cancers per mesothelioma death (Table 3). Corresponding \( R_2 \) estimates suggest there was between a 6% and 10% increase in lung cancer deaths for every mesothelioma death in 1000 deaths. The largest contributing study was the Paterson amosite factory in New Jersey (estimate 32), where both a large number of mesotheliomas (17 in 820 workers) and a very large excess lung cancer mortality were observed (SMR 4.8) (Seidman et al., 1986). In the only cohort with anthophyllite exposure (estimate 35), there were 12.5 excess lung cancers per mesothelioma death (Meurman et al., 1994).

**Mixed asbestos types** For the majority of cohorts asbestos exposure was mixed and their ratio estimates lay between the corresponding values for pure asbestos fibres. The summary SMR for lung cancer was 1.77 (95% CI 1.44, 2.20), which was less than that for crocidolite or amosite, but larger than that for chrysotile.


Asbestos-related lung cancer burden

### Table

| Asbestos Type | Subtotal (I², P) | Unit | (95% CI) |
|---------------|------------------|------|----------|
| Crocidolite   |                  |      |          |
| 2 – Nottingham gas masks | 0.34 (0.16, 0.70) | 1 – Canada gas mask canisters | 0.51 (0.19, 1.37) |
| 4 – South Africa crocidolite | 0.69 (0.38, 1.22) | 6 – Wittenoom mine/rib Australia | 0.78 (0.65, 0.93) |
| 5 – Tuscany rail | 1.00 (0.38, 2.60) | 3 – Leyland gas masks | 1.36 (0.48, 3.81) |
| Subtotal (I²= 29.0%, P< 0.218) | 0.71 (0.53, 0.94) | Crocidolite and chrysotile | 12 – Ferodo friction |
| 13 – South Africa asbestos factory | 0.20 (0.00, .) | 11 – Völkbrück cement | 0.50 (0.18, 1.39) |
| 14 – Norway cement | 2.06 (0.7, 2.21) | 7 – Rochdale men early cohort | 2.87 (1.55, 5.31) |
| 9 – Rochdale principle cohort | 8.17 (3.01, 22.18) | 10 – New Orleans plant | 50.00 (0.00, .) |
| 8 – Rochdale women | 1.44 (0.59, 3.49) | Mixed asbestos cohorts | 18– 42 – Swedish rail maintenance |
| Subtotal (I²= 85.3%, P< 0.001) | 2.00 (1.30, 3.66) | 66 – GB asbestos survey men | 3.73 (2.04, 7.63) |
| 19 – Tamworth cement | 1.05 (0.25, 4.47) | 47 – Gothenburg shipyard | 4.14 (2.66, 6.45) |
| 15 – Blackbull gas masks | 4.90 (1.16, 20.69) | 22 – Thetford company 3 | 34.90 (4.89, 248.83) |
| 21 – Quebec asbestos factory | 7.11 (3.52, 14.38) | 23 – Thetford company 4 | 10.95 (4.88, 24.56) |
| 24 – Quebec asbestos mine | 9.35 (2.20, 39.76) | 17 – Chongqing asbestos workers | 10.45 (2.54, 43.05) |
| 30 – Chrysotile textile workers China | 16.91 (8.37, 34.16) | 27 – North Carolina textile | 32.17 (10.29, 100.59) |
| 26 – South Carolina textile | 1.04 (0.41, 2.65) | 17 – Connecticut friction | 6.12 (3.58, 10.45) |
| 18 – Sweden cement | 10.00 (2.63, 37.67) | 28 – Greece asbestos cement | 1.80 (0.63, 5.16) |
| 29 – Chrysotile mines China | 3.73 (1.57, 8.86) | Amosite | 33 – South Africa amosite mines |
| Subtotal (I²= 53.1%, P< 0.007) | 4.56 (2.72, 7.63) | 34 – Tyres pipe insulation | 3.73 (1.57, 8.86) |
| 32 – Paterson amosite | 0.50 (0.18, 1.39) | 31 – Ustbridge insulation | 5.58 (2.24, 13.92) |
| Subtotal (I²= 0.0%, P= 0.393) | 4.04 (2.79, 5.87) | Mixed asbestos cohorts | 37 – Belgium cement |
| 38 – Devonport dockyard | 0.21 (0.11, 0.38) | 40 – Pennsylvania textile | 0.63 (0.58, 0.69) |
| 47 – Gothenburg shipyard | 1.09 (0.80, 1.47) | 66 – GB asbestos survey men | 1.05 (0.63, 1.75) |
| 42 – Swedish rail maintenance | 1.20 (0.63, 2.27) | 47 – GB asbestos survey women | 1.07 (0.45, 2.55) |
| 67 – GB asbestos survey women | 1.22 (0.66, 2.24) | 54 – Emila Romagna cement | 1.09 (0.80, 1.47) |
| 51 – Southern Sweden cement | 1.23 (0.60, 2.50) | 41 – Ontario cement | 1.20 (0.63, 2.27) |
| 43 – Pearl Harbour naval shipyard | 1.57 (0.59, 4.17) | 59 – East London women | 1.75 (0.59, 4.17) |
| 59 – East London men | 1.59 (1.8, 2.14) | 44 – Paray-Le-Monial | 1.68 (0.52, 5.04) |
| 53 – Italian rail | 1.74 (0.67, 4.51) | 46 – German asbestos workers (b) | 1.76 (0.73, 4.33) |
| 59 – German asbestos workers (a) | 1.96 (1.76, 2.19) | 52 – Asbestos insulation union | 1.96 (1.76, 2.19) |
| 58 – East London men | 2.12 (1.13, 3.99) | 57 – East London laggers | 2.15 (1.63, 2.84) |
| 53 – Italian rail | 2.18 (1.30, 3.66) | 60 – Genoa shipyard | 2.18 (1.30, 3.66) |
| 49 – New Orleans Plant 1 | 3.40 (0.83, 14.00) | 65 – Great Britain Eternit cement | 4.17 (2.46, 9.01) |
| 46 – Johns Manville retirees | 6.07 (2.93, 12.58) | 55 – Danish cement | 6.57 (2.04, 21.10) |
| 39 – Danish cement | 7.40 (0.98, 56.02) | 68 – Japan shipyard | 9.11 (4.53, 18.35) |
| 62 – Ontario pipe trade | 10.90 (1.50, 79.39) | 61 – Lithuanian cement | 10.90 (1.50, 79.39) |
| 63 – US Coast Guard shipyard | 10.95 (4.88, 24.56) | 50 – Finnish shipsyards | 34.90 (4.89, 248.83) |
| Subtotal (I²= 95.8%, P< 0.001) | 1.89 (1.38, 2.56) | 14 – Pearl Harbour naval shipyard | 1.80 (0.63, 5.16) |
| Subtotal (I²= 95.8%, P< 0.001) | 2012 Cancer Research UK |

Figure 2  Ratio of asbestos-related lung cancers to mesothelioma deaths, study-specific and random effects combined estimates by asbestos fibre type. Estimates of the ratio of excess lung cancer deaths to every mesothelioma death (R₁) in each study, by asbestos fibre type. P represents the percentage of the variance explained by regression of the contributing numerator on the denominator was higher for R₁ (> 95%) than for R₂ for crocidolite, crocidolite + chrysotile and for mixed asbestos cohorts, but was higher for R₂ than R₁ for chrysotile and amosite cohorts.

Mesothelioma deaths as a proportion of total mortality were half that for crocidolite, but higher than chrysotile or amosite (Table 3). There were between one and three excess lung cancers for every mesothelioma death in half of the cohorts, but the estimate in the two largest cohorts were very different, at 0.6 in men in the Great Britain Asbestos Survey and 2.0 in US and Canadian insulation workers (estimates 55 and 66, Table 1). For all mixed asbestos cohorts combined, there were 1.9 (95% CI 1.4, 2.6) excess lung cancer deaths for every mesothelioma death, although with large heterogeneity.

Comparison of the two ratio estimates  The percentage of the variance explained by regression of the contributing numerator on denominator was higher for R₁ (> 95%) than for R₂ for crocidolite, crocidolite + chrysotile and for mixed asbestos cohorts, but was higher for R₂ than R₁ for chrysotile and amosite cohorts.
Population attributable fractions in men

Table 4 provides, for 20 countries with large mesothelioma proportional mortality, PAFs (%) of male lung cancer deaths due to asbestos estimated using the crude and smoking-adjusted estimates of ratios $R_1$ and $R_2$ for exposure to mixed asbestos fibres, and smoking-adjusted ratios for crocidolite. The smoking adjustment (derived from 20% higher cohort smoking prevalence than the general population) is likely to underestimate ratios and PAFs, and can be considered a lower limit. In the countries listed, mesothelioma deaths ranged from 1 to 9 per 1000 deaths. If the ratio of ARLC to mesothelioma deaths were exactly 1, then mesothelioma deaths as a percentage of lung cancer deaths (ranging from 1% to 9% for these countries) would be the PAF (%) of lung cancer due to asbestos. For Australia, at the top of the table with the highest percentage of deaths from mesothelioma, using ratio estimates for crocidolite, we estimated that between 5.4% and 8.6% of lung cancer deaths in men are asbestos-related, based on $R_1$ and $R_2$, respectively. Similarly in the United Kingdom, New Zealand, South Africa and the Netherlands, where crocidolite was used among other asbestos fibres, PAFs ranged between 4% and 7%. For South Africa calculations based on $R_2$ estimates (PAF 6.7–8.4% for mixed fibres, 2.7% for crocidolite) are more suitable as total background mortality, which is incorporated into $R_2$-based estimates, is particularly high in this country during the HIV era. Applying the ratios for mixed asbestos exposures, PAFs for other countries lie between 3% and 7% using both ratio methods of estimation. For the United States, the estimated PAF in men was estimated to be 3.2–4.0% for mixed asbestos ($R_1$ estimates).

**DISCUSSION**

The ratios of ARLCs to mesotheliomas fall into three categories: (1) pure amphibole or mixed exposures causing high lung cancer risks and ARLC/mesothelioma ratios ranging from <1 for crocidolite, 1.4 to 2.5 for mixed types, to 4 or more for amosite and anthophyllite; (2) heavy prolonged chrysotile exposures causing high lung cancer risks and ARLC: mesothelioma ratios of the order of 10; and (3) shorter or less heavy chrysotile exposures causing lower lung cancer risks and little mesothelioma, between which there was little correlation and thus calculation of excess lung cancers from mesothelioma deaths after chrysotile exposure would not be reliable. Thus for all asbestos types other than crocidolite, the ARLC is larger than that for mesothelioma, but the low ARLC to mesothelioma ratio for crocidolite (0.71) does not imply that the lung cancer risk is small, only that it is slightly smaller than the high mesothelioma risk.

The ARLC: mesothelioma ratio in chrysotile cohorts may be dominated by two large errors. First, the lung cancer excess depends critically on the rates on which the SMR is based. Second, it seems likely that many of the mesotheliomas in such cohorts are actually due to amphibole exposure. These points are illustrated by the chrysotile miners and millers in Quebec (estimates 21–24). Their ARLC: mesothelioma ratio varied substantially, from 3.3 (22 mesotheliomas; 423 lung cancers, SMR 1.21) for cumulative exposures below 300 million particles per cubic foot (mpcf)-years to 31 (1 mesothelioma; 47 lung cancers, SMR 2.97) above 1000 mpcf-years. The lung cancer excess above 1000 mpcf-years is affected little by the choice of rates, but below 300 mpcf-years the lung cancer excess could be doubled or reduced to zero by a 20% change in expected rates. Furthermore, many mesotheliomas occurring in asbestos that is predominantly chrysotile may actually be due to other asbestos types. McDonald et al (1997) argued that the mesotheliomas among chrysotile miners and millers in Quebec were caused either by amphibole exposure elsewhere or by the tremolite that contaminated most Canadian chrysotile. Analysis of 22 lung samples from mesotheliomas in this cohort showed that 6 contained substantial amounts of crocidolite, and only 2 contained more chrysotile than tremolite despite their much heavier exposure to chrysotile. Tremolite, similarly to crocidolite

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**Table 4** Estimates of population attributable fractions (%) ranges of lung cancer due to exposure to mixed asbestos and crocidolite asbestos fibres

| Country   | No. of deaths/<sup>a</sup> | Mesothelioma deaths | Mixed asbestos fibres | Population attributable fraction of lung cancer due to asbestos, estimated for |
|-----------|----------------------------|---------------------|-----------------------|--------------------------------------------------------------------------------|
|           | Lung cancer | Mesothelioma | Per 1000 all-cause deaths | % Of lung cancer deaths<sup>b</sup> | R<sub>1</sub> | 1.5<sup>c</sup>–1.9 | R<sub>2</sub> | 2.2<sup>c</sup>–2.8 | Crocidolite | R<sub>1</sub> | 0.6<sup>c</sup>, R<sub>2</sub> | 1.2<sup>c</sup> |
| Australia | 12768       | 1156           | 7.8                    | 9.1                  | 13.6–17.2 | 14.7–18.0 | 5.4–8.6 |
| UK        | 90347       | 7362           | 6.9                    | 8.1                  | 12.2–15.5 | 13.2–16.2 | 4.9–7.7 |
| New Zealand | 3192     | 238            | 5.8                    | 7.5                  | 11.2–14.2 | 11.3–13.9 | 4.5–6.5 |
| Sweden    | 8386        | 491            | 3.2                    | 5.9                  | 8.8–11.1  | 6.5–8.1   | 3.5–3.7 |
| Netherlands | 29604    | 1629           | 6.2                    | 5.5                  | 8.3–10.5  | 12.0–14.8 | 3.3–6.9 |
| South Africa | 2995   | 133            | 0.8                    | 4.4                  | 6.7–8.4   | 1.8–2.3   | 2.7–10.0 |
| Iceland   | 274         | 12             | 3.7                    | 4.4                  | 6.6–8.3   | 7.5–9.3   | 2.6–4.2 |
| Norway    | 5506        | 216            | 2.9                    | 3.9                  | 5.9–7.5   | 6.1–7.6   | 2.4–3.4 |
| Finland   | 6557        | 252            | 2.7                    | 3.8                  | 5.8–7.3   | 5.5–6.9   | 2.3–3.1 |
| Malta     | 528         | 20             | 3.3                    | 3.8                  | 5.7–7.2   | 6.8–8.4   | 2.3–3.8 |
| Denmark   | 1810        | 55             | 2.6                    | 3.0                  | 4.6–5.7   | 5.4–6.8   | 1.8–3.0 |
| Italy     | 24126       | 729            | 3.4                    | 3.0                  | 4.5–5.7   | 7.0–8.7   | 1.8–3.9 |
| Germany   | 136953      | 4102           | 2.7                    | 3.0                  | 4.5–5.7   | 5.5–6.9   | 1.8–3.1 |
| France    | 99626       | 2900           | 2.9                    | 2.9                  | 4.4–5.5   | 5.9–7.4   | 1.7–3.3 |
| Luxembourg | 690       | 16             | 2.3                    | 2.3                  | 3.5–4.4   | 4.8–6.0   | 1.4–2.7 |
| USA       | 413529      | 8802           | 2.0                    | 2.1                  | 3.2–4.0   | 4.3–5.4   | 1.3–2.4 |
| Austria   | 8895        | 187            | 1.7                    | 2.1                  | 3.2–4.0   | 3.7–4.6   | 1.3–2.0 |
| Chile     | 6464        | 117            | 0.7                    | 1.8                  | 2.7–3.4   | 1.5–1.9   | 1.1–0.8 |
| Japan     | 185988      | 3010           | 1.4                    | 1.6                  | 2.4–3.1   | 3.1–3.9   | 1.0–1.7 |
| Spain     | 76606       | 978            | 1.4                    | 1.3                  | 19–24     | 2.9–36    | 0.8–1.6 |

<sup>a</sup>Based on the number of mesothelioma deaths in 1000 deaths, men aged 40–84, years 2001–2005, for countries using ICD 10 (WHO mortality data).<sup>b</sup>Note that if there were one asbestos-related lung cancer for every mesothelioma death, this percentage would be the PAF (%) of lung cancer due to asbestos. The ratio and thus PAFs are likely to be higher.<sup>c</sup>Corrected for confounding by smoking of up to 20% higher cohort smoking rates compared with the general population.
and amosite, is an amphibole that is cleared less rapidly from the lung than chrysotile. The vermiculite miners in Montana were included on this basis as vermiculite contains tremolite. Nevertheless, irrespective of the contribution of tremolite, it seems that prolonged heavy exposure to chrysotile causes a much larger excess of lung cancer than of mesothelioma.

**Heterogeneity in ratio estimates within and between cohorts**

Neither ratio \( R_1 \) or \( R_2 \) appeared to be more constant across all cohorts. Although it was expected that \( R_4 \) would more appropriately account for differential background lung cancer incidence rates, and thus be a more constant ratio, its denominator – ideally an age-adjusted mesothelioma mortality rate – could not be calculated – was mesothelioma proportional mortality and thus was additionally affected by differential background mortality rates. Nonetheless, PAF estimates using either ratio did not differ hugely.

We have considered the effect of fibre type on ratios; however, several other factors, discussed below, will affect within and between study ratio estimates. Stratifying by each factor could not be conducted owing to lack of data. The summary ratios provided here thus better characterise the overall ARLC–mesothelioma relationship across exposure circumstances and over a long period of time, and do not serve to precisely quantify lung cancer excess in a short time period.

(i) Dose–response relationship: Most formal risk assessment analyses assume that the relative risk for lung cancer is increased by each brief period of asbestos exposure in proportion to dose (intensity times duration), whereas the increase in the absolute mesothelioma rate is proportional to the dose weighted by the square or cube of latency. Such models imply that prolonged exposure beginning in middle age will cause a ratio of ARLC to mesothelioma more than 10 times greater than brief exposure at age 20 years (Peto et al., 1985). The ratio is thus age-dependent and affected by differences in the length of follow-up between studies. Exposure intensity also varies between and within cohorts, for example, if factory ventilation systems improve.

(ii) Death certificate reporting bias: Inaccurate recording of deaths may lead to possible overestimation of ratios, as shown by an autopsy-death certificate comparison in which false-negative mesotheliomas were likely to be recorded as lung cancers (Delendi et al., 1991). Special efforts to capture all mesothelioma deaths from medical records and mesothelioma registries would have reduced this bias here and mesothelioma-reporting accuracy should improve over time with the use of ICD-10.

(iii) Overall mortality rates: Although the use of a relative effect on lung cancer has been captured in \( R_2 \), its denominator would ideally be an age-standardised mesothelioma mortality rate. Instead the mesotheliomas per 1000 deaths are affected by changes in the overall risk of death. Mesothelioma proportional mortality will be higher in cohorts with lower mortality.

(iv) Confounding/efficacy modification by smoking and other lung carcinogens: Ratio estimates hinge on the assumption that SMRs for lung cancer are unbiased. Several cohorts specifically adjusted for smoking (estimates 11, 25, 29, 30, 68) and in some other estimates of smoking prevalence in subsets suggest that they were similar to that of the general population (estimates 43, 50, 51). Use of the PMR (1.28) rather than the SMR (1.89) for lung cancer was intended to reduce confounding by smoking (estimates 66, 67, Harding, 2010). The extent to which bias may be present in other cohorts depends on the social-class smoking gradient. Two recent cohorts commented on a higher smoking prevalence (estimates 61, 62) than in the general population, which may explain their high ratios. In addition, asbestos has a stronger effect on lung cancer in smokers than non-smokers, whereas smoking has little or no effect on mesothelioma. Thus, higher baseline lung cancer mortality rates may explain the higher ratios observed in United States and the European cohorts than in Israel (estimate 13, with a low lung cancer mortality rate; Tulchinsky et al., 1999). The great majority of cohorts included here were from Europe, the United States and Canada, where asbestos exposure occurred predominantly during the 1940s to 1970s when smoking prevalence was high. Estimates for Ontario pipe traders and two cohorts of shipyard workers \( (R_4 = 50 \text{ and } 63) \) may be underestimated if these workers also had exposure to other lung carcinogens, such as lead, chromium, cadmium and diesel exhaust.

**Population-level inferences**

For countries with the highest percent deaths from mesothelioma in men, estimates of the lung cancer PAF due to asbestos were between 3% and 8% for 2001–2005. In almost all of these countries, lung cancer made up 20–30% of cancer deaths, thus even 3–8% of this is a considerable contribution to the most common cause of cancer mortality in men in these settings. A few previous lung cancer-asbestos PAF estimates have been made. For the United Kingdom, the British Asbestos Systems Study included here had an \( R_2 \) value of 0.6, much lower than the other mixed asbestos cohorts. Darnton et al. (2006) obtained a similar estimate (\( R_2 \) between 0.7 and 1) from a population-based analysis of the relationship between lung cancer and mesothelioma PMRs in men in 131 occupational groups, adjusting for smoking, and a PAF of 2% to 3%. This is approximately half of the estimate found here (4.9% to 7.7% using crocidolite ratios, from Table 3), and the difference may be because their estimate was for a longer earlier period (1980–2000) than the current estimates (for 2001–2005), during which time mesotheliomas have increased as a percentage of lung cancer deaths (from 3.8% to 8.1%). However, as amosite was a major cause of mesothelioma in the United Kingdom (Rake et al., 2009), the lung cancer excess in the United Kingdom would be expected to be even higher. For Italy, Marinaccio et al. (2008) used a model-based approach to estimate the ARLC burden in men in 1980–2001 and found PAFs for lung cancer mortality of between 1.6% and 3.7%, that is, a ratio (\( R_2 \)) of between 0.68 and 1.37 excess lung cancers per mesothelioma. These estimates are similar to those of Darnton et al. (2006), and also suggest a slightly lower ratio of ARLCs to mesotheliomas than that based on our estimated ratios from mixed asbestos cohorts. In the United States, where amphiboles constituted a much smaller proportion of asbestos consumption than in Europe, estimates of the male lung cancer PAF for asbestos were 6% to 8% in the 1990s (Nicholson et al., 1982; Morabia et al., 1992), slightly lower than the estimate of 4.0–5.0% here. In Finland, where anthophyllite was mined extensively, 2.7 mesothelioma deaths per 1000 would lead to a PAF of 1% lung cancer. For the United States, Marinaccio et al. (2008) made similar estimates of a ratio of 1.37 excess lung cancers per mesothelioma. The asbestos-related cancer burden today is predominantly in Europe, North America, Australia, Japan, South Africa and parts of South America. However, the highest current consumption and exposure, and thus future burden, is in China, Russia, India, Kazakhstan, Ukraine, Thailand, Brazil and Iran. Exposure today is predominantly to chrysotile, either in a pure form or naturally...
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Conflict of interest

The authors declare no conflict of interest.

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REFERENCES

Acheson ED, Gardner MJ, Pippard EC, Grime LP (1982) Mortality of two groups of workers who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. Br J Ind Med 39: 344 – 348

Acheson ED, Gardner MJ, Winter PD, Bennett C (1990) Cancer in a factory using amosite asbestos. Int J Epidemiol 13: 3 – 10

Albin M, Jakobssohn K, Attewell R, Johansson L, Welinder H (1990) Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. Br J Ind Med 47: 602 – 610

Alies-Patin AM, Valéron AJ (1985) Mortality of workers in a French asbestos cement factory. 1940 – 1982. Br J Ind Med 42: 219 – 225

Battista G, Belli S, Compa B, Fiumalbi C, Grignoli M, Loi F, Orsi D, Paredes I (1999) Mortality due to asbestos-related causes among railway carriage construction and repair workers. Occup Med (Lond) 49: 536 – 539

Berry G (1994) Mortality and cancer incidence of workers exposed to chrysotile asbestos in the friction-products industry. Ann Occup Hyg 38: 539 – 546, 413

Berry G, Newhouse ML, Wagner JC (2000) Mortality from all cancers of asbestos-cement workers followed from 1943 through 1976. Ecotoxicol Environ Saf 51: 15 – 23

Dartnall AJ, McEvenny DM, Hodgson JT (2006) Estimating the number of mesothelioma deaths will be too unstable to be used to imply a small asbestos-related lung cancer burden. The major effect of the continuing use of this carcinogen will be on lung cancer. High smoking rates in men (e.g., 70% in Russia, 61% in China (World Health Organization, 2008)) in these countries will amplify the associated lung cancer burden. There is thus an urgent need for limiting exposure through strict regulation of asbestos use, and encouragement of smoking cessation to reduce mortality among formerly exposed workers.
Sichtelidis L, Chlodor D, Spyrratos D, Haidich AB, Fourkiotou I, Kakoura M, Patakas D (2009) Mortality from occupational exposure to relatively pure chrysotile: a 39-year study. *Respiration* 78: 63–68

Sluis-Cremer GK, Liddell FD, Logan WP, Beuzidenhout BN (1992) The mortality of amphibole miners in South Africa, 1946–1980. *Br J Ind Med* 49: 566–575

Smialyte G, Kirtinaitis J, Andersen A (2004) Mortality and cancer incidence among Lithuanian cement producing workers. *Occup Environ Med* 61: 529–534

Sullivan PA (2007) Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: update of a cohort mortality study. *Environ Health Perspect* 115: 579–585

Thomas HF, Benjamin IT, Elwood PC, Sweetnam PM (1982) Further follow-up study of workers from an asbestos cement factory. *Br J Ind Med* 39: 273–276

Tola S, Kalliomaki PI, Pukkala E, Asp S, Korkala ML (1988) Incidence of cancer among welders, plateers, machinists, and pipe fitters in shipyards and machine shops. *Br J Ind Med* 45: 209–218

Tomioka K, Natori Y, Kumagai S, Kurumatani N (2011) An updated historical cohort mortality study of workers exposed to asbestos in a refitting shipyard, 1947–2007. *Int Arch Occup Environ Health* 84: 959–967

Tulchinsky TH, Ginsberg GM, Iscovitch J, Shihab S, Fischbein A, Richter ED (1999) Cancer in ex-asperbestos cement workers in Israel, 1953–1992. *Am J Ind Med* 35: 1–8

Ulvestad B, Kjaerheim K, Martinsen JI, Damberg G, Wannag A, Mowe G, Andersen A (2002) Cancer incidence among workers in the asbestos-cement producing industry in Norway. *Scand J Work Environ Health* 28: 411–417

Virta RL (2006) Worldwide asbestos supply and consumption trends from 1900 through 2003, 1 February 2006

Wang X, Lin S, Yano E, Qiu H, Yu IT, Tse L, Lan Y, Wang M (2011) Mortality in a Chinese chrysotile miner cohort. *Int Arch Occup Environ Health* e-pub ahead of print 28 July 2011, doi:10.1007/s00420-011-0685-9

Wang XR, Yu IT, Qiu H, Wang MZ, Lan YJ, Tse LY, Yano E, Christiani DC (2012) Cancer mortality among Chinese chrysotile asbestos textile workers. *Lung Cancer* 73: 151–155

WHOSIS Mortality Database ICD-10 (2009) World Health Organization, Global Health Observatory, WHOSIS Mortality Database ICD-10, 21 April 2009. [http://www.who.int/whosis/mort/download/en/index.html](http://www.who.int/whosis/mort/download/en/index.html)

Woitowitz HJ, Lange HJ, Beierl I, Rathgeb M, Schmidt K, Ulm K, Giesen T, Woitowitz RH, Pache L, Rodelsperger K (1986) Mortality rates in the Federal Republic of Germany following previous occupational exposure to asbestos dust. *Int Arch Occup Environ Health* 57: 161–171

World Health Organization (2008) WHO report on the global tobacco epidemic, 2008: the MPower package. *Pop Dev Rev* 34: 581

Yano E, Wang ZM, Wang XR, Wang MZ, Lan YJ (2001) Cancer mortality among workers exposed to amphibole-free chrysotile asbestos. *Am J Epidemiol* 154: 538–543

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