Exposure to asbestos and the risk of colorectal cancer mortality: a systematic review and meta-analysis

Kyeongmin Kwak ,[1,2] Domyung Paek ,[1,3] Kyung Ehi Zoh [1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/oemed-2019-105735).

[1]Department of Environmental Health Sciences, Seoul National University Graduate School of Public Health, Seoul, Republic of Korea
[2]Department of Occupational and Environmental Medicine, Korea University Ansan Hospital, Ansan, Republic of Korea
[3]Institute of Health and Environment, Seoul National University, Seoul, Republic of Korea

Correspondence to
Kyung Ehi Zoh, Department of Environmental Health Sciences, Seoul National University Graduate School of Public Health, Seoul 08826, Republic of Korea; kezoh@snu.ac.kr

Received 30 January 2019
Revised 26 July 2019
Accepted 15 September 2019

To cite: Kwak K, Paek D, Zoh KE. *Occup Environ Med* Epub ahead of print: [please include Day Month Year]. doi:10.1136/oemed-2019-105735

ABSTRACT

Asbestos exposure is associated with mesothelioma and cancer of the lung, larynx and ovary. However, the association between asbestos exposure and colorectal cancer is controversial despite several systematic reviews of the literature, including a number of meta-analyses. We performed a systematic review and meta-analysis to evaluate quantitatively the association between exposure to asbestos and colorectal cancer. We searched for articles on occupational asbestos exposure and colorectal cancer in PubMed, EMBASE and Web of Science published before April 2018. In total, 44 articles were selected and 46 cohort studies were analysed. The overall pooled risk estimates and corresponding 95% CIs of the association between occupational asbestos exposure and colorectal cancer were calculated using a random-effects model. Subgroup analyses and sensitivity tests were also performed. There was a significantly increased risk of colorectal cancer mortality among workers exposed to asbestos occupationally, with an overall pooled SMR of 1.16 (95% CI: 1.05 to 1.29). The pooled SMR for colorectal cancer was elevated in studies in which the asbestos-associated risk of lung cancer was also elevated (1.43; 95% CI: 1.30 to 1.56). This implies that the risk of colorectal cancer mortality increases as the level of asbestos exposure rises. A sensitivity analysis showed robust results and there was no publication bias. Although the effect size was small and the heterogeneity among studies was large, our findings indicate that occupational exposure to asbestos is a risk factor for colorectal cancer.

Key messages

What is already known about this subject?

- Positive association between asbestos exposure and colorectal cancer has been reported in few studies; however, only limited evidences exist to support this relationship.

What are the new findings?

- Although several new studies have been conducted recently, there has been no new systematic review and meta-analysis since 2008.
- The results of the meta-analysis presented that occupational exposure to asbestos was significantly associated with colorectal cancer.
- The risk of colorectal cancer was higher among the studies in which asbestos-associated lung cancer risk was greater than twofold; this implies that the risk of colorectal cancer mortality increases at high level of asbestos exposure.

How might this impact on policy or clinical practice in the foreseeable future?

- The results might serve as additional scientific evidences that substantiate carcinogenic potential of asbestos to induce colorectal cancer in human.

INTRODUCTION

Asbestos exposure is associated with mesothelioma and cancer of the lung, larynx and ovary.[1] However, the association between exposure to asbestos and colorectal cancer has been controversial, despite several systematic reviews of literature, including a number of meta-analyses. Horna *et al*[2] conducted a meta-analysis in 1994 and found a non-significantly elevated summary SMR for colorectal cancer (overall SMR 1.10, 95% CI: 0.92 to 1.32). The US Institute of Medicine in 2006 conducted a meta-analysis of 23 cohort studies of the association between exposure to asbestos and colorectal cancer; the summary relative risk (RR) was 1.15 (95% CI: 1.01 to 1.31) in studies that compared any versus no exposure.[3] Gamble[4] reported in 2008 that the overall SMR of colorectal cancer in 22 cohort studies was 0.97 (95% CI: 0.89 to 1.05). The most recent International Agency for Research on Cancer (IARC) publication noted that positive associations between exposure to asbestos and colorectal cancer have been reported, but the IARC working group was evenly divided as to whether the evidence was strong enough to warrant classification as 'sufficient'.[5] Since then, several studies of the relationship between asbestos exposure and cancer mortality have been performed, but no up-to-date systematic review. Among the studies of cancer mortality due to asbestos performed after the IARC review, some reported a significant, positive association between asbestos and colorectal cancer, but others did not. Therefore, an updated systematic review and meta-analysis are needed.

Therefore, we performed a systematic review and meta-analysis to evaluate quantitatively whether occupational exposure to asbestos is associated with colorectal cancer.

METHODS

The systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[6] The protocol for systematic review was registered with the International Prospective Register of Systematic Reviews (registration number: CRD42018103589, available from: http://

www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018103589).

Selection of studies

On 2 April 2018, we searched PubMed, EMBASE and Web of Science using the following keywords: ("colon cancer" OR "colorectal cancer'" OR "cancer") AND ("asbestos" OR "crocidolite" OR "chrysotile" OR "amosite") AND "cohort" AND ("mortality" OR "incidence" OR "SIR" OR "SMR"). We excluded duplicate articles and those not in English. Two authors (KK and KEZ) screened the articles based on the title and abstract and read the full text to evaluate their eligibility according to the inclusion and exclusion criteria. In addition, we reviewed manually the reference lists of the included studies. Disagreements between the authors were resolved by discussion. If studies involving the same cohort had been published several times, only the latest article was included if the observation periods overlapped; if not, the results were integrated. If different cohorts were reported in the same article, we treated them as independent studies.

Inclusion criteria

The inclusion criteria were as follows: studies of workers exposed to asbestos, cohort studies and studies that reported mortality data for colorectal cancer (SMR or provision of data enabling calculation of the SMR).

Exclusion criteria

We excluded studies based on the following criteria: those that did not clearly define asbestos exposure; studies of environmental exposure to asbestos; those that reported only incidence data for colorectal cancer; studies that provided quantitative risk estimates other than the SMR (eg, RR, proportional mortality ratio, OR, HR); meta-analyses and reviews; and studies that could not be found.

Data extraction

From the included studies, we collected the first author, publication year, sex, country, industry type, asbestos type, cohort size, follow-up period, person-years of observation, follow-up rate (%), latency period, SMR and 95% CIs for lung cancer, as well as SMR values and 95% CIs for observed and expected deaths due to colorectal cancer. If colorectal cancer and rectal cancer were classified separately, SMRs were obtained by summing the observed and expected deaths. Small-intestinal cancer, sigmoid cancer and anal cancer were categorised as colorectal cancer (C17–C21 in International Classification of Diseases (ICD)-10, 152–154 in ICD-8 and ICD-9). If a study provided mortality data with and without latency, we analysed only the former. We used the 95% CIs in the articles if provided, and, if not, calculated the 95% CIs using the *eclpci* command in Stata/IC 15 (Stata, College Station, Texas, USA) from the observed and expected number of deaths.

Quality assessment

Two authors independently assessed the risk of bias of each study using the modified Newcastle-Ottawa Scale (NOS) tool, because the conventional NOS has difficulties for occupational cohort studies.[7] The modified NOS consists of the following five quality components: representativeness of the exposed cohorts, exposure assessment/reporting, comparability of the exposed and non-exposed cohorts, assessment of outcomes and adequacy of follow-up.[7] Disagreements were resolved by discussion.

Statistical analysis

Overall pooled SMR estimates and corresponding 95% CIs were calculated using random-effects models and a heterogeneity test. To assess heterogeneity among the studies, we used the I^2 statistic. The I^2 value ranges from 0% to 100% (I^2=0%–25%, no heterogeneity; I^2=25%–50%, moderate heterogeneity; I^2=50%–75%, large heterogeneity; I^2=75%–100%, extreme heterogeneity). We considered a value of I^2>50% to indicate substantial heterogeneity.[8] We used Begg's funnel plots and Egger's regression asymmetry test to identify publication bias. Subgroup analyses were performed by study region, type of industry, cohort size, follow-up duration, SMR for lung cancer, latency period and the quality components of the modified NOS tool to adjust for heterogeneity. Since colon and rectal cancers have different aetiologies, we also performed separate meta-analyses on studies reporting the results of colon cancer and on those regarding the results of rectal cancer. By carrying out these analyses separately, we calculated summary SMRs and their corresponding 95% CIs for colon cancer and rectal cancer, respectively. For the purpose of calculation, SMR for rectal cancer from Levin *et al*'s study,[9] which was 0, was replaced with the value of 0.1. Since smoking is an important confounder, subgroup analyses restricting to studies with smoking data were also carried out. Further, for studies that exhibited high mortality of lung cancer, summary SMRs were calculated taking available smoking information into consideration. A sensitivity analysis of the influence of individual studies was conducted to determine the robustness of the outcomes. All analyses were performed using Stata/IC 15 software.

RESULTS

Characteristics of the selected studies

We identified 1026 articles by searching PubMed, EMBASE and the Web of Science. After excluding non-English-language articles, we excluded a further 640 articles based on their title and abstract. After addition of 21 articles from the references, we performed a full-text assessment of 310 articles, resulting in selection of 44 articles for analysis. Among them, two articles by McDonald *et al*[10 11] were combined because they involved the same cohort with different follow-up periods. The articles of Peto *et al*[12] and Woitowitz *et al*[13] involved three and two cohorts, respectively, and so were analysed independently. Therefore, 46 studies were included in this meta-analysis (figure 1).

The studies included in the meta-analysis covered 1642 cases of colorectal cancer deaths. These studies were conducted in Europe, the USA, Canada, Australia and Asia between 1963 and 2018. Nineteen studies involved both males and females, and 24 and 3 studies involved only males and females, respectively. Ten studies were conducted in the textile industry, eight in mining and milling, eight in asbestos cement, four in insulation and two in shipbuilding. Other studies included cohorts of workers in asbestos product manufacturing, railroad shops, railway carriage construction and repair, petroleum refineries, asbestos removal and metalworking. Seven studies were not targeted at specific industries but involved cohorts of asbestos-exposed workers in several industries. Twenty-two studies provided information on smoking, but only two calculated the risk of colorectal cancer with adjustment for smoking. The remaining studies provided information only on the prevalence of current smokers or ever-smokers in the target cohort. Seven of these studies provided smoking information only for subgroups, not the entire cohort (table 1).

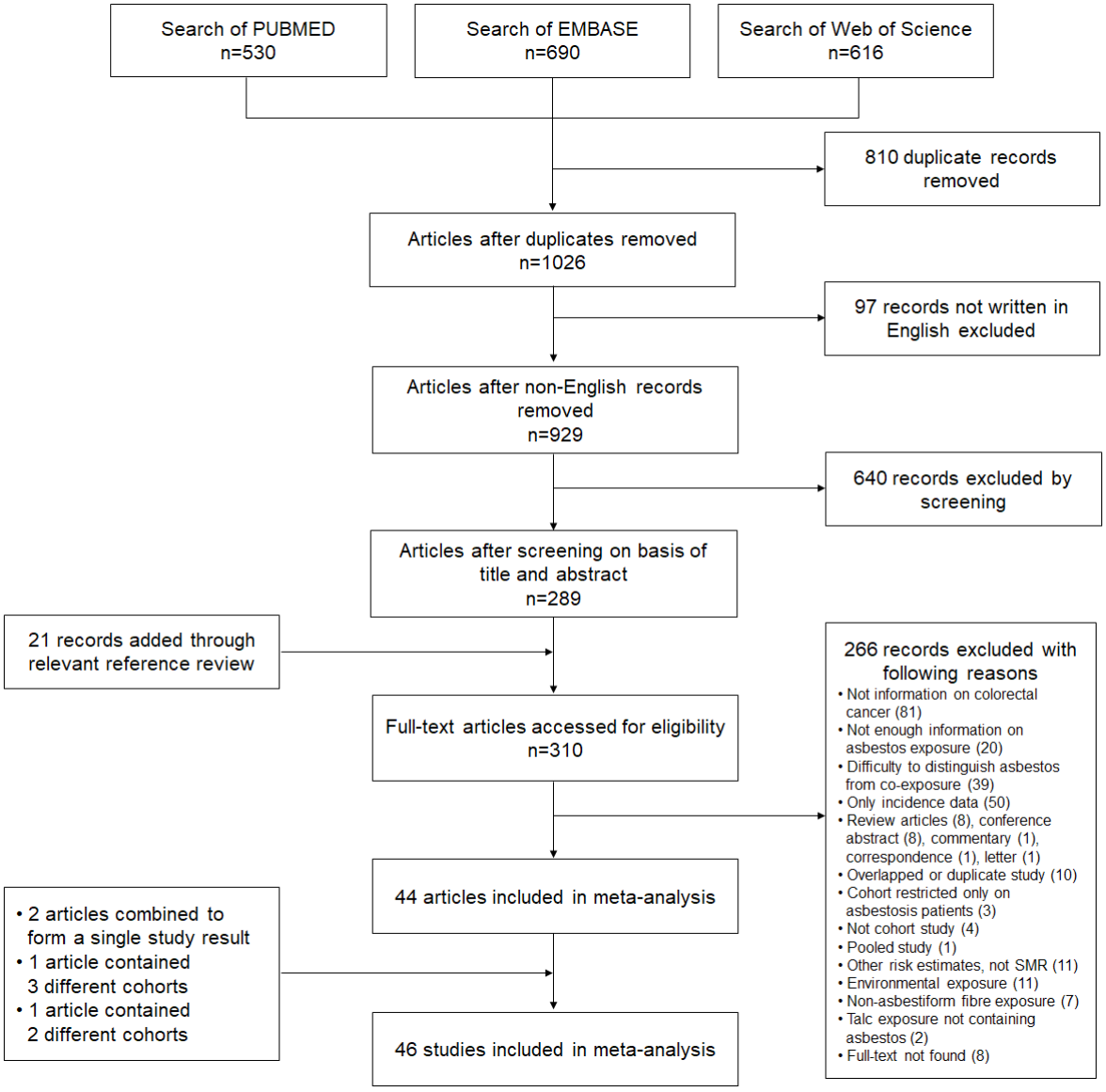

Figure 1 Flow diagram of selection of studies for the systematic review.

The result of a quality assessment of the studies is shown in online supplementary table 1. In terms of the representativeness of the exposed cohort, 35 studies that included asbestos workers from all or most areas of asbestos product factories or asbestos-using industries were rated as high quality (representative). For exposure, 26 studies with official workplace measurements or exposure data were rated as high quality (formal record). For comparability, 45 studies that calculated the SMR in comparison with a representative standard population group were rated as high quality (standardised). For assessment of outcome, 45 studies that used death statistics based on death certificates, National Cancer Registry data, and medical records were rated as high quality (formal record). Twenty-six studies in which more than 95% of the cohort were followed up were rated as high quality (virtually complete).

Overall meta-analysis

The overall pooled SMR in the random-effect meta-analysis was significantly increased to 1.16 (95% CI: 1.05 to 1.29), with large heterogeneity among the studies (I^2=62.0%, p<0.001) (figure 2).

Subgroup analysis

There was considerable heterogeneity, so subgroup analyses of related variables were performed. European (SMR 1.18; 95% CI: 1.03 to 1.35) and Australian (SMR 1.35; 95% CI: 1.12 to 1.62) cohorts had significantly higher risks of colorectal cancer mortality. The Australian cohorts had no significant heterogeneity, but the European cohorts showed moderate heterogeneity (I^2=44.5%, p=0.009). In small cohorts, the risk of colorectal cancer mortality was significantly elevated (SMR 1.29; 95% CI: 1.13 to 1.49), with no heterogeneity (I^2=0.0%, p=0.536). Workers in the insulation industry had a significantly increased risk of colorectal cancer mortality (SMR 1.49; 95% CI: 1.26 to 1.75), with no heterogeneity (I^2=4.0%, p=0.373). Long-term follow-up studies showed a significantly increased risk of colorectal cancer mortality (SMR 1.21; 95% CI: 1.07 to 1.37), with large heterogeneity (I^2=65.0%, p<0.001). Cohorts that did not consider latency had a significantly increased risk of colorectal cancer mortality (SMR 1.19; 95% CI: 1.06 to 1.35), with large heterogeneity (I^2=54.0%, p<0.001). Cohorts with a high mortality of lung cancer had a significantly higher risk of colorectal cancer mortality (SMR 1.43; 95% CI: 1.30 to 1.56),

Table 1 Characteristics of included cohort studies*

Study	Sex	Type of cancer	Type of industry	Country	Type of asbestos	Mortality of colorectal cancer			SMR of lung cancer	Latency (year)	Smoking information	Cohort size	F/U period	Person-years	F/U %	Comments
						O	E	SMR								
Mancuso and Coulter (1963)	Both	Small intestine, large intestine, rectum	Asbestos product manufacturing	USA	Mixed	5	3.52	1.42 (0.46 to 3.31)	3.39 (2.04 to 5.29)	NA	No	1495	1950–1960	NA	NA	SMR for intestine: 1.27 (0.26–3.70), rectum: 1.74 (0.21–6.28)
Selikoff *et al* (1980)	Men	Colon, rectum	Asbestos product manufacturing	USA	Amosite	11	5.2	2.12 (1.06 to 3.79)	5.94 (4.53 to 7.65)	20	Yes†	582	1961–1977	NA	NA	
Ohlson *et al* (1984)	Men	Colon, rectum	Railroad shop	Sweden	Mixed	15	20.9	0.72 (0.40 to 1.18)	1.05 (0.69 to 1.53)	20	Yes‡	3311	1951–1980	NA	99.6	
Acheson *et al* (1984)	Men	Colon, rectum	Insulation	USA	Amosite	10	7.6	1.32 (0.63 to 2.42)	2.1 (1.6 to 2.69)	NA	Yes‡	5969	1947–1979	NA	99	SMR for colon: 1.36 (0.50–2.97), rectum: 1.25 (0.34–3.20)
Peto *et al* (1985) - Cohort I	Men	Colon, rectum	Asbestos textile	UK	Chrysotile mainly	3	2.07	1.45 (0.30 to 4.24)	3.61 (2.2 to 5.57)	NA	No	145	1969–1973	NA	NA	
Peto *et al* (1985) - Cohort II	Women	Colon, rectum	Asbestos textile	UK	Chrysotile mainly	4	2.02	1.98 (0.54 to 5.07)	2.11 (0.57 to 5.39)	NA	No	283	1969–1973	NA	NA	
Peto *et al* (1985) - Cohort III	Men	Colon, rectum	Asbestos textile	UK	Chrysotile mainly	13	16.67	0.78 (0.42 to 1.33)	1.44 (1.16 to 1.76)	20	No	3211	1969–1973	NA	95.8	
Ohlson and Hogstedt (1985)	Men	Intestine	Cement factory	Sweden	Mainly chrysotile	11	5.9	1.86 (0.93 to 3.34)	1.23 (0.62 to 2.2)	NA	Yes‡	1176	1951–1982	26 931	99	
Woitowitz *et al* (1986) - Cohort I	Both	Colon, rectum	Various	Germany	Mixed	5	6.34	0.79 (0.26 to 1.84)	1.7 (1.11 to 2.49)	10	Yes	3070	1977–1982	14 283.75	98.1	
Woitowitz *et al* (1986) - Cohort II	Both	Colon, rectum	Various	Germany	Mixed	3	1.39	2.15 (0.45 to 6.31)	4.62 (2.38 to 8.06)	10	Yes	665	1977–1982	2528.11	98.1	
Seidman *et al* (1986)	Men	Colon, rectum	Insulation	USA	Amosite	22	11.9	1.85 (1.16 to 2.80)	5.41 (4.45 to 6.52)	5	No	820	1946–1982	NA	99.4	
Hodgson and Jones (1986)	Men	Colon, rectum	Various	UK	Mixed	14	27.4	0.51 (0.28 to 0.86)	1.36 (1.15 to 1.59)	10	Yes	33 079	1971–1981	NA	98.5	SMR for colon: 0.32 (0.11–0.76), rectum: 0.75 (0.34–1.42)
Gardner *et al* (1986)	Both	Large intestine, rectum	Asbestos cement	UK	Chrysotile	11	15.4	0.71 (0.36 to 1.28)	0.92 (0.64 to 1.28)	NA	No	2167	1941–1983	NA	96.4	SMR for large intestine: 0.65 (0.24–1.42), rectum: 0.81 (0.26–1.88)
Enterline *et al* (1987)	Men	Large intestine, rectum	Various	USA	Mixed	23	19.9	1.16 (0.73 to 1.73)	2.71 (2.14 to 3.38)	NA	No	1074	1941–1980	NA	97.1	
Hughes *et al* (1987)	Men	Colon, rectum	Cement factory	USA	Chrysotile, mainly	21	23.3	0.90 (0.56 to 1.38)	1.34 (1.14 to 1.57)	20	Yes‡	5492	1937–1982	NA	96.2	
Armstrong *et al* (1988)	Both	Intestine, rectum	Mining, milling	Australia	Crocidolite	14	12.28	1.14 (0.67 to 1.92)	2.64 (2.15 to 3.24)	NA	No	6916	1943–1980	180 190	72.3	
Piolatto *et al* (1990)	Both	Intestine	Mining	Italy	Chrysotile	3	2.3	1.30 (0.27 to 3.81)	1.05 (0.45 to 2.07)	20	No	1094	1946–1987	27 010	96.7	

continued

Table 1 continued

Study	Sex	Type of cancer	Type of industry	Country	Type of asbestos	Mortality of colorectal cancer			SMR of lung cancer	Latency (year)	Smoking information	Cohort size	F/U period	Person-years	F/U %	Comments
						O	E	SMR								
Botta *et al* (1991)	Both	Colon, rectum	Cement factory	Italy	Chrysotile, crocidolite	18	20.8	0.87 (0.51 to 1.37)	2.77 (2.29 to 3.31)	15	No	3367	1964–1986	57 494	97.9	
Selikoff *et al* (1992)	Men	Colon, rectum	Insulation	USA	Mixed	121	88.49	1.37 (1.13 to 1.63)	4.35 (4.10 to 4.60)	20	No	17 800	1967–1986	301 592.6	NA	
Sanden *et al* (1992)	Men	Intestine, rectum	Shipyard worker	Sweden	Chrysotile	9	8.2	1.10 (0.5 to 2.1)	1.08 (0.54 to 1.90)	20	Yes	1200	1978–1987	9248.6	NA	
McDonald *et al* (1980) (1993)	Men	Small intestine, colon, rectum	Mining, milling	Canada	Chrysotile	152	190.2	0.80 (0.68 to 0.94)	1.33 (1.22 to 1.45)	20	Yes	10 925	1910–1988	NA	90.6	
Rösler *et al* (1994)	Women	Colon, rectum	Various (most asbestos textile)	Germany	Mixed	3	3.1	0.96 (020 to 2.81)	3.39 (1.10 to 7.90)	10	Yes	616	1977–1988	6236	99.4	
Battista *et al* (1999)	Men	Intestine, rectum	Railway carriage construction and repair	USA	Chrysotile, crocidolite	6	6.45	0.93 (0.34 to 2.02)	1.24 (0.87 to 1.72)	NA	No	734	1970–1997	15 705	94.3	
Germani *et al* (1999)	Women	Intestine, rectum	Textile, asbestos cement	Italy	Mixed	11	5.05	2.18 (1.09 to 3.90)	4.83 (2.76 to 7.84)	NA	No	631	1980–1997	8831	99.4	
Szeszenia-Dabrowska *et al* (2000)	Men	Colon, rectum, anus	Asbestos cement factory	Poland	Mixed	11	6.3	1.75 (0.87 to 3.12)	0.84 (0.56 to 1.21)	NA	No	2616	1959–1991	54 129	96.5	
Berry *et al* (2000)	Both	Small intestine, colon, rectum	Asbestos textile, insulation	UK	Chrysotile, crocidolite, amosite	39	25.34	1.54 (1.09 to 2.10)	3.01 (2.64 to 3.43)	10	No	5100	1943–1980	85 291	NA	SMR for intestine: 1.90 (1.27–2.73), rectum: 0.99 (0.47–1.82)
Reid *et al* (2004)	Both	Colon, rectum	Mining, milling	Australia	Crocidolite	49	37	1.31 (0.99 to 1.74)	NA	NA	Yes†	6908	1979–2000	NA	NA	
Wilczyńska *et al* (2005)	Both	Colon, rectum, anus	Various	Poland	Mixed	34	21.81	1.56 (1.08 to 2.18)	1.34 (1.10 to 1.62)	NA	Yes‡	4497	1945–1999	118 742	93.1	SMR for colon: 1.76 (1.02–2.81), rectum/anus: 1.40 (0.82–2.24)
Hein *et al* (2007)	Both	Intestine, rectum	Asbestos textile	USA	Chrysotile	28	40.3	0.69 (0.46 to 1.00)	1.95 (1.68 to 2.24)	NA	No	3072	1940–2001	118 513	91.4	SMR for intestine: 0.57 (0.35–0.90), rectum: 1.25 (0.57–2.37)
Tsai *et al* (2007)	Men	Large intestine, rectum	Petroleum refinery and chemical	USA	Mixed	21	20.41	1.03 (0.64 to 1.57)	0.82 (0.63 to 1.05)	20	No	1222	1948–2003	25 792.5	98.2	SMR for large intestine: 1.04 (0.62–1.65), rectum: 0.94 (0.19–2.76)
Frost *et al* (2008)	Both	Colon, rectum	Asbestos removal	UK	Mixed	105	73.92	1.42 (1.16 to 1.72)	2.01 (1.81 to 2.21)	NA	Yes	52 387	1971–2005	NA	98	SMR for colon: 1.28 (0.98–1.64), rectum: 1.69 (1.22–2.28)

continued

Table 1 continued

Study	Sex	Type of cancer	Type of industry	Country	Type of asbestos	Mortality of colorectal cancer			SMR of lung cancer	Latency (year)	Smoking information	Cohort size	F/U period	Person-years	F/U %	Comments
						O	E	SMR								
Dement *et al* (2009)	Men (99.7%)	Intestine, rectum	Sheet metal worker	USA, Canada	Mixed	129	157.2	0.82 (0.69 to 0.98)	1.02 (0.94 to 1.11)	NA	Yes	17 345	1986–2004	207 442	NA	SMR for intestine: 0.84 (0.69–1.02), rectum: 0.70 (0.42–1.11)
Harding *et al* (2009)	Both	Colon, rectum	Various	UK	Mixed	480	353.2	1.36 (1.24 to 1.49)	1.87 (1.79 to 1.96)	NA	Yes	99 588	1971–2005	1 779 580	98.5	SMR for colon: 1.28 (1.14–1.44), rectum: 1.51 (1.30–1.74)
Loomis *et al* (2009)	Both	Intestine, rectum	Asbestos textile	USA	Mixed	48	45.76	1.05 (0.77 to 1.39)	1.96 (1.73 to 2.20)	NA	No	5770	1950–2003	181 640	NA	SMR for intestine: 0.93 (0.65–1.29), rectum: 1.59 (0.85–2.73)
Pesch *et al* (2010)	Men	Colon, rectum	Various	Germany	Mixed	7	9.1	0.77 (0.31 to 1.59)	0.39 (0.17 to 0.77)	NA	Yes	576	1993–2007	NA	NA	
Tomioka *et al* (2011)	Men	Colon, rectum	Ship repair worker	Japan	Mixed	4	3.56	1.12 (0.31 to 2.88)	1.97 (1.10 to 3.25)	NA	Yes	249	1947–2007	8467	95.2	
Menegozzo *et al* (2011)	Men	Intestine, rectum	Cement factory	Italy	Mixed	14	10.8	1.30 (0.71 to 2.18)	1.53 (1.22 to 1.89)	NA	No	1247	1965–2005	39 933	98.2	SMR for intestine: 1.14 (0.49–2.25), rectum: 1.57 (0.58–3.42)
Du *et al* (2012)	Both	Colon, rectum	Asbestos miner	China	Chrysotile	2	4.26	0.47 (0.05 to 1.30)	2.5 (1.85 to 3.24)	NA	Yes	1257	1981–2010	32 128	NA	
Wang *et al* (2013)	Both	Small intestine, colon, rectum	Asbestos textile	China	Chrysotile	4	3.38	1.18 (0.32 to 3.03)	3.76 (2.83 to 4.90)	NA	Yes	865	1972–2008	27 475	98.8	
Lin *et al* (2014)	Men	Colon, rectum	Mining, milling	China	Chrysotile	4	2.06	1.94 (0.76 to 4.99)	3.59 (2.76 to 4.66)	NA	No	1539	1981–2006	34 736	100	
Van den Borre and Deboosere (2015)	Men	Colon, rectum	Cement factory, asbestos products manufacturing	Belgium	Chrysotile mainly	3	3.52	0.85 (0.18 to 2.49)	1.75 (1.08 to 2.68)	10	No	1743	2001–2009	NA	NA	SMR for colon: 0.38 (0.01–2.14), rectum: 2.26 (0.27–8.18)
Pira *et al* (2016)	Both	Small intestine, colon, rectum	Asbestos textile factory	Italy	Mixed	33	23.57	1.40 (0.96 to 1.97)	2.96 (2.50 to 3.49)	NA	No	1977	1946–2013	74 126	98.1	
Levin *et al* (2016)	Men (99.2%)	Intestine, rectum	Pipe insulation	USA	Amosite	20	10.24	1.95 (1.19 to 3.02)	2.44 (1.96 to 3.00)	10	Yes‡	1130	1979–2013	NA	91.9	SMR for intestine: 2.40 (1.46–3.70), rectum: 0 (0–1.94)
Oddone *et al* (2017)	Both	Small intestine, colon, rectum	Asbestos cement factory	Italy	Chrysotile, crocidolite	33	35.88	0.92 (0.63 to 1.29)	1.48 (1.27 to 1.72)	NA	No	1818	1970–2014	47 536.1	98.9	SMR for intestine: 1.07 (0.71–1.56), rectum: 0.56 (0.21–1.22)

continued

Table 1 continued

Study	Sex	Type of cancer	Type of industry	Country	Type of asbestos	Mortality of colorectal cancer			SMR of lung cancer	Latency (year)	Smoking information	Cohort size	F/U period	Person-years	F/U %	Comments
						O	E	SMR								
Pira *et al* (2017)	Men	Small intestine, colon, rectum	Mining	Italy	Chrysotile	14	16.8	0.83 (0.45 to 1.40)	1.16 (0.87 to 1.52)	NA	No	1056	1946–2014	37 471	96.2	
Reid *et al* (2018)	Men	Colon, rectum	Mining, milling	Australia	Crocidolite	52	35.91	1.45 (1.08 to 1.90)	2.59 (2.30 to 2.91)	NA	Yes‡	4496	1940–2009	NA	NA	

*Reference lists were provided in online supplementary data.
†Smoking adjusted.
‡Incomplete smoking information.
E, expected number; F/U, follow-up; NA, not applicable;O, observed number.

without heterogeneity (I^2=0.0%, p=0.747). Subgroup analyses were performed for before and after 1965, because peritoneal mesothelioma was frequently misdiagnosed as colorectal cancer until the early 1960s.[14 15] Although the risk of colorectal cancer mortality was significantly increased (SMR 1.17; 95% CI: 1.01 to 1.36) with large heterogeneity (I^2=61.1%, p<0.001) in cohort studies initiated after 1965, the effect size and 95% CI were similar to those of studies started before 1965. In the studies that provided information on smoking, subgroup analyses according to the prevalence of current smokers and ever-smokers showed that the risk of colorectal cancer mortality was not significantly increased. Most studies did not provide data on smoking; in these studies the risk of colorectal cancer mortality was significantly increased (SMR 1.20, 95% CI: 1.07 to 1.34 (ever-smoking); SMR 1.21, 95% CI: 1.05 to 1.29 (current smoking)) with moderate heterogeneity (I^2=38.4%, p=0.028 (ever-smoking); I^2=36.9%, p=0.022 (current smoking)). Moreover, after excluding the studies evaluated as low quality by the modified NOS, all results, with the exception of the exposure-measurement quality component, were significant. Sixteen studies reported separate SMRs for colon/intestine cancer and rectal cancer, while two other studies reported SMRs only for intestine cancer. Random effect meta-analysis was performed on studies reporting separate SMRs for colon/intestine cancer and rectal cancer. Respective summary SMRs for colon/intestine cancer and rectal cancer were 1.15 (95% CI: 0.96 to 1.39) and 1.20 (95% CI: 0.98 to 1.47), the values of which approximated the result of overall pooled SMR for colorectal cancer while falling short of statistical significance (table 2).

Additional subgroup analysis considering smoking

The result of additional subgroup analyses restricting to studies with available smoking data was shown in online supplementary table 2. The overall pooled SMR was 1.15 (95% CI: 0.98 to 1.35); the effect size was comparable to that for all studies, but it was not statistically significant. The result of each subgroup analysis on studies with available smoking data was similar to that of all studies, but there were minor differences on the grounds of statistical significance. For both cohort studies implemented after 1965 and European cohort, loss of statistical significance resulted when analysis restricting to studies with smoking data was carried out. For Australian cohorts, small-sized cohorts, insulation industry cohorts, cohorts with no latency and cohorts with high mortality of lung cancer, statistical significance was increased after restriction. In particular, when studies with high mortality of lung cancer were analysed based on smoking information, SMRs for four studies that showed high ever-smoking prevalence was 1.60 (95% CI: 1.29 to 1.98), which was significantly increased. Similarly, summary SMR for five studies that showed low ever-smoking prevalence was 1.39 (95% CI: 1.15 to 1.68), which was significantly increased as well (online supplementary figure 1). Summary SMR for three studies that showed high current smoking prevalence was calculated to be statistically significant: 1.46 (95% CI: 1.22 to 1.75); on the contrary, that for two studies that showed low current smoking prevalence turned out statistically insignificant: 1.44 (95% CI: 0.56 to 3.66) (online supplementary figure 2).

Sensitivity test

Sensitivity tests were performed by removing each study in turn. The pooled risk estimates ranged from 1.15 to 1.18, and all were statistically significant (figure 3). The results of the meta-analysis

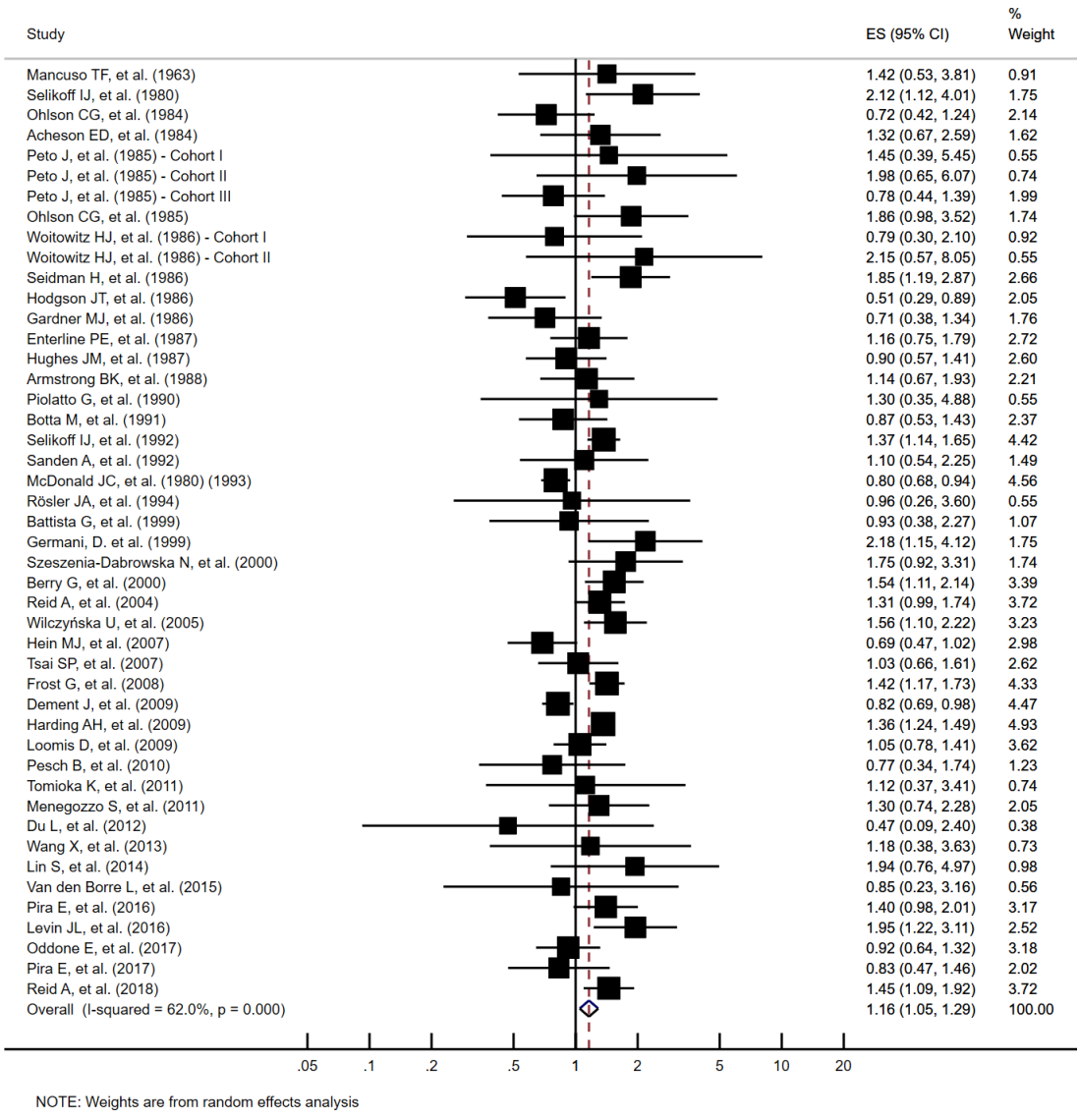

Figure 2 Forest plot of studies included in the meta-analysis of exposure to asbestos and the risk of colorectal cancer mortality. ES, effect size.

did not significantly vary according to the results of the individual studies.

Publication bias

Begg's funnel plot was symmetric (online supplementary figure 3), and Egger's regression asymmetry test was not significant (p-value for bias=0.645). Thus, there was no publication bias in the selected studies.

DISCUSSION

We quantitatively assessed the association between exposure to asbestos and colorectal cancer in a systemic review and meta-analysis. The results showed a significantly increased risk of colorectal cancer among workers exposed to asbestos, with an overall pooled risk estimate of 1.16 (95% CI: 1.05 to 1.29). A sensitivity analysis of the influence of individual studies showed robustness and there was no publication bias, suggesting that the results were reliable.

The pooled SMR for colorectal cancer was higher, at 1.43 (95% CI: 1.30 to 1.56) in the studies in which the SMRs of lung cancer were greater than twofold. Lung cancer is strongly associated with asbestos exposure and therefore an increased risk of lung cancer could be considered as evidence of high-level exposure to asbestos. Slightly more than half of the studies (26) in this meta-analysis used formal workplace measurements of asbestos. Among them, few studies included data for all workers. Some studies categorised asbestos exposure using only rough estimates. Therefore, it was impossible to classify levels of asbestos exposure accurately. Instead, the presence of an increased risk of lung cancer, which is associated with asbestos, was used as a substitute for high asbestos exposure. A similar approach to meta-analysis of the risk of cancer due to occupational exposure has been adopted to differentiate among levels of exposure.[16–19] It should also be considered that these results were confounded by smoking. It is possible that cohorts that exhibit high lung cancer mortality may also have high smoking prevalence. However, when analyses were carried out, taking smoking information into consideration, the proportion of studies with high smoking prevalence (ever smoking: 4 out of 9, current: 3 out of 5) was comparable to that of all studies (ever-smoking: 11 out of 21, current smoking: 7 out of 15). While we should be careful in formulating an interpretation since smoking information was not comprehensive enough, but we suggest a dose–response relationship between asbestos exposure and colorectal cancer.

Table 2 Pooled SMRs of subgroup analysis

	No of studies	Pooled SMR	Heterogeneity	
			I^2 (%)	P value
Study area				
North America (USA and Canada)	14	1.12 (0.93 to 1.35)	73.8	<0.001
Europe	25	1.18 (1.03 to 1.35)	44.5	0.009
Australia	3	1.35 (1.12 to 1.62)	0.0	0.710
Asia	4	1.25 (0.71 to 2.20)	0.0	0.518
Cohort size				
Small (<1500)	21	1.29 (1.13 to 1.49)	0.00	0.536
Large (≥1500)	25	1.10 (0.96 to 1.25)	75.4	<0.001
Type of industry				
Mining, milling	8	1.11 (0.84 to 1.46)	66.7	0.004
Insulation	4	1.49 (1.26 to 1.75)	4.0	0.373
Asbestos cement	8	1.06 (0.84 to 1.32)	23.6	0.241
Textile	10	1.19 (0.93 to 1.52)	49.7	0.037
Miscellaneous	9	1.10 (0.85 to 1.43)	66.2	0.003
Various	7	1.11 (0.83 to 1.48)	62.3	0.014
Follow-up duration				
Short (≤30 years)	21	1.08 (0.89 to 1.30)	54.7	0.001
Long (>30 years)	25	1.21 (1.07 to 1.37)	65.0	<0.001
Latency				
No latency	28	1.19 (1.06 to 1.35)	54.0	<0.001
Exist (5–20 years)	18	1.10 (0.90 to 1.35)	68.4	<0.001
Lung cancer SMR*				
Low (<2)	24	0.97 (0.83 to 1.13)	70.2	<0.001
High (≥2)	21	1.43 (1.30 to 1.56)	0.0	0.747
Smoking (ever) prevalence				
Data not available	25	1.20 (1.07 to 1.34)	38.4	0.028
Low (<75%)	11	1.05 (0.81 to 1.37)	62.1	0.003
High (≥75%)	10	1.21 (0.92 to 1.59)	77.5	<0.001
Smoking (current) prevalence				
Data not available	31	1.21 (1.05 to 1.29)	36.9	0.022
Low (<50%)	8	1.09 (0.82 to 1.44)	49.5	0.054
High (≥50%)	7	1.10 (0.84 to 1.45)	87.4	<0.001
Follow-up started year				
Early (1910–1965)	23	1.16 (0.997 to 1.342)	60.1	<0.001
Late (1966–2001)	23	1.17 (1.01 to 1.36)	61.1	<0.001
Study quality				
Representativeness: representative	35	1.14 (1.02 to 1.28)	62.0	<0.001
Exposure measurement: formal	26	1.11 (0.96 to 1.28)	60.0	<0.001
Comparability of groups: standard	45	1.16 (1.05 to 1.29)	62.0	<0.001
Assessment of outcome: formal	45	1.16 (1.05 to 1.29)	62.8	<0.001
Adequacy of follow-up: virtually complete	26	1.16 (1.02 to 1.32)	44.7	0.008
Types of cancer				
Colon or intestine	18	1.15 (0.96 to 1.39)	68.6	<0.001
Rectum	16	1.20 (0.98 to 1.47)	38.5	0.059

*Reid *et al*'s 2004 study did not provide SMR of lung cancer.

The risk of colorectal cancer was significantly high among insulation workers. In a study of the carcinogenic potency of asbestos using the US Environmental Protection Agency model, the risk of lung cancer was high among textile and insulation workers, but low among mining and milling workers, at the same asbestos concentration.[20] In particular, workers in the insulation industry, who are exposed to amosite, had the highest risk of lung cancer. In our review, all studies of the insulation industry involved amosite and had a higher risk of colorectal cancer compared with other industries. Although the target cancers differed, the results of our review are consistent with those of this previous study.

We conducted separate meta-analyses for studies reporting mortality of colon/intestine cancer and those reporting mortality of rectal cancer. The effect sizes derived for colon/intestine cancer and rectal cancer were comparable to that for colorectal cancer, although they fell short of statistical significance. Some literature suggest that the association between asbestos and colon cancer might be stronger than the one between asbestos and rectal cancer. In our study, however, there seemed to be no difference in the extent of associations. Both associations were not statistically significant, which might be attributed to the fact that only some of 46 studies were included in the separate meta-analyses.[5 19]

In addition, some studies that were included in our meta-analysis have classified small intestine cancer as colorectal cancer without distinguishing it from large intestine cancer, which goes against the norm wherein small intestine cancer is distinguished from colorectal cancer. However, we conjecture that the categorisation as such would have little influence on the overall result, since incidence of small intestine cancer is much lower than that of large intestine cancer.[21]

Several meta-analyses of the association between asbestos exposure and colorectal cancer have been published. In 1985, Morgan *et al*[22] reviewed 45 articles on exposure to asbestos and cancer and reported a slightly but non-significantly increased SMR for colorectal cancer (SMR 1.13; 95% CI: 0.97 to 1.30). In 1990, Weiss[23] reviewed 21 studies of asbestos exposure and colorectal cancer; the pooled SMR for colorectal cancer was not increased (SMR 0.97; p>0.05). In 1995, Weiss[24] reviewed 30 asbestos-exposure studies that reported mortality and incidence data; the overall RR for colorectal cancer was 0.99 (95% CI: 0.92 to 1.07). Gamble[19] reviewed 19 asbestos-exposure studies; the overall SMR for colorectal cancer was significantly increased to 1.48 (95% CI: 1.21 to 1.78) in seven studies with a lung cancer SMR ≥2. However, in studies with a lung cancer SMR <2, the overall SMR was not increased (SMR 0.95; 95% CI: 0.84 to 1.05). In 2008, Gamble[4] reviewed 22 cohort studies on asbestos exposure and GI cancer and found no increase in the overall SMR for colorectal cancer. Horna *et al*[2] performed a meta-analysis of 20 studies of the risk of colorectal cancer; the summary SMR for colorectal cancer was increased to 1.10 (95% CI: 0.92 to 1.32), but this was not significant. However, in eight studies reporting a lung cancer SMR >2, the summary SMR was significantly increased to 1.51 (95% CI: 1.29 to 1.76). Goodman *et al*[25] reviewed 69 asbestos-exposed cohort studies in relation to cancer mortality in 1999, among which 37 reported mortality due to colorectal cancer. The meta-SMR for colorectal cancer was significantly increased to 1.10 (95% CI: 1.03 to 1.17) in 28 studies without latency. However, in nine studies with latency and of ≥10-year duration, the meta-SMR was not increased (SMR 0.89; 95% CI: 0.71 to 1.08). The 2006 [3]Institute of Medicine meta-analysis of 23 cohort studies found a significantly increased summary RR to 1.15 (95% CI: 1.01 to 1.31) when comparing any to no exposure. When comparing high to no exposure, the lower-bound and upper-bound summary RRs were 1.24 (95% CI: 0.91 to 1.69) and 1.38 (95% CI: 1.14 to 1.67), respectively.[5] Among the above-mentioned articles, most did not report

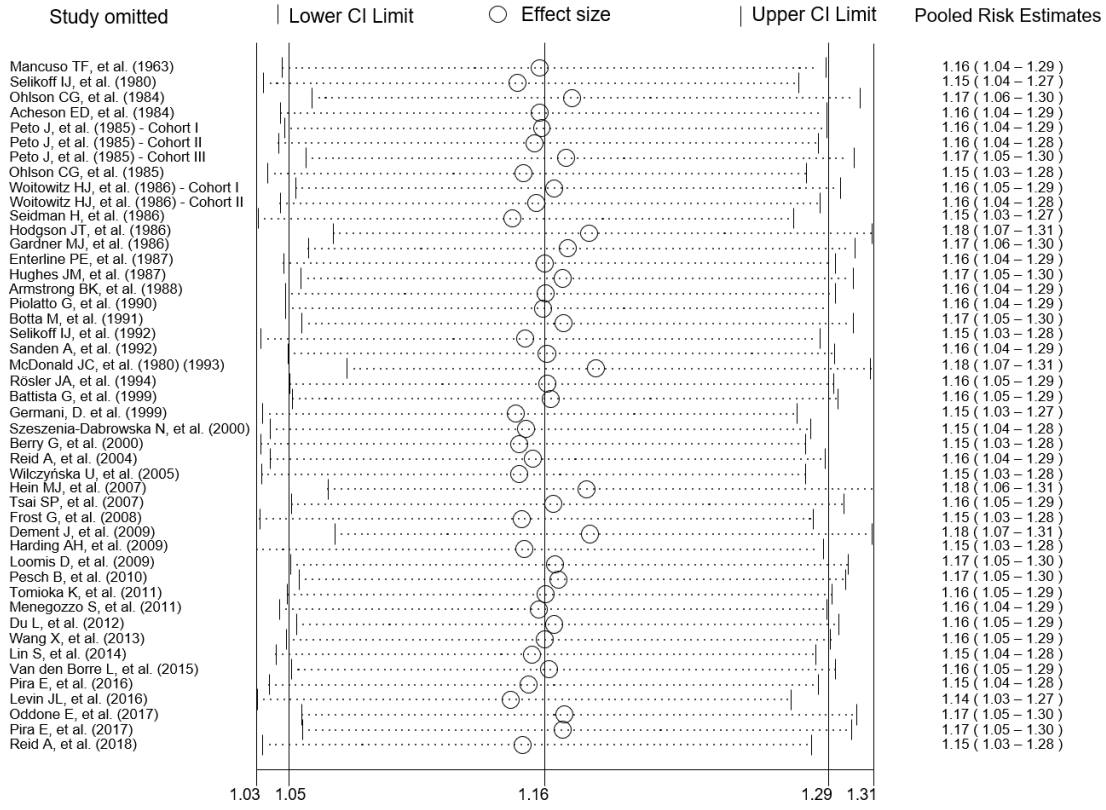

Figure 3 Sensitivity test by omission of individual studies.

a significantly increased association between asbestos exposure and colorectal cancer, while some showed a significantly increased overall SMR or RR. However, in meta-analyses that evaluated asbestos exposure levels indirectly using lung cancer SMRs, the summary estimates were significantly increased in the high-exposure studies and the effect sizes were greater than that calculated for all of the studies.

Induction of colon carcinogenesis by asbestos requires exposure of the lower gastrointestinal (GI) tract to asbestos fibres. Cook *et al*[26] reported that human urine sediments contained amphibole fibres, supporting the notion that asbestos fibres can transit the GI tract. Ehrlich *et al*[27 28] detected asbestos fibres and asbestos bodies in the colon of asbestos-exposed workers. In addition, an IARC review showed that asbestos fibres can penetrate the gut following ingestion.[29] Deposition of asbestos fibres in the respiratory mucosa after swallowing of sputum could facilitate their penetration of the lower GI tract.[30] Alternatively, asbestos could penetrate the lower GI tract after being consumed in drinking water,[31] but animal experimental studies regarding carcinogenicity of ingested asbestos have not revealed positive results.[32–34] In cohort studies of lighthouse keepers, however, incidence of colorectal cancer was found to be significantly increased for the group exposed to drinking water contaminated with asbestos.[35]In addition, Di Ciaula[36] recently reviewed several experimental and epidemiological studies and suggested the possibility in which ingestion of asbestos fibres by drinking of water was linked with colorectal cancer.

We used cancer mortality, not incidence, data in this review. Several studies have evaluated the agreement between death-certificate and cancer-registry data; of them Bedford *et al*[37] reported a high level of agreement—the positive predictive value of colorectal cancer mortality was 96.9%. Therefore, the use of death certificates to estimate cancer incidence is reasonable. Among the articles in this review, several retrospective cohort studies of the SIR used data from the National Cancer Registry. However, few countries have reliable cancer registration data, so we calculated the SMR using only mortality data.

This study had several limitations. First, the heterogeneity among the studies was large. Although a random-effects model was used to correct for this, such large heterogeneity implies inconsistent results, which limits their generalisation.[38] Next, most included studies did not consider risk factors for colorectal cancer (eg, red meat consumption, obesity, alcohol and smoking). More than half of the studies did not provide information on smoking; moreover, those that did used only the present prevalence of smoking. Only two studies adjusted for smoking when calculating the risk of colorectal cancer. In addition, colorectal cancer may have been misdiagnosed in the past; peritoneal mesothelioma was, until the early 1960s, frequently misdiagnosed as colorectal cancer.[14 15] In a subgroup analysis, we found no difference between studies initiated before and after 1965. However, the possibility that mortality due to colorectal cancer was exaggerated in prior studies cannot be completely ruled out. Finally, the overall effect size was small. Therefore, our result that asbestos exposure increases the risk of colorectal cancer should be confirmed in further studies.

Despite these limitations, this study has the following strengths. First, we performed a systematic review and meta-analysis study of the association between occupational exposure to asbestos and colorectal cancer by analysing studies performed in the last 10 years. Our results enhance our understanding of the controversial relationship between asbestos and colorectal cancer. Next, we included a greater number of studies than previous meta-analyses and a large number of deaths due to colorectal cancer (1642), resulting in considerable statistical power. Moreover, subgroup analyses according to study characteristics and

quality were performed to correct for the large heterogeneity and to identify factors that affect the relationship between asbestos and colorectal cancer. In these subgroup analyses, lung cancer mortality was separately categorised for each study, and cohorts with high exposure to asbestos were estimated based on the categorisation, enabling indirect evaluation of the dose–response relationship between asbestos and colorectal cancer.

In conclusion, in this systematic review and meta-analysis, the colorectal cancer mortality rate was increased significantly in workers exposed to asbestos. In particular, workers presumed to be highly exposed to asbestos had an increased colorectal cancer mortality rate, thus supporting the association between asbestos and colorectal cancer. Although the effect size of the overall pooled estimate was small and the heterogeneity among studies was large, our findings imply that occupational exposure to asbestos is a risk factor for colorectal cancer.

Acknowledgements We thank Textcheck (www.textcheck.com) for English language editing of our manuscript.

Contributors KK and KEZ searched literatures, identified relevant articles and reviewed full text. KK designed the study, analysed the data and drafted the manuscript. KEZ interpreted the data and revised the manuscript. DP suggested the study design, interpreted the data and revised the manuscript. All authors read and approved the final manuscript.

Funding This study was supported by the National Research Foundation of Korea (NRF) funded by the Korea government (MSIT) under grant NRF-2019R1A2C2007484

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Kyeongmin Kwak https://orcid.org/0000-0001-6296-8058
Domyung Paek http://orcid.org/0000-0003-4510-6362
Kyung Ehi Zoh http://orcid.org/0000-0002-2821-070X

REFERENCES

1 Paris C, Thaon I, Hérin F, *et al*. Occupational asbestos exposure and incidence of colon and rectal cancers in French men: the asbestos-related diseases cohort (ARDCo-Nut). *Environ Health Perspect* 2017;125:409–15.
2 Homa DM, Garabrant DH, Gillespie BW. A meta-analysis of colorectal cancer and asbestos exposure. *Am J Epidemiol* 1994;139:1210–22.
3 Institute of Medicine. *Asbestos: selected cancers*. Washington, DC: The National Academies Press, 2006: 216–29.
4 Gamble J. Risk of gastrointestinal cancers from inhalation and ingestion of asbestos. *Regul Toxicol Pharmacol* 2008;52(1 Suppl):S124–53.
5 International Agency for Research on Cancer (IARC). *A review of human carcinogens. Part C: arsenic, metals, fibres, and dust*. Lyon, France: IARC Monographs Evaluation of Carcinogenic Risks to Humans, 2012: 100. 219–309.
6 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
7 Alder N, Fenty J, Warren F, *et al*. Meta-analysis of mortality and cancer incidence among workers in the synthetic rubber-producing industry. *Am J Epidemiol* 2006;164:405–20.
8 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
9 Levin JL, Rouk A, Shepherd S, *et al*. Tyler asbestos workers: a mortality update in a cohort exposed to amosite. *J Toxicol Environ Health B Crit Rev* 2016;19:190–200.
10 McDonald JC, Liddell FD, Gibbs GW, *et al*. Dust exposure and mortality in chrysotile mining, 1910-75. *Occup Environ Med* 1980;37:11–24.
11 McDonald JC, Liddell FD, Dufresne A, *et al*. The 1891-1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976-88. *Occup Environ Med* 1993;50:1073–81.
12 Peto J, Doll R, Hermon C, *et al*. Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. *Ann Occup Hyg* 1985;29:305–55.
13 Woitowitz H-J, Lange H-J, Beierl L, *et al*. Mortality rates in the federal Republic of Germany following previous occupational exposure to asbestos dust. *Int Arch Occup Environ Health* 1986;57:161–71.
14 Elmes PC, Simpson MJ, Gibbs GW. Insulation workers in Belfast. A further study of mortality due to asbestos exposure (1940-75). *Occup Environ Med* 1977;34:174–80.
15 Smith DD. *The health effects of asbestos: an evidence-based approach*. Boca Raton, FL: CRC Press, 2015: 146–63.
16 Camargo MC, Stayner LT, Straif K, *et al*. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. *Environ Health Perspect* 2011;119:1211–7.
17 Welling R, Beaumont JJ, Petersen SJ, *et al*. Chromium VI and stomach cancer: a meta-analysis of the current epidemiological evidence. *Occup Environ Med* 2015;72:151–9.
18 Tomioka K, Saeki K, Obayashi K, *et al*. Risk of lung cancer in workers exposed to benzidine and/or beta-naphthylamine: a systematic review and meta-analysis. *J Epidemiol* 2016;26:447–58.
19 Gamble JF. Asbestos and colon cancer: a weight-of-the-evidence review. *Environ Health Perspect* 1994;102:1038–50.
20 Berman DW, Crump KS. Update of potency factors for asbestos-related lung cancer and mesothelioma. *Crit Rev Toxicol* 2008;38:1–47.
21 Pan SY, Morrison H. Epidemiology of cancer of the small intestine. *World J Gastrointest Oncol* 2011;3:1–42.
22 Morgan RW, Foliart DE, Wong O. Asbestos and gastrointestinal cancer. A review of the literature. *West J Med* 1985;143:60–5.
23 Weiss W. Asbestos and colorectal cancer. *Gastroenterology* 1990;99:876–84.
24 Weiss W. The lack of causality between asbestos and colorectal cancer. *J Occup Environ Med* 1995;37:1364–73.
25 Goodman M, Morgan RW, Ray R, *et al*. Cancer in asbestos-exposed occupational cohorts: a meta-analysis. *Cancer Causes Control* 1999;10:453–65.
26 Cook P, Olson G. Ingested mineral fibers: elimination in human urine. *Science* 1979;204:195–8.
27 Ehrlich A*et al*. Asbestos bodies in carcinoma of colon in an insulation worker with asbestosis. *JAMA* 1985;254:2932–3.
28 Ehrlich A, Gordon RE, Dikman SH. Carcinoma of the colon in asbestos-exposed workers: analysis of asbestos content in colon tissue. *Am J Ind Med* 1991;19:629–36.
29 Chouroulinkov I. Experimental studies on ingested fibres. *IARC Sci Publ* 1989;(90):112–26.
30 Miller AB. Asbestos fibre dust and gastro-intestinal malignancies. review of literature with regard to a cause/effect relationship. *J Chronic Dis* 1978;31:23–33.
31 Cook PM. Review of published studies on gut penetration by ingested asbestos fibers. *Environ Health Perspect* 1983;53:121–30.
32 Varga C. Asbestos fibres in drinking water: are they carcinogenic or not? *Med Hypotheses* 2000;55:225–6.
33 Donham KJ, Berg JW, Will LA, *et al*. The effects of long-term ingestion of asbestos on the colon of F344 rats. *Cancer* 1980;45:1073–84.
34 Ward JM, Frank AL, Wenk M, *et al*. Ingested asbestos and intestinal carcinogenesis in F344 rats. *J Environ Pathol Toxicol* 1980;3:301–12.
35 Kjærheim K, Ulvestad B, Martinsen JI, *et al*. Cancer of the gastrointestinal tract and exposure to asbestos in drinking water among lighthouse keepers (Norway). *Cancer Causes Control* 2005;16:593–8.
36 Di Ciaula A. Asbestos ingestion and gastrointestinal cancer: a possible underestimated hazard. *Expert Rev Gastroenterol Hepatol* 2017;11:419–25.
37 Bedford RL, Lourens SG, Lynch CF, *et al*. Utility of death certificate data in predicting cancer incidence. *Am J Ind Med* 2014;57:153–62.
38 Higgins JPT*et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.