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Occupational asbestos exposure and gastrointestinal cancers: systematic review and meta-analyses

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ABSTRACT

Objective To conduct meta-analyses of occupational asbestos exposure and oesophageal, stomach and colorectal cancer risk, including a critical exposure assessment approach.

Methods The search strategy was executed on MEDLINE, Embase, CINAHL, Scopus and Web of Science databases (March 2022, March 2024). Effect estimates (ORs, HRs, standardised incidence ratio and standardised mortality ratio) from eligible cohort and case-control studies were combined in random effects models. Meta-relative risks (mRRs) were calculated by cancer site and exposure characteristics. Investigators with occupational epidemiology and hygiene expertise came to a consensus on the estimates where there was confidence in significant asbestos exposure.

Results A total of 82 (oesophageal), 153 (stomach) and 144 (colorectal) papers met the inclusion criteria. Elevated mRRs were observed for any occupational asbestos exposure for oesophageal (1.17 (95% CI 1.07 to 1.29)), stomach (1.14 (95% CI 1.05 to 1.23)) and colorectal cancer (1.16 (95% CI 1.08 to 1.24)). There was consistency of mRR estimates and higher mRRs in meta-analyses where there was increased confidence in the categorisation of highly exposed workers, including among the highest exposed workers in exposure-response studies (oesophageal: 1.63 (95% CI 1.29 to 2.06); stomach: 1.28 (95% CI 1.09 to 1.52); colorectal: 1.29 (95% CI 1.09 to 1.53)), among asbestos insulation workers (oesophageal: 1.68 (95% 1.19 to 2.36); stomach: 1.53 (95% 0.93 to 2.51); colorectal: 1.59 (95% 1.14 to 2.23)) and among workers in cohorts with a twofold or greater risk of asbestos-related lung cancer (oesophageal: 1.40 (95% CI 1.14 to 1.71); stomach: 1.33 (95% CI 1.14 to 1.56); colorectal: 1.47 (95% CI 1.34 to 1.61)).

Conclusion The meta-analyses support a causal link between occupational asbestos exposure and the risk of oesophageal, stomach and colorectal cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prior authoritative evidence reviews found suggestive, limited or inadequate evidence for occupational asbestos exposure and the risk of gastrointestinal cancers.

WHAT THIS STUDY ADDS

⇒ In meta-analyses, we found elevated risks of oesophageal, stomach and colorectal cancer with occupational asbestos exposure and stronger risks in meta-analyses of studies where there was increased confidence in the categorisation of the highest exposed workers.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The evidence synthesis and consistency of evidence support a causal link between occupational asbestos exposure and the risk of gastrointestinal cancers that can inform prevention practices and workers' compensation policy for exposed workers.

BACKGROUND

Asbestos has been classified as carcinogenic to humans by the WHO's International Agency for Research on Cancer (IARC) and identified as a specific cause of pleural and peritoneal mesothelioma and cancers of the lung, larynx and ovary, primarily among occupationally exposed workers.[1] Epidemiological evidence for occupational asbestos exposure as a cause of gastrointestinal (GI) cancers among workers has been suggestive, limited or inadequate.

The Monograph on Asbestos by the IARC (2009)[1] and a prior systematic review by the United States National Academy of Sciences' Institute of Medicine (IOM) Committee on Asbestos (2006)[2] are the two most authoritative summaries of evidence on asbestos disease epidemiology. The IOM Committee concluded in 2006 that there was suggestive evidence for asbestos exposure as a cause of stomach and colorectal cancer and inadequate evidence for oesophageal cancer.[2] The IARC Working Group concluded in 2009 that there were positive associations, based on limited evidence, for asbestos exposure as a cause for pharynx and stomach and inadequate evidence for oesophageal cancer.[1] The Working Group was divided as to whether the evidence was strong enough to warrant the classification of asbestos as a cause of colorectal cancer.[1]

The Finnish Institute for Occupational Health (FIOH), in collaboration with the International Commission on Occupational Health, convened an international group of experts in 2014 to update the evidence for asbestos-related disease.[3] The FIOH consensus was in accordance with that of

the IARC review that there was consistency of evidence of an increased risk of stomach and colorectal cancers with asbestos exposure, especially for heavy and long-duration exposures, but that the evidence was not definitive.[3]

More recently, Peng and colleagues[4] published a systematic review and meta-analysis of 32 cohort mortality studies in 2015 and reported an overall elevated risk of stomach cancer with occupational asbestos exposure. Also in 2015, Fortunato and Rushton[5] published a meta-analysis of 40 mortality and 15 incidence cohort studies and reported an elevated risk of stomach cancer with occupational asbestos exposure and stronger elevated risks in meta-analyses of studies where there was also an increased risk of asbestos-related lung cancer and among workers in asbestos-related occupations. In 2019, Kwak and colleagues[6] published a systematic review and meta-analysis of 46 mortality studies and reported an elevated risk of colorectal cancer with occupational asbestos exposure, and stronger elevated risks where there was also an increased risk of asbestos-related lung cancer among workers, and among workers in an asbestos insulation-related occupation. Finally in 2021, Wu and colleagues[7] published a systematic review and meta-analysis of 34 cohort studies and reported an elevated risk of oesophageal cancer associated with occupational asbestos exposure and stronger elevated risks for the highest exposed workers and for workers in asbestos-related occupations.

The purpose of the current study was to conduct an updated systematic review and meta-analyses of the evidence for occupational asbestos exposure and the risk of GI cancers, given (a) the publication of many more relevant papers since the time of the IARC and IOM reviews, including the additional evidence from the systematic reviews published subsequently by Peng,[4] Fortunato and Rushton,[5] Kwak[6] and Wu[7] on colorectal, stomach and oesophageal cancer, respectively and (b) the opportunity to review three GI sites with the same methodology at the same time to investigate the consistency of findings.

Further, the current review and meta-analyses adopted a critical exposure assessment approach similar to that of the IARC review[1] and advocated for by experts in cancer epidemiology.[8] To assess studies evaluating the relationship between occupational asbestos exposure and GI cancers, the investigators agreed to an informativeness approach that prioritised the inclusion and meta-analyses of studies for which there was increasing confidence of sufficiently high and/or prevalent asbestos exposure. This informative approach is reflected in the selection of preferred estimates within and across eligible studies (eg, the most recent estimates, the estimates with the longest follow-up, and exposure based on measured levels); and the subgroup analyses of studies for workers with known exposure to asbestos (eg, mining, manufacturing), with exposure-response estimates among the highest exposed workers (eg, estimates based on measured levels, job exposure matrices, and/or expert assessment) and with asbestos exposure based on a twofold increased risk of lung cancer among workers. The robustness of these decisions was investigated in cumulative meta-analyses (stronger exposure assessment methods with time), meta-analysis for cohort versus case-control studies, incidence versus mortality estimates, meta-analyses excluding proportionate mortality ratio (PMR) estimates, meta-analyses using different preferred estimates (individual cohort study estimates vs combined cohort studies) and leave-one-out meta-analyses (influence of any one study). Traditional quality assessment approaches, developed for randomised controlled studies, pay little attention to exposure assessment methods that are key for a review of evidence focused on observational studies and occupational asbestos exposure.[9–11]

The current approach of an expert-informed assessment is consistent with calls that increased weight be given to exposure assessment and study 'informativeness' in reviews of evidence of exposures and cancers.[12]

This systematic review and meta-analysis study was conducted to answer the following primary questions:

- Does occupational asbestos exposure increase esophageal, stomach or colorectal cancer risk, and is there an exposure-response relationship by asbestos exposure characteristics?
- Does the esophageal, stomach or colorectal cancer risk co-vary with asbestos-related lung cancer risk?

METHODS

Literature search

This study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13 14] and the Cochrane Collaboration best practices for meta-analyses on health and medical topics.[15] The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO#CRD42022282524).[16 17]

The literature search strategy was developed by the investigators in collaboration with the health librarian at the University of British Columbia.[18] The search strategy included keywords and MeSH subject headings to identify cohort OR case-control study designs AND (GI) cancers AND occupational (asbestos) exposures. GI-specific cancer keywords were not included in the search for occupational cohort studies as sites are not always mentioned in the titles, abstracts or subject headings of these studies. Asbestos-specific keywords were not included in the search for case-control studies for the same reason. An additional search was conducted for occupational asbestos exposure AND GI cancers keywords only, as the study design is not always included in the titles, abstracts or subject headings of occupational epidemiological studies. References lists for prior evidence reviews[1 2 4–7] were searched for additional eligible studies. Online supplemental appendix 1 provides the full search strategy for MEDLINE via Ovid. This search strategy was adapted and executed on the Embase, CINAHL, Scopus and Web of Science databases. The search strategy was executed in March 2022, and re-run in March 2024 (executed on MEDLINE and Embase), resulting in 132 new records for screening following the removal of duplicates, and no new additional eligible studies.

Using Covidence,[19] all abstracts and full-texts were randomly assigned (avoiding assignment of a study to authors) and reviewed independently by pairs of investigators with occupational epidemiology and hygiene/exposure assessment expertise to make a determination of eligibility for inclusion. Disagreements on inclusion criteria were resolved by re-review and consensus.

Studies were included based on the following criteria:

- Original, epidemiological studies with cohort or (nested) case-control study designs.
- Studies that reported a quantitative effect estimate of the association (relative risk (RR), OR, HR, standardised mortality ratio (SMR), standardised incidence ratio (SIR) and PMR) between occupational asbestos exposure and oesophageal, stomach and/or colon/rectal/colorectal cancer sites among humans.
  - Studies of mixed occupational and environmental asbestos exposure or environmental exposure only were excluded.
  - Studies with estimates based on combined GI sites only or GI site(s) combined with other cancers only were excluded.

- No restriction on publication year, country/region or language.
  - Non-English publications were screened for inclusion by investigators with French, German, Italian, Spanish and Japanese language proficiencies or translated to English using Google Translate. If multiple papers were published for the same study/cohort, the English version was preferred.

The IARC Table Builder[20] was refined by the investigators for extracting the following data elements from included studies: first author, publication year, study design, study location, cancer outcome(s), number of cases, asbestos exposure measure(s) and source of exposure data, occupation(s) and/or industry(ies), asbestos fibre type(s), effect estimate(s), variance estimate(s) or confidence interval(s) and asbestos-related lung cancer effect estimates.

Meta-analyses

All meta-analyses were conducted using the Stata statistical software V.17.0[21] and considered Cochrane best practices.[22] Effect estimates were assumed to be equivalent to RRs and natural log transformed for meta-analyses.[23] Crude RRs were computed manually if only observed and expected counts were reported, and missing CIs computed using the Stata -eclpci- command that assumes a Poisson distribution. Effect estimates reported by strata only (eg, age, sex) were combined using random effect models to determine the overall effect estimate.

Only one independent effect estimate was included per meta-risk analysis if there were multiple analyses within a paper or multiple papers for the same cohort over time, with preference for the most informative estimates, as follows:

- the incidence verses mortality estimate;
- the estimate based on the longest follow-up period (usually the most recent paper);
- the estimate based on censoring at the last known date alive versus a cut-off date;
- the SMR or SIR estimates based on regional versus national population reference rates;
- the mortality estimate based on death certificates versus another data source;
- the estimate from pooled analyses of underlying cohorts (ie, larger sample sizes, longer follow-up) and
- the estimate that informed a specific meta-analysis for asbestos exposure characteristics (eg, by occupation, exposure-response relationship).

Meta-relative risks (mRRs) with associated 95% CIs were estimated using random-effects models to account for heterogeneity in the study estimates and a restricted maximum likelihood method to estimate the variance component parameters.[22 24 25] The mRRs and 95% CIs with the underlying effect estimates are presented in forest plots. Tests for heterogeneity were performed to quantify the degree of inconsistency between study results (Q, T^2 and I^2 statistics).[26 27]

Meta-analyses were conducted for overall pooled risk estimates of oesophageal, stomach and colorectal cancer for any asbestos exposure versus non exposure and for pooled risk estimates stratified by asbestos exposure characteristics, including for studies with dose-response estimates (high vs low exposure), asbestos-related occupations/industries (mining, insulating, cement manufacturing), asbestos-related lung cancer risks (RR<1.00, 1.00–1.99, 2.00+) and asbestos fibre-type (chrysotile, amphibole, mix, unknown).

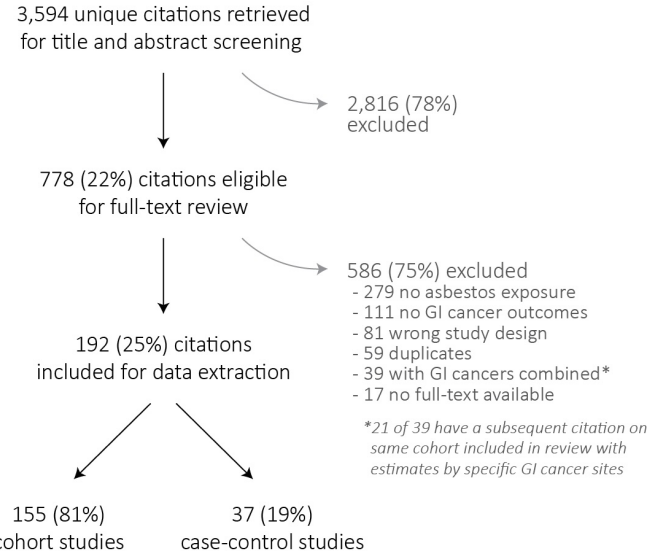


Figure 1 Flow chart for inclusion of studies in the systematic review and meta-analyses of occupational asbestos exposure and GI cancers. GI, gastrointestinal.

Sensitivity analyses were conducted to investigate the robustness of the results to the inclusion of any one study, the addition of studies over time, the preferred effect estimates when multiple estimates were available, the exclusion of PMR estimates and cohort versus case-control study design. Funnel plots were created to evaluate the potential for publication bias.

No ethics approval was required for this systematic review and meta-analysis study. This study was exempted from review by the governing university Office of Research Ethics because it relied exclusively on data that was in the public domain.

RESULTS

Literature search

A total of 3594 unique citations were retrieved across the combined search strategies and databases. Based on title/abstract and full-text screening, 192 publications/studies were included in the systematic review and meta-analyses of occupational asbestos exposure and GI cancers (figure 1). Of the 192 included studies, 155 (81%) were cohort and 37 (19%) case-control designs. A total of 82 studies (43%) investigated oesophageal cancer, 153 studies (80%) stomach cancer and 144 studies (75%) colorectal cancer. After the selection of preferred effect estimates as the most informative to the research questions and the selection of one independent estimate per cohort, a total of 56 studies contributed independent effect estimates to meta-analyses for oesophageal cancer, 90 studies to meta-analyses for stomach cancer and 82 studies to meta-analyses for colorectal cancer. Online supplemental appendix 2 provides the descriptive tables of the included studies for oesophageal (online supplemental table S2-1), stomach (online supplemental table S2-2) and colorectal (online supplemental table S2-3) cancers.

Meta-analyses results

Table 1 presents the mRRs with corresponding 95% CIs from the random effects meta-analyses models by GI site and stratified by asbestos exposure characteristics. Online supplemental appendix 3 provides the forest plots for each corresponding meta-analysis.

Overall, elevated mRRs were observed for oesophageal (1.17 (95% CI 1.07 to 1.29)), stomach (1.14 (95% CI 1.05 to 1.23))

Table 1 Meta-relative risks (mRRs) for the association between occupational asbestos exposure by gastrointestinal cancers site, overall and subgroup analyses defined by asbestos exposure characteristics

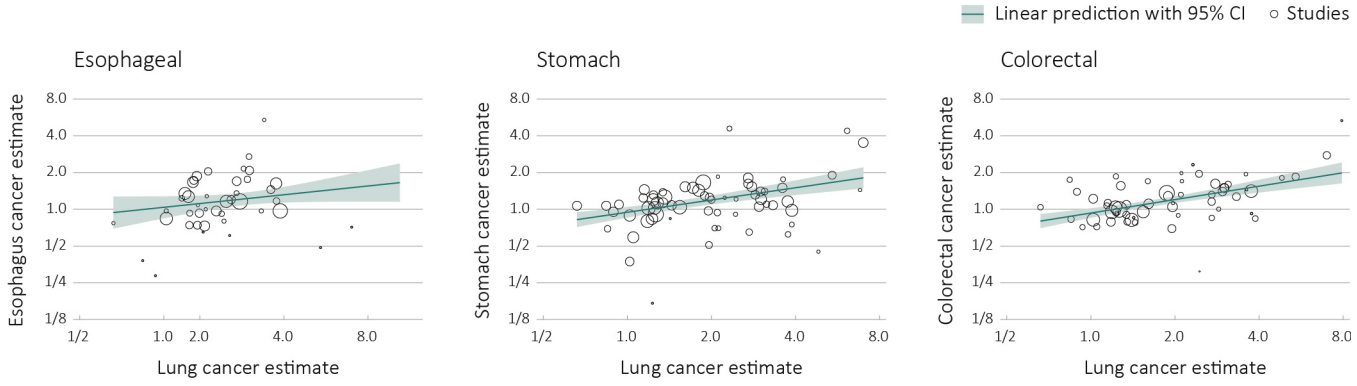
Asbestos exposure categorisation	Oesophageal cancer mRRs (95% CIs)	Stomach cancer mRRs (95% CIs)	Colorectal cancer mRRs (95% CIs)
Any versus non exposed	1.17 (1.07 to 1.29)	1.14 (1.05 to 1.23)	1.16 (1.08 to 1.24)
Major occupations/industries			
Asbestos-related insulation workers	1.68 (1.19 to 2.36)	1.53 (0.93 to 2.51)	1.59 (1.14 to 2.23)
Asbestos-related cement workers	1.12 (0.84 to 1.47)	1.14 (0.99 to 1.32)	1.21 (1.06 to 1.38)
Asbestos-related miners	1.13 (0.78 to 1.63)	1.30 (1.14 to 1.49)	1.15 (0.82 to 1.63)
All other occupations/industries	1.16 (1.02 to 1.32)	1.01 (0.91 to 1.13)	1.07 (0.99 to 1.16)
Asbestos-related lung cancer risk			
Risk ratios <1.00	0.53 (0.15 to 1.89)	0.81 (0.62 to 1.08)	1.05 (0.80 to 1.39)
Risk ratios 1.00–1.99	1.15 (1.02 to 1.29)	1.07 (0.95 to 1.20)	1.02 (0.93 to 1.11)
Risk ratios ≥2.00	1.40 (1.14 to 1.71)	1.33 (1.14 to 1.56)	1.47 (1.34 to 1.61)
Asbestos exposure-response			
Highest versus lowest exposed	1.63 (1.29 to 2.06)	1.28 (1.09 to 1.52)	1.29 (1.09 to 1.53)
Asbestos fibre type			
Chrysotile	1.17 (0.89 to 1.53)	1.09 (0.88 to 1.35)	1.05 (0.88 to 1.26)
Amphibole	1.16 (1.02 to 1.31)	1.35 (1.12 to 1.63)	1.38 (1.27 to 1.49)
Chrysotile and amphibole mix	1.44 (1.20 to 1.73)	1.21 (1.04 to 1.41)	1.23 (1.09 to 1.38)
Unclear/unknown	1.05 (0.85 to 1.30)	0.94 (0.84 to 1.06)	0.99 (0.89 to 1.10)

and colorectal cancer (1.16 (95% CI 1.08 to 1.24)) for any occupational asbestos exposure compared with non exposure. Heterogeneity was observed in the study effect estimates and CIs included in the overall pooled analyses with more heterogeneity observed among the studies of stomach (I^2=79.1%) and colorectal cancer (I^2=69.9%) than for oesophageal cancer (I^2=27.7%).

For occupational exposure classification, the highest mRRs were observed among asbestos insulators/insulation manufacturers for oesophageal (mRR=1.68 (95% CI 1.19 to 2.36)), stomach (mRR=1.53 (95% CI 0.93 to 2.51)) and colorectal cancer (mRR=1.59 (95% 1.14–2.23)). Elevated mRRs were also observed for stomach cancer among asbestos miners (mRR=1.30 (95% CI 1.14 to 1.49) and colorectal cancer among asbestos cement workers (mRR=1.21 (95% CI 1.06 to 1.38)). The remaining mRRs by occupational exposure classification ranged from 1.12 to 1.15. Heterogeneity was observed in the study effect estimates and CIs used in these meta-analyses by occupational exposure classification, with more heterogeneity observed among the studies for stomach (I^2 ranging from 0% to 75.2%) and colorectal cancer (I^2 from 20.8% to 67.5%) than for oesophageal cancer (I^2 from 0% to 30.3%).

Elevated mRRs were observed for oesophageal (mRR=1.40 (95% CI 1.14 to 1.71)), stomach (mRR=1.33 (95% CI 1.14 to 1.56)) and colorectal cancer (mRR=1.47 (95% CI 1.34 to 1.61)) in the meta-analyses of cohort studies where there was also a twofold or greater risk of asbestos-related lung cancer among workers. Further, using meta-regression (correlation) analyses and scatter plots (figure 2), the risk of GI cancers increased with the risk of asbestos-related lung cancer in the same cohort (regression coefficient (log-scale) for oesophageal (β=0.37 (95% CI 0.25 to 0.49)), stomach (β=0.33 (95% CI 0.21 to 0.46)) and oesophageal (β=0.24 (95% CI −0.02 to 0.50)) cancers). Heterogeneity was observed in the study effect estimates and CIs included in these meta-analyses by asbestos-related lung cancer risk in the same cohort, with more heterogeneity observed among the results for stomach cancer (I^2=39.4%) than for oesophageal (I^2=23.0%) or colorectal (I^2=0%) cancer.

In the meta-analysis of studies that reported an exposure-response relationship (table 1), elevated mRRs were observed



Weights: Random effects. Linear regression line and bubbles are weighted by inverse-variance. Estimates were analyzed on the log-scale and then exponentiated to relative risks for the figure.

Figure 2 Scatter plots and linear regression of asbestos-related lung cancer relative risk estimates by GI cancer relative risk estimates. GI, gastrointestinal.

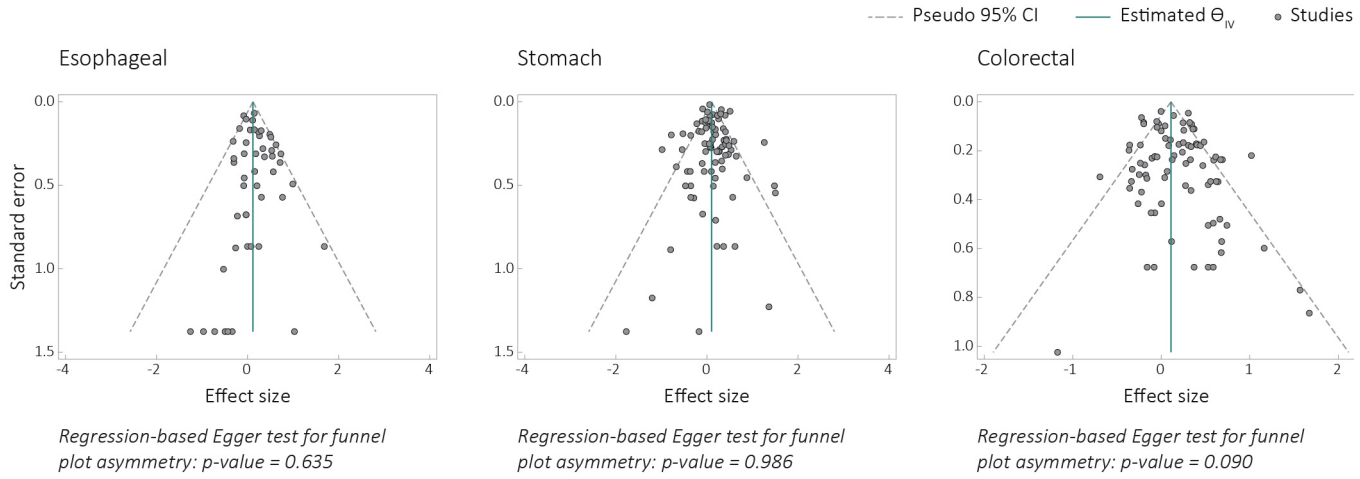


Figure 3 Funnel plots for studies included in the meta-analyses to investigate occupational asbestos exposure and GI cancer risk, by the type of GI cancer. GI, gastrointestinal.

for oesophageal (mRR=1.63 (95% CI 1.29 to 2.06)), stomach (mRR=1.28 (95% CI 1.09 to 1.52)) and colorectal cancer (mRR=1.29 (95% CI 1.09 to 1.53)) among workers in the highest asbestos exposure classifications compared with those in the lowest. Heterogeneity was observed in the study effect estimates and CIs included in these meta-analyses of exposure-response studies, with more heterogeneity observed among the results for stomach cancer (I^2=72.9%) than for colorectal (I^2=19.0%) or oesophageal (I^2=8.8%) cancer.

No discernable pattern in mRRs was observed for the risk of GI cancer by asbestos fibre type, except that the lowest mRRs were observed in meta-analyses of studies where the fibre type was not specified (ranging from 0.94 to 1.05). Elevated mRRs were observed for exposure to mixed fibres for oesophageal cancer (mRR=1.44 (95% CI 1.20 to 1.73)) and for exposure to amphibole-only fibres for stomach (mRR=1.35 (95% CI 1.12 to 1.63)) and colorectal (mRR=1.38 (95% CI 1.27 to 1.49)) cancer. There was more heterogeneity in the study effect estimates and CIs included in these subanalyses than in other meta-analyses due to a smaller number of studies within strata by fibre type.

Sensitivity analyses

The funnel plots (figure 3) for the meta-analyses were symmetric and the tests for asymmetry indicated minimal presence of small-study effects.[27] There was consistency of elevated mRRs in the leave-one-study-out sensitivity analyses (online supplemental figure S4 1a -c). Cumulative meta-analyses that incrementally recalculates the mRRs with the addition of each study chronologically resulted in more consistent estimates with less heterogeneity for all three cancer sites (online supplemental figures S4 2a-c). The elevated mRRs remained in a sensitivity analysis of cohort-only studies and in the analysis of case-control-only studies (online supplemental table S4-1). The elevated mRRs remained in a sensitivity analysis excluding PMR estimates (five of 82 estimates for oesophageal cancer studies, four of 153 estimates for stomach cancer studies and four of 144 estimates for colorectal cancer studies) (online supplemental table S4-2) and in an analysis of incidence versus mortality estimates (online supplemental table S4-3).

DISCUSSION

We observed elevated mRRs for oesophageal, stomach and colorectal cancer with occupational exposure to asbestos. The strongest mRRs were observed in studies among workers in the highest exposed groups, among workers with a history of exposure as asbestos insulators/insulation manufacturers and among workers where there was a twofold or greater risk of asbestos-related lung cancer in the same cohort. We observed consistency of elevated mRRs with increasing confidence in the assessment of (high) occupational asbestos exposure, and the results were robust to multiple sensitivity analyses.

This study represents the most comprehensive review yet of the epidemiological evidence of occupational asbestos exposure and GI cancers. The search strategy was designed to be inclusive of all peer-reviewed and published cohort and case-control studies to date, including mortality and morbidity cancer studies, English and non-English language studies and new studies published since the prior authoritative evaluations by IOM and IARC. Studies of the same cohort over time were included in the systematic review database to ensure the selection of the most informative independent effect estimate and to maximise the number of estimates available for stratified meta-analyses by asbestos exposure characteristics.

In the current review, the magnitude of the mRRs was stronger when the meta-analyses were based on studies where there was increased confidence in the classification of substantial occupational asbestos exposure (eg, where there was a twofold risk of lung cancer in the same cohort) and for which there was less observed heterogeneity in the effect estimates (eg, more recent studies with stronger methods). While causal inference is more challenging when the magnitude of the statistical relationship is closer to null, this does not negate the presence of a causal relationship. Many recently established causal relationships are based on small or moderately increased risks. These smaller risk estimates are probably close to the 'true' risk and not due to study limitations or incomplete adjustment for potential confounders. The consistency of risk estimates and the strength of association with increased confidence in higher asbestos exposure levels were crucial factors in drawing conclusions from the systematic review evidence.[27 28]

Relatively few of the included studies in the meta-analyses provided exposure-response estimates (29%, 44% and 30%

of oesophageal, stomach and colorectal cancer studies, respectively) and even fewer provided directly comparable exposure categories. However, exposure-response studies were considered the most informative based on quantitative exposure assessment methods using direct exposure measurements, job-exposure matrices and/or expert opinion and exposure metrics based on duration, intensity, frequency and/or cumulative exposure. While the assessment of 'high' asbestos exposure classification was relative to a study, the investigators are confident that these categories represented workers with the highest levels of asbestos exposure in their respective study samples, and that the consistency of elevated mRRs estimates for all three GI cancers in these highest exposure categories provides strong evidence of a relationship.

Some of the highest mRRs for all three GI cancers were observed among insulators and insulating manufacturing workers, an established high-risk group for asbestos-related disease.[1 29] Assessing risk defined by asbestos-related occupations yielded some heterogeneity, likely because exposure defined solely on occupation does not reflect elements of intensity or duration of exposure. Asbestos in insulation work is more prone to fraying, crumbling or abrading with an increased likelihood of airborne fibres and higher concentrations than with other types of industrial processes (*Monograph Table 1.3* [1]), and higher risks of GI cancers have been observed among insulation-related work compared with other asbestos-related work.[6]

The risk of asbestos-related lung cancer provides a strong measure of significant asbestos exposure (ie, high exposure contrasts in combination with methods that accurately captured and modelled these contrasts) for investigating the risk of GI cancers in the same cohort. In the current systematic review, the mRRs for all three GI cancers were positively correlated with the risk of asbestos-related lung cancer in their respective cohorts. Further, when restricting to studies with an RR of twofold or greater, there was consistency of stronger elevated mRRs for all three GI cancers.

The included studies did not provide adequate evidence to assess the risk of GI cancers by asbestos fibre type. Evidence for GI cancer risk by asbestos fibre type will remain a challenge as workers in different industries, eras and geographic locations are exposed to different types and sizes of asbestos fibres, and fibre type on its own is not a measure of dose.

The conclusion of a causal elevated risk of stomach and colorectal cancers with occupational asbestos exposure in the current systematic review is consistent with the reviews by IARC,[1] IOM (2006)[2] and FIOH (2014)[3] and with the more recent systematic reviews by Peng *et al* (stomach),[4] Fortunato and Rushton (stomach)[5] and Kwak *et al* (colorectal).[6] The conclusion of an elevated risk of oesophageal cancer with occupational asbestos exposure is stronger than that of the IOM and IARC reviews in 2006 and 2009/12, but consistent with the more recent systematic review by Wu in 2021.[7] An elevated risk for oesophageal cancer in the current review and the recent review by Wu may be a result of the inclusion of more well-designed studies (ie, 22 studies published since 2006) as this was the GI cancer that had the fewest studies/estimates in prior meta-analyses and where the evidence was assessed as inadequate or inconclusive. As demonstrated by the chronological sensitivity analysis, the consistency of the results has increased over time.

The relationship between occupational asbestos exposure and GI cancer risks may vary by smoking or alcohol consumption, as potential confounders of the relationship.[30] In the systematic review of asbestos and colorectal cancer by Kwak and colleagues,[6] metarisk estimates based on the subset of studies with smoking data were similar to estimates based on all studies. An investigation[31] of cancer risks by occupation using the Nordic Occupational Cancer database (~15M workers across 54 occupational categories) reported only minimal or moderate variation in risk estimates for oesophageal, colon and rectal cancers with the adjustment of smoking and alcohol. Further, it has been repeatedly demonstrated that only substantially different distributions of confounders by exposure groups would fully explain an exposure-response relationship, even for strong confounder associations such as for smoking and lung cancer.[32–35]

Heterogeneity was observed in the current meta-analyses as defined by the I^2 statistic. This was not unexpected because of the pooling of occupational epidemiological studies that include differences in study samples, control/comparison groups, duration of follow-up, case ascertainment, time period of asbestos exposure and exposure metrics. Differences in exposure metrics have been identified as a source of heterogeneity in meta-analyses of occupational epidemiological studies.[36] Overall, we observed consistency across stratified meta-analyses by exposure characteristics and in sensitivity analyses, showing elevated mRRs for GI cancers with occupational asbestos exposure.

This systematic review aimed to provide the most comprehensive systematic review of the epidemiological evidence on occupational asbestos exposure and the risk of GI cancers. Sensitivity analyses to investigate the robustness of the conclusions to the inclusion of different study designs and risk estimates revealed consistent elevated mRRs, including for the leave-one-study-out sensitivity analyses suggesting minimal influence from any one study on the findings. Cumulative meta-analyses produced more stable estimates and reduced heterogeneity with the inclusion of newer studies with stronger exposure assessment methods. Elevated mRRs persisted in sensitivity analyses of cohort-only studies, which typically provide stronger asbestos exposure assessment, and of case-control-only studies, which typically provide more thorough adjustment for potential confounders. The elevated mRRs also remained robust when excluding PMR estimates (six of 192 studies contributed PMRs to the meta-analyses) and in sensitivity analyses of incidence-only estimates (potentially prone to detection bias) and mortality-only estimates (often more precise outcome measures).

CONCLUSIONS

This evidence synthesis supports a causal link between occupational asbestos exposure and an elevated risk of oesophageal, stomach and colorectal cancer. We found consistency and stronger elevated risks in meta-analyses where there was increased confidence in higher asbestos exposures and stronger assessment methods, including among the highest exposed workers, among workers with significant exposure as a result of their work (eg, asbestos-related insulation) and among workers in cohorts where there was also a twofold or greater risk of asbestos-related lung cancer as a strong indicator of high-exposure contrasts in combination with methods that accurately captured and modelled these contrasts. There was heterogeneity in the studies included in the review, although sensitivity analyses indicate that there was minimal influence from any one study on the overall metaestimates or from publication bias. Unexplained heterogeneity was reduced, and the strength of association increased, in the meta-analyses of studies where there was increased confidence in higher exposures, and the cumulative meta-analyses with the addition of the most recent studies resulted in more consistent meta-risk estimates with less heterogeneity over time.

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