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Review article

Occupational benzene exposure and colorectal cancer: A systematic review and meta-analysis

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ABSTRACT

Recent reports suggest that benzene exposure may be associated with solid cancers, such as lung and bladder cancers. Instead, evidence on the association between benzene and colorectal cancer (CRC) is sparse. Thus, we aimed to summarize current literature on the association between occupational benzene exposure and CRC.

We searched Pubmed, Embase (through Ovid), and Scopus to retrieve cohort and nested case-control studies on the association between occupational benzene exposure and solid cancers. The search was initially completed in December 2022 and later updated in April 2024. We assessed quality of included studies using a modified version of Newcastle-Ottawa Scale. We computed pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) of CRC according to occupational benzene exposure, using the Paule-Mandel method.

Twenty-eight studies were included in the meta-analysis. Most of them were conducted in Europe or North America (82.1%) and were industry-based (89.3%). Pooled RRs comparing workers exposed to benzene with those who were unexposed for incidence and mortality were 1.10 (95% CI: 1.06, 1.15) and 1.04 (95% CI: 0.97, 1.11) for CRC, 1.12 (95% CI: 1.01, 1.24) and 1.08 (95% CI: 0.99, 1.19) for colon cancer, and 1.04 (95% CI: 0.94, 1.14) and 1.05 (95% CI: 0.92, 1.19) for rectal cancer, respectively. Only one study supported the occurrence of a dose-response relationship between occupational benzene exposure and CRC, while others found no increase in risk according to dose of exposure or duration of employment.

Our findings suggest that occupational benzene exposure may be associated with CRC. Further research with detailed assessment of individual-level exposure is warranted to confirm our results.

1. Introduction

With more than 1.9 million new cases and 900,000 deaths worldwide in 2022, colorectal cancer (CRC) is the third most common cancer type and the second leading cause of cancer death, respectively (Ferlay et al., 2024). In high-income countries in North America, Europe, and Oceania, incidence rates have been mostly stable or decreasing over recent years, while they are increasing in low- and medium-income countries in South America, Eastern Europe, and Asia (Keum and Giovannucci, 2019).

Besides genetic predisposition, main risk factors for CRC are obesity, lack of physical activity, diet, alcohol drinking, and tobacco smoking (Keum and Giovannucci, 2019). However, research has also focused on the identification of environmental and occupational factors associated with CRC (Oddone et al., 2014). Among them is exposure to benzene, which is a highly flammable and volatile aromatic hydrocarbon, liquid at room temperature. Benzene has historically been used as a solvent for organic materials, an additive to gasoline, metal degreaser, and starting and intermediate chemical in the synthesis of a number of materials and chemicals (both in the chemical and in the pharmaceutical industry) (IARC, 2018). Thus, occupational benzene exposure may occur in several industrial sectors, such as petroleum industry (including oil and gas extraction, as well as production, refining, and distribution of petroleum and derived products), coke production, petrochemical industry, automobile repair, rubber manufacturing, shoe manufacturing, firefighting, and operations entailing exposure to engine exhaust (IARC, 2018). As for the petroleum industry, in particular, benzene is a natural component of underground geological reservoirs, hence it occurs naturally in petroleum products (IARC, 2018). Additionally, although

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Abbreviations

Confidence interval (CI)
colorectal cancer (CRC)
cytochrome P450 (CYP)
hazard ratio (HR)
International Agency for Research on Cancer (IARC)
Nordic Occupational Cancer Study (NOCCA)
Newcastle-Ottawa Scale (NOS)
odds ratio (OR)
Patients, Exposure, Comparator, Outcomes, Study design (PECOS)
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
International Prospective Register of Systematic Reviews (PROSPERO)
relative risks (RRs)
standardized incidence ratio (SIR)
standardized mortality ratio (SMR)

benzene has been replaced as a solvent in paint and printing inks, these represented relevant sources of occupational exposure in the past, and may still be relevant in some low-income countries where it is still used (IARC, 2018).

Benzene is a known carcinogen for humans and its harmful effects on human health are due to its metabolites (IARC, 2018; Smith, 2010; Lovern et al., 2001). Benzene is considered a Group I carcinogen by the International Agency for Research on Cancer (IARC), mainly due to increased risk of leukemia following exposure (IARC, 2018). Recent reports also suggested that between benzene exposure may be a risk factor for some types of solid cancers, such as lung (Wan et al., 2023; Chiavarini et al., 2024) and bladder cancer (Hadkhale et al., 2017; Shala et al., 2023; Xie et al., 2024). However, current evidence on the association between benzene and CRC is sparse, and no meta-analysis of published epidemiological studies has been conducted so far, to our knowledge. Hence, we aimed to summarize current literature investigating the potential association between occupational benzene exposure and CRC.

2. Material and methods

We carried out a systematic review on the association between occupational benzene exposure and solid cancers, whose protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42022379720). The reporting of our review is compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021).

2.1. Search strategy and study selection

We searched Pubmed, Embase (through Ovid), and Scopus electronic databases to identify relevant studies. The search strategy was developed based on the Patients, Exposure, Comparator, Outcomes, Study design (PECOS) framework (Morgan et al., 2018), with the following structure:

Population/patients: workers in multiple industrial settings,
Exposure: major/substantial occupational benzene exposure,
Comparator: individuals not exposed to benzene or with the lowest exposure in the original study,
Outcomes: incidence and mortality of solid cancers,
Study design: cohort or nested case-control.

The complete search strategy for each database is reported in Supplementary Table 1. We completed the search in December 2022, and also updated it in April 2024.

Titles and abstracts of identified records were screened independently by two researchers. Full texts of retained records were thus evaluated independently by two researchers, following the same procedure. To retrieve additional relevant studies, we also conducted a manual search of reference lists of included studies, previous reviews, and last IARC Monograph on the topic (IARC, 2018). Discussion or involvement of a third researcher were used to solve any disagreements.

This report is part of a larger project on occupational benzene exposure and different solid cancers, although we report herein only results on CRC. During the selection process of the general project on solid cancers, we included identified articles if they were: (1) peer-reviewed reports with original data written in English, Italian, Spanish, German, or French, (2) studies on workers in industries and occupations in which benzene is a major occupational exposure or entailing substantial benzene exposure, based on current knowledge (e.g., petroleum industry workers, petrochemical industry workers, rubber manufacturing workers, shoe manufacturing workers) and for which an increased risk of leukemia has been reported (IARC, 2018), (3) studies investigating incidence or mortality of any types of solid cancers, (4) cohort studies or nested case-control studies, (5) studies reporting a relative measure of association, or allowing its computation based on reported data.

We excluded: (1) community-based cohort and nested case-control studies, if not reporting any exposure data (i.e., if based on occupations or job titles only), (2) case-control studies that were not nested within a cohort, (3) cross-sectional and descriptive studies, (4) conference proceedings, book chapters, theses, commentaries, and letters to editors, (5) systematic reviews or meta-analyses, (6) studies with results on leukemia, lymphoma, or myeloma only, (7) studies on non-occupational exposures, and (8) studies whose participants' main occupational exposure was not benzene.

The studies were considered industry-based if they were carried out among workers in a specific industrial setting/company, while they were considered community-based if they were conducted among the general population.

Hence, we included in this report and in the meta-analysis described herein only studies reporting estimates on CRC.

2.2. Data extraction and assessment of study quality

From each included study, two researchers independently extracted information regarding the following: author details, publication year, country, study design (cohort, nested case-control), study type (community-based, industry-based), period of employment, type of workers, participants' sex, type of cancer, outcome (incidence, mortality), and main results. Any disagreements were resolved by discussion or involvement of a third researcher.

Study quality was evaluated independently by two researchers with a modified version of Newcastle-Ottawa Scale (NOS) (Wells et al., 2019), which can be found in Supplementary Table 2. The modified version of NOS differed from the original one mainly for criteria used to assign scores to individual items and was intended for improved discrimination of fine differences in study quality between included studies. The modified scale includes 8 items and the possible total score ranged between 0 (highest risk of bias) and 10 (lowest risk of bias), given by the sum of scores for each individual item. Disagreements were solved by involving a third researcher.

2.3. Meta-analysis

We estimated pooled relative risks (RRs) and the corresponding 95% confidence intervals (CIs) for the association between occupational benzene exposure and CRC with Paule-Mandel method (Paule and Mandel, 1982), overall and by cancer type (colon cancer, rectal cancer).

Paule-Mandel method has shown better performance compared with other random-effects models (Veroniki et al., 2016; Langan et al., 2017). For studies reporting any relative measures of associations other than RR, including hazard ratio (HR), standardized mortality ratio (SMR), standardized incidence ratio (SIR), and odds ratio (OR), we considered all of them as valid approximations of RRs, since it is common practice in meta-analyses in the field of occupational epidemiology, and potential differences in study design were taken into account by avoiding a fixed-effects model in the analysis (McElvenny et al., 2004). Whenever stratified estimates based on the dose of exposure were available for a study, we included in the meta-analysis only those for the highest category, if possible. If needed, we combined different estimates from an individual study with an inverse variance fixed-effects model (e.g., for specific strata or separate estimates for colon and rectal cancers), before pooling them with those from other studies as described above. Instead, for studies reporting results for different cohorts separately, we combined them using Paule-Mandel method (Paule and Mandel, 1982), and then pooled them with estimates from other studies. For studies reporting no cases on cancer types of interest for our meta-analysis, we adopted a zero-cell correction entailing the addition of 0.5 to cells of the study-specific 2 × 2 table used for computation of the measure of association for the cancer type with no observed cases (Weber et al., 2020). The I^2 statistic, representing between-study variability in estimates due to heterogeneity rather than to chance, was used to evaluate

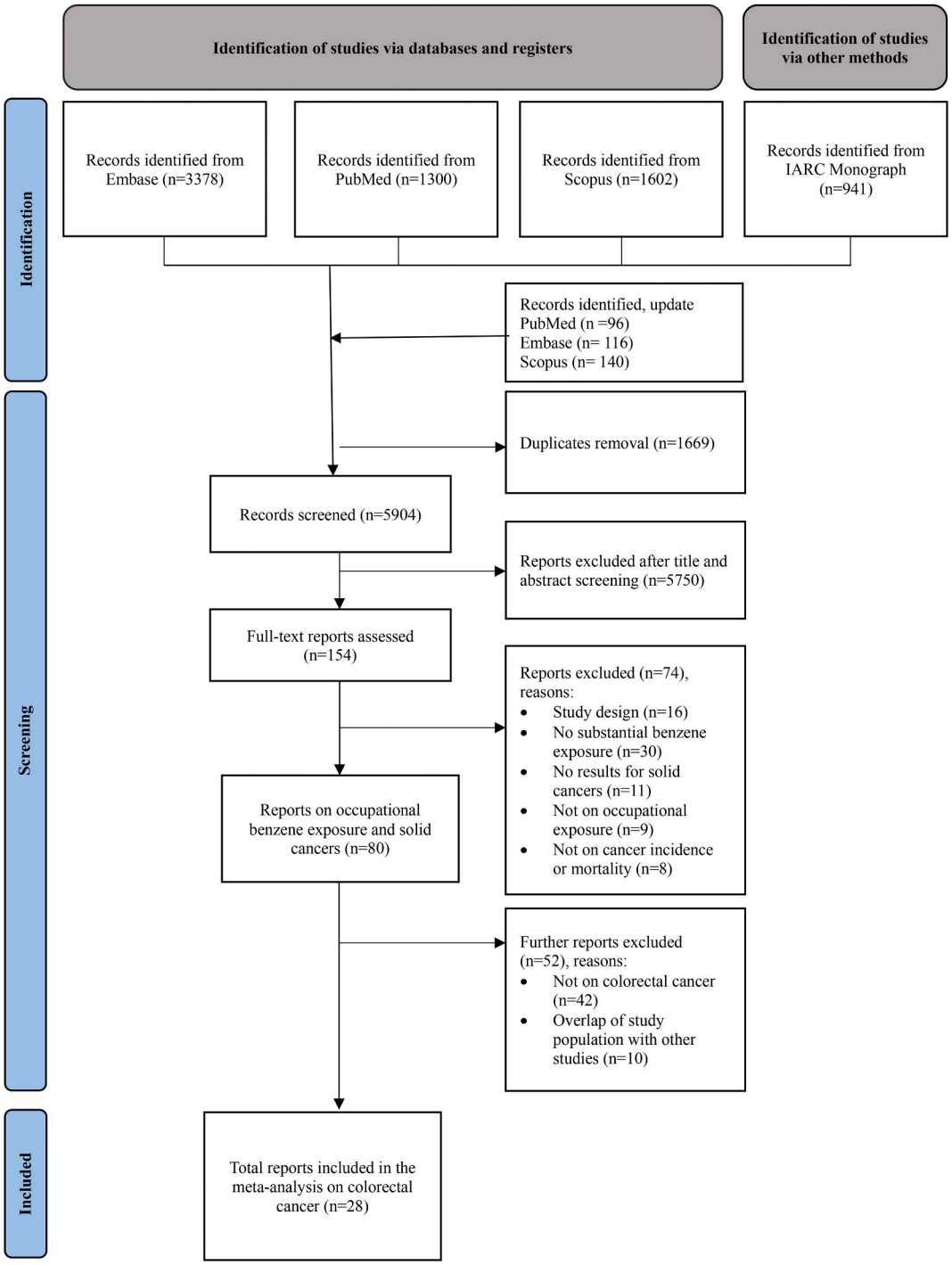

Fig. 1. Flowchart describing the study selection process.

statistical between-study heterogeneity (Higgins et al., 2003). It was considered low for values of the I^2 statistic lower than 30%, moderate between 30% and 59%, and high for values equal to 60% or higher (Alba et al., 2016).

We first analyzed data on incidence and mortality combined (with inclusion of estimates for incidence only for studies reporting both), and then separately by outcome. Analyses on incidence and mortality combined were based on the assumption of mortality being a valid indicator of incidence in studies reporting only data regarding the former.

We carried out five sets of sensitivity analyses: (1) we repeated the analysis using restricted maximum likelihood (REML) method to pool estimates from included studies, (2) we excluded one study at a time, (3) we restricted the analysis to male individuals, (4) we excluded study-specific estimates where the zero-cell correction was applied, and (5) we restricted the analysis to specific periods of employment (<1985, <1995). None of these sensitivity analyses were prespecified in the

Table 1
Main characteristics of included studies.

Study	Country	Study design	Type of study	Type of workers	Period of employment	Sex, male (%)	Outcome	NOS score
Rushton and Alderson, 1980	United Kingdom	Cohort	Industry-based	Oil refinery workers	1950–1975	100	M	7
Decoufle et al., 1983	USA	Cohort	Industry-based	White or blue-collar workers at a petrochemical plant where benzene was used	1947–1960	100	M	7.5
Guberan and Raymond, 1985	Switzerland	Cohort	Industry-based	Perfumery and flavor industry workers	up to 1964	100	I, M	8
Bond et al., 1986	USA	Cohort	Industry-based	Chemical workers exposed to benzene	1938–1970	100	M	7
Wong, 1987	USA	Cohort	Industry-based	Chemical workers exposed to benzene	1946–1975	100	M	8
Szeszenia-Dabrowska et al., 1991	Poland	Cohort	Industry-based	Rubber industry workers	1945–1973	100	M	6
Walker et al., 1993	USA	Cohort	Industry-based	Shoe manufacturing workers	1940–1979	32.4	M	9
Greenland et al., 1994	USA	Nested case-control	Industry-based	Workers at a transformer-assembly facility, exposed to benzene	up to 1984	100	M	6
Lagorio et al., 1994	Italy	Cohort	Industry-based	Gas station workers		86.6	M	7
Honda et al., 1995	USA	Cohort	Industry-based	Workers at a petroleum manufacturing plant	1942–1989	100	M	8
Satin et al., 1996	USA	Cohort	Industry-based	Oil refinery workers	1937–1983	88.9	M	7
Collingwood et al., 1996	USA	Cohort	Industry-based	Petroleum refinery workers	1946–1987		M	8
Fu et al., 1996	Italy, United Kingdom	Cohort	Industry-based	Shoe manufacturing workers	Italian cohort: 1950–1984	83.9	M	8
Lynge et al., 1997	Denmark, Finland, Norway, Sweden [a]	Cohort	Community-based	Service station workers		87.1	I	7
Gérin et al., 1998	Canada	Nested case-control	Community-based	Various		100	I	8.5
Bulbulyan et al., 1999	Russia	Cohort	Industry-based	Printing industry workers		0.0	M	8
Lewis et al., 2003	Canada	Cohort	Industry-based	Petroleum company workers		68.1	I, M	8
Sorahan et al., 2005	United Kingdom	Cohort	Industry-based	Various	up to 1967	93.0	I, M	8
Swaen et al., 2005	Netherlands	Cohort	Industry-based	Caprolactam workers exposed to benzene	1951–1968	100	M	6
Hoshuyama et al., 2006	China	Cohort	Industry-based	Iron and steel workers		100	M	8
Gun et al., 2006	Australia	Cohort	Industry-based	Petroleum industry workers		92.4	I, M	8.5
Budroni et al., 2010	Italy	Cohort	Industry-based	Petrochemical workers	1990–2001	100	I	6
Koh et al., 2011	Korea	Cohort	Industry-based	Manufacturing workers in a refinery/petrochemical complex	1960–2007	100	I, M	6
Bonneterre et al., 2012	France	Cohort	Industry-based	Chlorine chemical plant workers	1979–2002	100	I	7.5
Koh et al., 2014	Korea	Cohort	Industry-based	Temporary maintenance workers in a refinery/petrochemical complex	2002–2007	100	I, M	6
Linet et al., 2015	China	Cohort	Industry-based	Workers from various industries, exposed to benzene	1972–1987	53.9	M	8
Talibov et al., 2018	Finland, Iceland, Norway, Sweden	Nested case-control	Community-based	Various		49.9	I	9.5
Bonzini et al., 2019	Italy	Cohort	Industry-based	Oil refinery workers	1949–2011	100	M	8

I: incidence, M: mortality, NOS: Newcastle-Ottawa Scale.
[a] Included estimates are those for individuals from Denmark only, since study populations from Finland, Norway, and Sweden are included in (Talibov et al. (2018)).

protocol of our review. We also conducted subgroup analyses according to the following: study region (Europe, other), study quality (< median NOS score among reports with results on the same cancer type, ≥ median NOS score), study type (community-based, industry-based), and potential conflict of interest (based on reported authors' affiliation or industry sponsorship before or at the time of publication).

Eventually, we evaluated occurrence of publication bias using contour-enhanced funnel plots and Egger's tests (Higgins et al., 2019; Peters et al., 2008; Egger et al., 1997).

Analyses were conducted with Stata software version 18.0 (StataCorp LLC, College Station, Texas, USA).

3. Results

3.1. Selection process and study characteristics

Details regarding the study selection process are reported in Fig. 1. We screened 5904 records by title and abstract, and subsequently evaluated the full texts of 154 studies. Eighty of them reported relevant data on occupational benzene exposure and solid cancers, and 28 studies were included in the meta-analysis on CRC (Bonneterre et al., 2012; Bonzini et al., 2019; Gérin et al., 1998; Talibov et al., 2018; Szeszenia-Dabrowska et al., 1991; Bulbulyan et al., 1999; Sorahan et al., 2005; Rushton and Alderson, 1980; Decoufle et al., 1983; Satin et al., 1996; Greenland et al., 1994; Bond et al., 1986; Collingwood et al., 1996; Swaen et al., 2005; Lewis et al., 2003; Lynge et al., 1997; Fu et al., 1996; Lagorio et al., 1994; Walker et al., 1993; Wong, 1987; Gun et al., 2006; Hoshuyama et al., 2006; Budroni et al., 2010; Koh et al., 2011, 2014; Guberan and Raymond, 1985; Honda et al., 1995; Linet et al., 2015). Among them, 20 studies were also included in the meta-analysis on colon cancer (Bonneterre et al., 2012; Bonzini et al., 2019; Gérin et al., 1998; Talibov et al., 2018; Szeszenia-Dabrowska et al., 1991; Bulbulyan et al., 1999; Sorahan et al., 2005; Rushton and Alderson, 1980; Decoufle et al., 1983; Satin et al., 1996; Greenland et al., 1994; Bond et al., 1986; Collingwood et al., 1996; Swaen et al., 2005; Lewis et al., 2003; Lynge et al., 1997; Fu et al., 1996; Lagorio et al., 1994; Walker et al., 1993; Wong, 1987) and 17 on rectal cancer (Bonneterre et al., 2012; Bonzini et al., 2019; Gérin et al., 1998; Talibov et al., 2018; Szeszenia-Dabrowska et al., 1991; Bulbulyan et al., 1999; Sorahan et al., 2005; Rushton and Alderson, 1980; Decoufle et al., 1983; Satin et al., 1996; Greenland et al., 1994; Bond et al., 1986; Collingwood et al., 1996; Swaen et al., 2005; Lewis et al., 2003; Lynge et al., 1997; Fu et al., 1996).

Studies included in the meta-analysis were published between 1980 and 2019, and their characteristics are reported in Table 1. The majority of them were carried out in Europe (46.4%, n = 13) (Bonneterre et al., 2012; Bonzini et al., 2019; Talibov et al., 2018; Szeszenia-Dabrowska et al., 1991; Bulbulyan et al., 1999; Sorahan et al., 2005; Rushton and Alderson, 1980; Swaen et al., 2005; Lynge et al., 1997; Fu et al., 1996; Lagorio et al., 1994; Budroni et al., 2010; Guberan and Raymond, 1985) and in North America (35.7%, n = 10) (Gérin et al., 1998; Decoufle et al., 1983; Satin et al., 1996; Greenland et al., 1994; Bond et al., 1986; Collingwood et al., 1996; Lewis et al., 2003; Walker et al., 1993; Wong, 1987; Honda et al., 1995), and included only male study participants (57.1%, n = 16) (Bonneterre et al., 2012; Bonzini et al., 2019; Gérin et al., 1998; Szeszenia-Dabrowska et al., 1991; Rushton and Alderson, 1980; Decoufle et al., 1983; Greenland et al., 1994; Bond et al., 1986; Swaen et al., 2005; Wong, 1987; Hoshuyama et al., 2006; Budroni et al., 2010; Koh et al., 2011, 2014; Guberan and Raymond, 1985; Honda et al., 1995). Also, most included studies were industry-based (89.3%, n = 25) (Bonneterre et al., 2012; Bonzini et al., 2019; Szeszenia-Dabrowska et al., 1991; Bulbulyan et al., 1999; Sorahan et al., 2005; Rushton and Alderson, 1980; Decoufle et al., 1983; Satin et al., 1996; Greenland et al., 1994; Bond et al., 1986; Collingwood et al., 1996; Swaen et al., 2005; Lewis et al., 2003; Fu et al., 1996; Lagorio et al., 1994; Walker et al., 1993; Wong, 1987; Gun et al., 2006; Hoshuyama et al., 2006; Budroni et al., 2010; Koh et al., 2011, 2014; Guberan and Raymond, 1985; Honda et al., 1995; Linet et al., 2015).

Median NOS scores were 8.0 (interquartile range, IQR: 1.0) among studies included in the meta-analysis on CRC, 7.8 (IQR: 1.0) among those on colon cancer, and 7.5 (IQR: 1.0) on rectal cancer.

3.2. Meta-analysis

According to results of the meta-analysis on CRC incidence and mortality combined (Fig. 2), there was a positive association between occupational benzene exposure and CRC (RR: 1.10; 95% CI: 1.06, 1.14). Despite occasional differences, results were substantially similar in subgroup analyses according to study and participants' characteristics (Table 2). Use of REML method for pooling study-specific estimates instead of Paule-Mandel one did not change the result (Supplementary Fig. 1). Similarly, exclusion of one study at a time did not provide evidence for results being strongly dependent on a single study (Supplementary Fig. 2). When analyzing outcomes separately (Table 2), a positive association was confirmed for CRC incidence (RR: 1.10; 95%: 1.06, 1.15), while mortality showed a suggestive, albeit not significant, association (RR: 1.04; 95%: 0.97, 1.11). Also, no substantial differences were observed in subgroup and sensitivity analyses (Table 2). Only two studies evaluated the relationship between dose of exposure and CRC. One of them is a case-control study (n cases = 290,936, n controls = 1,454,680) nested within the Nordic Occupational Cancer Study (NOCCA) cohort, with 1:5 matching for country, sex, and year of birth, and adjustment for perceived physical workload and exposure to formaldehyde, ionizing radiation, and wood dust. In this study, an increasing trend ($p < 0.01$) of CRC according to the dose was found, with ORs of 0.99 (95% CI: 0.97, 1.02), 1.03 (95% CI: 0.99, 1.06), and 1.12 (95% CI: 1.05, 1.18) for low (≤4.3 ppm-years), intermediate (4.3–10.5 ppm-years), and high (>10.5 ppm-years) levels of exposure, respectively (Talibov et al., 2018). The other one is a cohort study of chemical workers exposed to benzene and did not find, instead, a clear trend of CRC mortality according to estimated SMRs, although the number of CRC deaths was limited (i.e., n = 12 among cohort participants exposed to benzene) (Wong, 1987). The latter study also reported no pattern of CRC mortality according to duration of employment (Wong, 1987).

The findings on colon cancer were in line with those on CRC (Fig. 3), showing a positive association for incidence and mortality combined (RR: 1.13; 95% CI: 1.07, 1.19). Similarly, stratified and sensitivity analyses carried out did not show substantially different results (Table 2 and Supplementary Figs. 3 and 4). Findings on separate outcomes were also similar to those on CRC, both for colon cancer incidence (RR: 1.12; 95% CI: 1.01, 1.24) and mortality (RR: 1.08; 95% CI: 0.99, 1.19), and results of sensitivity and subgroup analyses according to considered characteristics were also substantially similar (Table 2). One study, as mentioned above for CRC, found an increasing trend ($p = 0.01$) for colon cancer according to dose of exposure (Talibov et al., 2018). Other studies, instead, did not observe clearly defined patterns based on duration of occupational exposure or employment (Bonzini et al., 2019; Satin et al., 1996; Collingwood et al., 1996; Lewis et al., 2003) or based on levels of exposure derived from evaluation of duration, concentration, and frequency of exposure (Gérin et al., 1998).

The results of the meta-analysis on occupational benzene exposure and rectal cancer showed no clear association, both when considering incidence and mortality combined (Fig. 3, RR: 1.04; 95% CI: 0.96, 1.13) and incidence (RR: 1.04; 95% CI: 0.94, 1.14) or mortality (RR: 1.05; 95% CI: 0.92, 1.19) separately (Table 2). In line with results on CRC and colon cancer, also those on rectal cancer did not substantially differ when using REML method, when excluding one study at a time (Supplementary Figs. 3 and 5), or among subgroups of study and participants' characteristics (Table 2). No clear trend for rectal cancer according to dose of exposure or duration of employment was reported by included studies (Bonzini et al., 2019; Gérin et al., 1998; Talibov et al., 2018; Satin et al., 1996; Collingwood et al., 1996; Lewis et al., 2003).

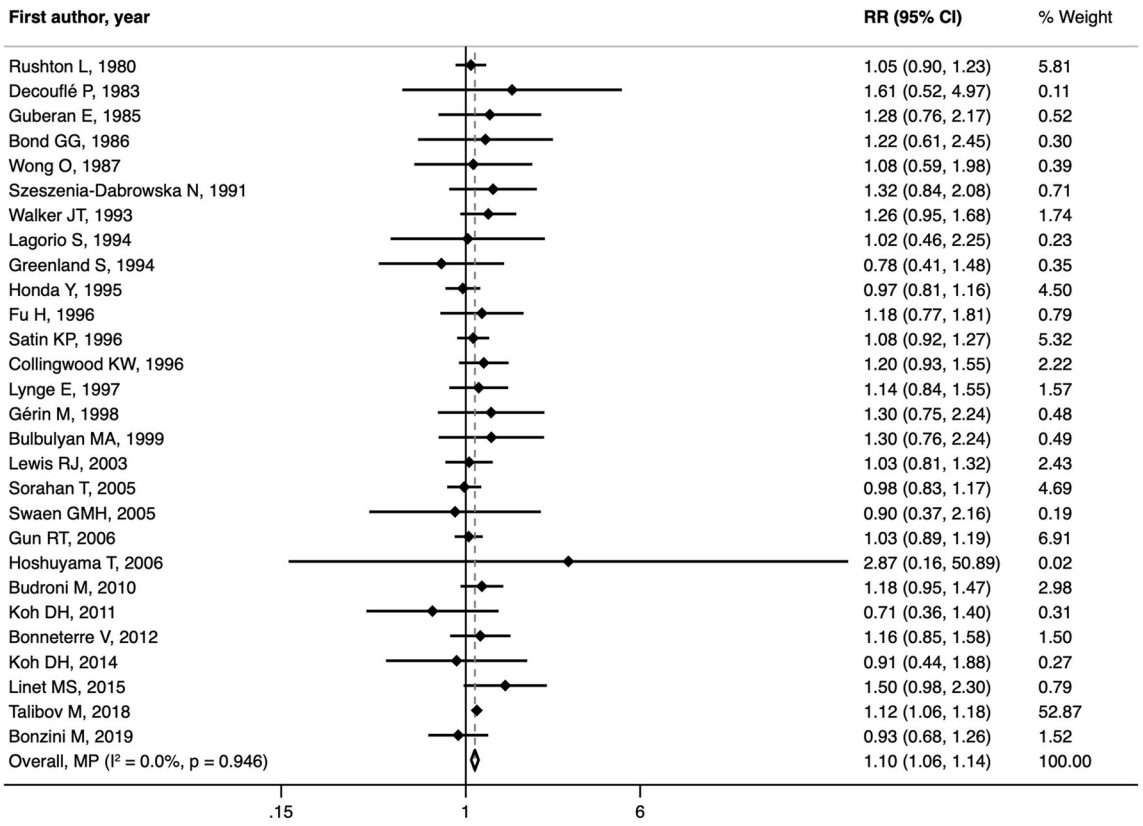

Fig. 2. Results of the meta-analysis on the association between occupational benzene exposure and colorectal cancer incidence and mortality combined.

A low degree of heterogeneity was observed for most of the analyses on all considered outcomes and cancers (Table 2).

Visual inspection of contour-enhanced funnel plots showed slight asymmetries in the area of no significance (Fig. 4 and Supplementary Fig. 6), although the results of Egger's test did not support the occurrence of publication bias ($p = 0.902$ for CRC incidence and mortality combined, $p = 0.419$ for CRC incidence, $p = 0.941$ for CRC mortality).

4. Discussion

The findings of our study suggest that occupational benzene exposure is associated with CRC, mainly due to a positive association with incidence. Results were similar for colon cancer, whose incidence showed an association with benzene. For all considered outcomes and CRC subtypes, subgroup and sensitivity analyses were substantially in line with these findings. Data on doses of exposure in included studies were limited, and the existence of a dose-response relationship was supported by one study (Talibov et al., 2018). A duration-risk relationship between length of employment and CRC was instead not supported by the studies included in our meta-analysis.

The liver is the main organ where metabolism of benzene occurs after its absorption in the body through inhalation or dermal absorption. Here, cytochrome P450 (CYP)-dependent metabolism leads to formation of toxic metabolites that are responsible for harmful effects of benzene on human health (IARC, 2018; Smith, 2010; Lovern et al., 2001). An especially relevant role in benzene metabolism has been suggested to be played by CYP2E1 isoenzyme (Smith, 2010; Lovern et al., 2001). Although primary metabolism of benzene occurs in the liver, it has been suggested to take place also in other organs, such as the bone marrow (involved in development of hematologic malignancies) (Smith, 2010; Lovern et al., 2001). Colorectal tissue has also been shown to express CYP isoenzymes, which could thus be involved in colorectal carcinogenesis (Bulus et al., 2019; Forsyth et al., 2014). Benzene metabolites might lead to CRC through DNA damage (including oxidative damage, strand breaks and gene mutations, formation of adducts), chromosomal aberrations, alterations of DNA repair mechanisms, promotion of cell proliferation and inhibition of cell death, epigenetic modifications, chronic inflammation, and immunosuppression (IARC, 2018).

Occupational exposure to any organic solvent, including benzene, has been reported to not be associated with colon or rectal cancer mortality in a previous meta-analysis of epidemiological studies on workers in various industrial settings (Chen and Seaton, 1996), hence in agreement with our findings suggesting associations for incidence but not for mortality. This previous meta-analysis did not specifically investigate exposure to benzene, but rather considered exposure to heterogeneous substances altogether. To our knowledge, no previous meta-analysis on the potential association between occupational benzene exposure and CRC has been published so far.

One of the main limitations of our meta-analysis is the lack of information regarding potentially relevant confounders in the primary studies that we included. Indeed, tobacco smoking, alcohol drinking, obesity, physical inactivity, and diet have been shown to play a key role in colorectal carcinogenesis (Keum and Giovannucci, 2019), yet most studies did not adjust for these factors, not allowing us to carry out related sensitivity analyses. These factors may mediate the effect of socioeconomic conditions, which could be expected to be related to both benzene exposure (i.e., blue collar workers may have higher exposure to benzene than white collar workers or workers performing also managerial or organizational tasks, and the latter may have a higher income and better socioeconomic conditions) and CRC. Similarly, most studies did not consider co-exposure with other occupational carcinogens, which may bias our estimates. Overall, unmeasured confounders may substantially contribute to the positive associations that we observed in our meta-analysis. Furthermore, only a limited number of included studies assessed benzene exposure among study participants, hence our meta-analysis is mostly based on occupations and industries entailing

Table 2
Results of the meta-analysis on the association between occupational benzene exposure and colorectal cancer, by study and participants' characteristics.

Outcome	Stratum	Colorectal cancer			Colon cancer			Rectal cancer		
		n studies	RR (95% CI)	I^2, p value	n studies	RR (95% CI)	I^2, p value	n studies	RR (95% CI)	I^2, p value
Incidence and mortality	**Overall**	28	1.10 (1.06, 1.14)	0.0%, 0.946	20	1.13 (1.07, 1.19)	0.0%, 0.878	17	1.04 (0.96, 1.13)	0.0%, 0.964
	Sex, male	24	1.08 (1.03, 1.13)	0.0%, 0.982	17	1.12 (1.06, 1.19)	0.0%, 0.937	14	1.01 (0.92, 1.11)	0.0%, 0.951
	Excl. zero-cell corrected estimates	27	1.10 (1.06, 1.14)	0.0%, 0.929	20	-[a]		16	1.04 (0.96, 1.13)	0.0%, 0.984
	Region									
	Europe	13	1.11 (1.06, 1.16)	0.0%, 0.933	11	1.12 (1.06, 1.19)	0.0%, 0.540	10	1.05 (0.97, 1.14)	0.0%, 0.986
	Other	15	1.07 (0.99, 1.15)	0.0%, 0.757	9	1.16 (1.03, 1.30)	0.0%, 0.934	7	0.95 (0.75, 1.21)	0.0%, 0.610
	$p_{heterogeneity}$		0.416			0.622			0.426	
	Study type									
	Community-based	3	1.12 (1.07, 1.18)	0.0%, 0.866	3	1.16 (1.08, 1.24)	0.0%, 0.616	3	1.02 (0.92, 1.14)	0.0%, 0.841
	Industry-based	25	1.07 (1.01, 1.13)	0.0%, 0.933	17	1.09 (1.00, 1.19)	0.0%, 0.867	14	1.06 (0.95, 1.19)	0.0%, 0.909
	$p_{heterogeneity}$		0.216			0.272			0.635	
	NOS score									
	<median	13	1.09 (1.00, 1.19)	0.0%, 0.949	10	1.12 (1.00, 1.25)	0.0%, 0.907	7	0.99 (0.82, 1.18)	0.0%, 0.931
	≥median	15	1.10 (1.05, 1.15)	0.0%, 0.680	10	1.14 (1.07, 1.20)	0.0%, 0.529	10	1.05 (0.97, 1.15)	0.0%, 0.823
	$p_{heterogeneity}$		0.869			0.827			0.511	
	Period of employment									
	<1985	11	1.07 (0.99, 1.17)	0.0%, 0.877	10	1.07 (0.97, 1.19)	0.0%, 0.536	8	1.05 (0.90, 1.23)	0.0%, 0.821
	<1995	14	1.08 (1.00, 1.16)	0.0%, 0.730	11	1.09 (0.99, 1.20)	0.0%, 0.575	9	1.06 (0.92, 1.23)	0.0%, 0.874
	Potential conflict of interest									
	Yes	12	1.04 (0.98, 1.11)	0.0%, 0.952	9	1.06 (0.95, 1.17)	0.0%, 0.721	8	1.08 (0.93, 1.25)	0.0%, 0.850
	No	16	1.13 (1.08, 1.18)	0.0%, 0.906	11	1.16 (1.09, 1.23)	0.0%, 0.920	9	1.03 (0.93, 1.13)	0.0%, 0.879
	$p_{heterogeneity}$		0.064			0.130			0.569	
Incidence	**Overall**	11	1.10 (1.06, 1.15)	0.0%, 0.803	6	1.12 (1.01, 1.24)	19.5%, 0.286	6	1.04 (0.94, 1.14)	0.0%, 0.648
	Sex, male	10	1.09 (1.04, 1.15)	0.0%, 0.914	5	1.14 (1.07, 1.23)	0.0%, 0.938	5	0.99 (0.89, 1.11)	0.0%, 0.695
	Excl. zero-cell corrected estimates	11	-[a]		6	-[a]		6	-[a]	
	Region									
	Europe	6	1.12 (1.06, 1.17)	0.0%, 0.763	4	1.09 (0.93, 1.26)	44.5%, 0.144	4	1.05 (0.95, 1.16)	0.0%, 0.659
	Other	5	1.03 (0.91, 1.16)	0.0%, 0.745	2	1.22 (0.94, 1.59)	0.0%, 0.470	2	0.79 (0.52, 1.19)	0.0%, 0.982
	$p_{heterogeneity}$		0.206			0.465			0.188	
	Study type									
	Community-based	3	1.12 (1.07, 1.18)	0.0%, 0.866	3	1.16 (1.08, 1.24)	0.0%, 0.616	3	1.02 (0.92, 1.14)	0.0%, 0.841
	Industry-based	8	1.05 (0.96, 1.14)	0.0%, 0.773	3	1.01 (0.83, 1.23)	27.6%, 0.251	3	1.07 (0.82, 1.40)	28.2%, 0.249
	$p_{heterogeneity}$		0.181			0.198			0.778	
	NOS score									
	<median	5	1.13 (0.97, 1.31)	0.0%, 0.676	2	1.21 (0.91, 1.59)	0.0%, 0.644	1	0.92 (0.55, 1.54)	na
	≥median	6	1.10 (1.05, 1.15)	0.0%, 0.591	4	1.09 (0.92, 1.30)	48.4%, 0.121	5	1.04 (0.94, 1.14)	0.0%, 0.534
	$p_{heterogeneity}$		0.756			0.551			0.658	
	Period of employment									
	<1985	2	1.01 (0.86, 1.19)	0.0%, 0.354	1	0.86 (0.67, 1.10)	na	1	1.13 (0.88, 1.45)	na
	<1995	2	1.01 (0.86, 1.19)	0.0%, 0.354	1	0.86 (0.67, 1.10)	na	1	1.13 (0.88, 1.45)	na
	Potential conflict of interest									
	Yes	3	1.03 (0.93, 1.14)	0.0%, 0.660	2	0.93 (0.73, 1.17)	12.4%, 0.285	2	1.17 (0.93, 1.46)	0.0%, 0.542
	No	8	1.12 (1.07, 1.17)	0.0%, 0.865	4	1.16 (1.09, 1.23)	0.0%, 0.808	4	1.01 (0.91, 1.12)	0.0%, 0.660
	$p_{heterogeneity}$		0.147			0.075			0.242	

(*continued on next page*)

Table 2 (*continued*)

Outcome	Stratum	Colorectal cancer			Colon cancer			Rectal cancer		
		n studies	RR (95% CI)	I^2, *p* value	n studies	RR (95% CI)	I^2, *p* value	n studies	RR (95% CI)	I^2, *p* value
Mortality	**Overall**	23	1.04 (0.97, 1.11)	0.0%, 0.540	16	1.08 (0.99, 1.19)	0.0%, 0.797	13	1.05 (0.92, 1.19)	0.0%, 0.978
	Sex, male	18	1.00 (0.92, 1.08)	0.0%, 0.804	13	1.06 (0.95, 1.19)	0.0%, 0.884	10	1.04 (0.89, 1.21)	0.0%, 0.937
	Excl. zero-cell corrected estimates	22	1.04 (0.97, 1.11)	0.0%, 0.492	16	-[a]		12	1.05 (0.93, 1.20)	0.0%, 0.995
	Region									
	Europe	9	1.03 (0.92, 1.14)	0.0%, 0.834	8	1.02 (0.89, 1.18)	0.0%, 0.552	7	1.06 (0.91, 1.23)	0.0%, 0.995
	Other	14	1.05 (0.93, 1.17)	20.6%, 0.229	8	1.13 (1.00, 1.28)	0.0%, 0.843	6	1.02 (0.78, 1.34)	0.0%, 0.621
	$p_{heterogeneity}$		0.815			0.310			0.813	
	Study type									
	Community-based	0	–		0	–		0	–	
	Industry-based	23	-[a]		16	-[a]		13	-[a]	
	$p_{heterogeneity}$									
	NOS score									
	<median	10	1.06 (0.95, 1.18)	0.0%, 0.614	8	1.10 (0.97, 1.25)	0.0%, 0.833	6	1.00 (0.82, 1.21)	0.0%, 0.876
	≥median	13	1.03 (0.93, 1.13)	8.9%, 0.356	8	1.06 (0.92, 1.21)	0.0%, 0.469	7	1.09 (0.92, 1.30)	0.0%, 0.924
	$p_{heterogeneity}$		0.642			0.653			0.473	
	Period of employment									
	<1985	11	1.06 (0.97, 1.16)	0.0%, 0.809	10	1.08 (0.97, 1.21)	0.0%, 0.544	8	1.02 (0.86, 1.20)	0.0%, 0.869
	<1995	14	1.07 (0.99, 1.15)	0.0%, 0.654	11	1.10 (0.99, 1.22)	0.0%, 0.591	9	1.03 (0.88, 1.21)	0.0%, 0.903
	Potential conflict of interest									
	Yes	11	1.01 (0.94, 1.10)	0.0%, 0.703	8	1.06 (0.95, 1.19)	0.0%, 0.623	7	1.03 (0.87, 1.21)	0.0%, 0.904
	No	12	1.10 (0.95, 1.28)	10.0%, 0.347	8	1.13 (0.95, 1.34)	0.0%, 0.694	6	1.09 (0.88, 1.34)	0.0%, 0.860
	$p_{heterogeneity}$		0.320			0.566			0.675	

[a] Same as corresponding overall estimate, na: not applicable, NOS: Newcastle-Ottawa Scale.

exposure to benzene. This may lead to exposure misclassification, likely non-differentially according to the outcome status, which may bias estimates towards the null. Even for similar occupations and industries, benzene exposure may vary between different cohorts due to potential differences in industrial processes and practices, including the use of personal protective equipment, whose use was not reported by included studies. Differences in exposure levels may occur even among participants within the same cohort, according to specific tasks carried out by each individual. Furthermore, variations in levels of exposure may also occur over time, due to change of industrial procedures, workers' tasks, and preventive measures, including the use of personal protective equipment. Although these are all potential sources of non-differential misclassification of the exposure, lack of data prevented us from evaluating whether these factors modify our results. One of the key aspects that may aid in evaluating causality in epidemiological research is the occurrence of a dose-response relationship between the exposure and the outcome. However, due to related data being available only in a limited number of included studies, we did not quantitatively assess how different aspects of exposure were related with CRC, including dose of exposure, workload, duration of employment or exposure, time since first and last exposure, and change in levels of occupational exposure during the life course. For the few studies reporting results according to these quantitative measures, categorization of continuous exposure metrics affected by nondifferential measurement error might have also led to differential misclassification, which may bias estimates both towards and away from the null (Flegal et al., 1991). Furthermore, most of the studies included in our meta-analysis were conducted in high-income countries, especially in Europe and North America, suggesting the need for further evidence from less developed countries, where incidence of CRC is on the rise (Keum and Giovannucci, 2019). Also, due to lack of data, it was not possible to evaluate whether the observed association changed according to different colon segments.

In summary, results of our meta-analysis suggest that occupations entailing benzene exposure may be associated with CRC. However, due to limitations of the studies that we included, further research is warranted, with particular emphasis on adjustment for relevant confounders, including co-exposure with other potential colorectal carcinogens in the occupational setting, and detailed assessment of benzene exposure at the individual level, possibly based on environmental monitoring data.

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CRediT authorship contribution statement

Michele Sassano: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Monireh Sadat Seyyedsalehi:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Paolo Boffetta:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Paolo Boffetta reports a relationship with the plaintiff and the defense in litigations involving benzene exposure that includes: paid expert

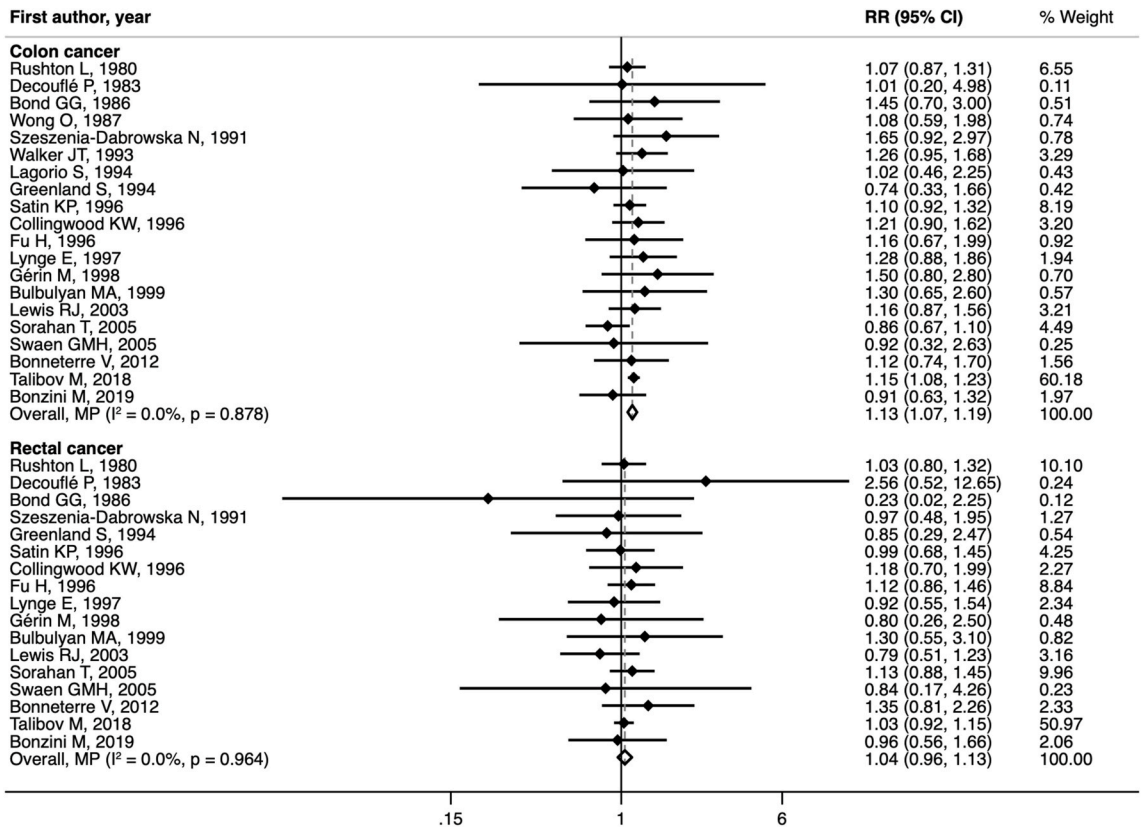

Fig. 3. Results of the meta-analysis on the association between occupational benzene exposure and colon and rectal cancer incidence and mortality combined.

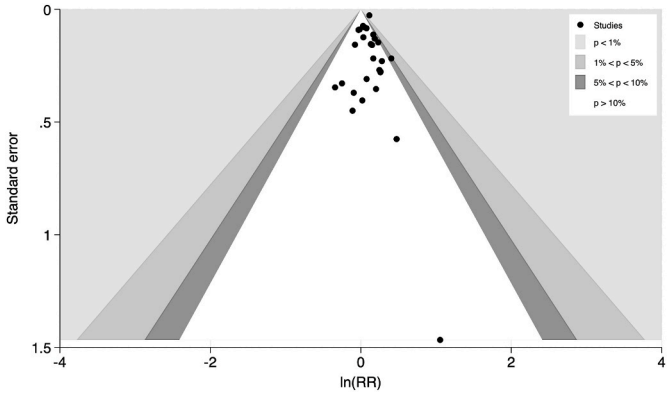

Fig. 4. Contour-enhanced funnel plot to explore small-study effect for colorectal cancer incidence and mortality combined.

testimony. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.119213.

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