The Innovation

Review

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Pei Yu,[1] Suying Guo,[2] Rongbin Xu,[1] Tingting Ye,[1] Shanshan Li,[1] Malcolm R. Sim,[1] Michael J. Abramson,[1] and Yuming Guo[1,*]
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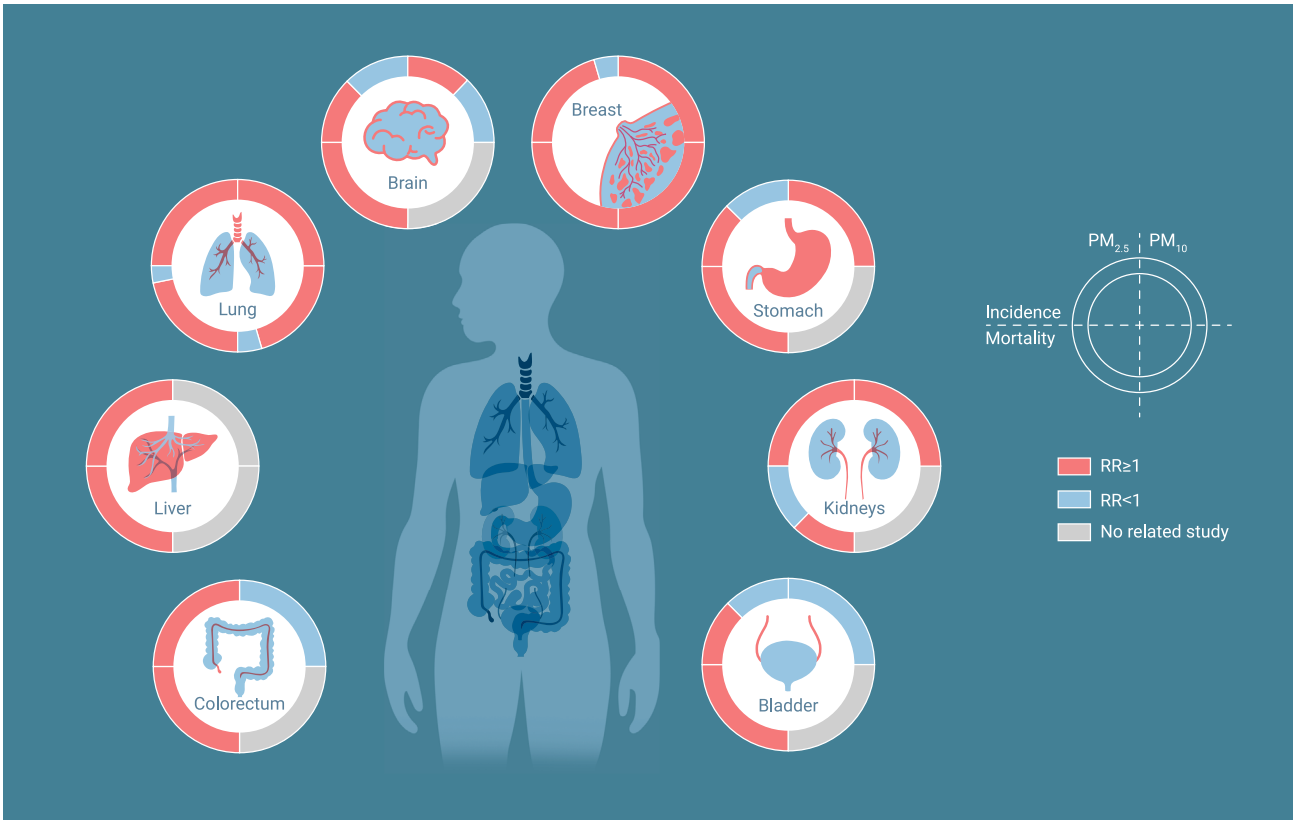
Graphical abstract



Public summary

- Updated evidence for the association between PM and lung cancer risk has been provided
- Associations between PM and cancer risks from 13 sites were summarized
- Further studies should be conducted to fill the research gaps

Review

Cohort studies of long-term exposure to outdoor particulate matter and risks of cancer: A systematic review and meta-analysis

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Robust evidence is needed for the hazardous effects of outdoor particulate matter (PM) on mortality and morbidity from all types of cancers. To summarize and meta-analyze the association between PM and cancer, published articles reporting associations between outdoor PM exposure and any type of cancer with individual outcome assessment that provided a risk estimate in cohort studies were identified via systematic searches. Of 3,256 records, 47 studies covering 13 cancer sites (30 for lung cancer, 12 for breast cancer, 11 for other cancers) were included in the quantitative evaluation. The pooled relative risks (RRs) for lung cancer incidence or mortality associated with every 10-μg/m^3 $PM_{2.5}$ or PM_{10} were 1.16 (95% confidence interval [CI], 1.10–1.23; I^2 = 81%) or 1.22 (95% CI, 1.02–1.45; I^2 = 96%), respectively. Increased but non-significant risks were found for breast cancer. Other cancers were shown to be associated with PM exposure in some studies but not consistently and thus warrant further investigation.

Keywords: particulate matter; air pollution; cancer; systematic review; meta-analysis

INTRODUCTION

Cancer is a major public health problem, with over 19 million incident cases and 9 million deaths globally in 2020.[1] To reduce the incidence and mortality of cancer, the known risk factors need to be controlled.

Air pollution, especially ambient particulate matter (PM), is a major environmental problem that can cause adverse health impacts.[2,3] Inhaled particles affect the lungs by causing chronic systemic inflammation, oxidative stress, and DNA damage to lung tissues.[4] In addition to depositing in airways, particles can also move into interstitial spaces between alveoli and circulate to other organs, which may be relevant for carcinogenic processes, although the potential mechanisms have not been fully explained.[5] Thus, PM should not only play a role in carcinogen progression in lung cancer, but also other cancers.

There have been some systematic reviews summarizing the relationship between PM and cancers. A previous meta-analysis by the International Agency for Research on Cancer (IARC) has summarized ambient PM exposure and lung cancer risk published before 2014. However, the search was conducted only in the PubMed database and included both cohort and case-control studies.[6] Similarly, a combination of all types of study design was conducted in some other articles.[7–9] In addition, some reviews pooled all respiratory tract diseases or cancers of different sites together.[8,10,11]

Combining studies with various designs may introduce more bias and heterogeneity. Therefore, to give more robust evidence and comprehensively summarize the relationship between PM and cancer risk, we conducted a systematic literature review and meta-analysis. Our aims were to examine the association between PM and cancer-specific risk among cohort studies and to examine differences in risk between various subgroups, such as by smoking status, histological subtypes, and exposure assessment methods.

METHODS

Search strategy

For this systematic review and meta-analysis, we searched MEDLINE, Embase, PsycInfo, CINAHL, EMCARE, and Scopus from the beginning of each database to 20 December 2019 and updated (last search 20 November 2020). Search terms included keywords related to cancer ("neoplasia," "tumor," "cancer," "melanoma," "leukemia," "lymphoma," "adenocarcinoma," "hemangioma"), combined with keywords related to PM with an aerodynamic diameter less than or equal to 2.5 or 10 μm ($PM_{2.5}$ or PM_{10}) ("fine particles," "particulate matter," "particulate air pollution," "$PM_{2.5}$," "PM_{10}") and specific study types ("cohort study," "follow-up study," "incidence study," "concurrent study," "prospective study," "retrospective study," "longitude study") (Table S1). We also extended the search to papers or reports cited in the literature, but not in the selected databases. We included studies if the design was a cohort study; the exposure of interest was measured $PM_{2.5}$ or PM_{10}; the endpoint of interest was cancer-specific incident or mortality; authors provided a risk estimate, such as a hazard ratio (HR), relative risk (RR), or odds ratio (OR) per unit; we excluded animal experiments, and those with no language restrictions. In addition, we also checked the references cited by World Health Organization (WHO) and IARC documents and in the articles. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed to identify the studies on ambient PM and cancer incidence or mortality.

Study eligibility criteria

The criteria used to select studies were: (1) the study was published in a scholarly peer-reviewed journal; (2) the study was designed as a cohort study, with ecological studies with data for both outcome and exposure collected only at an aggregated level excluded; (3) the exposure to PM was specifically defined as PM_{10} or $PM_{2.5}$; (4) individual outcomes for cancer (including total and site-specific cancers) were reported; (5) HR/relative risks (RR)/OR of PM exposure were reported; (6) quantitative estimates of the change in cancer incidence or mortality associated with every unit change of exposure to $PM_{2.5}$ and/or PM_{10} were reported or could be calculated from the published data; (7) for studies with overlapping study populations and time periods, only the study with the largest sample size and/or the longest follow-up period was selected for the meta-analysis.

Study selection

Two investigators (P.Y. and S.G.) conducted title and abstract screening independently and then reviewed the full text. Disagreements were resolved by discussion with a third reviewer (R.X.).

Data extraction

For each study, the following details were extracted: (1) reference details (authors and year of publication); (2) study details (name, country, study period, study population, case numbers, outcome assessment, concentrations of PM exposure, exposure time assessment, exposure source, and confounder adjustments); (3) effect (RR/HR/OR per unit exposure and 95% confidence interval [CI]); (4) subgroup details (exposure assessment method, smoking, gender, histological subtypes, lag time).

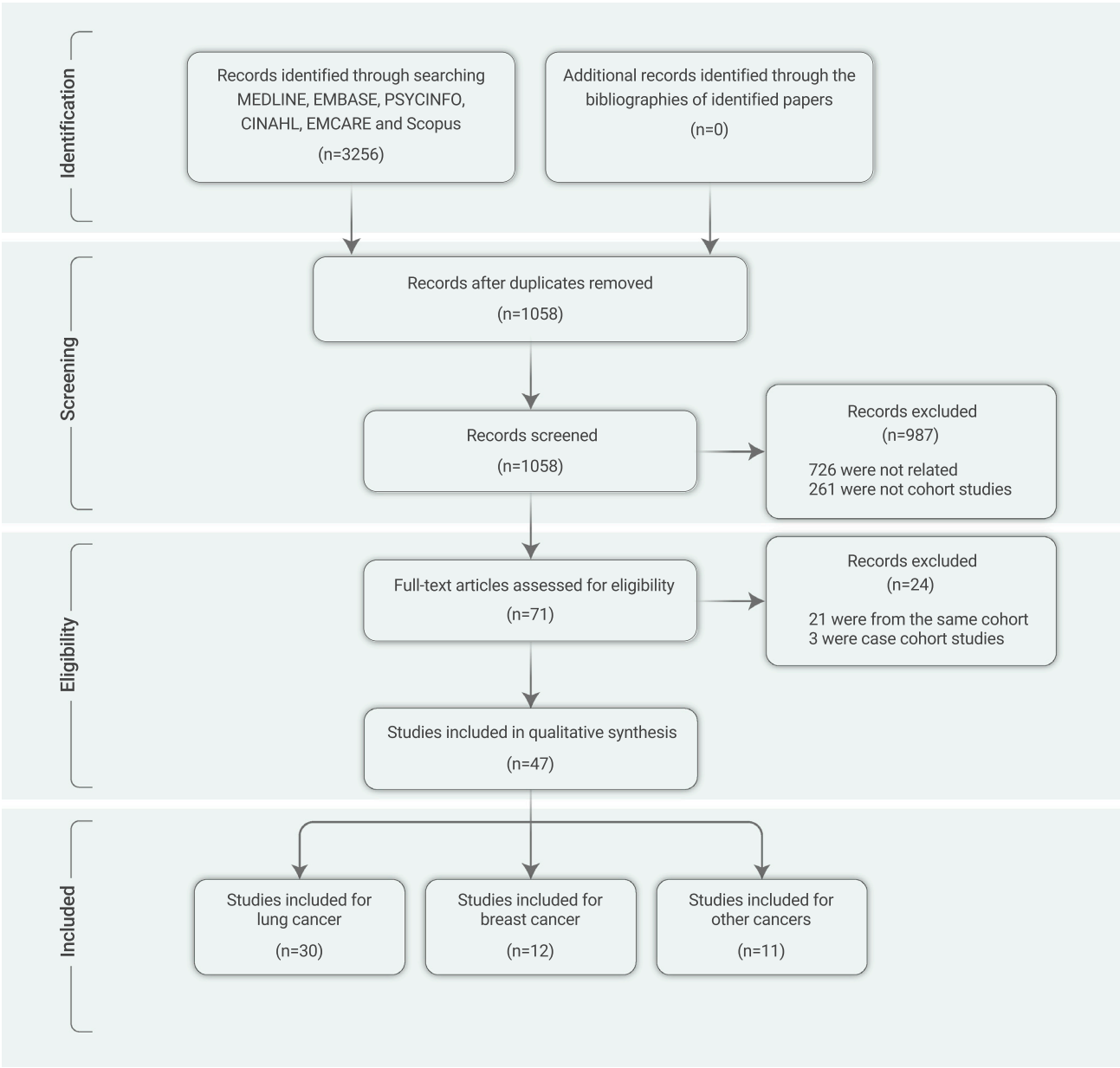

Figure 1. Study selection

Study quality assessment

We used the National Institute of Health (NIH) Quality Assessment of Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) to assess the study quality. The assessment was conducted by two authors (P.Y. and S.G.) independently and discussed with the third author (R.X.) for any disagreement. Nine items included in the assessment are shown in Table S2. Each item was equivalent to one score and the tallied score translated to a rating of quality. We considered articles that scored 9 as good quality; articles that scored 7–8 as fair quality, and 0–6 as poor quality. All studies included were evaluated to be good or fair (Table S3).

The overall quality of the evidence was evaluated by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system,[12,13] yielding a score between high, moderate, low, and very low. We considered the cohort studies as the sources with high-quality evidence, so all studies included were marked as high as a starting point. The original score could be upgraded/downgraded according to five downgrading (risk of bias, imprecision, inconsistency, indirectness, and publication bias) and three upgrading domains (dose-response trend, residual confounding, and the magnitude of associations). Tables S4–S9 show the overall judgment for the association between PM and the risk of cancer.

Data analysis

All results were estimated with standardized increments of a 10-μg/m^3 increase in exposures to $PM_{2.5}$ and PM_{10}. We calculated the RR for a standardized increment for each pollutant by applying the following formula:

$$RR_{standardised} = e^{\left(\frac{\ln\left(RR_{Origin}\right)}{Increment_{Origin}} \times Increment_{Standardised}\right)}$$

where ln is the log to the base e.

To evaluate the association between PM and cancer risk, a pooled RR ratio and 95% CI was calculated from the adjusted RR ratio and 95% CI in each study. To test heterogeneity across studies, we used the Higgins I^2 test to determine the percentage of the total variation. I^2 was computed as follows:

$$I^2 = 100\% \times (Q - df)/Q$$

where Q was Cochran's heterogeneity statistic and df indicated the degree of freedom. I^2 values ranged from 0% (no heterogeneity observed) to 100% (maximal heterogeneity), with values > 75% indicating substantial heterogeneity. A random-effects model based on the DerSimonian

Table 1. Summary of studies included in systematic review of cancer risk associated with PM exposure

Number	Reference	Study	Study period	Cancer	Outcome	Exposure (mean, SD)	Exposure time assessment	Exposure assessment	Covariate adjustment
1	Coleman et al. 2020[51]	Public National Health Interview Survey	1987–2014	cancer specific	mortality	$PM_{2.5}$ (10.7, 2.4)	1-, 5-, 10-, and 15-y moving average	fix monitor	age, sex, smoking status, education, income, BMI
2	Guo et al. 2020[55]	Taiwan National Death Registry	2001–2016	gastrointestinal cancer	mortality	$PM_{2.5}$ (26.57, 7.6)	2-y moving average	satellite	age, sex, smoking status, education, BMI, occupation
3	Bai et al. 2019[15]	OPHEC	2001–2015	lung and breast	incidence	$PM_{2.5}$ (10.8[b])	annual average	satellite	age, sex, education, income, histological subtype
4	Cheng et al. 2019[53]	CA MEC	1993–2010	breast	mortality	$PM_{2.5}$[c]; PM_{10}[c]	annual average	fix monitor	age, sex, smoking status, education, income, BMI, histological subtype
5	DuPre et al. 2019[52]	NHS and NHS-II	1988–2014	breast	mortality	$PM_{2.5}$ (13.3, 3.5 [NHS], 12.9, 3.1 [NHS-II]); PM_{10} (22.2, 6.9 [NIS], 21.3, 6.2 [NHS-II])	2-y moving average	fix monitor	age, sex, smoking status, BMI, histological subtype
6	Pope et al. 2019[23]	National Health Interview Survey	1986–2015	lung	mortality	$PM_{2.5}$ (10.7, 2.4)	1986–2015 average	fix monitor	age, sex, smoking status, education, income, BMI
7	White et al. 2019[45]	Sister Study	2003–2016	breast	incidence	$PM_{2.5}$[c]; PM_{10}[c]			Age, sex, smoking status, education, income, histological subtype
8	Yorifuji et al. 2019[38]	Basic health checkups in Okayama	2006–2016	lung	mortality	$PM_{2.5}$ (14, 1)	2006–2010 average	satellite	age, sex, smoking status, occupation, histological subtype
9	Andersen et al. 2018[58]	ESCAPE	1985–2008	brain	incidence	$PM_{2.5}$[c]; PM_{10}[c]	annual average	fix monitor	age, sex, smoking status, education, income, histological subtype
10	Cakmak et al. 2018[24]	CANCHEC	1991–2011	lung	mortality	$PM_{2.5}$[c]	7-y moving average	satellite	age, sex, education, income, occupation
11	Datzmann et al. 2018[49]	Saxony Semi-individual Cohort Study	2007–2014	cancer specific	incidence	PM_{10} (20.9, 15.47–26.3[e])	2007 concentration	LUR model	age, sex
12	Gandini et al. 2018[20]	LIFE MED HISS	1999–2008	cancer specific	incidence	$PM_{2.5}$[c]	annual average	fix monitor	age, sex, smoking status, education, income, BMI, occupation
13	Nagel et al. 2018[57]	ESCAPE	1985–2005	stomach and upper aerodigestive tract cancer	incidence	$PM_{2.5}$[c]; PM_{10}[c]	annual average	fix monitor	age, sex, smoking status, education, income, occupation, histological subtype
14	Pedersen et al. 2018[56]	ESCAPE	1985–2005	bladder	incidence	$PM_{2.5}$[c]; PM_{10}[c]	annual average	fix monitor	age, sex, smoking status, education, income, occupation
15	Villeneuve et al. 2018[46]	CNBSS	1980–2005	breast	incidence	$PM_{2.5}$ (9.50[d], 6.40–12.40[e])	annual average	satellite	age, sex, smoking status, education, BMI, occupation
16	Andersen et al. 2017[50]	Danish Nurse Cohort	1993–2013	breast	incidence	$PM_{2.5}$ (19.7, 3.5); PM_{10} (23.5, 3.9)	3-y moving average	fix monitor	age, sex, smoking status, BMI
17	Gharibvand et al. 2017[16]	AHS-II	2002–2011	lung	incidence	$PM_{2.5}$ (12.9, 3.7 [noncases]; 13.1, 4.0 [cases])	annual average	fix monitor	Sex, smoking status, education
18	Gharibvand et al. 2017[a 17]	AHS-II	2002–2011	lung	incidence	$PM_{2.5}$ (12.9, 3.7 [noncases]; 13.1, 4.0 [cases])	annual average	fix monitor	Sex, smoking status, education

(*Continued on next page*)

Table 1. *Continued*

Number	Reference	Study	Study period	Cancer	Outcome	Exposure (mean, SD)	Exposure time assessment	Exposure assessment	Covariate adjustment
19	Pedersen et al. 2017[59]	ESCAPE	1985–2012	liver	incidence	$PM_{2.5}$[c]	annual average	fix monitor	age, sex, smoking status, education, income, occupation, histological subtype
20	Pun et al. 2017[25]	Medicare beneficiaries	2000–2008	lung	mortality	$PM_{2.5}$ (12.5[d], 10.3–14.3[e])	12- to 60-mo moving average	fix monitor	Smoking status, education, income, BMI
21	Turner et al. 2017[54]	CPS-II	1982–2004	cancer specific	mortality	$PM_{2.5}$ (12.6, 2.8)	1999–2004 average	fix monitor	age, sex, smoking status, education, income, BMI, occupation
22	Yin et al. 2017[39]	Chinese men cohort	1990–2005	lung	mortality	$PM_{2.5}$ (43.7, 4.2–83.8[e])	2000–2005 average	satellite	age, sex, smoking status, education, BMI, occupation
23	Chen et al. 2016[41]	Northern China Cohort	1998–2009	lung	mortality	PM_{10} (144.34, 3.63)	1998–2009 time dependent	fix monitor	age, sex, smoking status, education, income, BMI, occupation
24	Hart et al. 2016[47]	NHS-II	1993–2011	breast	incidence	$PM_{2.5}$[c]; PM_{10}[c]	48-mo moving average	fix monitor	age, sex, smoking status, income, BMI, histological subtype
25	Jorgensen et al. 2016[60]	Danish Nurse Cohort	1993–2013	brain	incidence	$PM_{2.5}$ (19.7, 3.5); PM10 (23.6, 3.9)	3-y moving average	AirGIS	age
26	Raaschou et al. 2016[61]	ESCAPE	1994–2013	kidney	incidence	$PM_{2.5}$[c]; PM_{10}[c]	annual average	fix monitor	age, sex, smoking status, education, income, occupation
27	Tomczak et al. 2016[18]	CNBSS	1980–2004	lung	incidence	$PM_{2.5}$ (9.5, 3.44)	1998–2006 average	satellite	age, sex, smoking status, education, income, BMI, occupation, histological subtype
28	Wong et al. 2016[40]	Hong Kong Elderly Health services	1998–2011	cancer specific	mortality	$PM_{2.5}$ (33.7, 3.2)	1998–2001 average	fix monitor	age, sex, smoking status, education, income, BMI
29	Fischer et al. 2015[33]	DUELS	2004–2011	lung	mortality	PM_{10}[c]	2001 concentration	fix monitor	age, sex, BMI
30	Hart et al. 2015[21]	Netherlands Cohort Study	1986–2003	lung	incidence	$PM_{2.5}$ (18.2, 10)	1987–1996 average	fix monitor	age, sex, smoking status, education, income, BMI, occupation
31	To et al. 2015[48]	CNBSS	1980–2013	breast	incidence	$PM_{2.5}$ (12.5, 2.4)	1998–2006 average	satellite	age, sex, smoking status, education, income, BMI, occupation
32	Turner et al. 2015[26]	CPS-II	1984–2004	lung	mortality	$PM_{2.5}$ (12.6, 2.9)	1999–2004 average	fix monitor	age, sex, smoking status, education, income, BMI, occupation
33	Puett et al. 2014[44]	Nurses' Health Study	1994–2010	lung	incidence	$PM_{2.5}$ (13.1, 3); PM_{10} (21.6, 6)	72-mo cumulative average	fix monitor	age, sex, smoking status, education, income, BMI
34	Carey et al. 2013[36]	Clinical Practice Research Datalink	2003–2007	lung	mortality	$PM_{2.5}$ (12.9, 1.4); PM_{10} (19.7, 2.3)	2002 concentration	fix monitor	age, sex, smoking status, education, BMI
35	Cesaroni et al. 2013[35]	Rome Longitudinal Study	2001–2010	lung	mortality	$PM_{2.5}$ (23, 4.4)	1996–2001	FARM	Sex, education, income, occupation
36	Heinrich et al. 2013[34]	North Rhine-Westphalia cohort	1980s–2008	lung	mortality	PM_{10} (43.7, 34.8–52.5[e])	baseline year concentration	transformed from monitoring TSP	smoking status, income, occupation

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Table 1. *Continued*

Number	Reference	Study	Study period	Cancer	Outcome	Exposure (mean, SD)	Exposure time assessment	Exposure assessment	Covariate adjustment
37	Raaschou et al. 2013[22]	ESCAPE	1990s	lung	incidence	$PM_{2.5}$ (21.3, 2.7); PM_{10} (21.3, 2.7)	annual average	fix monitor	age, sex, smoking status, education
38	Hales et al. 2012[43]	New Zealand Census-Mortality Study	1996–1999	lung	mortality	PM_{10} (8.3, 8.4)	annual average	fix monitor	age, sex, smoking status, education, income
39	Lepeule et al. 2012[27]	Harvard Six Cities Study	1974–2009	lung	mortality	$PM_{2.5}$ (15.9[b])	3-y moving average	fix monitor	age, sex, smoking status, BMI
40	Hart et al. 2011[29]	Trucking company	1985–2000	lung	mortality	$PM_{2.5}$ (14.1, 4); PM_{10} (26.8, 6)	1985–2000 average	fix monitor	age, sex, occupation
41	Katanoda et al. 2011[42]	Three-prefecture Cohort Study	1995–2005	lung	mortality	$PM_{2.5}$ (10.8[b])	10-y average concentrations (1974–1983) before the baseline survey	fix monitor	age, sex, smoking status
42	Lipsett et al. 2011[30]	California Teachers Study	1999–2005	lung	mortality	$PM_{2.5}$ (15.6, 4.5); PM_{10} (29.2, 9.7)	annual average	fix monitor	age, sex, smoking status, education, income, BMI, occupation,
43	Turner et al. 2011[a 28]	CPS-II	1982–2008	lung	mortality	$PM_{2.5}$ (17.6,3.7)	1979–1983 and 1999–2000 average	fix monitor	age, sex, smoking status, BMI, occupation
44	Brunekreef et al. 2009[37]	NLCS-AIR Study	1986–1996	lung	mortality	$PM_{2.5}$ (28, 2.1)	1987–1996 average	fix monitor	age, sex, smoking status, income
45	Pope et al. 2002[31]	CPS-II	1982–1998	lung	mortality	PM_{10} (28.8, 5.9)	1979–1983 and 1999–2000 average	fix monitor	age, sex, smoking status, education, occupation
46	Abbey et al. 1999[32]	AHS	1973–1992	lung	mortality	PM_{10} (51.24, 16.63)	3-y moving average	fix monitor	age, sex, smoking status, education
47	Beeson et al. 1998[19]	AHSMOG Study	1973–1992	lung	incidence	PM_{10} (51, 16.52)	3-y moving average	fix monitor	age, sex, smoking status

AHS, Adventist Health Study; AHSMOG, Adventist Health Study on Smog; CA MEC, California Multiethnic Cohort; CANCHEC, Canadian Census Health and Environment Cohort; CNBSS, Canadian National Breast Screening Study; CPS-II, Cancer Prevention Study-II; DUELS, Dutch Environmental Longitudinal Study; ESCAPE, European Study of Cohorts for Air Pollution Effects; FARM, flexible air quality regional mode; LUR, land use regression; NHS, Nurses' Health Study; NLCS-AIR, Netherlands Cohort Study-AIR; OPHEC, Ontario Population Health and Environment Cohort; TSP, total suspended PM.
[a]Excluded in full analysis but included in subgroup analysis.
[b]SD not available.
[c]Mean concentration not available.
[d]Median value.
[e]Range.

and Laird method was used for calculating the overall RR and 95% CI values because the population and methodologies differed between the studies.[14]

Subgroup and sensitivity analyses were performed to evaluate the influences of selected studies and participant characteristics on pooled results. All analyses were performed with R software version 3.6.1 using the packages meta and metafor. This review was registered with PROSPERO, CRD42020161986.

RESULTS

Study characteristics

Out of 3,256 records identified by the search, 1,058 studies were given title screening after duplicates were removed. Abstracts of the papers retrieved in the electronic search were screened manually for topic relevance and 71 potentially relevant articles underwent a further full-text review. Finally, 47 articles were included in the statistical analyses (Figure 1). Thirty articles[15–44] were included in a meta-analysis of PM exposure and lung cancer risk.

For breast cancer, seven studies[15,45–50] took incidence as the endpoint, while another five studies[40,51–54] focused on mortality. There were 10 studies[49,51,54–61] reporting other cancers, which were reviewed but not included in the meta-analysis. No additional studies were identified by scanning the reference lists of previous studies or the WHO website.

Table 1 summarizes the details of the studies included in the systematic review sorted by the publication year. Most of the studies included in the review reported adverse impacts for cancers of lung, breast, stomach, liver, and kidney, although several studies reported RRs less than 1. The associations between PM_{10} and colorectal or brain cancers were still not clear.

PM and lung cancer

Because the case-fatality rate was high for lung cancer, mortality and incidence were comparable.[62] Thus, it was reasonable to include both outcomes within the same meta-analysis.[6] Thirty publications, including studies from the US, Europe, and Asia that covered total populations of 30.8 million and 10.6 million for $PM_{2.5}$ and PM_{10}, respectively, were included in the meta-analysis for lung cancer. Two publications[16,17] from the Adventist Health and Smog (AHSMOG) Study-2 were included. One study[17] that only reported adenocarcinoma of the lung was included in a subgroup analysis.

The overall pooled RRs of the change in lung cancer incidence or mortality per 10-$\mu g/m^3$ increase in exposure to $PM_{2.5}$ and PM_{10} were 1.16 (95% CI, 1.10–1.23) and 1.22 (95% CI, 1.02–1.45), respectively. The between-study variances for $PM_{2.5}$ and PM_{10} were 81% and 96%, respectively (Figures 2 and 3, estimation by region see Figure S1). Funnel plots for both $PM_{2.5}$ and

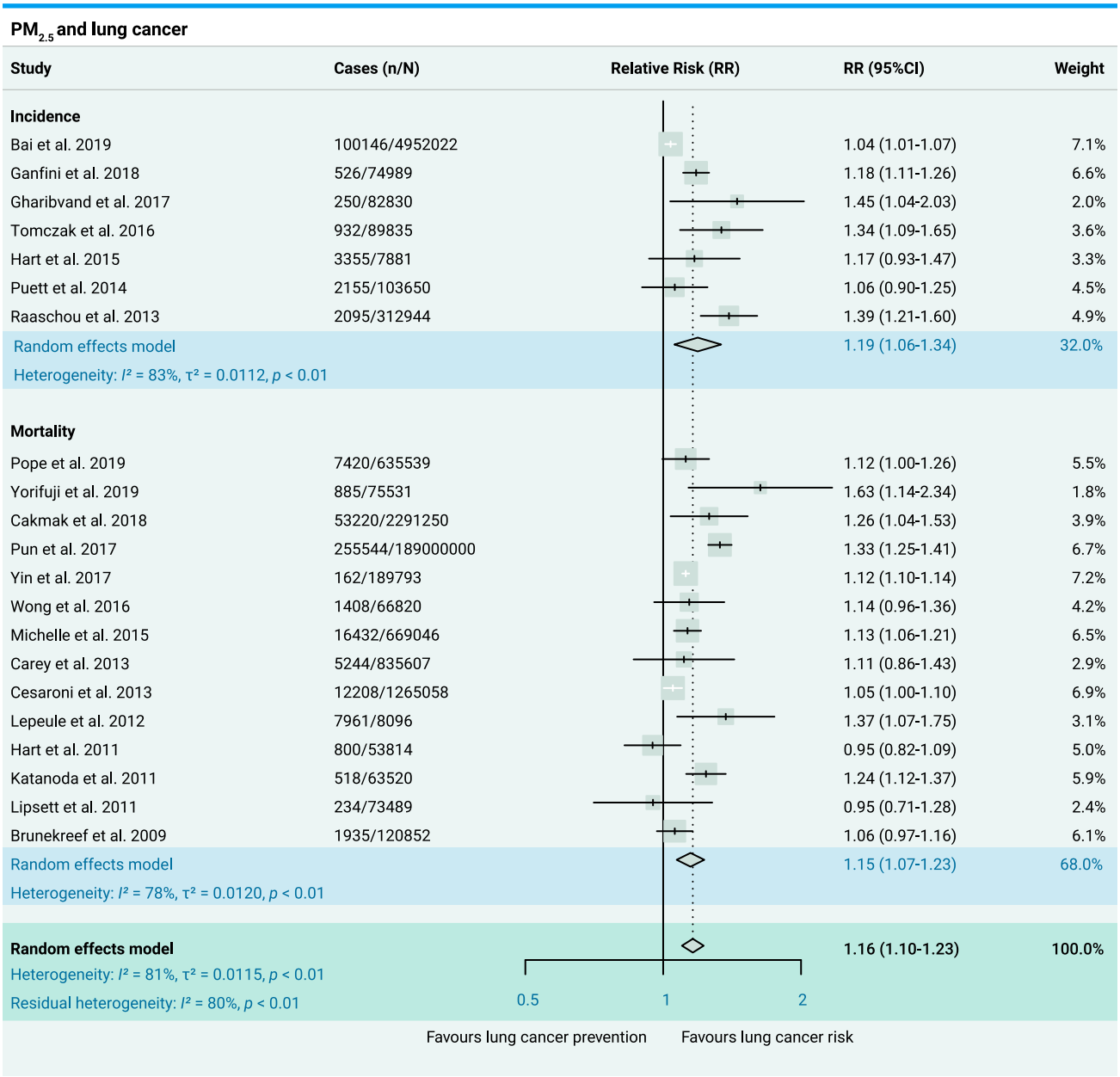

Figure 2. Estimates of lung cancer risk associated with a 10-μg/m^3 change in exposure to $PM_{2.5}$ overall and by outcome

PM_{10} were visually symmetrical. Trim and fill analyses were also conducted, showing no hypothetical negative studies were expected (Figure S2). In addition, the influence analyses showed that the overall findings remained stable after removing any specific studies (Table S10).

Figures 4 and 5 present subgroup analysis by region, sex, smoking status, and histological subtypes. There was no heterogeneity between different regions (p = 0.78). The estimated RR was highest among former smokers, then never smokers and current smokers for $PM_{2.5}$ exposure. The difference did not reach statistical significance between groups (p = 0.68). Only limited studies reported the association between PM_{10} exposure and lung cancer by smoking status. Studies that took age, sex, smoking status, education, income, and occupation exposure into account were also conducted in the meta-analysis. The RR was stable with various confounder adjustments. Associations between $PM_{2.5}$ and PM_{10} and risk for lung cancer by threshold are shown in Table S11. The RRs for studies reported the mean exposure concentration below the WHO air quality guideline threshold values of $PM_{2.5}$ (10 μg/m^3) and PM_{10} (20 μg/m^3) were slightly higher than those above the threshold.

PM and breast cancer

Figures 6 and 7 show the studies included in the meta-analyses of PM and breast cancer incidence and mortality, from total populations of 3.52 million and 2.06 million included for $PM_{2.5}$ and PM_{10}, respectively. The pooled RRs for breast cancer incidence and mortality associated with $PM_{2.5}$ were 1.03 (95% CI, 0.93–1.13) and 1.18 (95% CI, 0.81–1.73) per 10-μg/m^3 increase. Apart from Hart et al., (2016),[47] the other five studies all reported increased RR, but some were not statistically significant. For PM_{10}, the pooled RRs for breast cancer incidence was 1.05 (95% CI, 0.93–1.19) per 10-μg/m^3 increase (Figures 6 and 7, funnel plots see Figure S3). The number of studies included was insufficient to enable further subgroup analysis.

As breast cancer risk and prognosis vary by hormone receptor subtypes, subgroup analyses were conducted to examine possible different effects of

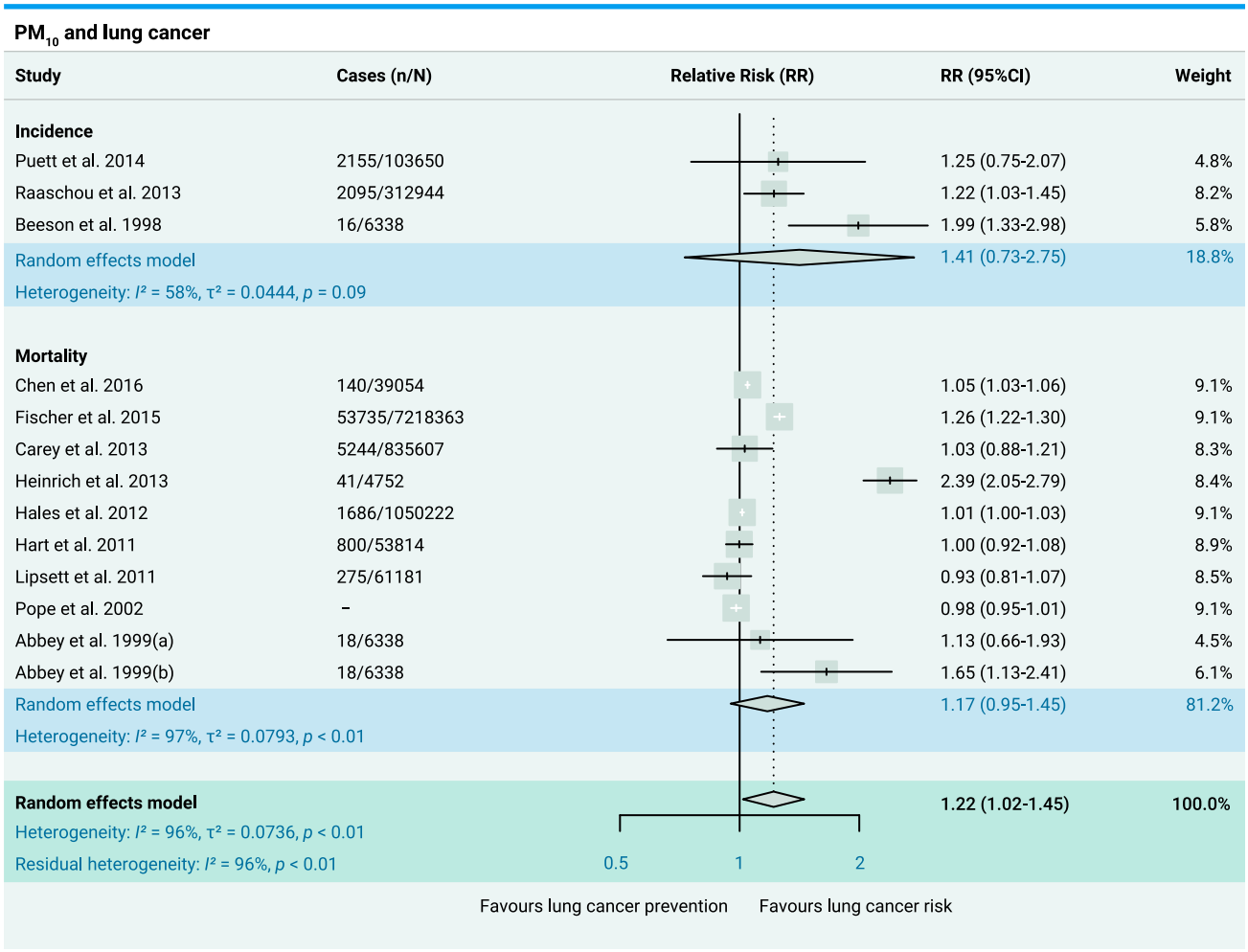

Figure 3. Estimates of lung cancer risk associated with a 10-μg/m^3 change in exposure to PM_{10} overall and by outcome

PM exposure on hormone receptor (estrogen receptor [ER]+ progesterone receptor [PR]+ versus ER− PR−) breast cancer in some studies, but no statistically significant differences were found.[45,47,53] There were also no differences between the risks of breast cancer for premenopausal or postmenopausal women.[46,47] Higher $PM_{2.5}$ was associated with higher stage I breast cancer mortality.[52] Women who smoked or with a higher body mass index (BMI; i.e., ≥30 kg/m^2) did not show a greater risk for breast cancer affected by $PM_{2.5}$.[48,51] No study reported male breast cancers.

PM and other cancers

Eleven studies reported other site-specific cancer risks associated with PM from North America (Public National Health Interview Survey[51] and CPS-II[54]), Europe (ESCAPE study,[56–59,61] Danish Nurse Cohort Study,[60] Saxony Semi-individual Cohort Study,[49] and LIFE MED HISS [Mediterranean Health Interview Survey Studies][20]), and Asia (Taiwan National Death Registry Study[55]). The LIFE MED HISS,[20] CPS-II,[54] and the National Health Interview Survey and mortality follow-up study in the US[51] found a higher risk of bladder cancer due to $PM_{2.5}$ exposure. However, there was no significant association between increased $PM_{2.5}$ and risk of bladder cancer incidence in ESCAPE and also no association between PM_{10} and bladder cancer mortality in a Spanish study.[56,63] Details for other cancers are presented in Figure 8.

When restricted to the never smokers, $PM_{2.5}$ mortality associations observed for cancers of stomach, liver, pancreas, cervix, and Hodgkin lymphoma were still significant.[51] The American CPS-II study reported statistically significant $PM_{2.5}$ associations with colorectal, kidney, and bladder cancer mortality, while the associations of $PM_{2.5}$ with kidney and bladder cancer appeared to be limited to men. Gastrointestinal and liver cancer mortality were reported to be associated with $PM_{2.5}$ exposure in Taiwan, but not stomach cancer. The association between PM and cancer-specific risks other than lung or breast were still unclear as the findings from various cohorts were inconsistent.

DISCUSSION

We conducted a systematic review and meta-analysis of the association between PM exposure and cancer incidence and mortality worldwide. This is the first up-to-date systematic review reporting the effect of PM exposure on all cancers comprehensively focusing on cohort studies, to our knowledge. This evidence supports regulatory authorities addressing community exposures to reduce the PM-related cancer risk.

Strong evidence suggests that cigarette smoke contributes to the development of various types of cancer, especially lung cancer.[64] The National Health Interview Survey study showed different $PM_{2.5}$-mortality associations with specific cancer types between the full cohort and non-smokers.[51] Seven studies reported the risk of $PM_{2.5}$ exposure on lung cancer in never smokers and current smokers, while six studies reported the risk in former smokers. The meta-analysis of these studies revealed higher $PM_{2.5}$-related lung cancer risk among former and never smokers than current smokers, although the findings were imprecise. The risk of outdoor $PM_{2.5}$ in current smokers might be obscured by the effect of smoking and an additive effect was shown

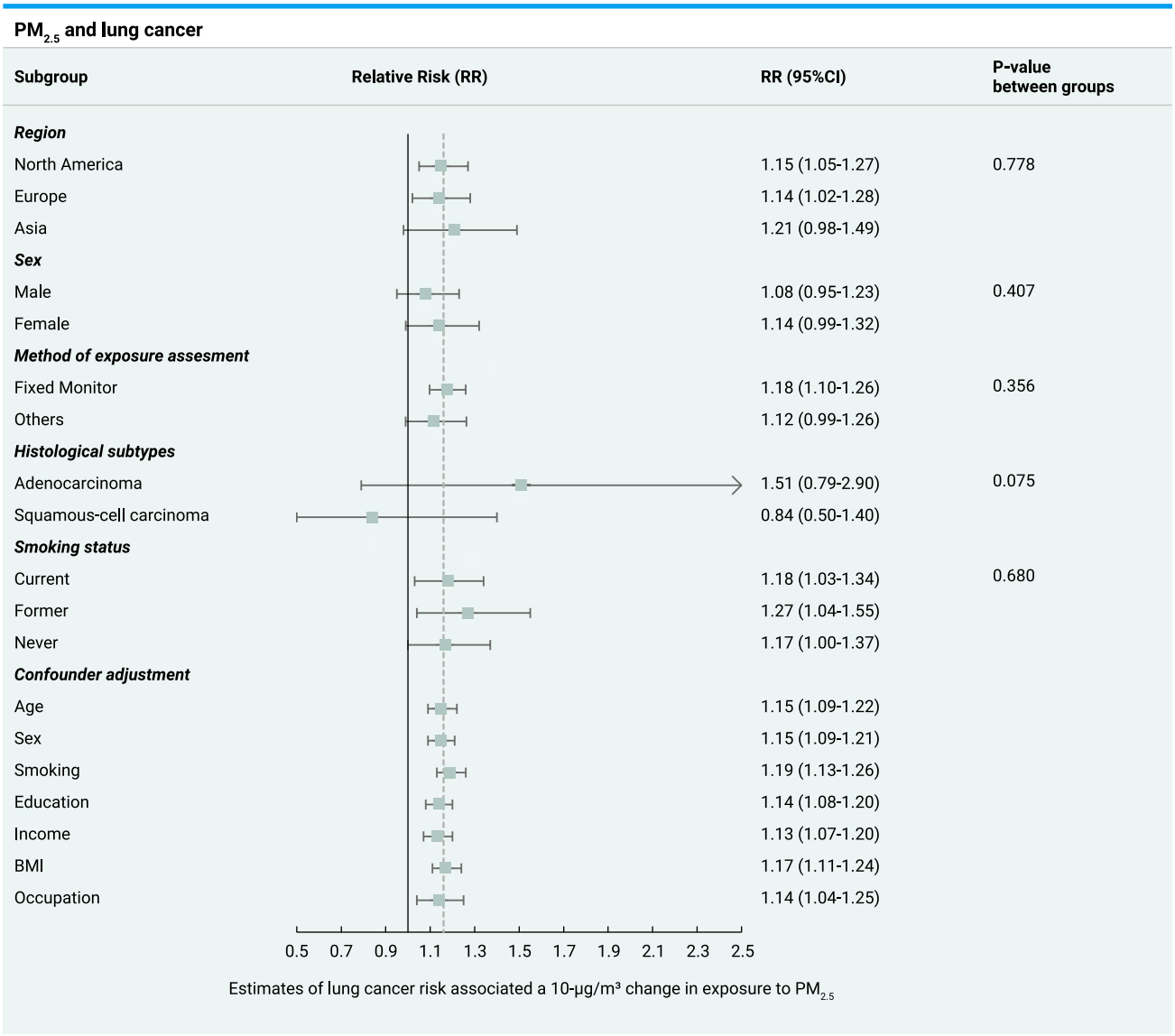

Figure 4. Estimates of lung cancer risks associated with a 10-μg/m^3 change in exposure to $PM_{2.5}$ by region, sex, method of exposure assessment, histological subtypes, and confounding adjustment

among never and former smokers. Another reason might be that many of the subjects had stopped smoking prior to diagnosis, as a result of medical advice for other diseases. Limited studies reported RR with other cancers to show robust evidence.

For lung cancer, the present findings provide more strength to the evidence than was found in previous reviews. Overall, our meta-analysis suggested that long-term exposure to PM was associated with increased risk of lung cancer, and the positive association remained when analyses were adjusted for confounders like age, sex, and smoking status. However, household air pollution, which is the key risk factor for lung cancer, was not adjusted in all studies since the data were unavailable. No difference in risk between geographical regions was found, nor between males and females, which was consistent with previous studies, thus it was reasonable to pool the data from all regions.[6,65] There was no significant heterogeneity between different regions, but we should be cautious when using the worldwide estimates because of heterogeneity between studies.

The pooled RRs for studies using fixed monitors were slightly higher than those using other data sources. Between-group differences were not significant for either $PM_{2.5}$ or PM_{10}, similar to the previous meta-analysis.[6] Considering the access to air pollution data, some cohort studies used the annual concentration at baseline instead of long-term exposure, while some others used the average concentration during the study period. There were limited studies using moving average concentrations to estimate the long-term PM exposure effect on lung cancer risk. Furthermore, only a third of the studies considered a time-varying effect of PM exposure in analysis, which may have led to miscalculation.

The ESCAPE study reported that only lung adenocarcinoma risk was associated with PM exposure.[22] Most studies reported total lung cancer risk affected by PM, while very few reported the results for lung cancer histological subtypes. Studies have shown a changing trend of different histological types of lung cancer. An increasing incidence of adenocarcinoma and a decreasing trend of squamous cell carcinoma incidence has been found in some countries, like China.[66] Therefore, cohort studies for total lung cancer cases cannot accurately reflect the role of PM on different histological types. The impact of PM on different histological subtypes of lung cancer requires further study. An ecological study published recently also showed $PM_{2.5}$ was associated with an increased risk of death from diseases such as

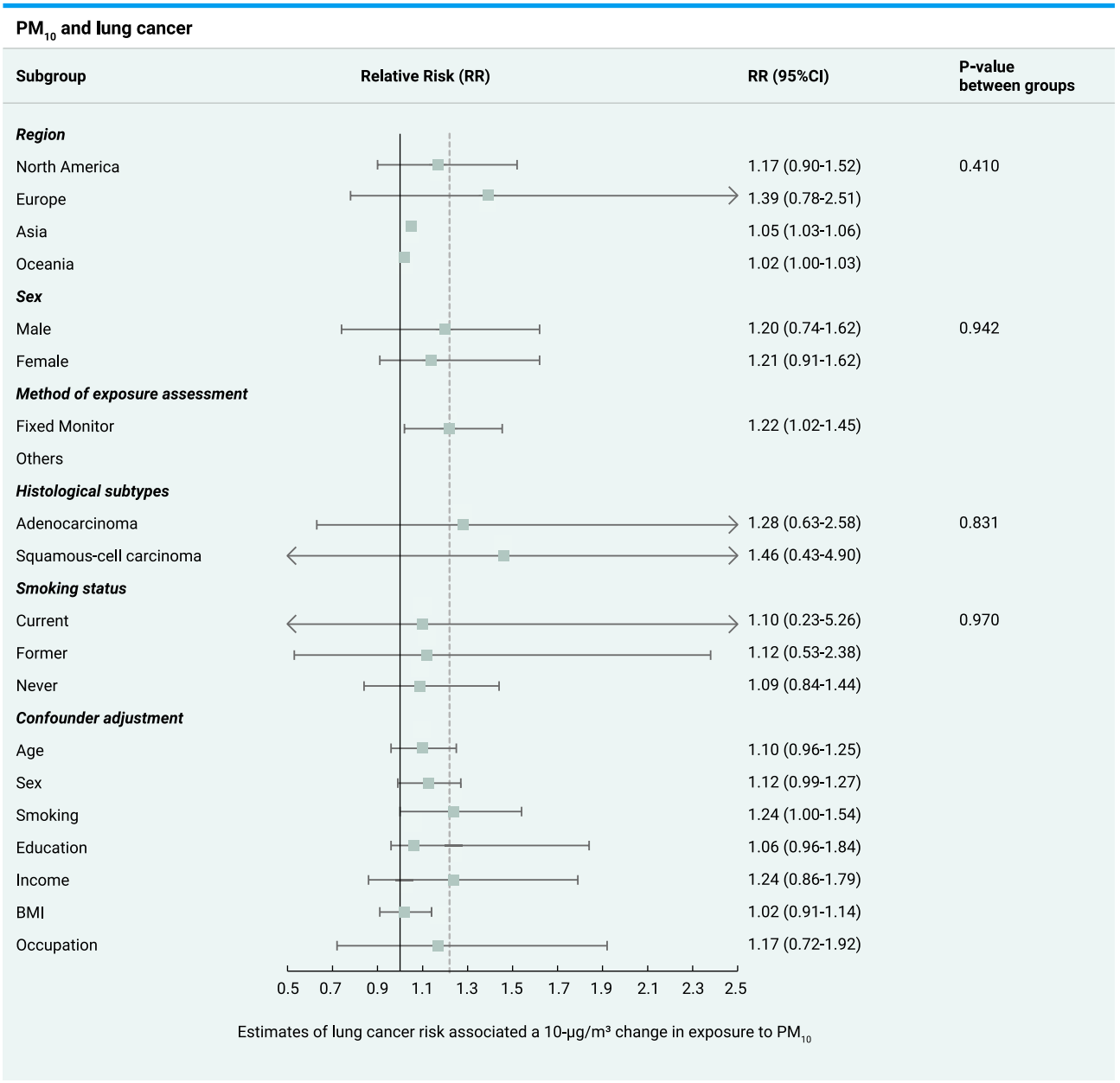

Figure 5. Estimates of lung cancer risks associated with a 10-$\mu g/m^3$ change in exposure to PM_{10} by region, sex, method of exposure assessment, histological subtypes, and confounding adjustment

cardiovascular and respiratory disease, even at low levels.[67] Two studies[36,43] included in our review reported average PM concentrations lower than the WHO air quality guideline threshold values for $PM_{2.5}$ (10 $\mu g/m^3$) and PM_{10} (20 $\mu g/m^3$).[68] The Effects of Low-level Air Pollution: A Study in Europe (ELAPSE), a large pooled cohort analysis, also suggested a linear to supra-linear shape of the $PM_{2.5}$ concentration-response function with no evidence of a threshold.[69]

For breast cancer, we did not find a statistically significant effect of PM exposure. The studies were too limited in number to analyze subgroups. Breast cancer is a disease with a higher survival rate compared with many malignant cancers, and the incidence and mortality rates vary greatly between different stages, subtypes, ages, and ethnicities.[62,70] As the 5-year survival rate is over 95% in patients diagnosed with stage I breast cancer, but about 30% in stage IV patients,[70] it would not be reasonable to pool all stages together to examine the association of PM exposure and breast cancer death without adjustment for treatment. When a stratified analysis was conducted of stage I breast cancer patients, $PM_{2.5}$ was associated with higher breast cancer-specific mortality.[52] A potential explanation for differences among studies may be that this finding is due to differences in the proportions of cancer stages.

Hormone receptor status is a key factor in breast cancer diagnosis and treatment. A potential mechanism of how PM could increase breast cancer risk is that estrogenic particles might move from the lung to breast tissue.[71] Only three articles reported the risks of PM on breast cancer stratified by hormone receptor status, but no significant differences were found between the risks for ER+ PR+ and ER− PR− breast cancers. The duration of hormone exposure is also important in breast cancer development. Two studies that were included reported the risks by menopausal status with no significant differences. Because of the rapid breast development and susceptibility of rapidly duplicating cells to environmental insults, puberty could be a critical period during which to assess the impact of exposures to $PM_{2.5}$ on the breast.[72,73] Limited studies focused on early lifetime

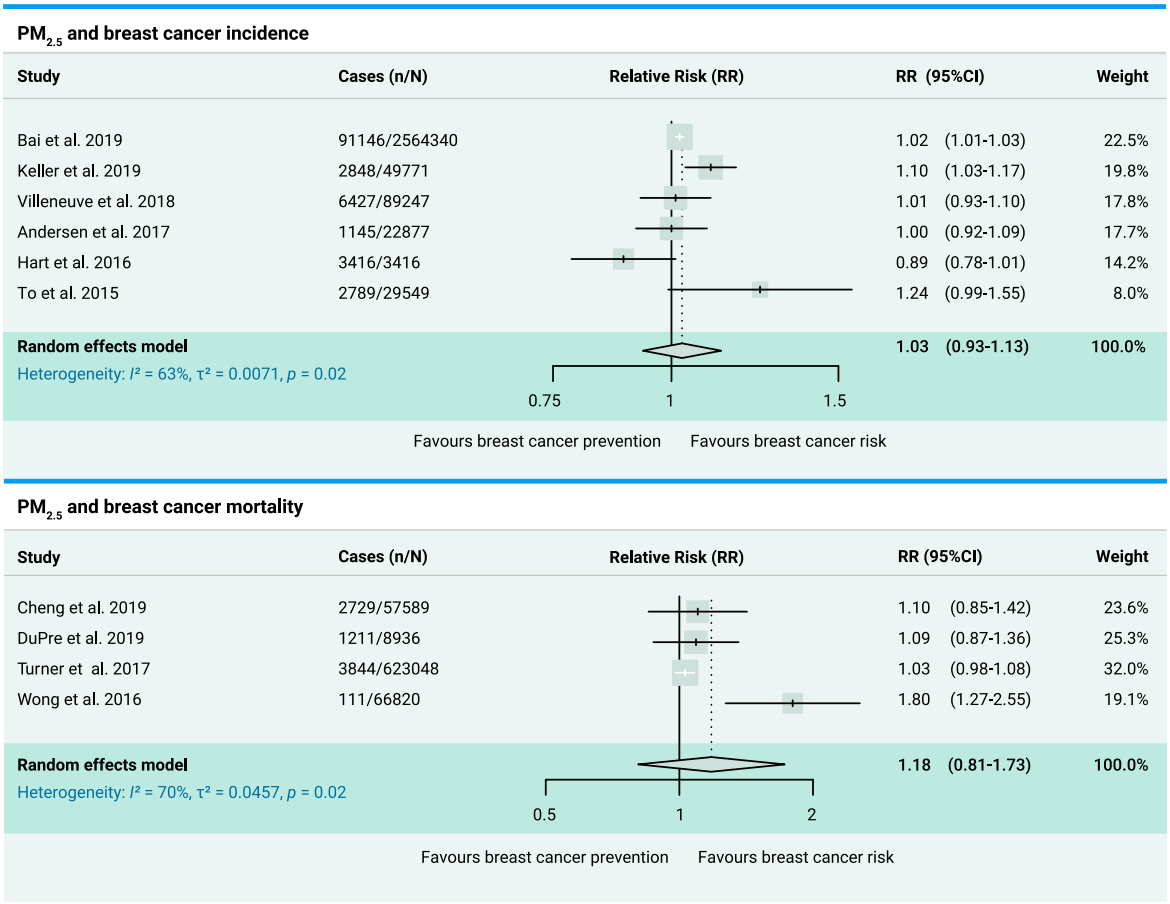

Figure 6. Estimates of breast cancer risk associated with a 10-μg/m^3 change in exposure to $PM_{2.5}$

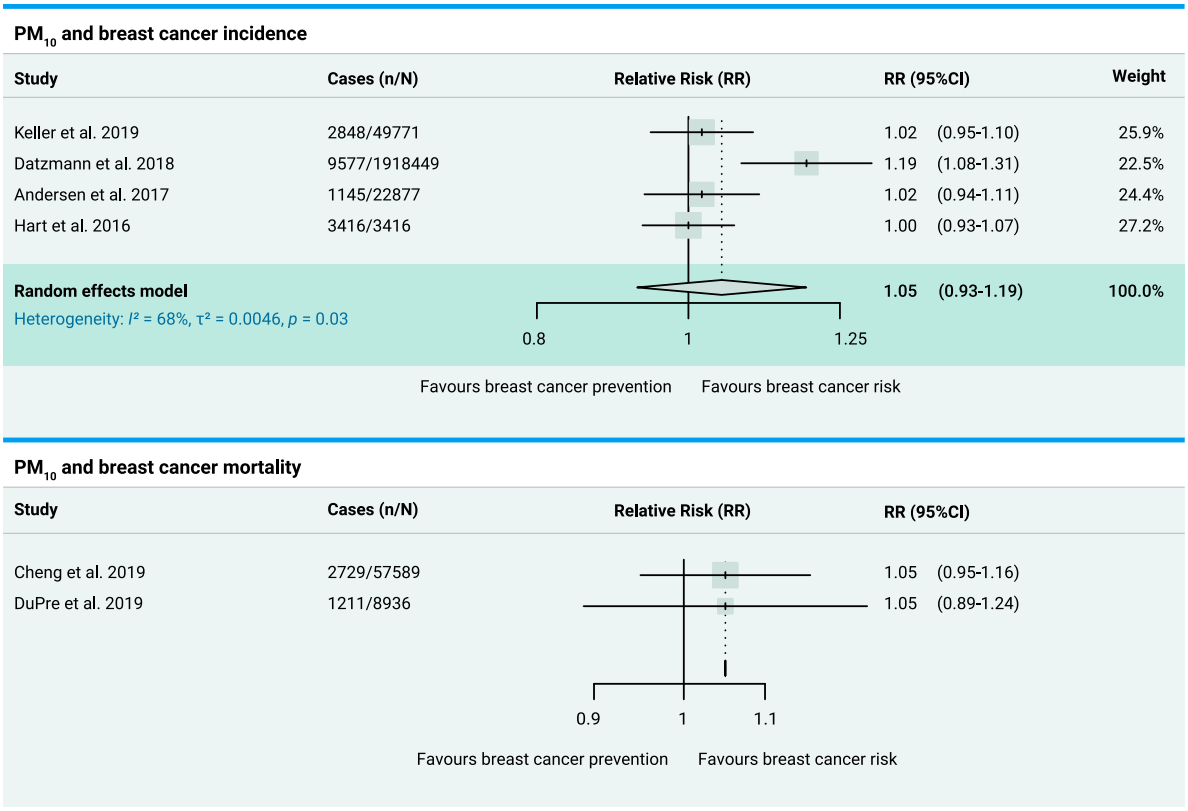

Figure 7. Estimates of breast cancer risk associated with a 10-μg/m^3 change in exposure to PM_{10}

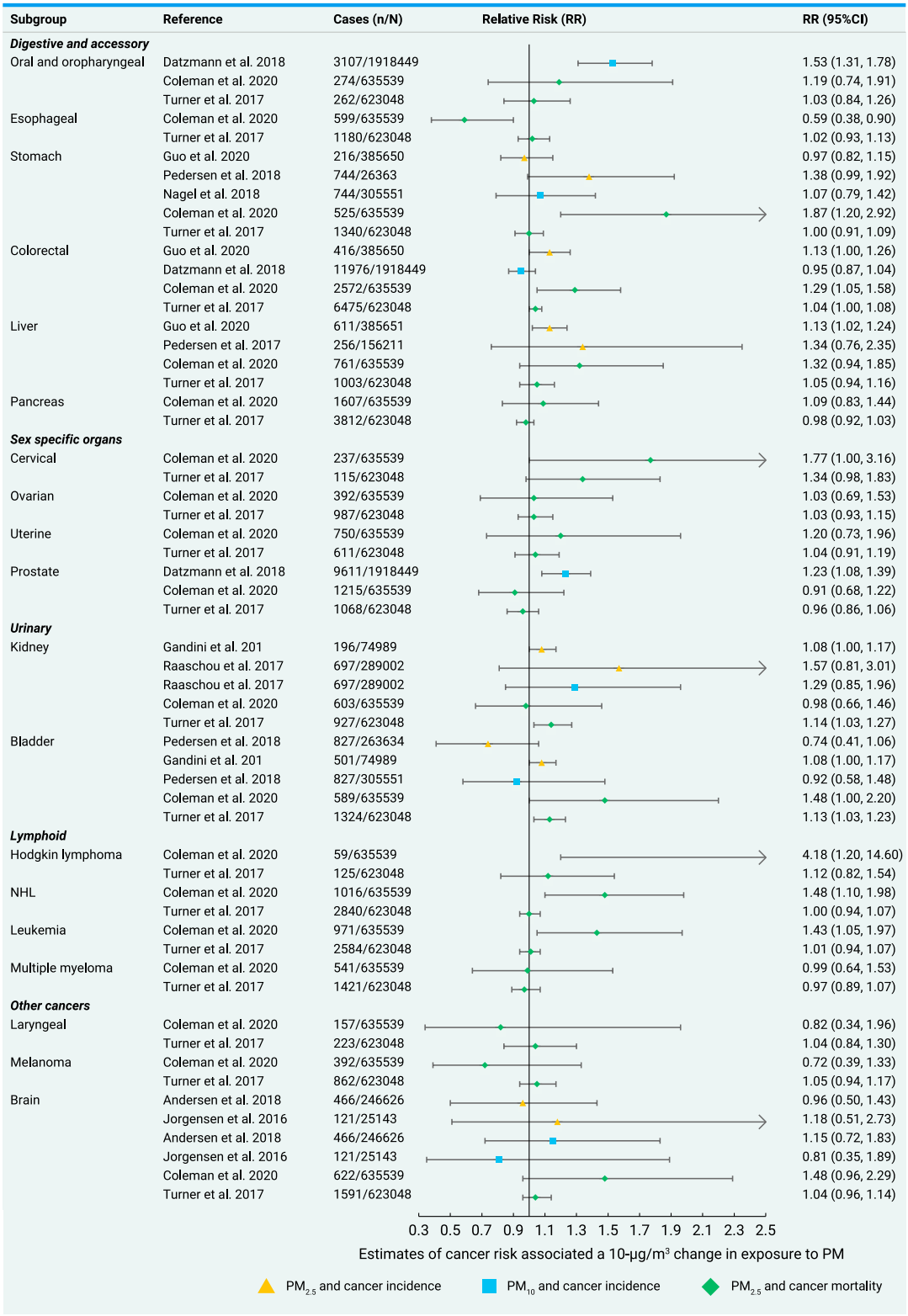

Figure 8. Estimates of other types of cancer risk associated with a 10-μg/m^3 change in exposure to $PM_{2.5}$ or PM_{10}

PM exposure to breast cancer risk. A sister study suggested that exposure to vehicular traffic-related air pollution during childhood may be associated with increased breast cancer.[74] After reviewing all these studies, there are still some research gaps to confirm whether PM exposure is a risk factor for breast cancer or not. More studies should be conducted to identify high-risk groups for PM.

Ambient air pollution was not significantly associated with incidence or death from most other cancers in the studies included. However, cancers

of oral cavity, stomach, bladder, kidney, prostate, liver, colorectum, and lymphoid tissues have been inconsistently associated with PM. PM-related bladder cancer risk was observed in several ecological studies. A study from Taiwan suggested an adverse effect of $PM_{2.5}$ on mortality,[75] which was in line with the study from the US.[76] The study using the Surveillance, Epidemiology, and End Results (SEER) program data in the US showed negative findings,[77] taking bladder cancer incidence as the outcome. Wang et al. showed the significant adverse effect of $PM_{2.5}$ on bladder cancer incidence, but a null effect on mortality in China.[78] Other studies reporting PM_{10}-related studies were also inconsistent with the cohort study included. Both a case-control study from Taiwan and an ecological study from Germany showed the risk of bladder cancer associated with increasing PM_{10} concentrations.[79,80] The inconsistent results, encompassing both incidence and mortality, could be due to the limited number of studies that were conducted in different regions with concentrations of exposure.

The inconsistent results apply not only in bladder cancer studies. Kidney cancer is another example, and inconsistent conclusions were shown within similar populations. Two cohort studies from Europe gave different conclusions on $PM_{2.5}$ and kidney cancer incidence, while studies from the US also showed different results for $PM_{2.5}$ and mortality from kidney cancer. In ESCAPE, only vanadium in $PM_{2.5}$ was found to be associated with kidney cancer,[81] which revealed particles from mixed oil burning and industry that might be carcinogenic to the kidney. As PM is a complex mixture of chemical composition related to the sources, more studies focusing on sources should be conducted to clarify these inconsistent results.

This is the first systematic review and meta-analysis summarizing the association between PM and cancer risk comprehensively with searching across six databases. Focusing on cohort studies should also give more robust evidence. However, there are still some limitations to our review. Firstly, high heterogeneity existed due to general differences in population demographics, exposure assessment methods, and the covariate adjustments in different studies. Secondly, large-scale studies of PM and lung cancer risk have not yet been published from some of the most polluted countries, such as India. Thus, the associations were not completely representative of the global population. Thirdly, although 30 articles were included for the lung cancer analysis, they were still insufficient to demonstrate a dose-response relationship by conducting meta-regression and also some subgroup analyses. Finally, the definitions of smoking status varied among studies, which may lead to misclassification.

CONCLUSION

Our systematic review has summarized cohort studies that aimed to find the association between ambient PM and cancer risk. Current studies provide evidence of an adverse effect of outdoor PM exposure on lung cancer. Further studies of air pollution and breast, bladder, and kidney cancer should be conducted as these research gaps still exist and need to be filled. However, regulatory authorities need to reduce community exposures to PM as much as feasible.

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Review

AUTHOR CONTRIBUTIONS

P.Y., Y.G., M.A., and S.L. designed the review. P.Y., S.G., and R.X. ran the literature search, screened records, and extracted data. P.Y., T.Y., and R.X. did statistical analyses. P.Y. and S.G. wrote the manuscript. Y.G., M.A., and S.L. provided scientific comments on the manuscript. All authors provided critical conceptual input, analyzed and interpreted data, and critically revised the report.

DECLARATION OF INTERESTS

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SUPPLEMENTAL INFORMATION

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