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Research article

# Association between urinary phthalates and phthalate metabolites and cancer risk: A systematic review and meta-analysis

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ABSTRACT

Phthalates, widely utilized in industrial products, are classified as endocrine-disrupting chemicals (EDCs). Although certain phthalate and their metabolites have been implicated in cancer development, the reported findings have exhibited inconsistencies. Therefore, we conducted the comprehensive literature search to assess the association between phthalate and their metabolites and cancer risk by identifying original studies measuring phthalates or their metabolites and reporting their correlation with cancer until July 4, 2023. The Odds Ratios (ORs) and corresponding 95% confidence intervals (CIs) were extracted and analyzed to estimate the risk. Pooled data from eleven studies, including 3101 cancer patients and 6858 controls, were analyzed using a fixed- or random-effects model based on heterogeneity tests. When comparing extreme categories of different phthalates and their metabolites, we observed a significant association between urinary phthalates and phthalate metabolites (MEHHP, MECPP, DBP and MBzP) and cancer risk. The findings of our meta-analysis reinforce the existing evidence that urinary phthalates and phthalate metabolites is strongly associated with cancer development. Further investigations are warranted to elucidate the underlying mechanisms of this association. These results may offer novel insights into cancer development.

## 1. Introduction

Endocrine-disrupting chemicals (EDCs) encompass a diverse array of exogenous compounds that disrupt the endocrine functions of the human body [1]. Phthalates, a class of chemicals within the wider umbrella of EDCs, are famous plasticizers and additives in

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industrial and daily products including medical devices, deodorants, cosmetics, food wrapping and toys [2]. Additionally, phthalates are unable to establish a stable coexistence with the other chemical constituents found in various industrial and daily products, leading to their easy release into the environment [3,4]. Therefore, phthalate exposure is ubiquitous in people of all age groups, via the oral route, inhalation, dermal contact and medical injection [5]. Phthalates could be divided into two categories: low molecular weight, such as dibutyl phthalate (DBP) and di-isobutyl phthalate (DIBP), and high molecular weight, such as di-(2-ethylhexyl) phthalate (DEHP) and di-isodecyl phthalate (DIDP) [6]. After entering the body, these phthalates undergo metabolism into monoesters [7,8]. For instance, DEHP could be metabolized into toxic and active mono-(2-ethylhexyl) phthalate (MEHP), subsequently converted to mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) through oxidation reactions. DBP could be metabolized into mono-n-butyl phthalate (MBP/MnBP) [9]. Generally, the phthalate metabolites are excreted or urinated as glucuronide conjugates. Therefore, urinary phthalate metabolites serve as valuable biomarkers for assessing human acute (short-term) exposure levels [7,10]. Recently, a series of phthalates and phthalate metabolites have been reported to be associated with several health outcomes, garnering great public attention in the world [11–13].

Cancer is one of the leading causes of death worldwide for its malignant progression and associated complications. About 10 million people die from cancer per year, with a projected increase to 28.4 million new cases by 2040 [14,15]. In the past decades, the patterns of cancer epidemiology has changed dramatically caused by multiple factors, such as environmental pollution, and unhealthy

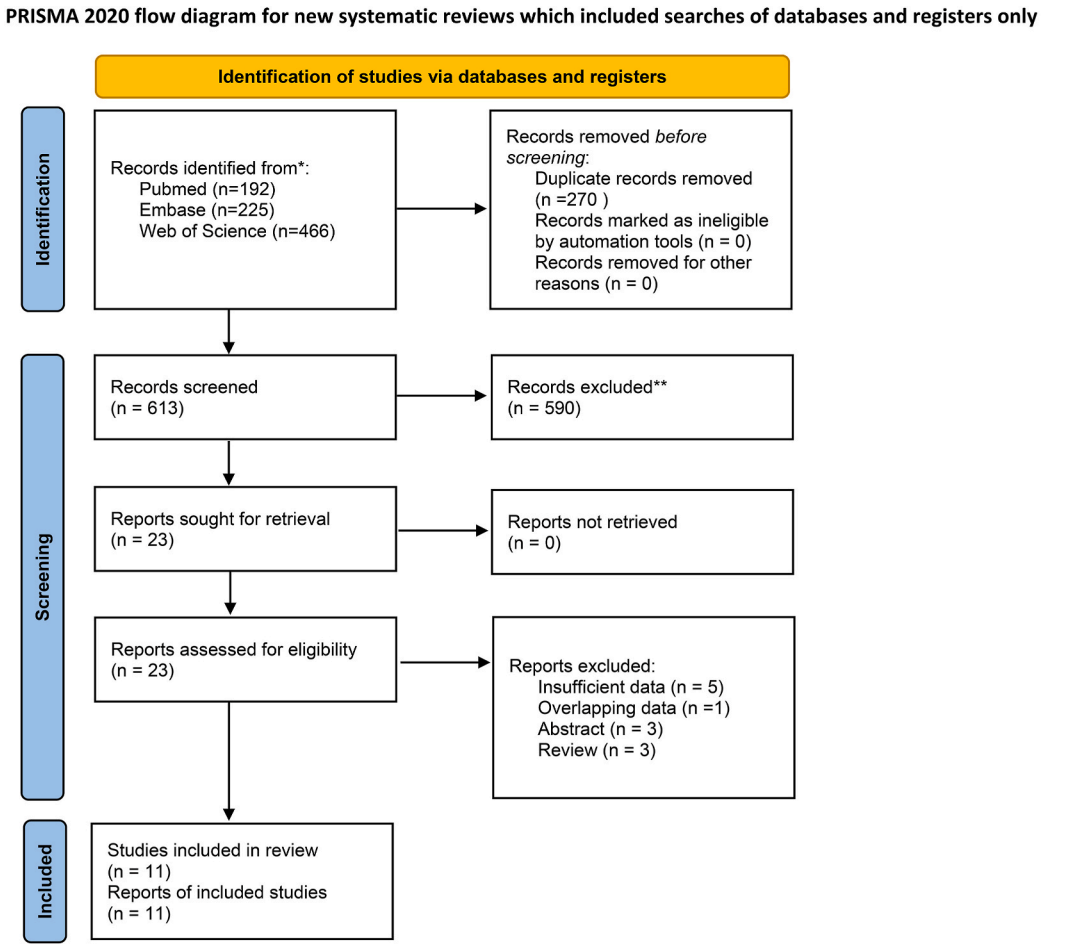


**Fig. 1.** Flow diagram of study identification.

**Table 1**
Characteristics of the studies included in the meta-analysis.

| First author | Country | Duration | Cancer | Sources | Sample | Detected phthalates and their metabolites | Detection method | Unit | Sample size | | Cases | | Controls | | Association | Confounders |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Publication year | | | type | | | | | | Case | Control | Age (years, Mean ± SD) | Male/ Female | Age (years, Mean ± SD) | Male/ Female | estimates | |
| Guo 2023 | China | From 2003 to 2010 | Prostate cancer | National Health and Nutrition Examination Survey (NHANES) data | urine | MnBP, MEP, MEHP, MBzP, MCHP, MiNP, MnOP, MnMP, MCPP, MEHHP, MEOHP, MiBP and MECPP | High-performance liquid chromatography-electrospray ionization tandem mass spectrometry (HPLC-ESI-MS/MS) | creatinine-corrected phthalate metabolite concentrations and ΣDEHP values were log10-transformed. | 100 | 1576 | 72.33 ± 8.73 | 100/0 | 59.72 ± 12.37 | 1576/0 | OR (T3 vs T1) | Adjusted for urine creatinine, age, BMI, race, education level, smoking status, diabetes and high blood pressure. |
| Mukherjee Das 2022 | India | From April 2018 to February 2020 | Breast cancer | Women who had come to the breast outpatient department (O.P.D) of the hospital complaining of having signs and symptoms of breast cancer. | urine | DMP, DEP, DBP, BBP, DEHP and DINOP | The enzyme Beta-Glucoronidase followed by Gas Chromatography coupled with Mass Spectrometry (GC-MS) analysis. | ng/g creatinine | 90 | 81 | 49.71 ± 11.4 | 0/90 | 49.70 ± 8.18 | 0/81 | OR (>median vs ≤ median) | Adjusted for covariates; age at marriage, education, BMI, first child birth, menarche, passive smoke exposure from husband's smoking habit and abortion history |
| Wu 2021 | USA | From 2001 to 2014 | Breast cancer | Patients living in Hawaii and California (primarily from Los Angeles County) | urine | MMP, MEP, MBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP and MCHP | State-of-the-art sensitive isotope-dilution orbitrap-based high-resolution accurate-mass liquid chromatography mass spectrometry (LC-MS) assay | ng/g creatinine | 1032 | 1030 | 66.7 ± 7.7 | 0/1032 | 66.8 ± 7.7 | 0/1030 | OR (T3 vs T1) | Adjusted for education, number of children, age at menarche, menopausal status, BMI at urine collection, neighborhood socioeconomic status at urine collection, smoking, alcohol intake, and Mediterranean |

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**Table 1** (*continued*)

| First author Publication year | Country | Duration | Cancer type | Sources | Sample | Detected phthalates and their metabolites | Detection method | Unit | Sample size Case | Control | Cases Age (years, Mean ± SD) | Male/ Female | Controls Age (years, Mean ± SD) | Male/ Female | Association estimates | Confounders |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | energy adjusted total score. |
| Sarink 2021 | USA | From 2001 to 2017 | Endometrial cancer | Patients from five main racial/ ethnicgroups included in the MEC. | urine | MBzP, MECPP, MEHHP, MEHP, MEOHP, MEP, MiBP, MMP, MnBP, PA phthalic acid, DBP and DEHP | Liquid chromatography high-resolution accurate-mass spectrometry | creatinine-adjusted urinary EDC metabolite excretion (ng/ mg) | 139 | 139 | 62 (59–69)[a] | 0/139 | 62 (59–69)[a] | 0/139 | OR (T3 vs T1) | Adjusted for BMI at specimen collection, diabetes, and the energy-adjusted alternate Mediterranean Diet Score from the baseline questionnaire (continuous). |
| Miao 2020 | China | From June to September 2017 | Thyroid cancer | Patients in the Cancer Hospital of Chinese Academy of Medical Sciences | urine | MBP, MEP, MEHP, MEOHP, MECPP and MEHHP | Ultraperformance liquid chromatography/ tandem mass spectrometry (UPLC-MS/MS) | ng/mL | 111 | 111 | 42.5 ± 11.4 | 25/86 | 42.5 ± 11.1 | 25/86 | OR (T3 vs T1) | NA |
| Liu 2020 | China | From March to December 2016 | Thyroid cancer | Patients in the Department of Thyroid and Breast Surgery, Central Hospital of Wuhan, China. | urine | MMP, MEP, MEHHP, MBP, MEOHP, MBzP and MEHP | Solid-phase extraction and high-performance liquid chromatography and tandem mass spectrometry | μg/g creatinine | 144 | 144 | 47.1 ± 11.6 | 40/ 104 | 44.9 ± 10.3 | 40/ 104 | OR (T3 vs T1) | Adjusted for gender, age, BMI, alcohol use, smoking status and income. |
| Chuang 2020 | China | From 1991 to 2010 | Prostate cancer | The Community-Based Cancer Screening Program was established between 1991 and 1992 in Taiwan. | urine | MMP, MEP, MnBP, MBzP, MiBP, MiNP, MEHP, MEHHP, MEOHP, MECPP and MCMHP | Solid phase extraction coupled with liquid chromatography/ electrospray ionization tandem mass spectrometry (LC-ESI-MS-MS) | μg/g creatinine | 80 | 156 | 57.74 ± 6.02 | 80/0 | 57.53 ± 6.00 | 156/0 | OR (T3 vs T1) | Adjusted for education and waist circumference. |
| Reeves 2019 | USA | From 1993 to 2013 | Breast cancer | Patients in theWomen's Health | urine | MEP, MBP, MHBP, ΣDBP, | Online solid phase extraction and high-performance | μg/g creatinine | 419 | 838 | 62.56 ± 6.93 | 0/419 | 62.46 ± 6.86 | 0/838 | OR (Q4 vs Q1) | Adjusted models include the following |

(*continued on next page*)

**Table 1** (*continued*)

| First author | Country | Duration | Cancer | Sources | Sample | Detected phthalates and their metabolites | Detection method | Unit | Sample size | | Cases | | Controls | | Association | Confounders |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Publication year | | | type | | | | | | Case | Control | Age (years, Mean ± SD) | Male/ Female | Age (years, Mean ± SD) | Male/ Female | estimates | |
| | | | | Initiative (WHI) prospective cohort. | | MiBP, MHiBP, ΣDiBP, MBzP, MCPP, MEHP, MEHHP, MEOHP, MECPP, ΣDEHP, MCOP and MCNP | liquid chromatography-electrospray ionization-tandem mass spectrometry | | | | | | | | | covariates: age; race/region; neighborhood socioeconomic status index; body mass index; alcohol use; smoking status; Gail risk score; postmenopausal hormone therapy use at enrollment; hormone therapy trial assignment; dietary modification trial assignment; and calcium and vitamin D trial assignment. |
| Parada 2018 | USA | From 1996 to December 31, 2014 | Breast cancer | Patients from the Long Island Breast Cancer Study Project (LIBCSP) | urine | MEP, MnBP, MiBP, MCPP, MBzP, MCOP, MCNP, MEHP, MEOHP, MEHHP, MECPP and ΣDEHP | Online solid-phase extraction followed by high-performance liquid chromatography-electrospray ionization-isotope-dilution tandem mass spectrometry | μg/g creatinine | 710 | 598 | 22–96[b] | 0/710 | 22–96[b] | 0/598 | OR (Q5 vs Q1) | Adjusted for age, age at menarche, education, menopausal status, hormone replacement therapy use, body mass index, and oral contraceptive use. |
| Morgan 2017 | USA | From 2003 to 2010 | Breast cancer | Patients in the National Health and Nutrition Examination Survey (NHANES) data | urine | MBP,MEP, MEHP, MBzP, MCCP, MEHHP, MEOHP, MIB, DEHP | NA | μg/g creatinine | 43 | 1964 | 65.2 ± 2.10[c] | 0/43 | 45.5 ± 0.43[c] | 0/ 1964 | OR (LOD≥50 % vs LOD<50 %) | Adjusted for age, race/ethnicity, BMI, age at menarche. |

(*continued on next page*)

**Table 1** (*continued*)

| First author | Country | Duration | Cancer | Sources | Sample | Detected phthalates and their metabolites | Detection method | Unit | Sample size | | Cases | | Controls | | Association | Confounders |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Publication year | | | type | | | | | | Case | Control | Age (years, Mean ± SD) | Male/ Female | Age (years, Mean ± SD) | Male/ Female | estimates | |
| López-Carrillo 2010 | México | From March 2007 to August 2008 | Breast cancer | Twenty-five tertiary hospital units, including Health Department (Secretaría de Salud), Social Security (Instituto de Seguridad y Servicios Sociales), and State Workers' Social Security hospitals, as well as university health centers. | urine | MEP, MBP, MiBP, MBzP, MCPP, MEHP, MEHHP, MEOHP, MECPP | Solid-phase extraction coupled with high-performance liquid chromatography/ isotope dilution/ tandem mass spectrometry | μg/g creatinine | 233 | 221 | 53.41 ± 12.78 | 0/233 | 53.83 ± 12.54 | 0/221 | OR (T3 vs T1) | Adjusted for current age, age of menarche, parity, and menopausal status plus phthalate metabolites: DEHP metabolites were adjusted for non-DEHP metabolites; MEP, MBP, MiBP, BBzP, and MCPP were adjusted for themselves plus the sum of DEHP metabolites. |

NA, not available.

[a] Data presented as median (interquartile range).

[b] Data presented as range.

[c] Data presented as mean ± standard error.

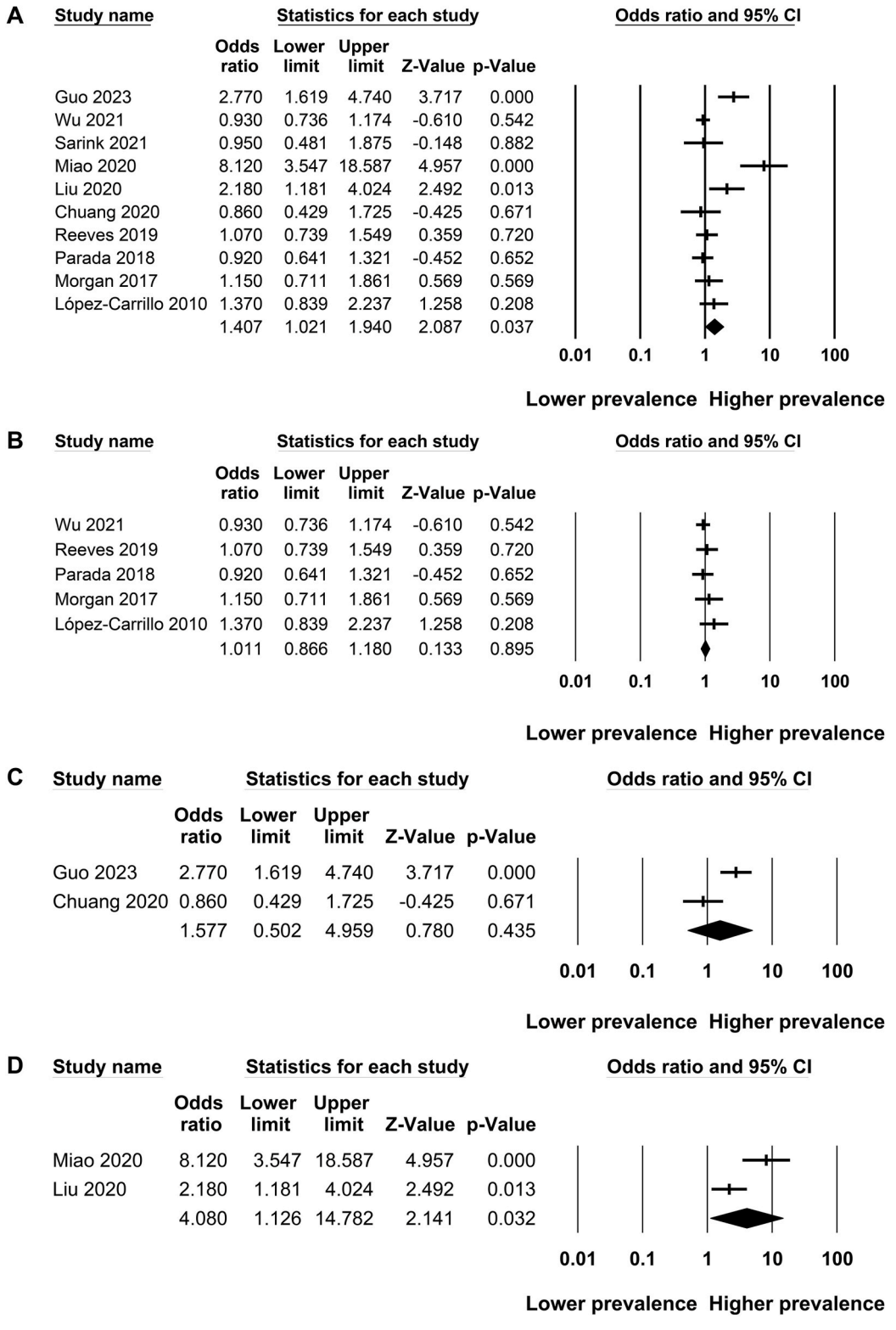
**Table 2**
Summary of meta-analysis results.

| Phthalate | Cancer | Studies | Case (n) | Control (n) | Tests of association | | | | Tests of heterogeneity | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Model | OR [95%CI] | Z | *P*-value | Q-value | *P*-value | $I^2$ (%) |
| MEP | Cancer | 10 | 3011 | 6777 | RE | 1.026[0.790–1.332] | 0.193 | 0.847 | 25.706 | 0.002 | 64.989 |
| | Breast cancer | 5 | 2437 | 4651 | RE | 0.982[0.696–1.387] | 0.101 | 0.920 | 15.992 | 0.003 | 74.988 |
| | Prostate cancer | 2 | 180 | 1732 | RE | 0.887[0.253–3.104] | 0.188 | 0.851 | 6.588 | 0.010 | 84.820 |
| | Thyroid cancer | 2 | 255 | 255 | FE | 1.301[0.828–2.045] | 1.142 | 0.253 | 1.731 | 0.188 | 42.232 |
| MnBP | Cancer | 10 | 3011 | 6777 | RE | 0.958[0.711–1.290] | 0.281 | 0.779 | 32.424 | <0.001 | 72.242 |
| | Breast cancer | 5 | 2437 | 4651 | FE | 0.917[0.781–1.077] | 1.054 | 0.292 | 4.453 | 0.348 | 10.179 |
| | Prostate cancer | 2 | 180 | 1732 | FE | 1.322[0.855–2.046] | 1.255 | 0.210 | 0.248 | 0.618 | 0.000 |
| | Thyroid cancer | 2 | 255 | 255 | RE | 0.597[0.070–5.056] | 0.473 | 0.636 | 20.08 | <0.001 | 95.020 |
| MEHP | Cancer | 10 | 3011 | 6777 | RE | 1.286[0.953–1.736] | 1.647 | 0.099 | 31.661 | <0.001 | 71.574 |
| | Breast cancer | 5 | 2437 | 4651 | FE | 0.983[0.831–1.162] | 0.203 | 0.839 | 2.445 | 0.654 | 0.000 |
| | Prostate cancer | 2 | 180 | 1732 | FE | 1.223[0.784–1.908] | 0.203 | 0.839 | 2.445 | 0.654 | 0.000 |
| | Thyroid cancer | 2 | 255 | 255 | RE | 5.235 [0.549–49.890] | 1.439 | 0.150 | 12.974 | <0.001 | 92.292 |
| MBzP | Cancer | 9 | 2900 | 6666 | RE | 0.824[0.668–1.017] | 1.806 | 0.071 | 14.862 | 0.062 | 46.170 |
| | Breast cancer | 5 | 2437 | 4651 | FE | 0.731[0.626–0.854] | 3.947 | **<0.001** | 3.365 | 0.499 | 0.000 |
| | Prostate cancer | 2 | 180 | 1732 | FE | 1.493[0.976–2.284] | 1.847 | 0.065 | 1.239 | 0.266 | 19.315 |
| MCHP | Cancer | 2 | 1132 | 2606 | RE | 0.866[0.449–1.670] | 0.429 | 0.668 | 4.962 | 0.026 | 79.845 |
| MCPP | Cancer | 5 | 1505 | 5197 | RE | 0.911[0.582–1.427] | 0.407 | 0.684 | 17.982 | 0.001 | 77.755 |
| | Breast cancer | 4 | 1405 | 3621 | RE | 0.758[0.544–1.055] | 1.641 | 0.101 | 6.405 | 0.093 | 53.164 |
| MEHHP | Cancer | 10 | 3011 | 6777 | RE | 1.407[1.021–1.940] | 2.087 | **0.037** | 42.02 | <0.001 | 78.582 |
| | Breast cancer | 5 | 2437 | 4651 | FE | 1.011[0.866–1.180] | 0.133 | 0.895 | 2.593 | 0.628 | 0.000 |
| | Prostate cancer | 2 | 180 | 1732 | RE | 1.577[0.502–4.959] | 0.780 | 0.435 | 6.798 | 0.009 | 85.290 |
| | Thyroid cancer | 2 | 255 | 255 | RE | 4.080 [1.126–14.782] | 2.141 | **0.032** | 6.259 | 0.012 | 84.022 |
| MEOHP | Cancer | 10 | 3011 | 6777 | RE | 1.217[0.958–1.547] | 1.608 | 0.108 | 23.057 | 0.006 | 60.967 |
| | Breast cancer | 5 | 2437 | 4651 | FE | 0.953[0.818–1.111] | 0.613 | 0.540 | 2.366 | 0.669 | 0.000 |
| | Prostate cancer | 2 | 180 | 1732 | RE | 1.721[0.876–3.380] | 1.577 | 0.115 | 2.226 | 0.136 | 55.066 |
| | Thyroid cancer | 2 | 255 | 255 | RE | 2.098[0.868–5.071] | 1.645 | 0.100 | 3.643 | 0.056 | 72.554 |
| MiBP | Cancer | 8 | 2756 | 6522 | FE | 1.024[0.882–1.189] | 0.315 | 0.752 | 11.248 | 0.128 | 37.765 |
| | Breast cancer | 5 | 2437 | 4651 | FE | 0.968[0.882–1.140] | 0.391 | 0.696 | 6.093 | 0.192 | 34.350 |
| | Prostate cancer | 2 | 180 | 1732 | FE | 1.229[0.800–1.889] | 0.942 | 0.346 | 1.432 | 0.232 | 30.143 |
| MECPP | Cancer | 8 | 2824 | 4669 | RE | 1.428[1.021–1.997] | 2.080 | **0.038** | 28.783 | <0.001 | 75.680 |
| | Breast cancer | 4 | 2394 | 2687 | RE | 1.075[0.829–1.394] | 0.545 | 0.586 | 6.425 | 0.093 | 53.307 |
| | Prostate cancer | 2 | 180 | 1732 | FE | 1.582[1.017–2.459] | 2.036 | **0.042** | 0.765 | 0.382 | 0.000 |
| DEHP | Cancer | 7 | 1581 | 5352 | RE | 1.391[0.918–2.108] | 1.557 | 0.120 | 23.381 | 0.001 | 74.338 |
| | Breast cancer | 4 | 1262 | 3481 | RE | 1.113[0.758–1.633] | 0.545 | 0.586 | 6.886 | 0.076 | 56.432 |
| | Prostate cancer | 2 | 180 | 1732 | RE | 2.194[0.781–6.160] | 1.492 | 0.136 | 5.147 | 0.023 | 80.572 |
| DBP | Cancer | 3 | 648 | 1058 | FE | 1.436[1.048–1.968] | 2.249 | 0.025 | 0.459 | 0.795 | 0.000 |
| | Breast cancer | 2 | 509 | 919 | FE | 1.389[0.990–1.950] | 1.902 | 0.057 | 0.194 | 0.659 | 0.000 |
| MMP | Cancer | 4 | 1395 | 1469 | RE | 0.976[0.543–1.753] | 0.083 | 0.934 | 12.61 | 0.006 | 76.209 |
| MEHP% | Cancer | 2 | 1176 | 1174 | FE | 1.136[0.888–1.454] | 1.015 | 0.310 | 1.823 | 0.177 | 45.135 |
| MCNP | Cancer | 2 | 1129 | 1436 | RE | 0.986[0.594–1.637] | 0.054 | 0.957 | 2.188 | 0.139 | 54.293 |
| | Breast cancer | 2 | 1129 | 1436 | RE | 0.986[0.594–1.637] | 0.054 | 0.957 | 2.188 | 0.139 | 54.293 |
| Total phthalates | Cancer | 3 | 272 | 2184 | FE | 0.905[0.587–1.397] | 0.449 | 0.653 | 1.320 | 0.517 | 0.000 |
| | Breast cancer | 2 | 133 | 2045 | FE | 0.746[0.428–1.302] | 1.031 | 0.303 | 0.140 | 0.708 | 0.000 |

RE, random-effects model; FE, fixed-effects model.

lifestyles [14]. A number of clinical studies suggested a strong correlation between exposure to environmental pollution and the incidence and mortality rates of cancer [16–18], which was consistent with results in animal models [19,20]. In addition, a series of studies have revealed that the disruption of the endocrine system plays significant roles in the development of breast cancer [21], prostate cancer [22], thyroid cancer [23], and endometrial cancer [24]. Moreover, endocrine therapy has been tried to treat these cancers mentioned above. It can be inferred from this that exposure to EDCs may contribute to risk of cancer.

As we all know, environmental phthalates and their metabolites are typical EDCs interacting with the estrogen receptor (ER), which




(caption on next page)

**Fig. 2.** Forest plot of the association between urinary MEHHP and risk of cancer. A: Cancer; B: Breast cancer; C: Prostate cancer; D: Thyroid cancer.

raises concerns regarding their potential impact on cancer incidence [25,26]. A large number of studies have assessed whether urinary phthalates and their metabolites and risk of cancers, including prostate cancer, breast cancer, endometrial cancer and thyroid cancer, have correlation [27–31]. However, the results were controversial. For breast cancer, López-Carrillo et al. found that urinary concentration of MBzP was significantly associated with breast cancer. However, there was no significantly association between urinary MBzP and breast cancer in some studies [32,33]. In addition, previous systematic review and meta-analyses mainly focused on phthalates and breast cancer, and ignored other types of cancers. Therefore, we conducted the study aimed to review and assess the correlation between urinary phthalates and their metabolites and the risk of tumorigenesis and cancer development.

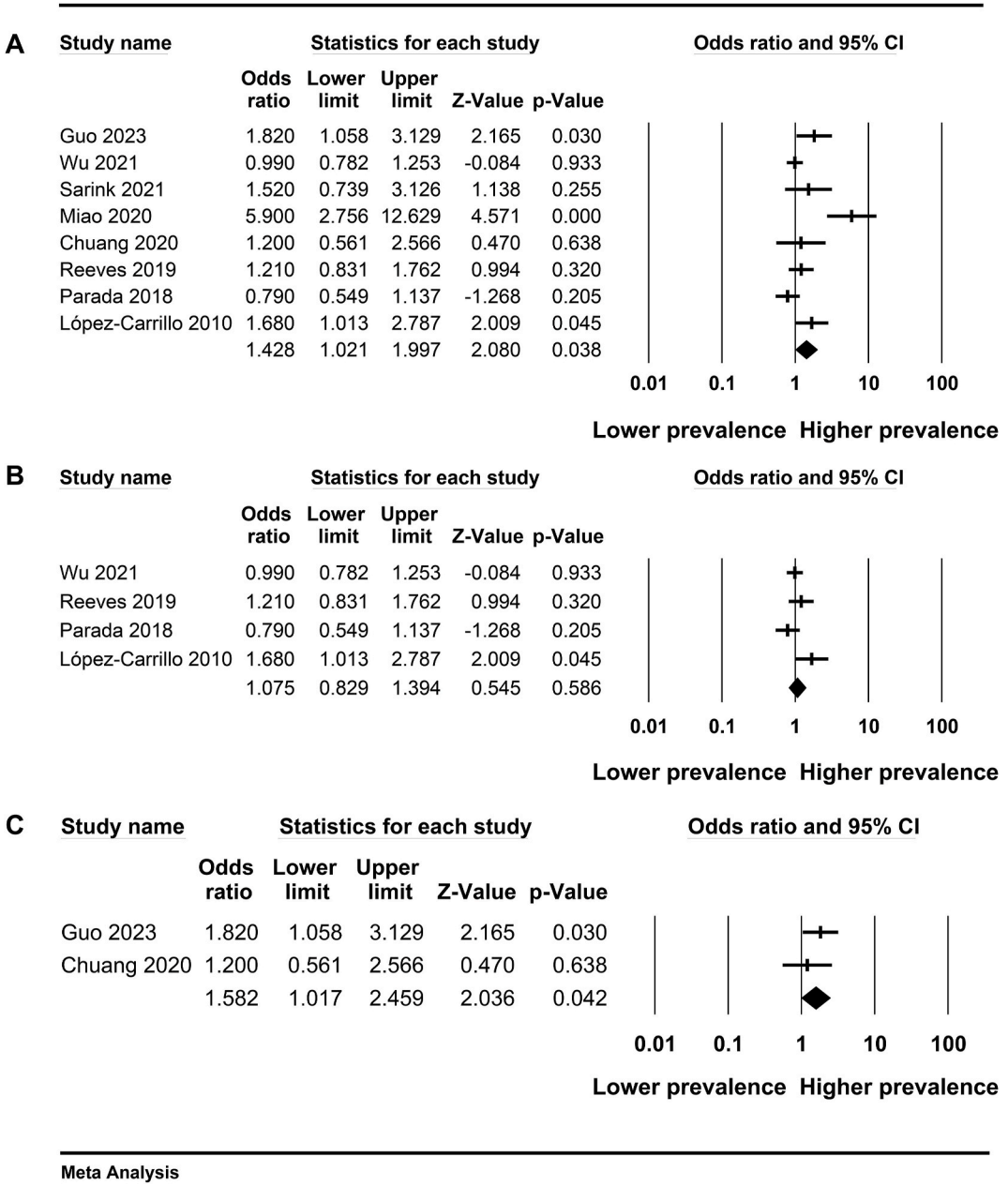



**Fig. 3.** Forest plot of the association between urinary MECPP and risk of cancer. A: Cancer; B: Breast cancer; C: Prostate cancer.

## 2. Material and methods

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guideline. This systematic review and meta-analysis was registered on PROSPERO (CRD42023449177).

### 2.1. Information sources and search strategy

We performed the systematic electronic search to obtain eligible records in the PubMed, Embase, and Web of Science databases up to July 4, 2023. The retrieval strategy included the terms: "neoplasm," "neoplasia," "tumor," "cancer," or "malignancy"; and "phthalate"; and "urine," or "urinary." In addition, we hand-searched the reference list of eligible records to get additional articles. All records were imported into the EndNote X9 software (Thomson Reuters, New York, NY, USA) for further analysis.

### 2.2. Eligibility criteria

Studies that met the following inclusion criteria were included: (1) clinical studies conducted on human; (2) studies evaluating the association between urinary phthalates and their metabolites concentrations and cancer; (3) studies published in English; (4) studies providing odds ratios (ORs) and their 95% confidence intervals (95% CIs) calculated based on the data of medians, tertiles, quartiles or quintiles of urinary phthalate levels. Studies that met the following inclusion criteria were excluded: (1) studies lacking sufficient data; (2) animal studies; (3) *in vitro* studies; (4) case reports, reviews, comments, or meeting abstracts.

### 2.3. Data extraction

According to the inclusion and exclusion criteria above, two independent authors (MM and YB) evaluated retrieved records, and identified available studies independently to reduce errors. A standardized Excel spreadsheet was used to record useful information extracted from the included studies. The following information was recorded: author, publication year, country, duration of studies, types of cancers, source of patients, types of phthalate metabolites, detection method for phthalate metabolites, sample size, age and gender of participants, association estimates and confounders. Discrepancies were resolved through deliberation involving a third author.

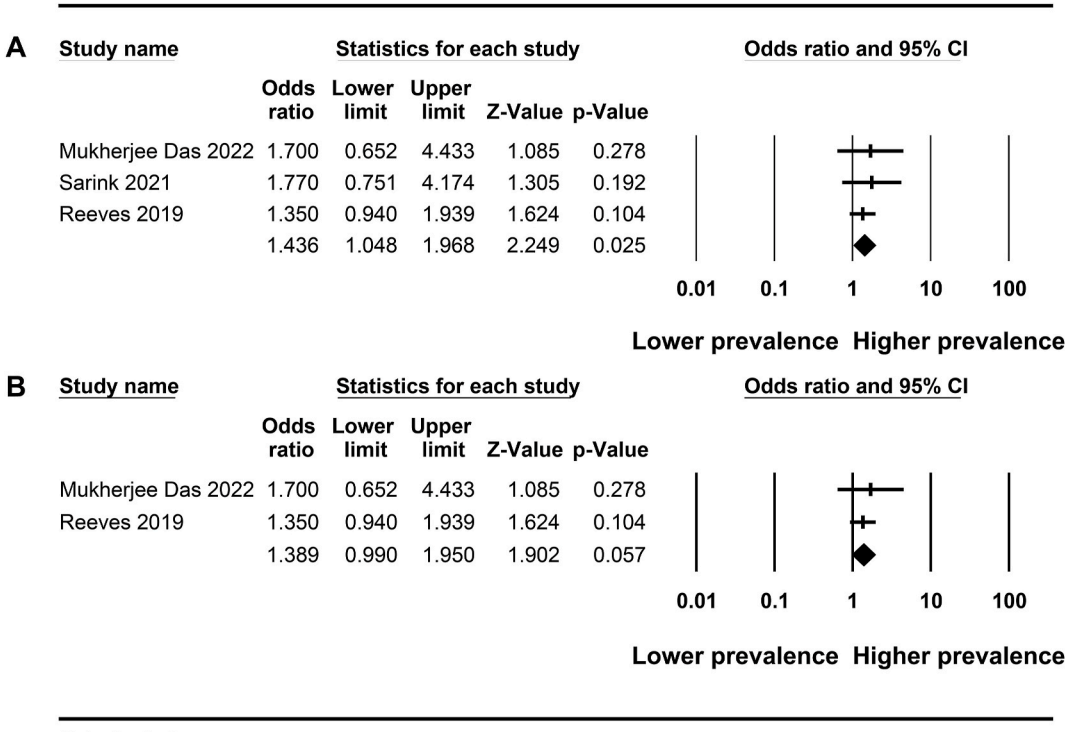



**Fig. 4.** Forest plot of the association between urinary DBP and risk of cancer. A: Cancer; B: Breast cancer.

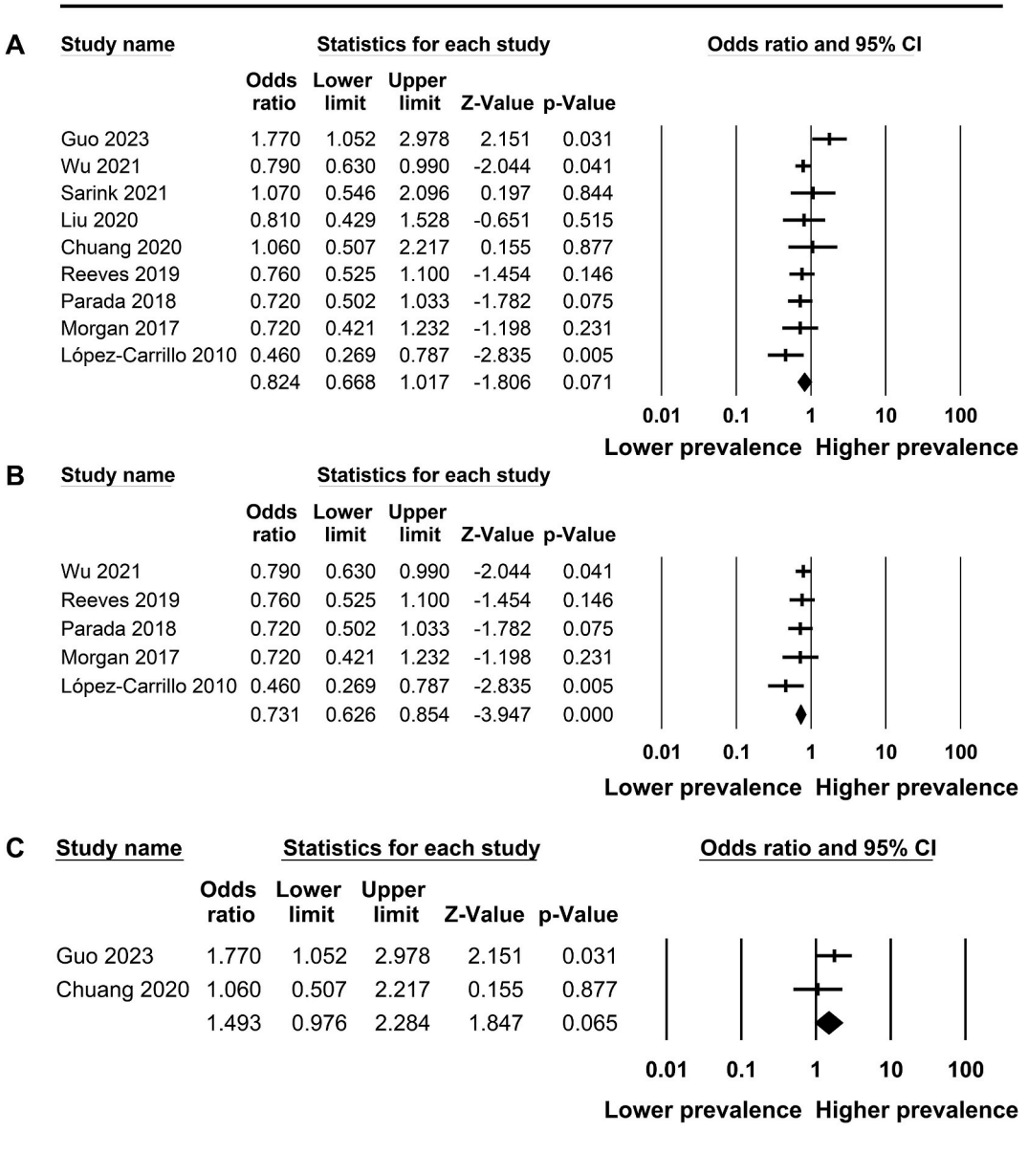



**Fig. 5.** Forest plot of the association between urinary MBzP and risk of cancer. A: Cancer; B: Breast cancer; C: Prostate cancer.

### *2.4. Statistical analysis*

As described in a previous study [34], the ORs and their corresponding 95% CIs were extracted from the most saturated models, when comparing extreme categories of exposure (the highest versus the lowest concentrations of phthalate metabolites). We pooled the ORs and corresponding 95% CIs to assess the strength of the association between each of urinary phthalates and their metabolites collected in the included studies and cancer risk. The selection of a fixed-effect model or random-effect model was based on the results of heterogeneity testing, which was measured using a chi-square-based and $I^2$ statistic. When the Q statistic $P$ was less than 0.10 or $I^2$ was more than 50%, suggesting that significant heterogeneity across studies existed, a random-effect model was employed to pool the ORs and 95% CIs; otherwise, a fixed-effect model was utilized [35]. Subgroup analyses were also conducted according to different types of cancers. In addition, publication bias was assessed through Begg's test and funnel plots. When the $P$-value $< 0.05$, it is considered statistical significance in the study. All analyses were performed using Comprehensive Meta-Analysis version 3 software (version 3; Biostat Inc).

## 3. Results

### 3.1. Literature search results

There were 883 records identified through the systematic electronic search with the combinations of retrieval search terms. Specifically, PubMed contributed 192 records, Embase contributed 225 records, and Web of Science contributed 466 records. Among the retrieved records, 270 duplicates were eliminated, and an additional 590 records were excluded due to unmatched titles or abstracts. Full-text reading enabled us to eliminate 12 records (5 records with insufficient data, 3 reviews, 1 record with overlapping data, and 3 abstracts). Details of the excluded studies through full-text reading are shown in Supplementary Table 1. According to the inclusion and exclusion criteria, 11 records (11 studies) with 3101 cancer patients and 6858 controls were included in the study at last [28–33,36–40]. The flow diagram is shown in Fig. 1.

### 3.2. Study characteristics

The included studies were performed in China (4 studies), USA (5 studies), India (1 study) and Mexico (1 study). These studies were published between 2010 and 2023. Of the eleven included studies, six were about breast cancer, two about prostate cancer, two about thyroid cancer, and one about endometrial cancer. Mass spectrometry analysis was employed to quantify urinary levels of phthalate metabolites in most of the included studies. There were twenty-nine phthalates or metabolites reported in the included studies, sixteen of which were analyzed based on extracted data. The other thirteen phthalates or metabolites were not analyzed for these only reported in one study. Ten of the studies reported results adjusted for creatinine. All of the included studies were related to prostate cancer, breast cancer, endometrial cancer and thyroid cancer. All participants were female in the included studies involving breast cancer or endometrial cancer, and all participants were male in the included studies involving prostate cancer. The overall population (men and women) was analyzed in two included studies involving thyroid cancer. The levels of phthalate metabolites were categorized into tertiles in seven included studies, into quartiles in one study, and into quintiles in one study. The other two included studies compared the level > median versus level ≤ median and LOD ≥ 50% versus LOD < 50% for phthalate metabolites, respectively. The detailed characteristics of all included studies are presented in Table 1.

### 3.3. Heterogeneity analysis

The heterogeneity analysis results indicated that there was no significant heterogeneity observed across studies in the overall analyses of MiBP ($I^2 = 37.765\%$, $P = 0.128$), DBP ($I^2 = 0$, $P = 0.795$), MEHP ($I^2 = 45.135\%$, $P = 0.177$) and total phthalates ($I^2 = 0$, $P = 0.517$), and there was obvious heterogeneity across studies for the other twelve phthalate metabolites (Table 2). Therefore, based on these findings, a fixed-effect model or random-effect model was selected.

### 3.4. Association of urinary phthalates and their metabolites and risk of cancer

There were eleven studies to evaluate the correlation between urinary levels of 16 phthalates and their metabolites and cancer. When comparing extreme categories, we observed significant associations between three specific phthalate and metabolites in urine and cancer risk. (for MEHHP: OR = 1.407, 95% CI 1.021–1.940, $P = 0.037$; for MECPP: OR = 1.428, 95% CI 1.021–1.997, $P = 0.038$; for DBP: OR = 1.436, 95% CI 1.048–1.968, $P = 0.025$) (Figs. 2A, 3A and 4A). In contrast, there was no statistically significant difference observed between urinary levels of other phthalates or phthalate metabolites, such as MBzP (OR = 0.824, 95% CI 0.668–1.017, $P = 0.071$) (Fig. 5A), and risk of cancer. In addition, subgroup analyses were conducted based on the types of cancers. We noted that the elevation of urinary MEHHP was significantly increased with the risk of thyroid cancer (OR = 4.080, 95% CI 1.126–14.782, $P = 0.032$) (Fig. 2D), instead of breast cancer or prostate cancer (Fig. 2B and C). Furthermore, a significant association between urinary levels of MECPP and prostate cancer, instead of breast cancer, was found (OR = 1.582, 95% CI 1.017–2.459, $P = 0.042$) (Fig. 3B and C). However, there was no significant association between urinary DBP and risk of breast cancer (Fig. 4B). Conversely, urinary MBzP significantly decreased risk of breast cancer (OR = 0.731, 95% CI 0.626–0.854, $P < 0.001$), instead of prostate cancer (Fig. 5B and C). The results are presented in Table 2.

### 3.5. Publication bias

Begg's test was conducted to quantitatively determine whether there was obvious publication bias in the included studies. Overall analyses of phthalate metabolites did not reveal any significant publication bias, except for MEHP ($P = 0.049$). Actually, it was a critical value, and the obvious publication bias may disappear as the number of included studies increases.

## 4. Discussion

Phthalate has been widely regarded as an environmental risk factor to human health. A large number of clinical studies have revealed that phthalate exposure was closely related to various diseases, including asthma [41], depression [42], diabetes [43] and infant allergic rhinitis [44]. In the past decade, scientific research has investigated whether there is an association between urinary phthalates and their metabolites and cancer, and people have tried to identify some main phthalate metabolites in urine of cancer

patients. The results were controversial. Although a meta-analysis conducted by Liu et al. assessed the correlation between urinary concentrations of eight phthalate metabolites and breast cancer, and revealed a negative association between MBzP and MiBP with breast cancer, it should be noted that this study had limitations such as a smaller sample size and analysis of fewer phthalate metabolites [27]. Thus, our study was designed as a meta-analysis with an expanded sample size and a broader range of phthalates and their metabolites to systematically verify the effects of phthalate on cancer.

To our knowledge, this is the most comprehensive meta-analysis on the association between urinary phthalates and their metabolites and cancer risk so far. Within this analysis, we systematically evaluated the relationship between various types of cancer and urinary phthalates and their metabolites. A series of urinary phthalates and their metabolites were analyzed in patients with various types of cancer. In overall analysis, the pooled results suggested that the elevation of urinary MEHHP, MECPP and DBP significantly increased the risk of cancer. Consistently, the levels of urinary MEHHP were obviously elevated in patients with thyroid cancer, and the levels of urinary MECPP were significantly increased in patients with prostate cancer compared with controls. The levels of urinary MBzP were negatively associated with breast cancer, which was in line with the previous meta-analysis.

Cancer is identified as one of the primary causes of mortality, seriously affecting global public health. The development of cancer is a complex and continuous dynamic process involving multiple genes and steps, and affected by environmental factors, lifestyle, and genetic mutations [45,46]. DBP and DEHP are ubiquitous in the environment and interfere with endocrine signaling, which may cause cancers of hormone sensitive organs, such as breast, prostate, testis and thyroid [47]. It has been indicated that DBP treatment stimulated both proliferation and invasion in bladder cancer, prostate cancer, and breast cancer cells [48–50]. In vitro, DEHP could activate the MAPK/AP-1 pathway and potentially enhance cell proliferation in prostate cancer cells [49]. Moreover, DEHP was reported to induce thyroid toxicity via endoplasmic reticulum stress [51]. DEHP can be rapidly metabolized when exposed to the human body. MEHHP and MECPP are the primary secondary metabolites of DEHP [52]. Clinical studies have suggested that MEHHP and MECPP exposure was associated with prostate cancer [28], thyroid cancer [31], breast cancer [40] and urothelial cancer [53]. In addition, MEHHP was reported to promote the survival of leiomyoma cells by increasing cellular tryptophan uptake, kynurenine production, and activating the aryl hydrocarbon receptor pathway [54]. All of the above evidence indicated that MEHHP, MECPP and DBP are closely correlated with the development of cancer, which are consistent with our results. Of course, we noted that there were no significant association between urinary DEHP, instead of its metabolites (MEHHP and MECPP), and cancer risk in our study. This may be because DEHP can be rapidly metabolized after exposure in the general population.

The exact mechanism of phthalate exposure on the development of cancer was still not clear. In fact, phthalates and their metabolites of phthalates display a unique mechanism of toxicity to the living body [10,55,56]. They could lead to abnormal cell proliferation, and promote invasive growth through regulating a number of biological processes, including oxidative stress [57], tumor-associated inflammation [58], and metabolic reprogramming [59]. A series of cell signaling pathways, such as TGF-β and ER signals [60], sonic hedgehog pathway [61], and Akt/NF-κB signaling pathway [62], were involved in carcinogenesis and metastasis. Thus, there seems to be a causal link between phthalates and their metabolites and cancer. The exact mechanisms behind this link may be vastly different, which requires more basic studies to explore in the future. It was worth noting that only four cancers (prostate cancer, breast cancer, endometrial cancer and thyroid cancer) were included in our study. The excluded studies were not involved with other types of cancers. Therefore, the results were also somewhat limited. Different types of cancer may have their own unique pathogenesis, and more well-designed studies are required to further verify the effects of different phthalates and their metabolites on different cancers.

Some limitations should be considered in our meta-analysis. Firstly, the sample size of our study was moderate. A series of subgroup analyses were carried out, but most of subgroups contained only 2 to 5 studies, which might result in biased results. Secondly, although we have tried our best to contact corresponding authors, some missing information in the included studies prevented us from performing a more comprehensive analysis. In addition, only three databases were used in our study, more databases can be considered in the future. Thirdly, moderate heterogeneity was observed in some overall and subgroup analyses, which may affect the results due to limited information in many included studies. Finally, cancer is gradually developing, and the included studies did not conduct a detailed longitudinal analysis, which could provide valuable insights into the role of phthalate in tumorigenesis and cancer development.

## 5. Conclusions

Our meta-analysis indicated that the levels of urinary MEHHP, MECPP, DBP and MBzP were significantly associated with cancer when comparing extreme categories. These findings strengthened the clinical evidence of correlation between cancer and phthalate exposure.

## Data availability

Data will be made available on request.

## CRediT authorship contribution statement

**Meng Meng:** Writing – original draft, Data curation, Conceptualization. **Yao Yang:** Investigation, Formal analysis. **Liang Song:** Software, Methodology. **Jian Peng:** Validation, Software. **Shenglong Li:** Writing – original draft, Validation, Data curation. **Zhengjun Gao:** Writing – review & editing, Resources, Project administration. **Youquan Bu:** Writing – review & editing, Conceptualization.

**Junwei Gao:** Writing – review & editing, Writing – original draft, Software, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

The authors confirm that there are no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29684.

## Abbreviations

| | |
|---|---|
| EDCs | endocrine-disrupting chemicals |
| ORs | odds ratios |
| CI | confidence intervals |
| MEP | monoethyl phthalate |
| MnBP | mono-n-Butyl phthalate |
| MEHP | mono-(2-ethylhexyl) phthalate |
| MBzP | mono-benzyl phthalate |
| MCHP | mono-cyclo-hexyl phthalate |
| MiNP | mono-isononyl phthalate |
| MCPP | mono-(3-carboxypropyl) phthalate |
| MEHHP | mono-(2-ethyl-5-hydroxy-hexyl) phthalate |
| MEOHP | mono-(2-ethyl-5-oxo-hexyl) phthalate |
| MiBP | mono-isobutyl phthalate |
| MECPP | mono-(2-ethyl-5-carboxy-pentyl) phthalate |
| DEHP | di-(2-ethylhexyl) phthalate |
| DBP | dibutyl phthalate |
| MMP | mono-methyl phthalate |
| MCNP | mono-carboxynonyl phthalate |
| MCOP | monocarboxyoctyl phthalate |
| MnOP | mono-n-octyl phthalate |
| MnMP | mono-n-methyl phthalate |
| DMP | dimethyl phthalate |
| DEP | diethyl phthalate |
| BBP | benzyl butyl phthalate |
| DINOP | di-n-octyl phthalate |
| MCMHP | mono-(2-carboxymethylhexyl) phthalate |
| MHBP | monohydroxybutyl phthalate |
| MHiBP | mono-hydroxyisobutyl phthalate |
| DiBP | di-isobutyl phthalate |

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