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Epidemiologic evidence of exposure to polycyclic aromatic hydrocarbons and breast cancer: A systematic review and meta-analysis

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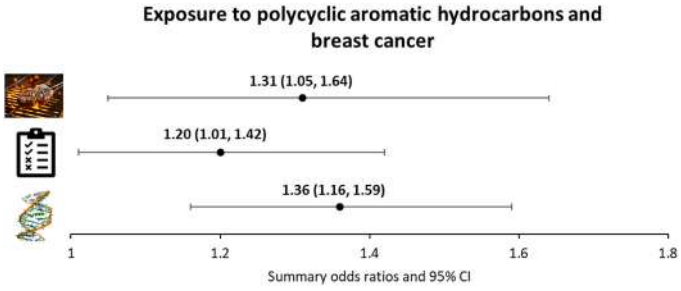
HIGHLIGHTS

- PAHs exposure was significantly and positively associated with BC.
- Some CYP1A1 and 1B1 polymorphisms and smoking strengthened PAHs and BC association.
- High intakes of fruit and vegetables attenuated PAHs and BC association.

GRAPHICAL ABSTRACT



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ABSTRACT

Breast cancer (BC) is the most frequently diagnosed cancer in women. However, only 58% of cases have been associated with known risk factors (reproductive, hormonal, lifestyles, and genetic), and the rest to unknown causes. Nevertheless, growing evidence suggests that exposure to environmental contaminants is an important risk factor for BC. Polycyclic aromatic hydrocarbons (PAHs) are formed during organic matter combustion, including smoking, grilled meat, and fuels, and are important carcinogenic constituents of environmental pollution. We examined the information generated by epidemiological studies evaluating the association between BC and PAHs exposure from multiple sources. Our work was conducted according to Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) guidelines. We searched PubMed, Web of Science, and Scopus from January 2000 to December 2019. A total of 124 records were identified, and only 23 articles met all inclusion criteria. Occupational and/or environmental exposure to PAHs

Abbreviations: AhR, (Aryl hydrocarbon Receptor); B[*a*]P, (Benzo[*a*]pyrene); BC, (Breast Cancer); BCRA1, (Breast Cancer 1); BCRA2, (Breast Cancer 2); CYP, (Cytochrome P450); ELISA, (Enzyme-Linked ImmunoSorbent Assay); ER, (Estrogen Receptor); ETS, (Environmental Tobacco Smoke); GC-FID, (Gas Chromatography with a Flame Ionization Detector); GC-MS, (Gas Chromatography-Mass Spectrometry); HPLC, (High Performance Liquid Chromatography); IARC, (International Agency for Research on Cancer); NTP, (National Toxicology Program); OH-PAHs, (Hydroxylated PAHs metabolites); PAHs, (Polycyclic aromatic hydrocarbons); PR, (Progesterone Receptor); SNPs, (Single nucleotide polymorphisms).

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was significantly associated with BC, irrespective of exposure being assessed by direct or indirect methods. CYP1A1 and CYP1B1 adverse polymorphisms, familial BC history and smoking status, significantly strengthened the association between PAHs exposure and BC, whereas high fruit and vegetable intake had antagonistic associations. The positive relationships obtained in the studies here reviewed indicated that PAHs exposure is a risk factor for BC. Research needs include the improvement of exposure assessment, particularly identification of specific PAHs, reconstruction of time-varying and distant past exposures and further studies on the interaction between known BC factors and modifiable diet and life-style factors allowing BC prevention and control.

1. Introduction

Breast cancer (BC) is the most frequently diagnosed neoplastic disease in women (IARC, 2020). Studies have shown that BC risk factors include age, sex, race, lifestyle, diet, body mass index, mammographic density, reproductive factors (early menarche, late menopause, old age at the first pregnancy, low parity, use of contraceptives or hormonal therapy), and genetic factors, such as mutations in *BCRA1* and *BRCA2* (breast cancer 1 and breast cancer 2) genes (Sun et al., 2017). However, only 58% of BC cases are related with these risk factors, hence 42% are of unknown causes. Therefore, identification of other factors may contribute to develop prevention strategies to reduce BC incidence, and the study of environmental causes has become of great importance because current research indicates that exposure to carcinogenic pollutants and/or estrogenic compounds for long periods are related to BC development (Engmann et al., 2017).

Polycyclic aromatic hydrocarbons (PAHs) are important constituents of environmental pollution (IARC, 2016). PAHs are formed in fuel and organic material combustion and are present in the environment at variable concentrations. (Zamora-León and Delgado-López, 2020). Regarding mechanisms of action, PAHs bind to the Aryl Hydrocarbon Receptor (AhR) and xenobiotic-metabolizing enzymes, such as cytochrome P450 (CYP) and, in conjunction with peroxidases, form electrophilic reactive intermediates. The generation of highly reactive epoxides, further hydrolyzed to dihydrodiols ("diols") and diol-epoxides may induce formation of DNA adducts and genetic mutations, and/or are metabolically converted to ortho-quinones, thereby generating reactive oxygen species triggering DNA damage (Henkler et al., 2012). A review on the relationship between epigenetic responses to traffic-related air pollution and BC was recently published (Sahay et al., 2019). In addition, PAHs are considered endocrine disruptors since they alter the activity and levels of endogenous hormones, such as thyroid, sex steroids (17β-estradiol, testosterone, and progesterone), and the expression of estrogen-metabolizing enzymes in a variety of experimental systems; however, some effects of PAHs are complex and at times contradictory, suggesting that their mechanisms have not been yet fully understood (Zhang et al., 2016). Notwithstanding, PAHs affect both female and male reproductive systems and strengthens their contribution for cancer development in organs strongly dependent on hormonal balance, such as the mammary gland. A systematic review on exposure to endocrine disruptors and BC risk was recently published (Rocha et al., 2021). Studies *in vitro* have shown that chrysene, pyrene, and benzo[*a*]pyrene (B[*a*]P) have estrogenic activity and that their hydroxylated metabolites are more potent activators of estrogen receptor α (ERα) than their parent compounds (Boonen et al., 2020; Sievers et al., 2013). Studies on experimental animals showed that via the Pregnane X Receptor, PAHs activate CYP3A4, which is involved in the oxidative metabolism of estrone, considered a crucial factor in the development and progression of BC (Luckert et al., 2013; Liu et al., 2019). A recent review illustrated the potential synergies between estradiol and B[*a*]P (Słowikowski et al., 2021).

Based on experimental animal studies, the International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence for the carcinogenicity of 13 individual PAHs, whereas 15 were reasonably anticipated to be human carcinogens by the National Toxicology Program (NTP). There are 22 priority PAHs listed by the U.S.EPA and European Union (Ali et al., 2021). Although certain occupations with high PAH exposure were classified by IARC as carcinogenic, the role of exposure to individual PAHs could not be defined because no specific epidemiological studies were identified (IARC, 2010; NTP, 2016). Several epidemiological studies have used biological samples to assess direct exposure, the more widely used are white blood cells, in which DNA adducts are determined, and urine where PAHs and their hydroxylated metabolites are measured (Santos et al., 2019; Rudel et al., 2014). On the other hand, other studies have indirectly estimated PAHs exposure by vehicular traffic emission and from other sources, such as consumption of tobacco (White et al., 2014), grilled and smoked meats (Fu et al., 2011; Di Maso et al., 2013) and other dietary intakes (Pratt et al., 2018), which are thought to be related to an increased BC risk. As compared with the vast literature on the association between lung cancer and PAHs exposure, the literature on BC is limited. The results of the association between PAHs and BC have been inconsistent and has led some authors to explore the interaction between exposure and BC in women carrying higher susceptibility variants in genes involved in DNA repair, tumor promotion, cell cycle control pathways, and PAH metabolism, as reviewed by Rodgers et al. (2018). However, to date, a systematic review on PAHs exposure and BC risk is not readily available; therefore, our aim was to perform a systematic review and meta-analysis of the epidemiologic evidence of exposure to PAHs from multiple sources, such as environmental, occupational, and diet, and its association with BC.

2. Methods

2.1. Search strategy

The systematic literature review was conducted in accordance with the Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) reporting guidance (Dekkers et al., 2019). We searched PubMed, Web of Science, and Scopus databases using a search strategy that incorporated terms for PAH, breast cancer, and study design (see Supplemental Table 1 for full search queries), with English as language restriction. The search included studies published from January 1st. 2000 to December 31st. 2019. Additional details are listed in Supplementary Table 1.

2.2. Selection criteria

The following criteria were met in the included studies: (1) original studies; (2) epidemiologic design (cohort, case-control, cross sectional); (3) presenting PAHs exposure assessment; (4) inclusion of histologically diagnosed BC patients. Studies were excluded if they did not reported measures of association between PAH exposure and BC. Titles and abstracts retrieved by our search were reviewed independently during the first phase of screening by LLC and YMS. Studies that met the inclusion criteria were carried forward to the full-text review. Studies deemed to be out-of-scope, based on the full-text review, were excluded with a documented rationale. Discrepancies between reviewers were discussed and resolved through consensus at each stage. Study search results, initial duplication, search review and study selection were managed using Excel.

2.3. Data extraction

We extracted the following information from each paper: 1) First author/year of publication, 2) Country, 3) Study design, 4) Sample size, 5) Type of PAH, 6) Exposure assessment, 7) PAHs concentration, 8) Effect modifiers, 9) Results, 10) Interaction results, 11) Covariates, and 12) Observations.

2.4. Risk of bias assessment

The risk of bias of prospective and retrospective studies was independently assessed by two authors (LLC and BGL), using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2014). Disagreements were discussed until a final score was obtained for each study. For retrospective studies, a maximum total score of 7 points obtained from the selection, comparability, and exposure components was considered. The maximum score for the selection component was 4 points (a-d), if the following criteria were met: a) Adequacy of the case definition (histologically confirmed cases or cases from a tumor registry, or cases captured in histopathology departments), b) Representativeness of cases (report of the percentage represented by included cases from total cases in the study area), c) Selection of controls (population or community controls), d) Definition of controls (without BC history). The maximum score for the comparability component was 1 (e) if e) Cases and controls were matched by design and/or confounders were adjusted for in the analysis. The maximum score for the exposure component was 2 points (f-g), if the following criteria were met: f) Determination of exposure (adducts or metabolites in urine, or questionnaires or other validated methods), g) Similar exposure assessment method for cases and controls. A total score of 0–2 indicated high risk, 3–4 a moderate risk, and 5–7 a low risk of bias. Likewise, for prospective studies a maximum total score of 8 points was considered, from the selection component (4 points; a-d), comparability (1 point; e), and outcome component (3 points; f-g), according to the following criteria: a) Representativeness of the exposed cohort (subjects from the general population were included), b) Selection of the unexposed cohort (drawn from the same cohort), c) Exposure determination (adducts or metabolites in urine or questionnaires or other validated methods), d) Demonstration that the event of interest was not present at the study onset (statement that participants affected with BC at the beginning of follow-up were excluded, e) Comparability of cohorts based on design or analysis (matching in the design and/or adjustment for confounders in the analysis), f) Evaluation of the event of interest (histologically confirmed cases or cases from a tumor registry, or cases captured in histopathology departments), g) The follow-up was long enough for the outcome to occur (at least 10 years), h) Adequacy of the follow-up cohorts (no more than 20% losses at the end of follow-up). A total score of 0–2 indicated high risk, 3–5 a moderate risk, and 6–8 a low risk of bias.

2.5. Meta-analysis

Summary association measures and 95% confidence intervals (CI) between the extreme categories of PAHs exposure and BC were estimated by the inverse of the variance method for the fixed effects model, and the DerSimonian and Laird's method for the random effects model (DerSimonian and Laird, 1986). Six studies (Lee et al., 2010; Niehoff et al., 2017; Mordukhovich et al., 2010; White et al., 2016; Rai et al., 2016; Labreche et al., 2010) were considered more than once in the meta-analysis since they provided information on different PAHs (1-Hydroxypyrene and 2-Naphthol) and/or sources (grilled/smoked meat intake, vehicular traffic, indoor stove/fireplace use). For two studies where association measures for two different periods were reported (Mordukhovich et al., 2016a, b), the result corresponding to the most recent period was considered. Heterogeneity was evaluated by means of the Q statistic, stratifying studies by design (case-control), exposure assessment (adducts, questionnaire or geographical modelling) and source of PAHs (grilled/smoked meat intake and indoor stove/fireplace use). The potential for publication bias was assessed using a funnel plot in conjunction with Begg's test (Begg, 1985; Begg and Mazumdar, 1994). All analyses were performed with the Stata 13 statistical software (StataCorp., College Station, TX, US).

3. Results and discussion

3.1. Selected studies

The electronic search returned 124 articles. We deleted 53 duplicates. Out of the 71 records screened based on their titles and abstracts, 55 were included in the full-text assessment. From the 55 eligible studies, we excluded 32 studies based on the inclusion/exclusion criteria. Ultimately, 23 studies were included for qualitative synthesis and 18 for the quantitative synthesis (Fig. 1). From these, 17 were case-control studies, seven studies provided results for PAHs-DNA or albumin adducts, five assessed exposures by questionnaire, and five by geographical modelling. From studies that measured PAHs by questionnaire, four provided results for grilled/smoked meat intake and two for indoor stove/fireplace use.

3.2. Characteristics of studies

Tables 1 and 2 summarize study characteristics. Studies were conducted in North American countries (United States and Canada, n = 19), Europe (Spain and Denmark, n = 2), Australia (n = 1) and China (n = 1). According to their design, most studies were case-control (n = 22), and one was an ecological study. In general, studies included 76 to 1508 BC patients. Assessment of PAHs included measurement of DNA adducts in blood or albumin adducts in plasma (n = 8), questionnaire and/or statistical models (n = 14) and urinary levels (n = 1). Age was a covariate considered in all studies, as well as total energy intake and the use of multivitamin supplements in those where exposure to PAHs was estimated through diet (Niehoff et al., 2017; Parada et al., 2017; Steck et al., 2007). Few studies considered simultaneously all the following covariates: smoking, alcohol consumption, risk factors for BC such as menopausal status, family history of BC, age at menarche, contraceptive use, hormonal therapy, and age at full-first pregnancy (Agudo et al., 2017; Mordukhovich et al., 2010, 2016b; Labreche et al., 2010; Gammon et al., 2002); education was considered in those studies where PAHs exposure was estimated by statistical models (Lee et al., 2019; Stults and Wei, 2018; Bonner et al., 2005). Several studies evaluated whether menopausal status, fruit and vegetable intakes, CYP450 genotypes, BMI, smoking, age at full-first pregnancy, and BC family history modified the association between PAHs and BC (Lee et al., 2019; Agudo et al., 2017; Parada et al., 2017; Mordukhovich et al., 2016b; Shen et al., 2006).

3.3. Risk of bias

No studies were at high risk of bias. Practically none of the retrospective studies reported the representativeness of their cases, and five used non-validated methods to determine PAHs exposure (Table 3). None of the prospective studies had a sufficient follow-up time for BC development, nor reported the percentage of losses at the end of the follow-up period (Table 4).

3.4. Assessment of exposure to polycyclic aromatic hydrocarbons using biological samples and its association with breast cancer

PAHs are always present as complex mixtures whose composition varies depending on the source and emission temperature (Campo et al., 2008). Therefore, selection of a reliable biomarker to assess exposure to multiple compounds is a crucial point. Most studies have measured exposure either as PAHs-DNA adducts in blood or urinary levels of PAHs

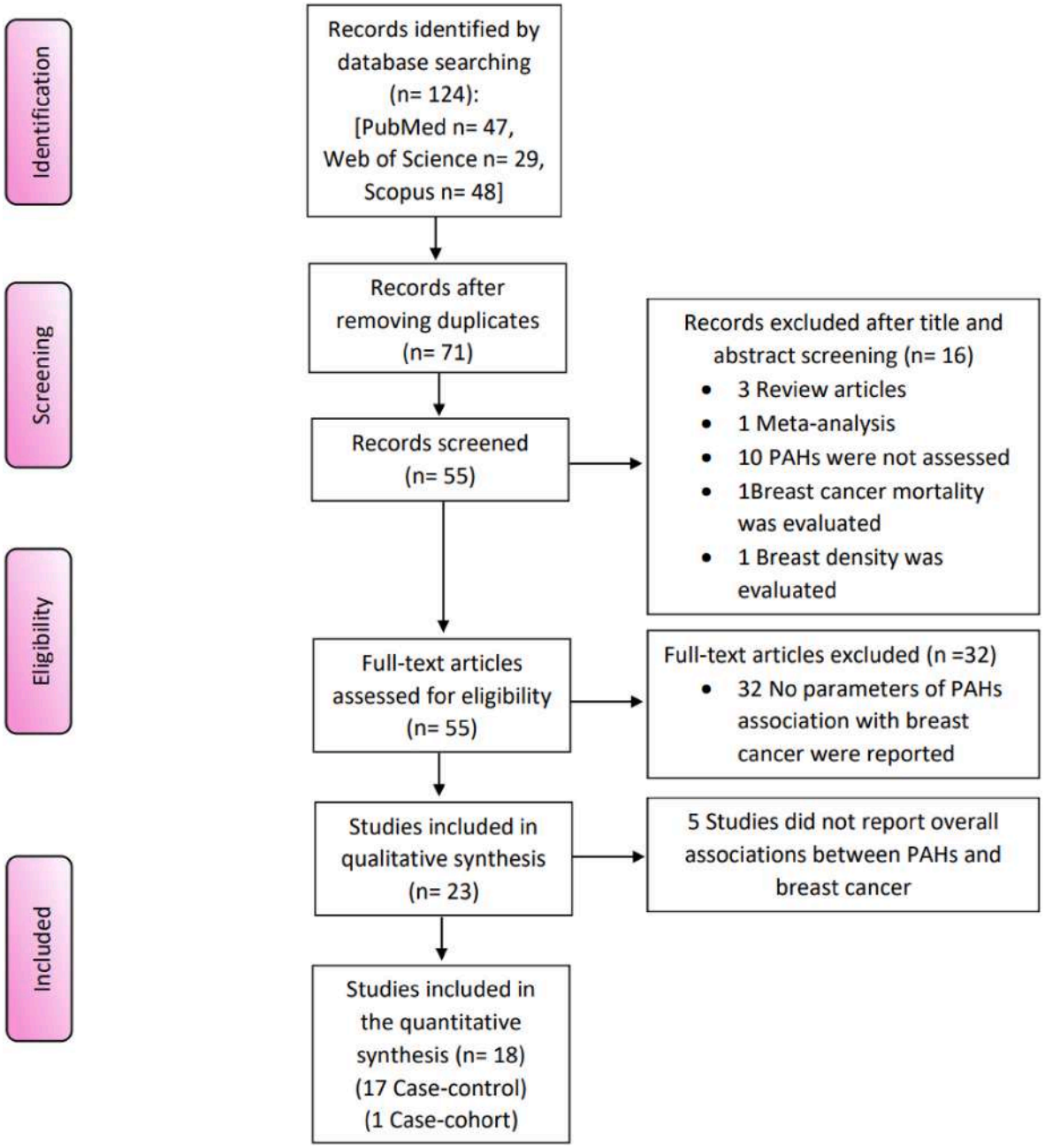

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram showing details of the process of study selection for inclusion in the systematic review and meta-analysis.

parent compounds or its hydroxylated metabolites allowing individualized exposure assessment. The majority of studies that measured PAH-DNA adducts in blood, also considered early markers for cancer, consistently showed positive associations with BC (Table 1); the odds ratios (OR) ranged from 1.01 (95% CI: 0.67, 1.52) (Gammon et al., 2002) to 4.38 (95% IC: 1.04, 18.50) (Li et al., 2002). Most studies used Enzyme-Linked ImmunoSorbent Assay (ELISA) to measure benzo(*a*) pyrene and structurally related PAH diol epoxide-DNA adducts (Mordukhovich et al., 2010; Gammon et al., 2002, 2004; Shen et al., 2006; Niehoff et al., 2017) or plasma PAH-albumin adducts (Shen et al., 2017). Two studies used ^{32}P-DNA post labeling assay, Agudo et al. (2017) measured aromatic DNA adducts in white blood cells, whereas Li et al. (2002) used DNA adduct formation in normal breast tissue obtained from participants and incubated *in vitro* with B[*a*]P. The post labeling assay is considered less specific because in addition to PAH-DNA adducts, it binds aromatic amines, hormones, and other hydrophobic compounds (Rodgers et al., 2018). There were only 4 studies assessing exposure by both PAH-adducts and questionnaire (Niehoff et al., 2017; Mordukhovich et al., 2010; Shen et al., 2006; Gammon et al., 2002), allowing a better exposure assessment. The main inconvenience of these methods is related with the invasive nature of blood collection, the special handling of materials used and proper storage during transport until analyses (Santos et al., 2019). Other studies have related PAH-DNA adducts with cancer in other organs, such as lung (Ceppi et al., 2017).

The concentration of PAHs and/or their hydroxylated metabolites in urine have been frequently used to assess recent exposures (De Craemer et al., 2016). In our review, only one study evaluated the association between BC and urinary levels of PAHs hydroxylated metabolites (1-OHPyrene and 2-Naphthol), as measured by high performance liquid chromatography (HPLC) and obtained a null association (Lee et al.,

Table 1
Assessment of exposure to polycyclic aromatic hydrocarbons using biological samples and breast cancer risk

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
1	Lee et al. 2010	China	Case-control	327 cases 654 controls	PAH metabolites	Urine	**Cases** 1-Hydroxypyrene (μmol/mol creatinine) Q1: ≤1.018 26.8% Q2: >1.018 to ≤1.563 24.5% Q3: >1.563 to ≤2.452 23.6% Q4: >2.452 25.1% 2-Naphthol (μmol/mol creatinine) Q1: ≤3.901 25.0% Q2: >3.901 to ≤6.162 25.1% Q3: >6.162 to ≤10.602 25.0% Q4: >10.602 25.0% **Controls** 1-Hydroxypyrene (μmol/mol creatinine) Q1: ≤1.018 28.0% Q2: >1.018 to ≤1.563 25.4% Q3: >1.563 to ≤2.452 23.6% Q4: >2.452 23.0% 2-Naphthol (μmol/mol creatinine) Q1: ≤3.901 25.0% Q2: >3.901 to ≤6.162 25.1% Q3: >6.162 to ≤10.602 25.0% Q4: >10.602 25.0%	–	**1-Hydroxypyrene** Q_2 vs. Q_1 OR = 0.90 (0.62–1.30) Q_3 vs. Q_1 OR = 0.83 (0.57–1.20) Q_4 vs. Q_1 OR = 0.91 (0.63–1.32) **2-Naphthol** Q_2 vs. Q_1 OR = 0.93 (0.64–1.35) Q_3 vs. Q_1 OR = 0.81 (0.56–1.18) Q_4 vs. Q_1 OR = 0.83 (0.58–1.21)	–	Age of baseline ±2 years, sample collection date <31 days + A.M./ P.M. match, antibiotic use in the past week, previous cancer history, and menopausal status	PAH metabolites were: 1-hydroxy-pyrene and 2-naphthol

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
2	Agudo et al. 2017	Spain	Case-cohort	305 cases 149 controls	Aromatic compounds	Blood DNA adducts	**Cases** P_{25} = 5.10 X 10^9 nucleotides P_{50} = 7.50 X 10^9 nucleotides P_{75} = 12.10 X 10^9 nucleotides **Controls** P_{25} = 4.20 X 10^9 nucleotides P_{50} = 7.80 X 10^9 nucleotides P_{75} = 10.90 X 10^9 nucleotides	**Menopausal status** Premenopausal Postmenopausal **BMI** <25 kg/m2 ≥25 to <30 kg/ m2 ≥30 kg/m2 **Age at first full-term pregnancy** Nulliparous <25 years ≥25 years **Smoking status** Never smoker	**Premenopausal** RR = 1.74 (1.25–2.45) **Postmenopausal** RR = 2.04 (1.36–3.05) **<25 kg/m2** RR = 2.76 (1.64–4.64) **≥25 to <30 kg/ m2** RR = 1.31 (0.98–1.77) **≥30 kg/m2** RR = 1.48 (0.99–2.21) **Nulliparous** RR = 1.38	PAHs x menopause status P = 0.94 PAHs x BMI P = 0.0001 PAHs x age at first full-term pregnancy P = 0.43 PAHs x smoking status P = 0.0002	Age, centre, season of blood extraction, education, physical activity, BMI, waist circumference, height, age at menopause, age at menarche, age at first full-term pregnancy, lactation, use of oral contraceptives, alcohol consumption,	The model for post-menopausal women included also ever use of hormonal replacement therapy. Menopause, BMI and age at first full-term pregnancy were excluded when used as variables of stratification.

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Table 1 (*continued*)

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
								Former smoker Current smoker	(0.70–2.73) **<25 years at first full-term pregnancy** RR = 1.44 (0.95–2.16) **≥25 years at first full-term pregnancy** RR = 1.69 (1.29–2.21) **Never smoker** RR = 1.34 (1.06–1.69) **Former smoker** RR = 2.89 (1.42–5.86) **Current smoker** RR = 2.19 (1.22–3.93)		total fat intake and energy intake	

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates
3	Niehoff et al. 2017	USA	Case-control	1006 cases 990 controls	PAH	Questionnaire and Blood DNA adducts	**Cases** Active smoking 55.6% ETS from spouse 52.0% Grilled/smoked meat 61.3% Synthetic log use 13.0% Vehicular traffic 5.6% PAH-DNA adducts 41.7% **Controls** Active smoking 44.4% ETS from spouse 48.0% Grilled/smoked meat 38.7% Synthetic log use 87.0% Vehicular traffic 94.4% PAH-DNA adducts 58.3%	**BMI:** < 25 kg/m2 ≥25 kg/m2 **Weight change:** Maintain Gain	**Active smoking** Ever vs. Never OR = 1.00 (0.83–1.21) **Environmental tobacco smoke from spouse** Ever vs. Never OR = 1.32 (1.09–1.60) **Grilled/smoked meat** 55+ servings vs. 0–54 servings OR = 1.52 (1.24–1.87) **Synthetic log use** Ever vs. Never OR = 1.44 (1.08–1.92) **Vehicular traffic** ≥95th percentile vs. < 95th percentile OR 1.30(0.85–1.97) **PAH-DNA adducts** Detectable vs. Non-detectable OR 1.10 (0.84–1.44)	BMI x Active smoking P = 0.9 BMI x Environmental tobacco smoke from spouse P = 0.3 BMI x Grilled/ smoked meat P = 0.5 BMI x Synthetic log use P = 0.01 BMI x Vehicular traffic P = 0.6 BMI x PAH-DNA adducts P = 0.1 Weight change x Active smoking P = 0.4 Weight change x Environmental tobacco smoke from spouse P = 0.3 Weight change x Grilled/smoked meat P = = 0.9 Weight change x Synthetic log use P = 1.0 Weight change x Vehicular traffic Not estimated Weight change x PAH-DNA adducts P = 0.6	Age, alcohol intake, marital status, parity, education, and energy intake.

ID	First author/year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates
4	Shen et al. 2017	USA	Case-control	80 cases 156 controls	PAH	Plasma albumin adducts	**Cases** Non-detectable: 36% <Median: 26.7% ≥Median: 37.3% **Controls**	**BOADICEA Risk Score** ≥3.4% <3.4%	**All women** <Median vs. Non-detectable OR = 1.59 (0.75–3.39) ≥ Median vs. Non-	PAHs x BOADICEA Risk Score P = 0.09	Age at blood draw, body mass index and smoking status

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Table 1 (*continued*)

ID	First author/year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates
							Non-detectable: 49.3% <Median: 25.3% ≥Median: 25.3%		detectable OR = 2.89 (1.25–6.69)		
5	Mordukhovich et al. 2010	USA	Case-control	1508 cases 1556 controls	PAH	Questionnaire and Blood DNA adducts	**Cases** Cigarette smoking history 100% Grilled and smoked meat 100% Detectable PAH-DNA 100% **Controls** Cigarette smoking history100.00% Grilled and smoked meat 94.79% Detectable PAH-DNA 60.47%	–	**Smoking status** Ever vs. Never OR = 0.94 (0.63–1.40) **Grilled and smoked meat** High intake vs. Low intake OR = 0.98 (0.66–1.46) **PAH–DNA adducts** Detectable vs. Nondetectable OR = 1.19 (0.63–2.25)	–	Age, final models were adjusted for daily alcohol intake when examining smoking exposure and age at menarche when examining PAH–DNA adducts
6	Shen et al. 2006	USA	Case-control	1067 cases 1110 controls	PAH	Questionnaire Blood DNA adducts	**Cases** **Non-detectable 9.9%** **Below median 14.7%** **Median and above 15.0%** **Controls** **Non-detectable 12.1%** **Below median 13.5%** **Median and above 15.5%**	IGHMBP2 Thr671Ala	**IGHMBP2 Thr671Ala AA genotype** **Below median vs. non-detectable 1.2 (0.9–1.8)** **Median and above vs. non-detectable 1.1 (0.8–1.6)** **AG + GG genotypes** **Below median vs. non-detectable 1.4 (1.0–1.9)** **Median and above vs. non-detectable 1.3 (1.0–1.9)**	IGHMBP2 Thr671Ala x PAH P = 0.30	Age

ID	First author/year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates
7	Gammon et al. 2004	USA	Pooled case-control	873 cases 941 controls	PAH	Blood DNA adducts	**Cases** Q1 26.1% Q2 17.8% Q3 20.0% Q4 15.6% Q5 20.2% **Controls** Q1 31.1% Q2 17.3% Q3 17.1% Q4 17.3% Q5 17.1%	–	Q_2 vs. Q_1 OR = 1.26 (0.95–1.67) Q_3 vs. Q_1 OR = 1.40 (1.06–1.85) Q_4 vs. Q_1 OR = 1.09 (0.82–1.45) Q_5 vs. Q_1 OR = 1.41 (1.07–1.86)	–	Age
8	Gammon et al. 2002	USA	Case-control	576 cases 427 controls	PAH	Questionnaire Blood DNA adducts	**Cases** **Q1 25.6%** **Q2 18.2%** **Q3 19.4%** **Q4 15.2%** **Q5 21.1%** **Controls** **Q1 31.6%** **Q2 16.9%** **Q3 17.2%** **Q4 17.2%** **Q5 16.9%**	–	All women: Q2 vs. Q1 OR = 1.45 (0.97–2.17) Q3 vs. Q1 OR = 1.48 (0.99–2.21) Q4 vs. Q1 OR = 1.01 (0.67–1.52) Q5 vs. Q1 OR = 1.49 (1.00–2.21)	–	Age, race, history of infertility problems, season of blood donation, religion, parity, total months of lactation , BMI at age 20, first-degree family history of breast cancer, age at first birth.
9	Li et al. 2002	USA	Case-control	76 cases 60 controls	Benzo (a) pyrene	Breast tissue DNA adducts	**Cases** ≤66.9 x 10^9 adducts 50% ≥66.9 x 10^9	–	≥66.9 x 10^9 adducts vs. ≤66.9 x 10^9 adducts	–	Age, ethnicity, smoking, alcohol use, family history of breast cancer, and CYP1A1,

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Table 1 (*continued*)

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates
							adducts 50% **Controls** ≤66.9 x 10^9 adducts 71.7% ≥66.9 x 10^9 adducts 28.3%		OR = 4.38 (1.04–18.50)		CYP1B1, and GSTM1 genotypes.

2010). However, several studies have associated these biomarkers with chronic diseases, such as diabetes mellitus and lung cancer (Khosravipour and Khosravipour, 2020; Singh et al., 2018), since their levels are much higher than in blood, a large sample volume could be easily collected, and its processing is less time consuming (Santos et al., 2019; Oliveira et al., 2016). The main limitations are differences in individual metabolism rate and that they indicate short exposures (days), as compared to DNA adducts that estimate exposure in the range of months (Miller-Schulze et al., 2013; Godschalk et al., 2003). In contrast, the association between urinary PAHs parent compounds and cancer has been rarely studied (Waidyanatha et al., 2003). Quantification of multiple urinary hydroxylated PAHs metabolites (OH-PAHs) and unmetabolized parent compounds have been proposed to obtain specific excretion profiles leading to a better exposure assessment (Campo et al., 2007). Other biological matrices, such as nails (Ma et al., 2021) and analytical methods, such as gas chromatography-mass spectrometry (GC-MS) or GC with a flame ionization detector (GC-FID), which have greater sensitivity and specificity to quantitate PAHs, may prove to be useful but have not been used to assess exposure in BC (Santos et al., 2019). BaP is used as a surrogate for estimating total PAHs exposure since its fraction is relatively stable in the PAHs complex (White et al., 2016).

In summary, our results indicate a positive association between BC and PAHs exposure, as measured through blood PAH-DNA adducts, whereas a null association was observed with urinary hydroxylated metabolites. A limitation of these studies is to understand how these measurements relate either to specific exposures or to the overall carcinogenic potency of the complex mixture of PAHs in the environment. The information currently available does not allow to identify the PAHs that can be more associated with BC development, since BAP and total suspended particles have been used as a surrogate for PAHs in many studies and only one study has measured two hydroxylated metabolites with null associations. In addition, the time frame of exposure is imprecise and may vary from months to a few years; nonetheless, levels at the time of study are assumed to reflect past exposures, since no biomarkers reflecting distant exposures are currently available Gammon et al. (2002); Ali et al. (2021).

3.5. *Assessment of exposure to polycyclic aromatic hydrocarbons by questionnaire and/or statistical methods and its association with breast cancer*

Questionnaires, air monitoring and statistical methods were indirect methods used to assess PAHs exposure and its association with BC Humans are exposed to PAHs through dietary sources, they are present in several categories of food and drinks as a complex mixture. The European Commission has identified four major PAHs in foods: benz[*a*] anthracene, chrysene, benzo[*b*]fluoranthene and (BaP), which may originate from environmental pollution and during food processing, such as smoking or roasting, along with preparation, as reviewed by Sampaio et al. (2021). A considerable number of epidemiological studies have examined the associations between diet and BC and most used questionnaires and formulas to estimate dietary intake (Niehoff et al., 2017; Parada et al., 2017; White et al., 2016; Mordukhovich et al., 2010. In our review, several studies reported null associations between a high intake of grilled-smoked meat and BC, except for the significant positive associations described by Niehoff et al. (2017) (OR = 1.52; 95% CI: 1.24, 1.87). Furthermore, women with high meat intake and additionally carrying CYP1B1 (GC) polymorphism (OR = 1.59; 95% CI: 1.15, 2.20) (Parada et al., 2017), or those carrying SULT1A1 polymorphism (Arg/Arg) (OR = 4; 95% CI: 1.4, 11.1) (Zheng et al., 2001) showed significant positive associations; both polymorphisms are involved in PAHs metabolism, i.e., phase I (DNA adducts formation) and phase II (PAH detoxification), respectively (Table 2).

Regarding environmental exposure, the use of indoor stove/fireplace and exposure to environmental tobacco smoke (ETS) were also assessed by questionnaire. The use of indoor stove/fireplace for more than seven years showed positive associations with BC, with ORs ranging from 1.11 (95% CI: 1.08, 1.92) (Niehoff et al., 2017) to 1.73 (95% CI: 1.11, 2.70) (White et al., 2014). Residential ETS passive exposure from spouse was positively associated with BC incidence (OR = 1.20, 95%CrI = 1.03, 1.40) (White et al., 2016), whereas Niehoff et al. (2017) described a positive association between postmenopausal BC and ETS (OR = 1.32; 95% CI: 1.09, 1.60), but not with active smoking. In contrast, associations were negative and significant for the high fruit/vegetable intake in women exposed to PAHs having ER + or PR + BC (OR = 0.66; 95% CI: 0.52, 0.83) or invasive BC (OR = 0.81; 95% CI: 0.66, 0.99) (Mordukhovich et al., 2016b) (Table 2). In these studies, BaP levels were used as a surrogate for all traffic PAHs.

A common method for assessing exposure to PAHs air pollution is environmental monitoring by geographic location, where it is often difficult to discriminate between emissions from coal and biomass combustion to those from gasoline and diesel vehicles (Ravindra et al., 2006). In general terms, these studies did not show significant associations between PAHs exposure and BC (Stults and Wei, 2018; Nie et al., 2007; Bonner et al., 2005) (Table 2). However, these studies considered only one source of exposure (total suspended particles, as a proxy for PAHs exposure), and participants may have been exposed to PAHs through other sources, such as diet, contaminated water, and tobacco smoke. In addition, other studies used statistical models to estimate exposure based on past PAHs air levels when exposure data on the study period were not available, but null associations with BC were reported (Ughade, 2013).

In terms of occupational exposure, estimated by a job-exposure matrix (JEM), most studies, except for Rai et al. (2016), showed significant positive associations between PAHs and BC. In highly exposed premenopausal women with BC family history, ORs ranged from 2.55 (95% CI: 1.34, 4.84) to 1.50 (95% CI: 1.04, 2.17) and the risk was related to the probability and duration of exposure, as inferred using a JEM based on a statistical model of coal tar pitch volatiles, another common PAH surrogate (Lee et al., 2019). A threefold increase for estrogen- and progesterone-positive tumors in postmenopausal women exposed to PAHs from petroleum sources, with risks appearing to be higher when exposures occurred at a younger age was reported by Labreche et al. (2010). Interestingly, the only study considering male BC reported a significantly increased risk in workers exposed to automotive gasoline and combustion products, with ORs ranging from marginally significant (2.0; 95% CI: 1.0, 1.40) to (5.4; 95% CI: 2.4, 11.9), respectively

Table 2
Assessment of exposure to polycyclic aromatic hydrocarbons by questionnaire and/or statistical methods and breast cancer risk

ID	First author/year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
10	Mordukhovich et al., 2016a	USA	Case-control	1508 cases 1556 controls	PAH	Questionnaire	–	**XPA-4A/G ERCC1 8092C/A ERCC4 Arg415Gln ERCC5 Asp1104His ERCC2 Lys751Gln ERCC2 Asp312Asn XRCC1 Arg399Gln XRCC1 Arg194Trp OGG1 Ser326Cys**	**All women 1960–1990** Q_3 vs. Q_1 OR = 1.04 (0.81–1.33) **1995** Q_3 vs. Q_1 OR = 1.01 (0.81–1.26)	1995 x XPA-4A/G P = 0.60 1995 x ERCC1 8092C/A P = 0.54 1995 x ERCC4 Arg415Gln P = 0.50 1995 x ERCC5 Asp1104His P = 0.23 1995 x ERCC2 Lys751Gln P = 0.04 1995 x ERCC2 Asp312Asn P = 0.87 1995 x XRCC1 Arg399Gln P = 0.90 1995 x XRCC1 Arg194Trp P = 0.54 1995 x OGG1 Ser326Cys P = 0.78 1960–1990 x XPA 24A/G P = 0.41 1960–1990 x ERCC1 8092C/A P = 0.63 1960–1990 x ERCC4 Arg415Gln P = 0.57 1960–1990 x ERCC5 Asp1104His P = 0.55 1960–1990 x ERCC2 Lys751Gln P = 0.50 1960–1990 x ERCC2 Asp312Asn P = 0.57 1960–1990 x XRCC1 Arg399Gln P = 0.59 1960–1990 x XRCC1 Arg194Trp P = 0.30 1960–1990 x OGG1 Ser326Cys P = 0.52	Age	PAH exposure was measured by vehicular traffic. No percentages of exposed cases were provided.

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results		Interaction results	Covariates	Observations
11	Mordukhovich et al. 2016b	USA	Case-control	1508 cases 1556 controls	Benzo [a] pyrene	Questionnaire	**Cases 1995** < 50th 40.18% 50 to < 75th 18.63%	**Fruit/ vegetable intake:** Low High **Menopausal**	**ER+ and PR+ breast cancer** 50th to < 75th vs. < 50th	**1995** ***In situ*** 50th to < 75th vs. < 50th OR = 1.20	**1995** Benzo(a) pyrene x fruit/ vegetable intake	5-year age group, educational level, annual household income, race, religion, parity, age at first birth,	Benzo(a)pyrene exposure was estimated from participants lifetime residential

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Table 2 (*continued*)

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results		Interaction results	Covariates	Observations
							75 to < 95th 15.98% ≥ 95th 4.44% **1960–1990** < 50th 16.18–17.70% 50 to < 75th 7.49–8.62% 75 to < 95th 5.83–6.89% ≥ 95th 1.52–1.85% **Controls 1995** < 50th 39.84% 50 to < 75th 21.20% 75 to < 95th 16.13% ≥ 95th 3.72% **1960–1990** < 50th 17.60–19.53% 50 to < 75th 8.09–9.12% 75 to < 95th 6.68–7.26% ≥ 95th 1.02–1.15%	**status:** Premenopausal Postmenopausal	OR = 0.69 (0.53–0.90) 75th to < 95th vs. < 50th OR = 0.82 (0.62–1.08) ≥ 95th vs. < 50th OR = 0.86 (0.52–1.41) **ER–/PR+, ER+/PR–, or ER–/PR– breast cancer** 50th to < 75th vs. < 50th OR = 0.68 (0.50–0.91) 75th to < 95th vs. < 50th OR = 0.78 (0.57–1.08) ≥ 95th vs. < 50th OR = 1.15 (0.68–1.94) **ER– and PR– breast cancer** 50th to < 75th vs. < 50th OR = 0.79 (0.54–1.16) 75th to < 95th vs. < 50th OR = 0.81 (0.52–1.24) ≥ 95th vs. < 50th OR = 1.67 (0.91–3.05) **ER+/PR–, ER–/PR+, or ER+/ PR+ breast cancer** 50th to < 75th vs. < 50th OR = 0.66 (0.52–-0.83) 75th to < 95th vs. < 50th OR = 0.81 (0.63–1.03) ≥ 95th vs. < 50th OR = 0.80 (0.50, 1.27)	(0.84–1.73) ≥ 75th vs. < 50th OR = 1.42 (0.99–2.02) **Invasive** 50th to < 75th vs. < 50th OR = 0.81 (0.66–0.99) ≥ 75th vs. < 50th OR = 0.97 (0.80–1.18) 75th to < 95th vs. < 50th OR = 0.93 (0.75–1.15) ≥ 95th vs. < 50th OR = 1.14 (0.79–1.66) **1960–1990** ***In situ*** 50th to < 75th vs. < 50th OR = 1.71 (0.92–3.19) ≥ 75th vs. < 50th OR = 1.63 (0.87–3.03) **Invasive** 50th to < 75th vs. < 50th OR = 0.90 (0.65–1.25) ≥ 75th vs. < 50th OR = 0.95 (0.69–1.31) 75th to < 95th vs. < 50th OR = 0.95 (0.68–1.32) ≥ 95th vs. < 50th OR = 1.35 (0.71–2.56)	P = 0.01 Benzo(a) pyrene x menopausal status P = 0.02 **1960–1990** Benzo(a) pyrene x fruit/ vegetable intake P = 0.04 Benzo(a) pyrene x menopausal status P = 0.50	body mass index, duration of hormonal replacement therapy use, duration of breastfeeding, duration of oral contraceptive use, lifetime average alcohol intake, lifetime average physical activity.	histories. Results in columns K and L were adjusted only by age.
12	Parada et al. 2017	USA	Case-control	988 cases 1021 controls	PAH	Questionnaire	–	Gene: CYP1A1 (rs1048943) CYP1B1 (rs10175338) CYP3A4 (rs2242480) Risk alleles	CYP1A1 (AA) High vs. Low Grilled-smoked meat intake OR = 1.21 (0.94–1.55) CYP1A1 (AG + GG) High vs. Low Grilled-smoked meat intake OR = 0.64 (0.23–1.80)		Grilled-smoked meat intake x CYP1A1 P = 0.03 Grilled-smoked meat intake x	Age at diagnosis, energy intake, fruit and vegetable intake, and multivitamin supplement use.	Low: 0–4296 times consumed, High: 4297–51,652 times consumed.

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Table 2 (*continued*)

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
									CYP1B1 (GC) High vs. Low Grilled-smoked meat intake OR = 1.59 (1.15–2.20) CYP1B1 (GT + TT) High vs. Low Grilled-smoked meat intake OR = 0.71 (0.50–1.02) CYP3A4 (CC) High vs. Low Grilled-smoked meat intake OR = 1.01 (0.78–1.30) CYP3A4 (CT + TT) High vs. Low Grilled-smoked meat intake OR = 1.59 (0.91–2.77) 0–3 risk alleles High vs. Low Grilled-smoked meat intake OR = 1.20 (0.92–1.55) 4–6 risk alleles High vs. Low Grilled-smoked meat intake OR = 0.97 (0.48–1.97)	CYP1B1 P<0.01 Grilled-smoked meat intake x CYP3A4 P = 0.07 Grilled-smoked meat intake x Risk alleles P = 0.44		

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
13	White et al. 2014	USA	Case-control	1508 cases 1556 controls	PAH	Questionnaire	**Cases** Ever use of any indoor stove/ fireplace 49.5% Wood 44.8% Synthetic Logs 16.4% Coal 5.8% Gas 1.5% **Controls** Ever use of any indoor stove/ fireplace 49.4% Wood 45.1% Synthetic Logs 13.0% Coal 4.9% Gas 1.4%	-	**Any indoor stove/ fireplace use** ≤11.6 years vs. No stove/ fireplace OR = 1.15 (0.87, 1.51) 11.7–21.6 years vs. No stove/fireplace OR = 1.00 (0.76, 1.32) 21.7–30.7 years vs. No stove/fireplace OR = 1.13 (0.87, 1.46) >30.7 years vs. No stove/ fireplace OR = 0.95 (0.72, 1.25) **Wood burning** ≤11.0 years vs. No stove/ fireplace OR = 1.07 (0.80, 1.42) 11.1–21.4 years vs. No stove/fireplace OR = 1.00 (0.75, 1.33) 21.5–30.9 years vs. No stove/fireplace OR = 1.20 (0.92, 1.55) >30.0 years vs. No stove/ fireplace OR = 0.88 (0.66, 1.17) **Synthetic log**	-	Age, age at menarche, history of breastfeeding, hormone therapy use, family history of breast cancer, parity, age at first birth, BMI, education, smoking history, alcohol intake, physical activity, race, religion, marital status.	Results stratified by number of GST variants: GSTA1, GSTT1, GSTM1, GSTP1 are included in the manuscript.

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Table 2 (*continued*)

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
									burning ≤6.9 years vs. No stove/ fireplace OR = 1.12 (0.68, 1.82) 7.0–16.7 years vs. No stove/ fireplace OR = 1.73 (1.11, 2.70) 16.7–24.8 years vs. No stove/fireplace OR = 1.29 (0.82, 2.03) >24.8 years vs. No stove/ fireplace OR = 1.50 (0.98, 2.31)			

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
14	Steck et al. 2007	USA	Case-control	1508 cases 1556 controls	Benzo (a) pyrene	Questionnaire	**Cases** **Low Fruit and Vegetable Intake** **Total BaPs from food** 0–56 53% 57–85 37% 86–309 10% **High Fruit and Vegetable Intake** **Total BaPs from food** 0–56 53% 57–85 35% 86–309 11% **Controls** **Low Fruit and Vegetable Intake** **Total BaPs from food** 0–56 5% 57–85 37% 86–309 58% **High Fruit and Vegetable Intake** **Total BaPs from food** 0–56 9% 57–85 30% 86–309 61%	-	**Low Fruit and Vegetable Intake** **Total BaPs from food** 57–85 vs. 0–56 OR = 1.10 (0.78–1.55) 86–309 vs. 0–56 OR = 1.10 (0.63–1.93) **High Fruit and Vegetable Intake** **Total BaPs from food** 57–85 vs. 0–56 OR = 1.47 (0.73–2.98) 86–309 vs. 0–56 OR = 1.09 (0.52–2.26)		Age, energy intake and multivitamin supplement use.	Benzo(a)pyrene was estimate from total grilled/barbecued and smoked meats intake.

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
15	White et al. 2016	USA	Case-control	1508 cases 1556 controls	Sources of PAH	Questionnaire and historical geographic model	**Cases** **Active smoking** 55.2% **Residential environmental tobacco smoke** 79.5% **Diet** 69.9% **Vehicular traffic** 6.0%	-	**Active smoking** OR = 1.02 (0.85–1.23) **Residential environmental tobacco smoke** OR = 1.10 (0.86–1.40) **Diet** OR = 1.13 (0.93,	-	Age at menarche, parity, lifetime alcohol intake, education, income, and the matching factor, 5-year age group.	-

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Table 2 (*continued*)

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
							Indoor stove/ fireplace use 49.7% **Controls** **Active smoking** 55.1% **Residential environmental tobacco smoke** 78.4% **Diet** 65.4% **Vehicular traffic** 5.0% **Indoor stove/ fireplace use** 49.7%		1.36) **Vehicular traffic** OR = 1.25 (0.85–1.76) **Indoor stove/ fireplace use** OR = 1.09 (0.90–1.31)			

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
16	Zheng et al. 2001	USA	Case-control	456 cases 900 controls	PAH	Questionnaire	**Cases** **Arg/Arg** Mostly well done 15.2% Rare/medium 30.4% Consistently well done 54.3% **Arg/His** Mostly well done 26.1% Rare/medium 26.1% Consistently well done 47.6% **His/His** Mostly well done 35.7% Rare/medium 35.7% Consistently well done 28.5% **Controls** **Arg/Arg** Mostly well done 42.9% Rare/medium 21.4% Consistently well done 35.5% **Arg/His** Mostly well done 37.1% Rare/medium 26.4% Consistently well done 36.3% **His/His** Mostly well done 44.7% Rare/medium 26.3% Consistently well done 28.9%	-	**Arg/Arg** Mostly well done vs. Rare/medium OR = 4.0 (1.4–11.1) Consistently well done vs. Rare/ medium OR = 3.6 (1.4–9.3) **Arg/His** Mostly well done vs. Rare/medium OR = 1.4 (0.6–3.1) Consistently well done vs. Rare/ medium OR = 1.8 (0.9–3.8) **His/His** Mostly well done vs. Rare/medium OR = 1.7 (0.5–6.1) Consistently well done vs. Rare/ medium OR = 1.0 (0.3–3.7)	-	Age, WHR, and number of live births.	
17	Lee et al., 2019	Canada	Case-control	1130 cases	PAH	Job exposure matrix	**Cases** None: 31.3% Low: 20.0%	**Menopausal status:** Premenopausal	**Premenopausal** Low vs. None OR = 1.12	PAHs x menopause status	Age, centre, education,	Categories of exposure are mg/m^3 of coal tar pitch volatiles in at least one job.

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ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
				1169 controls			Medium: 23.4% High: 25.3% **Controls** None: 39.7% Low: 20.1% Medium: 20.1% High: 20.1%	Postmenopausal **Family history of breast cancer:** Yes No	(0.74–1.68) Medium vs. None OR = 1.31 (0.91–1.90) High vs. None OR = 1.50 (1.04–2.17) **Postmenopausal** Low vs. None OR = 1.30 (0.96–1.76) Medium vs. None OR = 1.46 (1.07–2.00) High vs. None OR = 1.14 (0.82–1.57) **Family history** Low vs. None OR = 1.57 (0.89–2.76) Medium vs. None OR = 1.71 (0.91–3.20) High vs. None OR = 2.55 (1.34–4.84) **No family history** Low vs. None OR = 1.18 (0.90–1.55) Medium vs. None OR = 1.71 (1.05–1.76) High vs. None OR = 1.14 (0.87–1.49)	P>0.5 PAHs x Family history of breast cancer P = 0.03	ethnicity, smoking	None = 0 Low = 0.01–0.02 Medium = 0.03–0.07 High = 0.08–0.88

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
18	Rai et al. 2016	Australia	Case-control	1202 cases 1785 controls	PAH	Job exposure matrix	**Cases** Diesel exhaust 8.0% Gasoline exhaust 7.8% **Controls** Diesel exhaust 7.5% Gasoline exhaust 8.1%	-	**Diesel exhaust** Probable vs. None OR = 1.07 (0.81–1.41) **Gasoline exhaust** Probable vs. None OR = 0.98 (0.74–2.28)	-	Age	PAH exposure was measured through jobs where diesel and gasoline exhausts were present.
19	Labreche et al. 2010	Canada	Case-control	556 cases 613 controls	MAHs and PAHs	Job exposure matrix	**Cases** MAHs 3.4% PAHs from any source 7.7% PAHs from petroleum 5.0% **Controls** MAHs 2.7% PAHs from any source 6.6% PAHs from petroleum 3.2%	-	per 10-year increase of occupational exposure: Lifetime exposures MAHs OR = 1.27 (0.83–1.93) PAHs from any source OR = 1.21 (0.90–1.61) PAHs from petroleum OR = 1.52 (0.97–2.39) ER+/PR- OR = 2.44 (1.15–5.18) ER+/PR+ OR	-	Age, family history, age at oophorectomy, education, ethnicity, age at menarche, oral contraceptive use, duration of hormone replacement therapy use, total duration of breastfeeding, smoking status, alcohol consumption status, body mass index, age at first full-term pregnancy and proxy respondent status.	MAHs are monoaromatic hydrocarbons.ORs were stratified by hormonal phenotype.

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Table 2 (*continued*)

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
									= 1.65 (0.97–2.83) Exposures before age 36 years MAHs OR = 2.89 (0.96–8.71) PAHs from any source OR = 1.75 (0.99–3.10) PAHs from petroleum OR = 2.38 (1.00–5.67) ER+/PR- OR = 12.04 (1.39–104.4) ER+/PR+ OR = 5.22 (0.97–28.15)			
20	Hansen 2000	Denmark	Case-control	230 cases 12,880 controls	PAH	Employment history and worker status	**Cases** Unexposed 94.7% Exposed 5.2% Period of first exposure <1965 3.4% 1965–1974 1.7% Age at first exposure (years) <40 3.4% 40–66 1.7% **Controls** Unexposed 97.7% Exposed 22.7% Period of first exposure <1965 1.3% 1965–1974 0.8% Age at first exposure (years) <40 0.7% 40–66 1.4%	–	Exposed vs. unexposed OR = 2.5 (1.3–4.5) <1965 vs. unexposed OR = 2.8 (1.4–5.5) 1965–1974 vs. unexposed OR = 2.0 (1.0–4.0) <40 vs. unexposed OR = 5.4 (2.4–11.9) 40–66 vs. unexposed OR = 1.2 (0.4–3.3)	–	Birth year and socioeconomic status	Male breast cancer
21	Stults and Wei 2018	USA	Ecologic	-	PAH	Vehicular traffic	–	–	Traffic PAHs-breast cancer incidence β = 0.552 (0.278–0.826)	–	Sex, race, poverty, education level, smoking and obesity prevalence.	Outcome was breast cancer incidence.
22	Nie et al. 2007	Canada	Case-control	1068 cases 1944 controls	PAH	Vehicular traffic	**Cases** Q1 15.7% Q2 26.1% Q3 27.7% Q4 30.4% **Controls** Q1 25.1% Q2 25.1% Q3 25.4% Q4 24.2%	–	**Premenopausal** Q2 vs. Q1 OR = 1.86 (0.83–4.15) Q3 vs. Q1 OR = 2.14 (0.93–4.94) Q4 vs. Q1 OR = 2.07 (0.91–4.72)	–	Age, education, race, BMI, age at menarche, age at menopause, age at first birth, number of births, family history of breast cancer, previous benign breast disease, and year at interview.	Exposure to traffic emissions was examined at menarche.
23	Bonner et al. 2005	USA	Case-control	1166 cases	Benzo (a) pyrene	Total suspended	**Cases** <84 μg/m^3 2.3%	–	**Premenopausal** 84–114 vs. <84 OR = 1.96	–	Age, education, and parity	Total suspended particulates were used as *proxy* of benzo(a)-

(*continued on next page*)

Table 2 (*continued*)

ID	First author/ year of publication	Country	Study design	Sample size	Type of PAH	Exposure assessment	PAH concentration	Effect Modification	Results	Interaction results	Covariates	Observations
				2105 controls		particulates Air monitors	84–114 μg/m^3 14.9% 115–140 μg/m^3 39.5% >140 μg/m^3 43.1% **Controls** <84 μg/m^3 4.3% 84–114 μg/m^3 14.0% 115–140 μg/m^3 39.1% >140 μg/m^3 42.7%		(0.64–3.01) 115–140 vs. <84 OR = 2.23 (0.77–6.44) >140 vs. <84 OR = 1.78 (0.62–5.10) **Postmenopausal** 84–114 vs. <84 OR = 2.32 (0.89–6.10) 115–140 vs. <84 OR = 1.94 (0.77–4.86) >140 vs. <84 OR = 2.42 (0.97–6.09)			pyrene. The sample size from which ORs were calculated was: 521 cases and 804 controls.

Table 3
Quality assessment of retrospective studies based on the Newcastle-Ottawa Scale

Study	Selection (4)				Comparability (1)	Exposure (2)		Total score[a]	Risk of bias[b]
	Adequacy of case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls		
Niehoff et al., 2017	*		*	*	*	*	*	6	Low
Mordukhovich et al., 2010	*		*	*	*	*	*	6	Low
Shen et al., 2006	*		*	*	*	*	*	6	Low
Gammon et al., 2004	*		*	*	*	*	*	6	Low
Gammon et al., 2002	*		*	*	*	*	*	6	Low
Li et al., 2002				*	*	*	*	4	Moderate
Mordukhovich et al., 2016a	*		*	*	*	*	*	6	Low
Mordukhovich et al., 2016b	*		*	*	*	*	*	6	Low
Parada et al., 2017	*		*	*	*	*	*	6	Low
White et al., 2014	*		*	*	*	*	*	6	Low
Steck et al., 2007	*		*	*	*		*	5	Low
White et al., 2016	*		*	*	*	*	*	6	Low
Lee et al., 2019	*		*		*			3	Moderate
Rai et al., 2016	*		*	*	*	*		5	Low
Labreche et al., 2010	*	*			*			3	Moderate
Hansen, 2000	*		*	*	*		*	5	Low
Nie et al., 2007	*		*	*	*	*	*	6	Low
Bonner et al., 2005	*		*	*	*		*	5	Low

[a] Maximum number of stars for Selection is 4; Maximum for Comparability is 1; Maximum for Exposure is 2; Maximum for total score is 7.
[b] A total score of 0–2 indicates high risk, 3–4 a moderate risk, and 5–7 a low risk of bias.

comprising the period of first exposure (1965–1974) and having less than 40 years of age at first exposure, with risk tending to be highest for young workers (Hansen, 2000).

In summary, occupational and environmental exposure were positively associated with BC. However, direct comparisons between risks from occupational and non-occupational PAH sources may not be appropriate. Breast tissue is more sensitive to adverse effects when exposure occurs when breast cells are still proliferating (<40 years of life). High intakes of fruits and vegetables showed a negative association. PAHs exposure was estimated by indirect methods, such as dietary intake questionnaires, job-exposure matrix, and/or environmental monitoring; Nonetheless, there were important methodological differences between studies, and the possibility of exposure misclassification could not be ruled out. Recall bias may be a limitation for some of these studies, since occupational and environmental risk factors were collected retrospectively.

Table 4
Quality assessment of prospective studies based on the Newcastle-Ottawa Scale

Study	Selection (4)				Comparability (1)	Outcome (3)			Total score[a]	Risk of bias[b]
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up cohorts		
Lee et al., 2010	*	*	*		*	*			5	Moderate
Agudo et al., 2017	*	*	*		*	*			5	Moderate
Shen et al., 2017			*		*	*			3	Moderate
Zheng et al., 2001	*	*			*	*			4	Moderate

[a] Maximum number of stars for Selection is 4; Maximum for Comparability is 1; Maximum for Outcome is 3; Maximum for total score is 8.
[b] A total score of 0–2 indicates high risk, 3–5 a moderate risk, and 6–8 a low risk of bias.

3.6. Summary association between exposure to polycyclic aromatic hydrocarbons and breast cancer

The summary odds ratio for case-control studies on BC and PAHs exposure (including measurement of PAHs-DNA or albumin adducts, PAHs hydroxylated metabolites in urine, and PAHs sources by questionnaire) was 1.21 (95% CI: 1.11, 1.33; $I^2 = 44.1\%$; $p = 0.010$) (Fig. 2). After stratifying by types of PAHs exposure assessment, the positive association between PAHs and BC remained for PAHs-DNA or albumin adducts (summary OR = 1.36; 95% CI: 1.16, 1.59; $I^2 = 32.8\%$; $p = 0.178$), PAHs by questionnaire (summary OR = 1.20; 95% CI: 1.01, 1.42; $I^2 = 64.6\%$; $p = 0.015$), whereas a borderline summary odds ratio (summary OR = 1.12; 95% CI: 0.96, 1.31; $I^2 = 0.0\%$; $p = 0.423$) was found for PAHs by geographical modelling and BC. Grilled/smoked meat intake was positively associated with BC (summary OR = 1.31; 95% CI: 1.05, 1.64; $I^2 = 64.9$; $p = 0.036$), while a positive but non-significant association was found between indoor stove/fireplace use and BC (summary OR = 1.04; 95% CI: 0.89, 1.22; $I^2 = 0.0\%$; $p = 0.419$) (Table 5). No evidence of publication bias was observed (Begg's test $p = 0.065$) (Fig. 3).

3.7. Modifications of the association between PAHs and BC

Several studies stratified their results by variables, such as menopausal status, BMI, age at full-first pregnancy, smoking status, weight change, fruit and vegetable consumption, family BC history, genotypes of DNA binding (IGHMBP2), DNA repair (XPA, ERCC1-5, XRCC1, OGG1), genes involved in PAHs metabolism (CYPs 1A1, 1B1, 3A4), and p53 mutations. Most studies evaluated whether these variables modified the association between PAHs exposure and BC by means of statistical interaction tests (Table 2). For example, there were increases in BC risk in pre- and postmenopausal women when DNA adduct concentrations were doubled (RR = 1.61; 95% CI: 1.29, 2.01); in addition, a significant interaction with tobacco smoking and body mass index, with higher effect of DNA adducts on breast cancer risk among smokers and women with normal weight was observed (Agudo et al., 2017). In contrast, age at full-first pregnancy, BMI and weight change, as well as variants in genes involved in DNA repair and CYP3A4 did not modify the association between PAHs and BC (Niehoff et al., 2017; Parada et al., 2017; Mordukhovich et al., 2016a). However, high intake of vegetables and fruits significantly attenuated the association between PAHs and BC, whereas low consumption increased the risk (Mordukhovich et al., 2016b), consistent with studies reporting a negative correlation between PAH-DNA adduct formation and the intakes of fruit, vegetables, and flavonoids (Veglia et al., 2008). In general terms, inclusion of whole-grain, fiber, fruits, and vegetables within diets were associated with reduced cancer risk, with diet during early life (age <8 years) playing the strongest role (Kerr et al., 2017).

Regarding the influence of selected single nucleotide polymorphisms (SNPs) on BC incidence, the association PAHs-BC was stronger among CYP1A1 (AA) genotype carriers than in those carrying (AG + GG), probably by enhancing enzyme activity and increasing DNA adducts, in agreement with studies showing that most BC tumors constantly express CYP1A1, which may activate procarcinogens including PAHs (Parada et al., 2017). Furthermore, other studies have focused on associations between CYP1A1 SNPs and increased incidence of other types of cancer (Rodriguez and Potter, 2013). In addition, exposed women carrying the CYP1B1 (GC) SNP variant showed, a stronger association with BC than those with the (GT + TT) genotype (Parada et al., 2017).

Family history of BC and/or tobacco smoking also strengthened the association between PAHs exposure and -BC, as compared to women with no BC family history or nonsmokers (Lee et al., 2019; Agudo et al., 2017). The higher BC risk related to smoking was similar across racial/ethnic groups and ER and Progesterone Receptor (PR) status in the Multiethnic Cohort (Gram et al., 2019). In a pooled analysis of 14 prospective cohort studies of nearly one million women, smoking for more than 10 years before first birth was associated with an 18% higher BC risk, as compared with never smokers (Gaudet et al., 2017).

In summary, Familial BC history and smoking, significantly strengthened the association between PAHs exposure and BC, whereas high fruit and vegetable intake showed an antagonistic effect. CYP1A1, CYP1B1 and 3A4 genetic variants of phase I metabolizing enzymes may play a role in BC development and modify the positive association between grilled/smoked meat intake and BC (Parada et al., 2017). Information on active and passive smoking, grilled/smoked meat, synthetic log use, and residential history (used to determine vehicular traffic exposure) may give a better approximation of exposure (Mordukhovich et al., 2010; Niehoff et al., 2017).

Several issues that may affect interpretation of our findings need to be discussed. This review was restricted to English language articles present in PubMed, Web of Science and Scopus databases. In general terms, important limitations of the studies reviewed were that there was not a consistent examination and/or reporting of PAHs congeners present in the mixtures at which individuals were exposed, or the presence of other environmental pollutants (human exposome), as recently suggested by Bessonneau and Rudel (2019). These gaps of knowledge are

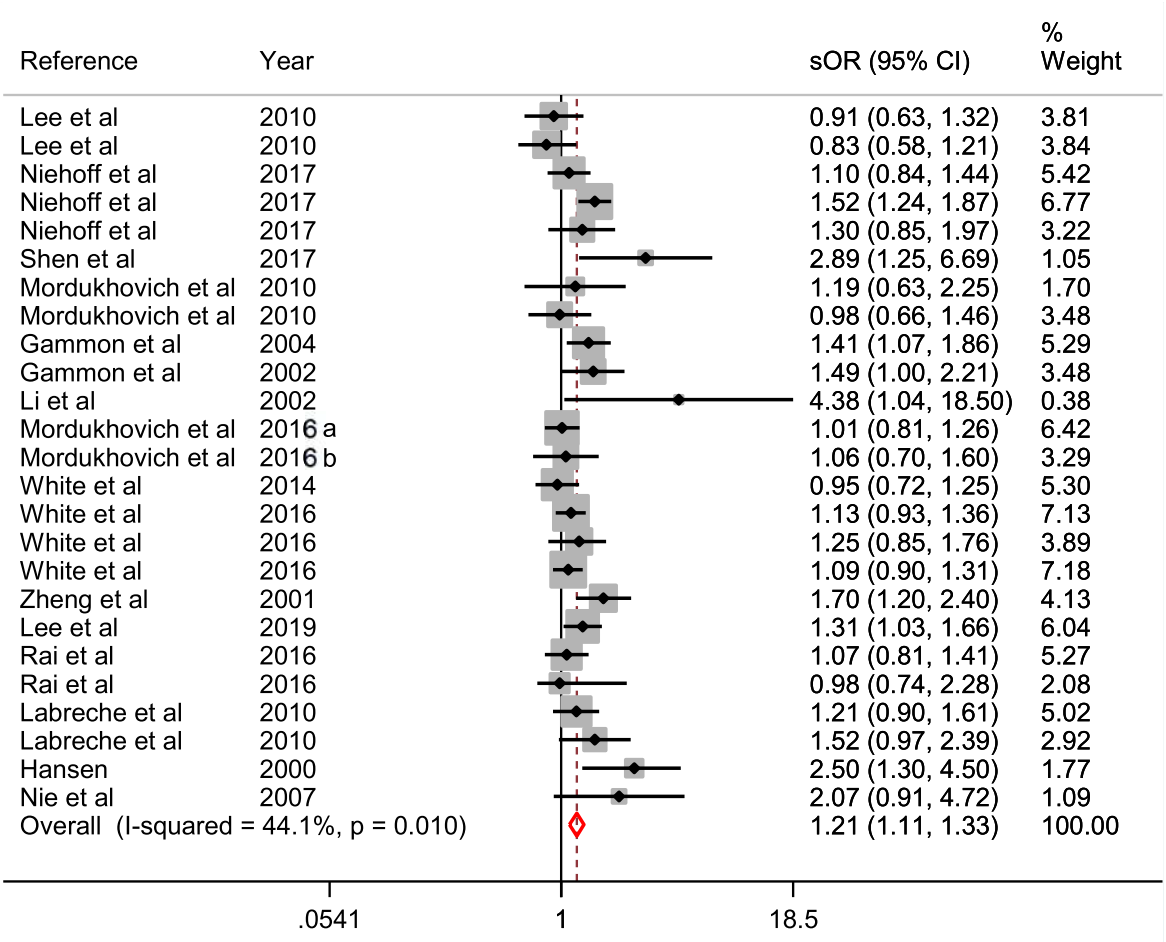

Fig. 2. Forest plot of PAHs exposure and breast cancer association in 17 case-control studies.

Table 5
Summary odds ratios for PAHs exposure and breast cancer by type of exposure assessment and PAHs source

PAHs	Number of studies	Summary OR	95% CI	I^2	Heterogeneity p-value	References
PAHs-DNA or albumin adducts	7	1.36	1.16, 1.59	32.8	0.178	Agudo et al., 2017 Niehoff et al., 2017 Shen et al., 2017 Mordukhovich et al., 2010 Gammon et al., 2004 Gammon et al., 2002 Li et al., 2002
PAHs by questionnaire	5	1.20	1.01, 1.42	64.6	0.015	Niehoff et al., 2017 Mordukhovich et al., 2010 White et al., 2014 White et al., 2016 Zheng et al., 2001
PAHs by geographical modelling	5	1.12	0.96, 1.31	0.0	0.423	Niehoff et al., 2017 Mordukhovich et al., 2016a Mordukhovich et al., 2016b White et al., 2016 Nie et al., 2007
Grilled/sked meat intake	4	1.31	1.05, 1.64	64.9	0.036	Niehoff et al., 2017 Mordukhovich et al., 2010 White et al., 2016 Zheng et al., 2001
Indoor stove/fireplace use	2	1.04	0.89, 1.22	0.0	0.419	White et al., 2014 White et al., 2016

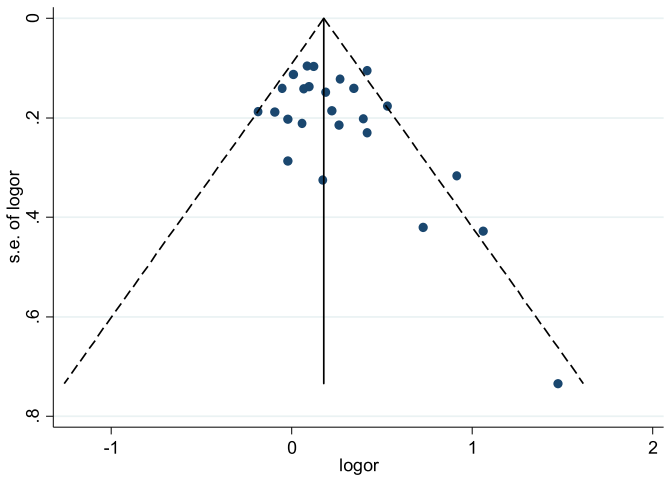

Fig. 3. Funnel plot of PAHs exposure and breast cancer association in case-control studies.

considered as research opportunities deserving further research.

4. Conclusion

This systematic review and meta-analysis provide a much-needed critical appraisal of the epidemiological evidence on the association between PAHs exposure and BC. Occupational and/or environmental exposure to PAHs were significantly and positively associated with BC, irrespective of exposure being assessed by direct or indirect methods, indicating that PAHs exposure is a risk factor for BC.

Research needs for future studies include: The improvement of exposure assessment, particularly on the identification of specific PAHs and reconstruction of time-varying and distant past environmental exposures, and in industrial processes considered carcinogenic by IARC (2010), such as coal gasification, coke production, paving and roofing with coal-tar pitch, and aluminum production. Additional studies on the interaction between known BC factors and modifiable diet and life-style factors which would allow prevention and control of BC are also needed.

Author contributions statement

LLC Conceptualization, Methodology. LLC and MEC Conceptualization and funding acquisition. BGL and LLC Methodology. YMS and MEC wrote the first draft of the manuscript. BGL validated the formal analysis. LLC and BGL performed Ms visualization. LLC supervised the findings of this work. MEC reviewed, edited, and provided insights on the overall manuscript. All authors read and approved the final manuscript.

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Ethical approval

This investigation was conducted using secondary data; therefore, approval of an Ethical Committee was not required.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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