

SYSTEMATIC REVIEW

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# Breast cancer determinants in low- to upper-middle-income countries: an umbrella review of meta-analyses of observational studies and an urgent call for implementation science

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## Abstract

**Introduction** Meta-analyses on breast cancer determinants in low- and middle-income countries (LMICs), including upper-middle-income countries (UMICs), often produce fragmented, context-specific findings. This umbrella review provides a consolidated synthesis to identify consistent risk factors and strengthen the evidence base for guiding targeted public health strategies.

**Methods and materials** In accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, we conducted a systematic search for meta-analyses across multiple databases. Study quality was assessed using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) tool. Data were analyzed using STATA version 14, applying a random-effects model to estimate pooled effect sizes with 95% confidence intervals. Forest plots were used to visualize determinants. Publication bias was assessed through funnel plots and Egger's test, while heterogeneity was evaluated using the I-squared ( $I^2$ ) statistic and Galbraith plots. Sensitivity analysis was performed to assess small-study effects.

**Results** Out of 1,515 publications reviewed, 35 met the inclusion criteria. Eight determinants of breast cancer showed convincing evidence under the random-effects model: being overweight (POR = 1.16, 95% CI: 1.09–1.23), oral contraceptive use (POR = 1.19, 95% CI: 1.11–1.27), family history of breast cancer (POR = 2.26, 95% CI: 1.84–2.67), age  $\geq 40$  years (POR = 1.82, 95% CI: 1.60–2.05), smoking history (POR = 1.22, 95% CI: 1.11–1.34), exposure to air pollution (POR = 1.03, 95% CI: 1.01–1.05), higher fruit and vegetable consumption (POR = 0.82, 95% CI: 0.71–0.92), and history of night work (POR = 1.14, 95% CI: 1.02–1.25).

**Conclusions** This umbrella review identified eight key breast cancer risk factors. Non-modifiable factors like age  $\geq 40$  and family history, along with modifiable factors such as overweight, smoking, oral contraceptive use, air pollution, and night shift work, increased the odds of breast cancer. Adequate fruit and vegetable intake was linked to reduced odds, suggesting a protective effect. We recommend that public health strategies promote healthy lifestyles and

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target high-risk groups through early screening and awareness campaigns, using evidence-based interventions to reduce the breast cancer burden.

**Keywords** Breast cancer, Determinants, Low- and middle-income countries, Upper-middle-income countries, Umbrella review

## Introduction

Breast cancer remains the most commonly diagnosed cancer and a leading cause of cancer-related death among women. In 2022, it represented 23.8% of all cancer cases and 15.4% of cancer deaths in women worldwide [1]. Most women diagnosed with breast cancer in high-income countries are likely to survive, while the survival rates are much lower for women in most low and middle-income countries [2, 3]. Breast cancer mortality is notably higher in transitioning regions such as Melanesia, Western Africa, Micronesia/Polynesia, and the Caribbean, where incidence rates are about 88% greater than in more developed regions like Australia/New Zealand, Western Europe, Northern America, and Northern Europe [4]. From 1990 to 2016, breast cancer incidence more than doubled in 60 out of 102 countries. Similarly, death rates doubled in 43 out of 102 countries [5].

Current estimates indicate that by 2030, approximately 2.7 million new breast cancer cases will be diagnosed annually worldwide, resulting in 870,000 deaths [6]. Mortality rates are rising significantly in Africa, with 2020 age-standardized death rates ranging from 20 per 100,000 women in Northern Africa to 27 per 100,000 in Western Africa [7, 8]. The overall pooled prevalence across the continent is reported at 48 per 100,000 [9]. In low- and middle-income countries, rising breast cancer incidence is driven by lifestyle changes such as delayed childbirth, reduced breastfeeding, early menarche, sedentary behavior, and poor diet, in addition to improved cancer detection and registration [10]. Female sex remains a major risk factor due to hormonal influences, particularly heightened estrogen and progesterone activity, which are strongly linked to increased breast cancer risk [11, 12]. Hormonal imbalances, including elevated endogenous estrogens and androgens, contribute to breast cancer risk in both premenopausal and postmenopausal women, as supported by large-scale cohort studies from the Endogenous Hormones and Breast Cancer Collaborative Group [13, 14]. Additional risk determinants include early menarche (under age 12), postmenopausal status, breastfeeding history, and a family history of cancer [15, 16]. These epidemiological trends highlight the urgent global health challenge posed by breast cancer, particularly in resource-limited regions, and emphasize the critical need for targeted prevention, early detection, and effective public health interventions to reduce disease burden and improve outcomes worldwide.

Despite numerous observational associations, the relationships between breast cancer and risk factors in low- and middle-income countries (LMICs), including upper-middle-income countries (UMICs), remain poorly understood. This is largely due to limited research infrastructure, inconsistent data quality, and sociocultural diversity that affect both risk factor expression and healthcare access. Existing systematic reviews often yield fragmented, context-specific findings, making it difficult to generalize results or inform targeted interventions. Furthermore, global cancer control strategies have traditionally prioritized high-income countries, resulting in a critical evidence gap for LMICs and UMICs. To address this, the present umbrella review systematically evaluates and synthesizes findings from existing reviews, emphasizing risk factors supported by robust epidemiological evidence. By consolidating diverse sources, this study aims to identify the most reliable determinants of breast cancer and inform more effective, context-appropriate public health strategies in these increasingly affected regions.

## Methods and materials

### Protocol development and registration

This umbrella review protocol was designed using preferred methods for reviewing available Systematic Review and Meta-Analysis (SRM) studies [17]. First, the existence of a similar umbrella review was checked on PROSPERO, and no similar studies were found to be registered. The protocol for this umbrella review was subsequently registered (CRD42024585671) with PROSPERO. Information related to the PROSPERO registration can be made available upon reasonable request from the primary author. The umbrella review focuses on systematically synthesizing existing systematic reviews and meta-analyses regarding the determinants of breast cancer.

### Searching strategy and information sources

Our umbrella review was conducted according to the guidelines for systematic reviews outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. We performed an umbrella review, which is a systematic collection and evaluation of multiple systematic reviews and meta-analyses on a specific research topic [19]. An umbrella review consolidates comparisons of a large number of existing systematic reviews and meta-analyses on the determinants into one

accessible and usable document [19, 20]. The methods for conducting an umbrella review are standardized, and in this work, we followed the same principles used in previously published umbrella reviews across various fields of research [20–22].

A thorough literature search was conducted using the PICO framework to review systematic reviews and meta-analyses on the determinants of breast cancer. Relevant studies were retrieved through an advanced computer search across various databases, including PubMed, PMC, MEDLINE, EMBASE, Web of Science Core Collection, SCOPUS, African Online Journals, and Google Scholar. A combination of keywords and MeSH terms was used to identify the studies. Snowballing and manual searches were also employed to find additional studies, including grey literature. This method involves reviewing the reference lists of relevant articles that are already included in the review. If a paper looks useful, the reference list of that paper is examined to find additional studies, which is why it is often called snowballing — the process helps the list grow as you move forward. This method is particularly useful for finding studies that may not have been indexed in the databases or were published in obscure journals. Search strategies were developed based on key concepts and search terms. The first concept was breast cancer, which included terms such as “ductal carcinoma,” “lobular carcinoma,” and “invasive breast cancer.” The second concept was determinant factors, encompassing terms like “risk factors,” “associated factors,” “predictors,” and “causes.” The third concept focused on systematic reviews and meta-analyses (SRM), with terms like “meta-analysis,” “systematic review,” and “review.” Literature searches were conducted independently by the four authors (MBD, MM, KB, and DZ), with any inconsistencies resolved through consensus. In cases where articles had incomplete information, the primary authors of the respective studies were contacted.

Search terms were used independently and/or in combination with ‘OR’ or ‘AND’ operators, including: ‘Breast Neoplasms’[Mesh] OR ‘Breast Carcinoma’[Mesh] OR ‘Breast Cancer Lymphedema’[Mesh] OR ‘Malignancy’ OR ‘Tumor’ OR ‘Unilateral Breast Neoplasms’[Mesh] OR ‘Triple Negative Breast Neoplasms’[Mesh] OR ‘Inflammatory Breast Neoplasms’[Mesh] OR ‘BRCA1 Protein’[Mesh] AND (‘Risk Factors’ OR ‘Associated Factors’ OR ‘Determinants’ OR ‘Predictors’ OR ‘Causes’) OR ‘Epidemiologic Factors’ OR ‘Women’ OR ‘Female’ AND (‘Meta-analysis’ OR ‘Systematic Review’ OR ‘Review’) AND (‘Developing Countries’ OR ‘Low-Income Countries’ OR ‘Middle-Income Countries’ OR ‘Lower-Middle-Income Countries’ OR ‘Upper-Middle-Income Countries’).

Additionally, the ‘Related Articles’ and ‘Cited by’ features in PubMed were used to identify further relevant

studies. All retrieved publications underwent a three-step parallel screening process—title, abstract, and full-text review—conducted independently by three authors (MBD, DZ, and MM) based on predefined inclusion and exclusion criteria. Reference lists of the included articles were also screened to identify additional eligible studies.

### Outcome measurements

The primary outcome of this review was the identification of determinants associated with breast cancer diagnosis. The secondary outcome focused on the prevalence of breast cancer diagnoses, defined as the proportion of individuals initially presenting with the disease at any stage.

### Eligibility criteria

#### Inclusion criteria

Systematic reviews and meta-analyses (SRMs) reporting at least one determinant of breast cancer among patients of any age and published in English were included. Eligible SRMs met the following criteria: (1) breast cancer as the primary outcome (2), a well-documented and reproducible literature search strategy (3), appraisal of included studies using a relevant quality assessment tool, and (4) use of a standard approach to pooling studies and reporting summary estimates. We included meta-analyses of observational studies (cross-sectional, case-control, and cohort) that investigated breast cancer determinants. Meta-analyses were retained if they included at least three studies reporting measures of association, standard errors, number of cases, and total sample size.

#### Exclusion criteria

Articles were excluded for the following reasons: (1) they did not measure the outcome of interest; (2) they were not published in English; or (3) they were narrative reviews, expert opinions, case reports, editorials, correspondence, abstracts, or methodological studies. We also excluded studies focused solely on risk factors for screening, diagnostic, or prognostic purposes. Additionally, systematic reviews and meta-analyses of genetic risk factors, letters to the editor, meta-analyses of randomized controlled trials (RCTs), and reviews lacking quantitative data synthesis were excluded. In cases where multiple meta-analyses addressed the same research question, we included the one with the largest number of primary studies and most comprehensive effect size data to avoid duplication.

### Data extraction and management

Three reviewers independently extracted data using a standardized form in Microsoft Excel. They screened and selected articles in three stages—title, abstract, and full-text review—with any disagreements resolved by

consensus. Eligible studies were imported into EndNote version 8, and duplicates were removed. Extracted data included: first author's last name, publication year, study setting, original study design, number of included studies, sample size, main findings, and methodological quality (using the AMSTAR-2 tool).

#### Quality assessment (risk of bias assessment)

To evaluate the methodological quality of the included studies, the Assessment of Multiple Systematic Reviews (AMSTAR 2) tool was used [23]. The updated AMSTAR version includes ten domains from the 2007 edition, with two of these being more detailed and four additional domains added, resulting in a total of 16 domains. Of these, seven are deemed critical, focusing on aspects such as protocol registration, literature search adequacy, justification for study exclusions, risk of bias assessment, appropriateness of meta-analytical methods, interpretation of results considering bias, and evaluation of publication bias impact [24]. The quality rating according to the AMSTAR 2 tool is as follows: (a) High quality: no or one non-critical weakness; (b) Moderate quality: more than one non-critical weakness; (c) Low quality: one critical flaw with or without non-critical weaknesses; (d) Critically low: more than one critical flaw with or without non-critical weaknesses [23]. Responses in the tool are categorized as “Yes,” “No,” “Cannot be answered,” or “non-applicable,” with “Yes” receiving a score of 1 and the others were receiving a score of 0. Articles are rated as “low quality” (scores 1 to 4), “medium quality” (5 to 8), and “high quality” (9 to 11). The final assessment score for each article was determined by agreement between two reviewers, with any disagreements referred to a third assessor. Articles deemed to have critically low-quality evidence were excluded from the umbrella review.

Given that this umbrella review synthesizes evidence from previously published systematic reviews and meta-analyses, the AMSTAR 2 tool was selected to evaluate their methodological quality. Unlike tools such as the Newcastle–Ottawa Scale (NOS), which are designed for assessing individual observational studies, AMSTAR 2 is specifically developed to appraise the quality of systematic reviews of both randomized and non-randomized studies. Its comprehensive criteria allow for a more accurate assessment of review-level evidence, which is essential for ensuring the credibility and reliability of umbrella review findings.

#### Statistical analysis

Data were extracted into Microsoft Excel and analyzed using STATA version 14. When multiple estimates were available for the same topic, either pooled estimates or ranges were used. Standard errors were computed using

the binomial distribution formula. Forest plots were used to illustrate the pooled determinants. Summary effect estimates (pooled odds ratios or relative risks) with 95% confidence intervals were calculated using a random-effects model; relative risks were converted to odds ratios when necessary.

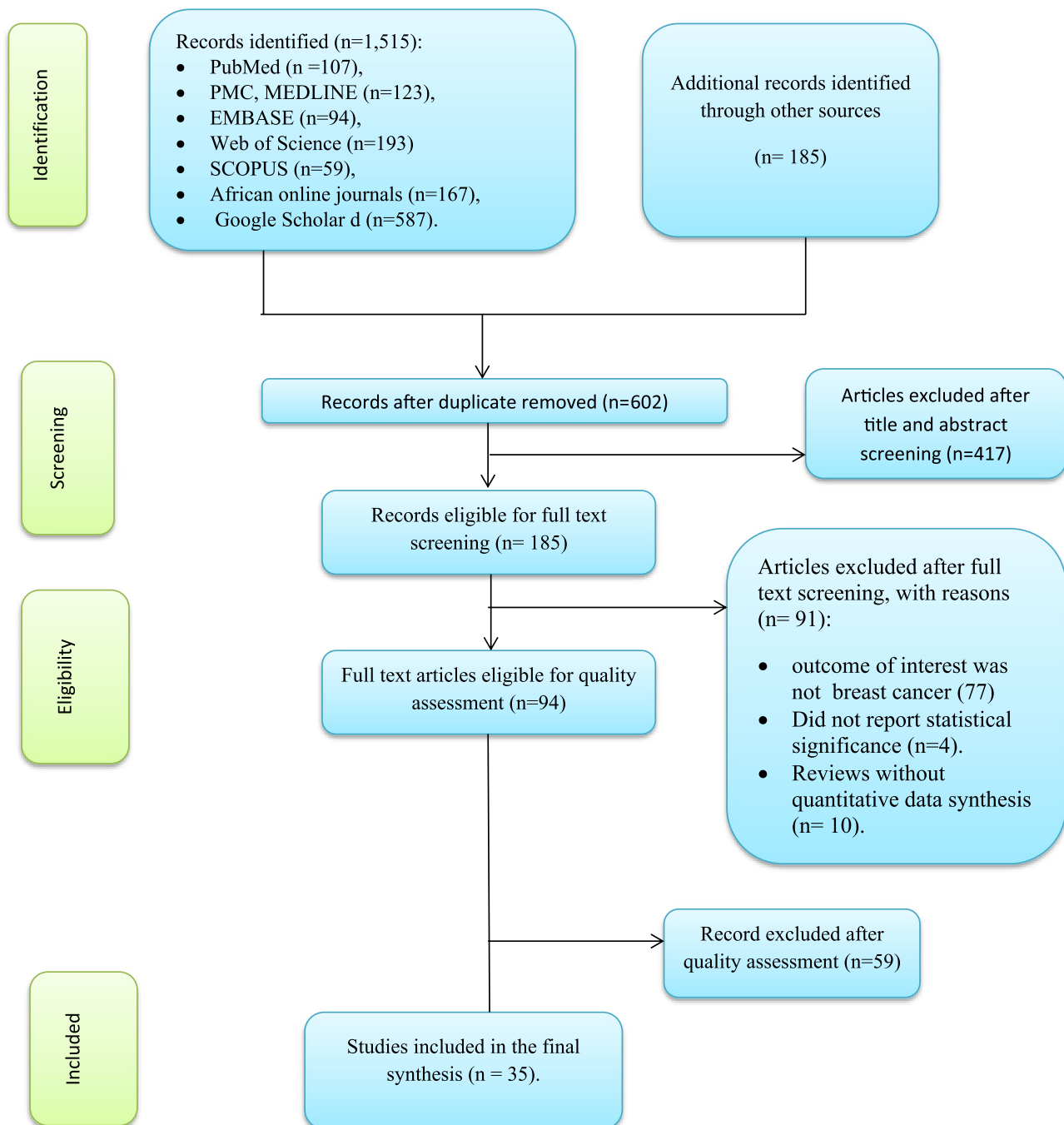
Publication bias was assessed using funnel plots and Egger's regression test. Heterogeneity was evaluated using Cochrane's  $Q$ ,  $I^2$  statistics, and  $p$ -values, with  $I^2$  interpreted as low (0–40%), moderate (30–60%), substantial (50–90%), and considerable (75–100%). A Galbraith Plot was used to visually assess heterogeneity and identify outliers. Types of heterogeneity included clinical, methodological, and statistical. Sensitivity analysis was performed to assess the impact of individual studies on pooled estimates.

## Results

### Study selection

In this umbrella review of meta-analyses of observational studies, the initial comprehensive database search identified a total of 1,515 publications. After eliminating duplicates, 602 unique records remained for the initial screening phase. Titles and abstracts of these records were carefully reviewed based on predefined eligibility criteria, which included relevance to breast cancer determinants, inclusion of quantitative synthesis, and reporting in English. As a result, 417 studies were excluded due to not meeting these criteria—primarily because they addressed unrelated topics, lacked relevant exposure or outcome measures, or were non-systematic in nature. This left 185 articles eligible for full-text screening. A detailed examination of the full texts led to the exclusion of 91 studies. Specifically, 77 were removed because they did not consider breast cancer as the primary outcome of interest, 4 failed to report statistically significant results necessary for pooled analysis, and 10 were narrative reviews or systematic reviews without meta-analytic (quantitative) synthesis (Fig. 1).

The remaining 94 articles then underwent a rigorous methodological quality assessment using the AMSTAR 2 tool. This step was crucial to ensure that only high-quality evidence contributed to the final synthesis. Based on this evaluation, 59 studies were excluded due to low methodological quality—such as lack of a clearly documented, systematic approach strategy, inadequate risk of bias assessment, or insufficient data pooling methods. Ultimately, 35 meta-analyses met all inclusion and quality criteria and were included in the final synthesis of this umbrella review. These studies formed the basis for identifying and quantifying the most credible determinants of breast cancer (Fig. 1).



**Fig. 1** PRISMA flow diagram showing the literature search, screening, and selection process for studies included in the umbrella review

### The characteristics of the studies included in the umbrella review

In this umbrella review of meta-analyses (MAs) of observational studies, 23 (65.7%) originated from upper middle-income countries (UMICs), while 12 (34.3%) were from low-income countries (LICs), suggesting greater research capacity or resource availability in UMICs. The articles were published between 2009 and 2024, reflecting recent trends in evidence synthesis. Regarding

quality assessment, 25 studies (71.4%) used the Newcastle–Ottawa Scale (NOS), 2 (5%) employed the Cochrane Collaboration’s risk of bias tool, 3 (7%) used the STROBE statement, and 4 (9.3%) applied other tools. Two studies (5.7%) did not perform any quality assessment, indicating variability in methodological rigor across studies (Table 1).

In terms of analytic models, 33 studies (77%) used the DerSimonian–Laird random-effects model to calculate

**Table 1** Characteristics of the eligible review papers included in the umbrella review on the determinants of breast cancer ( $n = 35$ ) in Low- to Upper-Middle-Income countries, 2025

| First author's last name and Year of Publication | Settings (location) | Design of the Original Studies | Number of Original Studies | Number of Primary Studies Included in MA | Total Sample Size | Main Findings                                                                                                                                                                                                                                 | Methodological Quality Assessment Tools Used |
|--------------------------------------------------|---------------------|--------------------------------|----------------------------|------------------------------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Liu X, et al., 2014 [25]                         | UMICs               | Case Control                   | 37                         | 32                                       | 430,898           | • Fruit and vegetable consumption was significantly associated with a reduced breast cancer risk (POR = 0.65; 95% CI: 0.43–0.99).                                                                                                             | None                                         |
| Yi YY, et al., 2017 [26]                         | LIC                 | Case Control                   | 56                         | 9                                        | 16,945            | • Air pollution was significantly associated with breast cancer risk (POR = 1.13; 95% CI: 1.07–1.20; $p < 0.0001$ ).                                                                                                                          | NOS                                          |
| Hidayat K et al., 2018 [27]                      | UMICs               | Cohort Study                   | 17,231                     | 24                                       | 33,606            | • Being overweight was associated with a 13% higher breast cancer risk in all women (POR = 1.13; 95% CI: 1.08–1.18) and a 14% higher risk in postmenopausal women (POR = 1.14; 95% CI: 1.08–1.20).                                            | NOS                                          |
| Berrington de Gonzalez A, et al., 2009 [28]      | UMICs               | Case Control                   | 32                         | 18                                       | 16,424            | • Women with a birth weight over 4000 g had a 20% higher breast cancer risk (POR = 1.20; 95% CI: 1.08–1.34).                                                                                                                                  | NOS                                          |
| Wang J et al., 2020 [29]                         | UMICs               | Cohort Study                   | 1,141                      | 20                                       | 52,904            | • Overweight increased the risk of BC by 0.89% per 1 kg/m <sup>2</sup> increase (POR = 1.01; 95% CI: 1.00–1.01).                                                                                                                              | NOS                                          |
| Dehesh T, et al., 2023 [30]                      | LIC                 | Cross-Sectional                | 10,662                     | 102                                      | 109,705           | • Overweight (obesity) is associated with an increased risk of breast cancer in women (POR = 1.26 (95% CI: 1.19–1.34).                                                                                                                        | NOS                                          |
| Pierobon M, et al., 2013 [31]                    | LIC                 | Case-Control                   | 267                        | 11                                       | 24,479            | • Obesity elevated breast cancer risk (POR = 1.24; 95% CI: 1.06–1.46), indicating a 24% higher risk in obese women compared to non-obese women.                                                                                               | NOS                                          |
| Arafat H, et al., 2021 [32]                      | LIC                 | Case Control and Cohort        | 1,211                      | 15                                       | 12,768            | • Modifiable factors (diabetes, hypertension, obesity, passive smoking) and non-modifiable factors (age, menopause, family history) significantly contribute to breast cancer risk.                                                           | Cochrane Collaboration                       |
| Dai Q, et al., 2009 [33]                         | MIC                 | Case Control                   | 15                         | 15                                       | 50,302            | • Menopausal Age > 50: 39% higher breast cancer risk (POR = 1.39; 95% CI: 1.22–1.57).<br>• Oral Contraceptive Use: Over double the breast cancer risk (POR = 2.12; 95% CI: 1.24–3.62).                                                        | NOS                                          |
| Kandy's W, et al., 2010 [34]                     | UMICs               | Case Control                   | 121                        | 79                                       | 72,030            | • Age at First Full-Term Pregnancy: OCs use before the first pregnancy increased breast cancer risk (POR = 1.14; 95% CI: 1.01–1.28).<br>• Duration of Use: OCs use for > 5 years modestly increased risk (POR = 1.09; 95% CI: 1.01–1.18).     | NOS                                          |
| Li L, et al., 2017 [35]                          | UMICs               | Case Control                   | 392                        | 20                                       | 15,427            | • OC use was associated with a 31% higher breast cancer risk (POR = 1.31; 95% CI: 1.18–1.45; $P < 0.00001$ ).                                                                                                                                 | NOS                                          |
| Conz L, et al., 2020 [36]                        | UMICs               | Case Control                   | 96                         | 8                                        | 9,234             | • OC use is associated with an increased risk of breast cancer, particularly among women aged 50 years and older (POR = 1.16; 95% CI: 1.06–1.28; $I^2 = 78\%$ ; $P < 0.01$ ).                                                                 | Downs and Black Instrument                   |
| Giersch J, et al., 2013 [37]                     | LIC                 | Cross-Sectional                | 6,476                      | 8                                        | 3,181             | • OC use was associated with a slight but significant increase in breast cancer risk (POR = 1.08; 95% CI: 1.00–1.17), with higher risk for more recent use.                                                                                   | NOS                                          |
| Shamshirian A, et al., 2020 [38]                 | LIC                 | Cross-Sectional                | 562                        | 39                                       | 25,592            | • Family History: Increased breast cancer risk (POR = 1.80; 95% CI: 1.47–2.12)<br>• Passive Smoking: Increased breast cancer risk (POR = 1.68; 95% CI: 1.34–2.03)<br>• Abortion: Increased breast cancer risk (POR = 1.84; 95% CI: 1.35–2.33) | NOS                                          |

**Table 1** (continued)

| First author's last name and Year of Publication | Settings (location) | Design of the Original Studies | Number of Original Studies | Number of Primary Studies Included in MA | Total Sample Size | Main Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Methodological Quality Assessment Tools Used |
|--------------------------------------------------|---------------------|--------------------------------|----------------------------|------------------------------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Xin Y, et al., 2015 [39]                         | UMICs               | Case-Control                   | 1,524                      | 16                                       | 9,324             | <ul style="list-style-type: none"> <li>Higher vegetable intake was positively significantly associated with breast cancer risk (AOR = 0.88 (95% CI: 0.77–1.01).</li> </ul>                                                                                                                                                                                                                                                                                                 | Cochrane Collaboration Tool                  |
| Nindrea RD, et al., 2017 [40]                    | LIC                 | Cross-Sectional                | 1,211                      | 15                                       | 14,963            | <ul style="list-style-type: none"> <li>Overweight (BMI): Increased breast cancer risk (POR = 1.61; 95% CI: 1.43–1.80)</li> <li>Oral Contraceptive Use: Modestly higher risk (POR = 1.27; 95% CI: 1.07–1.51)</li> <li>Family History: Significantly higher risk (POR = 2.53; 95% CI: 1.25–5.09)</li> <li>Age ≥ 40 Years: Increased risk (POR = 1.53; 95% CI: 1.34–1.76)</li> </ul>                                                                                          | NOS                                          |
| Liu H, et al., et al., 2020 [41]                 | UMICs               | Case Control                   | 1,283                      | 12                                       | 20,628            | <ul style="list-style-type: none"> <li>Overweight and obesity increase the risk of breast cancer, particularly after menopause.</li> </ul>                                                                                                                                                                                                                                                                                                                                 | Cochrane Collaboration Tool                  |
| Khoramdad M, et al., 2022 [42]                   | UMICs               | Case Control                   | 30,351                     | 24                                       | 12,460            | <ul style="list-style-type: none"> <li>OCP Use: Increased breast cancer risk by 35% (POR = 1.35; 95% CI: 1.11–1.63)</li> <li>Abortion History: 44% higher risk (POR = 1.44; 95% CI: 1.02–2.05)</li> <li>Smoking: Active and passive smoking increased risk by 83% and 86%, respectively</li> <li>Marriage Age (18–29 years): 22% increased risk (POR = 1.22; 95% CI: 1.02–1.47)</li> <li>Family History: 2.47 times higher risk (POR = 2.47; 95% CI: 1.83–3.33)</li> </ul> | NOS                                          |
| Solbana L, et al., 2023 [43]                     | LIC                 | Case Control                   | 52                         | 5                                        | 1,819             | <ul style="list-style-type: none"> <li>Family History of Cancer: More than double the breast cancer risk (POR = 2.39; 95% CI: 1.29–3.44)</li> <li>Early Menarche (&lt; 12 Years): Over three times higher risk (POR = 3.36; 95% CI: 1.68–5.04)</li> </ul>                                                                                                                                                                                                                  | NOS                                          |
| Wang H, et al., 2023 [44]                        | LIC                 | Case Control, Cohort           | 16,781                     | 76                                       | 5,184,024         | <ul style="list-style-type: none"> <li>Family History (Any Relative): Breast cancer risk over twice as high (OR = 2.21; 95% CI: 1.91–2.56)</li> <li>First-Degree Relatives: Risk increased further (POR = 2.46; 95% CI: 2.03–2.97)</li> </ul>                                                                                                                                                                                                                              | NOS                                          |
| Chen Ch, et al., 2008 [45]                       | UMICs               | Cohort and Case-Control        | 56                         | 19                                       | 9,345             | <ul style="list-style-type: none"> <li>Passive Smoking: Increased breast cancer risk by 62% (POR = 1.62; 95% CI: 1.39–1.85)</li> <li>Active Smoking: No significant association (POR = 1.04; 95% CI: 0.89–1.20)</li> </ul>                                                                                                                                                                                                                                                 | NOS                                          |
| Macacu A, et al., 2015 [46]                      | UMICs               | Case Control and Cohort        | 1,639                      | 86                                       | 14,678            | <ul style="list-style-type: none"> <li>Smoking was consistently associated with a moderate increase in breast cancer risk (AOR = 1.07; 95% CI: 1.02–1.13).</li> </ul>                                                                                                                                                                                                                                                                                                      | STROBE                                       |
| He Y, et al., 2022 [47]                          | UMICs               | Cohort and Case Control        | 19,746                     | 77                                       | 2,326,987         | <ul style="list-style-type: none"> <li>Active Smoking: 15% higher breast cancer risk (POR = 1.15; 95% CI = 1.11–1.20)</li> <li>Passive Smoking: 17% higher breast cancer risk (POR = 1.17; 95% CI = 1.09–1.24)</li> </ul>                                                                                                                                                                                                                                                  | NOS                                          |
| Possenti I, et al., 2023 [48]                    | UMICs               | Case-Control                   | 73                         | 63                                       | 47,456            | <ul style="list-style-type: none"> <li>Second-hand smoke (SHS) exposure increases breast cancer risk in non-smoking women, with the risk rising as exposure levels increase.</li> </ul>                                                                                                                                                                                                                                                                                    | STROBE                                       |
| Sollie M, et al., 2017 [49]                      | UMICs               | Cross-Sectional                | 12                         | 12                                       | 400,944           | <ul style="list-style-type: none"> <li>The findings revealed that current smokers had a 28% increased risk of breast cancer-specific mortality compared to never smokers (POR = 1.28; 95% CI: 1.17–1.41).</li> </ul>                                                                                                                                                                                                                                                       | STROBE                                       |
| Guo Q, et al., 2021 [50]                         | UMICs               | Case Control                   | 1,787                      | 15                                       | 13,234            | <ul style="list-style-type: none"> <li>Air pollution exposure was linked to a 9% higher risk of breast cancer (POR = 1.09; 95% CI: 1.02–1.16), but not breast cancer incidence.</li> </ul>                                                                                                                                                                                                                                                                                 | NOS                                          |
| Praud P, et al., 2023 [51]                       | UMICs               | Case Control, Cohort           | 925                        | 13                                       | 10,123            | <ul style="list-style-type: none"> <li>Traffic-related air pollution exposure was associated with a slight increase in breast cancer risk (POR = 1.015; 95% CI: 1.003–1.028).</li> </ul>                                                                                                                                                                                                                                                                                   | NOS                                          |

**Table 1** (continued)

| First author's last name and Year of Publication | Settings (location) | Design of the Original Studies | Number of Original Studies | Number of Primary Studies Included in MA | Total Sample Size | Main Findings                                                                                                                                                                                                                                         | Methodological Quality Assessment Tools Used |
|--------------------------------------------------|---------------------|--------------------------------|----------------------------|------------------------------------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Wie W, et al., 2021 [52]                         | UMICs               | Case-Control                   | 6,870                      | 18                                       | 15,896            | • Air pollution exposure associated with an increased risk of breast cancer (POR = 1.02 (95% CI: 1.01–1.04).                                                                                                                                          | NOS                                          |
| Manouchehri E, et al., 2021 [53]                 | UMICs               | Case-Control                   | 4,854                      | 26                                       | 1,313,348         | • Short-term night-shift work (less than 10 years) was associated with a 13% increased risk of breast cancer (POR = 1.13; 95% CI: 1.03–1.24).                                                                                                         | NOS                                          |
| Jia Y, et al., 2013 [54]                         | UMICs               | Case Control, Cohort           | 326                        | 13                                       | 7,345             | • Night shift work was associated with a 20% increased breast cancer risk (POR = 1.20; 95% CI: 1.08–1.33).                                                                                                                                            | NOS                                          |
| Kamdar B, et al., 2013 [55]                      | UMICs               | Cohort Study                   | 5,960                      | 15                                       | 13,234            | • Ever working night shifts was associated with a 21% increased breast cancer risk (POR = 1.21; 95% CI: 1.00–1.47).                                                                                                                                   | NOS                                          |
| Wei F, et al., 2022 [56]                         | UMICs               | Cohort Study                   | 470                        | 31                                       | 9,000,000         | • Night-shift work was associated with a 2.9% increased risk of breast cancer (POR = 1.029; 95% CI: 1.003–1.055).<br>• Long-term night-shift work (> 10 years) was linked to an 8.6% increased breast cancer risk (POR = 1.086; 95% CI: 1.032–1.142). | None                                         |
| Xue-Ou Liu et al. 2014 [57]                      | UMICs               | Case-Control, Cohort           | 452                        | 29                                       | 20,743            | • Overweight and obesity are associated with an increased risk of breast cancer (Overweight: POR = 1.13; 95% CI: 1.06–1.21, Obesity: POR = 1.26; 95% CI: 1.07–1.50).                                                                                  | NOS                                          |
| Farvid M, et al., 2021 [58]                      | LIC                 | Cohort Study                   | 66,817                     | 25                                       | 123,213           | • Higher intake of total fruits and vegetables is associated with a reduced risk of breast cancer (POR = 0.91; 95% CI: 0.87–0.95).                                                                                                                    | Health Quality Assessment Tool               |
| Aune D, et al., 2012 [59]                        | LIC                 | Cohort Study                   | 34,149                     | 15                                       | 12,765            | • High intake of fruits and vegetables, particularly fruits, is associated with a modest reduction in breast cancer risk (POR = 0.92; 95% CI: 0.86–0.98).                                                                                             | NOS                                          |
|                                                  |                     |                                | median, 1141               | Median: 18                               | Median: 16,424    |                                                                                                                                                                                                                                                       |                                              |

pooled odds ratios (ORs) with 95% confidence intervals (CIs), likely due to its ability to account for heterogeneity across studies. The median number of studies identified per meta-analysis was 1,141, with an average of 18 primary studies included, reflecting selective inclusion criteria or limitations in study quality. The median sample size across the included meta-analyses was 16,424 participants, indicating generally large-scale data synthesis efforts (Table 1).

### Risk of bias across studies

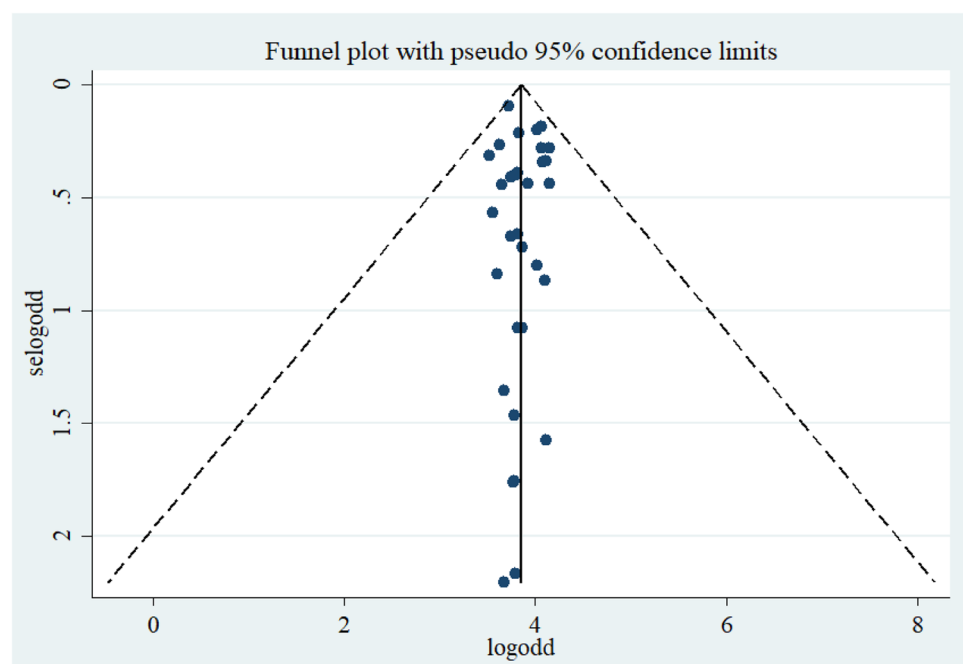
In this umbrella review, we assessed the risk of bias to enhance the transparency and credibility of our evidence synthesis. Publication bias was evaluated using funnel plots and Egger's test. The results indicated no significant evidence of publication bias, as effect sizes appeared normally distributed and symmetrically clustered around zero (Fig. 2).

This review assessed publication bias using Egger's test, yielding a p-value of 0.549, which suggests no evidence

of publication bias or small-study effects, as the result exceeds the conventional significance threshold ( $p < 0.05$ ), indicating that the funnel plot asymmetry is likely due to chance rather than systematic bias (Fig. 3).

The Galbraith plot is a diagnostic tool used in meta-analysis to visually assess heterogeneity and detect outlier studies. It plots the standardized effect size against its precision, helping to identify studies that may disproportionately influence overall results. In this umbrella review, the Galbraith plot was used to assess heterogeneity and identify potential outliers, showing no variation among the included studies (Fig. 4).

This umbrella review employed a random-effects model for sensitivity analysis to evaluate the influence of individual studies on the pooled estimates of breast cancer determinants. The analysis revealed no outlier studies, as all effect estimates fell within the confidence intervals, indicating consistent findings and supporting the robustness of the overall evidence. This suggests that no single study disproportionately influenced the results,



**Fig. 2** Funnel plot showing the 95% confidence limits for the determinants of breast cancer in low to upper-middle-income countries ( $n = 35$ ), 2025

| .                                  |          |           |       |           |                      |          |
|------------------------------------|----------|-----------|-------|-----------|----------------------|----------|
| Number of studies = 35             |          |           |       | Root MSE  | = .5562              |          |
| Std_Eff                            | Coef.    | Std. Err. | t     | P> t      | [95% Conf. Interval] |          |
| slope                              | 3.830749 | .0491926  | 77.87 | 0.000     | 3.730666             | 3.930832 |
| bias                               | .0896771 | .1482181  | 0.61  | 0.549     | -.2118749            | .3912292 |
| Test of H0: no small-study effects |          |           |       |           |                      |          |
|                                    |          |           |       | P = 0.549 |                      |          |

**Fig. 3** Egger's test results for detecting publication bias in studies on the determinants of breast cancer in low to upper-middle-income countries ( $n = 35$ ), 2025

which enhances the credibility and stability of the pooled estimates (Fig. 5).

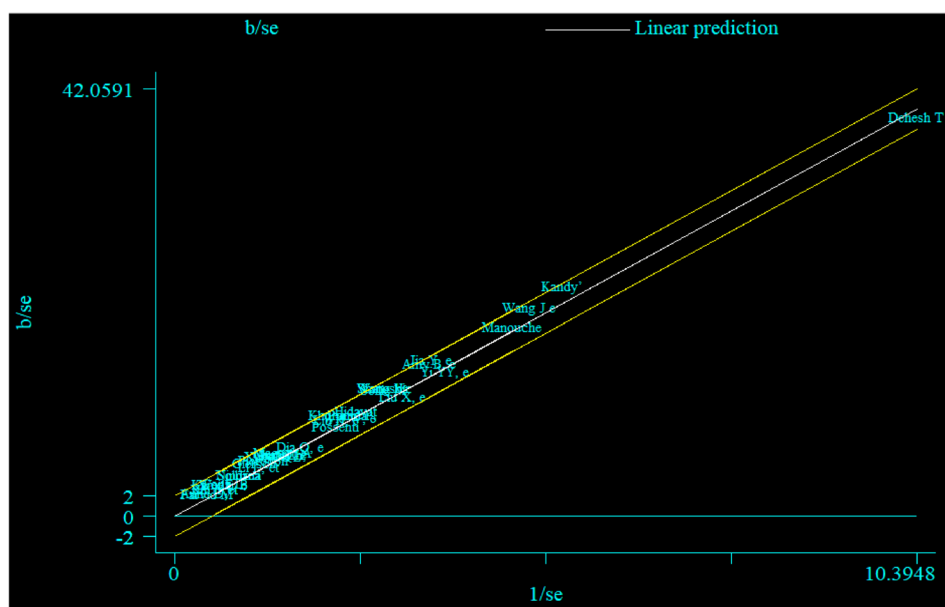
**Quality assessment of included meta-analyses studies**

To show the evidence class of the included studies, this umbrella review evaluated the quality of 35 meta-analyses using the AMSTAR-2 tool, resulting in a mean score of 6.3 (95% CI: 5.4–7.3) across 16 domains. Items were scored as No (0 points), Partial Yes (0.5 points), or Yes (1 point). While all meta-analyses conducted comprehensive literature searches and described study characteristics, most did not list excluded studies. The majority employed appropriate data analysis methods, addressed

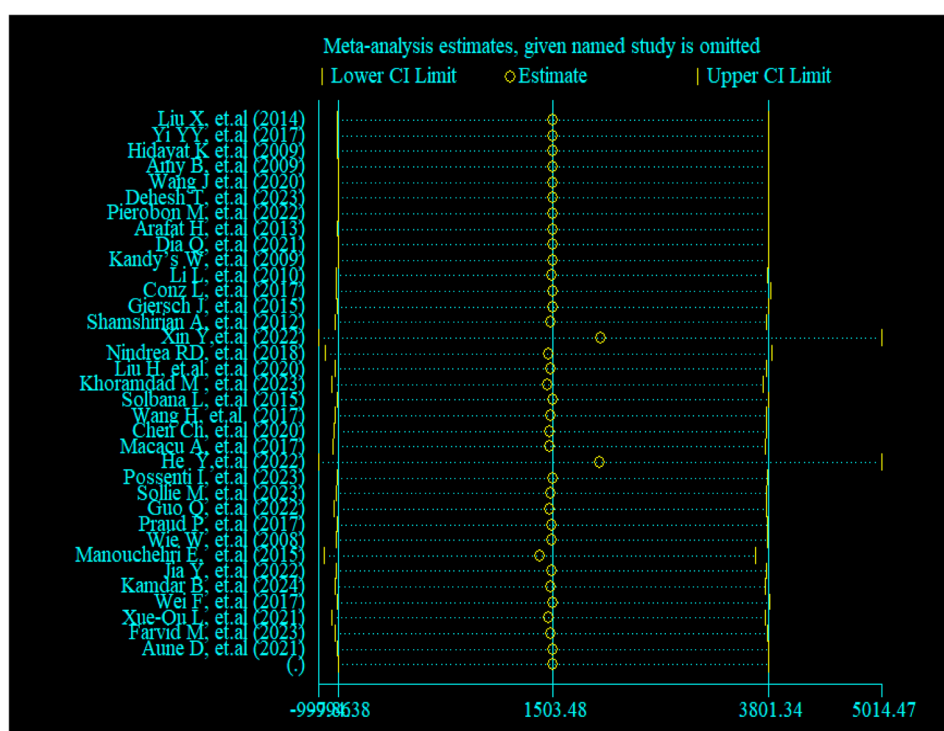
publication bias, and reported conflicts of interest (Supplementary Table 1).

**Meta synthesis of results on determinants of breast cancer**

After applying the credibility criteria quantitatively, eight determinants of breast cancer with convincing evidence of association under the random effects model were: being overweight [27, 29–31, 42, 60, 61], using oral contraceptives [33–37, 40, 41], having a family history of breast cancer [38, 40, 41, 43, 44, 62], being older ( $\geq 40$  years) [32, 41–44], having a history of smoking (both active and passive) [45–49], exposure to air pollution



**Fig. 4** Galbraith plot illustrating heterogeneity in the umbrella review of meta-analyses of observational studies on the determinants of breast cancer in low to upper-middle-income countries



**Fig. 5** Sensitivity analysis showing no outlier studies among the included articles estimating the pooled determinants of breast cancer, 2025 ( $n = 35$ )

[26, 50–52], having a history of night work [53–56], and fruit and vegetable intake [25, 39, 58, 59].

Among the eight significant determinants of breast cancer, seven were linked to higher risk. The following factors showed convincing evidence of association under the random effects model: Overweight (POR = 1.16, 95%

CI: 1.09–1.23) (Fig. 6A), Oral contraceptive use (POR = 1.19, 95% CI: 1.11–1.27) (Fig. 6B), Family history of breast cancer (POR = 2.26, 95% CI: 1.84–2.67) (Fig. 6C), Age  $\geq 40$  years (POR = 1.82, 95% CI: 1.60–2.05) (Fig. 6D), Smoking history (active and passive) (POR = 1.22, 95% CI: 1.11–1.34) (Fig. 6E), Air pollution exposure (POR

= 1.03, 95% CI: 1.01–1.05) (Fig. 6F), Fruit and vegetable intake (POR = 0.82, 95% CI: 0.71–0.92) (Fig. 6G), and Night shift work history (POR = 1.14, 95% CI: 1.02–1.25) (Fig. 6H). An overall assessment of these statistically significant associations is shown in Fig. 6A and H).

## Discussion

This umbrella review is the first to synthesize meta-analyses of observational studies from low- to upper-middle-income countries assessing the associations between various factors and breast cancer risk. Seven meta-analyses consistently showed that overweight individuals have a significantly higher odds of developing breast cancer compared to those with normal weight. This association is likely due to physiological mechanisms, including increased estrogen production from adipose tissue and elevated insulin levels, both of which are known to contribute to cancer development. These findings are consistent with existing literature, further reinforcing the strong association between excess body weight and an increased risk of breast cancer [63–65].

Empirical evidence showed that oral contraceptives (OCPs) are widely considered a safe, effective, and convenient form of contraception for many women [66–68]. However, our umbrella review found that seven meta-analyses reported a 19% increased risk of breast cancer among OCP users compared to non-users. This elevated risk may be due to the proliferative effects of estrogen and progesterone on hormone-sensitive tissues. Given that OCPs contain synthetic forms of these hormones, prolonged use could contribute to carcinogenesis. These findings align with previous reviews, which also reported an increased breast cancer risk associated with hormonal contraceptive use [68–70].

Our umbrella review found that six meta-analyses reported women with a family history of breast cancer had 2.26 times higher odds of developing the disease compared to those without such a history. This strong association is primarily due to inherited genetic mutations, particularly in the BRCA1 and BRCA2 genes, which significantly increase breast cancer risk. These findings are consistent with previous reviews that have consistently highlighted the impact of family history on breast cancer susceptibility [71].

In addition, five meta-analyses reported that women aged 40 and above had an 82% higher risk of developing breast cancer. This age-related increase may reflect the cumulative effects of cellular damage over time, which can contribute to oncogenesis. Our results are consistent with existing literature showing a strong correlation between advancing age and elevated breast cancer risk [72–74].

Our umbrella review found that five meta-analyses reported a 22% increased risk of developing breast cancer

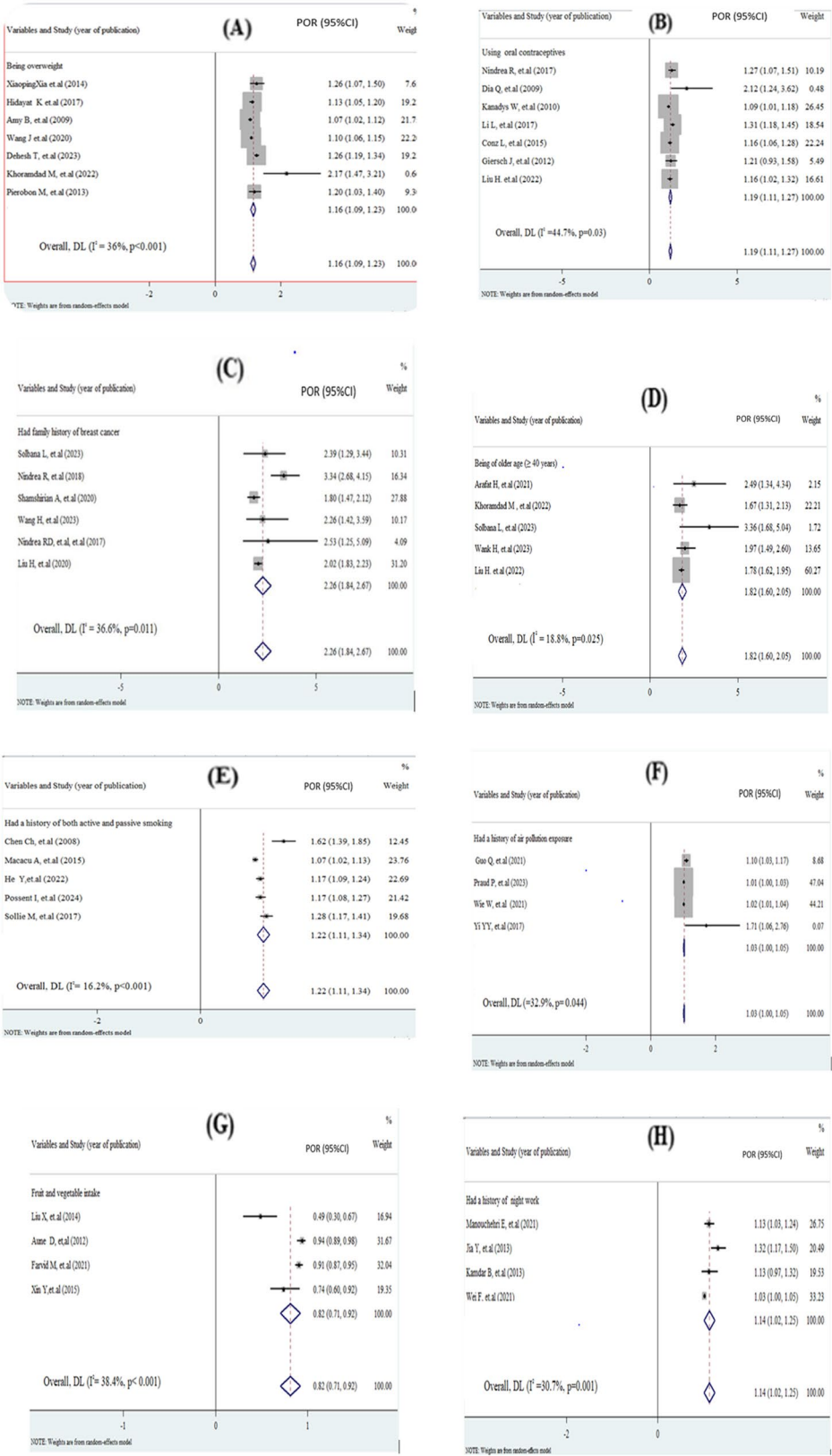
in women with a history of cigarette smoking, both active and passive, compared to non-smokers. This increased risk is likely due to carcinogenic compounds in tobacco smoke that can initiate or promote tumor development. Smoking is also associated with poorer breast cancer outcomes, including higher mortality and recurrence rates. These findings align with existing literature, which consistently shows a significant link between smoking and increased breast cancer risk in women with any history of tobacco exposure [73, 75–77].

This umbrella review found that four meta-analyses reported a 3% increase in the odds of developing breast cancer among women exposed to air pollution, particularly fine particulate matter (PM<sub>2.5</sub>), compared to those unexposed. This association may be due to PM<sub>2.5</sub>'s ability to penetrate deep into the lungs, enter the bloodstream, and potentially affect breast tissue. Air pollutants may also disrupt the structure and function of breast tissue. Previous reviews have observed a stronger link between PM<sub>2.5</sub> exposure and estrogen receptor-positive (ER+) breast cancer, suggesting that PM<sub>2.5</sub> may promote carcinogenesis through endocrine-disrupting mechanisms, but not in estrogen receptor-negative (ER-) subtypes [78–81].

Our synthesis of four meta-analyses of observational studies shows that higher fruit and vegetable intake is associated with an 18% reduction in the odds of developing breast cancer. While the evidence remains somewhat mixed, partly due to the diverse nature of breast cancer subtypes, this inverse relationship may be attributed to the presence of anti-carcinogenic compounds such as dietary fiber, vitamins C and E, and carotenoids. Several studies also support that increased fruit and vegetable consumption, especially among women with initially low intake, is linked to a reduced risk of breast cancer [82–85].

A synthesis of four meta-analyses revealed that women with a history of night work had a 14% higher risk of developing breast cancer compared to those without such exposure. This association may be explained by the disruption of circadian rhythms due to light exposure at night, which suppresses melatonin production. Reduced melatonin levels can, in turn, lead to increased estrogen production, a known risk factor for hormone-related cancers such as breast cancer. These findings are consistent with prior research, which has similarly identified an elevated breast cancer risk among women engaged in night shift work and exposed to artificial light during nighttime hours [86–88].

Lastly, based on the present review, specific intervention strategies tailored to the identified breast cancer determinants include community-based awareness campaigns, targeted screening initiatives, and risk-reduction programs such as lifestyle modifications. We have also



**Fig. 6** A through D illustrates selected determinants of breast cancer identified in the umbrella review ( $n = 35$ ). E through H, illustrates the determinants of breast cancer identified in Umbrella Review, 2024 ( $n = 35$ )

addressed implementation considerations in resource-limited settings by emphasizing the importance of leveraging existing primary healthcare infrastructure, integrating interventions into ongoing public health programs, and prioritizing cost-effective, culturally sensitive approaches. These additions aim to provide actionable insights for policymakers and healthcare practitioners.

### Implications of the study

This umbrella review emphasizes the importance of synthesizing summary evidence, particularly in regions where existing meta-analyses have produced inconclusive results—an issue particularly relevant in low-, middle-, and upper-middle-income countries. By providing a comprehensive assessment of breast cancer risk factors, this review offers practical insights for clinicians, policymakers, and stakeholders involved in women's health planning. For example, studies from sub-Saharan Africa and South Asia highlight the increasing burden of late-stage diagnoses and limited access to screening, often driven by socioeconomic factors, educational inequalities, and gaps in healthcare infrastructure [89, 90].

The findings underscore the need for future systematic reviews to explore additional, potentially region-specific risk factors, such as environmental exposures or cultural norms influencing health-seeking behavior [91, 92]. Furthermore, this review reinforces the significance of identifying consistently associated determinants—such as age, obesity, reproductive factors, and genetic predisposition—to guide targeted prevention strategies.

Health education remains a cornerstone intervention, especially in regions like Latin America and Southeast Asia, where community health worker engagement has shown promise in raising awareness and improving early detection [93, 94]. Emphasis must also be placed on expanding outreach into underserved and remote areas, where barriers to care are highest, and on promoting awareness among women, particularly mothers, about modifiable risk factors and effective mitigation strategies tailored to local contexts [95–97].

### Strengths and limitations of the study

This umbrella review has several key strengths. First, it minimized bias through comprehensive searches across multiple databases and independent study selection by four researchers. Second, it included studies published up to 2024 and used standardized quality assessment tools to ensure methodological rigor. These steps strengthen the credibility of the findings and increase their acceptance within the scientific community, particularly given the review's adherence to internationally recognized guidelines like PRISMA and AMSTAR. Third, by including studies from a broad geographical range—including low-, middle-, and upper-middle-income countries—the

review enhances the representativeness and policy relevance of the evidence, particularly for regions that are often underrepresented in global cancer research.

Limitations should be acknowledged. Despite a thorough search, some relevant studies may have been missed, which is a common limitation in literature reviews. Most studies were from middle- and upper-middle-income countries, limiting generalizability. Variations in study design and potential publication bias also affect the reliability of the findings.

### Conclusions and recommendations

This umbrella review identified eight key breast cancer risk factors. Non-modifiable factors like age  $\geq 40$  and family history, along with modifiable factors such as overweight, smoking, oral contraceptive use, air pollution, and night shift work, increased the odds of developing breast cancer. Notably, adequate fruit and vegetable intake was linked to reduced odds, suggesting a protective effect. These findings highlight the importance of standardized research methods and the need for evidence-based prevention strategies. We recommend that public health strategies promote healthy lifestyles and target high-risk groups through early screening and awareness campaigns, using evidence-based interventions and policy measures to reduce the breast cancer burden. Key priorities should include promoting early detection through antenatal and postnatal health services. Additionally, larger longitudinal and experimental studies are needed to further validate these associations.

### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12885-025-14499-w>.

Supplementary Material 1.

Supplementary Material 2.

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### Authors' contributions

All authors participated in data extraction, critical appraisal, analysis, drafting, or revising the article, approved the final version for publication, and agreed to be accountable for the work. Conceptualization: MBD. Data curation: MBD, MM, and DZ. Formal analysis: MBD, DZ, and KB. Investigation: MBD, KB and DZ. Methodology: MBD, AB, BF, CA and MH. Software: MBD, and DZ. Validation: AB and MH. Visualization: MBD, KB, and CA. Writing original draft: MBD, BF, CA and DZ. Writing—review and editing: MBD, BF, CA and KB.

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### Data availability

Data reported in this manuscript are available from the corresponding author on reasonable request.

# Declarations

## Ethics approval and consent to participate

No ethical approval was needed because the data was collected and analyzed from previously reported research where informed consent had been obtained from participants.

## Consent for publication

Not applicable.

## Competing interests

The authors declare no competing interests.

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