Review

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Assessing Lead Exposure by Biological Matrices Analysis and Links to Breast Cancer: A Critical Review of Experimental and Epidemiological Findings

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ABSTRACT

Lead (Pb), a ubiquitous environmental contaminant, is a toxic heavy metal known to interfere with enzymatic and hormonal processes. Its classification as a probable human carcinogen by international agencies has raised concerns about its potential role in cancer, including breast cancer (BC). This review critically examines epidemiological and experimental evidence linking Pb exposure to BC, emphasizing the impact of biological matrices used for Pb measurement on the consistency of findings. A systematic review following PRISMA guidelines was conducted. Eligible studies quantified Pb in breast tissues, blood, urine, hair, or toenails and assessed its association with BC risk. Animal studies and non-English publications were excluded. Twenty-seven studies (described in 23 publications) quantified Pb in human biological matrices: breast tissue (n = 6), urine (n = 6), blood (n = 9), hair (n = 4), and toenail (n = 2). Among them, 16 reported a positive association between Pb and BC risk (breast tissues: 4; urine: 3; blood: 6; hair: 3; toenails: 0). By contrast, 11 studies found no significant correlation (breast tissues: 2; urine: 3; blood: 3; hair: 1; toenail: 2). Four studies quantified Pb in different matrices, and the same results were obtained from analyses of breast tissue, blood, and hair. Discrepancies across studies included small sample sizes, heterogeneous demographic characteristics, insufficient follow-up, and different Pb assessment methods. While the majority of studies suggest a potential link between Pb exposure and BC, significant heterogeneity in study design and population selection limits definitive conclusions. Future research should standardize Pb measurement protocols in selected populations and explore mechanistic pathways to clarify this potential association and improve prevention strategies.

Keywords: Lead exposure; breast cancer; heavy metals; endocrine disruptors; biological matrices; environmental carcinogens

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Key Points

- Lead (Pb), a ubiquitous environmental contaminant, is a toxic heavy metal known to interfere with enzymatic and hormonal processes.
- The classification of lead as a probable human carcinogen by international agencies has raised concerns about its potential role in cancer, including breast cancer (BC).
- In our review, the majority of studies suggest a link between Pb exposure and BC.
- Future research should standardize Pb measurement protocols in selected populations and explore mechanistic pathways to clarify this potential association and improve prevention strategies.

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Introduction

Lead (Pb) is a heavy metal with the symbol Pb and atomic number 82. Lead is one of the densest metals (density: 11.34 g/cm^3) and has a long history of industrial use because of its malleability and high density (1). Although it has been phased out of many applications, such as paint and gasoline, it remains a pervasive environmental pollutant. Pb can persist in soil, dust, and water, leading to chronic human exposure through inhalation or ingestion (2, 3).

Pb exerts toxic effects even at low levels. It disrupts key biological processes, including heme synthesis and neurotransmission, and contributes to anemia and neurodevelopmental impairments (4, 5). Children and pregnant women are particularly vulnerable, as Pb crosses the placenta and affects fetal development (6-8). Chronic exposure may also impair the renal and reproductive systems (4). Acute or chronic Pb poisoning, whether domestic or occupational, is a serious condition, also called lead poisoning or saturnism. Blood lead level (BLL) is the most commonly used biomarker to assess lead exposure; the intervention threshold for children is set at 50 µg/L in most countries. Lead poisoning has long been recognized as an occupational disease. Due to higher Pb absorption in women, there are sex-specific occupational exposure limits (400 µg/L for men and 300 µg/L for women), making lead the only substance with different adult exposure limits by sex (9, 10).

Over the past decades, Pb has been scrutinized for its potential carcinogenicity. The U.S. Environmental Protection Agency and the U.S. Department of Health and Human Services have classified Pb compounds as probable or reasonably anticipated human carcinogens (11, 12). The International Agency for Research on Cancer classifies inorganic Pb as probably carcinogenic to humans (group 2A), based on sufficient evidence in animals and limited evidence in humans (13). Experimental findings suggest that Pb may act as a metallo-estrogen, mimicking estrogenic activity, promoting oxidative stress, inducing DNA damage, and influencing epigenetic regulation (14).

Given that breast cancer (BC) is a hormone-sensitive malignancy (15) and the leading cause of cancer-related death in women worldwide, interest has grown in investigating whether Pb contributes to BC development. Several studies have reported elevated Pb concentrations in BC patients (16-19), yet findings remain inconsistent, possibly due to differences in Pb measurement methods, the biological matrices used (e.g., blood, urine, hair, breast tissue, and toenails), and the study populations (20-25).

This review aimed to critically evaluate current experimental and epidemiological data on the relationship between Pb exposure and BC risk. A secondary goal was to assess the reliability of different biological matrices as biomarkers of Pb exposure, to guide future research and potential public health interventions.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (26).

Eligibility Criteria

We included prospective and retrospective cohort studies, case-control studies, and meta-analyses published in English before January 5, 2024. Eligible studies were required to assess the association between Pb exposure (occupational or non-occupational) and BC incidence, or to report Pb concentrations in biological matrices, including breast tissue, blood, urine, hair, and toenails. Animal studies, case reports, reviews, editorials, and studies published in languages other than English were excluded.

Search Strategy

A comprehensive literature search was performed in the PubMed, Scopus, and Web of Science databases through January 5, 2024, following PRISMA 2020 guidelines. The final search strategy combined controlled vocabulary (MeSH terms) and free-text keywords to maximize sensitivity.

PubMed search string:

((“lead”[MeSH Terms] OR “heavy metals”[MeSH Terms]) AND (“breast cancer”[MeSH Terms] OR “breast carcinoma”[All Fields] OR “mammary carcinoma”[All Fields] OR “mammary neoplasm”[All Fields])).

Scopus search string:

TITLE-ABS-KEY [(“lead” OR “Pb”) AND (“breast cancer” OR “breast carcinoma” OR “mammary carcinoma” OR “mammary neoplasm”)].

Study Selection and Data Extraction

Two reviewers (A.M. and S.E.B.) independently screened all titles, abstracts, and full texts for eligibility. Discrepancies between the two reviewers were resolved through discussion and consensus. When consensus could not be reached, a third reviewer (C.M. or M.G.) acted as an arbitrator. Full texts of eligible articles were reviewed in detail. Data extracted from each study included the first author, publication year, country of study, study design, population characteristics (sample size, age, recruitment period), biological matrix analyzed, and main findings. Only human studies were included.

Data Synthesis

Studies were categorized based on epidemiological data and/or the biological matrix used for Pb quantification. Results were synthesized narratively, and the strength of the association between Pb exposure and BC was assessed based on reported statistical significance. No meta-analysis was performed due to heterogeneity in study designs, Pb measurement methods, and outcome definitions.

All included case–control and cohort studies were evaluated using the Newcastle–Ottawa Scale, which assesses (Supplementary Table 1):

• Selection (0–4 points): representativeness of cases, selection of controls, ascertainment of exposure.

• Comparability (0–2 points): control for confounding factors (age, smoking, menopausal status).

• Exposure/Outcome (0–3 points): method of ascertainment, same method for cases and controls, non-response rate.

Results

Figure 1 presents the flowchart of the literature search and identification of relevant studies. A total of 27 studies (described in 23 publications) assessed the relationship between Pb content in biological matrices and BC risk (including one study on male BC and three studies where the gender of participants was not specified) (Figure 2).

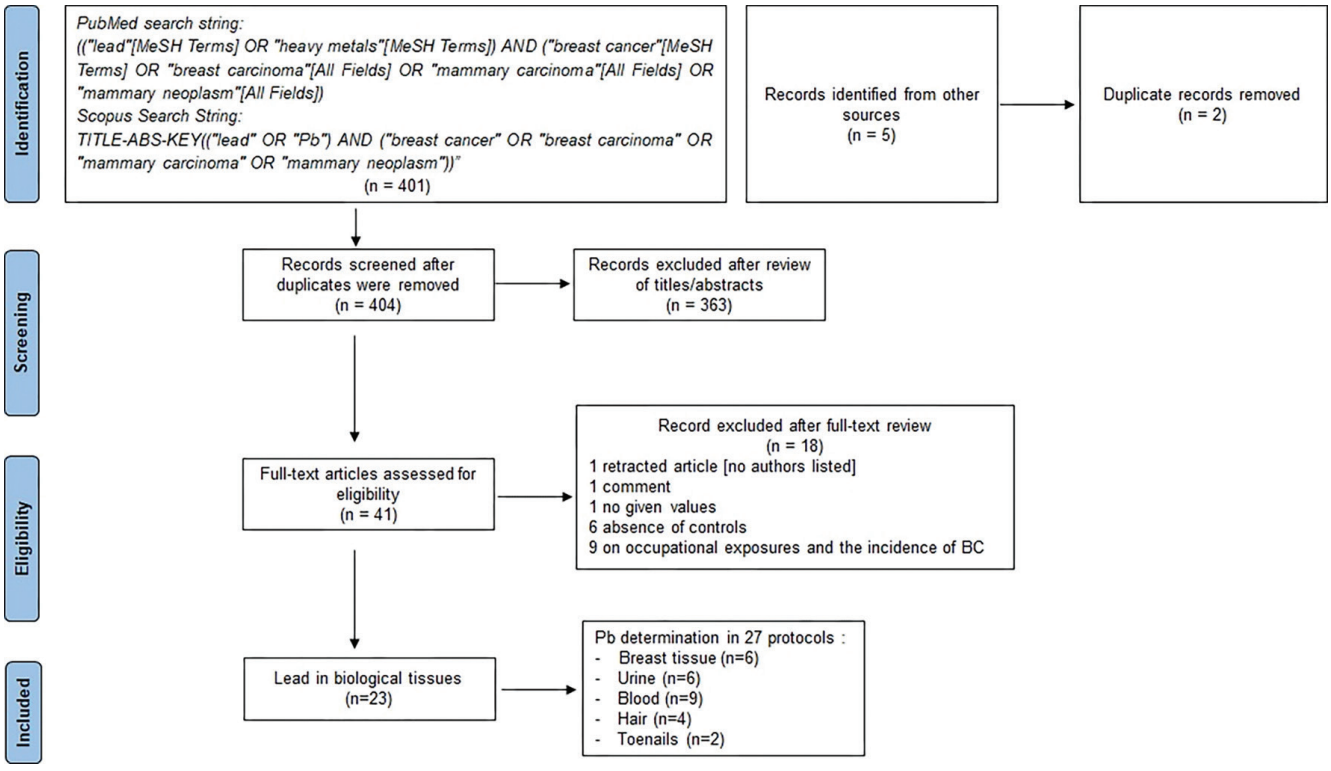

Figure 1. PRISMA flow chart of the procedure used to select the articles included in this review

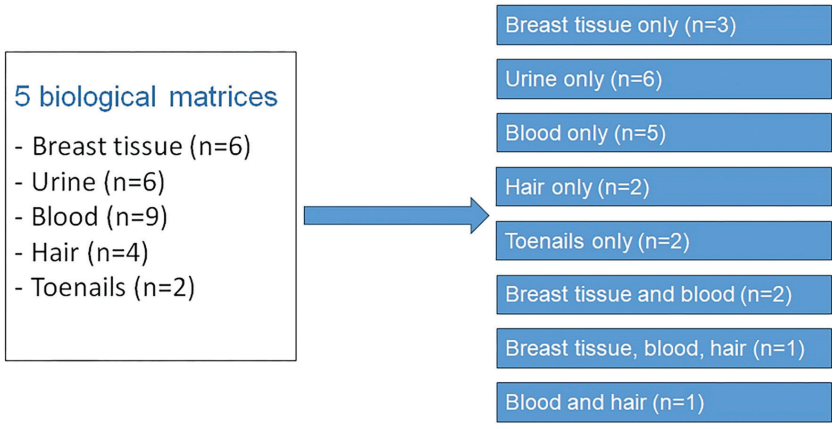

Figure 2. Pb determination in 23 publications including 27 protocols

Lead in Breast Tissues

Six studies (16-18, 20, 27, 28) analyzed Pb concentrations in breast tissue samples from BC patients and controls (Table 1a). Four of these studies reported significantly higher Pb levels in cancerous tissues (16-18, 28), suggesting a potential association with malignancy. For example, in 2006, Ionescu et al. (17) reported levels of 105 µg/kg in BC tissue versus 64 µg/kg. In 2022, Mansouri et al. (16) confirmed these findings, reporting a mean Pb concentration of 13.1 µg/kg in BC tissue versus 6.4 µg/kg in controls.

In contrast, two studies did not observe significant differences between cancerous and non-cancerous tissues. For example, Santoliquido et al. (27) found mean Pb levels of 0.60 µg/g in cancerous tissue compared to 0.68 µg/g in non-cancerous tissue, suggesting no notable variation. Recently, Anđelković et al. (20) investigated Pb levels in three types of operative specimens: benign breast lesions, malignant breast lesions, and surrounding tissue. The study included 55 women treated for BC. The control group consisted of 41 women with benign breast tumors. Pb levels were significantly higher in surrounding tissues than in tumors for both groups, but no significant differences in Pb levels were observed between the control and BC groups (Table 1a).

Two studies (19, 23), not included in our review (no control group), analyzed Pb concentration in surgical specimens obtained from BC patients treated for invasive ductal carcinoma and showed no significant differences between tumor and surrounding tissues.

Lead in Urine

Six studies evaluated urinary Pb levels in BC patients and controls (Table 1b). Three studies found significantly higher Pb concentrations in BC patients (29-31). In 2016, Burton et al. (31) reported significantly higher levels of Pb and Cu in BC patients, supporting their potential role as risk factors. Hu et al. (29), using NHANES data involving

2,795 women, reported a positive association between urinary Pb and BC in 2023, with an odds ratio of 2.22. Similarly, Bell et al. (30) (NHANES 2007–2016), published in 2023, reported significantly higher Pb levels in BC patients compared to healthy controls, with the highest Pb quartile showing a nearly threefold higher BC prevalence.

By contrast, McElroy et al. (22) found no association between urinary Pb and BC among women in Wisconsin. Interestingly, Men et al. (25) found no significant difference in Pb levels in BC patients, but they suggested a potential link between some other heavy metals and BC. Likewise, Mérida-Ortega et al. (32) reported no significant differences in Pb levels among BC patients in Northern Mexico, but identified metal combinations influencing postmenopausal BC risk.

Lead in Blood

Among nine studies assessing BLLs (Table 1c), six found a positive association with BC (18, 19, 33-36). For example, Siddiqui et al. (18) found significantly higher BLLs in malignant cases (20.33 µg/dL) than in benign cases (13.10 µg/dL) and in control subjects (6.14 µg/dL). Alatise and Schrauzer (19) found elevated BLLs that correlated with Pb content in breast tissue and hair, suggesting chronic exposure. Li et al. (35) observed significantly higher Pb levels in BC patients, along with arsenic, cadmium, and chromium, suggesting that environmental exposure to these metals might contribute to BC development. Wei and Zhu (36) also found significantly higher Pb levels in BC patients, supporting the hypothesis that Pb may contribute to BC through direct and indirect mechanisms. In 2024, Fernández-Martínez et al. (33) conducted a case-control study within the European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain cohort that analyzed metal exposure in 292 BC cases and 286 controls. Even though the values reported in their manuscript are similar between BC patients and controls, they found that high levels of certain metals, including Pb, were associated with an increased risk of BC, particularly in early-stage disease. Their analysis indicated a fourfold increase in BC risk associated with a specific metal exposure profile (33). Afridi et al. (34) studied male BC (MBC) patients and found elevated Pb levels in blood and serum compared to healthy males.

In contrast, in 2019, Gaudet et al. (37) found no association between Pb levels and BC risk in three cohorts from the USA, Italy, and Sweden. Similarly, Anđelković et al. (20) in 2022 compared BLLs between BC patients and healthy women, and found no significant difference. In 2023, Caini et al. (21) published the results of a nested case-control study within the Florence EPIC cohort, measuring six heavy metals in never-smokers. No significant association was found between Pb levels and BC risk.

Table 1a. Lead levels in breast tissue

Study	Country	*n* (cases/ controls)*	Pb in breast cancer cases	Pb in controls	Association	Conclusion
Anđelković et al. (20)	Serbia	55/41	91.89 ng/g	106.32 ng/g	No	Slight difference
Mansouri et al. (16)	Iran	63/63	13.1 µg/kg	6.4 µg/kg	Yes	Higher in malignant tissue
Ionescu et al. (17)	Czech Rep Germany	20/8	105 µg/kg	64 µg/kg	Yes	Higher in malignant tissue
Siddiqui et al. (18)	India	25/25	0.54 µg/g	0.40 µg/g	Yes	Higher in malignant tissue
Rizk and Sky-Peck (28)	ND	25/25	1.55 µg/g	1.33 µg/g	Yes	Higher in malignant tissue
Alatise and Schrauzer (19)	Nigeria	12/12**	0.11 µg/g	0.10 µg/g	No	Similar levels
Santoliquido et al. (27)	ND	20/20	0.60 µg/g	0.68 µg/g	No	Similar levels

*Controls are not considered when provided from the same breast with tumor
**No control for breast tissues

Table 1b. Lead in urine

Study	Country	*n* (cases/ controls)*	Pb in breast cancer (BC) cases	Pb in controls	Association	Conclusion
Hu et al. (29)	USA	210/2585	0.48 µg/L	0.37µg/L	Yes	Higher in BC patients
Bell et al. (30)	USA	106/3246	0.62 µg/g-creatinine	0.42 µg/g-creatinine	Yes	Higher in BC patients
Mérida-Ortega et al. (32)	Mexico	452/439	2.71 µg/g-creatinine	2.99 µg/g-creatinine	No	Slight difference
Men et al. (25)	China	106/38	75.0 µg/L	75.0 µg/L	No	Similar levels
Burton et al. (31)	USA	52/79	0.578 µg/L	0.388 µg/L	Yes	Higher in BC patients
McElroy et al. (22)	USA	246/254	0.86 µg/L	0.64 µg/L	No	Slight difference

*Controls are not considered when provided from the same breast with tumor
**No control for breast tissues

Lead in Hair

Four studies analyzed Pb in hair samples. Three of them reported significantly higher levels in BC patients (19, 34, 38). In 2010, in Nigeria, Alatise and Schrauzer (19) observed elevated Pb levels in BC patients (23.6 µg/g) compared to controls (10.3 µg/g). In India in 2014, Blaurock-Busch et al. (38) reported higher Pb concentrations in BC patients (11.42 µg/g) than in controls (2.15 µg/g), suggesting that Pb is a potential factor in BC development. Afridi et al. (34) reported significantly higher Pb levels in MBC patients (8.29±0.72 µg/g) than in healthy males (4.36±0.65 µg/g). In contrast, in Türkiye in 2011, Benderli Cihan et al. (39) found lower Pb levels in BC patients (3.794 µg/g) than in controls (6.196 µg/g), contradicting previous findings (Table 1d).

Lead in Toenails

In 2019, two studies by O'Brien et al. (40, 41), conducted in the USA, measured Pb in toenail samples and found no significant association with BC (Table 1e).

Table 1c. Lead in blood

Study	Country	*n* (cases/ controls)*	Pb in breast cancer (BC) cases	Pb in controls	Association	Conclusion
Fernández-Martínez et al. (33)	Spain	292/286	0.23 ng/mL	0.22 ng/mL	No	Slight difference
Caini et al. (21)	Italy	150/150	1.70 µg/L	1.70 µg/L	No	Similar levels
Anđelković et al. (20)	Serbia	55/41	1.17 µg/dL	1.36 µg/dL	No	Slight difference
Afridi et al. (34)	Pakistan	14/37	528 µg/L	239 µg/L	Yes	Higher in BC patients
Li et al. (35)	China	105/35	24.3 µg/L	16.0 µg/L	Yes	Higher in BC patients
Wei and Zhu (36)	USA	284/8976	1.52 µg/dL	1.08 µg/dL	Yes	Higher in BC patients
Alatise and Schrauzer (19)	Nigeria	12/12**	6.1 µg/dL	5.0 µg/dL	Yes	Higher in BC patients
Siddiqui et al. (18)	India	25/25	20.33 µg/dL	6.14 µg/dL	Yes	Higher in BC patients
Gaudet et al. (37)	USA	816/816	ND	ND	No	After the authors
	Italy	294/292				
	Sweden	325/325				

*Controls are not considered when provided from the same breast with tumor
**No control for breast tissues

Table 1d. Lead in hair

Study	Country	*n* (cases/ controls)*	Pb in in breast cancer (BC) cases	Pb in controls	Association	Conclusion
Afridi et al. (34)	Pakistan	14/37	8.29 µg/g	4.36 µg/g	Yes	Higher in BC patients
Blaurock-Busch et al. (38)	India	15/50	11.42 µg/g	2.15 µg/g	Yes	Higher in BC patients
Alatise and Schrauzer (19)	Nigeria	12/12**	23.6 µg/g	10.3 µg/g	Yes	Higher in BC patients
Benderli Cihan et al. (39)	Türkiye	52/52	3.794 µg/g	6.196 µg/g	No	Higher in healthy patients

*Controls are not considered when provided from the same breast with tumor
**No control for breast tissues

Table 1e. Lead in toenails

Study	Country	*n* (cases/ controls)*	Pb in breast cancer cases	Pb in controls	Association	Conclusion
O'Brien et al. (40)	USA	1217/1217	0.144 µg/g	0.134 µg/g	No	Slight difference
O'Brien et al. (41)	USA	111/110	0.117 µg/g	0.111 µg/g	No	Slight difference

*Controls are not considered when provided from the same breast with tumor
**No control for breast tissues

Discussion and Conclusion

In our review investigating the potential link between Pb exposure and BC risk, 16 of 27 studies that measured Pb in biological matrices, published in 23 manuscripts (16-22, 25, 27-41), reported an association between high Pb levels and BC. Among these 16 studies, 4 of 6 studies on breast tissue (16-18, 28), 3 of 6 studies on urine (29-31), 6 of 9 studies on blood (18, 19, 33-36), 3 of 4 studies on hair (19, 34, 38) reported a link between elevated Pb levels and risk of BC. The other 11 series reported no association: breast tissue in 2 publications (20, 27); urine in 3 publications (22, 25, 32); blood in 3 publications (20, 21, 37); hair in one publication (39); and toenails in 2 publications (40, 41).

These discrepancies can be explained by different hypotheses concerning the included populations, the type of BC, and the choice of biological matrix for Pb measurement.

Populations Included in Our Review

Age and hormonal status of participants vary considerably across the included series, whereas BC mainly affects menopausal women. This discrepancy in results could also arise from the diversity of countries in which the studies were conducted (China, India, Nigeria, European countries, USA). Moreover, two studies did not specify the sex of the participants (17, 28), and a third study (38) found a link between Pb in hair and BC in a mixed cohort. The number of participants varied widely, ranging from 12 to 816, with six studies having fewer than 50 participants. Finally, some publications did not mention follow-up; only one reported a follow-up of 25 years (33).

The Type and Characteristics of the BC

Histological BC characteristics are not always reported in sufficient detail to determine whether Pb could be linked to particular types of BC. For example, the study by Alatise and Schrauzer (19) found a link between Pb in breast tissues, blood, and hair, and infiltrating ductal carcinoma. Hu et al. (29) reported an association between Pb in urine and hormone-dependent BC in a study of 210 women in the USA. Burton et al. (31) mentioned in their publication that high urinary Pb levels may be associated with advanced stages of BC in women. These distinctions are critical, as Pb may not influence all BC types equally.

Pb Measurement Protocols

Concerning Pb measurement protocols, some studies analyzed Pb alone; others analyzed different metals, including Pb. For example, Mérida-Ortega et al. (32) studied the cocktail effect and the interactions of Pb and other metals in urine and their association with BC, showing that a mixture of metals (Sn, Cr, Ni, Sb, Al, and Pb) could be linked to BC in postmenopausal women. Such interactions may be crucial to understanding Pb's role as a co-carcinogen in environmental exposure contexts.

The Choice of the Biological Matrix

Regarding biological matrices, four studies permit comparison of Pb determination across different matrices: breast tissue and blood (18, 20); breast tissue, blood, and hair (19); and blood and hair (34). The results of these studies were comparable and led to the same conclusions. Except for toenails, all biological matrices appear to be conclusive. However, considering the lifetime of Pb in the body, urine and blood could indicate recent Pb exposure (42). In contrast, hair (43) and toenails (44) provide information on Pb exposure over the past few months. The only matrix that appears to reflect both past and recent Pb exposure is breast tissue.

In our review, two studies (40, 41) examined Pb levels in toenails and did not find a significant association between Pb and BC. These dosages had not been compared with dosages in other matrices. Consequently, it is difficult to determine whether toenails are a reliable biological matrix for studying the links between BC and heavy metals, including Pb.

Studies with Link Between Elevated Pb Level and BC Risk

Considering these limitations, when we included only well-designed studies that used four biological matrices (breast tissue, urine, blood, and hair), selected appropriate participant demographics, and excluded multi-metal exposure, the majority of studies (16/25) concluded that Pb exposure is associated with an increased risk of BC.

The BC incidence for each country, corresponding to the study year when available, is presented in Supplementary Table 2. Otherwise, we included the 2022 incidence data from GLOBOCAN. We have also included in this table the acceptable limits for lead in each country mentioned in this review (BLL and acceptable levels in drinking water), and the dates on which these values came into effect (45-58). The review's data show no consistent cross-country relationship between measured Pb concentrations in BC samples and national BC incidence. High-incidence countries (the USA, Italy, and Spain) typically exhibit low Pb concentrations in biological samples. Developing countries (India, Nigeria, and Pakistan) often exhibit higher Pb levels in patient specimens, yet BC incidence is lower. These discrepancies reflect methodological, environmental, and demographic differences, rather than a true causal Pb-BC relationship. The observed variations are more likely due to differences in study design, biological matrices, laboratory techniques, and population characteristics than to a direct causal link between Pb and BC incidence.

Table 2. Summary of strength of association between Pb levels and breast cancer by biological matrix

Biological matrix	Number of studies	Association	Interpretation
Breast tissue	6	4 positive, 2 null	Consistent relationship
Urine	6	3 positive, 3 null	Inconsistent
Blood	9	5 positive, 4 null	Stronger in high-exposure regions
Hair	4	3 positive, 1 null	Tendency toward positive association
Teonails	2	2 null	No consistent relationship
Overall	27	15 positive, 12 null	No consistent global relationship

When Comparing all available numerical data, Pb concentrations measured in BC specimens are generally lower in studies conducted after 2000 than in those before 2000.

In the studies before 2000 [Santiliquido (1976), Rizk (1984), Ionescu (2006), Siddiqui (2006) and Alatise (2010)]. Although published after 2000, these early studies used specimens collected before 2000 or before local Pb regulation took effect)), the observed ranges were:

• Breast tissue: 0.6–105 µg/kg (median = 50 µg/kg)

• Blood = 20 µg/dL

• Hair = 20 µg/g

Wheras in the studies after 2000 [Mansouri (2022), Andelkovic (2022), Afridi (2021), Li (2020), Wei (2019), Hu (2023), Bell (2023), Merida-Ortega (2022) and Benderli Cihan (2011)], the observed ranges were:

• Breast tissue = 0.09–13 µg/kg (median = 10 µg/kg)

• Blood =1.5–53 µg/dL (median = 2 µg/dL excluding Pakistan outlier)

• Hair = 3.8–8 µg/g

• Urine = 0.5–3 µg/L or µg/g creatinine

This temporal decrease aligns with the timeline of international lead-exposure regulations and environmental phase-outs. Nonetheless, the decline is not universal. Countries with weaker enforcement of environmental regulations or with ongoing environmental contamination (e.g., parts of South Asia or Africa) still report relatively high Pb levels among cancer patients.

A summary of interpretations (Table 2) shows that studies in high-exposure regions (e.g., Pakistan, India, Nigeria) reported positive associations between Pb concentrations in breast tissue, urine, blood, and hair and BC, whereas studies in low-exposure or post-regulation settings (e.g., USA, Europe) mostly reported null findings. The overall evidence remains inconsistent across matrices and study designs.

We find concordance between our results and those presented in this review and by Coradduzza et al. (59), indicating a link between Pb exposure and BC, particularly in blood samples. Consistent with our review, Coradduzza et al. (59) reported higher levels of Pb in biological samples from BC patients than in healthy controls. In plasma samples, Pb levels were 1.52-fold higher in BC patients than in controls. This suggests that exposure to Pb may influence blood lipid levels and other small-molecule metabolites involved in BC development.

Contrary to our findings in urine samples, studies investigating heavy metals in the urine of BC patients have shown that environmental exposure to Pb, together with Cd and Cr, may contribute to BC development (59).

Finally, consistent with our observations in hair samples, some studies on BC patients have reported higher levels of several elements in hair; nevertheless, the specific association of Pb levels in hair with BC appears less prominent than that of other metals (59).

In these studies, Pb exposure has been implicated in BC through various mechanisms, primarily due to its role as an endocrine disruptor and its ability to cause DNA damage. Pb can mimic estrogen, a hormone that plays a significant role in BC development, by activating estrogen receptors and promoting cell proliferation. This activity is similar to that of natural estrogens and can lead to increased expression of estrogen-regulated genes, contributing to tumor growth (60, 61).

Research on the mechanism involving Pb in BC is sparse. However, the predominant findings suggest a strong correlation between Pb and the pathogenesis of BC. Pb exerts a notable influence on both the expression and functionality of ERα. It promotes the proliferation of MCF-7 cells, reduces the steady-state levels of ERα protein and mRNA, triggers the activation of two estrogen-regulated genes, the progesterone receptor and pS2, and stimulates ERα in transient transfection assays (61). Figure 3 shows the mechanistic pathway of Pb-induced ER signaling activation (62, 63).

Furthermore, Pb, a nonessential metal, can mimic or interfere with the function of essential metals, leading to toxicity associated with BC (62, 64-66).

Additional research into the relationship between lead exposure and BC is justified. This should encompass studies tailored to specific geographic regions, extensive longitudinal investigations, and mechanistic analyses, all aimed at uncovering the pathways by which Pb exposure influences estrogen receptor signaling and promotes breast carcinogenesis. Exploring the interplay between non-essential lead and essential metals in BC development is also recommended (67).

Pb can also cause direct DNA damage and generate reactive oxygen species, leading to oxidative stress and potential mutations in breast cells. This damage can contribute to carcinogenesis by altering gene expression and inhibiting DNA repair mechanisms (68). Finally, Pb exposure may result in epigenetic modifications, such as altered gene expression caused by the displacement of zinc from transcriptional regulators. This can affect the regulation of genes involved in cell growth and differentiation, further promoting cancer development (68).

While substantial evidence links Pb exposure to BC, the relationship is not entirely straightforward. Additionally, interactions between Pb with other metals and nutrients, such as selenium, can influence its carcinogenic potential. Selenium, known for its anti-carcinogenic properties, can be antagonized by Pb, potentially exacerbating cancer risk (19).

The relationship between Pb and BC is complex and influenced by various factors, including environmental exposure levels and

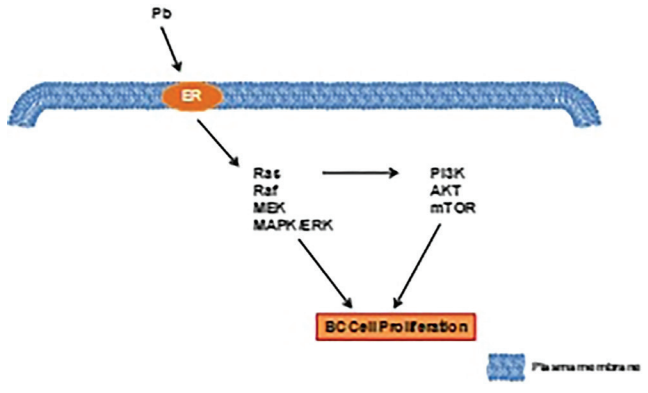

Figure 3. Signaling pathways involved in the associations between Pb and breast cancer

individual biological responses. Therefore, further research is needed to fully understand the mechanisms underlying potential Pb toxicity in BC cells.

While a majority of the reviewed studies suggest a potential association, particularly when Pb is measured in breast tissue, blood, urine, and hair, substantial variability in findings persists across different study designs. These inconsistencies underscore the importance of future studies that should prioritize larger cohorts, consider tumor heterogeneity, include both sexes and perform sex-stratified analyses, and account for cumulative exposures and metal interactions. Furthermore, prospective longitudinal studies with long-term follow-up are needed to strengthen causal inference and clarify the temporal relationship between Pb exposure and BC occurrence. Understanding the mechanisms by which Pb may influence BC development, such as endocrine disruption, oxidative stress, and epigenetic alterations, could inform more targeted public health prevention strategies.

Footnotes

Authorship Contributions

Concept: A.M., S.E.B., M.G., C.M.; Design: A.M., S.E.B., M.G., C.M.; Data Collection or Processing: A.M., S.E.B., M.G., C.M.; Analysis or Interpretation: A.M., S.E.B., M.G., C.M.; Writing: A.M., S.E.B., M.G., C.M.

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