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# Impact of heavy metals on breast cancer (Review)

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**Abstract.** Breast cancer is characterized by the uncontrollable proliferation and dissemination of abnormal cells in the mammary glands. It is a significant cause of mortality among women, with approximately one in eight females experiencing a breast cancer diagnosis in their lifetime. Multiple factors contribute to an elevated risk of developing breast cancer, encompassing sex, lifestyle choices, age, hormone usage, familial predisposition and exposure to environmental pollutants. Environmental pollution refers to the contamination of various components of the Earth's atmosphere, biology and physical systems. Heavy metal pollutants include copper (Cu), cadmium (Cd), nickel (Ni), lead (Pb), zinc (Zn) and manganese (Mn). Exposure to toxic heavy metals through inhalation, skin contact and ingestion poses significant risks to human health and organ function, including the breasts. Essential heavy metals, such as Cu, Zn, cobalt (Co) and iron (Fe), play crucial roles in various biochemical and physiological processes within organisms. Various techniques have been employed to analyze heavy metals, including ultraviolet-visible spectrophotometry, inductively coupled plasma, flame atomic absorption spectrophotometry, graphite furnace atomic absorption spectroscopy, atomic emission spectroscopy and proton-induced X-ray emission. Recent studies have suggested an association between variations in heavy metal metabolism and the occurrence and progression of breast cancer in human populations. Some studies have found increased levels of Cu and Cd and decreased Zn and Mn concentrations in patients with breast cancer compared to individuals without breast cancer. The present review aimed to explore the link between heavy metal exposure and breast cancer, providing insight into its potential effects on breast health and the significance of this association. Overall, heavy metals directly affect human health, particularly as regards breast cancer.

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*Key words:* heavy metals, breast cancer, genetic condition, environmental pollution, family history, human health

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## 1. Introduction

Cancer, as a genetic disorder, arises from the uncontrolled proliferation of cells (1). The human body comprises numerous cells that typically grow, divide and undergo natural cell death throughout the lifetime of an individual (2). In breast tissue, there is an aberrant multiplication and alteration of cells, often resulting in the formation of a tumor or lump (3). The primary site of origin for the majority of breast cancer cases is the lobules, or the ducts, which can potentially develop in multiple anatomical locations within the breast (3). Breast cancer is the most common cancer among women in the USA, with ~268,600 new cases of the invasive disease reported in 2019, including 48,100 cases of ductal carcinoma *in situ*. This constitutes a significant proportion, ranging from 15.2 to 30% of all newly reported cancer cases among women, depending on the sources considered (4-6).

Additionally, breast cancer is the primary contributor to cancer-related mortality among women globally, resulting in a significant and alarming toll of 684,996 fatalities (7). Breast cancer has been shown to be associated with various factors, such as sex, obesity, nulliparity, smoking and alcohol consumption (8,9). Environmental pollution directly affects breast cancer and human health, with development-related activities such as construction, transportation and manufacturing depleting natural resources and generating extensive waste. This waste contributes to global issues, including acid rain, global warming and the release of heavy metals by causing contamination of the water, air, soil and oceans (10,11).

Humans are exposed to heavy metals, which have a high density and are harmful to living creatures, by ingestion or inhalation. Exposure to these metals occurs through working or residing near industrial sites that utilize them and by their compounds and living near improperly disposed metal sites (12). Understanding and addressing the possible health issues associated with exposure to heavy metals is crucial in various situations, considering the diverse range of heavy metals involved, such as transition metals, lanthanides, metalloids and actinides (13,14). Heavy metals and their effects on human health have emerged as a pressing public safety concern, since excessive and inadequate levels of these minerals can lead to various potential adverse health effects (15). In recent years, a growing body of evidence suggests an association between diverse heavy metal metabolic pathways and the pathogenesis of breast cancer. Lappano *et al* (16) demonstrated that cadmium (Cd) exerts estrogenic effects and promotes the growth of breast cancer. Heavy metals such as copper (Cu), manganese (Mn) and zinc (Zn) have been linked to the occurrence and spread of breast cancer through the reactive oxygen species (ROS) pathway (17). The primary aim of the present review was to elucidate the influence of distinct heavy metals on breast cancer through an examination of recent relevant studies.

## 2. Breast cancer

Breast cancer refers to the abnormal growth and uncontrolled multiplication of cells within breast tissues (18). It is classified into various types based on conventional microscopic and morphological examinations. The majority of cases of breast cancer are carcinomas, malignancies that begin in epithelial cells. Specifically, breast cancers often manifest as adenocarcinomas, a group of carcinomas derived from glandular epithelial tissues. In some instances, breast tumor cells may exhibit a combination of these types or transform from *in situ* cancer to invasive structures, as commonly observed. Invasive ductal and invasive lobular carcinomas are the most common types, with invasive ductal carcinomas forming 70-80% of all breast cancer cases (19). Certain invasive breast cancers exhibit distinct characteristics or follow diverse developmental pathways, influencing their treatment strategies and prognosis (20).

Breast cancer often begins with no noticeable signs or symptoms, typically becoming evident when a lump forms in the breast or when the cancer spreads. While new lumps are a common sign, the majority of these are non-cancerous. Breast cancers are more likely to be cancerous if they are painless, firm masses with irregular edges (21,22). Changes in size, shape, texture, and skin alterations like rash, dimpling, or redness can also occur. Itching or redness around the nipples may be present. Fluid discharge from the nipples, breast discomfort and inflammatory breast cancer, which causes pain, redness and inflammation, are less common symptoms (23-25).

Breast cancer is the most prevalent type of cancer among women, accounting for ~30% of new female cancer cases annually (26). It is typically diagnosed at ~60 years of age, with rare cases in women <45 years of age (27). In the USA, a woman's lifetime risk of developing breast cancer is ~13%, or one in eight women. Globally, there were >2.3 million new breast cancer cases and 685,000 fatalities in 2020 (26-28). The incidence and mortality rates vary greatly across countries and regions. By the year 2040, it is estimated that there will be 3 million new breast cancer cases each year, with a corresponding increase in mortality rates (26-29). Addressing this growing burden, particularly in developing countries with high incidence and mortality rates, is crucial (29). Racial and ethnic disparities in breast cancer diagnosis are evident, with women of African origin receiving diagnoses at a younger age (average of 60 years) and experiencing a higher mortality rate compared to Caucasian women (average of 63 years) (27).

## 3. Breast cancer etiology

Breast cancer risk factors refer to the factors that contribute to an increased likelihood of developing the disease. Being female is the most prevalent risk factor, as females are more susceptible to breast cancer than males (30). However, it is essential to note that one or more risk factors do not guarantee a definitive diagnosis of breast cancer, just as the absence of risk factors does not exclude the possibility of developing the disease. The risk factors associated with breast cancer are summarized in Table I (31-35).

## 4. Heavy metals

Heavy metals, such as zinc, copper (Cu), chromium, Cd, lead (Pb), iron (Fe), nickel (Ni) and vanadium, are characterized by their high density, which is at least 5-fold greater than water (36). Metals can be classified into essential (harmless) and non-essential (toxic) (37). Essential heavy metals, when present in low quantities, are generally less harmful and play vital roles in the human body. They serve as coenzymes in biological processes, such as iron in hemoglobin and cobalt (Co) in vitamin B12. However, when essential heavy metals accumulate in high concentrations, they can become toxic and pose health risks. Conversely, non-essential heavy metals possess deleterious properties and exhibit toxicity toward living organisms, even when present in low concentrations (37).

Heavy metals occur naturally in the environment, primarily within the Earth's crust, and contribute significantly to environmental pollution. Human exposure to heavy metals is predominantly attributed to human activities, including mining, smelting, industrial utilization and the domestic and agricultural use of heavy metals (38-42). Heavy metals can represent a considerable risk even at low exposure levels due to their toxicity, which is strongly related to their mass (43). The escalating apprehension regarding the ecological and worldwide public health implications of heavy metal-induced environmental contamination is becoming increasingly prominent. Their widespread use in industries, agriculture and technology contributes to significant levels of human exposure (44).

Table I. Worldwide risk factors of breast cancer.

| Risk factors | Protective | Predisposing | Controversial | (Refs.) |
|---|---|---|---|---|
| Demographic | | | | |
| Female sex | | √ | | (29) |
| Age | | √ | | (29) |
| Blood group | | | √ | (30) |
| Reproductive | | | | |
| Menstruation age | | | √ | (31) |
| Late menopause age | | √ | | (31) |
| Complete-term pregnancy | √ | | | (31) |
| Abortion | | | √ | (31) |
| Period of ovulation | √ | | | (33) |
| Features of pregnancy | √ | √ | | (33) |
| Hormonal | | | | |
| Hormonal methods of birth control | | √ | | (33) |
| Medications that promote ovulation | | | √ | (31) |
| Hormone replacement after menopause | | √ | | (32) |
| Hereditary | | | | |
| Genetic influences | | √ | | (32) |

## 5. Heavy metals and human health

Essential heavy metals such as Zn, Cu, Fe and Co play crucial roles in the functioning of living organisms. Inadequate levels of these metals can adversely affect human health and may contribute to the development of various diseases (45). Heavy metals are sometimes referred to as trace elements due to the fact that they are found in living tissue at low concentrations (46).

Heavy metals have been found to impact different cellular organelles and components in biological systems, such as the cell membrane, mitochondria, lysosomes, endoplasmic reticulum, nuclei and numerous enzymes that play a role in the processes of detoxification, metabolism and damage repair. The interactions mentioned above can result in DNA damage, structural alterations and cellular mutations and eventually contribute to the development of cancer (47-49). Previous research has identified the production of ROS and the consequent induction of oxidative stress as the primary mechanisms underlying the toxicity and carcinogenicity of heavy metals, such as Cr, Pb, As, mercury and Cd (50-52). A summary of these metals, their origins, and their health consequences is presented in Table II (13,50-77).

## 6. Heavy metals and breast cancer

The role of heavy metals as environmental pollutants in promoting malignant tumor growth has gained recognition, particularly concerning breast cancer (78). Certain heavy metals, such as Cd, Cr, Ni, Cu, Pb and Hg, have been established as carcinogenic substances capable of inducing various types of cancer (79). Detecting biomarkers in various biological samples, such as blood, tissues, skin and nails, can provide valuable information regarding the effects of heavy metals on human health. This approach allows for the assessment of the influence of environmental factors, nutritional status and metabolism on heavy metal exposure and its potential health implications (80-84). However, the specific role of urinary levels of heavy metals and metabolomics profiles in the development of breast cancer is not yet fully understood, and further research is required to clarify this association (85).

Standardized analytical methods have been developed to quantify heavy metals in various sample types, such as tissue, serum, urine, toenails and hair. These methods include atomic fluorescence, graphite furnaces, atomic absorption, emission, mass spectroscopies and inductively coupled plasma techniques, which can operate with optical or mass discrimination (86-89). These methods have been extensively established and have a high accuracy when conducted in centralized laboratory facilities. However, they require specific infrastructure, time and skilled personnel. The proper storage and transportation of samples are crucial to avoid contamination, and only trained individuals with specialized knowledge can derive meaningful results.

Additionally, containers must be carefully inspected to rule out the possibility of heavy metal concentration changes during storage. Among the techniques employed for the quantitative analysis of heavy metals in environmental samples, atomic absorption spectrometry and atomic emission spectrometry are widely utilized. These cost-effective and user-friendly techniques enable high-throughput, quantitative metal content analysis in solids or liquids. Consequently, they can be applied in various fields (90,91).

## 7. Copper

Copper is a heavy metal with a reddish-brown color and belongs to the transition metals group 11 (IB) (54). It exhibits

Table II. Some heavy metals and their effects on human health.

| Heavy metal | Major source | Effects on human health | (Refs.) |
|---|---|---|---|
| Copper | Soil, plants, animals, mining, production, chemical industry and metal piping. | An essential element for growth, necessary for metabolism, deficiency causes anemia, a low number of white blood cells and skeletal bones. | (53-57) |
| Cadmium | Soil, rocks, wastewater and plants. | Cause cancer, lung damage, kidney disease, and bones damage. | (13,53) |
| Zinc | Meat, fish, legumes, nuts, and other dietary sources. | Essential trace element; functions in reproduction, immune function, and wound repair. | (58-69) |
| Manganese | Soil, many types of enzymes, nuts, tea, and parsley. | Necessary for growth, metabolism, antioxidant system, and normal brain and nerve function and can cause heart disease and cancer. | (66,68-73) |
| Nickel | Chocolate, fats, metal products, detergents, and cigarettes. | Cause many types of cancer, respiratory fever, heart disorders, and deficiency affect carbohydrates. | (53,74-77) |
| Lead | Air, soil, water, fossil fuel burning, and mining. | Cause cancer, nerve damage, weakness in fingers, and wrists, increase in blood pressure and anemia. | (13,53) |

moderate malleability and is essential for various enzymatic functions within the body, including monoamine oxidase and superoxide dismutase. Both copper deficiency and excess can lead to various health issues (92). Studies have suggested a potential association between copper exposure and an increased risk of the development of cancer, including breast cancer (55-57).

A previous systematic review of published studies found higher serum copper levels in patients with breast cancer than in healthy controls and patients with benign breast cancer (93). The highest copper levels have been found in advanced-stage malignant tissue (94). Additional research has reported a statistically significant elevation in serum copper levels in patients with breast cancer compared to controls (95). Other studies have reported similar findings, with increased serum copper levels in post-menopausal patients with breast cancer (96,97). Breast cancer development has been found to be associated with the involvement of copper-binding proteins and signaling pathways, including lysyl oxidase-like proteins and G protein-coupled estrogen receptor 1 signaling (98,99). Understanding the mechanisms underlying the role of copper in breast cancer is an area of ongoing research. In subgroup analyses by region, significantly higher copper concentrations in plasma and serum have been observed in breast cancer patients from Africa and Europe compared to participants without breast cancer. By contrast, no statistically significant changes have been observed between Asian patients with breast cancer and subjects without cancer (100). The copper levels in patients with breast cancer have been well-presented in the literature and a summary of these findings is presented in Table III (50-52,93,94,96,97,101-105).

## 8. Cadmium

Cadmium is a silvery-white metal belonging to group 12 (IIB) of the transition elements. It is often used for corrosion protection and as a pigment in glass and plastic. However, its usage has decreased due to its toxic and carcinogenic properties (106). Cadmium is a non-essential heavy metal found in soils and rocks, and exposure to cadmium can have detrimental effects on human health, including the potential development of cancer (13).

The urinary concentrations of cadmium have been shown to be considerably elevated in individuals diagnosed with breast cancer compared to the controls, as determined by the utilization of inductively coupled plasma techniques (107,108). Studies using atomic absorption and atomic emission spectroscopy have reported mixed results, with some demonstrating higher cadmium concentrations in patients with breast cancer and others finding no significant differences (100,109,110). Other studies have determined the evaluation of cadmium in sample tissue using different techniques, including atomic absorption spectroscopy, graphite furnaces and inductively coupled plasma. Generally, the cadmium concentration has been found to be significantly higher in patients with breast cancer compared to the controls, particularly in those patients in the metastatic stage. At the same time, no difference was found between cadmium levels in patients with benign stages (109,111-113). Hair samples from patients with breast cancer have also been found to have higher cadmium levels compared with those from healthy individuals (100).

The levels of cadmium can vary among populations due to factors, such as smoking, age, sex and nutritional status (111,112). Cadmium has been shown to be associated with the proliferation, transformation and metastasis of breast cancer cells through multiple pathways. These processes include its interaction with estrogen receptor $\alpha$, the activation of protein kinases and the promotion of the increased production of ROS (109,114-117). Understanding the role of cadmium in breast cancer development and progression is an active area of research. Copper levels in patients with breast cancer have been shown to be significantly increased in the majority of studies in the literature (Table IV) (109,114-117).

Table III. Copper levels in patients with breast cancer.

| Sample | Stages | Locations | Detection techniques | Frequency | (Refs.) |
|---|---|---|---|---|---|
| Plasma | Benign | Iraq | Atomic absorption spectroscopy | Non-significant difference | (978) |
| | Metastases | Iraq | Atomic absorption spectroscopy | Significant (increase) | (97) |
| | Metastases | Taiwan | Flame atomic absorption spectroscopy | Significant (increase) | (94) |
| | Metastases | India | UV-Visible Spectroscopy | Significant (increase) | (96) |
| | Metastases | Africa and Europe | Atomic absorption spectroscopy | Significant (increase) | (101-103) |
| Tissue | Metastases | Taiwan | Flame atomic absorption spectroscopy | Significant (increase) | (94) |
| | Metastases | USA | Inductively coupled plasma | Significant (increase) | (104,105) |
| Urine | Benign | Iraq | Atomic absorption spectroscopy | Significant (increase) | (97) |
| | Metastases | Iraq | Atomic absorption spectroscopy | Significant (increase) | (97) |
| Hair | Metastases | Iran | Inductively coupled plasma | Non-significant difference | (93) |
| | Metastases | USA | Inductively coupled plasma | Non-significant difference | (104,105) |
| Toenail | Metastases | USA | Inductively coupled plasma | Non-significant difference | (104,105) |

Table IV. Cadmium levels in patients with breast cancer.

| Sample | Stages | Locations | Detection techniques | Frequency | (Refs.) |
|---|---|---|---|---|---|
| Plasma | Metastases | Asian | Atomic absorption spectroscopy | Significant (increase) | (100) |
| | Metastases | Iraq | Atomic absorption spectroscopy | Significant (increase) | (110) |
| | Metastases | Serbia | Atomic emission spectroscopy | Non-significant difference | (109) |
| Tissue | Benign | Finland | Graphite furnace atomic absorption spectroscopy | Non-significant difference | (111) |
| | Metastases | Finland | Graphite furnace atomic absorption spectroscopy | Significant (increase) | (111) |
| | Metastases | Poland | Inductivity coupled plasma | Significant (increase) | (112) |
| | Benign | Lithuania | Atomic absorption spectroscopy | Non-significant difference | (113) |
| | Metastases | Lithuania | Atomic absorption spectroscopy | Significant (increase) | (113) |
| | Metastases | Serbia | Atomic emission spectroscopy | Significant (increase) | (109) |
| Urine | Metastases | United States | Inductively coupled plasma | Significant (increase) | (108) |
| Hair | Metastases | Asian | Inductively coupled plasma | Significant (increase) | (100) |
| | Metastases | Europe | Inductively coupled plasma | Significant (increase) | (100) |

## 9. Zinc

Zinc (Zn) is a silvery-white heavy metal belonging to group 12 (IIB) of the transition elements (118,119). It is essential for human health, playing a crucial role in immune function and metabolism (120). Zinc deficiency can lead to various health issues. Among these, weakened immune function is a notable consequence, rendering individuals more vulnerable to infections (121). Additionally, inadequate zinc levels can hinder the ability of the body to heal wounds, leading to delayed tissue and skin repair (122). Proper growth and development, particularly in children and adolescents, depend on zinc, and a deficiency can result in stunted growth and delayed sexual maturation (123). For reproductive health, both males and females require sufficient zinc, with males relying on it for sperm production and women needing it for healthy pregnancies and fetal development (124). Zinc deficiency has the potential to worsen skin conditions such as dermatitis and acne. Additionally, the role of zinc in taste and smell perception can lead to changes in these sensory functions (125). Gastrointestinal problems, including diarrhea and impaired nutrient absorption, can further manifest in cases of zinc deficiency (126). Thus, maintaining a balanced diet with an adequate zinc intake is crucial to preventing these health issues associated with zinc insufficiency.

Several studies have examined the levels of zinc in patients with breast cancer compared to healthy controls (58-65). In a previous study, in pre- and post-menopausal women, a significant decrease in serum zinc levels was observed in patients with breast cancer compared to the control group. Similarly, the urinary excretion of zinc was lower in patients with breast cancer than in the controls across all study groups (97). Reports indicate a notable decrease in zinc levels in the breast samples of individuals diagnosed with breast cancer compared to the

Table V. Zinc levels in patients with breast cancer.

| Sample | Stages | Locations | Detection techniques | Frequency | (Refs.) |
|---|---|---|---|---|---|
| Plasma | Metastases | Taiwan | Flame atomic absorption spectroscopy | Significant (decrease) | (94) |
| | Benign | Iraq | Atomic absorption spectroscopy | Significant (decrease) | (97) |
| | Metastases | Iraq | Atomic absorption spectroscopy | Significant (decrease) | (97) |
| | Metastases | Africa and Asia | Flame atomic absorption spectroscopy | Significant (decrease) | (100) |
| | Metastases | European and South America | Flame atomic absorption spectroscopy | Non-significant difference | (100) |
| Tissue | Metastases | India | Atomic emission spectroscopy | Significant (decrease) | (127) |
| | Metastases | USA | Atomic absorption spectroscopy | Significant (decrease) | (128) |
| Urine | Metastases | Iraq | Atomic absorption spectroscopy | Significant (decrease) | (97) |

controls (127,128). Another recent study found significantly reduced serum zinc concentrations in patients with breast cancer compared to healthy controls and women with benign breast diseases (129). Regional variations have been observed in the concentrations of zinc in patients with breast cancer and subjects without breast cancer (100). Zinc deficiency may occur due to impaired nutrient absorption or tumor-induced zinc extraction from the circulation (130,131). Further research is warranted in order to elucidate the exact role of zinc in breast cancer development and progression. The details of zinc levels in patients with breast cancer are provided in Table V (130,131).

**10. Manganese**

Manganese (Mn) is a crucial silvery transition metal classified within group 7 (VIIB) of the transition metals, serving as an essential trace element within the human body. It is typically found in low concentrations of ~11 mg in adults (71,72,132,133). Its significance lies in its pivotal role in various enzymes, particularly those involved in processes, such as photosynthesis and the defense against oxidative stress (73,134). Manganese serves as a constituent of the oxygen-evolving complex (OEC) within photosystem II during the process of photosynthesis. The OEC is accountable for the oxidation of water molecules and subsequent liberation of oxygen. The OEC is essential for the generation of oxygen and the conversion of light energy into chemical energy in the form of ATP and NADPH, which are vital for plant growth and energy production (135).

In terms of antioxidant defense, manganese is a cofactor for several enzymes, including manganese superoxide dismutase (MnSOD). MnSOD is a key antioxidant enzyme that functions to neutralize harmful superoxide radicals ($O_2$-) produced during cellular respiration. These radicals can cause oxidative damage to cellular components, including DNA, proteins and lipids. MnSOD helps protect cells from oxidative stress by converting superoxide radicals into less harmful molecules, such as oxygen and hydrogen peroxide (136). Manganese deficiency can give rise to severe health conditions, disrupting the intricate antioxidant mechanisms and rendering target organs more susceptible to carcinogens. Notably, it functions as an integral component of the SOD enzyme, which plays a critical role in antioxidant defense. The diminishment of manganese levels can disrupt the body's ability to counteract oxidative stress, thereby elevating the vulnerability of target organs to carcinogenic agents. As shown in Table VI, several investigations have compared manganese concentrations in patients with breast cancer and participants without breast cancer (97,100,137-139). Studies investigating manganese levels in patients with breast cancer have found lower concentrations of manganese in the plasma, serum and hair samples of patients with breast cancer compared to participants without breast cancer in Asia (100,137). However, the differences were not statistically significant in Europe (100). It is important to underscore that manganese, in its role as a contributor to antioxidant defense, may influence the ability of the body to manage oxidative stress and may affect the delicate equilibrium between oxidants and antioxidants in patients with breast cancer from a theoretical perspective (140,141). Nonetheless, it is essential to note that there is currently no direct empirical evidence establishing a direct connection between manganese and cancer development. Consequently, further research is warranted to comprehensively elucidate the precise role of manganese in the context of breast cancer.

However, there are currently no direct data linking manganese to cancer development. Further research is required to explore the association between manganese and breast cancer. This should include clinical studies across diverse populations, investigations into the potential benefits of manganese supplementation, and a better understanding of the mechanisms through which manganese affects antioxidant defenses. Exploring its role in cancer prevention, its use as a biomarker and conducting mechanistic analyses are essential.

**11. Nickel**

Nickel is a silvery-white metal categorized as a transition element belonging to group 10 (VIA) (54). It has a wide application in various industries, such as stainless-steel production, electroplating and foundries (142). Nickel is also an essential element in the metabolic processes of macromolecules in living organisms (74-77). The impact of nickel on human health is significant, as exposure to this metal can occur through inhalation, ingestion and drinking water, since nickel

Table VI. Manganese levels in patients with breast cancer.

| Sample | Stages | Locations | Detection techniques | Frequency | (Refs.) |
|---|---|---|---|---|---|
| Plasma | Benign | Iraq | Atomic absorption spectroscopy | Significant (decrease) | (97) |
| | Metastases | Iraq | Atomic absorption spectroscopy | Significant (decrease) | (97) |
| | Metastases | China | Atomic absorption spectroscopy | Significant (decrease) | (138) |
| | Metastases | Asia | Atomic absorption spectroscopy | Significant (decrease) | (100) |
| | Metastases | Europe | Atomic absorption spectroscopy | Non-significant difference | (100) |
| Tissue | Metastases | USA | Graphite furnace atomic absorption spectroscopy | Significant (increase) | (139) |
| Urine | Benign | Iraq | Atomic absorption spectroscopy | Significant (decrease) | (97) |
| | Metastases | Iraq | Atomic absorption spectroscopy | Significant (decrease) | (97) |
| Hair | Metastases | China | Inductively coupled plasma | Significant (decrease) | (138) |
| | Metastases | Asia | Inductively coupled plasma | Significant (decrease) | (100) |
| | Metastases | Europe | Inductively coupled plasma | Non-significant difference | (100) |

Table VII. Nickel levels in patients with breast cancer.

| Sample | Stages | Locations | Detection techniques | Frequency | (Refs.) |
|---|---|---|---|---|---|
| Plasma | Benign | China | Atomic absorption spectroscopy | Non-significant difference | (143) |
| | Metastases | China | Atomic absorption spectroscopy | Significant (increase) | (143) |
| | Metastases | Asia | Atomic absorption spectroscopy | Non-significant difference | (100) |
| Tissue | Metastases | Asia | Graphite furnace atomic absorption spectroscopy | Non-significant difference | (100-103) |
| Hair | Metastases | Asia | Inductively coupled plasma | Non-significant difference | (100) |

is present in the air, water sources and certain foods. While low levels of nickel are necessary for the functioning of the body, high levels of exposure can lead to an increased risk of developing various types of cancer (53).

Previous studies have examined the connection between nickel levels in serum and hair and breast cancer. Patients with breast cancer have been found to have significantly higher levels of nickel in their serum compared to healthy controls, even among those who have received treatment (143). Nickel levels in the hair of those with breast cancer have been found to be somewhat higher than those in the control group, although this difference did not reach statistical significance (143). Research that was carried out in Asia discovered that the levels of nickel in plasma/serum samples and hair samples did not differ significantly between individuals who had breast cancer and those who did not have breast cancer (100). Overall, no differences were observed between breast cancer cases and participants without breast cancer, as regards plasma/serum and hair specimens, including subgroup analyses. However, *in vitro* studies have provided insight into the potential mechanisms by which nickel may contribute to breast cancer development. One such mechanism involves nickel binding to estrogen receptor α in breast cancer cells, mimicking the effects of estradiol and promoting cell proliferation (144). An overview of the nickel levels in patients with breast cancer is presented in Table VII (144).

## 12. Lead

With an atomic number of 82 and an atomic weight of 207.2 g/mol, lead is a shiny gray metal known for its high density of 11.2 g/cm$^3$ (145,146). It falls under the category of transition elements, specifically group 14 (IVA) on the periodic table. Due to its relative abundance, low cost and desirable properties, lead is used in various industries, including batteries, plumbing and white paints (147). Lead is a heavy metal that can have detrimental effects on living organisms and is classified as a carcinogen capable of causing cancer (53). Prolonged exposure to lead can lead to numerous complications and diseases, such as damage to the nervous system, increased blood pressure, weakness in the extremities and anemia (13).

A previous study investigated lead levels in blood, healthy tissues, malignant tissues and serum (148). The findings indicated lower lead levels in cancerous tissue than in healthy tissue, while the serum lead levels in women with breast cancer did not significantly differ from those of the control group (148). In a previous systematic review and meta-analysis, as regards the lead concentration in Asia, no significant differences were found in plasma or serum. However, hair samples from patients with breast cancer exhibited significantly lower lead concentrations compared to participants without breast cancer (100). The number of studies analyzing lead levels in hair were limited, warranting further investigation

Table VIII. Lead levels in patients with breast cancer.

| Sample | Stages | Locations | Detection techniques | Frequency | (Refs.) |
|---|---|---|---|---|---|
| Plasma | Metastases | Asia | Inductively coupled plasma | Non-significant difference | (100) |
| | Metastases | Nigeria | Inductively coupled plasma | Significant (increase) | (149) |
| | Metastases | Serbia | Atomic absorption spectroscopy | Non-significant difference | (148) |
| Tissue | Metastases | Serbia | Atomic absorption spectroscopy | Significant (decrease) | (148) |
| | Metastases | Iraq | Atomic absorption spectroscopy | Significant (increase) | (110) |
| Urine | Metastases | USA | Inductively coupled plasma | Non-significant difference | (150s) |
| Hair | Metastases | Asia | Inductively coupled plasma | Significant (decrease) | (100) |

by region. In terms of the lead concentration in Asia, there were no discernible variations in lead content in plasma and serum samples (100). However, hair samples from breast cancer patients showed significantly lower lead concentrations compared to participants without breast cancer, although the number of hair-related studies were limited, necessitating further regional investigations (100). Another study found that patients with breast cancer had considerably higher blood lead levels than the controls (149). Similarly, in another study, lead concentrations were increased in patients with breast cancer compared to the control group (110). However, another study failed to reveal an association between elevated lead levels and an increased risk of developing breast cancer (150).

Overall, the analyses of lead levels in different samples and regions have exhibited varying results (Table VIII) (150). Lead concentrations in cancerous tissue and hair samples have exhibited some associations with breast cancer, while the analyses of blood lead levels have yielded inconsistent findings. The primary factor and pathway contributing to elevated lead (Pb) levels and the development of breast cancer involve estrogen receptor signaling. Lead can activate estrogen receptor $\alpha$, influencing estrogen target gene expression and promoting breast cancer cell proliferation (144). Additionally, lead, classified as a nonessential metal, can mimic or disrupt the functioning of essential metals, thereby leading to toxicity linked to breast cancer (151,152). Further research on the connection between lead exposure and breast cancer is warranted. This should include region-specific studies, large-scale longitudinal investigations, and mechanistic analyses to elucidate the mechanisms through which lead affects estrogen receptor signaling and promotes breast cancer. The interaction between non-essential lead and essential metals in contributing to breast cancer should be explored.

## 13. Conclusions and future perspectives

In summary, the findings of this study indicate a potential association between breast cancer and heavy metals. Recent research suggests that environmental contaminants, specifically heavy metals such as copper, cadmium, zinc, manganese, lead and nickel, may contribute to the development of various types of cancer, including breast cancer. The present review presented a detailed summary of the existing body of literature, revealing notable deficiencies in current research pertaining to the association between breast cancer and exposure to heavy metals. The investigation encompasses diverse sample types such as plasma, urine, tissue, hair and toenail samples, obtained from individuals afflicted with this medical condition. Consequently, it is imperative to comprehend the levels and evaluate the presence of heavy metals to facilitate early detection of cancer, particularly breast cancer. The reviewed articles indicate an increase in the concentration of copper and cadmium among patients with breast cancer compared to the controls. Conversely, zinc and manganese levels were observed to be lower in the patient group compared to the healthy groups. Moreover, no significant differences were observed in the levels of nickel in plasma, tissue, and hair samples between breast cancer cases and participants without breast cancer.

The present review highlights the importance of routinely assessing heavy metal levels in patients with breast cancer, as it has the potential to improve overall health outcomes and inhibit disease progression. It is recommended that future research endeavors concentrate on elucidating the specific roles of these heavy metals in breast cancer by conducting studies with larger sample sizes across diverse populations. Additional investigations are required in order to validate and expand upon the current knowledge regarding the functions of heavy metals in breast cancer pathogenesis.

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**Competing interests**

The authors declare that they have no competing interests.

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