Breast Cancer and Metals: A Literature Review

Safie Yaghoubi[1], Zero Breast Cancer

Janice Barlow, Zero Breast Cancer

Zero Breast Cancer

Non-Profit Organization

4340 Redwood Highway #C400

San Rafael, CA 94903

Philip H. Kass, PhD, Professor

Department of Population Health & Reproduction

University of California, Davis

1. Proofs to be sent to

Safie Yaghoubi

7 Oak Tree Court

San Rafael, CA 94903

Tel: 415/479-3719

Fax: 415/479-3712

safiey@zerobreastcancer.org

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4. List of abbreviations with explanations used

Reactive Oxygen Species (ROS)

Sulfhydryl (SH)

Tumor suppressor genes (p53, BRCA1 and BRCA2)

Abstract

Objective: To review the scientific evidence with respect to the *in vitro* and *in vivo* studies and epidemiological evidence for links between breast cancer and exposure to metals.

Data Sources and Extraction: PubMed was searched using the keywords “breast”, “mammary”, “carcinoma”, and “metals” for studies published in English between 1950 and 2006. Studies were reviewed and critiqued, with relevant data extracted.

Conclusions: There is growing evidence environmental contaminants such as metals play a role in disease, such as cancer. Based on a relatively small number of studies this literature review has uncovered important deficiencies and gaps in the current literature that assesses the link of the incidence of breast cancer to metal exposure.

Introduction/Background

Although the incidence of many types of cancer has declined in the United States over the last thirty years, the incidence of breast cancer globally has increased (Bray et al. 2004). Among women in the United States, breast cancer remains one of the most common cancers. By the end of 2007, an estimated 178,480 women are expected to be diagnosed with invasive breast cancer and 40,460 women will have died of breast cancer (American Cancer Society 2005). For many years, breast cancer incidence and mortality rates have been the highest in North America and Northern Europe (Verkooijen et al. 2003), intermediate in Southern Europe and Latin America, and the lowest in Asia and Africa (Parkin et al. 2005). Studies of immigrants to North America and Northern Europe (in which the immigrant populations quickly take on the higher incidence rates of the new countries) suggest that environmental factors, rather than genetic factors, are mainly responsible for this variation between countries (Parkin and Fernandez 2006).

Recently, there has been a growing interest in understanding whether exposure to toxic and cancer-causing (carcinogenic) chemicals contribute to the increasing number of breast cancer cases worldwide. Unfortunately, relatively few studies have investigated the impact of these environmental chemicals on general human health and even fewer have addressed the roles that known carcinogens, such as metals, may play a role in the initiation, promotion and progression of breast cancer.

Breast tissue is unique due to its complex hormonal influences and dramatic changes during various life events. Individual hormonal levels and metabolism are affected by environmental factors, and some frequently used chemical and metals have the ability to disrupt endocrine function, and thus mimic the effects of estrogen (Martin et al. 2006).

This paper reviews *in vitro* and *in vivo* studies, as well as epidemiological evidence for links between breast cancer and exposure to metals in all but occupational settings. This review covers studies published in English between 1950 and 2006, identified using a PubMed search. Metals for this review paper were selected from The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) Priority List of Hazardous Substances, 2005, or have appeared on the Agency for Toxic Substances and Disease Registry (ATSDR). A summary of the available evidence concerning the carcinogenicity of the selected metals, their source of exposure and the known routes of exposure are presented in Table 1.

Developmental Nature of Breast Cancer

Breast cancer is known to have a long latency period; there may be several decades between the initiation of the carcinogenic process and clinical detection (Colditz and Frazier 1995; Ostrowski et al. 1999). Environmental factors during embryogenesis, childhood, and adolescence may affect breast cancer occurrence in adulthood by enhancing or deterring carcinogenic processes (Cleaver et al. 2001). The embryo develops rapidly and toxic agents that do cross the placental barrier can have specific effects on organ development depending on the time at which the exposure occurs (Graeter and Mortensen 1996). Although breast tissue begins to differentiate by the fourth week of development, the breast is unusual among body parts in that it remains relatively unchanged until puberty or later.

A better understanding of the potential effects of exposure to metals *in utero,* during childhood and adolescence is particularly important. Children receive higher relative doses of metals from food than adults do because they consume more food per pound of body weight (Graeter and Mortensen 1996). Also, children absorb metals more readily through their intestinal tract than adults do (Wood 1974). Adolescence is characterized by hormonal changes

and the rapid proliferation of cells in incompletely differentiated tissues, including breast tissue. Thus, adolescence may be a more etiologically relevant period than adulthood for the study of potential causal and preventive determinants of breast cancers (Colditz and Frazier 1995).

Sources of Metals

Minerals, including metals, are naturally occurring elements found in the earth. Rock formations are made up of mineral salts. Rocks are gradually broken down into tiny fragments by erosion, a process that can take millions of years. The resulting sand accumulates, forming the basis of soil. Soil is teeming with microbes that utilize these tiny crystals of mineral salts which are then passed from the soil to plants. The plants are eaten by herbivorous animals. Minerals move up the food chain to humans following consumption of plants and herbivorous animals (Wood 1974). Aquatic organisms can also absorb and accumulate metals in their tissues, leading to an increase in contamination of the food chain (Bryan 1971).

Since the industrial revolution, humans have found an increasing number of uses for various metals in industry, agriculture, and medicine (Juracek and Ziegler 2006). These activities have increased exposure not only to metal-related occupational workers, but also to consumers of the various products (Adachi and Tainosho 2004). Metals like cadmium, arsenic, and zinc can be harmful pollutants when they enter the soil and water. Once in the environment, metals are almost impossible to eliminate because they do not decompose.

How Metals Enter the Cell

Metals get into the body through air, food, water, or dermal exposure. Metals have to cross the plasma membrane to enter the cell in order to exert toxicity. If a metal is in a lipophilic form, such as methyl mercury and arsenic compounds, it readily penetrates the membrane (Lakowicz and Anderson 1980). When bound to a protein, such as cadmium-metallothionein,

the metal is actively taken into the cell by endocytosis (Antila et al. 1996). Other metals, like lead may be absorbed by passive diffusion (Karmakar and Jayaraman 1988).

Effects of Metals on Enzyme Function

The mineral replacement process involves the idea of preferred minerals. Critical enzymes often require metal ions to function, and many of these show a "preference" for zinc in that this metal enables optimal enzyme activity. However, if zinc becomes deficient and exposure to cadmium or lead is sufficiently high, these will substitute for zinc in these critical enzymes (Lutzen 2004). Cadmium in particular, located just below zinc in the periodic table, has an atomic structure very similar to that of zinc. It fits quite well in the zinc binding sites of critical enzymes, such as RNA transferase. Enzymes assist in practically all cellular functions; metabolic enzymes catalyze the various chemical reactions within cells, such as energy production and detoxification. Toxic metals replace nutrient minerals in enzyme binding sites and enzyme inhibition may be caused by the interaction between the metal and a sulfhydryl (SH) group on an enzyme (Nikolic and Sokolovic 2004). Exposure to toxic metals can alter the activity levels of thousands of enzymes. An affected enzyme may function at as low as 5% of its normal activity and this may contribute to many health conditions ((Nikolic and Sokolovic 2004).

Genotoxic Effects of Metals in the Cell

Genotoxic effects of metals can be mediated either through metabolically activated electrophilic derivatives that interact with DNA and other macromolecules, or through direct binding of DNA (De Bont and van Larebeke 2004). Many metals have been shown to directly modify and/or damage DNA by forming DNA adducts that induce chromosomal breaks (Chakrabarti 2001).

Susceptibility to cancer is characterized by extensive DNA damage. This damage is thought to result from decreased repair capacity and/or by the direct carcinogenic interaction of metallic ions with DNA, as measured by DNA adducts (Kobayashi 1990; Hartwig et al. 2002). Presently, the most well-known genetic factors implicated in breast cancer are germ-line mutations in the breast cancer susceptibility genes BRCA-1 and BRCA-2 (Hunter et al. 2005). Mutations in BRCA-1 have been linked to the development of both breast and ovarian cancers. BRCA-2 mutations correlate with breast cancer in males as well as females. Identified genetic mutations appear in only 5%-10% of the cases (Hunter et al. 2005).

Metals and Oxidative Stress

Oxidative stress describes the steady state level of oxidative damage in a cell, tissue, or organ caused by reactive oxygen species (ROS). Oxidative stress occurs when the generation of ROS in a system exceeds that system's ability to neutralize and eliminate them. The imbalance can result from a disturbance in production or the distribution of antioxidants, as well as an overabundance of ROS from an environmental or behavioral stressor (Danilova 2006). Oxidative damage impacts the body's normal aging process and may contribute to certain diseases (Kirkwood 2002). It is apparent that ROS plays an important role in the etiology of diverse human pathologies such as carcinogenesis (Frenkel 1992), irradiation injury (Girotti and Thomas 1984), and tumor promotion (Girotti and Thomas 1984), in addition to the normal aging process (Jiang et al. 2001). The ability of ROS to damage cellular components, including DNA, is well documented (Halliwell and Aruoma 1991; Teebor 1998). Metals like arsenic, cadmium, chromium, lead, nickel, and others are a major source of oxidative stress (Wang et al. 2004; Leonard et al. 1998; Hei and Filipic 2004). Substantial data suggest that oxidative stress is involved in the development of breast cancer (Rossner 2006; Gammon 2002; Wu 2004).

Metals and Estrogen Receptors

Estrogen receptors (ER) are proteins that bind with high specificity and affinity to estradiol, the most potent and biologically active estrogen. Steroid hormones act on endocrine target cells in part by regulating gene expression. Recently the effect of arsenic on estrogen regulated genes in human breast cancer cell line MCF-7 was examined (Stoica et al., 2000a), and arsenic stimulated cell proliferation, and also mimicked the effects of estradiol. Also cadmium, which has been classified among the most important carcinogens, recently has been described to possess estrogen-like activity and acting like an endocrine disrupter (Garcia-Morales et al. 1994; Stoica et al. 2000b; Johnson et al. 2003). The rising level of environmental endocrine disruptors may not be the single cause of rising breast cancer rates during the last half of the century, but one of many factors that influence life time exposure.

Metals and Tumor Suppressor Genes

Tumor suppressor genes, such as p53, are known to participate in DNA repair by preventing the replication of damaged DNA in normal cells and promoting apoptosis of cells with abnormal DNA (Harris 1996; Greenblatt et al. 1994). The p53 gene has been associated with breast cancer development (IARC 2006, vol. 87) and p53 mutations have been identified in approximately 44% of invasive breast cancers (Armes et al. 1999). The p53 status has been shown to have an important role in the cellular response to metals in two breast cancer cell lines: MCF-7 and MDA-MB231. MDA-MB231 cells with mutant p53 are resistant to apoptosis when exposed to zinc (Ostrakhovitch and Cherian 2005).

The etiology of breast cancer may be among the most complicated of all cancers given the life long exposures to multiple endogenous and exogenous factors. Breast tissue may be more susceptible than other tissues to hormone mimicking metals. There is insufficient information

available to realistically determine the risks of breast cancer and other cancers from environmental metals that humans are exposed to regularly through our daily lives. It is critical to identify the roles of these potentially carcinogenic metals in the etiology of breast cancer, since breast cancer remains the leading cause of cancer death for women ages 25-54 and the second most common cause of cancer death for women of all ages (NCHS 2004).

Metals and Breast Cancer

Arsenic

The major source of human exposure to arsenic is through food. Micro-organisms convert arsenic to dimethylarsenate, which can accumulate in fish, providing a source for human exposure (ATSDR 2005). Arsenic compounds are lipid soluble and within 24 hours of absorption distribute throughout the body where they can bind to sulfhydryl (SH) groups on proteins. Arsenic may also replace phosphorus in bone tissue and be stored for years (Bartolome et al. 1999). Methylation efficiency in humans appears to decrease at high arsenic doses and studies show that aging is associated with a diminishing capacity to methylate inorganic arsenic, resulting in increased retention of arsenic in soft tissues (Tseng et el. 2005).

Endocrine factors play an important role in the etiology of breast cancer. Molecules that can bind to and activate the ER can potentially increase the risk of breast cancer (MartÃnez-Campa et al. 2006). In order to determine whether arsenic has estrogen-like activities, Stoica et al. (2000a) examined the effect of arsenite on estrogen regulated genes in the human ER-positive breast cancer cell line MCF-7. Arsenite blocked the binding of estrodiol to ER-alpha, acted as a ligand for ER activating it in the absence of hormone, suggesting that the metal interacts with the hormone binding domain of the receptor. It increased cell growth and mimicked the effects of estradiol, decreased the amount of ER-alpha and increased the expression of the progesterone

receptor. Arsenite was able to activate ER-alpha at concentrations as low as 1 nanomole, suggesting that arsenite is more potent than most known environmental estrogens. Kaltreider et al.(1999) in a recent study examined the effect of single low-dose arsenic, potentially directly relevant to human exposures, on binding of transcription factors in human MDA-MB-435 breast cancer and rat H4IIE hepatoma cells. These transcription factors were sensitive to toxic metal at low doses. The specific effects were dependent on the transcription factor, time, dose, and cell line. This study showed that alteration in gene expression may play a role in long term effects of low dose environmental exposures, such as in metal induced carcinogenesis. Regulation and activation of transcription factors is an important part of mediating cellular response to target genes by metals. However, pathways remain to be known.

Cadmium

Cadmium is a naturally occurring metal found in soil, rocks, and water. Human exposure to cadmium is primarily through food or industrial exposure to cadmium dust. Cadmium-containing products are rarely recycled. Instead, they are frequently dumped together with household waste, thereby contaminating the environment, especially if the waste is incinerated. Cadmium is a known cumulative toxin with a biological half-life of more than 10 years in humans. Thus, chronic low level exposure will eventually result in accumulation to toxic levels.

Cadmium has the potential to disrupt endocrine function by behaving like sex hormones (Stoica et al. 2000b). At low concentrations the metal mimics the effects of estradiol and binds with high affinity to the hormone-binding domain of ER-alpha. This binding involves several amino acids, suggesting that cadmium activates the receptor through the formation of a

complex with specific residues in the hormone-binding domain (Johnson et al. 2003; Stoica et al. 2000b).

Early puberty has been associated with breast cancer (Colditz and Frazier 1995; Hamilton and Mack 2003). A new study shows cadmium might also cause early puberty and possibly breast cancer (Johnson et al. 2003). Researchers at Georgetown University looked at two animal models. In the first model, they ovariectomized female rats, leaving them with no ability to produce estrogen. When exposed to the equivalent of the highest amount of cadmium allowed by the World Health Organization for drinking water, the rats experienced changes normally induced by estrogen, such as an enlarged uterus, thickening of the endometrial lining, and thickening of the mammary gland lining. Genes normally activated by the presence of estrogen were activated in the rats lacking ovaries. In a second model, pregnant animals were exposed to low doses of cadmium resulting in early puberty in their offspring. The experimental animal models such as Johnson et al. 2003 that exhibit complex interactions are needed for testing various mechanisms and methods for assessing the carcinogenic potential of metals.

A recent study has shown that even low doses and short term exposure to cadmium can cause specific DNA damage in breast tissue and may be a possible mechanism of action of cadmium on the cell cycle of human mammary cell lines (Roy et al. 2004). Cadmium significantly stimulated the growth of MCF-7 cells when compared with cells grown in estrogen-depleted medium, comparable with the degree of growth stimulated by estradiol (Roy et al. 2004). This study demonstrates that cadmium induces cell growth, and may have a possible role in the etiology or progression of breast cancer.

Available epidemiological evidence demonstrates that endogenous hormones play a role in the etiology of breast cancer and that there exists a convincing association between

elevated testosterone levels and postmenopausal breast cancer risk (Kaaks et al. 2005; Tamimi et al. 2006). A recent study by Nagata et al. investigated the association between urinary cadmium levels and estrogens and androgens in 164 postmenopausal Japanese women (Nagata et al. 2005). Their results revealed a significant positive association for cadmium exposure and testosterone levels. The cross-sectional nature of this study limits assessing the relationship between timing of cadmium exposure and hormonal changes. Cross-sectional studies may also involve length-biased sampling, over-representing cases with a long duration and under-representing those with a short duration of breast cancer. Also, the small sample size and possible confounding with other unmeasured factors makes the results of this study preliminary.

A study by McElroy et al. measured cadmium levels in urine samples in a population-based case-control study of 246 women, aged 20-69 years, with breast cancer. Breast cancer becomes more prevalent as women grow older, so the case and control groups were matched by age. After adjustment for currently accepted breast cancer risk factors, there was a significant increase in risk with increasing urine cadmium level (McElroy et al. 2006). Their results indicated a statistically significant two-fold increased breast cancer risk for women in the highest quartile of cadmium level compared with those in the lowest quartile. However the small sample size of this population based case-control study makes the absolute risk calculation unstable with large confidence intervals.

Chromium

The carcinogenic potential of chromium (VI) is well established for humans and experimental animals (Hayes 1997). However, the molecular mechanisms of damage after exposure to chromium are still not well understood. Chromium is not biologically accumulated; once absorbed it is rapidly excreted into the urine. Chromium (VI), which is not water soluble,

rarely occurs naturally and is more readily absorbed across cell membranes than chromium (III). There is accumulating evidence that metals, including chromium can interfere with distinct steps of diverse DNA repair systems (Hartwig and Schwerdtle 2002) as well as oxidative DNA lesions.

In order to study estrogen-like effects, chromium chloride was selected to perform a proliferation assay of MCF-7 human breast cancer cells and binding assays of the estrogen receptor. Results indicated that metal salt binds and activates ER, which stimulates the proliferation of MCF-7 cells. The effect of metal was blocked completely by anti-estrogen treatment suggesting their effects are mediated by ER alpha. Mutational analysis identified a few amino acids as a potential interaction site and suggested that metal anions activate ER through the formation of a complex within the hormone binding domain of the receptor (Martin et al. 2003). Environmental exposure to chromium is significant and this study shows that chromium compounds may pose a risk for endocrine-related disease such as breast cancer at environmentally relevant doses.

Coyle et al. (2005) conducted an ecological study to examine the effect of metals released into the environment from industrial sources in 254 Texas counties between 1988 and 2000. The authors performed univariate and multivariate analyses adjusted for race and ethnicity to examine the association of metal release with the average annual age-adjusted breast cancer rate at the county level. Coyle et al. (2005) showed with univariate analysis that chromium was positively associated with the breast cancer rates in Texas, which had 54,487 invasive breast cancer cases between 1995 and 2000. These aggregate county level environmental measures have insufficient control of factors that affect breast cancer incidence at the individual level. Additionally, individual exposures usually vary among members of each group and they may

remain unmeasured. Furthermore, control for confounders is more problematic in ecological analysis than in individual level analysis. To our knowledge there have been no other epidemiological studies of chromium and breast cancer.

Recently, hair analysis has been used to determine metal status in the human body. Kilic et al. (2004) collected hair samples from breast cancer patients and a cancer free control group. They compared the mean chromium content of breast cancer patients with controls. Their results showed an elevated mean concentration of chromium for breast cancer patients compared to the control group. Hair analysis may be a good tool for routine clinical screening of exposure to metals such as chromium. Collecting hair samples from patients is simple and analysis is easier because of the slow metabolic turnover rate of hair compared to serum element levels which vary in a day depending on the food intake.

Iron

Excessive iron is toxic because it reacts with peroxides, leading to the production of free radicals. Excess generation of free radicals within tissues can damage DNA, lipids, proteins and carbohydrates depending upon the cell type subjected to the oxidative stress. Estrogenic hormones appear to regulate the uptake of iron and its utilization in proliferative processes (Liehr and Jones 2001; Kawanishi et al. 2002).

In study by Thompson et al. (1991) female rats were injected with 1-methyl-1-nitrosourea in order to induce mammary tumors and subsequently randomized into one of three experimental groups fed a formulation with low, adequate, or excess amounts of iron. The low iron diet group had less mammary tumors compared to adequate or excess iron diet groups after 32 weeks. In another study by Diwan et al. (1997) female rats were randomized into four groups of 30 each. To induce mammary tumors, the first two groups received dimethylbenz[a]anthracene (DMBA)

in olive oil and the third group received only olive oil. Eight days later groups 2 and 3 received an injection of iron twice a week for 53 weeks. Group 4 was an untreated control. The size and location of tumors were recorded every week from the appearance of tumors. After 20 weeks of DMBA treatment, iron increased mammary tumor frequency two-fold compared with DMBA alone. Also, tumor frequency was higher and tumors were significantly larger in iron-treated rats. These studies (Thompson et al. 1991; Diwan et al. 1997) extended the cancer hypothesis evaluation of iron store to another organ, the breast and included the investigation of both iron deficiency and excess on the induction of mammary carcinogenesis. Their results indicated that the effect of excess iron to be more prominent than iron deficiency in the modification of mammary carcinogenesis. Iron may be a limiting nutrient to the growth and replication of a cancer cell. The public health implication of excess iron and cancer is important, given the use of iron-fortified foods and dietary supplements containing iron.

Geraki et al. (2002) investigated the correlations between the breast tissue levels of iron with the presence of breast cancer by using 40 healthy and 40 tumor samples. For iron the mean concentrations of specimens obtained from healthy individuals differed significantly from the mean concentrations of normal tissue adjacent to breast tumors (31% difference from the average) which was statistically significant. This apparent difference in iron concentrations between the two groups needs to be replicated with a larger number of samples. This study may yield important information for future studies.

Lead

The heavy metals of greatest concern for health in regard to drinking water exposure are lead and arsenic (ATSDR 2005). Lead in gasoline was removed during the early 1990s. Lead solder in food cans was banned in the 1980s and lead in paint was severely restricted in 1978 in

the U.S.

Both the nervous and reproductive systems are susceptible targets for lead toxicity. Lead exposure can cause male and female reproductive toxicity, miscarriages, and one of the most sensitive targets of this environmental toxin is the early stage embryo. Pregnancy and lactation have effects on blood lead concentrations (Rothenberg et al. 1994). In the first-half of pregnancy blood lead levels have been found to decrease because of increased fluid volume (Rothenberg et al. 1994). During late pregnancy and lactation blood lead levels have been found to increase.

Results of epidemiologic studies investigating the association of lead exposure with cancer are inconsistent and vary according to the type of cancers reported (Wong and Harris 2000; Steenland et al. 1992). The ability of lead to function as potent estrogens suggests that lead may be an important class of endocrine disrupters (Martin et al. 2003).

Siddiqui et al. (2003) analyzed blood, tumor tissue and breast adipose tissue from tumor free sections of mammary tissue of 25 women with malignant and 25 with benign breast tumors in order to investigate the association between environmental exposure to lead and risk of breast cancer in New Delhi, India. Blood lead was significantly higher in malignant cases than in those of benign and control. Also, lead level was insignificantly higher in malignant and benign tumor tissues when compared with normal tumor free breast tissue. It is reasonable to examine the possible association between the exposure to environmental lead and risk of breast cancer, given the known impact of lead on human health. The environmental exposure to lead is toxicologically significant to generate ROS, leading to oxidative damage, and/or may be the direct participation of lead in free radical reactions, which may increase risk of breast tumors.

There is some evidence for a connection between hormonal activity and lead exposure. Denham et al. (2005) conducted a study in order to look at the relationship of lead to timing of menarche among Akwesasne Mohawk girls aged 10 to 16.9 years old in New York, Ontario, and Quebec. Girls at or above the median blood lead level of 1.2_g/dL had a predicted age at menarche of 12.7 years. Girls below the median lead level had a predicted age at menarche of 11.8 years. They showed the findings were stable across analyses, both with and without controlling for SES, BMI and for other toxins. These results suggest that lead might have delayed maturation through changes in the endocrine system, rather than through delaying growth. However, interpretation of this study warrants caution because of the small sample size, 138 girls and the cross-sectional study design, and the possible occurrence of confounders beyond those tested, including genetic factors.

Nickel

Nickel is a rather common element, representing 0.018% of the earth's crust, compared to 0.0015% lead (ATSDR 2005). Nickel compounds are known carcinogens in both human and animal models (Feder et al. 1996; Harman 1981). There is evidence that the genotoxic effects of nickel compounds may be indirect through the inhibition of DNA repair systems (Rothenberg et al. 1994; ATSDR 1996). Carcinogenic actions of nickel compounds are thought to be mediated by oxidative stress, DNA damage, epigenetic effects, and the regulation of gene expression by activation of certain transcription factors (Leonard et al. 2004). Current studies have shown that heavy metals such as nickel can stimulate cell growth in estrogen receptor (ER) positive breast cancer cells, MCF-7 (Martin el al. 2003). A recent study (Ionsescu et al. 2006) has found highly significant nickel accumulation in 20 breast cancer tissue biopsies compared to controls. Since nickel has been known to inhibit the repair of damaged DNA (Beyersmann 2002) it has been

suggested that accumulation of nickel in breast tissue may be closely related to malignant growth process.

Zinc

Since zinc is essential for growth and cancer is characterized by uncontrolled growth, zinc accumulation suggests an involvement of zinc in breast tumorigenesis. Zinc is important to cell proliferation; however, it accumulates in mammary tumors and supports tumor growth (Sukumar et al. 1983; Lee et al. 2003). In one study twenty-one-day old female rats were assigned to a low-zinc, an adequate-zinc, or ad libitum control groups. On day 50, all rats were injected with 1-methyl-1-nitrosourea (MNU) to induce mammary tumors. MNU has been widely used in rodent models to induce diverse mammary tumors that differ in type and location of formation in the mammary gland for studying human breast cancer due to their similarities in hormone dependency. The carcinogenicity of MNU is due to its ability to induce a mutation in the H-ras oncogene (Lee et al. 2004). Results indicated low-zinc intake suppressed MNU-induced tumor incidence, tumor numbers and tumor multiplicity.

Geraki and Farquharson (2001) analyzed zinc concentration in breast tissue samples coming from biopsies, mastectomies or breast reduction surgeries. Samples were grouped as 10 normal and 14 pathological which included benign changes, carcinomas and fibroademomas. These measurements suggested significant elevation of zinc in the pathological tissues compared to normal tissues. Also Siddiqui et al showed that blood zinc was significantly higher in malignant cases than in those of benign and control (Siddiqui et al. 2006). These studies reveal that zinc accumulates in diseased samples compared to healthy samples. It is not known if the uncontrolled growth of cells in the tumor tissues accumulate more zinc to cope with the demands of the excessive dividing of the cells or if these metals play a role in tumorgensis.

Future research avenues

There is growing evidence that environmental contaminants such as metals play a role in disease genesis, such as cancer. Although studies on breast cancer and metals are limited, this review suggests that there may be a relationship between exposure to certain metal compounds and the risk of breast cancer. This review has uncovered important deficiencies in the current literature, it provides evidence for a possible link between metal exposure and incidence of breast cancer, and identifies priority areas that should motivate further studies. There remains a need for additional research, including:

- epidemiologic studies of occupational exposure to metals to monitor breast cancer incidence rates and to determine whether these metals and their species contribute to the development and growth of breast cancer
- studies on breast cancer incidence and environmental exposure to metals via all major pathways (air, water or diet) which may be assessed by biological monitoring of toxic metals in blood, urine, hair and nail samples.
- studies on the issues of timing with respect to latency and periods of breast vulnerability and exposure to potentially carcinogenic metals. Metal concentration may be assessed by using maternal and cord blood samples for exposures during early human development.
- studies to determine specific mechanisms of metal-induced DNA damage and the mechanisms by which metals can alter specific gene expression and signaling pathways
- studies to advance our understanding of how specific metals can act directly or indirectly to enhance known carcinogenic processes.

- studies on the mechanisms of carcinogenesis of two or more metals when they are present together. Environmental metals in nature rarely occur in isolation, and these metals may interact with each other.

In general, research on metals and cancer is limited, and there are relatively few experimental animal studies and even fewer epidemiologic studies on metals and breast cancer. Epidemiologic research is far more limited because very few of the metals identified as animal mammary carcinogens have been targeted in human breast cancer studies. There are some data on the effects of metals on cancer development in different organs, but very little on breast cancer (Table 1). Furthermore, expanding breast cancer research to include metals may provide an opportunity to identify additional modifiable environmental pollutants that may be contributing to the breast cancer incidence.

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Table 1: Summary of available evidence concerning carcinogenicity of metals, their compounds, route of exposure, source and use

Metals CAS#	***Route of Exposure***	***Known Target Organs &Health Effects***	***Known Lowest Safe exposure***	***Human Carcinogen***	***Animal Carcinogen***	***Natural Sources***	***Anthropogenic Sources & Use***
Arsenic 7440-38-2	Ingestion Inhalation Dermal	Lung, Skin, Lymph Gland, CVS NS Development	Urine, Adult <50 µg/L	IARC, Vol.: 84 (Group 1), 2004 Carcinogen	IARC, Vol.:84 2004, Limited Evidence	Earth's Crust	By-product of Copper & Lead Smelters, Glass ware, Paints Semiconductor Industry, Pesticide
Cadmium 7440-43-9	Ingestion Inhalation Dermal	Lung, Kidney Breast	Adult, Blood < 5 µg/L	IARC, Vol.: 58 (Group 1), 1993 Carcinogen	IARC, Vol.: 58 1997 Carcinogen	Soils, Rocks Water	Rechargeable Batteries, Mining Household Waste, Burning Coal Industry
Chromium (VI) 7440-47-3	Ingestion Inhalation	Lung, Breast	Urine < 30 µg/g	IARC, Vol.: 49 (Group 1), 1990 Carcinogen	EPA, IRIS 1998 Carcinogen	Air, Soil	Chrome Plating, And Leather Tanning
Iron 7439-89-6	Ingestion Inhalation Dermal	Gastrointestinal Tract, Kidney Liver, CVS		IARC, Vol.: 34 (Group 1), 1987 Carcinogen	IARC, Vol.: 34 1987 Carcinogen	Earth's Crust	Used in making Steel, Welding
Lead 7439-92-1	Ingestion Inhalation Dermal	Brain, Liver, CNS, LBW Decreased Sperm Count Reduced Growth, Slowed Cognitive Development Spontaneous Abortions	Blood, Adult <30 µg/dL Children < 10 µg/dL	IARC, Vol.: 87 (Group 2A), 2006 Probably	IARC, Vol.: 87 2006 Carcinogen	Earth's Crust Soil, Water	Burning Fossil Fuel, Batteries, Pipes Lead Processing Facilities, Electrical Mining, Traps and Solder
Nickel 7440-02-0	Ingestion Inhalation Dermal	Lung, Skin, Kidneys Nasal, Breast	Urine, Adult < 5 µg/L	IARC, Vol.: 49 (Group 1), 1990 Carcinogen	IARC, Vol.: 49 1997 Carcinogen	Volcanoes Water Soil	Rechargeable Batteries, Welding Fossil Fuel Combustion, Glass Bottle Production, Coin & Jewelry Making
Zinc 7440-66-6	Ingestion Inhalation Dermal	Gastrointestinal Tract Immune System, Blood Pancreas		No	No	Earth's Crust Soil, Air Water	Pennies, Dry Cell Batteries, Drug Industry, Hazardous Waste Sites Producing Rubber, Preserving Wood

Footnote: Carcinogenic to humans (Group 1), probably carcinogenic to humans (Group 2A), possibly carcinogenic to humans (Group 2B), Not classifiable as to its carcinogenicity to humans (Group 3), Cardiovascular system (CVS), Central Nervous System (CNS), Low Birth Weight (LBW)