REVIEW PAPER

Environmental and chemical risk factors for breast cancer: A review of the current understanding of environmental toxic metal-induced breast malignancies, Nigeria perspective

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Abstract

Breast cancer is the most commonly diagnosed cancer in women worldwide, with an increasing number of new cases each year. The incidence of breast cancer is sadly increasing at the same time as environmental toxicants, particularly in Africa nations like Nigeria. Toxic metals are significant environmental pollutants and their toxicity results in harmful health effects. Numerous studies have described environmental exposure of humans to toxic metals in African populations, and the most commonly implicated toxic metals include arsenic, cadmium, chromium, copper, lead and nickel, all of which impact negatively on human health and the environment. Recently some of these toxic metals have been linked to the development of different types of cancers including breast cancer. Given the large burden of the morbidity and mortality associated with breast cancer, it is of the upmost importance to identify predisposing risk factors so that appropriate preventive strategies that could reduce cancer incidence can be developed and implemented. Therefore, this review aims at elucidating the role of environmental toxic metals in the development of breast cancer.

Biological: Toxicology. Keywords: Nigeria, breast cancers, environmental toxic metals

1.0 Introduction

Breast cancer is the most common type of cancer in women and it is the second leading cause of cancer death among women[1]. Itis also seen in men, but it is rare. It displays clonal cell proliferation, like other cancers, and has diverse histological presentations. Breast cancer is currently the most common type of cancer worldwide, with 2.26 million cases recorded in 2020[2]. It is the most common cancer among women both in developed and developing countries, and a major cause for public health concern[2]. It has been predicted that the worldwide incidence of female breast cancer will reach approximately 3.2 million new cases per year by 2050[3]. These numbers reflect the magnitude of breast cancer incidence, its effect on society worldwide and the need for urgency for preventive and treatment measures. The incidence of breast cancer has been on the rise in developing countries like Nigeria, thought the incidence is higher in the developed countries than in the developing countries[1]. Although breast cancer occurs in women of all races, a disparity exists in diagnosis, mortality, and survival[4]. For example, African American women have a 42% higher breast cancer death rate compared to Caucasian women despite recent advancements in management of the disease[5]. Among African American women, a 10-year report between 2000 and 2010 indicated that breast cancer

mortality increased from 30.3% to 41.8% and that at the advanced stage, 5% of breast cancers are detected among Caucassian women compared to 8% of breast cancers among African women[6]. It is disconcerting to note that although incidence in the African region was, despite rising, relatively lower than on other continents except from Asia, its age-standardized death rate was the highest globally. Nigeria, the most populous African nation, has the highest mortality rate[7].

Recently, breast cancer is the leading cause of cancer deaths, representing about 25% of all cancer cases and approximately 18% of deaths are attributed to it in Nigeria as seen in Figure 1[8]. Studies have revealed that the majority of Nigerian women, both in rural and urban regions, have little to no understanding of the risk factors and symptoms of the disease[9].

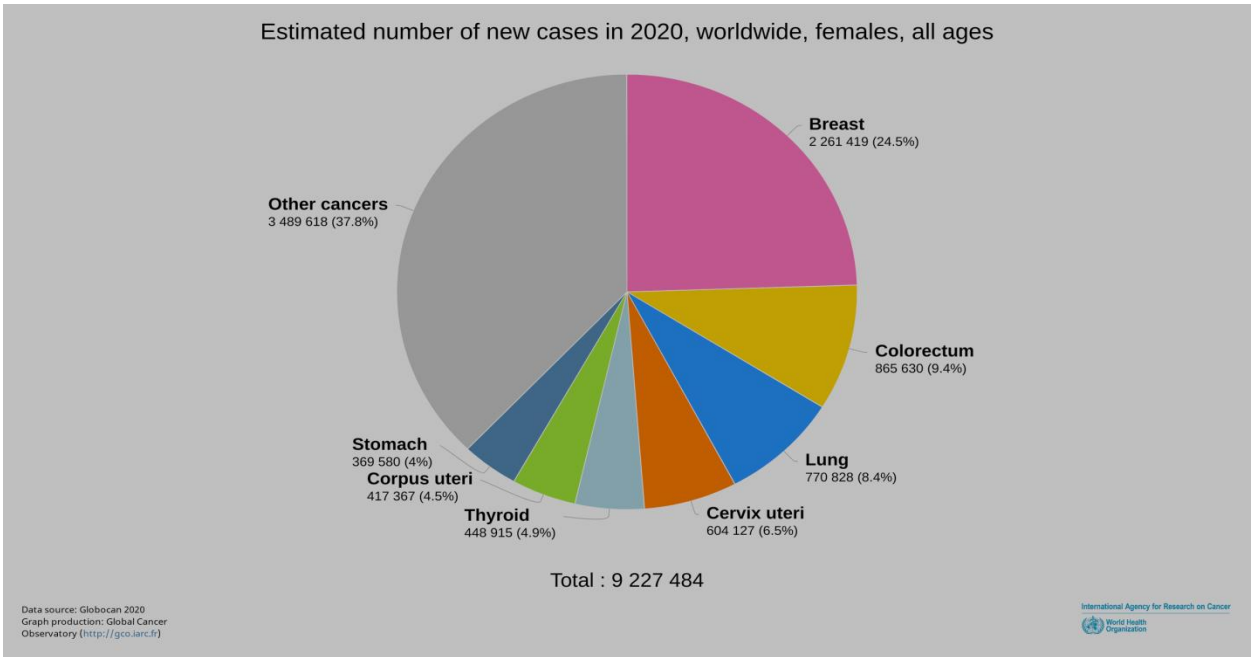

Figure 1: Number of new cases in 2020, females, all ages, Nigeria;

Source: Global Cancer Observatory, 2021

Race/ethnicity, advanced age, age at menarche, and age at first life birth are among the risk factors for developing breast cancer. Additionally, germline mutations in the tumour suppressor genes, breast density, radiation exposure, obesity, estrogen exposure, and environmental pollutants are other risk factors[10].

Breast cancer is typically discovered in Nigerian women at an advanced stage, so survival rateis poor[11], because patients do not routinely do their breast examinations and not many of them get routine mammograms. Breast cancer cases in Nigeria have historically been low, but they are increasingly rising as a result of urbanization and lifestyle modifications. The incidence of breast cancer is sadly increasing at the same time as environmental toxicants, particularly in emerging nations like Nigeria due to inadequate waste management, indiscriminate mining activities, and overall disrespectful environmental stewardship; this is supported by recent studies that suggest that environmental wastes are largely responsible for breast cancer[12].

These review aims at elucidating the role of environmental toxic metals in the development of breast cancer, and hence provide adequate information on the dangers of chronic exposure to toxic metals. This will encourage minimal exposure to environmental toxins and encourage policies by the

government that will reduce environmental toxicants, improve health facilities, and support inexpensive and early detection of breast cancer.

2.0 Pathogenesis of Breast Cancer

The aetiology of breast cancer is multi-factorial with the interplay of several genetic and environmental factors. These may act independently or in combination, especially in high-risk individuals. Genetic predisposition is one of the most intellectually intriguing factors associated with increased risk for breast cancer. The growing knowledge base about the fundamental changes in gene structure and expression involved in tumorigenesis suggest that patterns of risk can be precisely defined on a person-by-person basis.

Mutations in tumor suppressor genes including BRCA1, BRCA2, and CHEK2 that cause loss-of-function in the germline are responsible for the clonal proliferation of mammary gland cells that results in a carcinoma. These genes are involved in DNA repairs to maintain genomic integrity. These mutations might be spontaneous or inherited. Their phenotypic expressions are influenced by their surroundings.

The inherited defective genes are the cause of familial/hereditary breast cancer. The ataxia-telangiectasia mutated (ATM) gene recognizes DNA damage when it occurs in a cell and the cell cycle is stopped by CHEK2 and p53 genes. At this moment, BRCA1, BRCA2, and CHEK2 start an attempt to repair the DNA. When the repair fails, the cell goes through apoptosis. The cells with damaged DNA survive and spread this mutation that will eventually cause cancer in the presence of defective genes involved in carrying out the vital physiological duties of DNA repairs[13, 14]. Other risk factors for sporadic breast cancers include hormone exposure, gender, age at menarche and menopause, past pregnancy, and exogenous estrogen. Environmental variables have a role as well. These factors include exposures to radiations and chemicals with estrogen-like effects and toxic metals which this review aims to explore.

3.0 Exposure to Toxic Metals as Risk factor for Breast Cancers

Toxic metals are relatively dense metallic elements, some of which are hazardous or deadly even at low concentrations, and are distinguished by their potential for bioaccumulation and non-biodegradation[15]. There are many different toxicants in our surroundings that have negative effects on human health. The majority of these toxins are hazardous metals, such as mercury, cadmium, arsenic, lead, and aluminum. The air, water, soil, plants, animals, cigarettes, and other products contain these heavy metals, which are ubiquitous. Over time, they build up in the body and cause toxicity-related diseases like cancer, hypertension, infertility, anemia, emphysema, osteomalacia, and cognitive decline[16]. In recent years interest has risen in the possibility that exposures to environmental pollutants, such as the toxic metals, mercury and cadmium, could be risk factors for breast cancer. These toxic metals have been examined in numerous epidemiological studies and tissue investigations in relation to breast cancer, which is crucial since synergistic effects of toxic metals in causing cellular damage are progressively being recognized[17, 18]. Consuming meals contaminated with these toxicants can result in acute, chronic, or latent toxicity. When compared to other routes, eating contaminated food accounts for more than 90% of human exposure to harmful substances.

3.1 Cadmium (Cd)

Cadmium is a widely known toxic metal that mostly gets into the environment during the manufacture of zinc[19]. Due to its extremely very long biological half-life, chronic exposure to cadmium poses dangerous threat particularly to human health, taking approximately 10 years to induce kidney injury, which is the main organ for long-term Cd accumulation[20]. Smoking is one of the main non-occupational sources of Cd exposure for people, but for non-smokers, exposure is primarily caused

through contaminated water, air, and food[21]. In contrast to non-smokers, smokers were shown to have significantly greater amounts of Cd in body tissues. Additionally, a number of variables, including age, sex and nutritional status affect Cd absorption in the body[22]. For instance, women's higher blood and urine Cd concentrations compared to men's are likely due to their lower iron (Fe) status[22].Cd accumulation increases with age due to the body's tendency to store the metal and its extremely slow rate of elimination. In general, epidemiological research looking into Cd exposure using various approaches generally supports the idea that Cd exposure might increase the risk of breast cancer development in women; the submission that occupational exposure to Cd increases the incidence of breast cancer in African-Americans and Caucasian further buttresses this fact. Rising industrial activity had increased the exposure to cadmium toxicity and chronic exposure to Cd in the environment and biological tissues has significant potential negative consequences on health[23]. In a study carried out in Nigeria, breast cancer was linked with increased serum cadmium levels[24]and according to Mona et al. 2010[25]breast cancer patients had greater tissue and urinary concentrations of cadmium than non-cancer patients. Higher cadmium concentrations were linked to ER/PR negative breast tumors, according to an early study by Kresovich et al, 2019[26] involving 676 Chicago breast cancer patients. Also, another study reported that postmenopausal breast cancer is more likely to occur in areas with greater airborne hazardous metal concentrations, particularly cadmium[27]. Higher concentrations of cadmium were seen in breast tissues of breast cancer patients than non- cancer patients[27]. Cadmium is a divalent metal that acts as a metalloestrogen and its possible link with the development of breast cancer might be via the stimulation of estrogen receptor alpha(ERa). This stimulation leads to switching on of pro-survival genes such as c-myc (a master regulator of cellular metabolism and proliferation) and Cyclin D1 alongside other genes associated with cell growths like Insulin-like Growth Factor 1(IGF-1). The work of Alonso-Gonzales et al, revealed the estrogenic impact of cadmium by observing the development of lobulo-alveolar structures in the mammary gland of ovariectomized mice after intra-peritoneal administration of cadmium[28]. It has also been demonstrated that prolonged exposure to cadmium causes breast cancer cells to develop into more aggressive, invasive carcinomas that are resistant to the chemotherapy drug, 5-fluorouracil. Cadmium also prevents p53 from being activated after long-term exposure.

Cadmium has a number of cellular effects which include modification of bio-molecules, modulation of DNA structure and genotoxic consequences. Specifically, Cd is known to impair DNA repair mechanisms and apoptosis[29]. Cadmium is also a competitive antagonist of zinc which is well known for its role in DNA repair mechanisms. This toxic metal had also been implicated in oxidative stress; a phenomenon widely recognized for its role in DNA damage[23]. Cadmium is reported to impair the p53 gene, a protein involved in tumor suppression through a number of mechanisms including apoptosis and it also induces cancer by genotoxic or non-genotoxic mechanisms[30, 31]. Cadmium's ability to inhibit DNA repair has been demonstrated repeatedly and it has been implicated in the alteration of epigenetics[32]which is a recently recognized mechanism of gene expression that does not involve DNA sequence alteration. Exposure to cadmium results in chromosomal aberrations, sister chromatid exchange, DNA strand breaks, and DNA-protein crosslink in a variety of cell lines[33]. One of the most precarious types of DNA damage is a break in a DNA strand; if the break is poorly repaired, it can cause severe chromosomal rearrangements, aneuploidy, and eventually malignancy. Maintaining genomic integrity is greatly aided by DNA repair, and defects in the repair enzyme systems are known to encourage the growth of a tumour. A human hamster hybrid (AL) cell type, CD59 locus, known to be particularly effective in detecting mutations including significant deletions, has been revealed to be susceptible to cadmium-induced mutation[34]. One of the mechanisms of breast cancer promotion may be based on Cd-induced epithelial-mesenchymal transition, mediated by downregulation of miR-30 followed by upregulation of Snail – master regulator of epithelial-mesenchymal transition; Cd elevates CpGdemethylation and enrichment of specific transcription

factors in the gene promoter of oncogenic PRMT5 and EZH2 methyl-transferases resulting in their elevated expression in breast cancer cells, as the mechanism of epigenetic toxicity[35]. Also, Cd may promote breast cancer cell proliferation, migration and invasion by impaired autophagosome formation, resulting from Cd-induced inhibition of ACSS2 expression, and further enhancement of H3K27 acetylation in the gene promoter region of key autophagy factor (ATG5)[36].

3.2 Arsenic

Arsenic had been in use as a pharmaco-therapeutic agent and humans are exposed to it via drinking water, skin contact or inhalational route[37]. It exists in organic and inorganic forms. A recent study in Nigeria, found that at least 46 % of the beverages in the Nigerian market contain arsenic in quantities well over the prohibitive level set by the United States Environmental Protection Agency (USEPA) guideline[38]. There is therefore increase risk of exposure considering habitually high/large volume intake of these beverages both in the young and the old especially during the dry seasons[38].

A change to ER/HER2/PR negative basal-like breast cancer cells was reported by Xu et al where the effects of chronic low dosage exposure to inorganic arsenic on breast epithelial cell lines was studied[39]. Arsenic alters the mitochondrial metabolism of reactive oxygen species by accumulating acetylated manganese superoxide dismutase (MnSOD) with inhibition of sirtuin, a tumor suppressor gene[40]. The hypoxia-induced factor 2a (HIF2a) is activated by the acetylated manganese superoxide dismutase inducing the normal epithelial cells of the mammary gland to become malignant[40].Lopez–Carillo et al[41], reported that people who have genetic ability to methylated arsenic have two-fold odds for developing breast cancer. They continued by stating that people who have higher urinary levels of methylated methylarsonic (MMA) compared to unmethylated inorganic arsenic are more likely to develop breast tumors that are ER-positive, HER2-negative, and PR-positive[41]. Selmin et al in 2016[42] asserted that treatment of cancer cells with NaAs111 (sodium arsonate) results in a decrease in the expression of ER and BRCA1. Arsenic exposure can also trigger epigenetic alteration in a number of cellular processes, which can result in malignancy. Inorganic arsenite has been shown to inhibit DNA mismatch repair, which can lead to genomic instability, activation of pathways linked to uncontrolled cell proliferation, transition of epithelial cells to mesenchymal cells, stimulation of inflammation and angiogenesis via activation of NFkB and VEGF, and increased cellular tyrosine phosphorylation, which can result in aberrant cell signaling and buildup of reactive oxidative species; all promoting cell death[43, 44].Previous work has also found that exposure to inorganic arsenic can result in chromosomal abnormalities, stimulation of sister chromatid exchange, and the silencing of DNA methyl-transferases which can inhibit the cell repair cycle and additionally interfere with important tumor suppressor genes like p16[44].

3.3 Lead (Pb)

Pb is a metalloestrogen of major concern in Nigeria due to its many industrial and domestic uses, its presence as tetraethyl lead in gasoline, and the largely uncontrolled dumping of its residues contaminating the soil and the water supplies in many parts of the country[45]. A large portion of the Nigerian population especially the children is chronically exposed to Pb even at low dose. A study revealed that excessive use of alcohol and tobacco, undue exposure to exhaust from vehicles using leaded gasoline, exclusive use of wells as sources of drinking water and increased consumption of the Nigerian table salt may all be pathways for increased Pb burden in the country[46]. Another study also suggested depressed immune status in workers occupationally exposed to Pb in Nigeria[47]. Other significant sources of airborne Pb in Nigerian cities include the use of fire-wood for cooking, manufacturing industries such as cottage industries, and most especially those with poor or no pollution control measures. Garbage burning in the open, which is a common practice for waste management; the burning of household and commercial waste, wood, paper products, plastics, discarded tires, battery casings, agricultural wastes, etc, increase Pb release into the environment[47]. It

was reported in a study done at Abeokuta, South West, Nigeria that occupationally Pb-exposed auto-mechanics exhibited mean blood and hair Pb levels of 48.50 ± 9.08 µg/dL and 17.75 ± 5.16 µg/g, respectively which is higher than levels measured in occupationally unexposed controls, 33.65 ± 10.09 µg/dL in blood and 14.30 ± 5.90 µg/g in hair from the same city[48]. In a study to evaluate the degree of lead exposure and renal function tests in Port Harcourt, Nigeria, it was found that occupationally exposed participants had higher mean blood lead levels (50.37 ± 24.58 µg/dL) than controls[49].

Several studies have found a link between blood level of lead and breast cancer. Many epidemiological researches showing association of tissue lead levels with female breast cancers included other toxic metals like cadmium and mercury. This was the case in the work of Wei and Zhu 2020[50] in which they examined sample from 9260 American women; it was discovered that the higher blood levels of Pb and Cd significantly increases the likelihood of breast cancer in the women. Alasia et al, reported elevated concentrations of Pb in the blood and hair specimen of Nigerian patients diagnosed with infiltrating ductal carcinoma of the breast[49]. Pb had been shown to induce many epigenetic alterations which are possibly one of the mechanisms by which it causes malignancies[51].In a study carried out at Obafemi Awolowo University, Ile-Ife, Nigeria, higher levels of Pb were found in blood and head hair samples of newly diagnosed patients with breast cancer, all with infiltrating ductal carcinoma, the most common form of breast cancer in Nigeria[45]. Alatise also reported that the Pb levels in hair samples of the studied patients were directly correlated with the volumes of their tumors suggesting tumor growth-promoting effects of Pb[45].

Lead had been linked with alterations in the functions of tumor-regulating genes and DNA damage, simultaneously impeding DNA damage repair. In a trial where mice were exposed to Pb, it was submitted that Pb induces ROS production and alters the function of specific genes by altering the sequence of the genes[52].Another significant report in connection to Pb's ability to impair typical cellular physiological processes was evidence of its effect in controlling common transcriptional reactions where Pb is substituted for zinc which is a metal catalyst for several important enzymatic processes regulating DNA structure[52].

3.4 Mercury

Mercury exists in three forms namely: the elemental form(Hg) which is largely considered as non-toxic, the organic (such as ethyl mercury and methyl mercury), and the inorganic form such as Hg^{+} and Hg^{2+}[53]. Both the organic and the inorganic species are considered toxic and carcinogenic. Mercury as a xenoestrogen (i.e. metalloestrogen) binds to estrogen receptors and causes increased transcription of genes that are regulated by estrogen thereby causing the proliferation of estrogen-dependent cells[54]. According to WHO report in Nigeria, not less than 850,690 people are at risk of mercury poisoning. In March 2019, the Federal Ministry of Health (FMoH) of Nigeria and WHO identified some communities in 12 states in Nigeria as having the highest risk of poisoning from mercury as a result of mercury-dependent artisanal and small-scale gold mining[55].

Gaudet et al, on treating MCF7 breast cancer cells in an in vitro experiment with low and high doses of methylmercury, demonstrated that methylmercury induces proliferation of cancer cells at low doses and apoptosis at high doses[56]. Martin et al comparing the effect of low dose mercuric chloride on cancer cells showed that the cells that were treated with it had 2- to 5-fold increase in rate of proliferation compared to the untreated cells[57]. Mercury was found in both the cancer and normal breast tissues when laser-ablation inductively coupled plasma mass spectrometry (LA ICP-MS) was used to measure mercury concentrations in mastectomy tissues of patients with invasive ductal breast carcinoma[58]; this serves as additional evidence of mercury's contribution to the development of breast cancer. Toxic metals like mercury have the potential to cause cancer directly through gene mutations,

epigenetic alterations, or by functioning as estrogen-simulating agents after binding to estrogen receptors[59, 60]. Mercury interferes with DNA repair mechanisms, and mutations in genes such as *BRCA1* that play a part in DNA repair and are associated with breast cancer, suggesting that these environmental toxins and gene mutations may disrupt DNA repair mechanism[61, 62]. Atmospheric mercury has been reported to be the most strongly associated with breast cancer according to White in 2019[27]. Mercury is known to have estrogen-simulating properties[63] as well as the potential to cause genetic mutations[62] and epigenetic changes, and it can also promote proliferation of malignant breast epithelial cells[64]. The amount of mercury in breast milk has been extensively studied because of concerns about transfer of the toxic metal to the fetus[65]. Mercury transporters have been described in human breast glands and these could facilitate the transfer of mercury from the systemic circulation into breast epithelial cells and secretions[66]. Mercury was usually present in only a small percentage of lobules within individual samples. This is probably because mercury transporters (such as breast cancer resistance protein, BRCP/ABCG2) are normally found in many capillaries, but in only a few lobules, in the human breast[67].Mercury transporters are probably needed to move circulating mercury into the luminal epithelial cells in the breast capillaries, where it is subsequently transferred into the lumen secretions as shown in figure 2[58].

It has been suggested that the export protein BRCP facilitates the secretion of nutrients into milk, but that there is typically little chance of xenotoxins contaminating the milk[66]. The ability to produce free radicals (ROS), as well as the disruption of DNA, whether connected to transcription processes, changes in the maintenance of its molecular structure are the mechanisms at play[45]. Also, mercury has the ability to reduce levels of glutathione[45], a naturally occurring antioxidant, thereby enhancing the production of reactive oxygen species. Cells that are exposed to oxidative stress have been demonstrated to have increased rates of lipidperoxidation, which has been proposed as another functional mechanism by which mercury induces malignancies[12]. Within the cells, mercury has been implicated to influence the function of microtubules, which by their activity can disrupt cellular mitosis[68].

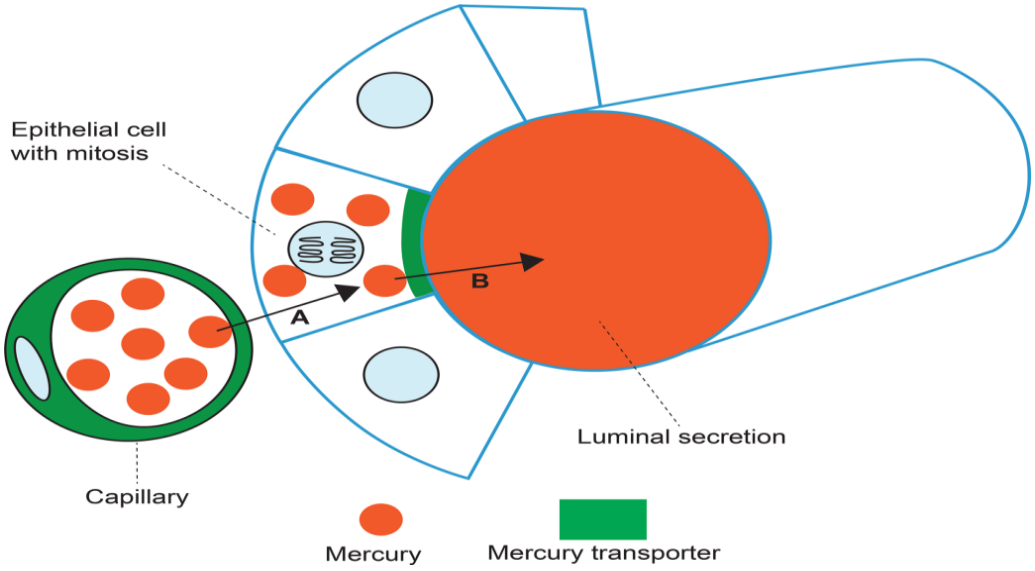

Figure 2: Proposed transfer of circulating mercury through breast epithelial cells into ductules. (A) A capillary with mercury transporters transfers circulating mercury into a luminal epithelial cell. (B) An epithelial cell with apical mercury transporters transfers mercury into the lumen of the breast ductule. Luminal epithelial progenitor cells that are undergoing mitoses may be particularly vulnerable to the genotoxic effects of mercury[58].

3.5 Chromium (Cr)

Cr is found in the earth's crust and seawater and is a naturally occurring toxic metal released during industrial processes[69]. Cr has multiple oxidation states ranging from −2 to + 6, in which the trivalent and hexavalent forms are the most common stable forms[70]. Cr (VI) is related to a series of diseases and pathologies while Cr (III) is required in trace amounts for natural lipid and protein metabolism and also as a cofactor for insulin action[71, 72]. The primary route of exposure is inhalation, while oral ingestion of contaminated water and food or direct dermal contact with products containing chromium are other potential routes.

Chromates have been known to be potent inducers of cancer in exposed workers. *In vitro* studies indicate that both Cr(VI) and Cr(III) induce genotoxicity in culture cells, although mechanisms of their toxicity may be different. Cells exposed to chromium complexes, especially Cr(VI) species, can generate a diverse array of DNA lesions, including SSB, alkali-labile sites, DPCs, DNA–amino acid cross-links and chromium–DNA adducts, as well as the formation of protein–Cr(III)–DNA cross-links, the most likely cause of mutations in Cr(VI)-treated cells. *In vivo* experiments have demonstrated that Cr(VI) is carcinogenic, but the carcinogenicity of Cr(III) is uncertain[73].

3.6 Aluminum(Al)

Aluminum (Al) is the most widely distributed metal in the environment[74] occurring naturally in the trivalent state (Al^{+3}) as silicates, oxides and hydroxides, but it may be combined with other elements such as chlorine, sulphur, fluorine, as well as form complexes with organic matter[75]. Exposures to Al occur in occupations associated with mining and processing of ore, scrap metal recycling, deployment and use of Al-containing compounds and products, and during engagement in Al metal cutting, sawing, filing and welding. Aluminum Phosphide is a cheap, effective and commonly used pesticide by farmers in Nigeria. It is used as a rodenticide, insecticide and fumigant for stored cereal grains to kill small verminous mammals such as moles and rodents. It is the most common cause of poisoning among agricultural pesticides, and it liberates lethal phosphine gas when it comes in contact either with atmospheric moisture or with hydrochloric acid in the stomach[76].

Aluminum is a metalloestrogen, a type of inorganic xenoestrogen that is capable of binding to cellular estrogen receptors and mimicking the actions of physiological oestrogens[77]. The most commonly used aluminum-based compounds in underarm cosmetic products (UCP) are aluminum chloride and aluminum chlorohydrate. The human breast tissue is exposed to aluminium from many sources including diet and personal care products, but dermal application of aluminium-based antiperspirant salts provides a local long-term source of exposure. Recent measurements have shown that aluminium is present in both tissue and fat of the human breast but at levels which vary both between breasts and between tissue samples from the same breast[12]. Recently a study found increased levels of aluminum in non-invasively collected nipple aspirate fluids taken from breast cancer patients (mean 268 ± 28 μg/l) compared with control healthy subjects (mean 131 ± 10 μg/l) providing evidence of raised aluminum levels in the breast microenvironment when cancer is present[12] . This environmental carcinogen accumulates in the human breast, transforming MCF-10A human mammary epithelial cells and inducing DNA double-strand breaks (DSB). These effects have been exhibited *in vitro* with similar concentrations of aluminum to those measured in the human breast[12]. Not only do aluminum salts trigger DNA DSB, they can lead to oxidative stress, proliferation, and interference in estrogen action before and with metastasis. The concentrations of aluminum in the culture medium transform the MCF-10A human mammary epithelial cells, therefore enabling them to produce tumors that can metastasize[78].

4.0 Future Direction

The Nigerian environment is laden with metallic toxicants and other hydrocarbon carcinogens. With the rapid expansion of industrialization and mining activities that are just beginning in the developing countries, it is to be anticipated that cadmium, lead, mercury and so on will further be released into the atmosphere, water sources and landfills. Future toxicology research involving large populations in Nigeria and molecular studies that will further elucidate the impact of toxic metals in the development and progression of breast cancer are encouraged.

5.0 Conclusions and Recommendations

Toxic metals are ubiquitous. Most of these metals have been designated as carcinogens and they have been identified as some of the causes of breast cancer. Unregulated mining activities, chronic low exposure in pesticides, cosmetics, industrial wastes, locomotive machines and inappropriate recycling of waste in Nigeria should be addressed by government and lasting solutions provided. Public health interventions and policies should also be implemented that will reduce the level of exposure to these toxic metals.

List of Acronyms

- Vascular endothelial growth factor (VEGF)
- United States Environmental Protection Agency (USEPA)
- Federal Ministry of Health (FMoH)
- World Health Organization (W. H.O)
- Laser-Ablation Inductively Coupled Plasma Mass Spectrometry (LA-ICP)
- Underarm Cosmetic Products (UCP)
- Double-Strand Breaks (DSB)
- Insulin-like Growth Factor 1 (IGF-1)
- Reactive Oxygen Species (ROS)
- Deoxyribonucleic acid (DNA)

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