

## Environmental Chemical Risk Factors of Breast Cancer in Nigeria: Chemicals in Skin Lightening Products

Olumide YM\*, Ayanlowo OO, Akinkugbe AO and Otofrowei E

Department of Medicine, College of Medicine of the University of Lagos, Surulere, Idiaraba, Lagos, Nigeria

### \* Corresponding Author

Yetunde Mercy Olumide, Emeritus Professor of Medicine, Department of Medicine, College of Medicine of the University of Lagos, Surulere, Idiaraba, Lagos, Nigeria.  
Tel: +234 803 344 6614, Email: mercyolumide2004@yahoo.co.uk

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### Abstract

Two monstrous female health-related issues are currently engaging the attention of the global community viz, (i) the chemical skin-lightening issue and (ii) the rising female breast cancer issue. Since the skin-lightening chemicals are notable endocrine disruptors, a research question has been entertained for a possible link between skin lightening cosmetics and breast health.

Mercury and hydroquinone have been used as skin lightening agents for more than five decades since the inception of the skin bleaching practice. Methylmercury is IARC Group 2B carcinogen. Methylmercury and hydroquinone have immunotoxic, embryotoxic and endocrine disruptor (ED) effects, hence, breast cancer risk factors. Mercury chloride has shown some carcinogenic activity. Hydroquinone causes the release of Trimethylamine (TMA) and N-Nitrosodimethylamine (NDMA), members of the family of extremely potent carcinogens which are EDs hence risk factors for breast cancer. Skin bleachers release fumes of TMA and NDMA which may be of environmental public health importance (like tobacco smoke) to non-bleachers. Oxybenzone and Titanium dioxide, the main ingredients in sunscreen chemicals, often incorporated in skin-lightening products are carcinogens and Endocrine disrupting chemicals, hence breast cancer risk factors. Other notable EDs in skin lightening cosmetics are phthalates, and heavy metals contaminants. These chemicals are modifiable breast cancer risk factors; there is need for public health approach to long-term prevention of breast cancer.

**Keywords:** Breast Cancer, Skin lightening chemicals, Methylmercury, N-Nitrosodimethylamine, Oxybenzone, Public health approach

## Background

Possible links have been suggested between skin lightening cosmetics and breast cancers. This study explores the relevance of the active ingredients in skin lightening products which have been used since the inception of the skin-lightening practice (over five decades) in Nigeria. These chemicals are mercurials, hydroquinone, heavy metal contaminants and oxybenzone and Titanium dioxide in sunscreens.

## Introduction

The use of chemicals to lighten the skin colour is a global practice and has no boundaries because we live in a globalized world. The chemicals are constituents of cosmetic products used to deliberately alter the skin colour in naturally dark skin people e.g. homeland and diasporic Africans or to even-out the tone of the skin colour by Caucasians with unevenly sun-tanned skin and other pigmented skin blemishes e.g. melasma and freckles. The global epidemiology of skin lightening (bleaching) has been comprehensively characterized in the two-volume book by Olumide [1]. The clinical complications of chronic use of skin lightening cosmetics have also been described [2]. Nigeria is the most populous African nation and is in the lower middle-income group. Two monstrous health-related issues are currently engaging the attention of the global community: the chemical skin-lightening issue and the rising female breast cancer issue. Breast cancer is the most common type of cancer and cause of cancer-related mortality among women worldwide, but the burden is not evenly distributed as regards incidence, mortality and survival between different countries and regions. Recent attention has focused on the rising rates of breast cancer across Africa [3]. Globocan's 2018 cancer statistics shows that Nigeria has one of the highest incidences and 5-year prevalence rate of breast cancer globally. Furthermore, Nigeria's age-standardized mortality rate ranked highest globally [4]. In many African countries, between 25 and 80% of women regularly use skin lightening products. The motives for total body surface skin lightening translate to three words—'security,' 'self-worth,' and 'significance.' Light skin tone can be transformed into social capital (social networks), symbolic capital (esteem or status), or even economic capital (high-paying job or promotion). The drivers and enablers of the skin bleaching culture are formidable. Nigeria has about the world's highest percentage of women engaged in skin lightening. According to the World Health Organization, 77% of women in Nigeria use skin lightening products [5]. The recognized risk factors for breast cancer have

not been examined in interaction with environmental chemical exposures. The research question is then entertained if there is a possible link between the chemicals in skin lightening products and the raging breast cancer burden.

## Context

Skin lightening products classically contain steroids, mercury, hydroquinone, sunscreen (UV Filters) notably oxybenzone, titanium dioxide, phthalates found in fragrance, and heavy metals contaminants. Skin lightening products are available as topical preparations—creams, serums, soaps, intimate wash etc. They are also marketed as pills, injectables and beverages e.g. tea. Once initiated into the use, usually in adolescence, the products are used to maintain the light skin for life. Hence, the products are used for several decades except visible cosmetically disfiguring complications occur e.g. exogenous ochronosis. Pregnant women also intensify the use of the chemicals to attenuate the hormone induced darkening of the skin in pregnancy. Some mothers also use the products on their babies. All these chemicals are known endocrine disruptors. Breast cancer's is an endocrine dependent malignancy.

Endocrine Disrupting Compounds (EDCs) are defined by the Endocrine Society as "an exogenous [non-natural] chemical, or mixture of chemicals, that interferes with any aspect of hormone action [6]." Endocrine Disrupting Compounds (EDCs) are also called Xenoestrogens, "environmental hormones," or "estrogen mimics."

The breast can be extremely vulnerable at times of growth and change such as puberty and pregnancy. Increased lifetime exposure to estrogen, other hormones and higher exposures in early life links many of the established risks factors for breast cancer and are a key factor in the disease development [7]. Timing of exposure can be more important than dose. Female breast tissue may be more susceptible to environmental influences because of changes in the breast through puberty, menstruation, pregnancy and menopause. None of the established risk factors directly causes the disease. Furthermore, the unborn baby (the fetus) can be extremely vulnerable to the development of various serious diseases later in life which may not be manifest at birth. Such serious diseases include developmental, neurological, or cancerous, including breast cancer [7].

Many common environmental chemicals are mammary gland carcinogens in animal studies [8]. They activate relevant hormonal pathways, or enhance mammary gland susceptibility to carcinogenesis. Breast cancer long latency and multifactorial etiology make evaluation of these chemicals in humans challenging. For chemicals previously identified as mammary gland toxicants, epidemiologic studies and evidence of exposures during biologically relevant windows of organogenesis (in utero, adolescence, and pregnancy) help to assess relevance of the toxicants to the disease when diagnosed. The cause of most breast cancer is unknown, but a new study found that women exposed in the womb to the now banned pesticide in the USA, dichlorodiphenyltrichloroethane (DDT), have a quadrupled risk of developing the disease. Women who were exposed to the pesticide during the 1950s and 1960s are just now reaching the age of heightened breast cancer risk. In addition, daughters exposed to the higher levels of DDT were more likely to be diagnosed with aggressive tumors and advanced stages of the disease, according to the study. Although it has been banned throughout most of the world, DDT is still used in Africa to kill mosquitoes that carry malaria, which sickens 200 million people worldwide every year [9].

Finally, obtaining prevalence rates on use of skin lightening products is challenging. Skin bleaching is a highly stigmatized practice in most countries in Africa which people are unwilling to discuss and often keep to themselves as a secret. Unless they have problems they are not likely to reveal the habit and even when complications compel them to seek, medical help, they tend to deny the use of skin bleaching agents but would rather divert the attention of the dermatologist/health care provider to an imaginary causal “allergy” from diet. Some studies have also shown that some analphabetic women genuinely do not know that the cosmetic product they are using contain skin lightening chemicals. It is therefore not sufficient to base studies solely on questionnaires; the products used should also be analyzed for the active ingredients when possible. In countries with highly repressive laws on skin bleaching (like the Gambia) [1], the patient will never admit the use of bleaching agents.

### **Racial disparities in breast cancer**

Breast cancer is widely recognized as a highly heterogeneous disease, commonly characterized by the gene or hormone receptor expression pattern of the tumor. Black – White racial disparities in breast cancer subtype have been identified and are etiologically distinct [10]. African – Americans are 2 to 3 times more likely to develop estrogen receptor negative (ER-), estrogen

and progesterone receptor negative (ER-/PR-), or triple negative tumors (ER-, PR- and human epidermal growth factor receptor, HER2 negative), subtypes of the disease. This statistically significant disparity has meaningful clinical implications, as hormone receptor negative (HR-) tumors are associated with larger and higher-grade carcinomas at the time of diagnosis and are not responsive to current endocrine-based treatments such as Tamoxifen and Herceptin. As a result, women diagnosed with HR- tumors have higher rates of five – year cancer – related mortality than women diagnosed with other types of breast cancer regardless of tumor stage at the time of diagnosis. It is noteworthy that Nigerian breast cancer patients have identical subtypes [11], clinical and behavioral characteristics as African Americans i.e. triple negative tumors, early age of onset, clinically aggressive and poor prognosis. As a result, identifying factors that influence the development of HR- breast cancer may be critical to developing upstream interventions to reduce mortality disparities.

Several interplay of factors have been hypothesized as responsible for these racial disparities. Some of them are several lifestyle characteristics of Africans and African Americans which include the use of skin lighteners and hair relaxers. In a recent breast health study in Ghana [12], a country in West Africa, researchers conducted a breast health study to shed further light on the relationship of skin lighteners and hair relaxers on breast cancers among African women. This was a population-based case-control study using a questionnaire to ascertain past/present use of skin lighteners. The researchers concluded that “This study does not implicate a substantial role for skin lighteners as breast cancer risk factors.” It is worthy of note that the study did not search for any of the chemicals in skin lightening products e.g mercury in the cancerous breast tissue (obtained through biopsy/mastectomy), nor did the study look for biomarkers of any of the chemicals e.g in urine/blood. It is also worthy of note that history of use of skin lightening products is not often reliable as stated above. However, the researchers concluded that “given that the constituents of skin lighteners have biologic plausibility for exerting effects on cancer risk, it would seem worthwhile for the exposure to continue to be evaluated in future studies of women of African descent.”

### **Past Intervention strategies**

Relentlessly sustained intervention strategies have been made by various organizations to create awareness of the health hazards associated with the use of skin lightening chemicals [1]. All available mass communication media—print, electronic,

mainstream and social have been deployed to create awareness, but the use has continued unabated and instead the use of the products has increased. Highly repressive government regulations aimed at prohibiting both the manufacture, sale and advertising of any kind of skin lightener in some African countries have not produced the desired effect because the products are demand driven [1].

### Product pandemic

Currently, there is a formidable subterranean online manufacturers, marketers and suppliers for the products and anyone can have the products delivered at one's doorstep sameday just by the click of the mouse. Often the manufacturers of the products are unknown; the products are mislabeled, misbranded or counterfeit. Over the last few years this 'product pandemic' has led to a flood of cheap and affordable over the counter (OTC) products touted to be the 'next best thing' for lightening the skin. Indeed currently someone wanting to buy an ordinary body cream or lotion would be hard pressed to find one that doesn't contain a bleaching agent among the hundreds that do; and even those believed to be non-bleaching are not always so. Some of the promotional claims on the product include:

- To make you flawless and confident
- Antiaging soap, slimming soap etc

Indeed online schools are available for training in mixing ingredients for bleaching. Skin bleachers come from all socio-demographic variables and professional groups which regrettably, include doctors, nurses, pharmacists school teachers and workers in government regulatory agencies against the products. Hence, a new and credible approach to intervention strategies are imperative.

Breast cancer is not like any other cancer. Chemical exposure have generational implications. In an under-resourced milieu for health services as exists in Nigeria and indeed many sub-Saharan African countries, it is easy to settle for less than optimal performance in scientific research. Research activities are generally confined to the gathering of rapid situational assessment of diseases (e.g point prevalence rates of diseases). Breast cancer's long latency and multifactorial etiology make evaluation of risk assessment of environmental chemicals and lifestyle exposures in humans challenging. Furthermore, statistically powerful epidemiologic studies require a large volume of women, a long duration, high costs and substantial – often unattainable exposure information.

### Objective of study

Research on risk factors of breast cancer has not engaged the merited attention it deserves in sub-Saharan Africa and this has been highlighted by Brinton et al. [13] The objective of this study is to provide a systematic review of the literature as regards the relationship between the chemicals in skin lightening products as potential breast cancer risk factors. This review should

- serve as a springboard for explosive research activities on chemical risk factors of breast cancer
- stimulate innovative multi-, inter-, and trans-disciplinary research on skin lightening products as breast cancer risk factors and build robust study designs on the subject
- prescribe science-backed practical ways to mitigate exposure to hazardous personal care products which are breast cancer risk factors as there is need for public health approach to long term prevention.

### Method of study

The study is part of an extensive systematic review study on Environmental Chemical risk factors for breast cancer. This is a systematic review study of chemicals already identified as ingredients in skin-lightening products. For each chemical we entered the following search terms into PubMed, Google Scholar, Global Health and Africa Journals Online: 'endocrine disruptors', "Breast Cancer"

### Mercury

Mercury occurs naturally in the earth's crust. It is released into the environment from volcanic activity, weathering of rocks and as a result of human activity. Human activity is the main cause of mercury releases, particularly coal-fired power stations, residential coal burning for heating and cooking, industrial processes, waste incinerators and as a result of mining for mercury, gold and other metals. Mercury is a toxic metal that has been used by humans for centuries as a constituent of medicines, scientific instruments, fungicides and other items.

## Mercury in skin lightening cosmetics [14-16]

Mercury is a common ingredient found in skin lightening soaps and creams. It is also found in other cosmetics, such as eye makeup cleansing products and mascara. Skin lightening soaps and creams are commonly used in certain African and Asian nations.

Mercury in cosmetics exists in two forms: inorganic and organic. Inorganic mercury (e.g. ammoniated mercury) is used in skin lightening soaps and creams. Organic mercury compounds (thiomersal [ethyl mercury] and phenyl mercuric salts) are used as cosmetic preservatives in eye makeup cleansing products and mascara.

The amount or concentration of mercury in a product may be labelled on the packaging or in the ingredient list. Names to look for include mercury, Hg, mercuric iodide, mercurous chloride, ammoniated mercury, amide chloride of mercury, quicksilver, cinnabaris (mercury sulfide), hydrargyri oxydum rubrum (mercury oxide), mercury iodide or "poison"; directions to avoid contact with silver, gold, rubber, aluminium and jewellery may also indicate the presence of mercury. However, companies selling products that contain mercury, do not always list it as an ingredient. Levels of mercury in urine have been found to correlate with the use of skin lightening products [17-21].

## Evidence of high mercury levels in cosmetics

The Food and Drug Administration (FDA) limits the amount of mercury in cosmetic products to trace amounts, 1ppm. Hamann et al [22] conducted a spectrometric analysis of mercury content in 549 skin lightening products purchased online in the United States, Taiwan, and Japan and Sri Lanka. 33 (6.0%) contained mercury above 1000 ppm. In all, 45% of mercury-containing samples contained mercury in excess of 10,000ppm. Of the skin lightening products purchased in the United States, 3.3% were found to contain mercury in excess of 1000ppm.

It is difficult to estimate how many people have been affected by mercury poisoning from cosmetics because screening for it is not routine. The kidneys are the major sites of inorganic mercury deposition; renal damage includes reversible proteinuria, acute tubular necrosis, and nephrotic syndrome. In environment like Nigeria where there are many other causes of renal damage, it is often difficult to associate chronic renal failure to mercury in cosmetics [23-25]. Studies in US revealed high levels of mercury in some Hmong and Latina women linked to skin lightening

cosmetics and in samples of lightening cosmetics from Chicago, Los Angeles, New York, and Phoenix in the US [26-33]. High concentrations of mercury found in 10 products analyzed in Nigeria, ranged from 5.52µg/L - 57.80µg/L [34]. Most products on sale in Nigeria are imported, hence users of the products in Nigeria are exposed to cosmetics with high levels of mercury [34].

## Public health concern of mercury in skin-lightening products

The use of mercury-containing cosmetic products was found to be of public health concern and can contaminate the home. [35] Mercury from the soap and cream is transferred through the drainage system into the environment, where it enters the organisms either as inorganic mercury compounds or is converted by bacterial action to organic mercury such as methylmercury. Methylmercury is readily incorporated into the food chain and concentrated in fish and fish-eating birds, which when eaten by humans, the results can be fatal like in Minamata in Japan [36]. Pregnant women who have eaten fish containing methylmercury transfer this mercury very efficiently to their fetuses. Consequently, their new-born babies have higher mercury contents in their blood than their mothers [37]. Skin lightening cosmetics manufactured in Mexico and brought into USA by an immigrant was found to release measurable levels of mercury vapor [38]. Close household contacts had elevated urinary concentrations through inhalation of hazardous toxic mercury vapor, a phenomenon akin to non-tobacco smokers at risk due to inhalation of smoke from smokers.

## Mercury as a breast cancer risk factor

The International Agency for Research on Cancer (IARC) has classified methylmercury as "possibly carcinogenic to humans" (Group 2B) [39]. Mercury has the potential to induce malignant growth through several specific mechanisms like other heavy metals: ability to generate free radicals; disruption of DNA molecular structure; and the maintenance system [40]. However, there are several proposed carcinogenic mechanisms of mercury that are either unique to this metal, not observed in most heavy metals such as its role in reducing the body's concentration of glutathione, a natural antioxidant [41]. Oxidative stress on cells has been shown to elevate rates of lipid peroxidation, another mechanism associated with carcinogenesis [42]. It has also been proposed that mercury can affect the microtubules in cells, which, can disrupt cellular division [40]. The 'estrogenicity' of mercury was examined in MCF-7cells [43]. Mercuric chloride

stimulated both estrogen receptor-dependent transcription and increased proliferation of MCF-7 cells [43]. Mercury is a weak estrogen mimic. Methylmercury reacts with sulfhydryls and could interact with protein thiol groups such as those located in the ligand-binding domain of the estrogen receptor to stimulate MCF-7 cell proliferation [44].

### Hydroquinone as breast cancer risk factor

Recent studies indicated that co-exposure to hydroquinone and other phenolic compounds can greatly potentiate the toxic effects of the individual compounds, causing cytotoxic, immunotoxic, mutagenic, and clastogenic effects. [45] Animal testing of hydroquinone showed immunity-weakening side effects and an impact on the endocrine system, and by default humans. In addition to its classification as a likely carcinogen, it has also been implicated as a disruptor of vital human functions and systems, including the immune system.

Fish odor syndrome in chronic skin bleachers—potential for N-nitrosodimethylamine (a carcinogen)

Trimethylamine and N-nitrosodimethylamine are endocrine disruptors [46] and may be risk factors for breast cancers. Chronic skin bleachers exude an offensive odour like the “fish odour syndrome” (FOS) [47] also known as trimethylaminuria, due to excretion of trimethylamine (TMA) in the breath, urine, sweat, saliva, and vaginal secretions. Trimethylamine is a volatile tertiary aliphatic amine that is derived from the diet either directly from the consumption of foods containing TMA, or by the intake of food containing precursors such as trimethylamine-N-oxide (TMNO), choline and L-carnitine. Following oral absorption in humans, TMA undergoes efficient N-oxidation to TMNO, a reaction catalyzed by the Flavin-containing monooxygenase (FMO) isoform 3 enzyme. TMNO subsequently undergoes excretion in the urine, breath and sweat although, evidence also suggests that metabolic retro-reduction of TMNO can occur. Primary Trimethylaminuria is a condition that is characterized by a genetically determined deficiency in FMO3 enzyme activity. Secondary Trimethylaminuria occurs following processes that interfere with the action of the enzyme. Hydroquinone, an antioxidant can cause the fish odour by reducing the ability to oxidize trimethylamine in chronic bleachers. Whilst TMA and TMNO are generally regarded as non-toxic substances, they are of clinical interest because of their potential to form the carcinogen—N-nitrosodimethylamine, a member of a family of extremely potent carcinogens [48]. It has been observed in

rats that ethanol enhances the hepatic carcinogenic effect of NDMA [49], suggesting that alcohol may induce cancer from exposure to small doses of the carcinogen in normal life. Skin bleachers exude fumes of TMA which may be of environmental public health importance (like tobacco smoke) to non-bleachers because of the potential to form carcinogenic NDMA.

This use of hydroquinone in cosmetics is banned in some countries, including the member states of the European Union under Directive 76/768/EEC: 1976 [50] due to numerous safety issues and serious toxicity concerns in Europe, Japan, and several other countries [51]. The WHO recommends restrictions to over-the-counter sale because of inadequate labelling of hydroquinone containing lightening creams and concentrations exceeding the permitted limit.

### The Nigerian Scenarios and need for Zero Tolerance for HQ based cosmetic products

Ofondu [20], studied the concentrations of hydroquinone in 10 cosmetic products sold in Nigeria. The levels of hydroquinone ranged from 0.09 - 30.8mg% (mean 15.2mg%). These products are easily imported into countries with weak regulatory and screening as well as no standard conditions for manufacturing. Several studies have been conducted in various countries that confirmed non-compliance. Odumosu et al [52] in a study found hydroquinone up to 6.2% in the analyzed product while Oyedeji et al [53] found up to levels 5.035% in the analyzed products.

### The need for highly sensitive, simple, fast, and economic test for hydroquinone

Manufacturers globally are aware of the ban on hydroquinone in cosmetics in several countries, including Nigeria. Many packages for skin lightening products have boldly written “HYDROQUINONE FREE”. Other names used in ingredient labeling to camouflage the identity includes Quinol, Tequinol, Benzene-1,4-diol, Idrochinone, 1-4 dihydroxy benzene, 1,4 hydroxy benzene, 1,4-Benzenediol, p-Diphenol, Hydrochinone, p-hydroxylphenol, Hydrochinonium, and Hydroquinol. Hydroquinone is a possible impurity of tocopheryl acetate (synthetic Vitamin E) which is very common in facial and skin cleansers, facial moisturizers and hair conditioners often labelled as tocopheral, tocopheral linoleate, and “toco.” Hence, there is need for a highly sensitive, simple, and fast method to test the products.

## Sunscreen Chemicals in Skin Lightening Products— Oxybenzone, Titanium dioxide

Skin lighteners inhibit the formation of melanin the natural sun-protecting pigment in the skin against the adverse effects of sunlight such as photoageing and skin cancers. Sunscreen chemicals are incorporated in the skin-lightening products to prevent the development of these adverse effects. Oxybenzone, also known as benzophenone-3, is the regular ingredient in sunscreens, personal care products like facial moisturizer/treatment, and products with sun protecting factor (SPF), lip balm, lipstick, moisturizers, anti-aging creams, conditioner and fragrance for women [54].

### Sunscreens (UV Filters)

Research has discovered that many sunscreens contain chemicals that mimic estrogen in the body, disrupt the endocrine system, and can significantly induce breast cancer development. Evidence that UV filters are breast cancer risk factors are as follows:

- They readily penetrate the skin and have been found in breast tissue of women who had mastectomy for breast cancer [55]. UV filters have also been identified in human placental tissue [56] and milk [57], and in adult blood and urine samples [58,59].
- Many chemicals used as UV filters in personal care products are estrogen mimics and endocrine disruptors [60].
- Some of these chemicals have been shown in laboratory studies to increase the growth and proliferation of breast cancer cells [61]. Others were found to increase the migration and invasive activity of human breast cancer cells [62].
- Animal studies have also shown that exposure to some UV filters in utero can affect the development of reproductive organs, while other studies have shown that exposure to some UV filters could affect the thyroid gland [63].

### Titanium dioxide

Titanium dioxide has been classified by the International Agency for Research on Cancer (IARC) as a group 2B Carcinogen “possibly carcinogen to humans [64].” Titanium dioxide (TiO<sub>2</sub>) nanoparticles are known to be bioactive and have unexpected toxicological outcomes. It induces reactive oxygen species (ROS) – mediated cytotoxicity and genotoxicity. Titanium dioxide nanoparticles induce apoptosis by interfering with epidermal growth factor receptor (EGFR) signaling in human breast cancer cells [65].

## Heavy metals contaminants in skin lightening products

Some scientists assayed a broad spectrum of over the counter (OTC) cosmetic skin lightening and personal care products sold in Nigeria for potentially toxic metals other than hydroquinone and mercury [66-68]. They identified metals such as copper, nickel, cobalt, cadmium, iron, chromium, lead, aluminum, zinc, manganese, and magnesium in substantial levels. These toxic metals are either intentionally added to cosmetics or present as impurities in the raw materials.

### Metals and Breast carcinogenesis

Heavy metals are metallo-estrogens and are breast cancer risk factors. Trace metals and metals induced oxidative stress have been implicated in breast carcinogenesis. The relationship between metals and breast cancer was articulated by Gray JM et al [69]. Higher accumulations of iron, nickel, chromium, zinc, cadmium, mercury, and lead have been found in cancerous breast biopsies compared to biopsies taken from the breast of women without breast cancer. These metals were found in higher concentrations in serum and urine from women diagnosed with cancer as compared with those without cancers. Laboratory studies have shown that metals including copper, cobalt, nickel, lead, mercury, methylmercury, tin, cadmium, and chromium have estrogenic effects on breast cancer cells (MCF -7) cultured in vitro, with cadmium expressing the highest level of estrogenic activity.

As regards regulatory aspects, the eight metals are all banned from being intentionally added to cosmetics in EU, Canada, and US but also in other countries that uses the EU or US legislations. Anyway they are permitted as impurities according to good manufacturing practices and if they are safe for human health, but limits have been established only for some metals, for others as Co, Cr and Ni limits are still lacking. The data collected in this review revealed three key findings: (i) metals are present in cosmetics at concentrations above what is considered “technically avoidable” and so many cosmetics are not in compliance with legislation on impurities; (ii) there is difference between what level of metal is safe and what is technically avoidable and so the limits suggested for impurities do not necessarily provide a sufficient level of protection for humans and should be lowered Bocca et al. [70] reviewed the regulatory aspects of eight metals of concern in cosmetics. They are antimony (Sb), arsenic (As), cadmium (Cd), Chromium (Cr), cobalt (Co), mercury (Hg), nickel (Ni) and lead (Pb). This was because they are banned as

intentional ingredients in cosmetics, have draft limits as potential impurities in cosmetics and are known as toxic.

Alatise and Schrauzer [71] at Ile-Ife, Osun State, Nigeria found higher levels of Pb in blood and head hair samples of patients with infiltrating ductal carcinoma breast cancer, the most common form, than in controls. Lead levels in hair samples were directly correlated with tumor volumes, while Se levels were inversely correlated with the tumor volumes, consistent with the anti-proliferative effects of Se. Elements, like Cd, Hg, Cr, Sn, and As, were detected in the scalp hair at significantly lower levels than Pb. The researchers concluded that there is evidence that the breast cancer patients were chronically exposed primarily to lead at levels sufficient to abolish the cancer-protecting effects of Selenium. This suggests that measures to reduce the burden of lead and other industrial metals must become an essential part of public health programs to reduce breast cancer risk of Nigerian women.

Olaiya et al. [72], applied particle-induced X-ray emission (PIXE) spectroscopy to investigate the levels of trace elements in breast tissues (cancerous and non-cancerous) and whole blood and reported similar findings. Selenium (Se), Zinc (Zn) and Chromium (Cr) were significantly elevated in the malignant tissues inferring that low or high levels of some trace elements in the malignant or non-malignant tissues could be an early indicator of their carcinogenic role, through formation of free radicals or other reactive oxygen species that adversely affect DNA, causing cancer-related diseases. The researchers recommended that for result reliability and correct assessment of the role of trace elements in initiation, promotion, progression, or inhibition of cancer in various organs, there is a need for acquisition of more data from different regions using age, gender, dietary habit, and lifestyle.

### Phthalates

Phthalates are multifunctional chemicals that are used in a variety of consumer products including cosmetics and personal care products. They are hormonally active compounds which are often reported under the terms 'fragrance; 'perfumes' or 'flavours'. Urinary concentrations of MEP showed a positive relationship with the number of personal care products used. The results suggest that the use of some personal care products contribute to phthalate body burden that deserves attention due to its potential impact on breast health [73].

### Homemade concoctions for skin bleaching

In Nigeria, a backyard industry for manufacturing skin lightening products has emerged [1]. Various additives are used to "enhance" the bleaching effect of over-the-counter products and possibly, make them affordable. Some of the additives for the concoctions are African black soap, lemon or lime juice, sulfur powder, potash, potassium alum, tooth paste, liquid milk, pulverized naphthalene (camphor balls)—a moth proofing agents, Vitamin C tablets, hair relaxers, detergents, shampoo, laundry bleach, battery acid, mercury containing antiseptic soaps, Cam wood, papaya, honey, indeed the list is endless. All these are made into a paste, in varied and assorted combinations, applied on the skin and left overnight, before being washed off the following morning to prepare for the day's work. In East Africa [74], *mkorongo* is a potent mix of Jik, (laundry bleach), talcum powder, hair relaxer, mashed raw potatoes (for the starch) and battery acid. This is mixed with over-the-counter products like Clear Tone or Ambi, which women then smear all over their naked bodies.

The mode of application of the products "Body works/ Exfoliation" also promotes maximum percutaneous absorption of the chemicals. This has been discussed comprehensively [1].

### Special considerations on use of the skin lightening products on babies

The surface area of a child's skin relative to body weight is greater than adults. As a result, the potential dose of a chemical following dermal exposure is likely to be about 1.4 times greater in children than in adults [75]. In addition, children are less able to detoxify and excrete chemicals, and their developing organ systems are more vulnerable to damage from chemical exposures, and more sensitive to low levels of hormonally active compounds [76]. Children also have more years of future life to develop disease triggered by early exposure to chemicals [76]. Therefore, there are well-documented concerns regarding children's sensitivity to harmful substances and the use on babies calls for extreme caution [1].

## Conclusion

The use of chemicals in cosmetics to lighten the skin colour has been on for several decades largely by homeland and diasporic Africans and Asians. Several adverse health complications, some of which are life-threatening to the users, have been consistently documented by researchers. However, the raging female breast cancer issue has brought to the fore, the need to explore the possible link of these chemicals as potential breast cancer risk factors because commonly used skin lightening chemicals are potent endocrine disruptors and notable carcinogens.

Breast cancer is not like any other cancer. Chemical exposure has generational implications. This systemic review study on these chemicals should serve as a stimulus for future explosive studies on the relevance of these chemicals as modifiable breast cancer risk factors. The need to explore the impact of adverse environmental chemical exposures to breast health in Nigeria informed the study as there is need for public health approach to long term prevention of breast cancer. It is expected that this study will be a wake-up call for regulators and manufacturers on choice of safe chemicals in cosmetics. Furthermore, in underserved populations as exist in sub-Saharan Africa, proffered solutions are generic in nature and mutually beneficial.

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