Introduction

Data of the European Cancer Registries indicate that the incidence of breast cancer, which is the most common cancer among women, tends to increase not only in postmenopausal but also in very young women (under the age of 35 years).

The potential causes of breast cancer are genetic predisposition, long-term hormonal replacement therapy, alcohol, environmental pollution, and possibly modern lifestyle. The controversial results of several studies suggest that certain everyday-use products (including cosmetic ingredients) may be linked to breast cancer. Some of these ingredients, such as ethylene oxide, have recently been classified by the International Agency for Research for Cancer as carcinogenic and mutagenic to humans, with sufficient evidence of carcinogenicity for breast cancer. Other ingredients, such as xenoestrogens, are chemicals which have an estrogen-like effect or disrupt the normal metabolism of the natural estrogen and thus act as carcinogens. Some of them have been shown to result in DNA damage in animal and human mammary epithelial cells and, therefore, have the potential to generate genomic instability in the breast tissue. Examples of xenoestrogens with such properties include parabens, aluminium salts, phthalates, or bisphenol A. No sufficient epidemiological data on humans have been published so far, and the effects of a mixture of chemicals to which women are exposed during lifetime on the incidence of breast cancer have not been investigated. However, the results of the available studies emphasize the need for analysis of adverse environmental factors, which, in addition to a genetic predisposition and natural aging, may contribute to the increased incidence of breast cancer.

Ethylene oxide

Ethylene oxide is important for the production of detergents, thickeners, solvents, plastics, and various organic chemicals. It is also found in fragrances. Recently, it has also...
been commonly used to manufacture popular brands of shampoo, other cosmetics, and sterilizing agents until the International Agency for Research on Cancer (IARC) classified it as carcinogenic and mutagenic to humans, with sufficient evidence of carcinogenicity in humans for lymphoid and breast malignant neoplasms.7-10

Although, according to the European legislation, the use of ethylene oxide as a cosmetic ingredient is prohibited, it still remains as residual impurity during cosmetic manufacture.5 Other potential environmental factors associated with an increased risk of breast cancer are xenoestrogens, chemicals exerting an estrogen-like effect in the body or capable of disrupting the normal metabolism of natural estrogen and thus acting as carcinogens.11 Currently, there are some 160 xenoestrogens that may be involved in breast cancer development. Women are the largest group of consumers of cosmetic products, which may be a significant source of xenoestrogens.

Numerous epidemiological, clinical, and experimental studies conducted over more than a century have confirmed that it is particularly the prolonged exposure to higher concentrations of estrogen that plays a central role in the development and progression of breast cancer.12,13 An example of such substances are numerous chemicals with estrogenic properties such as parabens, aluminium salts, and phthalates.

Parabens Parabens, the alkyl esters of p-hydroxybenzoic acid (methylparaben, ethylparaben, propylparaben, n-butylnparaben, and isobutylparaben), continue to be widely used as antimicrobial preservatives in products used by humans, including most of the cosmetics (body creams, antiperspirants, sunscreen products, lotions, or shampoos) and pharmaceuticals, but also food.13-15 Elder16 identified parabens in 99% of the cosmetics tested. Janjua et al.17 demonstrated that parabens can be rapidly absorbed through the skin into the human body even from a single dose of a body care product and long-term exposure results in the accumulation of these chemicals.

The measurement of intact esters in human breast cancer tissue sparked an international debate in 2004 because of estrogenic properties of parabens.18 Furthermore, the incidence of about 60% of breast cancers in the upper outer quadrant of the breast suggested that there was a relationship between the chemicals applied underarm and the development of breast cancer.19 Although the higher incidence of breast cancer in the upper outer quadrant may be partly related to the higher proportion of target epithelial tissue in this particular region, an increase in cancer rates in this region over the recent decades cannot be explained solely by tissue distribution and it must have an additional yet unidentified component.19 Any increase in the disproportionality of breast cancer in the upper outer quadrant may be parallel to the increasing use of cosmetics in the underarm area.19

In 2012, Barr et al.13 measured paraben levels in different regions of healthy breast tissue (without cancer). Except propylparaben (which was observed at higher levels in the upper outer quadrant compared with other breast regions), the other parabens had similar concentrations in different breast regions.13 They also found similar concentrations of parabens in the breast tissue of women who reported to be current, past, or nonusers of underarm cosmetics. It suggests that parabens originate also from other sources than underarm cosmetics.13 It is possible that these chemicals enter the body via skin application of any other body care product and parenterally from food or medicines taken by patients.13,20 Several European studies have confirmed the presence of parabens in urine, blood, human milk samples, and semen in the European population. It is also possible that systemically absorbed low-dose chemicals might accumulate and result in diffusion to the breast region13,17,19,20 However, the above clinical studies did not establish a clear correlation between parabens and breast cancer development.

Experimental studies evaluated the mechanism of action of parabens and their effect on the incidence of breast cancer. A number of studies have reported that they act mainly by an in-vivo mechanism mediated by the estrogen receptor (ER).11-13,21 Although parabens have been termed “weak estrogens” because of their low-binding affinity to the ER, their level of response to the growth of human breast cancer cells in vitro may be the same as that of 17β-estradiol when sufficient concentrations are present.21

The estrogenic activity of some cosmetic products with parabens has recently been confirmed again by the development of gynecomastia in 3 prepubertal boys as a consequence of the topical application of body oils. Gynecomastia resolved after product use was discontinued.22 In Denmark, since January 2011, propyl and butyl parabens have not been allowed for use in products for children under the age of 3. This decision was based on the possibility of high systemic absorption from an immature metabolism and skin barrier dysfunction.22 It is also possible that estrogen activity of parabens only affects estrogen-positive cancers because not all breast cancers are estrogen-dependent.13 This issue requires further research.

Prusakiewicz et al.24 have confirmed that parabens can also inhibit sulfation of estrogens through inhibition of sulfotransferase enzymes, which suggests that parabens may also indirectly enhance estrogen effects through elevation of free estradiol levels.24 Notwithstanding parabens being inactive in classic assays for mutagenicity and carcinogenicity, recent studies have reported that parabens may cause DNA damage.25

In 2012, Khanna et al.26 were the first to demonstrate that parabens can induce a transformed phenotype in human breast epithelial cells (MCF-10A) in vitro. The transformation of human
mammary epithelial cells is an approved model of carcinogenesis in vitro and can be a potential link between parabens and breast carcinogenesis, which was not recognized previously.26

Wróbel and Gregoraszczuk7 have revealed that parabens stimulate the proliferation of human breast cancer cells (MCF-7) by increasing estradiol secreting and aromatase activity, whereas the mechanism of growth stimulation of the human breast epithelial cells (MCF-10A) is unknown and requires further research.

The strength of an association between weak estrogen-like compounds in body care products and breast cancer in women is still limited by the lack of human epidemiological studies. Only 2 epidemiological studies have attempted to directly address the issue of underarm cosmetic (containing parabens and aluminium) use and breast cancer. Darbre and Harvey19 reported that there was no difference in the current use of antiperspirant/deodorant products between breast cancer patients and nonaffected matched controls. However, the study is limited by the lack of a nonuser population and of a discussion on the usage patterns in the past. By contrast, another study on the population of breast cancer patients reported that patients who used more antiperspirant products were diagnosed with breast cancer at an earlier age.19 This study suggested a dose–response relationship to chemical exposure and sensitivity at a younger age, consistent with the patterns of breast cancer development, but it did not exclude other risk factors or consider the possibility that cosmetic use was simply higher in younger women.

Within the European Union, parabens have been permitted for use in cosmetic products with a maximum concentration of 0.4% each and a total maximum concentration of 0.8%. In the United States, the Cosmetic Ingredient Review has recommended the same maximum paraben concentrations as those suggested by the European Union. However, it should be noted that the European Union recommendations are only guidelines, and manufacturers are not required to follow them.20

Phthalates Phthalates, other chemicals with potential estrogen action, are mainly used as plasticizers and are commonly found in a variety of household, food, and cosmetic products such as hair cosmetics, deodorants, nail polishes, and lotions.14 In humans, phthalates have been detected in matrices such as blood, urine, saliva, amniotic fluid, breast milk, and cord blood.14,28-30 The major pathway of exposure to phthalates is the oral route, though inhalation and dermal absorption may also contribute to this exposure.14,28-30 Phthalates have been reported to affect multiple biochemical processes in humans and animals. These include the effects on reproduction such as damage to sperm, early onset of puberty in women, anomalies of the reproductive tract, infertility, and adverse outcomes of pregnancy.14,28-30

Most studies on the mechanisms of phthalate-induced breast cancer focus on the estrogenic activity of phthalates, which impairs the endocrine function of steroid receptors.14,24-30 Furthermore, phthalates have been reported to block cell-to-cell communication, which is typical for tumor-promoting chemicals.28-30 They also affect cell proliferation and inhibition of tamoxifen-induced apoptosis in ER-positive MCF-7 cells but not in ER-negative MDA-MB-231 cells.28-30 Intriguingly, numerous in-vivo and in-vitro studies have shown that phthalates exhibit only a weak estrogenic activity in breast cancer cells, suggesting that they may contribute to cancer development also through ER-independent mechanisms. In an experimental study, Hsieh et al.25 demonstrated that phthalates, by stimulating the cell surface aryl hydrocarbon receptor (AhR) (a ligand-activated transcription factor belonging to the basic helix-loop–helix family), induce proliferation and invasiveness of ER-negative breast cancer.29

Epidemiological evidence suggests that the risk of breast cancer increases following exposure to diethyl phthalate in the environment.29 In a case-control study, urinary mono-ethyl phthalate (MEP) levels were also positively associated with breast cancer.29 Women with the highest levels of MEP were 2.2 times more likely to develop breast cancer than those with the lowest levels. For premenopausal women, this association became stronger—the odds ratio was even higher at 4.13.30

Other chemical compounds with estrogenic activity on breast cancer cell lines and potentially disruptive endocrine effects that are used in everyday consumer products, including cosmetics, are alkylphenols such as benzyl salicylate, benzyl benzoate, and butylphenyl methylpropional or triclosan.12,20

In 2011, a bill of law was adopted at first reading by the French National Assembly: “The manufacturing, import and selling of products containing phthalates, parabens, or alkylphenols are prohibited”.70

Bisphenol A Bisphenol A (BPA) is used as a plasticizer to soften plastics and increase their flexibility, and as an antioxidant in cosmetics. BPA has a short physiological half-life but because of continuous environmental exposure, it is routinely detected in human blood, placenta, cord (fetal) blood, fetal liver, and breast milk.11,20,31,32 The disruptive endocrine effects of BPA mainly concern the sexual function and hormone levels in male adults. These effects may be caused by low BPA doses but appear in the long term. In men, potential adverse effects of phthalates include hypospadias, cryptorchidism (if exposed in utero), and impaired hormone levels, while in women—early puberty. BPA binds to ER-α and ER-β and reverses antiestrogen and chemotherapy-induced cytotoxicity in cancer cell lines.11,20,31-33 BPA induces upregulation of AKT (v-Akt murine thymoma viral oncogene homolog) in association
with increased proliferation and decreased apoptosis of the epithelial cells in the breast tissue of lactationally exposed rats as well as histological changes associated with mouse mammary carcinogenesis after in-utero exposure. 20,31-33 These effects are specific to breast tissues because BPA treatment of adipocytes and leukemia cells reduces phosphorylation of the serine/threonine protein kinase AKT and promotes terminal differentiation and cell death. 20

The IARC does not have ratings for BPA with respect to human carcinogenicity although it may form DNA adducts in vitro and inhibit mitotic spindle activity. 33,34

**Aluminium salts** Aluminium salts are used as an active antiperspirant agent in underarm cosmetics, but they are also present in antacids, food, and aluminium-based adjuvants in vaccinations. However, application of aluminium-based antiperspirant salts (which are xenoestrogens) to the underarm results in a high level of long-term exposure in the local area of the human breast. 12,20,35-38

Flarend et al. 38 demonstrated the unequivocal absorption of aluminium across the skin and its excretion in urine. Studies using human breast tissue have shown that aluminium can be measured in a range of breast structures (malignant and healthy breast tissues) at higher levels than those in the blood. 28 Clinical consequences of the dermal absorption of antiperspirant salts were described in a case study in 2004 reporting bone pain and fatigue associated with toxic blood levels of aluminium, both of which disappeared after discontinuing antiperspirant use. 71,38

Much more recently, aluminium has been shown to result in DNA damage in animal and human mammary epithelial cells and, therefore, has the potential to generate genomic instability in breast tissues. 28 Moreover, the ability of aluminium to increase the growth of MCF10A human breast epithelial cells in semi-solid suspension culture shows that aluminium can affect anchorage-independent growth, which is a parameter related to tumor growth in vivo. 39 Other authors described how exposure to aluminium salts can increase migratory and invasive properties of human breast cancer cells, the changes of which are essential for cell metastasis. 38

MCF10A cells do not have detectable levels of either the ER-α or ER-β protein but overexpression of ER-α (not ER-β) can enhance suspension growth by estradiol in these cells, so it remains to be determined whether aluminium might act by increasing the levels of ER-α in the cells or whether the mechanism is non-ER mediated. 21,35-38

Additionally, aluminium salts have been described as pro-oxidant, proinflammatory factors in the breast microenvironment in both in-vitro and in-vivo models and, as such, they promote carcinogenesis. 25-38

So far, very few epidemiological studies have attempted to address the issue of exposure to antiperspirant and risk of breast cancer development. Two studies reported no association between the use of antiperspirant products and breast cancer. 40,41 By contrast, 1 study on the population of breast cancer patients reported that those who used antiperspirants more often were diagnosed with cancer at an earlier age. 28 However, since genomic instability has been reported in outer breast quadrants of healthy women, the region of disproportionate breast cancer incidence and local site of antiperspirant application, a stronger correlation might be noted if studies were more specifically focused on an association with antiperspirant use and breast cancer development in women with defective DNA repair systems such as BRCA1/2 carriers. 38

The main aim of the current research was to investigate whether the concentrations of aluminium measured in the human breast could have similar in vivo effects to those observed in the cells in vitro, and this would be aided by the identification of biomarkers specific for aluminium action.

Although single chemicals considered in isolation may or may not reach the levels in the human breast that are equivalent to those needed for measurable effects in vitro, the environmental reality is that the breast is continuously exposed to many different chemicals. Furthermore, the mixtures of the chemicals with estrogenic action can also increase an estrogenic response at low levels of estradiol, as may be found at times of low estrogen concentrations in the menstrual cycle, before puberty, or after menopause.

Unfortunately, there have been no epidemiological studies that would investigate not only the effect of a single substance but also of a mixture of xenoestrogens on the incidence of breast cancer in women. A selection of a homogeneous population is necessary to make such studies reliable, but this is difficult in practice. Humans do not live in a controlled environment. People are exposed to numerous substances at any given time, including those they encounter at work, school, or home; in the food they eat; and in the air they breathe. It is very unlikely that they know exactly what they have been exposed to or that they would be able to remember all of their exposures if asked by a researcher. Moreover, usually many years, often decades, pass between the exposure to a carcinogen and the development of cancer. Therefore, it can be very hard to definitely link any particular exposure to cancer. An additional issue is the occurrence of so called hidden carcinogens, which do not cause cancer themselves but, under certain conditions, when combined with other substances, have carcinogenic properties or increase the carcinogenic effects of other substances.

All of the above findings are important in that they have led an increasing number of cosmetic companies to discontinue addition of these chemicals into cosmetics. Therefore, it is crucial to continue research into the effects of diverse environmental factors, cosmetic ingredients, food...
products, and air pollution, which may contribute to the increased incidence of cancer, especially when combined with a genetic predisposition and natural aging.

REFERENCES
Związek między kosmetykami codziennego użytku a rakiem piersi u kobiet

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SŁOWA KLUCZOWE
kosmetyki, rak piersi

STRESZCZENIE
Dane Krajowego Rejestru Nowotworów wskazują, że zapadalność na raka piersi, który jest najczęstszym nowotworem u kobiet, ulega zwiększeniu nie tylko u kobiet po menopauzie, lecz także u bardzo młodych. Potencjalnymi przyczynami raka piersi są: predyspozycja genetyczna, przedłużony czas hormonalnej terapii zastępczej, alkohol, skażenie środowiska i prawdopodobnie nowoczesny styl życia. Kontrowersyjne wyniki wielu badań wskazują, że niektóre produkty codziennego użytku (obejmujące składniki kosmetyków) mogą mieć związek z występowaniem raka piersi. Niektóre z tych składników, np. tlenek etylenu, zostały zakwalifikowane przez Międzynarodową Agencję Badań nad Rakiem jako karcynogen i substancja mutagenna u ludzi, przy czym istnieją wystarczające dowody na powiązanie tych substancji z rakiem piersi. Inne, np. ksenoestrogeny, są substancjami chemicznymi o właściwościach podobnych do działania estrogenu lub zaburzających normalne działanie estrogenów i w ten sposób wywierają działanie karcynogenne. Wykazano, że niektóre z nich uszkadzają DNA ludzkich i zwierzących komórek nablonkowych piersi i w ten sposób prowadzą do niestabilności genomu w tkance piersi. Przykładem ksenoestrogenów o takich właściwościach są np. parabeny, sole aluminium, ftalany czy bisofenol A. Nie opublikowano do tej pory wystarczająco przekonujących badań epidemiologicznych na ludziach oraz nie oceniano wpływu mieszanki wielu substancji, na których działanie narażone są kobiety w ciągu całego życia. Niemniej jednak wyniki opublikowanych badań wskazują na konieczność analizy niepożądanych skutków działania środowiska, które w połączeniu z genetyczną predyspozycją i ze starzeniem się mogą przyczyniać się do zwiększenia zapadalności na raka piersi.

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