Cosmetics and breast cancer: can chemicals applied to the skin affect human breast biology?

Professor Philippa D Darbre
Professor in Oncology, School of Biological Sciences, University of Reading, Reading, UK.

Correspondence to:
E: p.d.darbre@reading.ac.uk

In 2001, I proposed the hypothesis that regular dermal application of chemical constituents contained in underarm cosmetics are a contributory factor in the rising incidence of breast cancer [1]. This was supported by the unexplained disproportionality of breast cancer incidence in the upper outer quadrant of the breast, where more than half of breast cancers originate, and where chemicals are applied to the underarm and left on the skin allowing for low levels to be absorbed over long periods of time [2,3]. In the intervening years, it has become evident that the presence of many hundreds of pollutant chemicals, including chemicals in underarm products, can be measured in human breast tissue, and that many are genotoxic and/or oestrogenic, thereby affecting breast cells [4]. The breast's high fat content provides a good milieu because many of these chemicals are lipophilic.

Breast cancer was recorded in ancient Egypt and classical Greece, but the incidence is now rising quite rapidly. Advances have been made in its early detection and risk factors have been identified, but prevention cannot become a reality without more insight. Although inherited loss of function of the BRCA1/BRCA2 DNA repair genes, diet, radiation and alcohol are known risk factors, the main influence on the development of breast cancer is lifetime exposure to oestrogen [5]. Reduction in oestrogen action through the use of antioestrogens or aromatase inhibitors is the basis for the success in endocrine therapy as treatment for breast cancer [6]. With oestrogen being such a central component of breast cancer, the potential contribution of environmental chemicals with oestrogenic activity needs to be taken more seriously [4]. These chemicals may enter the human body by inhalation (pesticides, herbicides, cleaning products, personal-care aerosols), oral intake (water, food, plastic packaging, pharmaceuticals, oral hygiene products) or dermal absorption (cosmetics, personal care products, soft furnishings, clothing) [4]. Sources of environmental oestrogenic compounds are given in Figure 1, and examples of oestrogenic components present specifically within cosmetics/personal care products are given in Figure 2. Relevant references to the evidence

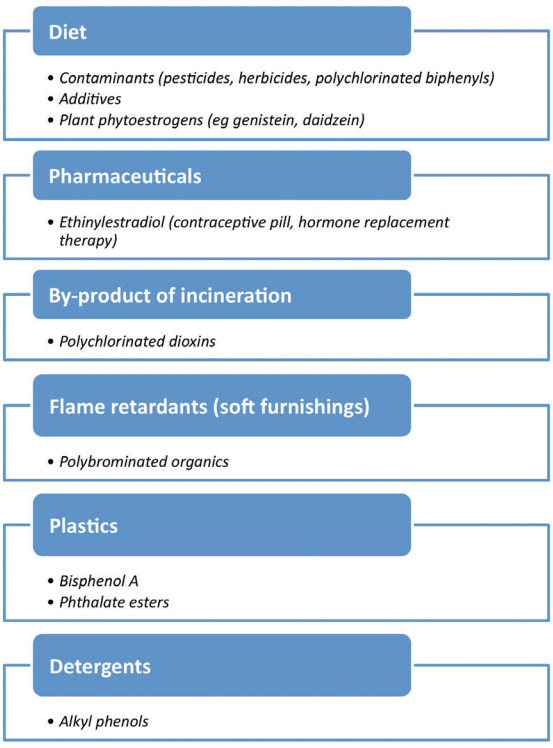

Figure 1 (left): Environmental sources of exposure of the human breast to compounds with oestrogenic activity (see reference 4 for associated references).

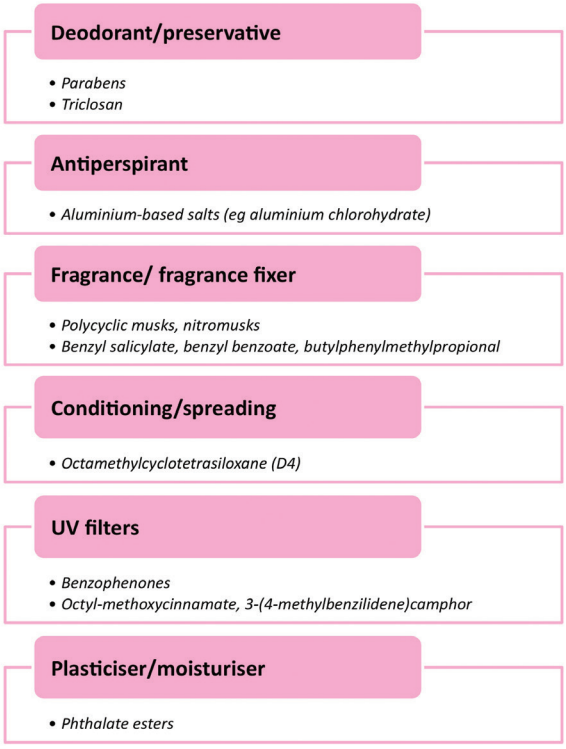

Figure 2 (right): Chemical components of cosmetic products which have been shown to possess oestrogenic activity (see reference 4 for associated references).

for their oestrogenic activity can be found in ref [4]. None of these sources are exclusive because, for example, exposure to pesticides and herbicides may be through contaminants in diet as well as through spraying, and because many of these chemicals are used in a wide range of consumer products.

Dermal absorption

It has been shown that topical application of cosmetic chemicals can result in rapid dermal uptake. In Denmark, Janjua et al. [7,8] showed that topical application of creams containing parabens, phthalates and UV filters [9] can result in measurable increases in these chemicals in the blood and urine within hours. Flarend et al. [10] traced absorption of isotopically-labelled aluminium (26Al) into blood from topical application to the underarm of aluminium-based antiperspirant salts. An average of 5.9+/-2.1% of a dose of topically applied Triclosan cream was absorbed within 48h [11]. It has been shown there is a reduction in urine concentrations of the following – phthalates, parabens, benzophenone-3 and triclosan – through cessation of exposure by consumer choice of products lacking these chemical components [12], which clearly shows that these burdens can be reduced by individual choice.

Dermal absorption can lead to physiological consequences

The "Mortician's Mystery" published in the *New England Journal of Medicine* in 1988 [13] describes the development of gynecomastia (enlargement of breasts in a man) and hypogonadotropic hypogonadism (due to impaired gonadotropin levels) in an embalmer with long-term exposure of his hands to embalming creams. He had a normal pubertal development and fathered seven children, but over a decade suffered progressive loss of libido, decrease in testicular size and marked breast development, all of which were reversed within a year by simply wearing gloves for his work [13]. Thus exposure of the hands to these creams had affected breast development. Pre-pubertal gynecomastia has been reported in three boys (28 months, 33 months, 8 years of age) following indirect exposure to topical oestrogen-containing creams used by their mothers [14], and gynecomastia has also been seen following exposure to cosmetics containing lavender and tea-tree oils [15].

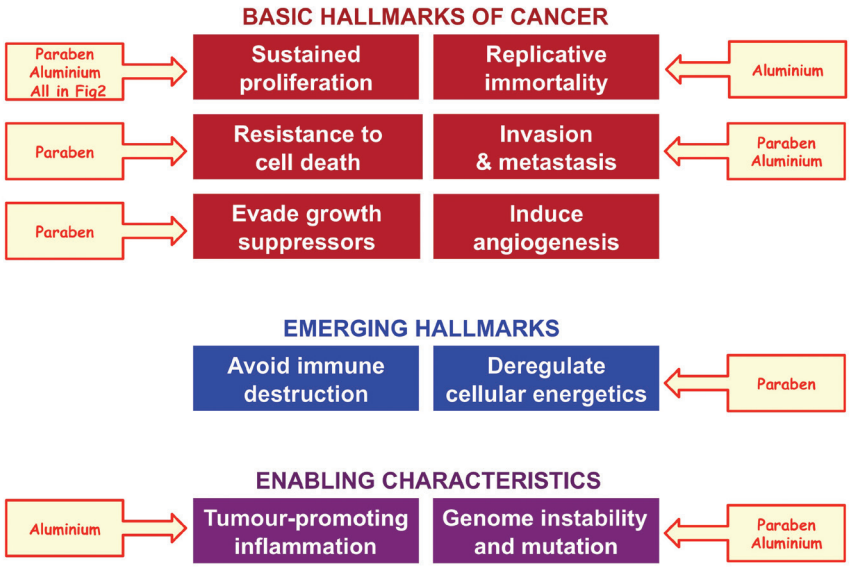

Figure 3. The hallmarks of cancer [19] which have been demonstrated following exposure to parabens [20] or aluminium [21]. Six basic hallmarks (red), two emerging hallmarks (blue), two enabling characteristics (purple) [19].

These issues are not confined to men. A 36-month girl in Italy had premature breast development (thelarche), together with menstruation and uterus enlargement, caused by exposure to components in her mother's hair lotion [16]. Another case describing physiological consequences following dermal absorption of cosmetic chemicals was in a patient who presented with bone pain and extreme fatigue associated with exposure to aluminium-based antiperspirants. Plasma aluminium levels fell from 4μM to within the normal range (0.1-0.3μM) when she stopped using the antiperspirant, and the associated symptoms also disappeared [17].

Case for a link with breast cancer

The reversal of symptoms after ceasing to use a product implies that it was involved in their causation. However, since cancer is so seldomly reversible, a different approach has to be taken when cancer is suspected as an end-point of an adverse response. Given that animal models are of limited value in extrapolating to human situations [18], and that the effects of chemicals cannot be studied directly in the human breast in vivo, an approach to investigating the implications of the presence of mixtures of cosmetic chemicals (alone and in combination) at real-life concentrations on the human breast relies on human breast epithelial cell culture models. The hallmarks of cancer, as defined by Hanahan and Weinberg [19], offers a focus on which to assess the ability of the chemicals to influence processes leading to cancer development in breast cells. Using this approach, parabens showed four of the six basic hallmarks, one of the two emerging hallmarks and one of the two enabling characteristics [20]. Aluminium has also been shown to influence three of the basic hallmarks and both enabling characteristics [21]. Figure 3 summarises an emerging picture of how parabens and aluminium may influence different hallmarks in breast cells. What is needed is to understand how the many other components of cosmetics interact. For example, all the components of cosmetics with oestrogenic activity given in Figure 2 can influence proliferation of oestrogen-responsive human breast cancer cells [4] and therefore have the potential to influence the hallmark of sustained proliferation. With such a large number of cosmetic chemicals that can influence a single hallmark, there is a potential for the different chemicals to act in an additive manner at lower doses [22,23]. The more chemicals known to enter human breast tissue, the greater the possibility that a mixture of them might cover all the hallmarks; if the concentration is sufficient, then cancer could be the outcome in due course.

Case for a link with benign breast disease

Gross cystic breast disease is the most common benign breast disorder [24]. Although not life-threatening in itself, the finding of a cyst causes stress and treatment can be invasive. Furthermore, some cyst types are associated with increased risk of breast cancer development [24,25]. Since Al-based antiperspirant salts act by blocking sweat ducts [26] and cysts arise as blocked breast ducts [24,25] in the adjacent region of the body, I previously suggested that breast cysts might arise as a result of the long-term use of antiperspirant from which sufficient Al has been absorbed by the underlying breast tissues [1]. The incidence of breast cysts is more frequent in the upper outer quadrant of the breast [27], which coincidentally is the site of application of antiperspirant to the underarm. Since Al levels are higher in breast cyst fluids than blood or milk [28], further consideration needs to be given to the possibility that antiperspirants induce cyst formation. If excessive use of antiperspirant leads to this benign disorder, then avoiding it could be a non-invasive strategy for prevention and treatment.

Conclusions and regulatory considerations

Chemical contamination of human breast tissue and milk results from modern human behaviour [4]. The sources are varied, but they will include chemicals in cosmetics and other widely used personal-care products. Whilst it may not be possible to avoid exposure to many contaminants in air and diet, personal choices can be made to reduce or eliminate exposure to those in cosmetics. Stopping using them will reduce body burdens, as urine measurements show [12]. To date, cosmetic ingredients have received far less regulatory attention than other chemicals to which the human population is exposed. Within the European Union, the Cosmetics Directive (76/768/EEC) was set up in 1976 to allow for recommendation and ongoing review of chemical components published at intervals by the Scientific Committee on Consumer Safety (SCCS), but since 2013 this has been replaced by the European Union Cosmetics Products Regulation (Regulation EC No1223/2009) [4]. In the United States, regulation of cosmetic chemicals is the responsibility of the Food and Drug Administration (FDA), and many manufacturers are altering their formulations in response to growing consumer demand [29]. Although there is no definitive proof of a link to breast cancer, there is certainly a substantial body of evidence of human breast tissue containing chemical components used in cosmetics, and of their potential to act at low doses in the long-term not only as individual chemicals, but as complex mixtures with the inherent ability to cause adverse effects on human breast biology, even cancer.

REFERENCES

1. Darbre PD. *Underarm cosmetics are a cause of breast cancer.* Eur J Cancer Prevention 2001;10:389-93.
2. Darbre PD. *Recorded quadrant incidence of female breast cancer in Great Britain suggests a disproportionate increase in the upper outer quadrant of the breast.* Anticancer Res 2005; 25: 2543-50.
3. Darbre PD, Charles AK. *Environmental oestrogens and breast cancer: evidence for combined involvement of dietary, household and cosmetic xenoestrogens.* Anticancer Res 2010; 30: 815-28.
4. Darbre PD (ed). *Endocrine disruption and human health.* Elsevier Academic press, New York, 2015.
5. Key TJ, Verkasalo PK, Banks E. *Epidemiology of breast cancer.* Lancet Oncol 2001; 2: 133-40.
6. Lonning PE (ed). *Endocrinology and treatment of breast cancer.* Clin Endocrinol Metab 2004; 18: 1-130.
7. Janjua NR, Mortensen GK, Andersson AM et al. *Systemic uptake of diethyl phthalate, dibutyl phthalate, and butyl paraben following whole-body topical application and reproductive and thyroid hormone levels in humans.* Environ Sci Technol 2007; 41: 5564-70.
8. Janjua NR, Frederiksen H, Skakkebaek NE et al. *Urinary excretion of phthalates and paraben after repeated whole-body topical application in humans.* Int J Androl 2008; 31: 118-30.
9. Janjua NR, Kongshoj B, Andersson AM et al. *Sunscreens in human plasma and urine after repeated whole-body topical application.* JEADV 2008; 22: 456-61.
10. Flarend R, Bin T, Elmore D et al. *A preliminary study of the dermal absorption of aluminium from antiperspirants using aluminium-26.* Food Chem Toxicol 2001; 39:163-8.
11. Queckenberg C, Meins J, Wachall B et al. *Absorption, pharmacokinetics, and safety of triclosan after dermal administration.* Antimicrobial Agents and Chemotherapy 2010; 54:570-2.
12. Harley KG, Kogut K, Madrigal DS et al. *Reducing phthalate, paraben and phenol exposure from personal care products in adolescent girls: findings from the HERMOSA intervention study.* Environ Health Perspect 2016; (EPub ahead of print).
13. Finkelstein JS, McCully WF, MacLaughlin DT et al. *The Mortician's Mystery.* New Engl J Med 1988; 318: 961-5.
14. Felner EI, White PC. *Prepubertal gynecomastia: indirect exposure to estrogen cream.* Pediatrics 2000; 105: e55, 1-3.
15. Henley DV, Lipson N, Korach KS et al. *Prepubertal gynecomastia linked to lavender and tea tree oils.* New Engl J Med 2007;356:479-85.
16. Guaneri MP, Brambilla G, Loizzo A et al. *Estrogen exposure in a child from hair lotion used by her mother: clinical and hair analysis data.* Clin Toxicol 2008; 46:762-4.
17. Guillard O, Fauconneau B, Olichon D et al. *Hyperaluminemia in a woman using an aluminium-containing antiperspirant for 4 years.* Am J Med 2004;117:956-9.
18. Davis D. *The secret history of the war on cancer.* Basic Books (Perseus Group) New York, 2007.
19. Hanahan D, Weinberg RA. *Hallmarks of cancer: the next generation.* Cell 2011; 144:646-74.
20. Darbre PD. Harvey PW. *Pararbens can enable hallmarks and characteristics of cancer in human breast epithelial cells: a review of the literature with reference to new exposure data and regulatory status.* J Appl Toxicol 2014;34:925-38.
21. Darbre PD. *Aluminium and the human breast.* Morphologie 2016;100:65-74.
22. Darbre PD, Fernandez MF. *Environmental oestrogens and breast cancer: long-term low-dose effects of mixtures of various chemical combinations.* J Epidemiol Comm Health 2013;67:203-205.
23. Charles AK, Darbre PD. *Combinations of parabens at concentrations measured in human breast tissue can increase proliferation of MCF-7 human breast cancer cells.* J Appl Toxicol 2013;33:390-8.
24. Mannello F, Tonti GAM, Papa S. *Human gross cyst breast disease and cystic fluid: bio-molecular, morphological, and clinical studies.* Breast Cancer Res Treat 2006;97:115-29.
25. Mannello F, Malatesta M, Gazzanelli G. *Breast cancer in women with palpable breast cysts.* Lancet 1999;354:677-8.
26. Laden K, Felger CB. *Antiperspirants and deodorants.* Cosmetic Science and Technology series, vol 7, New York: Marcel Dekker. 1988.
27. Haagensen CD. *Diseases of the breast.* 2nd ed., W.B. Saunders, Philadelphia, 1971.
28. Mannello F, Tonti GA, Darbre PD. *Concentration of aluminium in breast cyst fluids collected from women affected by gross cystic breast disease.* J Appl Toxicol 2009;29:1-6.
29. Kessler R. *More than cosmetic changes: taking stock of personal care product safety.* Environ Health Perspect. 2015; 123: A121-A127.