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Breast cysts and aluminium-based antiperspirant salts

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ABSTRACT

On the basis that aluminium-based antiperspirant salts are designed to block apocrine sweat ducts of the axilla, and that breast cysts result from blocked breast ducts in the adjacent region of the body, it has been proposed that breast cysts may arise from antiperspirant use if sufficient aluminium is absorbed into breast tissues over long-term usage. This review collates evidence that aluminium can be absorbed from dermal application of antiperspirant salts and describes studies measuring levels of aluminium in breast tissues, including in breast cyst fluids. It is notable that breast cysts, as for breast cancers, start most frequently in the upper outer quadrant of the breast, which is the region closest to the site of underarm antiperspirant application. Mechanistic evidence is reviewed for a link between aluminium levels in breast tissue, cyst formation and development of breast cancer. If excessive use of antiperspirant is a cause of breast cysts, then reduction or cessation of use could provide a preventative or even treatment strategy. Furthermore, if cyst formation from antiperspirant use is an indicator of increased risk for breast cancer, then reduction in use of antiperspirant could also provide a strategy for reducing breast cancer risk.

INTRODUCTION

Cystic disease of the breast is a common benign disorder of breast biology which results from blockage of breast ducts and is classified according to the size of the cysts formed [1]. If the cysts are small and typically visible only by microscopy, the condition is termed "microscopic cystic disease". Due to the small size of such cysts, diagnosis is usually only made when there is another lesion present and therefore the frequency and significance of microscopic cysts remain largely unknown. When the cysts are palpable and over 3mm in diameter, the condition is termed Gross Cystic Breast Disease (GCBD). The larger size of the cysts enables them to be clinically diagnosed and GCBD has been reported to occur in up to 7% of women living in western countries [1]. This makes GCBD the most commonly diagnosed benign breast disorder [1,2]. Although not life-threatening in itself, development of cysts causes anxiety, and treatment is invasive. GCBD arises from dilation and/or obstruction of ductal terminal lobular units (Figure1) which, due to retention of fluid, then swell up to form fluid-filled sacs [1,2]. Although gross cysts are known to be associated with retention of fluid and secretory material linked to the metabolic activity of the lining epithelial cells [1,2], the molecular basis of cyst formation and the reasons why cysts arise so frequently in western women remain to be identified. Aluminium-based salts are used as the active antiperspirant agent in underarm cosmetics to reduce sweating in the underarm area [3]. The main salts used are aluminium chloride, aluminium

chlorohydrate and aluminium zirconium chlorohydrate glycine complexes [3]. Their mechanism of action is thought to involve the formation of a physical plug at the top of the sweat ducts which is composed of a mixture of damaged cells and precipitated aluminium salts [3]. This plug then prevents the escape of sweat onto the skin surface which would otherwise generate odour from bacterial action on the sweat as it lingers on the skin. On the basis that antiperspirant formulations are designed to block apocrine sweat ducts of the axilla, and that breast cysts result from blocked breast ducts in the adjacent region of the body (Figure1), it has been hypothesised that breast cysts may arise from antiperspirant use if sufficient aluminium is absorbed into breast tissues [4-6]. Since antiperspirant salts are applied frequently to the underarm region and left on the skin, this allows for a continuous dermal exposure which could result in absorption of aluminium and deposition into underlying breast tissues. This might then give rise to subsequent blockage of breast ducts if sufficient aluminium were absorbed or accumulated over long term usage. Aluminium complexes have been previously linked to the development of granulomas at the site of antiperspirant application [7,8] and the use of aluminium-based vaccines is also known to cause itching nodules locally at the site of vaccination [9,10].

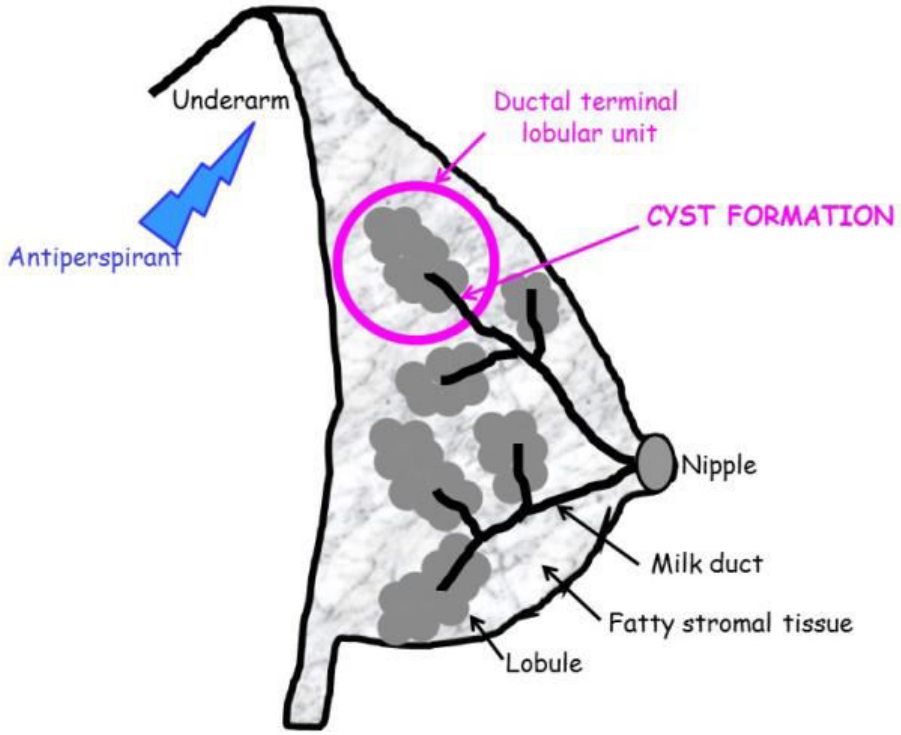

Figure 1: Structural features of the human breast showing the sites of breast cyst formation. The human breast is composed of a series of ducts and lobules which are lined with epithelial cells and are embedded in fatty stromal tissue. It is the lining epithelial cells which produce the milk which then flows down the ducts to the nipple. Breast cysts result from blocked ducts in the ductal terminal lobular units indicated in pink. Aluminium-based antiperspirant salts are used to block sweat ducts in the underarm region (indicated in blue): if sufficient aluminium were absorbed over time, could the breast ducts not also become blocked by the same mechanism?

DERMAL ABSORPTION OF ALUMINIUM FOLLOWING UNDERARM APPLICATION OF ANTIPERSPIRANT

In 2001, a report was published by Flarend and colleagues which demonstrated the principle that aluminium could be taken up through the skin following application of antiperspirant to the human underarm [11]. In this study, an antiperspirant formulation was applied which included the ^{26}Al isotope and thus allowed aluminium to be traced from application to the human underarm into blood and urine [11]. Conclusions from this research were that aluminium uptake from a single application was small [11], but long-term effects of low-dose uptake have yet to be studied. This is pertinent to breast tissue in particular because this is the site adjacent to antiperspirant application and also because breast tissue contains high levels of calcium phosphate which would generate a favourable chemical environment for aluminium deposition. In 2004, this was followed by a clinical case report documenting physiological consequences following absorption of aluminium from use of underarm antiperspirant [12]. Uptake of aluminium in a human subject was measured as rising to 4μM in the blood following the underarm antiperspirant use, and this was associated with clinical symptoms of bone pain and fatigue [12]. The report documents clearly that the high plasma aluminium levels and associated symptoms resulted from antiperspirant use because when antiperspirant use was stopped, the aluminium levels fell back to the normal range (0.1-0.3μM) and symptoms ceased [12].

THE EFFECT OF SHAVING ON TRANSDERMAL UPTAKE OF ALUMINIUM

Current cultural practices have led to aluminium-based antiperspirant salts being applied to the underarm region often after shaving. Shaving is a procedure which can create abrasions in the skin, loss of stratum corneum and damage from hair removal [13]. This procedure could therefore be expected to result in increased transdermal uptake of aluminium, and *in vitro* studies provide supporting evidence for this. Using a Franz diffusion cell and a stripping procedure as a model for shaving, aluminium has been shown to be absorbed to a greater extent through stripped than intact skin [14]. Absorption of aluminium from a stick formulation containing aluminium chlorohydrate showed aluminium absorption of 1.81μg/cm^2 for intact skin but this was increased to 11.5μg/cm^2 for stripped skin [14]. The Cosmetics Directive of the European Union [15] recommends that these aluminium salts should not be applied "to irritated or broken skin" which conflicts with these current practices of shaving prior to antiperspirant application and therefore ignores the regulatory advice [15]. Furthermore, recent calculations by the BfR in Germany estimate that antiperspirant use, in conjunction with prior shaving, may result in absorption of aluminium at levels exceeding tolerable weekly intake guidance, and accordingly women have been advised in their report not to shave prior to antiperspirant use [16].

MEASUREMENT OF ALUMINIUM IN BREAST CYST FLUID

Aluminium plays no known functional role in biological systems, but due to the activities of man [17], increasing levels of this non-essential metal are being found in biological tissues [18]. The source of the aluminium cannot be specifically identified in such measurements because the human population is now exposed through diet, vaccines and antacids as well as through antiperspirant use [6]. However, research has identified aluminium as now present in several human breast tissue structures (Figure 2) [6], and measurements have reported that aluminium is widely present in breast tissue at levels varying from 4 to 437 nmol/g dry weight [19]. If breast cysts result from blockage of breast ducts through an aluminium-mediated mechanism, aluminium should also be measurable in breast cyst fluids, and indeed, measurement has shown that aluminium is widely present in breast cyst fluids, at levels varying from 11 to 330 μg/L [20] (Figure 2). Classification of gross cysts into two types based on histology and on ion/protein/hormone concentrations in the cyst fluid has enabled aluminium levels to be measured separately in type 1 and type 2 cyst fluids. Median levels of aluminium have been found to be higher in type 1 (150μg/L) (range 80-330 μg/L) than in type 2 (32μg/L) (range 11-39 μg/L) breast cyst fluids, and both were higher than in blood serum (6μg/L) (range 3-9μg/L) [20]. The reasons for and consequences of the different levels of aluminium in the type 1 and type 2 cyst fluids remains to be determined, but they might explain the different Na^+ / K^+ion concentrations reported in the two cyst types [2,21]. Type 1cyst fluids have low Na^+ / high K^+ ion concentrations ($Na^+/K^+<3$),

whilst, by contrast, type 2 cyst fluids contain high Na^+ / low K^+ ion concentrations ($Na^+/K^+>3$) [2,21]. Since the electrolyte composition of the breast cyst fluid will depend on the Na^+/K^+-ATPase activity of the lining epithelial cells, and since chronic exposure to aluminium has been shown to alter cellular Na^+/K^+-ATPase activity [22,23], differences in ion concentrations between the two main cyst types might be explained by the differences in aluminium levels in the cyst fluid.

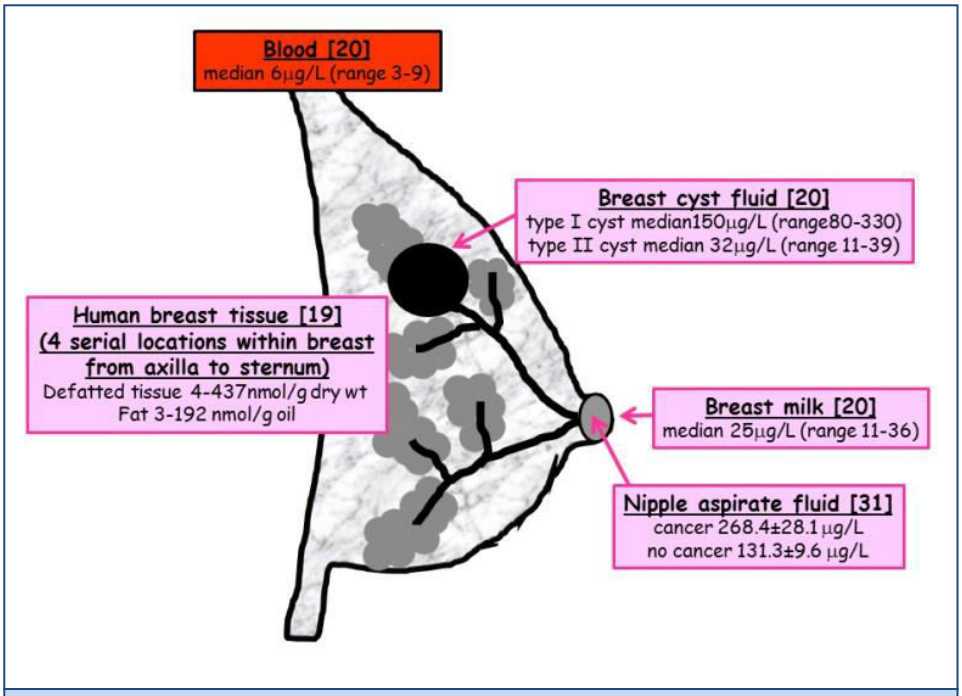

Figure 2: Human breast tissue structures in which aluminium has been measured as present: references are indicated in parentheses.

DISPROPORTIONATE INCIDENCE OF CYSTS IN THE UPPER OUTER QUADRANT OF THE BREAST

It is notable that breast cysts occur more frequently in the upper outer quadrant compared with other regions of the breast [1]. An explanation of this disproportionate incidence is lacking other than there being more target ductal tissue in that region [1]. However, coincidentally this is the location adjacent to the site of application of antiperspirant to the underarm. If this were an explanation, then it might be expected that aluminium levels would be higher in that region of the breast. Indeed, measurements of aluminium concentrations at four serial locations across the breast showed that the aluminium content of defatted tissue was significantly higher in the outer than the inner breast regions [19]. A similar disproportionate incidence also occurs for breast cancers in the upper outer quadrant of the breast [24,25]. Whilst national statistics are not collated for breast cysts, national statistics offices for England, Wales and Scotland have collected information concerning the site of incidence of cancer in the breast since 1979, and these data show that over half of breast cancers start in the upper outer quadrant (Figure 3) [24,25]. Furthermore, a rising incidence in that specific region over recent decades [24,25] cannot be explained solely by more epithelial tissue in that region, and the hypothesis of a link between increasing use of underarm antiperspirant and breast cancer has also been proposed [24,25].

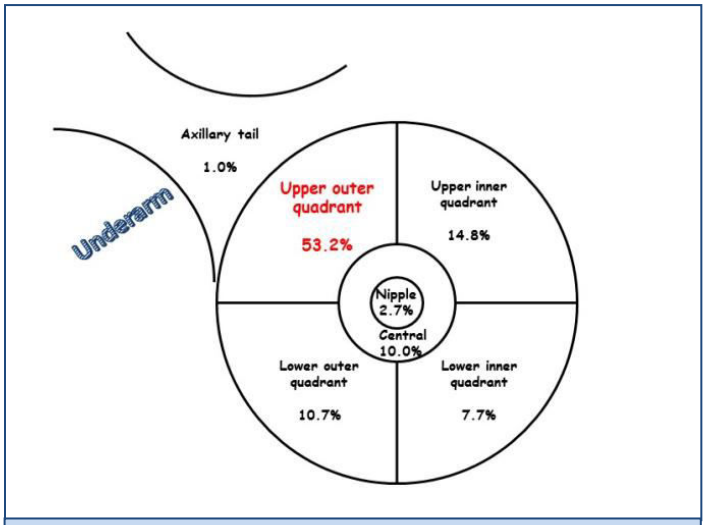

Figure 3: More than half of breast cancers originate in the upper outer quadrant of the breast. In the UK, incidence is recorded annually in the seven regions of the breast shown here and the percentage proportion of total incidence in each region is shown as published for the year of 2006 [25].

IS THERE A LINK BETWEEN BREAST CYSTS AND SUBSEQUENT DEVELOPMENT OF BREAST CANCER?

Over the years, several studies have suggested that the presence of gross cysts may be linked with a higher subsequent risk of breast cancer development [1,2,21,26-28]. Notably, the highest incidence of cysts is in women of the 35-50 age group with a sharp decline after menopause [1,2] whilst 80% of breast cancers occur later in life in the over 50 age group [29], which provides a compatible timeline for such a link. Many epidemiological studies have concluded that there is an increased frequency of subsequent breast cancer in women who have had GCBD but not all [2]. This indicates that GCBD is not a precancerous lesion in itself, but is suggestive of an associated increased risk [30]. Since some studies have suggested that those with type 1 cysts may be at greater risk [2,21,26-28,30], and it was the type 1 breast cyst fluids which contained the higher levels of aluminium [20], further research is justified to test whether tissue levels of aluminium might provide a prognostic indicator. It might be that levels of aluminium high enough in the breast tissue to block a breast duct and cause formation of a cyst would be indicative of rising levels of aluminium in the breast tissue in general, which if not checked or reversed, could eventually lead to development of cancer.

IS THERE A LINK BETWEEN ALUMINIUM-BASED ANTIPERSPIRANT SALTS AND DEVELOPMENT OF BREAST CANCER?

Many studies have now been published suggesting a potential link between exposure of the human breast to aluminium and development of breast cancer. In terms of exposure scenarios, some tissue measurements report higher levels of aluminium in breast tissue of women with breast cancer. Using nipple aspirate fluid, which is secreted by ductal and lobular epithelial cells of the breast and therefore reflects the breast microenvironment, aluminium, was measured at higher levels in samples from breast cancer patients than from women who did not have cancer at the time of sampling [31]. The mean level of aluminium in the nipple aspirate fluids from women with breast cancer was 268.4+/-28.1 μg/L but in unaffected women was 131.3+/-9.6 μg/L [31]. Using breast tissue, other studies have also reported higher levels of aluminium in malignant breast tissue than in adjacent unaffected tissue [32-35]. Only few epidemiological studies have attempted to address any link between antiperspirant use and breast cancer. An early epidemiological study reported that within a population of breast cancer patients, those who used more antiperspirant were diagnosed at a younger age with breast cancer [36]. However, two other epidemiological studies failed to find any

association between antiperspirant use and breast cancer [37,38]. These early studies were impeded by the difficulty in finding control populations of women who had never been exposed to antiperspirant or who even understood the difference between antiperspirant and deodorant. A more recent epidemiological study from Austria used actual tissue measurements of aluminium as a quantitative indication of exposure, and reported associations both between antiperspirant use and aluminium levels in breast tissue and between aluminium tissue levels and development of breast cancer at young age [39]. Recent animal model studies back up the concept that exposure of non-transformed breast epithelial cells to aluminium salts can cause alterations to the cells which result in transformation and subsequent growth of the cells into tumours in mice [40]. *In vitro* studies have shown that exposure to aluminium can enable development of several of the hallmarks of cancer [41,42] in breast epithelial cells including genomic instability, inappropriate proliferation and increased migration/invasion [6]. In addition, aluminium is a metalloestrogen [43] and exposure to excessive oestrogen is a risk factor for breast cancer [44]. With regard to DNA damage, aluminium has been shown to result in DNA damage in a micronucleus assay [45] and in Comet assays [46,47] *in vitro*, and *in vivo* using a zebra fish model [48], which support the potential for aluminium to generate genomic instability in cells and tissues. Aluminium chloride has been shown to induce DNA double strand breaks in non-transformed MCF10A human mammary epithelial cells [49], and in these same cells, to induce anchorage-independent growth in a soft agar assay [49] which is considered predictive of tumour growth in an animal [50]. Furthermore, exposure of MCF10A cells to aluminium chloride or aluminium chlorohydrate has been shown to cause down regulation of both mRNA and protein for BRCA1 [51], which is a gene critical for DNA repair in breast cells, so much so that inherited defects are known to be associated with increased breast cancer risk [52,53]. With regard to migration and invasion, *in vitro* models have revealed that long-term exposure (>20 weeks) to aluminium salts can increase migratory and invasive properties of human breast cancer cells in culture [54,55]. Such alterations are characteristic of the metastatic process [56] and are especially pertinent to breast cancer where the major cause of mortality is from tumour growth at metastatic sites rather than at the primary site in the breast [44].

DISCUSSION AND CONCLUSIONS

Published evidence is broadly supportive of proposed links between the presence in breast tissue of excessive aluminium from antiperspirant use and both breast cyst formation and breast cancer development. Further evidence over a longer time frame has suggested an association between GCBD and subsequent development of breast cancer. It would seem likely that mechanisms would be different, with aluminium acting in breast cyst formation through a physical mechanism involving obstruction of ducts, but in breast cancer through intracellular molecular alterations leading to development of hallmarks of cancer in target epithelial cell(s). Such a basic difference in mechanisms would be consistent with the lack of any direct links but rather with more nebulous associated risks. Aluminium has a long-established toxicological profile of cellular actions, and it could be that the excessive build-up of aluminium leading to duct obstruction is indicative of rising tissue aluminium levels which could lead to subsequent cancer formation if left unchecked. However, the stochastic and multi-step requirements for cancer development would also be consistent with the lack of any direct link. In particular, the strong link between excessive oestrogen exposure and breast cancer development [44] would be a complicating interacting factor. However, with such a high proportion of both cysts and cancers starting in the same region of the breast (upper outer quadrant), and if aluminium build-up in the tissues is mechanistically involved, then it becomes questionable as to whether the diagnosis of a cyst should be a relief or rather a warning sign of aluminium build-up in the region of the breast most prone to cancer incidence, and this needs further research. If excessive use of antiperspirant is a cause of breast cysts, then reduction or cessation of use could provide a non-invasive preventative or even treatment strategy. Furthermore, if excessive cyst formation is an indicator of increased risk for breast cancer, then reduction in use of antiperspirant could also provide a strategy for reducing breast cancer risk. Anecdotally, several women from the general public have told me of their experiences of breast cysts which disappeared following cessation of antiperspirant use. These observations need to be followed up by controlled clinical studies. However, if breast

cysts could be reversed simply by ceasing use of antiperspirant, then this could reduce the health service burden of this common benign breast condition. Furthermore, the implied anecdotal reversibility could be exploited to investigate cause and effect. Several studies have now reported gynecomastia (excessive breast growth) in men following dermal exposure to cosmetic products containing oestrogenic compounds and these products have been identified as causative because symptoms reversed upon cessation of exposure [57,58]. Such studies where reversibility of symptoms can be linked to cessation in use of a specific product are becoming important approaches to identifying effects of endocrine disrupting agents [59]. Since cancer is not a reversible condition, such studies need to be performed in conditions linked to cancer, and the association between GCBD and breast cancer provides one possible opportunity. For this reason, studies should now be performed to test the hypothesis that cessation in use of aluminium-based antiperspirant salts could prevent or reverse breast cyst formation.

Conflict of interest

The author has no conflict of interest.

REFERENCES

1. Haagensen CD. (1971). Diseases of the breast. 2nd Edition. Philadelphia: W.B.Saunders.
2. Mannello F, Tonti GAM, Papa S. (2006). Human gross cyst breast disease and cystic fluid: bio-molecular, morphological, and clinical studies. Breast Cancer Res Treat. 97: 115-129.
3. Laden K, Felger CB. (1988). Antiperspirants and deodorants: cosmetic science and technology series. 7. New York: Marcel Dekker.
4. Darbre PD. (2001). Hypothesis: Underarm cosmetics are a cause of breast cancer. Eur J Cancer Prev. 10: 389-393.
5. Darbre PD. (2003). Underarm cosmetics and breast cancer. J Appl Toxicol. 23: 89-95.
6. Darbre PD. (2016). Aluminium and the human breast. Morphologie. 100: 65-74.
7. Skelton HG 3rd, Smith KJ, Johnson FB, Cooper CR, Tyler WF, et al. (1993). Zirconium granuloma resulting from an aluminum zirconium complex: a previously unrecognized agent in the development of hypersensitivity granulomas. J Am Acad Dermatol. 28: 874-876.
8. Montemarano AD, Sau P, Johnson FB, James WD. (1997). Cutaneous granulomas caused by an aluminum-zirconium complex: an ingredient of antiperspirants. J Am Acad Dermatol. 37: 496-498.
9. Habs H, Simon B, Thiedemann KU, Howe P. (1997). Aluminium. Environ Health Criteria. 194: 1-207.
10. Bergfors E, Trollfors B, Inerot A. (2003). Unexpectedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccines from a single manufacturer. Vaccine. 22: 64-69.
11. Flarend R, Bin T, Elmore D, Hem SL. (2001). A preliminary study of the dermal absorption of aluminium from antiperspirants using aluminium-26. Food Chem Toxicol. 39: 163-168.
12. Guillard O, Fauconneau B, Olichon D, Dedieu G, Deloncle R. (2004) Hyperaluminemia in a woman using an aluminum-containing antiperspirant for 4 years. Am J Med. 117: 956-959.
13. Turner GA, Moore AE, Marti VPJ, Paterson SE, James AG. (2007). Impact of shaving and anti-perspirant use on the axillary vault. Int J Cosmet Sci. 29: 31-38.
14. Pineau A, Guillard O, Fauconneau B, Favreau F, Marty MH et al. (2012). *In vitro* study of percutaneous absorption of aluminum from antiperspirants through human skin in the Franz™ diffusion cell. J Inorg Biochem. 110: 21-26.
15. (1976). European Union Cosmetics Directive 76/768/EEC.
16. (2014). Federal Institute for Risk Assessment, Germany. Aluminum-containing antiperspirants contribute to the absorption of aluminum. Opinion number 007/2014.
17. Exley C. (2003). A biogeochemical cycle for aluminium? J Inorg Biochem. 97: 1-7.
18. Exley C. (2009). Darwin, natural selection and the biological essentiality of aluminium and silicon. Trends Biochem Sci. 34: 589-593.
19. Exley C, Charles LM, Barr L, Martin C, Polwart A, et al. (2007). Aluminium in human breast tissue. J Inorg Biochem 101: 1344-1346.
20. Mannello F, Tonti GA, Darbre PD. (2009). Concentration of aluminium in breast cyst fluids collected from women affected by gross cystic breast disease. J Appl Toxicol. 29: 1-6.

21. Malatesta M, Mannello F, Sebastiani M, Cardinali A, Marcheggiani F, et al. (1998). Ultrastructural characterization and biochemical profile of human gross cystic breast disease. Breast Cancer Res Treat. 48: 211-219.
22. Silva VS, Duarte AI, Rego AC, Oliveira CR, Goncalves PP. (2005). Effect of chronic exposure to aluminium on isoform expression and activity of rat Na/K-ATPase. Toxicol Sci. 88: 485-494.
23. Silva VS, Nunes MA, Cordeiro JM, Calejo AI, Santos S, et al. (2007). Comparative effects of aluminum and ouabain on synaptosomal choline uptake, acetylcholine release and (Na+/K+)ATPase. Toxicology. 236: 158-177.
24. Darbre PD. (2005). Recorded quadrant incidence of female breast cancer in Great Britain suggests a disproportionate increase in the upper outer quadrant of the breast. Anticancer Res. 25: 2543-2550.
25. Darbre PD. (2010). Environmental oestrogens and breast cancer: evidence for a combined involvement of dietary, household and cosmetic xenoestrogens. Anticancer Res. 30: 815-827.
26. Angeli A, Dogliotti L, Naldoni C, Orlandi F, Puligheddu B, et al. (1994). Steroid biochemistry and categorization of breast cyst fluid: relation to breast cancer risk. J Steroid Biochem Molec Biol. 49: 333-339.
27. Bruzzi P, Dogliotti L, Naldoni C, Bucchi L, Costantini M, et al. (1997). Cohort study of association of risk of breast cancer with cyst type in women with gross cystic disease of the breast. BMJ. 314: 925-928.
28. Dixon JM, McDonald C, Elton RA, Miller WR. (1999). Risk of breast cancer in women with palpable breast cysts: a prospective study. Lancet. 353: 1742-1745.
29. Key TJ, Verkasalo PK, Banks E. (2001). Epidemiology of breast cancer. Lancet Oncol. 2: 133-140.
30. Mannello F, Malatesta M, Gazzanelli G. (1999). Breast cancer in women with palpable breast cysts. Lancet. 354: 677-678.
31. Mannello F, Tonti GA, Medda V, Simone P, Darbre PD. (2011). Analysis of aluminium content and iron homeostasis in nipple aspirate fluids from healthy women and breast cancer-affected patients. J Appl Toxicol. 31: 262-269.
32. Mulay IL, Roy R, Knox BE, Suhr NH, Delaney WE. (1971). Trace-metal analysis of cancerous and noncancerous human tissues. J Natl Cancer Inst. 47: 1-13.s
33. Ng KH, Bradley DA, Looi LM. (1997). Elevated trace element concentrations in malignant breast tissues. Br J Radiol. 70: 375-382.
34. Millos J, Costas-Rodriguez M, Lavilla I, Bendicho C. (2009). Multiple small volume microwave-assisted digestions using conventional equipment for multielemental analysis of human breast biopsies by inductively coupled plasma optical emission spectrometry. Talanta. 77: 1480-1496.
35. Romanowicz-Makowska H, Forma E, Brys M, Krajewska WM, Smolarz B. (2011). Concentration of cadmium, nickel and aluminium in female breast cancer. Pol J Pathol. 4: 257-261.
36. McGrath KG. (2003). An earlier age of breast cancer diagnosis related to more frequent use of antiperspirants/deodorants and underarm shaving. Eur J Cancer Prev. 12: 479-485.
37. Mirick DK, Davis S, Thomas DB. (2002). Antiperspirant use and the risk of breast cancer. J Natl Cancer Inst. 94: 1578-1580.
38. Fakri S, Al-Azzawi A, Al-Tawil N. (2006). Antiperspirant use as a risk factor for breast cancer in Iraq. East Mediterr Health J. 12: 478-482.
39. Linhart C, Talasz H, Morandi EM, Exley C, Lindner HH, et al. (2017). Use of underarm cosmetic products in relation to risk of breast cancer: a case-control study. EBioMedicine. 21: 79-85.
40. Mandriota SJ, Tenan M, Ferrari P, Sappino AP. (2016). Aluminium chloride promotes tumorigenesis and metastasis in normal murine mammary gland epithelial cells. Int J Cancer. 139: 2781-2790.
41. Hanahan D, Weinberg RA. (2000). The hallmarks of cancer. Cell. 100: 57-70.
42. Hanahan D, Weinberg RA. (2011). Hallmarks of cancer: the next generation. Cell. 144: 646-674.
43. Darbre PD. (2006). Metalloestrogens: an emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. J Appl Toxicol. 26: 191-197.

44. Miller WR. (1996). Estrogen and Breast Cancer. London: Chapman and Hall.
45. Banasik A, Lankoff A, Pislulak A, Adamowska K, Lisowska H, et al. (2005). Aluminum-induced micronuclei and apoptosis in human peripheral-blood lymphocytes treated during different phases of the cell cycle. Environ Toxicol. 20: 402-406.
46. Lankoff A, Banasik A, Duma E, Ochniak H, Lisowska T, et al. (2006). A comet assay study reveals that aluminium induces DNA damage and inhibits the repair of radiation-induced lesions in human peripheral blood lymphocytes. Toxicol Lett. 161: 27-36.
47. Lima PD, Leite DS, Vasconcellos MC, Cavalcanti BC, Santos RA, et al. (2007). Genotoxic effects of aluminum chloride in cultured human lymphocytes treated in different phases of cell cycle. Food Chem Toxicol. 45: 1154-1159.
48. Pereira S, Cavalie I, Camilleri V, Gilbin R, Adam-Guillermin C. (2013). Comparative genotoxicity of aluminium and cadmium in embryonic zebrafish cells. Mutat Res.750: 19-26.
49. Sappino AP, Buser R, Lesne L, Gimelli S, Bena F, et al.(2012). Aluminium chloride promotes anchorage-independent growth in human mammary epithelial cells. J Appl Toxicol. 32: 233-243.
50. Shin SI, Freedman VH, Risser R, Pollack R. (1975). Tumorigenicity of virus-transformed cells in nude mice is correlated specifically with anchorage independent growth *in vitro*. Proc Nat Acad Sci USA. 72: 4435-4439.
51. Farasani A, Darbre PD. (2015). Effects of aluminium chloride and aluminium chlorohydrate on DNA repair in MCF10A immortalised non-transformed human breast epithelial cells. J Inorg Biochem. 152: 186-189.
52. Roy R, Chun J, Powell SN. (2011). BRCA1 and BRCA2: different roles in a common pathway of genome protection. Nat Rev Cancer. 12: 68-78.
53. Apostolou P, Fostira F. (2013). Hereditary breast cancer: the era of new susceptibility genes. BioMed Res Internat. 2013: 747318.
54. Darbre PD, Bakir A, Iskakova E. (2013). Effect of aluminium on migratory and invasive properties of MCF-7 human breast cancer cells in culture. J Inorg Biochem. 128: 245-249.
55. Bakir A, Darbre PD. (2015). Effect of aluminium on migration of oestrogen unresponsive MDA-MB-231 human breast cancer cells in culture. J Inorg Biochem. 152: 180-185.
56. Scheel C, Weinberg RA. (2012). Cancer stem cells and epithelial-mesenchymal transition: concepts and molecular links. Semin Cancer Biol. 22: 396-403.
57. Finkelstein JS, McCully WF, MacLaughlin DT, Godine JE, Crowley WF. (1988). The Mortician's Mystery. Gynecomastia and reversible hypogonadotropic hypogonadism in an embalmer. N Engl J Med. 318: 961-965.
58. Henley DV, Lipson N, Korach KS, Bloch CA. (2007). Prepubertal gynecomastia linked to lavender and tea tree oils. N Engl J Med. 356: 479-485.
59. Darbre PD. (2015). Endocrine disruption and human health. Academic Press/Elsevier: NY.