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Aluminium and breast cancer: Sources of exposure, tissue measurements and mechanisms of toxicological actions on breast biology

Philippa D. Darbre [a,*], Ferdinando Mannello [b], Christopher Exley [c]

[a] School of Biological Sciences, University of Reading, Reading RG6 6UB, UK
[b] Department of Biomolecular Sciences, Section of Clinical Biochemistry and Cell Biology, University of 'Carlo Bo', Urbino 61029, Italy
[c] Birchall Centre, Lennard-Jones Laboratories, Keele University, Staffordshire ST5 5BG, UK

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ABSTRACT

This review examines recent evidence linking exposure to aluminium with the aetiology of breast cancer. The human population is exposed to aluminium throughout daily life including through diet, application of antiperspirants, use of antacids and vaccination. Aluminium has now been measured in a range of human breast structures at higher levels than in blood serum and experimental evidence suggests that the tissue concentrations measured have the potential to adversely influence breast epithelial cells including generation of genomic instability, induction of anchorage-independent proliferation and interference in oestrogen action. The presence of aluminium in the human breast may also alter the breast microenvironment causing disruption to iron metabolism, oxidative damage to cellular components, inflammatory responses and alterations to the motility of cells. The main research need is now to investigate whether the concentrations of aluminium measured in the human breast can lead *in vivo* to any of the effects observed in cells *in vitro* and this would be aided by the identification of biomarkers specific for aluminium action.

1. Introduction

We are living in the aluminium age [1] which means that we are faced with a burgeoning exposure to a non-essential metal [2]. Aluminium is biologically available [3] and has been linked to many human diseases including neurological disorders [4]. Recent research has identified aluminium associated with several human breast structures and this aluminium may be linked to the topical application of aluminium salts as antiperspirants [5,6]. Herein we have examined the recent evidence which links exposure to aluminium with the aetiology of breast cancer.

Breast cancer is not a new disease because it was recorded in ancient Egypt and in the writings of classical Greece [7]. However, the increasing incidence worldwide over recent decades is unprecedented and has led to the breast becoming the site of greatest cancer incidence in women [8]. Breast cancer can occur in men albeit with lower frequency and incidence of male breast cancer is rising in some Western countries [9]. Risk factors have been identified but underlying environmental causes remain unknown. Breast cancer incidence is influenced by age but the majority incidence over age 50 in some Western countries such as the UK can be seen at younger ages in the East [8]. Inherited susceptibility can be traced through family history in 5–10% of breast cancers and this may be associated with loss of function of the breast cancer susceptibility genes BRCA1/2 which are needed for efficient DNA repair [10]. However, this still begs the question as to the source of the underlying DNA damage for which repair is inadequate and increasing penetrance of the BRCA1/2 genes in some populations demonstrates an additional unidentified environmental component [11]. Lifestyle factors such as radiation exposure, alcohol and diet are components of risk but the main identified risk factors are hormonal and in particular linked to increased life-time exposure to oestrogen through physiological variations associated with early menarche, late menopause, late age of first pregnancy or lack of breast-feeding [12] and through personal decisions to use oral contraceptives [13] or hormone replacement therapy [14]. Widespread screening by mammography has shown that high breast density is also a risk factor which increases still further in the presence of proliferative benign breast disease [15].

In addition to the rising incidence of breast cancer, there are also other characteristics of breast cancer which remain unexplained. In the UK, in the early 1970s, fewer than 10% of breast tumours were ductal, lobular or medullary but by the end of the 1990s, ductal carcinomas alone were reported to comprise 60% of all breast cancer cases [16]. In addition, the relative proportion of breast tumours which contain oestrogen receptors (ERs) and are oestrogen responsive for growth has also been reported to be rising [17]. Another notable change has been in the socioeconomic status of women with breast cancer. In the UK, breast cancer has been rising faster among affluent women an observation which is not explained solely by compliance with screening and which is in marked contrast to the widening deprivation gap

* Corresponding author at: School of Biological Sciences, University of Reading, Hopkins Building, Reading, RG6 6UB, UK. Tel.: +44 118 378 7035; fax: +44 118 378 6642.
E-mail address: p.d.darbre@reading.ac.uk (P.D. Darbre).

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observed with other types of cancer [16]. However, perhaps the largest unexplained clinical observation in breast cancer is the disproportionate incidence in the upper outer quadrant of the breast which has risen from 47.9% in 1979 to 53.3% in 2006 in England/Wales and from 38.3% in 1980 to 57.0% in 2006 in Scotland [18,19]. Although this may relate in part to the higher proportion of target epithelial tissue in that region of the breast [20], the increase year by year in this region over recent decades [18,19] cannot be explained by tissue distribution and must have a further unidentified component. Is it possible that the increasing use of antiperspirant which parallels breast cancer incidence [21] could also be an explanation for greater numbers of ductal tumours (antiperspirant is designed to block ducts), tumours in more affluent women (cosmetic products are expensive luxuries) and disproportionate incidence of breast cancer in the upper outer quadrant (the local site of application of antiperspirant)?

2. Sources of exposure to aluminium for the human breast

The human population is exposed to aluminium in many ways in everyday living and including the diet [4], the dermal application of personal care products [22], use of antacids [4] and aluminium-based adjuvants in vaccinations [23]. However, application of aluminium-based antiperspirant salts to the underarm provides a specific high and lifetime exposure level in the local area of the human breast. The salts used include aluminium chloride, aluminium chlorohydrate and aluminium zirconium chlorohydrate glycine complexes [22]. Aluminium chlorohydrate is limited to 25% *w/v* by the Food and Drug Administration (FDA) of the USA and aluminium zirconium chloride hydroxide complexes are limited in cosmetics to 20% *w/v* by the FDA and in the European Union (EU) [24]. Both the USA and EU [24] include statements that these products should not be applied to broken, damaged or irritated skin, but current cultural practices can include shaving before antiperspirant application, a procedure which can create abrasions in the skin, loss of stratum corneum and irritation from hair removal [25], thereby negating the specific warning by the FDA and EU [24].

Very few epidemiological studies have attempted so far to address the issue of exposure to antiperspirant and risk of breast cancer development. Two studies have reported no association between use of antiperspirant products and breast cancer [26,27]. By contrast, one study has reported within a population of breast cancer patients that those who used more antiperspirant were diagnosed at an earlier age with breast cancer [21]. However, since genomic instability has been reported in outer breast quadrants of healthy women [28,29], the region of disproportionate breast cancer incidence [18,19] and local site of antiperspirant application, a stronger correlation might be noted if studies were more specifically focused on an association with antiperspirant usage and breast cancer development in women with defective DNA repair systems such as BRCA1/2 or ATM carriers [30]. This is especially relevant since these genes function to repair double strand breaks in the DNA [30] and aluminium has been shown recently to cause DNA double strand breaks in human breast epithelial cells [31] (see Section 5).

3. Dermal absorption of aluminium through human skin

Since aluminium salts in underarm cosmetics are applied frequently, often multiple times a day, and are left on the skin, the human breast area is subjected to a continuous dermal exposure. The extent to which such continuous exposure with frequent reapplication and prior shaving could lead to absorption of aluminium at low levels into underlying tissues has only recently attracted research effort.

Although it is often assumed that unbroken skin would provide a barrier to the transdermal uptake of aluminium, in a seminal piece of research using an antiperspirant formulation which included ^{26}Al, Flarend and colleagues [32] demonstrated the unequivocal absorption of aluminium across the skin and its excretion in urine. Only two subjects were used in this experiment on aluminium absorption from antiperspirant and it was of note that these two individuals showed significantly different rates of urinary excretion of topically applied ^{26}Al. Conclusions from this study were that uptake was small but due consideration needs now to be given to the long-term effects of low-dose uptake and whether over the longer term, aluminium might accumulate in certain tissues. *In vitro* studies using a Franz diffusion cell have shown that aluminium from antiperspirant salts can be absorbed through human skin but to a greater extent through stripped than intact skin [33]. Comparison of aluminium chlorohydrate from a stick formulation showed aluminium absorption of 1.81 μg/cm^2 for intact skin but this was increased to 11.5 μg/cm^2 for stripped (a procedure equivalent to shaving) skin [33].

The ability of dermal absorption of aluminium from underarm antiperspirant application to give rise to physiological consequences was reported in a clinical case study in 2004 [34]. This report documents uptake of aluminium from underarm antiperspirant use in a human subject to a potentially toxic level of 4 μM in blood plasma and describes associated clinical symptoms of bone pain and fatigue. The report leaves little doubt that the high plasma aluminium and associated symptoms resulted from antiperspirant use because when antiperspirant use was stopped, the aluminium levels fell back to the normal range (0.1–0.3 μM) and bone pain and fatigue ceased [34].

4. Concentrations of aluminium measured in human breast structures

Studies using human breast tissue have shown that aluminium can be measured in a range of breast structures at levels which are higher than in blood (Table 1) [35–42]. Several studies, although not all, have reported higher levels of aluminium in malignant breast tissue than in adjacent unaffected tissue (Table 1) [35–42]. A study in 2007, using unaffected breast tissue from a breast with a primary tumour present, compared aluminium concentrations in both the defatted tissue and in the fat itself and revealed that levels in the defatted tissue varied from 4 to 437 nmol/g dry weight and in the fat from 3–192 nmol/g oil [37]. Interestingly, for each individual, as opposed to mean tissue level, the aluminium content of defatted tissue was significantly higher in the outer than the inner breast regions which could be compatible with the aluminium originating at least in part from cosmetic application to the underarm area [37]. However, this gradient of aluminium was not observed in the fat taken from these tissues [37,43] and so future studies will need to measure aluminium in the tissue and fat separately, especially since breast is a fatty tissue and fat content can vary between tissue samples. From these studies, it is evident that methodological development is still needed for assessment of the significance of differences in aluminium concentrations reported in human breast tissues and due consideration must continue to be given to all possible sources of contamination during sampling or reasons for variation in aluminium measurements in different compartments of the human breast.

Aluminium has been measured also in nipple aspirate fluid where it was found at higher levels in samples from breast cancer patients than from non-affected women [41]. Nipple aspirate fluid is secreted by ductal and lobular epithelial cells of the breast and therefore reflects the breast microenvironment. Since it can be collected non-invasively, it has been used in numerous studies to identify biomarkers of women at increased risk of breast cancer development. The mean level of aluminium in 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 [41].

Aluminium has been measured also in breast cyst fluids at higher levels than in blood or milk [42]. Gross cystic breast disease is the most common benign breast disorder caused by obstruction of ductal terminal lobular units and retention of fluid. Gross cysts can be classified into two types based on histology and on ion/protein