Commentary

A Case-control Study Adds a New Piece to the Aluminium/Breast Cancer Puzzle

CrossMark

Stefano J. Mandriota

Laboratoire de Cancérogenèse Environnementale, Fondation des Grangettes, Chêne-Bougeries, Switzerland

ARTICLE INFO

Breast cancer (BC) is a heterogeneous group of human neoplasias in which age, family history of BC and hormone exposure are well-established risk factors. Epidemiological data indicate that environmental factors largely contribute to BC incidence. For instance, migrants from eastern Asia, where the BC incidence is generally lower than in Western populations, develop the same rate of BC as the Americans, after having moved to the USA (Key et al., 2001). In addition, specific BRCA mutations lead to BC earlier in life in patients born after 1940, compared to those born before that year (King et al., 2003). Much remains to be understood regarding the identity and relative contributions of environmental factors to breast cancer incidence.

The incidence of BC has increased in industrialized Countries since, approximately, the second half of the 1960′s. A topological redistribution has also been observed, the majority of tumors occurring nowadays in the upper outer quadrant of the breast. Based on these observations, P. Darbre first hypothesized that the daily application of antiperspirants to the underarm area could be responsible for these effects (Darbre, 2016, and references therein).

Aluminium – mainly in the form of aluminium chloride and aluminium chlorohydrate - is a main component of the large majority of commercialized antiperspirants. In addition to preventing sweating – probably by physically obstructing sweat glands – aluminium is absorbed through the skin. Significant amounts of aluminium are present in the human breast (reviewed by Darbre, 2016). The reasons for this accumulation are not understood. Intriguingly, aluminium-based antiperspirants have been widely commercialized since approximately the end of 1950′s, thus preceding the abovementioned increase in BC by a few years. Aluminium has no recognized biological function.

The classical approach for the assessment of an environmental carcinogen consists of both experimental and epidemiological investigations. On the experimental front, existing studies have focused on the effects of aluminium on cultured mammary epithelial cells.

Concentrations of aluminium in the range of those measured in the human breast transform MCF-10A human mammary epithelial cells and NMuMG mouse mammary epithelial cells *in vitro* after several weeks of culture. In MCF-10A cells, these effects were preceded by the induction of DNA double strand breaks (DSB), of which the repair is often intrinsically mutagenic, and were not reversible following aluminium withdrawal from the culture medium, thus suggesting a genetic modification of the cells. Consistent with this hypothesis, mammary epithelial cells cultured in the presence of aluminium accumulate mutations (Sappino et al., 2012; Mandriota et al., 2016; and our unpublished data). However, it is still unclear whether aluminium is a true mutagen, or if it selects for mutations already present in the mammary epithelial cell lines. When injected into NOD-SCID or nude mice, NMuMG cells transformed *in vitro* by aluminium form tumors and metastasis, whereas untreated controls do not (Mandriota et al., 2016). In other studies, aluminium increased the migratory and invasive properties of MCF-7 or MDA-MB-231 human breast cancer cells *in vitro* (Darbre et al., 2013; Bakir and Darbre, 2015). As it is true for other metals and known carcinogens, aluminium is not detectably mutagenic in bacteria (Sappino et al., 2012). Altogether, these results support the hypothesis that aluminium is an environmental breast carcinogen. Epigenetic effects might contribute to aluminium-induced cellular transformation.

On the epidemiological front, studies investigating the link between aluminium and BC have led to conflicting results. In a retrospective study using the data from 437 BC patients, McGrath (2003) reported that frequency of antiperspirant/deodorant (collectively referred to as UCP: underarm cosmetic product) use, in combination with underarm shaving, was associated with a BC diagnosis at an earlier age. The effect was particularly marked in women who started UCP use before the age of 16. In another retrospective study, using the data of 813 BC patients, Mirick et al. (2002) found no association between UCP use and BC risk. The latter study did not collect information on frequency or age of use. Neither study measured the levels of aluminium in the breasts of cancer cases or controls.

In this issue of *EBioMedicine*, a new retrospective study (Linhart et al., 2017) analyzing the data from 209 BC cases and 209 healthy controls, revealed an association between self-reported UCP use and BC risk. The association was statistically significant for patients who reported using UCP more than once a day when they were under the age of 30. Importantly, this study also measured the aluminium content of a large subsample of BC cases and controls, and found that self-reported UCP use correlates with higher aluminium content in the breast. It is worth

highlighting that the concentrations of aluminium measured in BC cases are in the range of those that transform mammary epithelial cells *in vitro* (Sappino et al., 2012; Mandriota et al., 2016).

The subgroup exhibiting a statistically significant association between UCP use and BC risk is small (27 patients) and recall biases may exist in this kind of study. Also, it is currently unclear how exactly aluminium could reach and distribute within the mammary gland once applied to the axilla. In addition, if a link between UCP use and BC is confirmed by future studies, one should consider the possibility that a UCP component other than aluminium is the potentially involved carcinogen. Therefore, additional studies are required to confirm that UCP use is associated with BC risk, and that the involved carcinogen is aluminium. Notwithstanding these limitations, the observations by Linhart et al. add an important new piece of work to the aluminium/BC story.

Disclosure

The author declares no conflicts of interest.

References

Bakir, A., Darbre, P.D., 2015. Effect of aluminium on migration of oestrogen unresponsive MDA-MB-231 human breast cancer cells in culture. J. Inorg. Biochem. 152, 180–185.

Darbre, P.D., 2016. Aluminium and the human breast. Morphologie 100, 65–74.

Darbre, P.D., 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.

Key, T.J., Verkasalo, P.K., Banks, E., 2001. Epidemiology of breast cancer. Lancet Oncol. 2, 133–140.

King, M.C., Marks, J.H., Mandell, J.B., New York Breast Cancer Study Group, 2003. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 302, 643–646.

Linhart, C., Talasz, H., Morandi, E.M., Exley, C., Lindner, H.H., Taucher, S., Egle, D., Hubalek, M., Concin, N., Ulmer, H., 2017. Use of underarm cosmetic products in relation to risk of breast cancer: a case-control study. EBioMedicine http://dx.doi.org/10.1016/j.ebiom.2017.06.005.

Mandriota, S.J., Tenan, M., Ferrari, P., Sappino, A.P., 2016. Aluminium chloride promotes tumorigenesis and metastasis in normal murine mammary gland epithelial cells. Int. J. Cancer 139, 2781–2790.

McGrath, K.G., 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.

Mirick, D.K., Davis, S., Thomas, D.B., 2002. Antiperspirant use and the risk of breast cancer. J. Natl. Cancer Inst. 94, 1578–1580.

Sappino, A.P., Buser, R., Lesne, L., Gimelli, S., Béna, F., Belin, D., Mandriota, S.J., 2012. Aluminium chloride promotes anchorage-independent growth in human mammary epithelial cells. J. Appl. Toxicol. 32, 233–243.