

Breast Cancer and Exposures from the Physical Environment:

Introduction and Overarching Issues

In May 2007, 200 leading environmental scientists convened in the Faroe Islands north of Scotland to consider the human health effects of early-life exposures to environmental toxicants. This gathering, the International Conference on Fetal Programming and Developmental Toxicity, resulted in a signed declaration that made headlines around the world, for example, in the Los Angeles Times.¹ The Faroes Statement warned that low-level exposures to common environmental chemicals during fetal life and early infancy increase risks for various health problems later in life. According to the document, these problems include diabetes, attention deficit disorders, obesity, infertility, and thyroid disorders. They also include breast cancer.² Singled out for mention were the common pesticide atrazine and the common plastics ingredient, bisphenol A, which, according to the document's consensus statement, can alter breast development in early life in ways that increase susceptibility to breast cancer in adulthood.

The Faroes Statement goes on to call for a fresh approach to research on breast cancer and other diseases that recognizes a new paradigm of toxicologic understanding:

"The old paradigm, developed over four centuries ago by Paracelsus, was that 'the dose makes the poison.' However, for exposures sustained during early development, the most important

issue is that 'the timing makes the poison.' This extended paradigm deserves wide attention....Among the mechanisms involved, particular concern is raised about changes in gene expression due to altered epigenetic marking, which may not only lead to increased susceptibility to diseases later in life, but the effects may also be passed on to subsequent generations."²

Andreas Kortenkamp, a toxicologist at the University of London, has likewise called for a new approach to breast cancer that recognizes the existence of *critical periods* in early life and during development that sensitize the breast to carcinogenesis by hormonally active chemicals. Emphasizing the biological plausibility of such an approach, Kortenkamp points out that the majority of cancers arise from the terminal end buds of the breast ducts. Any environmental chemical that increases the number of cells in the end buds during early life or that delays the maturation of these structures can raise the risk for cancer—even without direct genetic damage.^{3,4} The weed killer atrazine, to which 60 percent of the U.S. population is exposed daily, is such a chemical. In laboratory animals, atrazine exposure *in utero* retards the maturation of the mammary gland in puberty and increases the number of end buds.^{5,6} The insecticide DDT may also be such a chemical. A study of women in Oakland, California has found that high serum levels of DDT predicted a five-fold increased risk of breast cancer among women exposed prior to age 14. Women exposed

after age 14 showed no link between blood levels of DDT and breast cancer.⁷

For environmental exposures that do induce genetic damage, such as ionizing radiation, timing of exposure also matters. Among atomic bomb survivors in Hiroshima and Nagasaki, for example, breast cancer increased significantly only among those exposed during puberty.⁸ More recently, a study of breast cancer patients who had been treated previously with radiation therapy for childhood cancers found a link between timing of radiation exposure and the development of HER2-positive tumors: the highest risk occurred in patients irradiated within four years of menarche.⁹ And yet, in spite of evidence such as this, conventional epidemiological and toxicological testing does not routinely take into account developmental differences at the time of exposure.

Many leading researchers, including Kortenkamp, have also urged increased attention to *chemical mixtures* in environmental health research. Real-life exposures to environmental agents, these researchers point out, are not limited to one chemical but, most often, result from low-level exposures to a changing kaleidoscope of chemicals, some of which may operate down similar molecular pathways.^{3, 4, 10-12}

A recent Spanish study, for example, demonstrated that breast cancer risk among women was associated with the body burden of all estrogenic chemical contaminants, excluding natural hormones.¹³ Among grazing sheep in Scotland, males exposed *in utero* to a cocktail of chemicals found in sewage sludge developed testicular abnormalities,¹⁴ while females reared on

pastures treated with sewage sludge showed abnormalities in mammary gland development.¹⁵ In lab animals, exposure to dioxin in fetal life sensitizes mammary glands to carcinogenic assault by other chemical agents in later life.⁵ More specifically, dioxin-exposed breast tissue is less able to fend off the damage caused by subsequent free radical exposure.¹⁶ And yet, again, conventional testing has not routinely taken into account the effects of low-level exposures to chemicals in combination. Like atrazine, bisphenol A has been detected in ground water and private wells.^{17, 18} What is the risk for a young girl whose drinking water contains both?

Exposures from the physical environment may also play a role in the breast cancer story if they *amplify the effects of known risk factors*. Early puberty – especially early menarche – is a well-established risk factor for breast cancer. As age of menarche decreases, overall risk of breast cancer increases.¹⁹ Menarche before age 12, for example, raises breast cancer risk by 50 percent when compared to menarche at age 16.²⁰ Environmental factors that hasten the timing of sexual maturation may thus contribute to breast cancer risk. Some researchers have posited that greater use of estrogen- or placenta-containing hair preparations may be contributing to the falling age of puberty among U.S. black girls.^{21, 22} If so, they may also contribute to racial disparities in breast cancer. In addition, chemicals in the physical environment may contribute to early puberty – and thereby to breast cancer risk – if they shorten human gestation, lower birth weight, or increase the risk for obesity and insulin dysregulation. All of these factors are associated with earlier sexual maturation in girls.^{20, 23-25}

Identifying Gaps in Breast Cancer Research

In contrast to early puberty, breast-feeding is a reproductive factor known to lower breast cancer risk, especially among post-menopausal women.²⁶ Thus, chemical exposures that interfere with lactation may increase the risk for breast cancer. Some organochlorine chemicals have been associated with shortened duration of breast-feeding among nursing mothers in North Carolina and Mexico^{27, 28} and decreased milk volume among mothers in the Netherlands.²⁹ And yet, although pubertal timing and duration of breast-feeding are both known to modify breast cancer risk, little research has explored the impact of the physical environment on these two reproductive factors.

In sum, a fresh approach to the question of breast cancer's environmental roots would take up the question of chemical mixtures, would consider the timing of exposure, (with an emphasis on exposures that happen in utero and in early life), and would expand the search to include environmental agents with the power to modify known reproductive risk factors.

The chapters of this report that follow do not, for the most part, take this tack. Instead, they summarize the evidence—from *in vitro*, animal, and human studies—for individual environmental agents in isolation from one another. While there are obvious shortcomings to this kind of analysis, the hope is that the atomized organization of these chapters will, nevertheless, inspire the reader to consider the various ways in which these individual agents might interact with one another in a web of causality and, in so doing, will reveal potential avenues of inquiry that would be fruitful to pursue. As two new papers reveal, exposure to

mammary gland carcinogens is widespread.³⁰ Many of these have not yet been included in human studies.³¹ Among the 216 compounds identified as mammary carcinogens in animals, 73 are found in food or consumer products; 35 are air pollutants; and 29 are produced in the U.S. in large amounts.³⁰ Thus, even using old-fashioned criteria – investigating one mammary carcinogen at a time using conventional toxicological research – we still have much to learn about how to identify chemical contributors to breast cancer and eliminate them from the environment.

Understanding the role of industrial chemicals and other environmental factors in the story of breast cancer, a disease characterized by complexity and multi-causality, will require bringing the best time-honored techniques of traditional toxicology and epidemiology together with holistic approaches that, so advise the authors of the Faroes Statement,² focus on systems and tissue biology.

References

1. Cone M. Common chemicals pose danger for fetuses, scientists warn [newspaper article]. In: Los Angeles Times. Los Angeles, CA, USA: Los Angeles Times, 2007 May 25. Available at <http://www.commondreams.org/archive/2007/05/25/1445/>.
2. Grandjean P, Bellinger D, Bergman A, Cordier S, Davey-Smith G, Eskenazi B, Gee D, Gray K, Hanson M, Van der Hazel P, Heindel JJ, Heinzow B, Hertz-Picciotto I, Hu H, Huang TT-K, Jensen TK, Landrigan PJ, McMillen C, Murata K, Ritz B, Schoeters G, Skakkenbaek NE, Skerfving S, Weihe P. The Faroes statement: health human effects of developmental exposure to chemicals in our environment. *Basic & Clinical Pharmacology & Toxicology*. 2007, doi: 10.1111/j.1742-7843.2007.00114.x (available at <http://dx.doi.org/>).
3. Kortenkamp A. Environmental Contaminants and Breast Cancer: The Growing Concerns about Endocrine Disrupting Chemicals (a briefing paper for WWF-UK). Surrey, UK: WWF-UK, 2006. Available at http://assets.panda.org/downloads/breast_cancer_report_1.pdf.
4. Kortenkamp A. Breast cancer, oestrogens and environmental pollutants: a re-evaluation from a mixture perspective. *Int J Androl*. 2006, 29(1):193-8.
5. Birnbaum LS, Fenton SE. Cancer and developmental exposure to endocrine disruptors. *Environ Health Perspect*. 2003, 111(4):389-94.
6. Rayner JL, Enoch RR, Fenton SE. Adverse effects of prenatal exposure to atrazine during a critical period of mammary gland growth. *Toxicol Sci*. 2005, 87(1):255-66.
7. Cohn BA, Wolff MS, Cirillo PM, Sholtz RI. DDT and breast cancer in young women: new data on the significance of age at exposure. *Environ Health Perspect*. 2007, doi:10.1289/ehp.10260 (available at <http://dx.doi.org/>).
8. McGregor H, Land CE, Choi K, Tokuoka S, Liu PI, Wakabayashi T, Beebe GW. Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki, 1950-69. *J Natl Cancer Inst*. 1977, 59(3):799-811.
9. Castiglioni F, Terenziani M, Carcangiu ML, Miliano R, Aiello P, Bertola L, Triulzi T, Gasparini P, Camerini T, Sozzi G, Fossati-Bellani F, Menard S, Tagliabue E. Radiation effects on development of HER2-positive breast carcinomas. *Clin Cancer Res*. 2007, 13(1):46-51.
10. Porter WP, Jaeger JW, Carlson IH. Endocrine, immune, and behavioral effects of aldicarb (carbamate), atrazine (triazine) and nitrate (fertilizer) mixtures at groundwater concentrations. *Toxicol Ind Health*. 1999, 15(1-2):133-50.

Identifying Gaps in Breast Cancer Research

11. Schettler T. Toward an ecological view: complex systems, health, and disease. *San Francisco Medicine*. 2006, 79(1):12-5.
12. Snedeker S. Environmental estrogens: affects on puberty and cancer risk. *The Ribbon - A Newsletter of the Cornell University Program on Breast Cancer and Environmental Risk Factors (BCERF)*. 2007, 12(1):5-7.
13. Ibarluzea Jm J, Fernandez MF, Santa-Marina L, Olea-Serrano MF, Rivas AM, Aurrekoetxea JJ, Exposito J, Lorenzo M, Torne P, Villalobos M, Pedraza V, Sasco AJ, Olea N. Breast cancer risk and the combined effect of environmental estrogens. *Cancer Causes Control*. 2004, 15(6):591-600.
14. Paul C, Rhind SM, Kyle CE, Scott H, McKinnell C, Sharpe RM. Cellular and hormonal disruption of fetal testis development in sheep reared on pasture treated with sewage sludge. *Environ Health Perspect* . 2005, 113(11):1580-7.
15. Fowler P, Gordon K, Thow C, Cash P, Miller D, Lea R, Rhind S. Dietary sewage sludge exposure disrupts ewe mammaryogenesis [conference proceeding]. Presented at the 13th Annual General Meeting of the Association of Clinical Embryologists, Fertility 2007 Conference; University of York, Heslington, York, UK. Heslington, York, UK: University of York, 2007.
16. Jenkins S, Rowell C, Wang J, Lamartiniere CA. Prenatal TCDD exposure predisposes for mammary cancer in rats. *Reprod Toxicol*. 2007, 23(3):391-6.
17. Rudel RA, Melly SJ, Geno PW, Sun G, Brody JG. Identification of alkylphenols and other estrogenic phenolic compounds in wastewater, septage, and groundwater on Cape Cod, Massachusetts. *Environ Sci Technol*. 1998, 32(7):861-9.
18. Kolpin DW, Barbash JE, Gilliom RJ. Occurrence of pesticides in shallow groundwater of the United States: initial results from the National Water-Quality Assessment Program. *Environ Sci Technol*. 1998, 32(5):558-66.
19. Anderson WF, Matsuno RK, Sherman ME, Lissowska J, Gail MH, Brinton LA, Yang XR, Peplonska B, Chen BE, Rosenberg PS, Chatterjee N, Szeszenia-Dabrowska N, Bardin-Mikolajczak A, Zatonski W, Devesa SS, Garcia-Closas M. Estimating age-specific breast cancer risks: a descriptive tool to identify age interactions. *Cancer Causes Control*. 2007, 18(4):439-47.
20. Grumbach MM, Styne DM. Puberty: ontogeny, neuroendocrinology, physiology, an disorders. In: Larsen PR. *Williams Textbook of Endocrinology*. Philadelphia, PA, USA: W.B. Saunders, 2003; pp. 1115-286. (ISBN: 9780721691961)

California Breast Cancer Research Program

21. Donovan M, Tiwary CM, Axelrod D, Sasco AJ, Jones L, Hajek R, Sauber E, Kuo J, Davis DL. Personal care products that contain estrogens or xenoestrogens may increase breast cancer risk. *Med Hypotheses*. 2007, 68(4):756-66.
22. Tiwary CM. Premature sexual development in children following the use of estrogen- or placenta-containing hair products. *Clin Pediatr (Phila)*. 1998, 37(12):733-9.
23. Biro FM, Khoury P, Morrison JA. Influence of obesity on timing of puberty. *Int J Androl*. 2006, 29(1):272-7; discussion 286-90.
24. Neville KA, Walker JL. Precocious pubarche is associated with SGA, prematurity, weight gain, and obesity. *Arch Dis Child* . 2005, 90(3):258-61.
25. Slyper AH. The pubertal timing controversy in the USA, and a review of possible causative factors for the advance in timing of onset of puberty. *Clin Endocrinol (Oxf)*. 2006, 65(1):1-8.
26. Shantakumar S, Terry MB, Teitelbaum SL, Britton JA, Millikan RC, Moorman PG, Neugut AI, Gammon MD. Reproductive factors and breast cancer risk among older women. *Breast Cancer Res Treat*. 2007, 102(3):365-74.
27. Gladen BC, Rogan WJ. DDE and shortened duration of lactation in a northern Mexican town. *Am J Public Health*. 1995, 85(4):504-8.
28. Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, Thullen J, Tingelstad J, Tully M. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: effects on growth, morbidity, and duration of lactation. *Am J Public Health*. 1987, 77(10):1294-7.
29. Boersma ER, Lanting CI. Environmental exposure to polychlorinated biphenyls (PCBs) and dioxins. Consequences for longterm neurological and cognitive development of the child lactation. *Adv Exp Med Biol*. 2000, 478:271-87.
30. Rudel RA, Attfield KR, Schifano JN, Brody JG. Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. *Cancer*. 2007, 109(S12):2635-66.
31. Brody JG, Moysich KB, Humblet O, Attfield KR, Beehler GP, Rudel RA. Environmental pollutants and breast cancer: epidemiologic studies. *Cancer*. 2007, 109(12 Suppl):2667-711.