HOW USEFUL IS MEASUREMENT OF ENVIRONMENTAL CHEMICALS IN HUMAN MILK IN INVESTIGATIONS OF BREAST CANCER ETIOLOGY?

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Introduction

The etiology of breast cancer is complex and multifactorial. Risk factors for increased breast cancer risk include[1, 2]: nulliparity, late age at first pregnancy, early menarche, late menopause, inheritance of high-penetrance susceptibility genes, increasing age, exposure to ionizing radiation, and environmental factors. Environmental factors, including exposure to xenobiotic compounds, diet, and lifestyle, have been the subject of numerous scientific inquiries. Yet studies investigating possible associations with xenobiotic compounds such as persistent organochlorine compounds in women have yielded inconsistent results (as summarized and reanalyzed by Laden et al.[3]).

Recommendations to monitor human milk as part of an effort to explore breast cancer etiology[4] have been made, noting that "Like no other body fluid, breast milk reflects the internal contamination of the target organ for breast cancer." The hypothesis that human milk is an effective fluid for understanding potential environmental links to breast cancer is explored in this paper by first considering the evidence relating to the biological plausibility of environmental chemicals in human milk as contributors to the etiology of breast cancer and then considering, from an epidemiological perspective, the practicality of using measurements of environmental chemicals in human milk as exposure measures in investigations of breast cancer etiology.

Methods and Materials

A survey of the literature on research into the potential relationship between breast cancer and environmental chemicals in human milk, and human milk biomonitoring relating to breast cancer etiology was conducted. The survey included literature on environmental chemicals found in an array of breast tissues and fluids.

Results and Discussion

Biological plausibility of a role for environmental chemicals in human milk in breast cancer etiology

There are several lines of evidence and reasoning that support the possibility of a relationship between exposure to certain lipophilic compounds (such as organochlorine compounds) and breast cancer: First, these compounds are stored in lipids, and are in contact with mammary epithelial cells. Second, some organochlorine compounds act as xenoestrogens, and it has been hypothesized that the estrogenic activity related to these compounds can stimulate breast cell proliferation and induce or promote cancer[5]; however, not all researchers agree with this hypothesis[5, 6].

Third, it has been reported that increased duration of breastfeeding is associated with a decreased risk of breast cancer; one plausible hypothesis for this association relates to the depuration of chemicals such as organochlorines during lactation, resulting in a reduced body burden of these chemicals. Others have critically reviewed the association between history of breastfeeding and decrease in risk of breast cancer in the mother, and found that the protective effect of prolonged breastfeeding is mainly limited to premenopausal women and is a relatively weak effect[7]. In addition, having been breast-fed (which would result in increased body burdens of PBTs in infants as compared to formula-fed infants[8]) does not appear to result in increased breast cancer risk in pre- or post-menopausal women[9]; in addition, breastfed children have a lower risk of developing Hodgkin's disease[10].

Human milk extracts have shown positive results in tests for genotoxic activity; research comparing the breast cells and milk from human milk samples collected early and late in lactation indicates that the genotoxicity of the milk does not appear to decrease during the course of lactation[11]. Because concentrations of many persistent lipophilic compounds decline over the course of lactation[12], this finding suggests that chemicals other than the persistent lipophilic compounds may be responsible for the genotoxicity found in human milk extracts. There is evidence that mutagenic agents in breast lipids and human milk are moderately polar lipophilic compounds of low molecular weight[1], whereas most persistent organic compounds (e.g., the PBTs) are highly lipophilic. For DDT compounds, it has been noted that the decline in body burdens of these compounds over the past few decades has coincided with an increase in incidence of breast cancer, suggesting that DDT does not play an etiologic role for breast cancer[6]. In sum, this information suggests that breast cancer research on compounds other than traditionally monitored PBTs would be more fruitful than limiting the focus solely to PBTs.

Other avenues for understanding breast cancer etiology may lie in studying dietary links. For example, the relationship between diet (specifically, the consumption of well-done cooked meats) and breast cancer may be related to the detection of heterocyclic amines cooked meats and in human milk[13]. Polycyclic aromatic hydrocarbons (PAHs) are another class of chemicals which have been shown to be mammary carcinogens in laboratory animals. These chemicals are also present in cooked foods and as DNA adducts in human mammary epithelial cells[14].

Overall, while not compelling, the evidence suggests that there may be a relationship between persistent environmental chemicals in human milk and breast cancer, and that further investigation of this possibility could be worthwhile.

Human milk as an exposure measure in breast cancer etiology studies.
As a medium for assessment of exposure to breast tissue, human milk has certain advantages: In particular, it can be obtained relatively non-invasively and it comes into direct contact with breast tissue. It can also be used to assess infant exposures during breast-feeding and to carry out corresponding risk assessments[12, 15]. If the milk is collected in a consistent manner from a well-defined population, it can be compared with a large amount of internationally collected information from other areas and countries. This comparison can provide some measure of relative population exposures to these chemicals. However, the question of whether human milk as a biomonitoring tool for persistent, lipophilic compounds will advance the state of understanding of environmental causes of breast cancer is more complex.

Epidemiology seeks associations between exposures and disease incidence, with the ultimate aim of finding true causal relationships and identifying key exposures that may be reduced or eliminated. For breast cancer, measurement of environmental chemicals in human milk has the advantages that it can be obtained non-invasively and involves chemicals that actually come into contact with breast tissue at a time of life that may be etiologically meaningful in breast cancer development. However, such measurements also have major limitations. First, human milk can be obtained only from women who have children. It has been reported that women who have breastfed children are at lower risk of breast cancer than women who have not breastfed children[16]. Thus, seeking breast cancer associations with lipophilic environmental chemicals in human milk is immediately limited to the sub-group of women (albeit a large one) who are at lower risk for breast cancer. The second limitation is that, for most women, the age at which breast cancer occurs is much later than the age at which lactation took place. So, to carry out an analytic epidemiological study (cohort or nested case-control) with the possibility of meaningful results, it would be necessary to collect human milk samples from a large cohort of women and store the samples, or maintain the analytical results, until a sufficient proportion of the cohort had developed breast cancer. No such study has yet been published. Such studies that have been done have generally used blood serum or breast tissue samples to obtain exposure measures. Because human milk sampling and the availability of sufficiently sensitive chemical analytic methods is relatively recent, it may still be several decades before the results of a study seeking associations between breast cancer and chemical levels could be anticipated, even if such a study is already underway.

The alternative, which could be carried out in a shorter time, is an ecological study -- examining breast cancer rates across different areas in relation to measurement data for comparable human milk samples from those areas. However, as with all ecological studies, such a study has inherent limitations. In particular, it is not possible to examine potential confounding factors. It is possible that there are many determinants of breast cancer that correlate at a population level with degree of exposure to persistent lipophilic environmental chemicals. For example, fat intake is a likely determinant of organochlorine exposure, and it is a risk factor for breast cancer[17]. Therefore, at an ecological level, it may confound the association with organochlorine levels in human milk. Secondly, the timing of the exposure measurement is not necessarily appropriate. Exposures influencing breast cancer rates may have occurred many years previously and these would not necessarily be reflected by contemporaneous measurements of environmental chemicals in milk from women without breast cancer.

Conclusions

There is plausibility in the view that PBTs present in human milk may play a role in the etiology of breast cancer. However, there are practical difficulties in using human milk PBT measurements as exposure measures in epidemiological studies investigating breast cancer etiology, although if such a study were to be carried out it could provide valuable information. The best approach may be to incorporate human milk sample collection into a large prospective cohort study of women's health. Given the current expense of comprehensive chemical analysis, these samples could be stored frozen until (probably decades later) a sufficient sample of the cohort had developed breast cancer. Stored samples for the study subjects and an appropriately selected control group could then be chemically analyzed as part of a nested case-control study design. As with all human milk studies, the study plan should incorporate a process for communicating to women the benefits of breastfeeding to the mothers and infants, so that the research does not result in reductions in breastfeeding among study participants who may interpret the message of the study as "breastfeeding is unsafe"[18]. Other types of breast tissues/ fluids may also prove useful in shedding

light on the of the relationship (if any) between environmental chemicals (including those from dietary sources) and breast cancer[1, 19, 20, 21, 22].

The views expressed in this paper are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

References

1. Phillips, D.H., Martin, F.L., Williams, A., Wheat, L.M.C., Nolan, L., Cole, K.J., Grover, P.L.; (2002) Environmental and Molecular Mutagenesis, 39,143.
2. Adami, H.-O., Signorello, L.B., Trichopolous, D.; (1998) Cancer Biology 8, 255.
3. Laden, F., Colman, G., Iwamoto, K., Alberg, A.J., Berkowitz, G.S., Freudenheim, J.L., Hankinson, S.E., Helzsouer, K.J., Holford, T.R., Huang, H.-Y., Moysich, K.B., Tessari, J.D., Wolff, M.S., Zheng, T., Hunter, D.J.; (2001) Journal of the National Cancer Institute 92(10), 768.
4. California Senate Bill SB 689, April 22, 2003. http://info.sen.ca.gov/pub/bill/sen/sb_0651-0700/sb_689_bill_20030422_amended_sen.pdf
5. DeBruin, L.S., Josephy, P.D.; (2002) Environmental Health Perspectives 110(1), 119.
6. Safe, S.; (1997) Environmental Health Perspectives 105(3), 675.
7. Lipworth, L., Bailey, L.R., Trichopoulos, D.; (2000) Journal of the National Cancer Institute 92(4), 302.
8. LaKind, J.S., Berlin, C., Park, C., Naiman, D.Q., Gudka, N.J.; (2000) Journal of Toxicology and Environmental Health, Part A 59, 605.
9. Titus-Ernstoff, L., Egan, K.M., Newcomb, P.A., Baron, J.A., Stampfer, M., Greenberg, E.R., Cole, B.F., Ding, J., Willett, W., Trichopoulos, D.; (1998) Journal of the National Cancer Institute 90(12), 921.
10. Davis, M.K.; (1998) International Journal of Cancer S11, 29.
11. Martin, F.L., Cole, K.J., Harvey, D., Weaver, G., Williams, J.A., Millar, B.C., Phillips, D.H., Grover, P.L.; (2000) Carcinogenesis 21(4), 799.
12. LaKind, J.S., Berlin, C., Naiman, D.Q.; (2001) Environmental Health Perspectives 109, 75.
13. DeBruin, L.S., Martos, P.A., Josephy, P.D.; (2001) Chemical Research in Toxicology 14, 1523.
14. El-Bayoumy, K.; (1992) Chemical Research in Toxicology 5(5), 585.
15. LaKind, J.S., Birnbach, N., Borgert, C.J., Sonawane, B.R., Tully, M.R., Friedman, L.; (2002) Journal of Toxicology and Environmental Health 65(22), 1909.
16. Collaborative Group on Hormonal Factors in Breast Cancer. (2002) The Lancet 360, 187.
17. Bradlow, H.L., Sepkovic, D.W.; (2002) Ann NY Acad Sci 963, 247.
18. Bates, M.N., Selevan, S.G., Ellerbee, S.M., Gartner, L.M.; (2002) Journal of Toxicology and Environmental Health Part A 65, 1867.
19. Rundle, A., Tang, D., Hibshoosh, H., Estabrook, A., Schnabel, F., Cao, W., Grumet, S., Perera, F.P.; (2000) Carcinogenesis 21, 1281.
20. Malatesta, M., Mannello, F., Bianchi, G., Sebastiani, M., Gazzanelli, G.; (2000) Journal of Clinical Laboratory Analysis 14, 330.
21. Klein, P.M., Lawrence, J.A.; (2002) Environmental and Molecular Mutagenesis 39, 127.
22. Martin, F.L., Cole, K.J., Weaver, G., Williams, J.A., Millar, B.C., Grover, P.L., Phillips, D.H.; (1999) Biochemical and Biophysical Research Communications 257, 319.