A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP13777.

Invited Perspective: New Motivations and Future Directions for Investigating Environmental Risk Factors for Breast Cancer

Rena R. Jones[1] *and Alexandra J. White*[2]

[1]Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health (NIH), Department of Health and Human Services (DHHS), Rockville, Maryland, USA
[2]Epidemiology Branch, National Institute of Environmental Health Sciences, NIH, DHHS, Research Triangle Park, North Carolina, USA

https://doi.org/10.1289/EHP13777

Refers to https://doi.org/10.1289/EHP13233

As the most commonly diagnosed cancer in women, and the primary cause of cancer death in women globally,[1] breast cancer continues to be a significant public health issue. Although widely recognized risk factors, such as genetic mutations, reproductive history, and lifestyle choices, contribute to breast cancer risk, they do not account for a majority of the disease,[1–3] and many of these factors are not easily intervened upon. Moreover, although some modifiable risk factors have been identified, incidence rates continue to increase for certain groups.[4] The identification of new risk factors, particularly those that lend themselves to intervention, are needed. Epidemiologic evidence is accumulating in support of a role for various environmental chemicals in breast cancer etiology, including ambient air pollution, personal care products, and persistent organic pollutants, such as some pesticides.[5] Given their widespread nature and the potential for policy changes or public health interventions to reduce exposure, environmental chemicals are promising targets for addressing breast cancer incidence.

In this issue of *Environmental Health Perspectives*, Kay et al.[6] update their prior list[7] of mammary carcinogens by drawing upon the key characteristics framework developed by the International Agency for Research on Cancer. In doing so, they broadened the approach to identifying mammary carcinogens by incorporating information on chemical bioactivity, including both genotoxicity and endocrine disruption. In particular, the inclusion of biologic activity of endocrine-disrupting compounds (EDCs), which are frequently encountered in daily life, is important given the hormonally influenced nature of most breast cancer types. In this new effort combining carcinogenicity and mechanistic bioactivity data, the authors have compiled a list of compounds relevant to breast cancer that can be used to help prioritize chemicals for study and to enhance prevention efforts.

Research on exogenous chemicals and breast cancer risk has been limited, in part due to sparse environmental measurements[8] and other relevant data. For many agents on the list compiled by Kay et al., the epidemiologic evidence for cancer is derived primarily from high-exposure occupational settings, in which women tend to be underrepresented[9] and which likely reflect different exposure patterns and routes of exposure than typically occur in the ambient environment. Another issue is the possibility that environmental risk factors are contributing to the increasing incidence of early-onset breast cancers (i.e., those diagnosed in women <50 years of age).[10] Some of this increase is likely attributable to greater screening and early detection,[10,11] but exposure to harmful chemicals long before breast cancer occurs may also be relevant. Growing epidemiologic evidence indicates that EDC exposure—particularly during specific vulnerable life stages, including during the prenatal period, early life, puberty, pregnancy, and menopausal transition—may affect breast cancer risk.[12] Research on exposures occurring during these windows of susceptibility has the potential to advance our understanding and prevention of breast cancer.

Studying the environmental etiology of breast cancer comes with considerable challenges as well as exciting opportunities. Given the long latency of the disease and opportunity for women to experience complex, cumulative exposures to numerous mammary carcinogens over their lifetime, exposure characterization is a major challenge for epidemiologic studies. For example, assessing exposures during the aforementioned critical windows requires creative study design approaches. Newly developed statistical methods for analyzing exposures to mixtures offer improvements in evaluating the risk associated with multiple, correlated exposures to better reflect real-world exposure patterns, accounting for co-occurring exposure to multiple chemicals. Targeted exposure measurement approaches, informed by this new list and used in conjunction with new analytic mixture methods for identifying the "bad actors" among correlated exposures, may be the key to moving the needle in identifying novel environmental contributors to breast cancer risk.

The consideration of multiple endocrine-disrupting pathways, including steroidogenesis and estrogen receptor (ER) agonism and the enrichment of EDC activity among mammary carcinogens, is a nice addition to this work. Nearly half of all mammary carcinogens evaluated by Kay et al. show both endocrine and genotoxic activity, which underscores the importance of considering multiple biologic pathways. In addition, as the authors note, evaluation of chemicals independently may not represent the effect of multiple exposures or mixture effects on breast cancer risk. However, information on individual effects can be enlightening in the setting of limited correlation among multiple chemicals. It can also be useful when using *a priori* data to inform mixture analyses when correlation between compounds is very high and the associations are challenging to disentangle.

Despite the efforts made here to better characterize and prioritize the chemicals to which we are exposed, difficulties remain. The number of industrial chemicals in U.S. commerce is large,[13] and many are not routinely measured,[8] indicating a need for future studies to expand the agents considered for inclusion in analyses. Indeed, among the EDCs newly identified by Kay et al. as potential rodent mammary carcinogens that also exhibited genotoxicity, including some widely used chemicals, cancer studies were absent for more than half. The list is also a constantly moving target, with new chemicals introduced into the environment at unpredictable intervals.[14] Untargeted exposure assessment approaches, although not always scalable, may therefore complement targeted strategies.

Address correspondence to Rena R. Jones, 9609 Medical Center Dr., Room 6E606, Rockville, MD 20850 USA. Telephone: (240) 276-7292. Email: rena.jones@nih.gov

The authors declare they have no conflicts of interest related to this work to declare.

Received 7 August 2023; Revised 21 September 2023; Accepted 4 December 2023; Published 10 January 2024.

Note to readers with disabilities: *EHP* strives to ensure that all journal content is accessible to all readers. However, some figures and Supplemental Material published in *EHP* articles may not conform to 508 standards due to the complexity of the information being presented. If you need assistance accessing journal content, please contact ehpsubmissions@niehs.nih.gov. Our staff will work with you to assess and meet your accessibility needs within 3 working days.

Our opinion is that understanding of the role of these environmental chemicals on the development of breast cancer will be most critically informed by combining data from robust exposure studies with those from epidemiologic investigations.

Finally, we note that nonhormonal etiologic mechanisms have received comparatively less study than endocrine disruption pathways. In part because these tumors comprise less than a quarter of breast cancers,[15] the etiology of ER-negative tumors is not well understood. These cancers have been linked to environmental exposures in a small number of studies[16–18] and are also important from a public health perspective because of their poorer prognosis.

Despite decades of research and extensive public health interest, how the environment influences breast cancer risk is not well understood. Improving our knowledge of risk factors for breast cancer is crucial to reducing its incidence and alleviating the overall burden it imposes. The addition of new environmental targets should spur focused future investigations with the potential to identify new risk factors for this disease.

References

1. Brinton LA, Gaudet MM, Gierach GL. 2017. Breast cancer. In: *Cancer Epidemiology and Prevention*. 4th ed. Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, eds. Oxford, UK: Oxford University Press, 861–888.
2. Campeau PM, Foulkes WD, Tischkowitz MD. 2008. Hereditary breast cancer: new genetic developments, new therapeutic avenues. Hum Genet 124(1):31–42, PMID: 18575892, https://doi.org/10.1007/s00439-008-0529-1.
3. Martin AM, Weber BL. 2000. Genetic and hormonal risk factors in breast cancer. J Natl Cancer Inst 92(14):1126–1135, PMID: 10904085, https://doi.org/10.1093/jnci/92.14.1126.
4. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, et al. 2022. Breast cancer statistics, 2022. CA Cancer J Clin 72(6):524–541, PMID: 36190501, https://doi.org/10.3322/caac.21754.
5. Rodgers KM, Udesky JO, Rudel RA, Brody JG. 2018. Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. Environ Res 160:152–182, PMID: 28987728, https://doi.org/10.1016/j.envres.2017.08.045.
6. Kay JE, Brody JG, Schwarzman M, Rudel RA. 2023. Application of the key characteristics framework to identify potential breast carcinogens using publicly available *in vivo*, *in vitro*, and *in silico* data. Environ Health Perspect 132(1):017002, https://doi.org/10.1289/EHP13233.
7. Rudel RA, Attfield KR, Schifano JN, Brody JG. 2007. Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. Cancer 109(suppl 12):2635–2666, PMID: 17503434, https://doi.org/10.1002/cncr.22653.
8. Muir DCG, Getzinger GJ, McBride M, Ferguson PL. 2023. How many chemicals in commerce have been analyzed in environmental media? A 50 year bibliometric analysis. Environ Sci Technol 57(25):9119–9129, PMID: 37319372, https://doi.org/10.1021/acs.est.2c09353.
9. Friesen MC, Beane Freeman LE. 2023. Identifying occupational risk factors for cancer in women: a need for further action. Occup Environ Med 80(9):522–523, PMID: 37429726, https://doi.org/10.1136/oemed-2023-108948.
10. Ugai T, Sasamoto N, Lee HY, Ando M, Song M, Tamimi RM, et al. 2022. Is early-onset cancer an emerging global epidemic? Current evidence and future implications. Nat Rev Clin Oncol 19(10):656–673, PMID: 36068272, https://doi.org/10.1038/s41571-022-00672-8.
11. Zhao JX, Liying X, Sun J, Song M, Wang L, Yuan S, et al. 2023. Global trends in incidence, death, burden and risk factors of early-onset cancer from 1990 to 2019. BMJ oncology 2(1):e000049, https://doi.org/10.1136/bmjonc-2023-000049.
12. Terry MB, Michels KB, Brody JG, Byrne C, Chen S, Jerry DJ, et al. 2019. Environmental exposures during windows of susceptibility for breast cancer: a framework for prevention research. Breast Cancer Res 21(1):96, PMID: 31429809, https://doi.org/10.1186/s13058-019-1168-2.
13. U.S. EPA (U.S. Environmental Protection Agency). 2023. Toxics Substances Control Act Chemical Substance Inventory. Last updated 24 October 2023. https://www.epa.gov/tsca-inventory [accessed 1 September 2023].
14. U.S. EPA. 2023. Chemical Data Reporting. Trends: CDR Trend Summary. Last updated 31 March 2023. https://www.epa.gov/chemical-data-reporting/trends [accessed 1 September 2023].
15. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. 2014. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 106(5):dju055, PMID: 24777111, https://doi.org/10.1093/jnci/dju055.
16. Rhee J, Medgyesi DN, Fisher JA, White AJ, Sampson JN, Sandler DP, et al. 2023. Residential proximity to dioxin emissions and risk of breast cancer in the Sister Study cohort. Environ Res 222:115297, PMID: 36642125, https://doi.org/10.1016/j.envres.2023.115297.
17. White AJ, Gregoire AM, Fisher JA, Medgyesi DN, Li L, Koutrakis P, et al. 2022. Exposure to particle radioactivity and breast cancer risk in the Sister Study: a U.S.-wide prospective cohort. Environ Health Perspect 130(4):047701, PMID: 35377195, https://doi.org/10.1289/EHP10288.
18. Xiao Q, Gierach GL, Bauer C, Blot WJ, James P, Jones RR. 2021. The association between outdoor artificial light at night and breast cancer risk in Black and White women in the Southern Community Cohort study. Environ Health Perspect 129(8):087701, PMID: 34379524, https://doi.org/10.1289/EHP9381.