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Environmental exposures, breast development and cancer risk: Through the looking glass of breast cancer prevention

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ABSTRACT

This review summarizes the report entitled: Breast Cancer and the Environment: Prioritizing Prevention, highlights research gaps and the importance of focusing on early life exposures for breast development and breast cancer risk.

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1. Introduction

This supplement of *Reproductive Toxicology* focuses on Environmental Impacts on Breast Development and Disease. A Congressionally mandated report, published in 2013 from an expert panel of non-federal and federal scientists and breast cancer advocates, provides illustrative evidence that environmental exposures across the lifespan may have an effect on breast development and breast cancer risk, recurrence, and survival decades later and identifies major research gaps. Moreover, the report, entitled *Breast Cancer and the Environment: Prioritizing Prevention*, [1] emphasizes the value of using the animal–human paradigm to unravel the dynamic, complex contributions of environmental exposures to breast development and breast cancer. With a better understanding of these relationships, we can identify strategies for breast cancer prevention. The *Breast Cancer and the Environment: Prioritizing Prevention* report provides a context and framework for the papers in this supplement, each of which addresses a different aspect of the environmental impact on breast development and disease.

2. The Breast Cancer and the Environment: Prioritizing Prevention report

The reasons why the Interagency Breast Cancer and the Environmental Research Coordinating Committee (IBCERCC) called for a prevention approach arose from several factors. For one, despite decades of research, the number of women diagnosed with breast cancer continues to rise. In 2014, an estimated 233,000 women and 2400 men in the United States were diagnosed with breast cancer, and approximately 40,000 women died from it [2]. Worldwide, breast cancer is the most commonly diagnosed malignancy and the leading cause of cancer death in women, accounting for approximately 14% of cancer deaths [3,4]. Another reason stems from the vast majority of breast cancer cases in women with no family history, suggesting that environmental factors may increase breast cancer risk. Since environmental factors can be identified and modified, focusing on these factors presents a tremendous opportunity to prevent breast cancer. Yet another reason is the potential for environmental exposures throughout the life course and decades prior to the diagnosis of breast cancer to modify early breast development or occur at a vulnerable period such as the age at menarche and influence risk for breast cancer. Noting these reasons for a focus on prevention and especially environmental exposures that alter breast development or cancer risk over the life course, the report

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finds that prevention is the key to reducing the emotional, physical, and financial burden of a disease that takes a tremendous toll on all of us and on our health care system.

The aims of this commentary are to: (1) summarize the current knowledge about environmental exposures and breast cancer and identify gaps in knowledge where further research is needed, and (2) delineate major recommendations from the Interagency Breast Cancer and Environment Research Coordinating Committee (IBCERCC) report. The articles in this Supplement collectively address a strategy recommended in the IBCERCC report; namely to emphasize the life course approach and therefore we describe several aspects of the life course approach that may influence the effect of environmental exposures on breast development and cancer risk. Further we discuss using the animal–human paradigm to unravel the dynamic, complex contributions of environmental exposures to breast development and breast cancer risk, recurrence, and survival.

On October 8, 2008, the Breast Cancer and Environment Research Act was signed into law [5]. The Act required the Secretary of the Department of Health and Human Services (DHHS) to establish an Interagency Breast Cancer and Environment Research Coordinating Committee (IBCERCC) of federal and nonfederal members to examine the current state of breast cancer and the environment research and make recommendations for eliminating any knowledge gaps in this area. Specifically, the charge to the committee was to: (1) review federal research efforts concerning the environmental and genomic factors related to breast cancer; (2) identify scientific advances in breast cancer research and outline key research questions, methodologies, and knowledge gaps. (3) Develop a comprehensive strategy for accelerating transdisciplinary, innovative, and collaborative research on breast cancer and the environment across federal agencies and in partnership with nonfederal organizations. (4) Determine how to increase public participation in decisions about breast cancer research and the optimal mode of dissemination of information on research progress. As part of the task to examine breast cancer and the environment, the IBCERCC initially framed a definition of the environment. The environment included: (1) lifestyle and behavioral factors, such as alcohol intake, diet and physical activity; (2) chemical agents that people are exposed to through food, pesticides, industrial pollutants, consumer products, and medications; (3) physical agents, such as radiation from medical and other environmental sources; and (4) social and cultural influences, such as family, community, psychological, and societal factors that may influence breast cancer risk. The focus on the physical and chemical components of the environment became preeminent as the committee developed the report because other areas noted above had been addressed by recent reports [6].

3. A summary of the current knowledge about environmental exposures and breast cancer

The IBCERCC reviewed and summarized current knowledge about breast cancer and the environment based on two premises:

- Premise 1: Timing matters. There are windows of susceptibility during the life course when environmental exposures could influence breast development and breast cancer. The timing of exposures therefore may be essential to observe an effect. To understand the role of the environment in the etiology of breast cancer, we must understand life stages when the breast is most susceptible to environmental insults. Little research to date has focused on environmental exposures across the life course or prior to adult years at diagnosis. Thus this supplement addresses a major gap in knowledge identified in the report.

The report noted that the majority of the studies on breast cancer and the environment to date have looked for environmental exposures at or around the time of diagnosis, when the causative exposures could have occurred decades earlier. The report delineated those factors that are recognized and accepted, those that have some evidence from either animal and/or human research and then identified knowledge gaps. The risk factors that are accepted or for which there is some evidence include:

- Accepted risk factors include: family history, rare and common genetic variants, breast density, benign breast disease, steroid hormones and reproductive factors, physical activity, alcohol consumption, radiation exposure, and adult body mass index, weight gain, and height.
- Some evidence exists linking the following factors to breast cancer: diet, body mass index in earlier years, and weight throughout life including birthweight, inflammation, light at night, other hormones besides steroid hormones' and growth factors, psychosocial factors, chemical exposures, and tobacco smoke.

Research findings in the past five to eight years highlight the importance of early life exposures on risk for breast cancer or early breast development. In one study, girls who were then aged 8–11 years and who were born weighing 4000 g or more (*i.e.* the high birthweight) were at higher risk for early breast development based on Tanner breast pubertal staging 2+ than girls of the same age but born of normal birthweight (2500–3999 g) after taking into account maternal prenatal conditions like gestational diabetes and smoking in pregnancy that may confound the birthweight–breast development association [7]. A review of the research on early life exposures and breast cancer identified that the high birthweight were at higher risk for breast cancer, especially for women diagnosed in their premenopausal years more than postmenopausal breast cancer [8]. A study of DDT exposure and risk of early breast cancer demonstrated that there may be a potential window of susceptibility for girls before 14 years of age when the exposure is associated with risk [9]. Another study focused on why women who have preeclampsia, a condition in pregnancy characterized by placental deficiency of the aromatization of androgens into estrogens, and their daughters of that pregnancy are at significantly lower risk for breast cancer than women who were not diagnosed with preeclampsia [8,10]. Of note, offspring of preeclampsia pregnancies have lower cord blood levels of insulin-like growth factor one (IGF-1) than offspring of normotensive pregnancies and daughters of preeclampsia pregnancies experience breast development later than daughters of women without preeclampsia; the lower IGF-1 levels experienced by the fetus might have contributed to delayed breast development and reduced breast cancer risk in later years [11,12].

We need more research on other exposures early in life that can lead to strategies for breast cancer prevention. Just as we now have the vaccine for Human Papilloma Virus to reduce risk for cervical cancer which is offered in adolescence, we look forward to the day when there are preventative strategies for breast cancer.

- Premise 2: Transdisciplinary research is necessary to accelerate knowledge about environmental exposures and understand the mechanisms related to breast cancer risk. The animal to human research paradigm provides an optimal approach to discovery of windows of susceptibility, mechanisms underlying and pathways related to derangement of normal breast development and cancer risk. This paradigm rests on the commitment to learning and conducting research in a transdisciplinary environment. We understand that results from animal research may not be directly applicable to humans. In our review, we considered both observational research and clinical trials in humans that

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