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Editorial

Refining the Focus on Early Life and Adolescent Pathways to Prevent Breast Cancer

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Studies have consistently demonstrated that early life adiposity is inversely related to pre- and postmenopausal breast cancer independent of adult weight gain (1-3). Early life period, particularly pubertal and early adult, represents one of the critical "windows of susceptibility" to breast cancer, when mammary epithelial cells proliferate exponentially but remain incompletely differentiated making them susceptible to various exposures (4). Early life adiposity may impact growth in height and female reproductive organ maturation as reflected in lower height growth velocity and earlier age at menarche (5,6) but does not impact final attained height (5) and is potentially related to other intermediate markers of breast cancer risk such as benign breast disease (7), mammographic breast density, and breast tissue features (8-10). Mechanisms for the inverse association identified to date include alterations in clonal pools, endogenous hormone, and insulin growth factor 1 levels across pre- and postmenopausal years, as well as mammographic breast density (11,12).

Transcriptomics, the study of a complete set of RNA transcripts produced by the genome, allows the identification of genes that are differentially expressed in tissues (13) and offers great potential to provide novel insights on this topic. Transcriptomics was recently used to demonstrate that several genes in inflammation and estrogen activation pathways are differentially expressed in the breast tissues of overweight and obese adolescent girls compared with those of age-matched nonoverweight or nonobese girls (14). Notably, there is considerable overlap in the breast transcriptome of adolescent girls and adult women (14).

In this issue of the Journal, Wang et al. (15) report on the associations of early life adiposity with the transcriptome of breast tumor and tumor-adjacent histologically normal tissue, collected as part of the Nurses' Health Studies. Information on early life adiposity was obtained from study participants using the validated 9-level Stunkard pictogram. Transcriptomic profiling was done using Glue Grant Human Transcriptome Array 3.0 and 2.022. The investigators performed differential gene expression analysis and gene set enrichment analyses as well as molecular pathway analysis using Hallmark gene sets. The investigators adjusted for several confounders, including body mass index (BMI) at the time of breast cancer diagnosis, indicating that the associations identified are independent of adult obesity. In analyses corrected for multiple testing, no individual gene was statistically significantly differentially expressed by early life body size. Gene set enrichment analyses, however, revealed 4 gene sets (2 gene sets downregulated and 2 gene sets upregulated) that were affected by early life body size in estrogen receptor–positive (ER+) tumors and 15 gene sets (14 gene sets downregulated and 1 gene set upregulated) in ER-negative (ER-) tumors. Higher early life size was associated with downregulation of cellular proliferation pathways (MYC targets variant 1) in both ER+ and ER- tumors, indicating that early life adiposity has a real biologic effect on pathways that drive breast cancer development. It is notable that several pathways, including those related to immune response/inflammation and PI3K/AKT/mTOR signaling, were downregulated in ER- tumors but not in ER+ tumors. Thus, Wang et al. have used transcriptomics to demonstrate how early life adiposity acts on different pathways to reduce the life-time risk of ER+ and ER- tumors, emphasizing the etiological differences in the tumor subtypes, especially the role of nonhormonal mechanisms in ER- tumors.

Many of the associations identified are biologically plausible. For instance, downregulation of MYC targets variant 1 by larger early life adiposity in both ER+ and ER- tumors fits in with expectations based on the functions of MYC. MYC regulates the transcription of genes involved in cell division, stem cell differentiation and MYC overexpression is associated with increased breast cancer risk (16). Further, higher adulthood BMI is associated with increased breast cancer risk, and MYC target variant 1 is upregulated by higher adulthood BMI (17). On the other hand, the upregulation of tumor necrosis factor–α signaling via NFκB in ER+ tumor by early life adiposity is surprising and needs

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validation in other studies. The biologically plausible expectation is for early life adiposity to downregulate NFκB expression. NFκB is pro-inflammatory and oncogenic and drives breast cancer development and progression (18), which has led to preclinical studies testing the utility of targeting NFκB signaling in mammary cancer prevention. Nevertheless, some data suggest a more complex interplay between NFκB and other signaling pathways (eg, PI3K/AKT/mTOR and epidermal growth factor receptor) in carcinogenesis (19). NFκB is a master regulator of diverse cellular processes but is also controlled by other signaling pathways (18), hence, future studies should evaluate potential crosstalk between these pathways in the context of early life adiposity and breast cancer.

There are 3 key implications from this analysis. First, the use of hallmark gene sets by Wang et al. (15) to identify biologically relevant pathways is a notable strength and an important benchmark for future studies to follow. If the analyses had been limited to looking at individual genes only, the findings would have been null, and the novel biological insights gained using hallmark gene sets would have been missed. Second, the strong associations of early life adiposity with immune response/inflammation and PI3K/AKT/mTOR signaling in ER- tumors underscore the need to design studies targeting these pathways to reduce the incidence of ER- tumors. Third, although findings in relation to early life and adolescent adiposity are well established in epidemiologic literature, the study brings focus to the separate pathways of early adiposity from later adult weight gain, with the effect of early life adiposity being more prominent on nonhormonal pathways compared with adult weight gain acting mainly through hormonal pathways. Clearer separation of these pathways in future breast cancer studies may improve insights to the burden of adult weight gain and the protection of childhood and adolescent adiposity.

Refining insights into pathways that are separate from adult adiposity and offer lifelong reduction in breast cancer risk is urgent given the global burden that is already high and rising with economic development. Such deeper understanding of the pathways through which childhood lifestyle and adiposity modify breast cancer risk can open new avenues for preventive interventions. Lack of prevention options for premenopausal breast cancer (more than 20% of global breast cancer burden) calls for immediate funding of more extensive studies of these pathways and how they can be targeted in breast cancer prevention.

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Data Availability

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