



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

Graham A. Colditz , MD, DrPH,^{1,2,*} Adetunji T. Toriola , MD, PhD^{1,2}

¹Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St Louis, MO, USA and ²Alvin J. Siteman Cancer Center, Barnes-Jewish Hospital and Washington University School of Medicine, St Louis, MO, USA

*Correspondence to: Graham A. Colditz, MD, DrPH, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8100, St Louis, MO, 63110, USA (e-mail: colditzg@wustl.edu).

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 NF κ B in ER+ tumor by early life adiposity is surprising and needs

validation in other studies. The biologically plausible expectation is for early life adiposity to downregulate NF κ B expression. NF κ B is pro-inflammatory and oncogenic and drives breast cancer development and progression (18), which has led to preclinical studies testing the utility of targeting NF κ B signaling in mammary cancer prevention. Nevertheless, some data suggest a more complex interplay between NF κ B and other signaling pathways (eg, PI3K/AKT/mTOR and epidermal growth factor receptor) in carcinogenesis (19). NF κ B 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.

Funding

Dr Toriola is supported by the grants R37CA235602 and R01CA246592 and Dr Colditz by Breast Cancer Research Foundation award 20-028.

Notes

Role of the funders: The funders had no role in the writing of this editorial or the decision to submit it for publication.

Disclosures: The authors declare no potential conflicts of interest.

Author contributions: Drs Colditz and Toriola jointly outlined the editorial, drafted and reviewed text, and then accepted the final version.

Data Availability

Not applicable.

References

1. Rosner B, Eliassen AH, Toriola AT, et al. Weight and weight changes in early adulthood and later breast cancer risk. *Int J Cancer*. 2017;140(9):2003-2014.
2. Gao C, Patel CJ, Michailidou K, et al. Mendelian randomization study of adiposity-related traits and risk of breast, ovarian, prostate, lung and colorectal cancer. *Int J Epidemiol*. 2016;45(3):896-908.
3. Richardson TG, Sanderson E, Elsworth B, et al. Use of genetic variation to separate the effects of early and later life adiposity on disease risk: Mendelian randomisation study. *BMJ*. 2020;369:m1203.
4. Fenton SE. Endocrine-disrupting compounds and mammary gland development: early exposure and later life consequences. *Endocrinology*. 2006;147(6):S18-24.
5. Berkey CS, Gardner JD, Frazier AL, et al. Relation of childhood diet and body size to menarche and adolescent growth in girls. *Am J Epidemiol*. 2000;152(5):446-452.
6. Berkey CS, Frazier AL, Gardner JD, et al. Adolescence and breast carcinoma risk. *Cancer*. 1999;85(11):2400-2409.
7. Berkey CS, Willett WC, Frazier AL, et al. Prospective study of growth and development in older girls and risk of benign breast disease in young women. *Cancer*. 2011;117(8):1612-1620.
8. Alimujiang A, Imm KR, Appleton CM, et al. Adiposity at age 10 and mammographic density among premenopausal women. *Cancer Prev Res*. 2018;11(5):287-294.
9. Oh H, Rice MS, Warner ET, et al. Early life and adult anthropometrics in relation to mammographic image intensity variation in the Nurses' Health Studies. *Cancer Epidemiol Biomarkers Prev*. 2020;29(2):343-351.
10. McCormack VA, dos Santos Silva I, De Stavola BL, et al. Life-course body size and perimenopausal mammographic parenchymal patterns in the MRC 1946 British birth cohort. *Br J Cancer*. 2003;89(5):852-859.
11. Hankinson SE, Colditz GA, Hunter DJ, et al. Reproductive factors and family history of breast cancer in relation to plasma estrogen and prolactin levels in postmenopausal women in the Nurses' Health Study (United States). *Cancer Causes Control*. 1995;6(3):217-224.
12. Su X, Hankinson SE, Clevenger CV, et al. Energy balance, early life body size, and plasma prolactin levels in postmenopausal women. *Cancer Causes Control*. 2009;20(2):253-262.
13. Wang Z, Gerstein M, Snyder M. RNA-Seq: a revolutionary tool for transcriptomics. *Nat Rev Genet*. 2009;10(1):57-63.
14. Burkholder A, Akrobetu D, Pandiri AR, et al. Investigation of the adolescent female breast transcriptome and the impact of obesity. *Breast Cancer Res*. 2020;22(1):44.
15. Wang J, Peng C, Askew C, et al. Early life body adiposity and the breast tumor transcriptome. *J Natl Cancer Inst*. 2020.
16. Xu J, Chen Y, Olopade OI. MYC and breast cancer. *Genes Cancer*. 2010;1(6):629-640.
17. Heng YJ, Wang J, Ahearn TU, et al. Molecular mechanisms linking high body mass index to breast cancer etiology in post-menopausal breast tumor and tumor-adjacent tissues. *Breast Cancer Res Treat*. 2019;173(3):667-677.
18. Wang W, Nag SA, Zhang R. Targeting the NF κ B signaling pathways for breast cancer prevention and therapy. *Curr Med Chem*. 2014;22(2):264-289.
19. Huttunen JE, Pfeifferle AD, Russell SC, et al. Oncogenic PI3K mutations lead to NF κ B-dependent cytokine expression following growth factor deprivation. *Cancer Res*. 2012;72(13):3260-3269.