LAY ABSTRACT

TITLE: Inverse association between estrogen receptor-α DNA methylation and breast composition in adolescent Chilean girls

JOURNAL: Binder et al. Clinical Epigenetics (2018) 10:122

AUTHORS: Alexandra M Binder[1†], Leah T Stiemsma[1†], Kristen Keller[2], Sanne D van Otterdijk[3], Verónica Mericq[4], Ana Pereira[4], José L Santos[5], John Shepherd[6] and Karin B Michels[1*]

INSTITUTIONS:
* Correspondence: k.michels@ucla.edu
Alexandra M Binder and Leah T Stiemsma are co-first authors.
† Alexandra M Binder and Leah T Stiemsma contributed equally to this work.
1 Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles 90095, USA
2 Department of Biostatistics, Fielding School of Public Health, University of California, Los Angeles 90095, USA.
3 Institute for Prevention and Cancer Epidemiology, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg im Breisgau, Germany.
4 Institute of Nutrition and Food Technology, University of Chile, Santiago, Chile. 5 Department of Nutrition, Diabetes and Metabolism, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile.
6 Population Sciences in the Pacific Program, University of Hawaii Cancer Center, Honolulu, HI 96813, USA.

This is attributed to the BCERP grant: U01 ES026130

SCIENTIFIC ABSTRACT

Background
Estrogen receptor-α (ER-α) is a transcriptional regulator, which mediates estrogen-dependent breast development, as well as breast tumorigenesis. The influence of epigenetic regulation of ER-α on adolescent breast composition has not been previously studied and could serve as a marker of pubertal health and susceptibility to breast cancer. We investigated the association between ER-α DNA methylation in leukocytes and breast composition in adolescent Chilean girls enrolled in the Growth and Obesity Cohort Study (GOCS) in Santiago, Chile. Breast composition (total breast volume (BV; cm3), fibroglandular volume (FGV; cm3), and percent fibroglandular volume (%FGV)) was measured at breast Tanner stage 4 (B4). ER-α promoter DNA methylation was assessed by pyrosequencing in blood samples collected at breast Tanner stages 2 (B2; n = 256) and B4 (n = 338).

Results

After adjusting for fat percentage at breast density measurement, ER-α methylation at B2, and cellular heterogeneity, we observed an inverse association between B4 average ER-α DNA methylation and BV and FGV. Geometric mean BV was 15% lower (95% CI: − 28%, − 1%) among girls in the highest quartile of B4 ER-α methylation (6.96–23.60%) relative to the lowest (0.78–3.37%). Similarly, FGV was 19% lower (95% CI: − 33%, − 2%) among girls in the highest quartile of B4 ER-α methylation relative to the lowest. The association between ER-α methylation and breast composition was not significantly modified by body fat percentage and was not influenced by pubertal timing.

Conclusions
These findings suggest that the methylation profile of ER-α may modulate adolescent response to estrogen and breast composition, which may influence breast cancer risk in adulthood.

LAY ABSTRACT

Estrogen-receptor-α (ER-α) is a gene that affects breast development. Before genes can make proteins, they must be activated or ‘turned on’. DNA methylation is one of the ways our cells control which genes are activated. Our research group studied how different patterns of DNA methylation that control ER-α activation can affect how breasts develop during adolescence. To study this, we measured ER-α DNA methylation in blood and breast development in girls in Santiago, Chile. We found that girls with the same age and total body fat had smaller breasts if ER-α DNA methylation increased from the beginning of puberty to later in adolescence. This shows that this gene is important in influencing breast development during puberty. We also studied ER-α methylation and the amount of fat and tissue in the breast. We already know that adults with more breast tissue (dense breasts) have a higher risk of breast cancer. Our study showed that an increase in ER-α DNA methylation during puberty was linked to less breast tissue (less dense breasts) in girls with similar total body fat. An increase in ER-α DNA methylation during puberty is related to breast characteristics that reduce cancer risk in adults. Future research is needed to see if this relationship is consistent as women age. If so, ER-α DNA methylation in blood may serve as a valuable predictor of future breast cancer risk. Our research was supported by two funding agencies; a National Institutes of Health grant R01CA158313 from the National Cancer Institute, and by the Breast Cancer and the Environment Research Program (BCERP) award U01ES026130 from the National Institute of Environmental Health Sciences and the National Cancer Institute.