# Study identifies molecular differences between primary breast cancer and its metastases

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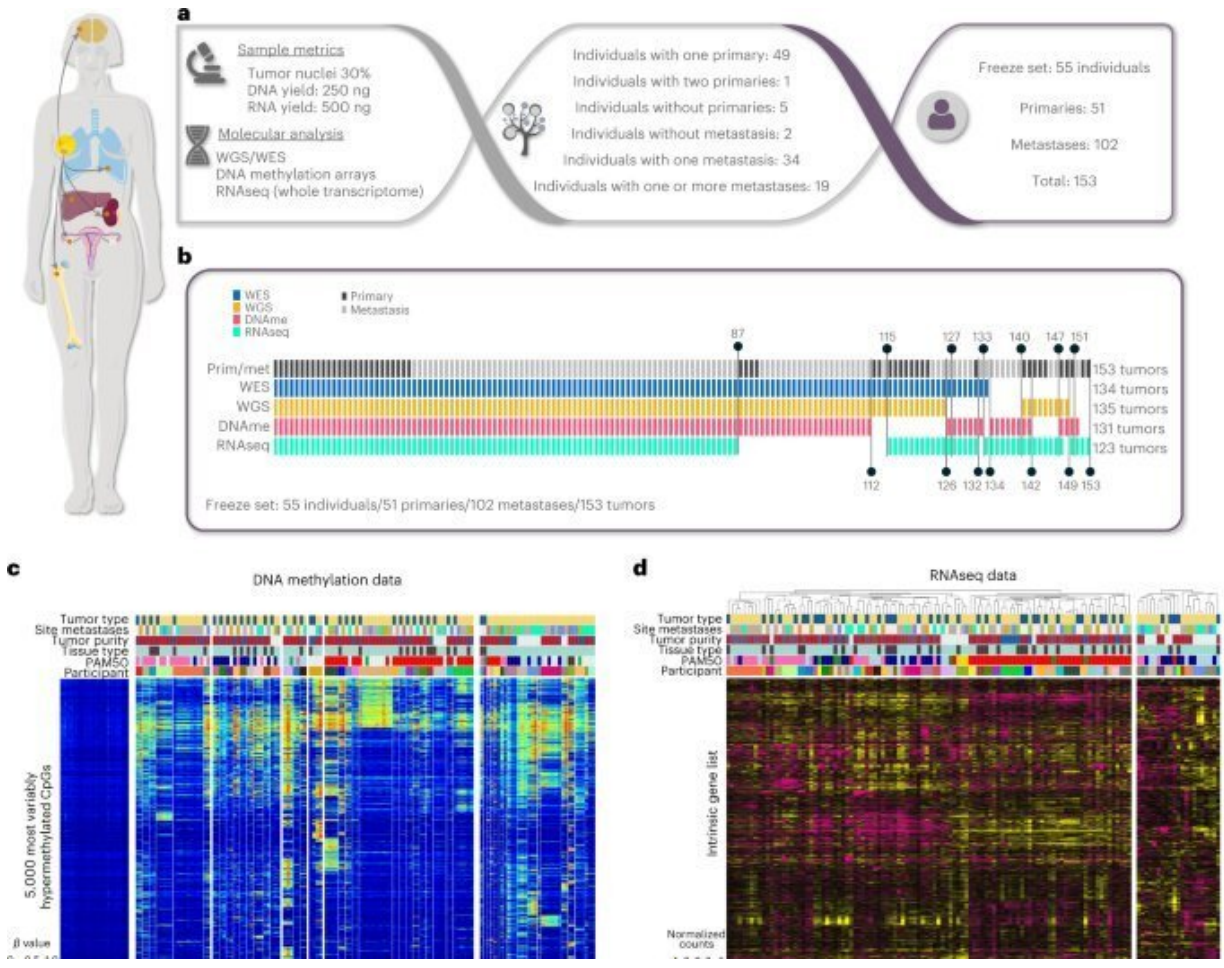


Study design and global genomic patterns of metastatic breast tumors. a, Cohort description of the AURORA Metastatic Project. b, Diagram of the shared or individual tumor DNA methylation, WGS/whole-exome sequencing (WES) and RNAseq data successfully performed on each of the 55 participants; DNAme,

DNA methylation; prim, primary; met, metastasis. c, Global profiling of the DNA methylation landscape using the top 5,000 most variable cancer-associated hypermethylated CpGs in 97 paired and 34 unpaired primary and metastatic tumors. Samples were intentionally ordered by participant to visually inspect the within-participant conservation of DNA methylation patterns. d, Supervised hierarchical cluster analysis of 102 paired and 21 unpaired primary and metastatic RNA-sequenced tumors using the so-called 1,900 intrinsic gene list (~1710 genes found in this dataset)21. e, OncoPrint panel of DNA somatic mutations displaying 37 of the most frequently mutated genes in 41 primary and 93 metastatic tumors. The percentage on the right indicates the mutation frequency of each gene across samples; LumA, Luminal A; LumB, Luminal B, Claudin, Claudin-low; normal, normal-like; Del, deletion; Ins, insertion. This figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license. Credit: *Nature Cancer* (2022). DOI: 10.1038/s43018-022-00491-x

A multi-institutional national study has identified unique molecular features responsible for the development and progression of metastatic breast cancer. One of the key features involves changes in the immune system that are due, in part, to methylation of the HLA-A gene; methylation is the addition of a small chemical group to a DNA molecule. Focal deletions, or the loss of part of the HLA-A gene, were also found and were mutually exclusive from samples with DNA methylations. In this study, methylation and focal deletions resulted in fewer immune cells being available to attack cancer cells.

The findings appeared Dec. 30, 2022, in *Nature Cancer*.

The study, led by the AURORA US Metastasis Network Project, is one of the first to use multiple genomic platforms to analyze primary (original) tumors and their paired metastases; most earlier studies looked at primary cancers, or metastases, in isolation from each other. In this

new study of 55 women with metastatic breast cancer, the researchers collected tumor tissue that represented 51 primary cancers and 102 paired metastases.

"This study involved extensive collaboration among many institutions to advance our understanding of breast cancer," said Charles M. Perou, Ph.D., the May Goldman Shaw Distinguished Professor of Molecular Oncology, co-leader of the UNC Lineberger Comprehensive Cancer Center's Breast Cancer Research Program and corresponding author of this study. "Our knowledge of breast cancer biology comes from studies of original tumors, but when people die of breast cancer, it is from the metastatic disease, so our lack of understanding of the biology of metastasis hinders patient care."

The researchers found that T cells and B cells, which largely direct anti-tumor immune response, were notably fewer in metastases. They also looked at differences between various sites of metastasis; liver and brain metastasis showed lower levels of immune cell response compared to levels of immune cells found in lung metastases.

"We found that around 17% of metastatic tumors had reduced expression of a gene that affects cellular immunity and showed a reduced ability of immune cells to infiltrate their environment and fight off cancer cells," said Susana Garcia-Recio, Ph.D., an assistant professor in Perou's lab at UNC Lineberger and co-lead author of this study.

In addition to Garcia-Recio, the paper's other co-lead authors are Toshinori Hinoue, Ph.D., Van Andel Institute, Grand Rapids, MI; Gregory L. Wheeler, Ph.D., and Benjamin J. Kelly, MS, Nationwide Children's Hospital, Columbus, OH; and Ana C. Garrido-Castro, MD, Dana-Farber Cancer Institute, Boston.

"This finding represents but the first half of the AURORA US

Metastasis Network Project as researchers have recently launched a clinical trial to help collect more samples," said Nancy E. Davidson, MD, Executive Vice President of Clinical Affairs at Fred Hutchinson Cancer Center, Seattle, and one of the founders of AURORA. "Results of analyses of the samples from the trial will be added to the current data, thereby enabling better detection of genomic changes to truly enhance our understanding of the disease."

"We saw changes in biology in about 30% of patients, including loss of immune activation, especially in liver and brain metastases," said Lisa A. Carey, MD, ScM, FASCO, deputy director of clinical science and the L. Richardson and Marilyn Jacobs Preyer Distinguished Professor in Breast Cancer Research at UNC Lineberger and study author. "Many of these changes occurred through mechanisms that can be reversed or treated. For this reason, we are very excited about the potential for improved treatment of metastatic disease, or even prevention of metastases themselves, based on this effort."

"This crucial study—which identifies a new target for potentially controlling metastatic disease—demonstrates the value of broad-based collaborative research by people united by their dedication to a vital mission," said Larry Norton, MD, founding scientific director of the Breast Cancer Research Foundation.

"We owe our patients a tremendous round of thanks for helping us advance these research efforts and for any contributions they make in the future," said Perou. "We are currently mimicking a lot of these genetic findings in our mouse models, where we are testing new treatments and making real progress, which we hope will pay off for patients in the near future."

**More information:** Susana Garcia-Recio et al, Multiomics in primary and metastatic breast tumors from the AURORA US network finds

microenvironment and epigenetic drivers of metastasis, *Nature Cancer* (2022). DOI: 10.1038/s43018-022-00491-x