Study Finds Racial Disparity in Tumor Microenvironment Among Women With Breast Cancer

Differences in the tumor environment may help explain why Black women are more prone to aggressive breast cancer.

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Study Finds Racial Disparity in Pro-metastatic Tumor Microenvironment Among Women With Residual Breast Cancer After Neoadjuvant Chemotherapy

Residual tumors from Black patients with estrogen receptor (ER)-positive/HER2-negative primary breast cancer treated with neoadjuvant [pre-surgery] chemotherapy (NAC) had a higher score of a biomarker of distant metastatic recurrence than tumors from white patients, according to data presented at the San Antonio Breast Cancer Symposium, held December 6-10, 2022.

“Black women with breast cancer are more likely to be diagnosed with advanced-stage disease, have lower access to care, and have triple-negative disease, all of which contribute to higher mortality rates compared with white women,” said Maja H. Oktay, MD, PhD, professor and co-leader of the Tumor Microenvironment and Metastasis Program at the NCI-designated Montefiore Einstein Cancer Center, professor of pathology at Albert Einstein College of Medicine, and senior author of the study. “The results from our study demonstrate differences in the tumor microenvironment of Black women that may partly explain the racial disparities in the outcomes of ER-positive/HER2-negative breast cancer, the most common breast cancer subtype in both white and Black women.”

Previous research by Oktay and collaborators led to the identification of three-cell structures in primary breast tumors in which an invasive tumor cell partially inserted into a blood vessel wall is bound to an endothelial cell and a macrophage, and all three are in direct and stable contact. “We have used the term tumor microenvironment of metastasis (TMEM) doorways because these structures serve as portals for tumor cells to enter the blood circulation,” said Oktay.

Oktay and her colleagues showed that the density of TMEM doorways in the primary untreated tumors, as measured by the TMEM doorway score, is a prognostic biomarker for the development of distant metastatic recurrence in ER-positive, HER2-negative patients.

“We have also shown that NAC increases the TMEM doorway score and produces pro-metastatic changes in the tumor microenvironment in some women, uncovering a previously unrecognized mechanism of resistance to chemotherapy,” Oktay explained. “Although numerous prospective clinical trials and population-based studies have shown that chemotherapy reduces the risk of recurrence and death when given before or after surgery to patients with locally advanced breast cancer and prolongs survival for patients with metastatic breast cancer, we suspect that in some patients NAC may prime the tumor to more efficiently disseminate tumor cells into the blood stream. Identifying this mechanism of resistance may allow us to develop new treatment strategies to reverse it.”

Oktay and team conducted a retrospective, multi-institutional study of TMEM doorway score and macrophage density in patients with unilateral, invasive breast cancer who received NAC to determine whether the TMEM doorway score can provide prognostic information about the residual disease after NAC, and whether there were racial differences in the TMEM doorway score in the residual disease.

In the study cohort, 96 patients self-identified as Black and 87 as white. The TMEM doorway score was determined in the residual breast cancer tissues after pre-operative chemotherapy using previously validated multiplex staining and automated scoring method. The researchers analyzed the relationship between TMEM score, macrophage density, and distant recurrence-free survival (DRFS), defined as the time from surgery to first distant recurrence.

Study results showed that 49% of Black patients developed distant recurrence, compared to 34.5% of white patients, and that Black women were more likely to receive mastectomy than white women (69.8% and 54%, respectively), and have higher-grade tumors.

Tumors from Black patients had more macrophages and a higher TMEM doorway score than tumors from white patients in the entire cohort and in the ER-positive/HER2-negative subset, but not in the triple-negative subset.

Adjusting for race, age, surgery type, tumor size, lymph node status, tumor grade, and tumor subtype, high TMEM doorway score was associated with worse DRFS: The risk of distant recurrence approximately doubled in patients with high TMEM score compared with patients with intermediate/low TMEM score in the entire cohort. A similar trend was observed in the ER-positive/HER2-negative subgroup, although not statistically significant. There was no association between high TMEM score and increased risk of distant recurrence in women with triple-negative breast cancer.

“Our study provides a potential explanation for the persistent racial disparities in ER-positive/HER2-negative breast cancer outcomes that are not fully explained by disparities in social determinants of health, including access to care or treatment,” said Oktay.

According to Oktay, one of the limitations of this study relates to the fact that the team did not evaluate the TMEM doorway density in the tumors before NAC. Further, the study did not demonstrate that chemotherapy increases the number of TMEM doorways in Black women more

than in white women.

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