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

SAN ANTONIO – Residual tumors from Black patients with estrogen receptor (ER)-positive/HER2-negative primary breast cancer treated with neoadjuvant 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 percent of Black patients developed distant recurrence, compared to 34.5 percent of white patients, and that Black women were more likely to receive mastectomy than white women (69.8 and 54 percent, 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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Abstract

GS1-02

Racial disparity in tumor microenvironment and outcomes in residual breast cancer treated with neoadjuvant chemotherapy

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Background: Black, compared to White women with localized breast cancer have higher mortality and worse distant recurrence free survival (DRFS). This has been attributed to social determinants of health and higher prevalence of triple negative breast cancer (TNBC) in Black compared to White women. Recent studies indicate that racial disparity in outcome is present in patients with estrogen receptor-positive (ER+), but not ER- disease, in particular in patients with residual disease after neoadjuvant chemotherapy (NAC). It has been shown that in some patients NAC may induce pro-metastatic changes in tumor microenvironment, such as increased density of tumor associated macrophages and portals for cancer cell dissemination to distant sites called TMEM doorways (TMEM score). TMEM score correlates with metastasis in patients with ER+/HER2- breast cancer. We hypothesized that racial disparity in DRFS

in patients with residual ER+/HER2- disease is due to enhanced pro-metastatic components (macrophage and TMEM doorway density) in the tumor microenvironment post-chemotherapy in Black compared to White women. **Methods:** We performed a retrospective, multi-institutional study of TMEM score and macrophage density in the residual disease after NAC from 196 patients diagnosed with unilateral invasive ductal cancer of breast between 2004 and 2014. 99 patients self-identified as Black and 97 as White. TMEM doorways were visualized by triple immunohistochemistry for macrophages (CD68), tumor cells (panMena), and endothelial cells (CD31). The evaluation of TMEM score and macrophage density was done using automated image analysis. Tumor characteristics and patient survival were compared between Black and White patients. The relationship between TMEM score, macrophage density and DRFS was examined by log-rank test and multivariate Cox regression model. The covariates in Cox model included TMEM score, age (continuous), race (Black vs White), surgery type (mastectomy vs lumpectomy), tumor stage (T3 vs T1; T2 vs T1), lymph node status (positive vs negative), and tumor subtype (triple negative [TN] vs ER+/HER2-; other vs ER+/HER2-). **Results:** Black compared to White women were more likely to develop distant recurrence (49.5% vs 34%, p=0.04), receive mastectomy (69.7% vs 51.5%, p=0.014), and have higher grade (p=0.001). Tumors from Black patients had more macrophages and a higher TMEM score in the entire cohort (p=0.004; p=0.001 respectively) and in the ER+/HER2- subset (p=0.008; p=0.008 respectively), but not in the TNBC subset. High TMEM score was associated with worse DRFS in all patients (p=0.004) and in the ER+/HER2- (p=0.03), but not in TNBC. In multivariate Cox model, TMEM score was an independent prognostic factor in the entire cohort (HR, 1.92; 95%CI, 1.15-3.22; p=0.01) and trended towards significance in ER+/HER2- disease (HR, 2.13; 95%CI, 0.96-4.71; p=0.06). TN, compared to ER+/HER2- cancers had higher TMEM score (p=0.01), and macrophage density (p=0.001). **Conclusion:** Racial disparity in outcome in patients with localized breast cancer may be due to a more pronounced pro-metastatic response to chemotherapy in Black, compared to White patients with ER+/HER2- disease. Thus, higher prevalence of TNBC in Black patients may not be the controlling factor in racial disparity.

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