Editorial Commentary

Race, ethnicity, and clinical outcomes in hormone receptor-positive, human epidermal growth factor 2 negative (HER2–), node negative breast cancer in the randomized TAILORx trial: gaps in biologic and social determinants of health

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Introduction

As a result of significant innovations in breast cancer treatments, outcomes for breast cancer patients have greatly improved in the last decade. Despite breast cancer mortality rates decreasing in the general population, large racial disparities exist, with mortality remaining higher and declining more slowly among Black women than White women in the United States (1). In spite of higher breast cancer incidence rates in White women, the death rates are 1.9–2.6 times higher in Black women less than 50 years old (2). While Black patients commonly present at a more advanced disease stage and are more likely to have triple negative breast cancer, most breast cancer incidences and mortalities in Black women are related to estrogen receptor positive (ER+), human epidermal growth factor 2 negative (HER2–) disease (2). Previous observational studies and cohort studies were limited by multiple confounding factors such as differences in distribution of age, stage, co-morbidities, molecular status, access to diagnostics (Oncotype Dx), and treatment.

TAILORx, one of the largest prospective randomized control trials, enrolled 9,719 patients with ER+/HER2– early stage breast cancer including relatively large subgroups of racial minorities (Black n=693, Asian n=405, Hispanic =889, other/unknown race n=432) (3,4). Patients were assigned to treatment based on their 21-gene recurrence score (RS): patients with a RS ≤10 received endocrine therapy alone, patients with a RS ≥26 received chemoendocrine therapy and women with a midrange score of 11–25 were randomized to receive either endocrine therapy alone or chemoendocrine therapy. These patients were limited in the number of co-morbid conditions, deemed fit enough to receive chemotherapy, had comparable stage disease and a comparable proportion of patients in each RS category. Despite similar baseline characteristics in both groups, a post-hoc analysis of the TAILORx study conducted by Albain *et al*. highlighted notable disparities in invasive disease-free survival, relapse free interval, distant relapse free interval, and overall survival in Black women compared to White women (4). In this commentary, we review the available data from this analysis to help explain the observed racial disparity.

TAILORx: review on racial disparities

Most studies to date examining racial disparities in the breast cancer population are either observational or cohort studies. TAILORx represented a unique opportunity to examine whether these differences held true in a randomized and controlled early-stage breast cancer cohort. This study adjusted for multiple factors including age, tumor size (>2 *vs.* ≤2 cm), histologic grade (high *vs.* medium *vs.* low *vs.* unknown), continuous oncotype RS, and insurance status. While this trial had a large sample of each racial minority subgroup, with 693 individuals who self-

identified as Black, this still represented less than 10% of the overall trial population and was much smaller than the 8,189 individuals who self-identified as White.

Low clinical risk was defined as tumor ≤3 cm and low grade; ≤2 cm and intermediate grade; or ≤1 cm and high grade and high clinical risk was defined as any tumour not meeting low clinical risk criteria (5). This binary method of clinical risk categorization has been used previously in the MINDACT trial and is an accepted method of risk assessment (6). TAILORx primarily included a lower risk population, with 95% of tumours being less than 3 cm and 80% being low to intermediate in grade.

In the study, there were moderate interracial differences in age, menopause, tumour size, grade, and clinical risk. White women had proportionally fewer patients with high clinical risk disease. It was also noted that Black women more frequently had a loss of the progesterone receptor (14.1% compared to 9.6% in White women and 9.3% in Asian women). The loss of the progesterone receptor is associated with more cancer resistance to hormonal treatment and worse clinical outcomes (7). Another factor that was different among groups that was not adjusted for, given the data was only available for 950 patients in the trial, was BMI, with a high BMI (>30 kg/m^2) noted in 44.6% of Whites, 59.0% of Blacks, 18.8% of Asians and 39.3% of other/unknown races.

Although randomization was not stratified by race, the proportion of tumors with intermediate [11–25] and high [26–100] RS were comparable among racial subgroups, including the proportion of those with a score of greater and less than 18. In terms of low RS (<11), Asians had the greatest proportion at 20%, compared to Whites and Blacks at 16.6% and 15.4% respectively. That there were no major differences in RS makes it unlikely that differences in proliferation and invasion genes, as measured by the RS assay, explain the disparities in clinical outcomes between Black and White patients in this study.

In the RS 11–25 cohort, even after adjusting for multiple clinical risk factors using multivariate analysis, Black race compared with White race was still associated with inferior invasive disease-free survival (HR =1.43, 95% CI: 1.13 to 1.82), distant relapse-free interval (HR =1.60, 95% CI: 1.07 to 2.41), and overall survival (HR =1.51, 95% CI: 1.06 to 2.15). This corroborates previous data pointing to worse outcomes in the Black population. This analysis reveals that racial disparity cannot be explained by differences in the 21-gene RS, estrogen, progesterone or HER2 expression, clinicopathologic factors, or the type of treatment (endocrine/chemotherapy) prescribed. Consistent with the results from the entire randomized cohort, both Black and White women with RS 11 to 25 equally did not benefit from adjuvant chemotherapy.

Discussion

One question that arises from this subgroup analysis of race and ethnicity from TAILORx is whether the RS comprehensively captures a breast tumour's entire biologic behavior and prognosis. Previous studies that have shown a strong disparity in clinical outcomes between races among ER+/HER2– breast cancer patients demonstrated a higher frequency of basal-like breast cancer in Black women (8). Dowsett *et al.* compared the Oncotype Dx RS to the PAM50 risk of recurrence (ROR) score, which identifies intrinsic breast cancer subtypes (luminal A/B, HER2 enriched, basal-like). ROR segregated more patients to a higher risk category and fewer to an intermediate risk category than the oncotype Dx RS (9). Another study using PAM50 found that Black women had a higher ROR compared to White women after standardizing for clinical covariates (10). Therefore, the difference in disease-free and overall survival between the Black and White ER+/HER2– breast cancer population could be explained by differences in tumour biology that are not accounted for by Oncotype Dx RS.

Another possible contributor to the racial disparity observed in TAILORx is the impact of obesity on outcomes, as this was not adjusted for in the analysis. It is known that obesity rates are higher in Black women than White women and that obesity is associated with inferior outcomes in patients with ER+/HER2– breast cancer (11). However, prior studies suggested that obesity alone does not explain the racial disparity observed (12,13). The study by Sparano *et al.* (13) which performed multivariable analyses including race and obesity, revealed that Black race was associated with inferior disease-free, breast-cancer specific and overall survival only in patients who were not obese. The mechanism of endocrine resistance caused by obesity is not quite understood but is believed to be related to elevated circulating levels of estrogens released from the peripheral adipose tissue, and decreased sex hormone-binding globulin, which lead to increased insulin resistance and higher levels of insulin-like growth factor-1 (12,14).

One limitation of TAILORx was the lack of monitoring of adherence or compliance to endocrine therapy. Endocrine therapy is the main treatment modality in ER+/HER2– breast cancer patients, and poor adherence and

compliance is known to impact disease-free survival (15). There is a growing body of evidence that Black women are at increased risk of under-treatment with endocrine therapy as they are less likely to initiate treatment and less likely to adhere to treatment (16). Adherence and compliance can be affected by multiple factors including socioeconomic status, education, patient counselling and health-care system access. Black women have reported less social support from survivorship networks, a higher endocrine therapy side effect burden and decreased communication with treating physicians (17).

Socioeconomic factors are key determinants of health. Although a meta-analysis conducted in 2006 demonstrated that African American ethnicity was a significant predictor of poor outcome, even after accounting for socioeconomic status (18), it is known that fewer than 5% of published breast cancer studies take into account race/ethnicity, economic status, education level, health insurance status and other social factors (19). Therefore, it is critical that the social determinants of health are more robustly included in cancer research and that greater efforts are made to promote better access to health care services.

There is some evidence that racial differences in pharmacokinetics might impact efficacy of endocrine therapies. For example, tamoxifen metabolism into its major active metabolite endoxifen might be reduced through the alteration of the cytochrome p450 and 2D6 systems leading to lower bioavailability of the active drug in Black women receiving tamoxifen (20). Potential differences in pharmacokinetics and pharmacogenetics could also explain a higher burden of self-reported endocrine therapy-related side effects in Black women. Despite that, burden of endocrine-related side effects did not seem to correlate with treatment adherence (17). In support of our hypothesis on the differential efficacy of endocrine therapy between races, a post-hoc analysis of MA.17 (n=5,187) comparing letrozole versus placebo after 5 years of adjuvant tamoxifen showed that racial minorities (n=462, 8.9%), which included 179 (3.5%) Black women, did not seem to benefit from letrozole compared to placebo (21).

Conclusions

The findings from the TAILORx substudy add to the growing body of evidence that racial disparities in breast cancer-related survival exist. The factors contributing to this are complex, and likely include both biological and social determinants of health. Greater representation of racial and ethnic minorities is strongly needed in clinical trials, and further research is required to elucidate contributing factors to the racial disparities.

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