RESEARCH LETTER

Hormone Receptor Status of Second Breast Cancers in Women With Triple-Negative Breast Cancer

A personal history of breast cancer is a strong risk factor for subsequent breast malignant neoplasm.[1,2] Adjuvant endocrine therapy for hormone receptor (HR)-positive disease reduces this risk. Women with triple-negative breast cancer (TNBC) will not reap chemoprevention benefits because subsequent in-breast events (SBE) are expected to recapitulate the biomarker expression of the first cancer regardless of whether the SBE represents a new primary tumor (in either breast) or a true local recurrence. We evaluated this assumption.

Supplemental content

Methods | A prospectively maintained database was used to identify female patients with nonmetastatic TNBC diagnosed between January 1, 1998, and December 29, 2017. The Weill Cornell Medicine Institutional Review Board approved this cohort study and waived informed consent because deidentified data were used. We followed the STROBE reporting guideline.

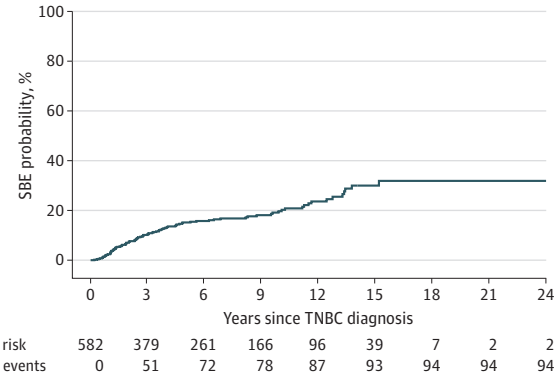
We evaluated HR status for any SBE, grouping local recurrences and second primaries together. Tumors with estrogen receptor (ER) or progesterone receptor (PR) staining greater than 1% on immunohistochemistry were considered HR positive. Self-reported race and ethnicity (Asian, Black, Hispanic or Latino, White, other) were included because of higher prevalence of TNBC in Black women. Categorical variables were compared by Fisher exact test; continuous variables were compared by Wilcoxon (for 2-group comparisons) or Kruskal-Wallis (for multiple groups) rank sum test. SBE incidence was evaluated using the Aalen-Johansen estimator.

All *P* values were 2-sided, with statistical significance set at $P < .05$. Analyses were performed between October 2022 and December 2023 using R 4.3.1 (R Project for Statistical Computing).

Results | Five hundred ninety-seven patients (median [IQR] age, 56 [46-66] years) were identified. Among 552 patients with available race and ethnicity data, 42 (7.6%) identified as Asian, 86 (15.6%) Black, 6 (1.1%) Hispanic or Latino, 393 (71.2%) White, and 25 (4.5%) other. Overall, 208 tumors (41.3%) were detected on screening mammography and 12 (2.3%) on screening magnetic resonance imaging. *BRCA1/BRCA2* sequence variations were found in 69 of 229 patients (30.1%) who underwent genetic testing.

Most cases were invasive ductal carcinoma (521 of 570 [91.4%]), T1 and T2 lesions (402 of 458 [87.8%]), and node negative (346 of 457 [75.7%]). Of 559 patients, 418 (74.8%) underwent primary surgery and 132 (23.6%) received neoadjuvant chemotherapy. Additionally, 363 patients (64.8%) attempted lumpectomy and 236 (42.2%) ultimately underwent mastectomy; 117 (21.2%) underwent contralateral prophylactic mastectomy. Among patients with available adjuvant treatment information, 311 of 476 (65.3%) received chemotherapy, and 327 of 468 (69.9%) received radiation.

Figure 1. Incidence of Second In-Breast Events (SBEs) Among Patients With Triple-Negative Breast Cancer (TNBC)



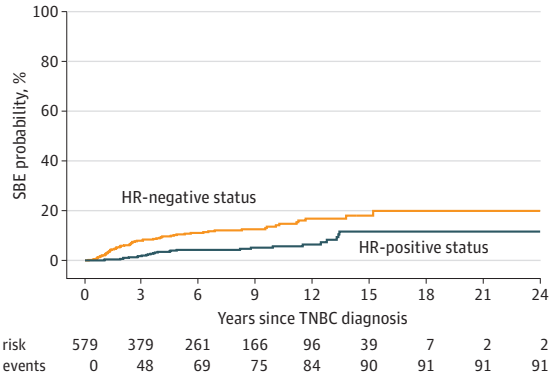
Median (IQR) follow-up was 5.88 (2.22-10.60) years. Ninety-five of 582 patients (16.3%) with documented outcome information developed SBE; median (IQR) time to detection was 2.74 (1.29-5.42) years. Seventeen SBEs (17.9%) were contralateral tumors. Neither race and ethnicity, histological type, nor treatment sequence was associated with SBE risk.

Sixty of 93 SBEs (64.5%) were TNBC; 23 (24.2%) were ER-positive, including 15 over 10%; 18 (19.0%) were PR-positive, and 65 (68.4%) were ER- and PR-negative SBEs. Median (IQR) time to developing SBE was 3.60 (2.54-9.33) years for ER-positive SBE, 4.48 (3.35-12.20) years for PR-positive SBE, and 2.37 (1.19-4.82) years for HR-negative SBE.

Six of 94 SBEs (6.4%) were ductal carcinoma in situ; 4 (66.7%) were HR-positive. Five-year SBE incidence was 0.15 (95% CI, 0.12-0.18); 0.10 (95% CI, 0.08-0.13) for HR-negative SBE, and 0.04 (95% CI, 0.03-0.07) for HR-positive SBE (**Figures 1** and **2**). Five-year overall survival was 93.5% (95% CI, 91.3%-95.8%).

Discussion | Patients with TNBC are typically not offered chemoprevention. Although SBE incidence is low,[1] the findings suggest that chemoprevention may be reasonable for patients with TNBC because approximately one-third (30.1% in this cohort) of the neoplasms will be HR-positive. Studies of low-dose tamoxifen for chemoprevention suggest preserved risk-reducing benefits with favorable tolerance.[3] Furthermore, the TNBC phenotype is based on lack of expression for ER α; ongoing translational research suggests tamoxifen therapy may be associated with improved outcomes in TNBC expressing ER β.[4,5] Study limitations include the retrospective, single-institution design.

Figure 2. Incidence of Second In-Breast Events (SBEs) Among Patients With Triple-Negative Breast Cancer (TNBC), Stratified by Hormone Receptor Status



No. at risk	579	379	261	166	96	39	7	2	2
No. of events	0	48	69	75	84	90	91	91	91

Hormone receptor (HR)–negative status includes both estrogen receptor– and progesterone receptor–negative. HR-positive status includes estrogen receptor– and/or progesterone receptor–positive.

These findings are hypothesis-generating. Additional studies of HR expression in SBE after TNBC are warranted.

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Accepted for Publication: December 28, 2024.

Published Online: March 12, 2025. doi:10.1001/jamasurg.2025.0100

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Author Contributions: Dr Newman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Eden, Johnson, Newman.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Eden, Syrnioti, Johnson, Moore, Zhou, Newman.
Critical review of the manuscript for important intellectual content: Eden, Liu, Zhou, Newman.
Statistical analysis: Syrnioti, Liu, Zhou, Newman.
Obtained funding: Newman.
Administrative, technical, or material support: Syrnioti, Johnson, Newman.
Supervision: Moore, Zhou, Newman.

Conflict of Interest Disclosures: Dr Newman reported receiving salary support from Susan G. Komen, the Breast Cancer Research Foundation, and the Fashion Footwear Association of New York Shoes for a Cure during the conduct of the study. No other disclosures were reported.

Data Sharing Statement: See the Supplement.

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