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Sex Disparity Observed for Oncotype DX Breast Recurrence Score in Predicting Mortality Among Patients with Early Stage ER-Positive Breast Cancer

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ABSTRACT

Purpose: Prognostic value of Oncotype DX Breast Recurrence Score (RS) in male patients with breast cancer is understudied. We evaluated associations of RS with overall mortality in male patients with breast cancer and compared it with female counterparts.

Experimental Design: With a cohort of 848 male and 110,898 female patients with breast cancer identified from the National Cancer Database (2010–2014), we estimated HRs and 95% confidence intervals (CI) for overall mortality associated with RS using Cox regression models. RS was evaluated continuously, as well as by categorization following respective traditional ($\leq$17, 18–30, and $\geq$31) and TAILORx ($\leq$10, 11–25, and $\geq$26) cutoffs.

Results: RS was positively associated with mortality in male patients (HR = 1.13; 95% CI, 1.02–1.26 per unit RS increment) up to RS > 21, after which the risk plateaued. Among female patients, mortality began to increase with RS only when RS > 23 (HR = 1.02; 95% CI, 1.01–1.02 per unit of RS increment). The intermediate- (HR = 5.37; 95% CI, 1.79–16.11) and high-risk diseases (HR = 4.28; 95% CI, 1.22–14.97) defined by TAILORx, but not traditional cutoffs established for female patients, were associated with elevated mortality risk in men even after adjustment for demographic, clinical characteristics, and treatments, except chemotherapy.

Conclusions: RS is associated with mortality in male patients with breast cancer at a much lower threshold than that for female patients. Studies are needed to establish specific guidelines for RS thresholds for male patients with breast cancer.

Introduction

The Oncotype DX Breast Recurrence Score (RS) is a 21-gene marker based on expression of 16 tumor-associated genes and 5 reference genes, which was initially developed to quantify the likelihood of distant recurrence in female patients with estrogen receptor–positive (ER+) and node-negative breast cancer, with a high RS indicating a higher risk of distant recurrence (1). Since its development, the predictive and prognostic values of RS in female patients with breast cancer have been validated in several prospective clinical trials, including the National Surgical Adjuvant Breast and Bowel Project B-20 trial, Southwest Oncology Group-8814 trial, and Trial Assigning Individualized Options for Treatment (TAILORx; refs. 2–5). Currently, RS is recommended in clinical practice to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer, especially for those who present with ER+, human epidermal growth factor receptor 2-negative (HER2−), and node-negative diseases (6).

For male patients with breast cancer, who account for approximately 1% of all breast cancers, diagnostic and treatment approaches are in large part based on evidence generated from female patients (7). A vast majority of male patients with breast cancer are characterized with ER+ or progesterone receptor–positive (PR+), as well as HER2− diseases, in accordance to indications of RS testing (8). However, it has not been well investigated whether RS is predictive to treatment efficacy and/or prognosis among men with breast cancer.

It has been suggested that male breast cancer may have a different etiology/biology from that of female (9). A recent study, which included 322 male patients with breast cancer from the Surveillance Epidemiology and End Results (SEER) Program, revealed that male patients with breast cancer with higher RS had worse crude survival than those with lower RS (10), although the independent predictive or prognostic values of RS in men were not evaluated.

To fill this knowledge gap, we examined the association between RS and overall mortality in male patients with breast cancer using data from the National Cancer Database (NCDB) and compared it with that of female patients.

Materials and Methods

Patients with a primary breast cancer diagnosis and RS testing between 2010 and 2014 were identified from the NCDB, which captures 70% of newly diagnosed cancers each year across the United States. Patients with ER+, HER2−, and stage I or II invasive breast cancers between 2010 and 2014 were included. Patients who received no surgery (n = 23) were excluded (**Fig. 1**). Because only completely deidentified information was provided by the NCDB, this study was approved by the Vanderbilt University Medical Center Institutional

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Oncotype DX Breast Recurrence Score (RS) has been well validated and recommended to be used to select female patients with estrogen receptor–positive, HER2-negative early stage breast cancer with a high recurrence risk for chemotherapy. Our study showed that, in routine oncology practice setting, RS predicts total mortality in both male and female patients with breast cancer but following distinct patterns. This finding highlights the need to develop RS categorization specifically for male patients with breast cancer. Studies on sex-specific pathogenic alterations in breast cancer are needed to clarify the underlying mechanisms.

Review Board as a human subject exempt project, for which no informed consent is needed. This study was conducted in accordance with the Declaration of Helsinki.

Data on demographic characteristics, including age at diagnosis, race, year of diagnosis, urban/rural residence, estimated annual household income and educational attainment at the zip code level, insurance, treating facility, region, and distance to care were gathered from the NCDB. Available clinical characteristics included tumor size, nodal status, PR status, histology type, Nottingham combined histologic grade (grade), lymphovascular invasion (LVI), and Charlson/Deyo score. Data on receipt of treatment (yes/no only) were obtained from the NCDB, including chemotherapy, radiotherapy, and endocrine therapy. Information on breast surgery type was also collected.

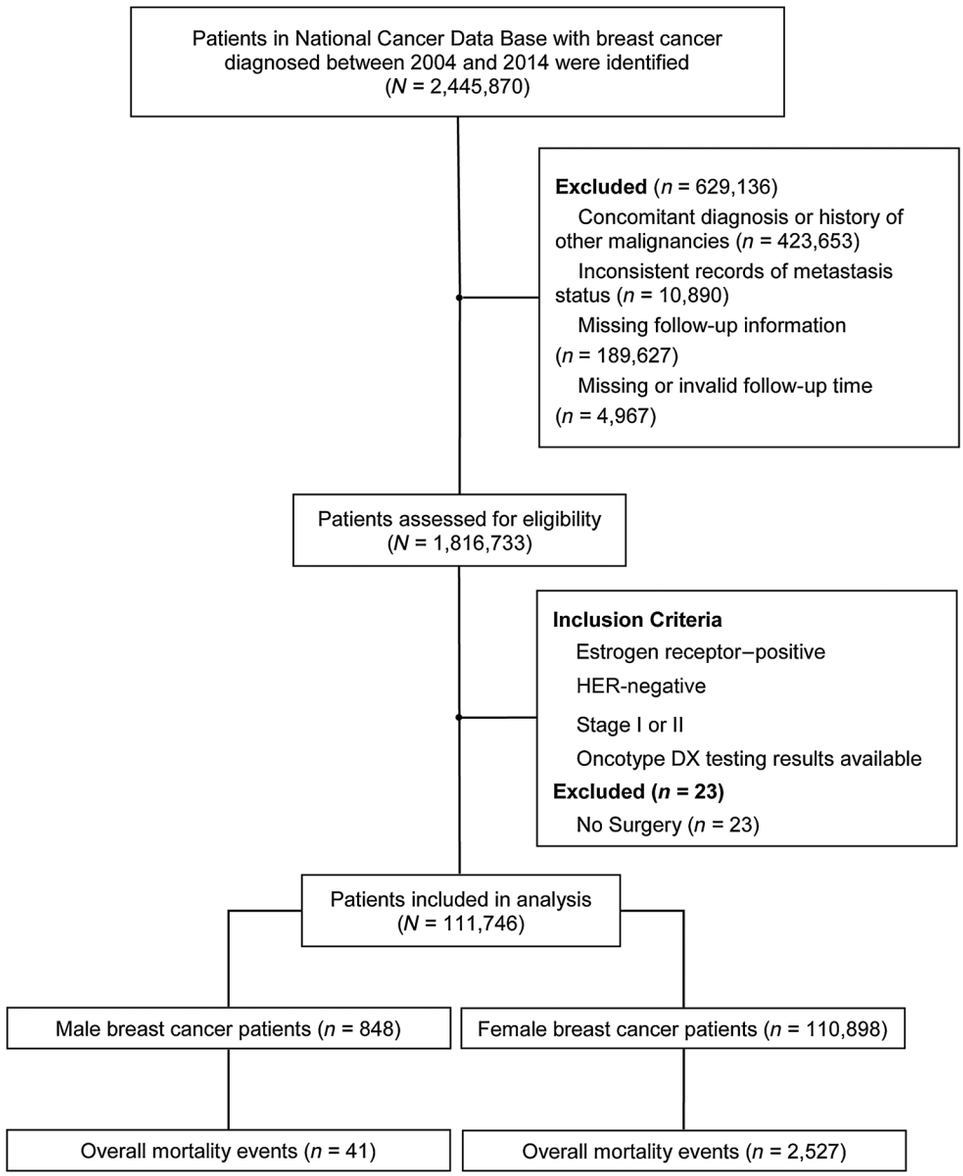

Figure 1.
Study flowchart.

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Table 1. Characteristics of patients with breast cancer with Oncotype DX RS testing.

Characteristics	Male ($N = 848$, %)	Female ($N = 110{,}898$, %)	*P*
Age [years, mean ± SD (range)]	61.9 ± 10.4 (26–88)	58.3 ± 10.5 (18–90)	<0.001
RS (mean ± SD (range)]	16.6 ± 12.0 (0–100)	17.2 ± 10.1 (0–100)	0.15
RS			<0.001
0–10	34.7	23.4	
11–17	23.8	36.1	
18–25	24.1	26.0	
26–30	6.6	6.6	
31–100	10.8	7.9	
Follow-up time (months, median)	39.5	40.1	0.06
Deaths	41	2,527	
Race			0.01
White	86.4	87.0	
Black	10.0	7.6	
Other	2.7	4.4	
Unknown	0.8	0.9	
Year of diagnosis			0.25
2010	12.3	13.8	
2011	20.3	17.8	
2012	20.5	20.1	
2013	23.3	23.0	
2014	23.6	25.3	
Nottingham combined histologic grade			<0.001
I	20.5	30.0	
II	52.4	50.6	
III	21.0	14.1	
Unknown	6.0	5.3	
Histology type			<0.001
Ductal	83.0	73.9	
Lobular	3.4	11.7	
Other	13.6	14.4	
Positive PR	92.7	90.9	0.29
Positive lymph vascular invasion	18.2	13.2	<0.001
Tumor size (mm, mean ± SD)[a]	19.7 ± 9.5	17.3 ± 12.3	<0.001
Lymph node metastasis	19.0	16.9	0.12
Comorbidity	19.9	14.5	<0.001
Mastectomy	74.4	32.8	<0.001
Chemotherapy	22.6	23.4	0.49
Endocrine therapy	86.0	93.0	<0.001
Radiotherapy	32.1	67.9	<0.001

[a]Exact tumor size was not available for 5 male patients and 590 female patients.

Statistical analysis

The primary outcome was overall survival (OS), defined as months from cancer diagnosis to death of any cause or to last contact. Patients lost to follow-up were censored at last contact. Demographic, clinical, and treatment characteristics of male and female patients were compared using χ^2 tests for categorical variables and Student *t* tests for continuous variables. Descriptive analyses were also carried out among patients who were eligible for Oncotype DX test to compare patients with RS tests and those without RS tests. Five-year OS across RS groups, defined by traditional and TAILORx cutoffs in men and women, were estimated and compared using the Kaplan–Meier method and log-rank test.

The age-adjusted RS–mortality association was evaluated using restricted cubic spline function (11) by treating RS as a continuous variable, with three knots (model automatically generated) placed. Patients were also stratified into respective low-, intermediate-, and high-risk groups based on traditional cutoffs (≤17, 18–30, and ≥31; ref. 1) and TAILORx cutoffs (≤10, 11–25, and ≥26; ref. 12). Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association of RS groups with overall mortality in male and female patients separately. The HRs and 95% CIs were derived with (i) adjustment for age alone, (ii) additional adjustment for demographic characteristics, clinical characteristics, and treatments, except chemotherapy, and (iii) further adjustment for chemotherapy. Fully adjusted associations between chemotherapy utilization and overall mortality were further evaluated among patients with intermediate risk defined by traditional or TAILORx cutoffs. Similar analyses were not performed for high-risk patients because of the small sample size and high chemotherapy rate in male patients with breast cancer. Given that the TAILORx Trial showed a significant interaction between chemotherapy treatment and age (≤50 years vs. >50 years; ref. 5), the abovementioned Cox regression analyses were also conducted with stratification by age in women. Because of the small number of male patients aged ≤50, age-specific analyses were

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only conducted in male patients with age >50. Tests for interactions between RS groups and sex were conducted using maximum likelihood tests comparing fully adjusted models with and without the interaction terms.

Sensitivity analyses were conducted after excluding patients with lymph node metastasis based on post-operative evaluation, or those who did not receive endocrine therapy (n = 25,755). Ten female patients who died within 90 days after surgery were also excluded in the sensitivity analysis to rule out the potential influence of treatment-related deaths. All statistical tests were based on two-sided probability, with the significance level set at $P < 0.05$, and performed using R 3.5.1 (R Foundation).

Results

A total 848 male and 110,898 female patients were included in the final analysis of this study, accounting for 24.9% ($n = 3,400$) and 30.5% ($n = 363,958$) of all male and female patients, respectively, who were eligible for Oncotype DX test (i.e., ER+, HER2−, and stage I or II invasive breast cancer). In comparison with male patients who were eligible for but did not take Oncotype DX test, male patients who took the test were younger (61.9 ± 10.4 vs. 64.9 ± 12.3; $P < 0.001$), and tended to have smaller tumor size (19.7 ± 9.5 mm vs. 21.2 ± 17.0 mm; $P = 0.02$), lower proportion of lymph node metastasis (19.0% vs. 36.2%; $P < 0.001$), lower grade (grade I: 20.5% vs. 21.8%; $P = 0.02$), and lower proportion of LVI (18.2% vs. 22.7%; $P < 0.001$). However, after excluding patients who had lymph node metastasis and who did not receive endocrine therapy, patients with and without RS test only showed a significant difference in tumor grade (grade I: 23.2% vs. 26.0%, for patients with and without RS test, respectively; $P = 0.03$; Supplementary Table S1, online only).

Overall, among patients who had RS results, the average RS in men was comparable with that in women (16.6 ± 12.0 vs. 17.2 ± 10.1, respectively; $P = 0.15$), and so was the proportion of patients with RS < 26 (82.6% vs. 85.5%, respectively). However, the respective proportion of patients with RS ≤ 10 and RS ≥ 31 was higher in men than women (RS ≤ 10: 34.7% vs. 23.4%; RS ≥ 31: 10.8% vs. 7.9%; $P < 0.001$ for both; **Table 1**). Chemotherapy utilization increased with higher RS in both men and women; among patients with RS ≥ 26, 70.9% of men and 74.8% of women received chemotherapy (**Table 2**).

Table 2. HRs (95% CI) for total mortality associated with the RS categories.

	Male patients				Female patients			
	Deaths/patients	CT (%)	ET (%)	HR (95% CI)	Deaths/patients	CT (%)	ET (%)	HR (95% CI)
Continuous scale								
Age-adjusted	41/848	22.6	86.0	1.02 (1.01–1.04)	2,527/110,898	23.4	93.0	1.03 (1.03–1.03)
Adjusted[a]	41/848	22.6	86.0	1.02 (0.99–1.05)	2,527/110,898	23.4	93.0	1.02 (1.02–1.02)
Fully adjusted[b]	41/848	22.6	86.0	1.02 (0.99–1.05)	2,527/110,898	23.4	93.0	1.02 (1.02–1.03)
Traditional cutoffs[c]								
Age-adjusted								
Low risk	14/496	6.2	88.5	Reference	1,158/65,935	6.7	93.5	Reference
Intermediate risk	19/260	34.2	82.3	2.75 (1.38–5.49)	869/36,174	39.3	93.4	1.32 (1.21–1.44)
High risk	8/92	78.3	82.6	3.06 (1.28–7.32)	500/8,789	83.0	88.2	3.07 (2.76–3.41)
Adjusted[a]								
Low risk	14/496	6.2	88.5	Reference	1,158/65,935	6.7	93.5	Reference
Intermediate risk	19/260	34.1	82.3	1.82 (0.83–4.00)	869/36,174	39.3	93.4	1.27 (1.16–1.39)
High risk	8/92	78.3	82.6	1.35 (0.45–4.06)	500/8,789	83.0	88.2	2.23 (1.96–2.54)
Fully adjusted[b]								
Low risk	14/496	6.2	88.5	Reference	1,158/65,935	6.7	93.5	Reference
Intermediate risk	19/260	34.1	82.3	1.69 (0.74–3.86)	869/36,174	54.3	94.6	1.31 (1.20–1.44)
High risk	8/92	78.3	82.6	1.15 (0.34–3.91)	500/8,789	85.1	91.2	2.46 (2.13–2.84)
TAILORx cutoffs[d]								
Age-adjusted								
Low risk	4/294	6.8	88.1	Reference	489/25,929	4.4	92.9	Reference
Intermediate risk	23/406	16.5	86.0	4.60 (1.59–13.32)	1,289/68,882	18.5	93.7	1.05 (0.94–1.16)
High risk	14/148	70.9	81.8	7.15 (2.35–21.72)	749/16,087	74.8	90.0	2.44 (2.18–2.74)
Adjusted[a]								
Low risk	4/294	6.8	88.1	Reference	489/25,929	4.4	92.9	Reference
Intermediate risk	23/406	16.5	86.0	5.37 (1.79–16.11)	1,289/68,882	18.5	93.7	1.06 (0.96–1.18)
High risk	14/148	70.9	81.8	4.28 (1.22–14.97)	749/16,087	74.8	90.0	1.92 (1.68–2.18)
Fully adjusted[b]								
Low risk	4/294	6.8	88.1	Reference	489/25,929	4.4	92.9	Reference
Intermediate risk	23/406	16.5	86.0	5.33 (1.77–16.08)	1,289/68,882	18.5	93.7	1.07 (0.97–1.19)
High risk	14/148	70.9	81.8	3.56 (0.93–13.58)	749/16,087	74.8	90.0	2.05 (1.78–2.37)

Abbreviations: CT: chemotherapy, ET: endocrine therapy.

[a]Adjusted for: age (continuous), race, grade, histology type, PR status, tumor size, lymph nodal status, LVI, comorbidity, surgery, endocrine therapy, radiotherapy, education, income, insurance, and year of diagnosis (strata).

[b]In addition adjusted for chemotherapy.

[c]Traditional cutoffs: low risk, RS ≤ 17; intermediate risk, RS 18–30; and high risk, RS ≥31. On the basis of the fully adjusted model, $P_{interaction}$ between RS and sex was 0.10.

[d]TAILORx cutoffs: low risk, RS ≤10; intermediate risk, RS 11–25; and high risk, RS ≥ 26. On the basis of the fully adjusted model, $P_{interaction}$ between RS and sex was 0.008.

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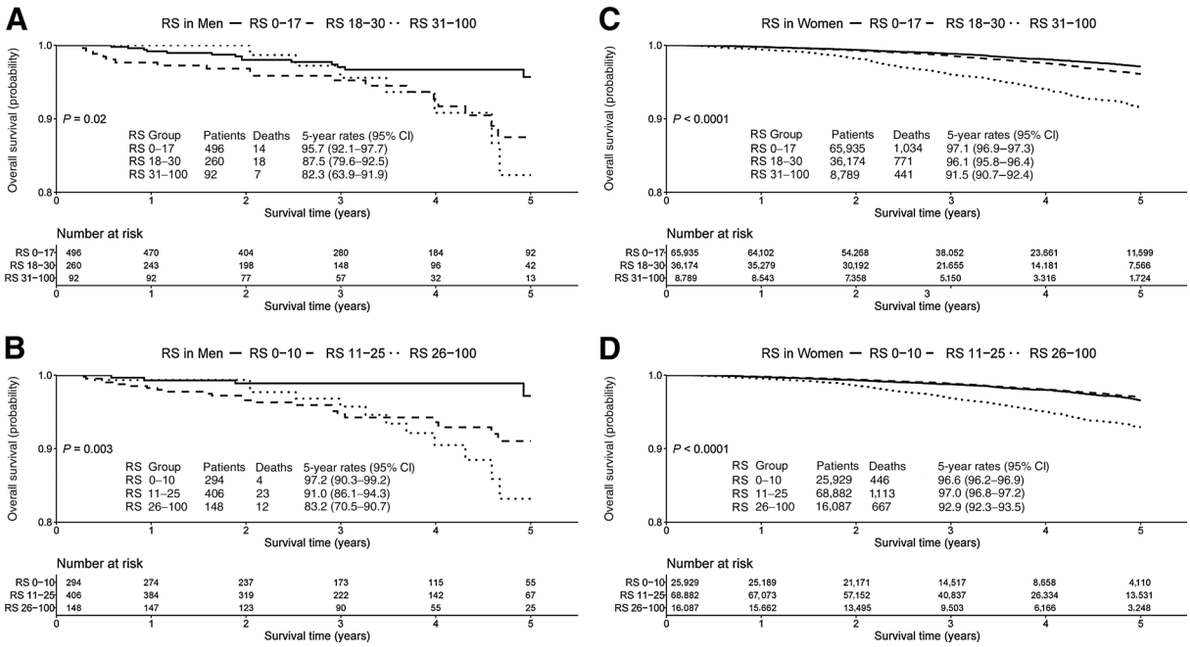

Figure 2.

Five-year OS by Oncotype DX RS for male and female patients with breast cancer. **A,** Five-year survival curve for male patients according to traditional RS cutoff (i.e., 0–17, 18–30, and 31–100); **B,** Five-year survival curve for male patients according to TAILORx RS cutoff (i.e., 0–10, 11–25, and 26–100); **C,** Five-year survival curve for female patients according to traditional RS cutoff (i.e., 0–17, 18–30, and 31–100); **D,** Five-year survival curve for female patients according to TAILORx RS cutoff (i.e., 0–10, 11–25, and 26–100).

Estimates of 5-year OS differed significantly across RS groups in both men and women (**Fig. 2**). When evaluated using TAILORx cutoffs, the 5-year OS was 97.2% (95% CI, 90.3%–99.2%), 91.0% (95% CI, 86.1%–94.3%), and 83.2% (95% CI, 70.5%–90.7%) for men with RS 0–10, RS 11–25, and RS 26–100, respectively ($P = 0.003$). In women, patients with RS 0–10 and RS 11–25 had similar 5-year OS of 96.6% (95% CI, 96.2%–96.9%) and 97.0% (95% CI, 96.8%–97.2%), respectively; both were higher than that of the RS 26–100 group (92.9%, 95% CI, 92.3%–93.5%; $P < 0.001$). When estimated using traditional RS cutoffs, 5-year OS was 95.7%, 87.5%, and 82.3% for men with RS 0–17, RS 18–30, and RS 31–100, respectively ($P = 0.02$). Respective corresponding rates in women were 97.1%, 96.1%, and 91.5% ($P < 0.001$).

RS was associated with increased mortality risk in male patients until RS > 21 (fully-adjusted HR = 1.12, 95% CI, 1.02 to 1.24 per unit RS increment), after which the risk plateaued. In female patients, however, mortality risk began to increase only with a RS > 23 (fully-adjusted HR = 1.02, 95% CI, 1.01 to 1.02 per unit RS increment). Test for non-linearity was significant in both groups (**Fig. 3**).

Traditional cutoffs for RS were not significantly associated with mortality in male patients (**Table 2**). Based on TAILORx cutoffs, after adjustment for demographic factors, clinical characteristics, and treatments, except chemotherapy, male patients with RS 11–25 (HR = 5.37; 95% CI, 1.79–16.11) or ≥26 (HR = 4.28; 95% CI, 1.22–14.97) had a higher mortality risk compared with those with RS ≤ 10. Additional adjustment for chemotherapy resulted in little attenuation of HR for the intermediate-risk group (HR = 5.33; 95% CI, 1.77–16.08), but some attenuations for the high-risk group (HR = 3.56; 95% CI, 0.93–13.58). In comparison, female patients in the high-risk group had a 2.0-fold (fully adjusted HR = 2.05; 95% CI, 1.78–2.37 for TAILORx cutoffs) to 2.5-fold (fully adjusted HR = 2.46; 95% CI, 2.13–2.84 for traditional cutoffs) elevated risk of mortality compared with their low-risk counterparts. Women with RS 11–25 did not have higher mortality risk compared with those with RS ≤ 10 (fully adjusted HR = 1.06; 95% CI, 0.96–1.18; **Table 2**). Significant interactions between sex and RS group were observed for TAILORx cutoffs ($P_{interaction} = 0.008$) but not for traditional cutoffs ($P_{interaction} = 0.10$). These associations were observed in male patients age > 50 years and in female patients irrespective of age ≤50 or >50 years (Supplementary Tables S2 and S3; online only). Analyses restricted to female patients who did not receive chemotherapy showed that, in comparison with RS ≤ 10, RS ≥ 26 was associated with an increased mortality (HR = 2.00; 95% CI, 1.69–2.37), but RS 11–25 was not significantly associated with mortality (HR = 1.08; 95% CI, 0.97–1.21). Similar analyses could not be conducted in men due to the small sample size.

Additional chemotherapy was associated with lower risk of mortality among women with RS 18–30 (HR = 0.83; 95% CI, 0.71–0.97), and nonsignificant reduction in mortality among women with RS 11–25 (HR = 0.89; 95% CI, 0.76–1.05; **Table 3**). When stratified by age, the lower mortality risk associated with chemotherapy was only observed among older women with RS 18–30 (HR = 0.82; 95% CI, 0.69–0.97), but not among those aged ≤50 with RS 18–30 (HR = 0.96; 95% CI, 0.64–1.44), or among those with RS 11–25 regardless of age (i.e., HR = 0.97, 95% CI, 0.65–1.44 for women aged ≤50; HR = 0.87, 95% CI, 0.73–1.04 for women aged >50; Supplementary Table S4, online only). No significant association between chemotherapy and mortality was observed among male patients with intermediate-risk; that is, RS 18–30 (traditional cutoffs: HR = 1.37; 95% CI, 0.32–5.82) or RS 11–25 (TAILORx cutoffs: HR = 3.50; 95% CI, 0.98–12.53), although these analyses were based on a much smaller sample size (**Table 3**). Similar analyses by age at diagnosis could not be done in male cases due to a small sample size.

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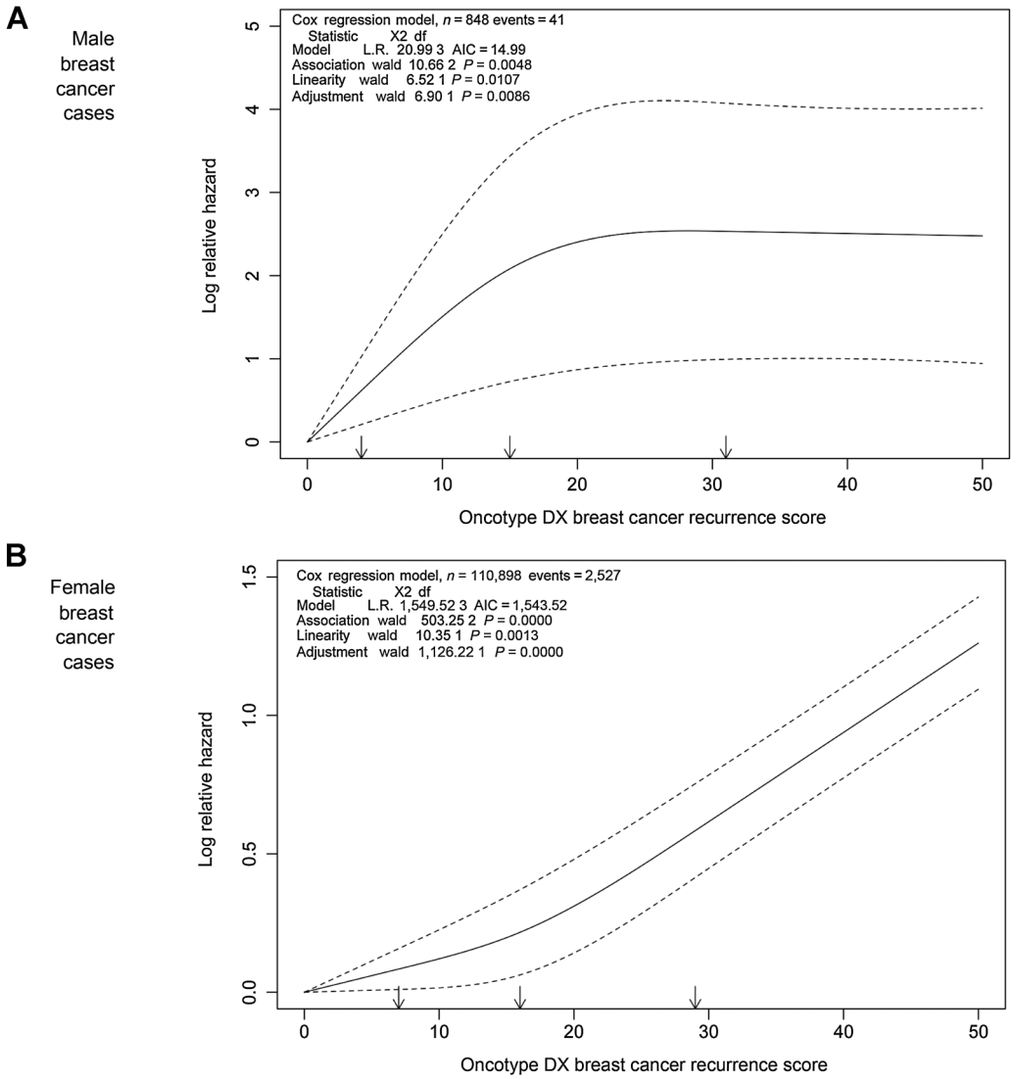

Figure 3.

Association pattern between total mortality curve and Oncotype DX RS in male and female patients with breast cancer. **A,** Association pattern for male patients with breast cancer. **B,** Association pattern for female patients with breast cancer. Results were generated from restricted cubic spline regression with adjustment for age and RS as a continuous variable.

Sensitivity analyses excluding patients with lymph node metastasis, or those who did not receive endocrine therapy, showed overall similar patterns (**Table 3**; Supplementary Table S5, online only).

Discussion

In this large-scale registry-based study, we found that distribution and association patterns of RS with mortality in male patients with breast cancer were different from those in their female counterparts. RS was prognostic for mortality among male patients, but with a lower threshold than that for female patients. Little benefit from chemotherapy was observed for those with intermediate-risk male patients, defined either by TAILORx or traditional cutoffs, although this group, overall, was at high mortality risk.

The RS algorithm was developed on the basis of multigene profiles from female patients with breast cancer to quantify the risk of distant recurrence (1). Despite the overall similar averaged RS between men and women, we observed higher proportions of both high and low RS in male patients with breast cancer than their female counterparts. This is similar to previous reports based on data from the SEER Program, as well as those from a single institution (10, 13, 14). The observed differences in RS distribution between men and women suggest that male breast cancer may have distinct biology and different prognostic factors compared with female patients. Studies have suggested that pathogenic mutations and epigenetic alterations involved in male breast carcinogenesis do not exactly overlap with those of women (15). For example, *BRCA2* and *CHEK2* mutations were more frequent in male compared with female cases (16). A study by Massarweh and colleagues revealed that, among patients with breast cancer with RS testing, men in comparison with women had higher mean expression levels for ER-related genes, as well as proliferation- and invasion-related

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Table 3. HRs (95% CI) for total mortality associated with chemotherapy status among intermediate-risk patients[a].

	Male patients			Female patients		
	Deaths/patients	ET (%)	HR (95% CI)	Deaths/patients	ET (%)	HR (95% CI)
All patients						
RS 18–30						
No chemotherapy	11/164	85.4	Reference	575/21,460	93.1	Reference
Chemotherapy	8/89	80.1	1.37 (0.32–5.82)	282/14,217	94.3	0.83 (0.71–0.97)
RS 11–25						
No chemotherapy	17/329	88.4	Reference	1,075/54,902	93.9	Reference
Chemotherapy	6/67	79.1	3.50 (0.98–12.53)	194/12,750	94.5	0.89 (0.76–1.05)
Patients with negative lymph node and receipt of endocrine therapy[b]						
RS 18–30						
No chemotherapy	8/126	100.0	Reference	385/17,475	100.0	Reference
Chemotherapy	4/54	100.0	1.15 (0.02–8.72)	155/10,307	100.0	0.80 (0.66–0.98)
RS 11–25						
No chemotherapy	12/252	100.0	Reference	733/44,243	100.0	Reference
Chemotherapy	3/39	100.0	4.89 (0.46–52.34)	98/8,141	100.0	0.87 (0.70–1.09)

Note: Adjusted for: age (continuous), race, grade, histology type, PR status, tumor size, LVI, comorbidity, surgery, radiotherapy, education, income, insurance, and year of diagnosis (strata). Lymph nodal status and endocrine therapy status were also included for adjustment when analysis was conducted within all populations.
Abbreviation: ET: endocrine therapy.
[a]Patients with unknown chemotherapy status were excluded from this analysis.
[b]Four female patients with RS 18–30 and 8 female patients with RS 11–25 who died within 90 days after surgery were excluded from this analysis. No male patients died within 90 days after surgery.

genes (10). Future comparative studies on sex-specific pathogenic alterations in breast cancer may provide more insight on underlying mechanisms.

In female breast cancer, prognostic values of RS on cancer outcome, as well as predictive values of chemotherapy benefit, have been well validated in both clinical trials and routine practice settings (3–5, 17), and RS has been recommended for clinical utility (18). Our findings on the prognostic and predictive values of RS on female patients with breast cancer are consistent with previous reports (4, 17–19). We found that female patients with RS 11–25 had only a modest increased mortality compared with those with RS $\leq$ 10. We also found no overall mortality benefit of chemotherapy for women with RS 11–25, irrespective of age (i.e., $\leq$50 or >50), which is generally in-line with results from TAILORx Trials (5, 20). These findings support the 2018 National Comprehensive Cancer Network guidelines to increase the risk cutoff to 26 for female patients with breast cancer (21), as well as the updated clinical practice guidelines by the American Society of Clinical Oncology (6). We carried out additional analyses for women aged $\leq$50 with RS 16–25, for whom a chemotherapy benefit on distant recurrence-free survival was recently reported in the TAILORx Trial (20). We found a borderline significant overall mortality benefit for this group of patients (HR = 0.84; 95% CI, 0.70–1.00; not reported in the tables). These results support the validity of our findings.

To the best of our knowledge, the prognostic and predictive values of RS in male patients with breast cancer have not been well evaluated. In our study, we found significantly different 5-year OS in men across RS groups, either defined by traditional or TAILORx cutoffs, especially when evaluated using the TAILORx cutoffs. This is consistent with the study of Massarweh and colleagues, which used data from the SEER Program and estimated OS and breast cancer specific survival (BCSS) for 322 male patients with breast cancer, according to traditional RS cutoffs (10). They also observed significantly different 5-year OS and BCSS estimates across RS groups in the entire study male population, although the differences did not remain significant in 276 male patients without node metastasis ($P = 0.22$ for OS, and $P = 0.08$ for BCSS, respectively). In our study, after adjustment for demographic, clinical, and treatment factors, we found that a much lower RS cutoff for risk classification is needed for male compared with female patients with breast cancer. TAILORx cutoffs, but not traditional cutoffs, were associated with significantly increased mortality among male patients with breast cancer. Interestingly, the association for the high-risk group was only modestly attenuated after additional adjustment for chemotherapy, and chemotherapy was not significantly associated with mortality among male patients with RS 11–25 or those with RS 18–30. This may suggest that RS may only be associated with total mortality but not robustly predict the benefit of adjuvant chemotherapy for male patients with breast cancer. However, the sample size for the analysis related to chemotherapy is small. In addition, our study was not equipped to investigate the predictive value of Oncotype DX due to the lack of detailed treatment information and compliance data in the NCDB. It is noteworthy that treatment for male breast cancer, including those based on the RS categorization, is primarily based on the knowledge gained from clinical trials conducted in female patients (8). In addition, previous studies have shown that compliance to treatments was poorer in men than women (22, 23). Furthermore, there may be biological differences between male and female breast cancer (9). Thus, studies directly evaluating whether RS is predictive to treatment in male patients with breast cancer are warranted.

The strengths of our study include the relatively large sample size and generalizability. Our study included 848 male patients with both RS results and mortality data, which is larger than the previous SEER-based study, which included only 322 male patients with survival data (10). Compared with the SEER Program, which covers 28% of the U.S. population (24), the NCDB captures approximately 70% of newly diagnosed cancer cases across the United States, further enhancing the generalizability of our study. In our analysis, we also accounted for a wide range of clinical covariates, including information on endocrine therapy, which was the backbone of systemic treatment for patients with ER+ breast cancer, but which was not covered in the previous

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SEER data–derived study. However, our study has limited statistical power for subgroup analyses, including age- and chemotherapy-specific analyses, and these findings should be interpreted with caution. We included all patients with RS results in our study, some of whom may not be qualified for receiving Oncotype DX test, according to the current guideline. We conducted additional analysis restricting our analysis to populations strictly following the inclusion criteria of the TAILORx Trial (i.e., ER+, HER2−, node-negative, tumor size 1.1–5.0 cm, and ages 18–75 years; ref. 5). We found that 70.9% of those female patients had low clinical risk (CR, defined by tumor size and grade), and 29.1% had high CR (data was not shown in tables), in exact agreement with proportions reported in the TAILORx Trial (5). The RS–mortality association remained little changed among these patients. Furthermore, our findings were not materially changed in sensitivity analysis when patients who had lymph node metastasis or did not receive endocrine therapy were excluded. In addition, patients with RS results had generally comparable biologic characteristics to those who were eligible for but did not take Oncotype DX test. All these indicate that bias related to patient selection is not a major concern for our study. A major limitation for our study is that information on recurrence and causes of death was not recorded in the NCDB, and thus, BCSS could not be evaluated. Lack of information on genetic tests (e.g., *BRCA* mutation) is also a limitation. Finally, the follow-up time was relatively short, and subsequent analyses with long-term follow-up are warranted.

In conclusion, among routine oncology care populations with early-stage breast cancer, RS is prognostic for total morality in both male and female patients, but with distinct association patterns. Mortality increased in much lower ranges of RS for male than female patients with breast cancer. Studies are needed to develop RS categorization specifically for male patients with breast cancer.

Disclosure of Potential Conflicts of Interest

I.A. Mayer is an employee/paid consultant for Novartis, Genentech, Astra-Zeneca, Lilly, GlaxoSmithKline, Immunomedics, Macrogenics, and Seattle Genetics, and reports receiving commercial research grants from Pfizer and Genentech. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The American College of Surgeons and the Commission on Cancer are not responsible for conclusions drawn from the data.

Authors' Contributions

Conception and design: F. Wang, S. Reid, T. Pal, I.A. Mayer, X.-O. Shu
Development of methodology: S. Reid, T. Pal, X.-O. Shu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T. Pal, C.E. Bailey, X.-O. Shu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): F. Wang, T. Pal, X.-O. Shu
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T. Pal, X.-O. Shu
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References

1. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817–26.
2. Sparano JA, Paik S. Development of the 21-gene assay and its application in clinical practice and clinical trials. J Clin Oncol 2008;26:721–8.
3. Mamounas EP, Tang G, Fisher B, Paik S, Shak S, Costantino JP, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J Clin Oncol 2010;28:1677–83.
4. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24:3726–34.
5. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 2018;379:111–21.
6. Andre F, Ismaila N, Henry NL, Somerfield MR, Bast RC, Barlow W, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: ASCO Clinical Practice Guideline Update—integration of results from TAILORx. J Clin Oncol 2019;37:1956–64.
7. Miao H, Verkooijen HM, Chia KS, Bouchardy C, Pukkala E, Larønningen S, et al. Incidence and outcome of male breast cancer: an international population-based study. J Clin Oncol 2011;29:4381–6.
8. Giordano SH. Breast cancer in men. N Engl J Med 2018;378:2311–20.
9. Fentiman IS. Male breast cancer is not congruent with the female disease. Crit Rev Oncol Hematol 2016;101:119–24.
10. Massarweh SA, Sledge GW, Miller DP, McCullough D, Petkov VI, Shak S. Molecular characterization and mortality from breast cancer in men. J Clin Oncol 2018;36:1396–404.
11. Harrell F Jr. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York City, NY: Springer-Verlag; 2001.
12. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 2015;373:2005–14.
13. Altman AM, Kizy S, Yuan J, Denbo JW, Jensen EH, Hui JYC, et al. Distribution of 21-gene recurrence scores in male breast cancer in the United States. Ann Surg Oncol 2018;25:2296–302.
14. Turashvili G, Gonzalez-Loperena M, Brogi E, Dickler M, Norton L, Morrow M, et al. The 21-gene recurrence score in male breast cancer. Ann Surg Oncol 2018; 25:1530–5.
15. Rizzolo P, Silvestri V, Tommasi S, Pinto R, Danza K, Falchetti M, et al. Male breast cancer: genetics, epigenetics, and ethical aspects. Ann Oncol 2013;24: viii75–viii82.
16. Pritzlaff M, Summerour P, McFarland R, Li S, Reineke P, Dolinsky JS, et al. Male breast cancer in a multi-gene panel testing cohort: insights and unexpected results. Breast Cancer Res Treat 2017;161:575–86.
17. Dowsett M, Cuzick J, Wale C, Forbes J, Mallon EA, Salter J, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J Clin Oncol 2010;28:1829–34.
18. Harris LN, Ismaila N, McShane LM, Andre F, Collyar DE, Gonzalez-Angulo AM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016;34:1134–50.

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19. Ibraheem AF, Press DJ, Olopade OI, Huo D. Community clinical practice patterns and mortality in patients with intermediate oncotype DX recurrence scores: who benefits from chemotherapy? Cancer 2019;125:213–22.
20. Sparano JA, Gray RJ, Ravdin PM, Makower DF, Pritchard KI, Albain KS, et al. Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer. N Engl J Med 2019;380:2395–405.
21. National Comprehensive Cancer Network. Breast cancer (Version 4.2019). Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
22. Kiluk JV, Lee MC, Park CK, Meade T, Minton S, Harris E, et al. Male breast cancer: management and follow-up recommendations. Breast J 2011;17:503–9.
23. Venigalla S, Carmona R, Guttmann DM, Jain V, Freedman GM, Clark AS, et al. Use and effectiveness of adjuvant endocrine therapy for hormone receptor–positive breast cancer in men. JAMA Oncol 2018;4:e181114.
24. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34.

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