Associations of Breast Cancer Risk Prediction Tools With Tumor Characteristics and Metastasis

Johanna Holm, Jingmei Li, Hatet Darabi, Martin Eklund, Mikael Eriksson, Keith Humphreys, Per Hall, and Kamila Czene

ABSTRACT

Purpose
The association between established risk factors for breast cancer and subtypes or prognosis of the disease is not well known. We analyzed whether the Tyrer-Cuzick–predicted 10-year breast cancer risk score (TCRS), mammographic density (MD), and a 77-single nucleotide polymorphism polygenic risk score (PRS) were associated with breast cancer tumor prognosticators and risk of distant metastasis.

Patients and Methods
We used a case-only design in a population-based cohort of 5,500 Swedish patients with breast cancer. Logistic and multinomial logistic regression of outcomes, estrogen receptor (ER) status, lymph node involvement, tumor size, and grade was performed with TCRS, PRS, and percent MD as exposures. Cox proportional hazard models were used to estimate hazard ratios (HRs) of distant metastasis.

Results
Women at high risk for breast cancer based on PRS and/or TCRS were significantly more likely to be diagnosed with favorable prognosticators, such as ER-positive and low-grade tumors. In contrast, by age, the associations of TCRS with favorable prognosticators were restricted to women younger than age 50. Women scoring high in both TCRS and PRS had a lower risk of distant metastasis (HR, 0.69; 95% CI, 0.49 to 0.98). MD was not associated with any of the examined prognosticators.

Conclusion
Women at high risk for breast cancer based on genetic and lifestyle factors were significantly more likely to be diagnosed with breast cancers with a favorable prognosis. Better knowledge of subtype-specific risk factors could be vital for the success of prevention programs aimed at lowering mortality.

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INTRODUCTION

Breast cancer is a heterogeneous disease, with both environmental and genetic causes. Currently known risk factors can be used in prediction modeling to identify women at risk for disease, as a necessary step for improving early detection, as well as offering preventative interventions. The Tyrer-Cuzick model has been developed to identify women at increased risk for breast cancer, incorporating hormonal, lifestyle, and reproductive risk factors, together with family history, in the estimation of risk. Additionally, large-scale genome-wide association studies have identified many low-risk common variant single-nucleotide polymorphisms (SNPs) that partially explain disease occurrence when analyzed as a polygenic risk score (PRS). Recently, a PRS based on 77-SNP variants was developed to predict breast cancer risk. Another factor used for risk prediction is mammographic density (MD), one of the strongest risk factors for breast cancer. These tools show future promise for determining breast cancer risk in healthy women, and their use has been suggested to improve performance when used in combinations.

Identification of women at high risk for breast cancer is a pivotal part of successful clinical prevention aimed at lowering disease mortality. Importantly, if disease burden and mortality are to be lowered, it is necessary to be able to identify women at risk for all subtypes of the disease. However, the prediction tools mentioned earlier may be differentially associated with subtypes of
the disease, given previous findings of separate etiologies for distinct molecular subtypes of breast cancer.9-11 We investigated whether Tyrer-Cuzick–predicted 10-year breast cancer risk score (TCRS), PRS, and percent MD values differed, on average, according to tumor prognosticators and metastasis in a large population-based cohort of breast cancer patients in Sweden.

**RESULTS**

Descriptive statistics for the cohort are listed in Table 1. Of the 5,500 women, 5,232 had information on TCRS, 4,927 had information on PRS, and 3,488 had a prediagnostic MD measurement. Most women were postmenopausal (70%); the median age was 59 years, with a range of 23 to 79 years. In the cohort, TCRS ranged from 0.23% to 28.86%, with a median of 3.13% (standard deviation [SD], 2.26%). Percent MD ranged from 0.001% to 91.5%, with a median of 19.19% (SD, 13.5%), and PRS ranged from 0.23% to 28.86%, with a median of 3.13% (SD, 2.26%). Spearman's rank correlation coefficient was -0.004 between TCRS and PRS, -0.12 between TCRS and MD, and 0.04 between PRS and MD.

Table 2 shows the results of binomial and multinomial logistic regression of TCRS, PRS, and MD, overall and stratified by age. TCRS was associated with ER status, grade, and lymph node involvement (ER-negative odds ratio [OR], 0.80; 95% CI, 0.72 to 0.90; lymph node-positive OR, 0.77; 95% CI, 0.68 to 0.87; grade 3 OR, 0.79; 95% CI, 0.69 to 0.90; Table 2), but not with tumor size. Associations remained in women younger than age 50 at diagnosis but were not shown in women aged 50 to 79 years at diagnosis. On finer age stratification, these effects were driven by associations in women aged 40 years or younger (Appendix Table A1, online-only).

The PRS was associated with several prognosticators. Each 1-SD increase in the score was associated with smaller, low-grade, hormone-positive tumors (ER-negative OR, 0.88; 95% CI, 0.74 to 0.87; tumor size greater than 40 mm OR, 0.86; 95% CI, 0.76 to 0.99; grade 3 OR, 0.86; 95% CI, 0.77 to 0.93; Table 2). In analyses stratified by age at diagnosis, patterns of associations were similar in both young and old women. MD was positively associated with lymph node metastasis and tumor size in crude analysis, but showed null associations with grade and ER status. After adjusting
for age at diagnosis, no prognosticator was associated with MD (Table 2). Further adjustments for body mass index, hormone replacement therapy use, and menopausal status did not change estimates (not shown). In analyses stratified by age at diagnosis, no distinct differences were observed (Table 2).

Table 3 shows the results from analyses of TCRS and MD by ER status and of PRS weighted by ER-positive and ER-negative disease. The same pattern was observed for TCRS among ER-positive disease, as in the overall analysis, with a high score being more common in low-grade, lymph node-negative patients. Among ER-negative disease, no prognosticator was associated with TCRS. Analysis using the ER-positive weighted PRS yielded point estimates similar to the main PRS, whereas the ER-negative weighted score was associated with ER-negative receptor status. MD was not associated with any tumor characteristic in any of the strata. There was a nonsignificant trend of high-grade cancer among ER-negative patients with high MD (Table 3).

Sensitivity analysis using 5-year TCRS yielded results similar to the main analysis using 10-year TCRS. The associations for both scores were driven by effects among patients with early-onset disease (Appendix Table A1, online-only). Sensitivity analysis excluding women with a family history of breast cancer revealed more pronounced effect sizes for TCRS, whereas no change was shown for PRS or MD (Appendix Table A2, online-only).

Because TCRS and PRS were not correlated but showed associations between ER and grade in the same direction, we analyzed the combined effect of TCRS and PRS. Women scoring above the median in both TCRS and PRS had more favorable tumor characteristics than did those scoring below the median on both measures (ER-negative OR, 0.52; 95% CI, 0.41 to 0.66; grade 3 OR, 0.56; 95% CI, 0.43 to 0.78; Fig 1).

We further studied the combination of high TCRS and PRS on the risk of being diagnosed with a distant metastasis. For women scoring above the median in both TCRS and PRS, an approximately 30% decreased risk of a distant metastasis was shown (HR, 0.69; 95% CI, 0.49 to 0.98; Table 4). The lowered risk was restricted to patients younger than 50 years of age at diagnosis (HR, 0.20; 95% CI, 0.05 to 0.84), with null associations in women aged 50 or older (Table 4). Neither PRS nor MD were individually associated with a risk of distant metastasis in our cohort, but there was a protective effect for TCRS (HR, 0.69; 95% CI, 0.50 to 0.93), slightly attenuated by adjusting for age and prognosticators (Table 4). No violations of the proportionality assumptions were shown.

DISCUSSION

For breast cancer risk prediction models to aid in lowering disease mortality, they should ideally be able to predict both aggressive and less aggressive subtypes of the disease. We found that women at high risk for breast cancer based on the TCRS or PRS, or both, were significantly more likely to be diagnosed with low-grade, ER-positive cancers. TCRS was also associated with lymph node involvement, and PRS was also influenced by tumor size. The
<table>
<thead>
<tr>
<th></th>
<th>TCRS</th>
<th>PRS</th>
<th>MD*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Women</td>
<td>Women &lt; 50 years</td>
<td>Women ≥ 50 years</td>
</tr>
<tr>
<td><strong>ER status</strong></td>
<td></td>
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<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Negative</td>
<td>0.80 (0.72 to 0.90)</td>
<td>0.57 (0.39 to 0.81)</td>
<td>0.91 (0.81 to 1.02)</td>
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<td><strong>Lymph node status</strong></td>
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<td>1.00 (ref)</td>
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<tr>
<td>Positive</td>
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<td>0.76 (0.55 to 1.01)</td>
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<td><strong>Tumor size</strong></td>
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<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
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<tr>
<td>20-40 mm</td>
<td>0.96 (0.90 to 1.03)</td>
<td>0.81 (0.64 to 1.03)</td>
<td>1.02 (0.95 to 1.10)</td>
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<tr>
<td>&gt; 40 mm</td>
<td>0.97 (0.84 to 1.11)</td>
<td>0.50 (0.29 to 0.87)</td>
<td>1.13 (0.99 to 1.28)</td>
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<td><strong>Grade</strong></td>
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<td>1.00 (ref)</td>
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<td>0.96 (0.62 to 1.47)</td>
<td>1.11 (0.98 to 1.26)</td>
</tr>
<tr>
<td>3</td>
<td>0.79 (0.69 to 0.90)</td>
<td>0.73 (0.46 to 1.15)</td>
<td>0.94 (0.61 to 1.10)</td>
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</tbody>
</table>

NOTE. Values are OR (95% CI). ORs with 95% CIs are shown per 1-SD increase. Boldface type indicates associations significant at alpha = 0.05.
Abbreviations: ER, estrogen receptor; MD, mammographic density; OR, odds ratio; PRS, polygenic risk score; ref, reference; SD, standard deviation; TCRS, Tyrer-Cuzick-predicted 10-year risk score.
*Age-adjusted.
Table 3. Binomial and Multinomial Logistic Regression of Tyrer-Cuzick–Predicted 10-Year Risk Score and Mammographic Density Stratified by ER Status and Polygenic Risk Score Weighted on ER-Positive Disease and ER-Negative Disease

<table>
<thead>
<tr>
<th>ER status</th>
<th>TCRS All Women</th>
<th>ER-Positive</th>
<th>ER-Negative</th>
<th>Overall</th>
<th>ER-Positive</th>
<th>ER-Negative</th>
<th>PRS* All Women</th>
<th>ER-Positive</th>
<th>ER-Negative</th>
<th>MD† All Women</th>
<th>ER-Positive</th>
<th>ER-Negative</th>
</tr>
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<tbody>
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<td>Positive</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Negative</td>
<td>0.80 (0.72 to 0.90)</td>
<td>0.80 (0.74 to 0.87)</td>
<td>0.76 (0.70 to 0.83)</td>
<td>1.14 (1.05 to 1.24)</td>
<td>1.00 (ref)</td>
<td>0.93 (0.83 to 1.04)</td>
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<td>0.93 (0.83 to 1.04)</td>
<td>1.00 (ref)</td>
<td>0.93 (0.83 to 1.04)</td>
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<td>Lymph node status</td>
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<tr>
<td>Negative</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
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<td>1.00 (ref)</td>
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<tr>
<td>Positive</td>
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<td>0.76 (0.65 to 0.89)</td>
<td>1.01 (0.78 to 1.26)</td>
<td>0.98 (0.91 to 1.10)</td>
<td>0.99 (0.90 to 1.09)</td>
<td>1.03 (0.93 to 1.13)</td>
<td>1.11 (0.98 to 1.25)</td>
<td>1.13 (0.97 to 1.30)</td>
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<td>1.00 (ref)</td>
<td>0.93 (0.83 to 1.04)</td>
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<tr>
<td>Tumor size</td>
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<tr>
<td>&lt; 20 mm</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
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<td>1.00 (ref)</td>
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<td>1.00 (ref)</td>
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<td>20-40 mm</td>
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<td>0.96 (0.88 to 1.05)</td>
<td>0.92 (0.77 to 1.11)</td>
<td>0.94 (0.88 to 1.00)</td>
<td>0.92 (0.87 to 0.98)</td>
<td>1.07 (0.99 to 1.14)</td>
<td>1.03 (0.95 to 1.12)</td>
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<td>&gt; 40 mm</td>
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<td>1.00 (ref)</td>
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<td>Grade</td>
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<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
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<td>1.03 (0.91 to 1.15)</td>
<td>1.38 (0.59 to 3.02)</td>
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<td>1.02 (0.93 to 1.13)</td>
<td>1.05 (0.95 to 1.15)</td>
<td>1.02 (0.87 to 1.16)</td>
<td>1.03 (0.90 to 1.18)</td>
<td>1.85 (0.60 to 5.75)</td>
<td>1.00 (ref)</td>
<td>0.93 (0.83 to 1.04)</td>
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<tr>
<td>3</td>
<td>0.79 (0.69 to 0.90)</td>
<td>0.84 (0.72 to 0.98)</td>
<td>1.03 (0.45 to 2.35)</td>
<td>0.86 (0.77 to 0.95)</td>
<td>0.82 (0.74 to 0.92)</td>
<td>1.11 (1.00 to 1.24)</td>
<td>0.87 (0.75 to 1.01)</td>
<td>0.84 (0.74 to 1.00)</td>
<td>2.10 (0.70 to 6.36)</td>
<td>1.00 (ref)</td>
<td>0.93 (0.83 to 1.04)</td>
<td></td>
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</table>

NOTE. Values are OR (95% CI). Odds ratios with 95% CIs are shown per 1-SD increase. Boldface type indicates associations significant at alpha = 0.05.
Abbreviations: ER, estrogen receptor; MD, mammographic density; OR, odds ratio; PRS, polygenic risk score; ref, reference; SD, standard deviation; TCRS, Tyrer-Cuzick-predicted 10-year risk score.
*All analysis was conducted for all patients.
†Age-adjusted.
influence of PRS was age independent, in contrast to TCRS, which was only associated with tumor characteristics in young women. We further found that the risk of being diagnosed with distant metastasis was significantly lower in women at increased risk for breast cancer, according to both TCRS and PRS. MD showed null associations with all tumor prognosticators under study and seems therefore to be a general risk factor for breast cancer.

To the best of our knowledge, no study has previously addressed how tumor prognosticators vary with the predicted breast cancer risk using the Tyrer-Cuzick model. Several of the lifestyle and reproductive risk factors determining the score have been shown to be positively associated with ER-positive disease,\(^1\) in agreement with our results. We found that patients with a high TCRS were more likely to have ER-positive tumors, and the largest effect sizes were shown when excluding patients with a family history of breast cancer, thus restricting the score to signifying hormonal and lifestyle risk factors. Stratified analysis revealed that these main effects were driven by associations in women younger than 40 years of age. This suggests that risk factors incorporated in the Tyrer-Cuzick model are less useful when aiming to identify aggressive breast cancer in young women, but may work well as a general tool for postmenopausal cancers. Moreover, if high-risk young women according to TCRS are at risk for developing ER-positive subtypes, TCRS could be a tool for identifying healthy

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**Table 4. Cox Regression Modeling of Hazard Ratios of Distant Metastasis**

<table>
<thead>
<tr>
<th>Model 1*</th>
<th>No. of Events</th>
<th>All Women</th>
<th>No. of Events</th>
<th>Women &lt; 50 years</th>
<th>No. of Events</th>
<th>Women ≥ 50 years</th>
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</thead>
<tbody>
<tr>
<td>TCRS</td>
<td>164</td>
<td><strong>0.69 (0.50 to 0.93)</strong></td>
<td>69</td>
<td>0.83 (0.38 to 1.82)</td>
<td>95</td>
<td>0.83 (0.54 to 1.25)</td>
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<tr>
<td>PRS</td>
<td>145</td>
<td>0.91 (0.66 to 1.26)</td>
<td>38</td>
<td>0.66 (0.35 to 1.25)</td>
<td>107</td>
<td>0.99 (0.68 to 1.45)</td>
</tr>
<tr>
<td>MD</td>
<td>85</td>
<td>1.13 (0.74 to 1.74)</td>
<td>18</td>
<td>0.50 (0.14 to 1.73)</td>
<td>67</td>
<td>1.17 (0.72 to 1.90)</td>
</tr>
<tr>
<td>TCRS/PRS combined</td>
<td>129</td>
<td><strong>0.69 (0.49 to 0.98)</strong></td>
<td>39</td>
<td><strong>0.20 (0.05 to 0.84)</strong></td>
<td>90</td>
<td>1.02 (0.66 to 1.53)</td>
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</table>

<table>
<thead>
<tr>
<th>Model 2†</th>
<th>No. of Events</th>
<th>All Women</th>
<th>No. of Events</th>
<th>Women &lt; 50 years</th>
<th>No. of Events</th>
<th>Women ≥ 50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCRS</td>
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<td>0.74 (0.53 to 1.06)</td>
<td>69</td>
<td>0.98 (0.44 to 2.20)</td>
<td>95</td>
<td>0.82 (0.54 to 1.25)</td>
</tr>
<tr>
<td>PRS</td>
<td>145</td>
<td>0.90 (0.65 to 1.25)</td>
<td>38</td>
<td>0.66 (0.35 to 1.25)</td>
<td>107</td>
<td>0.99 (0.68 to 1.45)</td>
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<tr>
<td>MD</td>
<td>85</td>
<td>1.10 (0.68 to 1.76)</td>
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<td>0.47 (0.13 to 1.64)</td>
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<td>1.22 (0.74 to 2.02)</td>
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<td>TCRS/PRS combined</td>
<td>129</td>
<td>0.80 (0.56 to 1.15)</td>
<td>39</td>
<td><strong>0.23 (0.06 to 0.98)</strong></td>
<td>90</td>
<td>1.01 (0.66 to 1.53)</td>
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<table>
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<th>Model 3‡</th>
<th>No. of Events</th>
<th>All Women</th>
<th>No. of Events</th>
<th>Women &lt; 50 years</th>
<th>No. of Events</th>
<th>Women ≥ 50 years</th>
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<tr>
<td>TCRS</td>
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<td>0.73 (0.51 to 1.04)</td>
<td>69</td>
<td>1.10 (0.48 to 2.49)</td>
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<td>PRS</td>
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<td>38</td>
<td>0.66 (0.35 to 1.26)</td>
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<tr>
<td>MD</td>
<td>85</td>
<td>1.04 (0.64 to 1.69)</td>
<td>18</td>
<td>0.44 (0.12 to 1.65)</td>
<td>67</td>
<td>1.15 (0.69 to 1.91)</td>
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<td>TCRS/PRS combined</td>
<td>129</td>
<td>0.81 (0.56 to 1.18)</td>
<td>39</td>
<td>0.26 (0.06 to 1.10)</td>
<td>90</td>
<td>0.93 (0.61 to 1.43)</td>
</tr>
</tbody>
</table>

**NOTE.** Values are No. of events or HR (95% CI). HRs are shown for overall analysis and stratified to old and young women. TCRS, PRS, and MD HRs represent women in the top quartile of the scores being compared with women in the lowest quartiles. For TCRS/PRS combined, HRs represent women above median of TCRS and PRS. Boldface type indicates associations significant at alpha = 0.05.

Abbreviations: HR, hazard ratio; MD, mammographic density; PRS, polygenic risk score; TCRS, Tyrer-Cuzick–predicted 10-year risk score.

*Adjusted for calendar period.
†Adjusted for calendar period and age (continuous).
‡Adjusted for calendar period, age (continuous), estrogen receptor status, lymph node involvement, and tumor size. For TCRS, also adjusted for grade.
women who could be offered prophylactic treatment with anti-
estrogens, such as tamoxifen.

Interestingly, associations with grade and lymph node status
remained within the strata of ER-positive cancers; thus, we
observed an effect beyond ER status. High-grade ER-positive
cancers are more often of the luminal B subtype, a type found
with younger age of onset, whereas low-grade ER-positive tumors
are commonly of the subtype luminal A.\textsuperscript{18} Given the over-
representation of luminal A breast cancers in most populations
in which the etiology has been studied, a bias among currently
known risk factors toward luminal A might explain the associa-
tions. The distribution of TCRS within molecular subtypes is of
great interest for addressing this hypothesis in future work.

The associations between the 77-SNP PRS and tumor
prognosticators are in agreement with the one previous study
addressing a similar question.\textsuperscript{19} In contrast to TCRS, the PRS
findings were independent of age. This would be expected with
genetic markers if they predict disease independent of age-of-onset
patterns. Beyond ER status, we also found an association with
tumor grade. This is not altogether surprising, because there is a
modest correlation between ER status and grade. When stratifying
our analysis by ER status, all associations with grade disappeared
within both strata (data not shown). The reason for the PRS bias
toward ER-positive tumors is likely because of the abundance of
ER-positive cancers in SNP discovery cohorts. Studies designed to
challenge this issue have identified SNPs associated with ER-
negative disease,\textsuperscript{20} and the ER-negative weighted PRS would be
an important tool to examine, in addition to the overall PRS, when
assessing individual risk. We found ER-negative weighted PRS to be
associated with ER-negative disease, thus showing potential as a
complement to the overall PRS score for identification of healthy
women at risk for aggressive disease.

Of the three risk prediction tools characterized in this study,
MD has been studied most thoroughly for associations with tumor
prognosticators. Our results are consistent with the outcome of a
meta-analysis on MD and ER status, showing null associations,\textsuperscript{21}
and the null associations with lymph node involvement and size,
after adjusting for age, are consistent with most other published
literature.\textsuperscript{22} In our study, we could not replicate the previous
finding of an association between MD and an increased risk of ER-
negative breast cancer in young women.\textsuperscript{23}

Both PRS and TCRS were associated with favorable tumor
prognosticators, and women scoring high in both tools may be
even more likely to have favorable disease outcomes, as judged by
effect sizes from combinatorial analysis. The survival analysis
supported these findings because women above the median in both
PRS and TCRS were at decreased risk of distant metastasis. Again,
the effects were constrained to women younger than age 50. In this
group, adjusting for standard prognosticators did not alter the
effect size substantially, although the statistical significance was
lost. Given that young patients are at highest risk of metastasis,\textsuperscript{24}
our results warrant further investigation in future studies. How-
ever, this is the first study of TCRS/PRS and survival, and this
part of our results should be interpreted with caution until
replication in independent cohorts can be performed. Our
survival analysis suggests that young women at risk for
aggressive disease may be classified as low-risk women by both
TCRS/PRS prediction tools.

Our study has limitations that should be discussed. The
survivor bias arising from including women alive in 2009 might
influence our findings. We performed sensitivity analysis, restricting
to women diagnosed between 2004 and 2008, but saw no consid-
erable changes to point estimates. Moreover, we had no information
of history of benign breast disease, one of the components of the
Tyrer-Cuzick model. Although we do not believe that such a history
is associated with any of the tumor characteristics under study, this
should be kept in mind when comparing with future studies. Family
history was restricted to first-degree relatives, which could under-
estimate the effects of family history on risk. However, because the
Tyrer-Cuzick shows a high-penetrance genetic risk, the model
should not be sensitive to the loss of information on distant relatives.
Finally, our results are representative of a homogenous Scandinavian
population and may not translate to other ethnic groups and
geographical regions.

The main strengths of this work lie in the high quality of the
Swedish health registers, combined with the availability of automated
MD estimates, questionnaire data, and genotype information for each
patient. We addressed our study question in a population-based cohort
of breast cancer patients with a large number of participants, thereby
generating high external validity. The regional cancer register provides
near-complete information on tumor prognosticators and good
follow-up for distant metastasis; moreover, the completeness of the
cause of death register ensures reliable censoring information, and the
reader-independent MD measurements limit any observer bias.

In conclusion, to our knowledge, we showed for the first time
that a high risk of breast cancer, based on TCRS and PRS, is
associated with favorable tumor prognosticators and a reduced risk
of being diagnosed with distant metastasis. PRS weighted on ER-
negative disease should be considered for identifying women at risk
for aggressive disease. Our results support the hypothesis that
breast cancer subtypes have different etiologies and highlight the
need to identify risk factors separately for distinct breast cancer
subtypes and ages of onset. Better knowledge of subtype-specific
risk factors and understanding of disease etiology may be vital for
the success of primary prevention and screening programs aimed
at lowering mortality.

Glossary Terms

**Cox proportional hazards regression model:** a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

**hazard ratios:** the ratio of the hazard rate in one group (eg, a group of treated patients) to the hazard rate in another group (eg, an untreated control group of patients). The hazard rate is the probability of a specified event, such as death or cancer recurrence, occurring during a short time interval. The hazard ratio, therefore, is a measure of the relative probability of an event occurring at any given point in time.

**logistic regression analysis:** a multivariable regression model in which the log of the odds of a time-fixed outcome event (eg, 30-day mortality) or other binary outcome is related to a linear equation.
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Association of Breast Cancer Risk Prediction Tools With Tumor Characteristics and Metastasis

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## Appendix

### Table A1. Binomial and Multinomial Logistic Regression of TCRS and TCRS5 Versus Tumor Prognosticators, Stratified by Age: ≤ 40, 41 to 50, 51 to 60, > 60 Modeled per 1-SD Increase

<table>
<thead>
<tr>
<th></th>
<th>Women ≤ 40 (n = 298)</th>
<th>Women 41 to 50 (n = 1,063)</th>
<th>Women 51 to 60 (n = 1,785)</th>
<th>Women &gt; 60 (n = 2,354)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ER positive</strong></td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td><strong>ER negative</strong></td>
<td>0.37 (0.15 to 0.86)</td>
<td>0.99 (0.67 to 1.43)</td>
<td>0.90 (0.75 to 1.07)</td>
<td>0.89 (0.74 to 1.05)</td>
</tr>
<tr>
<td><strong>Lymph node negative</strong></td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td><strong>Lymph node positive</strong></td>
<td>0.31 (0.10 to 0.81)</td>
<td>0.86 (0.62 to 1.11)</td>
<td>0.95 (0.77 to 1.12)</td>
<td>0.94 (0.78 to 1.10)</td>
</tr>
<tr>
<td><strong>Tumor &lt; 20 mm</strong></td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td><strong>Tumor 20 to 40 mm</strong></td>
<td>0.90 (0.42 to 1.91)</td>
<td>0.89 (0.73 to 1.10)</td>
<td>1.08 (0.97 to 1.21)</td>
<td>0.96 (0.86 to 1.07)</td>
</tr>
<tr>
<td><strong>Tumor &gt; 40 mm</strong></td>
<td>1.04 (0.33 to 3.27)</td>
<td>0.69 (0.39 to 1.23)</td>
<td>1.05 (0.84 to 1.32)</td>
<td>1.14 (0.97 to 1.33)</td>
</tr>
<tr>
<td><strong>Grade 1</strong></td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>0.61 (0.13 to 2.87)</td>
<td>1.18 (0.72 to 1.92)</td>
<td>1.29 (1.03 to 1.63)</td>
<td>1.10 (0.87 to 1.18)</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>0.70 (0.16 to 3.00)</td>
<td>1.35 (0.81 to 2.25)</td>
<td>1.00 (0.77 to 1.30)</td>
<td>0.89 (0.73 to 1.07)</td>
</tr>
</tbody>
</table>

**NOTE.** Values are OR (95% CI). Boldface type indicates associations significant at alpha = 0.05. Abbreviations: ER, estrogen receptor; OR, odds ratio; Ref, reference; SD, standard deviation; TCRS, Tyrer-Cuzick-predicted 10-year risk; TCRS5, Tyrer-Cuzick-predicted 5-year risk.

### Table A2. Binomial and Multinomial Logistic Regression of Each Tool Versus Tumor Prognosticators in Women Without Family History: TCRS, PRS, and MD Modeled per 1-SD Increase

<table>
<thead>
<tr>
<th></th>
<th>TCRS</th>
<th>PRS</th>
<th>MD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ER positive</strong></td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td><strong>ER negative</strong></td>
<td>0.71 (0.56 to 0.89)</td>
<td>0.77 (0.70 to 0.84)</td>
<td>0.92 (0.81 to 1.04)</td>
</tr>
<tr>
<td><strong>Lymph node negative</strong></td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td><strong>Lymph node positive</strong></td>
<td>0.43 (0.33 to 0.56)</td>
<td>1.01 (0.91 to 1.13)</td>
<td>1.07 (0.93 to 1.24)</td>
</tr>
<tr>
<td><strong>Tumor &lt; 20 mm</strong></td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td><strong>Tumor 20 to 40 mm</strong></td>
<td>0.96 (0.87 to 1.07)</td>
<td>0.95 (0.88 to 1.03)</td>
<td>1.07 (0.97 to 1.18)</td>
</tr>
<tr>
<td><strong>Tumor &gt; 40 mm</strong></td>
<td>0.70 (0.48 to 0.99)</td>
<td>0.82 (0.70 to 0.95)</td>
<td>0.95 (0.77 to 1.18)</td>
</tr>
<tr>
<td><strong>Grade 1</strong></td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>1.01 (0.81 to 1.27)</td>
<td>1.03 (0.93 to 1.15)</td>
<td>0.98 (0.85 to 1.13)</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>0.43 (0.33 to 0.59)</td>
<td>0.85 (0.76 to 0.96)</td>
<td>0.89 (0.75 to 1.05)</td>
</tr>
</tbody>
</table>

**NOTE.** Values are OR (95% CI). MD is adjusted for age. Boldface type indicates associations significant at alpha = 0.05. Abbreviations: ER, estrogen receptor; MD, mammographic density; OR, odds ratio; PRS, polygenic risk score; Ref, reference; SD, standard deviation; TCRS, Tyrer-Cuzick predicted 10-year risk; TCRS5, Tyrer-Cuzick predicted 5-year risk.