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The 21-Gene Recurrence Score in Special Histologic Subtypes of Breast Cancer

A Population-Based Study

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Context. — Recurrence score (RS) testing was developed and validated in invasive ductal and rare lobular carcinomas, although it is used for all special types of breast cancers.

Objective. — To determine association of histologic type (HT) and RS, specifically high-risk RS.

Design. — We used RSs linked to Surveillance, Epidemiology, and End Results program registries of invasive breast cancers diagnosed in 2004 through 2015. Multivariable logistic regression was used to evaluate association between HT and high-risk RS. Relationships between HT and low-, intermediate-, and high-risk RS were compared with χ² test. Kaplan-Meier curves were compared using log-rank test.

Results. — A total of 110,318 patients had RS testing. Of these, 23,220 (21%) had low, 70,822 (64.2%) intermediate, and 16,276 (14.8%) high RS. Histologic types were 80,476 (73%) ductal, 12,713 (11.5%) lobular, 12,449 (11.3%) mixed, 2,151 (2%) mucinous, 610 (0.6%) tubular, 382 (0.4%) micropapillary, 365 (0.3%) salivary, 208 (0.2%) papillary, 49 (0.04%) medullary, 26 (0.02%) metaplastic, 26 (0.02%) neuroendocrine, and 863 (0.8%) unknown. The distribution of low-, intermediate-, and high-risk RS was significantly different among HTs. Higher percentages of high-risk RS were identified in patients with ductal, medullary, and metaplastic types (P < .001). The odds of having high-risk RS were lower for some HTs, including micropapillary, after multivariable adjustment (P < .05). The low number of estrogen receptor–positive medullary and metaplastic carcinomas tested had higher odds of having high-risk RS. In T1 and T2 tumors, when ductal, lobular, mixed, and other types combined were compared, the mortality was different.

Conclusions. — This population-based study of RS in HTs showed high-risk RSs are identified in traditionally good prognostic subtypes. Micropapillary carcinoma has lower odds of high-risk RS even after multivariable adjustment.

Oncotype Dx Breast Recurrence Score (Genomic Health Inc, Redwood City, California; currently Exact Sciences, Madison, Wisconsin), is a 21-gene RT-PCR assay and recurrence score (RS) algorithm that quantifies the likelihood of distant recurrence in patients with estrogen receptor (ER)–positive breast cancer. Among women with early-stage ER-positive breast cancer, the RS is used to determine which patients are more likely to benefit from adjuvant chemotherapy.1 In the Trial Assigning Individualized Options for Treatment (TAILORx),2 3 risk groups were defined as low (RS <11), intermediate (RS 11–25), and high (RS >25). The TAILORx trial showed that chemoendocrine therapy had similar efficacy to endocrine therapy alone in women with intermediate risk (RS 11–25), although some benefit of chemotherapy was found in intermediate-risk women 50 years of age or younger.3,4 Although the data for the RS testing were derived from the analysis of invasive ductal carcinoma, no special type, and a small proportion of lobular cancers, RS testing is used for all special types of breast cancers. Histologic types have not typically been included in the clinical trials of RS. The purpose of this study is to determine association of histologic types and RS, specifically high-risk RS—the group that would need systemic therapy—and histologic type as predictor of breast cancer specific death.

MATERIALS AND METHODS

Data Set and Subjects

We used 21-gene assay results from Genomic Health’s clinical laboratory (2004–2015) linked to the National Cancer Institute’s Surveillance Epidemiology and End Results Program (SEER) registries of breast cancer cases diagnosed from 2004 through 2015, the most recent linked data available in SEER at the time of the start of this study, released in April 2020 based on November 2019 submissions by 18 registries. It is estimated that more than

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Table 1. Breast Cancer Histologic Type Groups

| Group | ICD-O-3 Code |
|-------|-------------|
| Ductal |             |
| Invasive ductal carcinoma, NOS | 8500 |
| Infiltrating ductal carcinoma | 8521 |
| Paget disease and infiltrating ductal carcinoma | 8541 |
| Lobular |             |
| Lobular carcinoma, NOS | 8520 |
| Mixed |             |
| Infiltrating duct and lobular carcinoma | 8522 |
| Adenocarcinoma with mixed subtypes | 8255 |
| Mixed cell adenocarcinoma | 8323 |
| Infiltrating duct mixed with other types of carcinoma | 8523 |
| Infiltrating lobular mixed with other types of carcinoma | 8524 |
| Micropapillary |             |
| Ductal carcinoma, micropapillary | 8507 |
| Salivary gland and rare types |             |
| Malignant tumor, giant cell type | 8003 |
| Malignant tumor, clear cell type | 8005 |
| Lymphoepithelial carcinoma | 8082 |
| Clear cell adenocarcinoma, NOS | 8310 |
| Glycogen-rich carcinoma | 8315 |
| Apocrine adenocarcinoma | 8401 |
| Intraductal papillary-mucinous carcinoma, invasive | 8453 |
| Secretory carcinoma | 8502 |
| Epithelial myoepithelial carcinoma | 8562 |
| Adenoid cystic carcinoma | 8200 |
| Cribriform carcinoma | 8201 |
| Polymorphous adenocarcinoma | 8525 |
| Carcinoma with osteoclast-like giant cells | 8035 |
| Papillary |             |
| Papillary carcinoma, NOS | 8050 |
| Papillary squamous cell carcinoma | 8052 |
| Papillary adenocarcinoma, NOS | 8260 |
| Papillary microcarcinoma | 8341 |
| Medullary |             |
| Medullary carcinoma | 8510 |
| Atypical medullary carcinoma | 8513 |
| Metaplastic |             |
| Spindle cell carcinoma | 8032 |
| Pseudosarcomatous carcinoma | 8033 |
| Squamous cell carcinoma | 8070 |
| Adenocarcinoma with squamous metaplasia | 8570 |
| Metaplastic carcinoma | 8575 |
| Carcinosarcoma | 8980 |
| Adenosquamous carcinoma | 8560 |
| Neuroendocrine |             |
| Large cell neuroendocrine carcinoma | 8013 |
| Small cell carcinoma | 8041 |

Table 1. Continued

| Group | ICD-O-3 Code |
|-------|-------------|
| Combined small cell carcinoma | 8045 |
| Carcinoid tumor | 8240 |
| Neuroendocrine carcinoma, NOS | 8246 |
| Atypical carcinoid | 8249 |
| Unknown |             |
| Neoplasm, malignant | 8000 |
| Carcinoma, NOS | 8010 |
| Pleomorphic carcinoma | 8022 |
| Adenocarcinoma, NOS | 8140 |
| Scirrhous carcinoma | 8141 |
| Solid carcinoma | 8230 |
| Adenocarcinoma with neuroendocrine features | 8574 |
| Inflammatory carcinoma | 8530 |
| Intraductal papillary adenocarcinoma with invasion | 8503 |
| Paget disease (T > Tis) | 8540 |
| Encapsulated papillary carcinoma (T > Tis) | 8343 |
| Intracystic carcinoma (T > Tis) | 8504 |

Abbreviations: ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results.

*The presence of invasive carcinoma was confirmed by tumor size (T) greater than in situ (Tis) both in the American Joint Committee on Cancer (AJCC) variable and in the Collaborative Stage (CS) variable in SEER data, which are quality controlled by SEER coders.

93% of results from Oncotype DX for cases residing in SEER regions are linked to a registry case. Demographic and clinicopathologic information as well as survival for each case were obtained from the SEER data. Eligible cases were those with ER-positive breast cancer (International Classification of Diseases for Oncology, 3rd edition codes C50.0–C50.9; SEER recode 26000) diagnosis according to SEER variables. Patients younger than 18 years, men with breast cancer, and those with stage 4 disease were excluded. Cases with missing data (such as histologic type) were also excluded. Although RS testing was done in a relatively low number of patients with stage 0/Tis, T4, HER2-positive cases (Table 1), these were not included in further analyses. The study protocol was determined to have exempt status by the University of Utah Institutional Review Board (Salt Lake City). Patients were stratified into low-risk (RS <11), intermediate-risk (RS 11–25), and high-risk (RS >25) subgroups according to TAILORx trial cutoffs. Variables and Histologic Subgroups

We extracted patient age at the time of diagnosis, tumor grade, progesterone receptor (PR) status, HER2 status, tumor size, lymph node status, stage, 21-gene RS, chemotherapy, breast cancer–specific death, and histologic subtype of tumors. International Classification of Diseases for Oncology 3rd edition codes were used to group carcinomas (Table 1).

Statistical Analysis

We used multivariable logistic regression to evaluate associations between histologic types and high-risk RS. Relationships between histologic type and low-, intermediate-, and high-risk RS were compared with \( \chi^2 \) test, rather than a regression model, as this was just a secondary, descriptive analysis, where showing the observed percentages, rather than adjusted percentages, was thought to be informative. Kaplan-Meier curves were plotted and compared using log-rank test. \( P \) values of <.05 were considered statistically significant. Statistical analyses were completed using Stata software, version 16.0 (StataCorp, College Station, Texas).
RESULTS

Patient Characteristics

A total of 110,318 women were identified in SEER registries diagnosed between 2004 and 2015 who had RS testing and were 18 years of age or older at the time of diagnoses. Their characteristics are listed in Table 2. The most common histologic type was invasive ductal carcinoma (80,476; 72.95%). A small number of carcinomas with medullary features, metaplastic carcinomas, and neuroendocrine carcinomas were also hormone receptor–positive and had RS testing (Table 1). The majority of the patients tested for RS had tumors less than 2 cm (T1) and negative axillary lymph nodes (N0) and were HER2 negative. HER2 status was reliably collected only after 2010 in the SEER database (Table 2). Close to 15% (16,276 of 110,318) of patients had high-risk RS.

Association of Histologic Tumor Type With RS

The distribution of low-, intermediate-, and high-risk RS was significantly different among histologic types and when each histologic type was compared with all others ($P < .001$) (Figure 1). Significantly higher percentages of high-risk RS were identified in patients with ductal, medullary, and metaplastic types when compared with other histologic subtypes ($P < .001$). One medullary carcinoma that was low-risk RS was from a woman 50 years of age or older with a grade 3 tumor and negative lymph nodes (N0). Both of the low-risk RS metaplastic carcinomas were from women age 50 years or older; one each was grade 1 and grade 2, and one had N0 and the other N1 lymph node status.

Lobular, tubular, mucinous, and papillary types were significantly less likely to have high-risk RS compared with other types.

Association of Histologic Tumor Type With High-Risk RS

The TAILORx trial showed that chemoendocrine therapy has similar efficacy to endocrine therapy alone in women with intermediate-risk (RS 11–25) breast cancer, with no benefit in women older than 50 years and only some benefit of chemotherapy in women younger than 50 years. Therefore, we investigated if histologic tumor types are predictive of high-risk RS, the only RS subgroup that will require systemic chemotherapy in most if not all women. The odds of having high-risk RS were lower for lobular, mixed, mucinous, tubular, and micropapillary types compared with ductal type when all patients over 18 years of age were considered (all $P < .05$). This difference persisted after multivariable adjustment for clinicopathologic characteristics (age, grade, PR status, tumor size, and lymph node status) (Table 3). A similar difference was seen among women 50 years and older (Table 3). The low number of ER-positive medullary and metaplastic carcinomas that were tested had higher odds of having high-risk RS compared with ductal type carcinoma (Table 3). Of the 984 high-risk RS lobular carcinomas, 887 (90.1%) were from women 50 years of age or older, 173 (17.6%) were grade 1, 593 (60.3%) grade 2, 140 (14.2%) grade 3, 78 (7.9%) unknown grade, 819 (85.5%) N0, 121 (12.3%) N1, 9 (0.9%) N2, 5 (0.5%) N3, and 8 (0.8%) unknown lymph node status. Of the 22 high-risk RS tubular carcinomas, 18 (81.8%) were from women 50 years of age or older, 17 (77.3%) were grade 1, 2 (9.1%) grade 2, 1 (4.5%) grade 3, 2 (9.1%) unknown grade, 21 (95.5%) N0, and 1 (4.5%) N1. Of the 170 high-

Table 2. Characteristics of Patients Who Underwent Recurrence Score (RS) Testing

| Characteristic                      | No.  | %    |
|------------------------------------|------|------|
|                                    | (n = 110,318) |      |
| Histologic type                    |      |      |
| Ductal                             | 80,476 | 72.95 |
| Lobular                            | 12,713 | 11.52 |
| Mixed                              | 12,449 | 11.28 |
| Mucinous                           | 2,151  | 1.95  |
| Unknown                            | 863    | 0.78  |
| Tubular                            | 610    | 0.55  |
| Micropapillary                     | 382    | 0.35  |
| Salivary gland and rare types      | 365    | 0.33  |
| Papillary                          | 208    | 0.19  |
| Medullary                          | 49     | 0.04  |
| Metaplastic                        | 26     | 0.02  |
| Neuroendocrine                     | 26     | 0.02  |
| Progesterone receptor status       |      |      |
| Positive                           | 97,798 | 88.65 |
| Negative                           | 10,295 | 9.33  |
| Unknown                            | 2,225  | 2.02  |
| HER2 status*                      |      |      |
| Positive                           | 1,546  | 1.4   |
| Borderline                         | 1,698  | 1.54  |
| Negative                           | 75,293 | 68.25 |
| Unknown                            | 1,857  | 1.68  |
| Cases before 2010*                 | 29,924 | 27.13 |
| Grade                              |      |      |
| I                                  | 30,672 | 27.8  |
| II                                 | 58,721 | 53.23 |
| III                                | 17,796 | 16.13 |
| Unknown                            | 3,129  | 2.84  |
| Tumor size                         |      |      |
| Tis                                | 7      | 0.01  |
| T1 (<2 cm)                         | 81,110 | 73.52 |
| T2 (2–5 cm)                        | 25,820 | 23.41 |
| T3 (>5 cm)                         | 1,822  | 1.65  |
| T4                                 | 267    | 0.24  |
| Unknown                            | 1,292  | 1.17  |
| Lymph nodes                        |      |      |
| N0                                 | 94,047 | 82.25 |
| N1                                 | 14,842 | 13.45 |
| N2                                 | 538    | 0.49  |
| N3                                 | 174    | 0.16  |
| Unknown                            | 717    | 0.65  |
| TAILORx RS risk group              |      |      |
| Low (<11)                          | 23,220 | 21.05 |
| Intermediate (11–25)               | 70,822 | 64.2  |
| High (RS >25)                      | 16,276 | 14.75 |
| Chemotherapy                       |      |      |
| No/unknown                         | 86,463 | 78.38 |
| Yes                                | 23,855 | 21.62 |

Abbreviation: TAILORx, Trial Assigning Individualized Options for Treatment.

* HER2 status was reliably collected in Surveillance, Epidemiology, and End Results registries only after 2010.
risk RS mucinous carcinomas, 119 (70%) were from women 50 years of age or older, 61 (35.9%) were grade 1, 77 (45.3%) grade 2, 19 (11.2%) grade 3, 13 (7.6%) unknown grade, 159 (93.5%) N0, and 11 (6.5%) N1. Of the 16 high-risk RS papillary carcinomas, 11 (68.8%) were from women 50 years of age or older, 2 (12.5%) were grade 1, 9 (56.3%) grade 2, 5 (31.3%) grade 3, 14 (87.5%) N0, and 11 (6.5%) N1.

Survival
Kaplan-Meier curves for breast cancer–specific death are shown in Figures 2 and 3. Because most of the women in this cohort who were tested for RS did not have adverse prognostic factors such as ER-negative, HER2-positive, or advanced cancer, the number of events (breast cancer–specific deaths) was very low or zero for some groups in the relatively short follow-up period. Therefore, these histologic

Table 3. Odds Ratios (ORs) for High-Risk Recurrence Score (RS) Among All Women and Women 50 Years of Age or Older Diagnosed With Breast Cancer in 2004–2015 Who Had RS Testing by Histologic Types, Surveillance, Epidemiology, and End Results Registriesa

| Histologic Type                     | All Ages | 50 Years and Older |
|------------------------------------|----------|--------------------|
|                                    | No.  | %  | OR  | CI  | P  | No.  | %  | OR  | CI  | P  |
| Ductal                             | 7836  | 73.44 | 0.47 | 0.43 | 0.50 | 60  | 72.57 | Reference |
| Lobular                            | 12528 | 11.66 | 0.63 | 0.59 | 0.68 | .001 | 10358 | 12.46 | 0.45 | 0.45 | 0.50 | .001 |
| Mixed                              | 12255 | 11.4 | 0.55 | 0.48 | 0.64 | .001 | 9861 | 11.56 | 0.55 | 0.55 | 0.65 | .001 |
| Mucinous                           | 2117  | 0.56 | 0.61 | 0.39 | 0.97 | .04 | 1610 | 1.93 | 0.60 | 0.60 | 0.91 | .01 |
| Micropapillary                     | 607   | 0.51 | 0.71 | 0.58 | 0.96 | .03 | 312  | 0.42 | 0.42 | 0.85 | .004 |
| Salivary gland and rare types      | 378   | 0.35 | 0.76 | 0.51 | 1.11 | .15 | 244  | 0.29 | 0.49 | 0.49 | 1.22 | .27 |
| Papillary                          | 204   | 0.19 | 0.67 | 0.39 | 1.17 | .13 | 174  | 0.21 | 0.26 | 0.26 | 0.96 | .04 |
| Medullary                          | 48    | 0.04 | 9.65 | 3.77 | 24.73 | <.001 | 34  | 0.04 | 2.64 | 2.64 | 20.75 | <.001 |
| Metaplastic                        | 26    | 0.02 | 7.34 | 2.55 | 21.15 | <.001 | 20  | 0.02 | 1.63 | 1.63 | 14.73 | .01 |
| Neuroendocrine                     | 25    | 0.02 | 0.70 | 0.23 | 2.17 | .46 | 21  | 0.03 | 0.06 | 0.06 | 1.47 | .14 |
| Total                              | 107480 | 100 | 83136 | 100 |

a Bold text designates statistical significance.

*P from a multivariate logistic regression, adjusted for grade, progesterone receptor status, tumor size, lymph node status, and age.
groups were combined under “other.” In patients with both 2 cm or smaller (T1) and larger than 2 cm (T2) tumors the mortality was significantly different \( P < .01 \) among the 4 groups. There was no difference in breast cancer–specific mortality among the histologic groups in patients with negative lymph nodes (N0) or with 3 or fewer positive lymph nodes (N1), although \( P \) value approached statistical significance \( (P = .053) \) for the lymph node–negative group (Figure 2, A through D). When breast cancer–specific mortality was compared in women with low-, intermediate-, and high-risk RS, there were no significant differences among ductal, lobular, mixed, and “other” histologic types in low- or high-risk RS groups (Figure 3, A through C).

A Cox proportional hazards model showed no significant association between histologic type and breast cancer–specific death after adjusting for clinicopathologic variables including age, tumor size, lymph node status, PR status, and chemotherapy, although there were no (medullary and metaplastic) or a low number of deaths (micropapillary) in some histologic groups, precluding hazard ratio estimates in these groups (data not shown).

### DISCUSSION

Invasive ductal carcinoma constituted close to 73% of invasive carcinomas tested for RS in women with ER-positive breast cancer. Some histologic types are rare and/or are ER negative a majority of the time, resulting in relatively lower numbers tested for RS even in a large registry such as SEER. Recurrence score testing is recommended for patients with ER-positive, HER2-negative breast cancer.\(^6\) Although excluded in this study, occasionally HER2-positive cases are also tested for RS.\(^7\)

There was significant association between histologic types and RS risk groups. Medullary, metaplastic, and ductal types were more likely to have high-risk RSs when compared with all other histologic types. When adjusted for tumor size, lymph node status, grade, patient age, and PR status, medullary and metaplastic types had higher odds of having high-risk RSs compared with the reference, ductal-type carcinoma. Mucinous, tubular, mixed, and micropapillary carcinomas had lower odds of having high-risk RSs. All histologic types, including special types with favorable prognosis that were previously reported by some groups to have exclusively low- or intermediate-risk RSs, \(^8,9\) Eight percent of mucinous carcinomas in SEER had high-risk RSs, similar to the 8.6% reported by Wang et al\(^10\) and higher than what was reported by Ding et al\(^11\) both of which studies used the traditional cutoff for high-risk RS (RS >30). In the 4th edition of the World Health Organization (WHO) classification of breast cancer.
tumors, carcinomas with prominent lymphoplasmacytic infiltrate—medullary carcinoma, atypical medullary carcinoma, and invasive carcinomas of no special type with medullary features—were grouped in the category of carcinomas with medullary features. In the 5th edition, these were included with basal-like and medullary in a combined morphologic subset under the category of invasive carcinoma of no special type. In this cohort, from 2015 and before, medullary and atypical medullary carcinoma diagnoses constituted a small percentage of cases tested for RS. Less than 10% of medullary cancers are ER positive. Because many of the 16 nonreference genes (MKI67, CCNB1, MYBL2, BIRC5, ALK1A) in RS testing are proliferation related, it is not surprising that medullary carcinomas with high mitotic index will have high-risk RS (even after adjusting for grade). Metaplastic carcinomas are a heterogeneous group of tumors, even at the histologic level, with low ER positivity rates. When positive, medullary and metaplastic carcinomas may have lower ER positivity, contributing to higher RS. Although pure micropapillary carcinomas are rare, accounting for 1% to 2% of all invasive breast cancers with high propensity for lymphovascular invasion and lymph node metastasis, recent studies, including a meta-analysis, showed a similar or even favorable overall survival compared with ductal carcinoma in adjusted models. Excluding about 10% of those hormone receptor-negative cases, which were shown to be associated with poor outcome, ER-positive micropapillary carcinomas are less likely to have high-risk RS. In this study micropapillary carcinomas had a similar proportion of high-risk RS compared with ductal carcinomas after adjusting for multiple factors, including lymph node status. However, they were more likely to have low-risk RSs compared with many other histologic subtypes, including ductal and lobular carcinomas.

Defining phenotypes based on morphology by grading and assigning a histologic type have been the standards of pathology reports for a very long time. It was known that some histologic types were associated with better outcome mainly because they were less likely to be associated with axillary lymph node metastasis. Introduction of microarray-based expression profiling studies brought the heterogeneity of the cancers to the forefront. Apart from invasive lobular carcinomas, special types of carcinomas were mostly excluded in original high-throughput microarray-based expression profiling studies. Weigelt et al included 113 special types of breast cancer in microarray-based analysis to show that most special types of cancers are more homogeneous than invasive ductal carcinomas of no special type and consistently fall into one of the molecular subgroups (such as luminal, HER2, basal-like). There were 2 exceptions: lobular cancers, which, when pleomorphic and expressing HER2, did separate out from the common luminal type lobular cancers, and apocrine cancers, which failed to form a separate cluster. The RS has low discriminatory power for ER-negative tumors and is validated for ER-positive carcinomas. Although follow-up information was not available, Weigelt et al also did RS and 70-gene signature (MammaPrint) testing in specialized types of breast cancer. Recurrence score testing showed that 17 of 22 lobular (77%), 10 of 10 medullary (100%), 20 of 20 metaplastic (100%), 4 of 8 micropapillary (50%), 7 of 19 mucinous (37%), and 6 of 10 neuroendocrine carcinomas (60%) were high risk. The proportion of high-risk RSs within each special histologic subtype was much higher compared with this study, mainly because either a smaller proportion or none of the special types included were ER positive (18 of 22 [82%] lobular, 0 of 10 [0%] medullary, 0 of 20 [0%] metaplastic, 8 of 8 [100%] micropapillary, 18 of 19...
[94.7%] mucinous, and 9 of 9 [100%] neuroendocrine carcinomas were ER positive).24

Many special types of breast cancer have very good prognosis, although some patients will develop regional and distant recurrences. Laenkholm et al,25 using a different test, demonstrated that Prosigna-PAM50’s risk of RS added significant information for distant recurrence in postmenopausal patients with special subtypes with either larger than 2-cm tumor size or 1 to 3 positive nodes. In this study, the follow-up can be considered short for hormone receptor–positive breast cancer, and there was very little or no breast cancer–specific mortality in some groups. In the lymph node–negative group, breast cancer–specific mortality approached significance; however, there was no difference in mortality in lymph node–negative or –positive (1–3 lymph node) groups. There was no significant difference in breast cancer–specific mortality within low- and high-risk RS groups when ductal, lobular, mixed, and all other histologic subtypes together were compared. We did not compare mortality of all 11 histologic types because there were no breast cancer–related deaths in 2 (medullary and metaplastic) and fewer than 5 deaths in 5 (micropapillary, neuroendocrine, papillary, salivary and rare, tubular) histologic types even in this large, registry-based study (data not shown).

Research on RSs of special types of breast cancer has been limited and addressed in only small studies until now. Although this is a retrospective, registry-based study without an independent pathology review to confirm the specific histologic type and grade, it is the largest population-based study of RSs in histologic types that showed high-risk RSs identified in traditionally good prognostic subtypes. Some special subtypes, including micropapillary carcinoma, have lower odds of high-risk RS even after adjusting for grade, PR status, tumor size, lymph node status, and age.

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