



# Relationship of pathological features and a 21 gene expression assay in younger versus older women with node-negative endocrine receptor-positive breast cancer

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## Abstract

**Purpose** Determining the need for adjuvant chemotherapy in estrogen receptor (ER)+ disease can be influenced by pathological characteristics and gene expression assays [i.e., Oncotype Dx recurrence scores (RSs)]. The primary objective of this study is to investigate the relationship between the RSs and pathological markers in younger (<50) versus older (≥50) women with early-stage node-negative ER+ breast cancer.

**Methods** This was a single academic-center retrospective cohort study. Subjects who underwent Oncotype gene expression testing were retrospectively and sequentially identified. 436 Subjects were identified of which 344 were eligible for analysis (133 younger subjects < 50 years of age, and 211 older subjects ≥ 50 years). Pathological data assessed included the progesterone receptor (PR), histological grade (grade), Ki-67, and P53. A multivariable regression analysis was performed using age, PR, and grade as predictor variables for RS. Adjusted  $R^2$  was determined. To investigate the primary objective, subjects were stratified based on age, PR, and grade status in that sequence. Within each tumor subtype as determined by PR and grade statuses, the RSs in the younger versus older age group were compared using Student's  $t$ -test and the differences in the 95% confidence interval limits in RS means calculated. Age influence on adjuvant chemotherapy recommendation was also assessed by stratifying subjects based on age (<50 vs. ≥50) and then by RS risk group (≤10, 11–25, ≥26). Subsequently, the proportions of younger versus older subjects within identical RS risk groups who were explicitly advised by their oncologist to proceed with chemotherapy as documented in their electronic health records were compared using  $\chi^2$  test.

**Results** Based on the multivariable regression analysis, the adjusted  $R^2$  was 0.229232 and RS was found to be independent of age ( $p=0.7169$ ). Between younger and older subjects with tumors with similar PR and grade pathological features, the differences in the RS were insignificant ( $p>0.05$ ). Chemotherapy was recommended in younger versus older women, in 0% when the RS was ≤10, 39% and 40% when the RS was 11–25 ( $p=0.82$ ), and 100% and 98% when the RS was ≥26 ( $p=0.51$ ), respectively.

**Conclusions** The relationship between pathological features and RS is consistent irrespective of age; therefore, models predicting RS may be applicable irrespective of age.

**Keywords** Oncotype Dx · Adjuvant chemotherapy · Hormone-positive breast cancer · Young women with breast cancer

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## Introduction

Breast cancer is the leading cause of cancer death in women worldwide, and in the US breast cancer is the most common non-dermatologic cancer in women [1, 2]. Due to early screening and self-examination, the majority of patients in the US and other developed countries present with early-stage disease [3, 4]. However, determining the benefit from adjuvant chemotherapy for patients with early-stage breast cancer can be complex without knowledge of tumor biology

and recurrence patterns. For patients with estrogen receptor (ER)+ and human epidermal growth factor receptor 2 neu (HER2)– lymph node-negative breast cancer, the Oncotype Dx recurrence score (ODx RS) may be used to assess the risk of recurrence and to determine whether patients may benefit from adjuvant chemotherapy [5].

ODx platform is a reverse-transcriptase-polymerase-chain-reaction-based assay that evaluates the expression of 5 reference genes and 16 cancer-related genes including ER, HER2, and Ki-67 [6]. A RS is generated which can be used to stratify ER+ node-negative patients with breast cancer into low ( $\leq 10$ ), intermediate (11–25), or high ( $\geq 26$ ) risk groups to help determine benefit from adjuvant chemotherapy. The Trial Assigning Individualized Options for Treatment (TAILORx) study has confirmed that participants with ER+ HER2– node-negative breast cancer and a low ODx RS ( $\leq 10$ ) have very low 5-year recurrence rates with endocrine therapy alone, and those with intermediate scores (11–25) may not benefit from adjuvant chemotherapy in addition to endocrine therapy [5, 7]. An exploratory analysis in women less than 50 years of age did suggest modest benefits in those with RSs 16–25. Notably, however, younger patients in studies investigating ODx RS are under-represented, which is of concern since younger women tend to have more aggressive disease and TAILORx data suggest possible benefit to chemotherapy at lower ODx RS (a RS of 16–25 may have benefit to chemotherapy in patients younger than 50) [8–14]. Indeed, only one-third of patients in the TAILORx study were under 50 years of age [ $n = 3054$ , (6665 over 50)].

The correlation between ODx RS and standard pathology has been described in numerous studies, and data suggest that ODx RS may be inferred by standard pathology; however, most patients in these studies are older and data regarding the relationship between standard pathology to ODx RS in younger women are limited [11, 15–20]. In this study, we investigate the relationship between the ODx RS and pathological markers between younger ( $< 50$ ) and older ( $\geq 50$ ) women with early-stage ER+ breast cancer.

## Methods

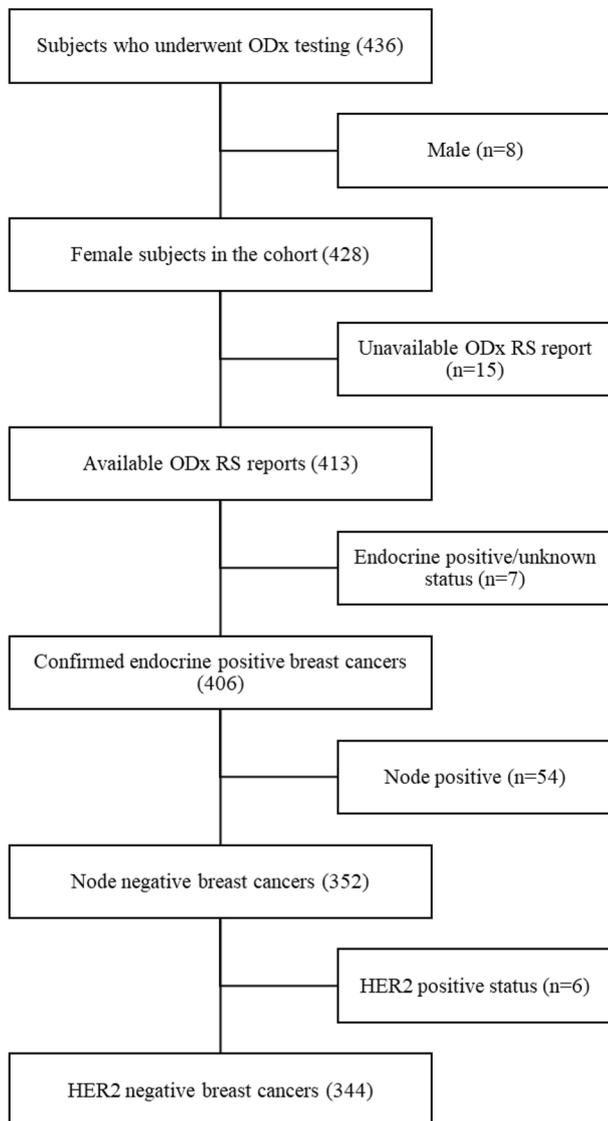
This was a single academic-center retrospective cohort study. After approval by the Northwestern Internal Review Board, we retrospectively and sequentially identified subjects who had undergone ODx testing ( $n = 436$ ) between January 2002 and December 2012. Clinical and pathological information on these subjects was extracted via the institutional electronic data warehouse and by chart reviewing. Specifically, we obtained ER, progesterone receptor (PR), Ki-67, HER2, P53, grade, and node statuses as well as sex, race, ethnicity, tumor size, breast surgery type, radiation,

and adjuvant chemotherapy administration information. We excluded men ( $n = 8$ ) as well as subjects with missing RS reports ( $n = 15$ ), subjects with unknown or ER+ breast cancers ( $n = 7$ ), subjects with positive nodes ( $n = 54$ ), and subjects with HER2+ tumors ( $n = 6$ ) in that sequence. 344 Women subjects with ER+ HER2– node-negative breast cancer and available ODx test reports were eligible for analysis. A multivariable regression analysis was performed using age, PR, and grade as predictor variables and RS as the dependent variable. Adjusted  $R^2$  was determined, and the relationship between RS and age was assessed. Histological grade was assessed per institutional standards, and PR, Ki-67, and P53 using standard immunohistochemistry (IHC) methods. Pathological markers from core biopsy specimens were assessed ( $n = 262$ ), but if unavailable, surgical specimen staining results were obtained ( $n = 82$ ). American Society of Clinical Oncology and College of American Physicians guidelines were used in determining the status of ER ( $\geq 1\%$  by IHC), PR ( $\geq 1\%$  by IHC), and HER2 (0 or +1 by IHC or if +2 a negative FISH test [HER2-to-CEP17 ratio  $< 2$  with HER2 copy number  $< 4$ ]) [21]. Institutional cutoffs were used for P53 (positive if  $\geq 10\%$ ) and Ki-67 (low  $\leq 10$ , intermediate 11–20, high  $\geq 21$ ).

To investigate the primary objective, subjects were stratified based on age, PR status, and grade status in that sequence. Within each tumor subtype as determined by PR and grade statuses, the RSs in the younger versus older age group were compared using Student's *t*-test and the differences in the 95% confidence interval (CI) limits in RS means calculated. Patterns in physician adjuvant chemotherapy recommendations were also assessed in younger versus older subjects within each ODx RS risk category (low  $\leq 10$ , intermediate 11–25, high  $\geq 26$ ) by chart review. Adjuvant chemotherapy was deemed recommended or not recommended if a physician explicitly noted on the subject's medical record that they had a conversation with the subject where they did or did not recommend adjuvant chemotherapy. In this study, physician chemotherapy recommendations do not reflect whether subjects received or did not receive chemotherapy. Subjects who did not have any clear chemotherapy recommendations from their oncologists ( $n = 24$ ) or subjects who were enrolled in clinical trials, i.e., received non-standard therapy ( $n = 8$ ) were excluded from the analysis of chemotherapy recommendation trends.

## Results

Between January 2002 and December 2012, 436 subjects who had undergone ODx testing in our institution were identified. Based on the criteria for inclusion and exclusion, 344 women subjects were eligible for analysis (Fig. 1). Among eligible subjects, 133 (39%) were classified as younger



**Fig. 1** Study flow chart showing step-wise exclusion algorithm based on eligibility

(age < 50) and 211 (61%) older (age  $\geq$  50). There was no difference in RS in the two age groups (17.9, SD 8.1 in the younger age group vs. 19.4, SD 9.7 in the older age group,  $p=0.13$ ). Additionally, upon multivariable regression analysis (where age, progesterone status, and histological grade were used as the predictor variables and RS as the dependent variable), the adjusted  $R^2$  was found to be 0.229232. Additionally, similar to the NSABP studies, RS was found to be independent of age ( $p=0.7169$ ). Both progesterone status and histological grade had a significant influence on RS ( $p<0.0001$  for both predictor variables). The distribution of subjects among the three ODx RS risk stratifications was similar in the two age groups ( $p=0.19$ ). However, there was a larger proportion of subjects in the younger age group

(age < 50) with PR+ breast cancer ( $p=0.007$ ), and younger patients tended to have smaller tumors than older subjects ( $p=0.002$ ). Despite there being no difference in surgical management between younger and older subjects ( $p=0.18$ ), there was a smaller proportion of younger subjects who received radiotherapy ( $p=0.02$ ). No significant differences were observed in other clinical and pathological features (Table 1).

Younger and older subjects were stratified in four groups based on PR and grade statuses (PR+ grade 1, PR+ grade 2/3, PR– grade 1, PR– grade 2/3). Between younger and older subjects with tumors with similar PR and grade pathological features, there were no significant differences in the 95% CI limits of RS means ( $p>0.05$ ; Table 2).

Patterns in physician chemotherapy recommendations within ODx RS risk groups (low  $\leq$  10, intermediate 11–25, high  $\geq$  26) were found to be similar in the two age groups (Table 3). Chemotherapy was not recommended in 100% of younger (age < 50,  $n=24/24$ ) and older (age  $\geq$  50,  $n=33/33$ ) subjects with low ODx RS (RS  $\leq$  10), while chemotherapy was recommended in 100% of younger subjects ( $n=18/18$ ) and 98% of older subjects ( $n=42/43$ ) who had high ODx RS (RS  $\geq$  26, OR 1.02 95% CI 0.47–2.23,  $p=0.51$ ). In the intermediate ODx RS risk group (RS 11–25), chemotherapy was recommended in 39% of younger subjects ( $n=29/75$ ) and 40% of older subjects ( $n=48/119$ ; OR 0.82 95% CI 0.56–1.65,  $p=0.82$ ).

## Discussion

In patients with ER+, HER2–, node-negative breast cancers, we demonstrate that RSs in younger subjects are comparable to those of older patients with similar tumor biology based on PR and grade statuses. We also demonstrate that breast cancers with pathological characteristics associated with inferior outcome (PR+ and grade 2/3) are associated with higher RS ( $p<0.05$ ) irrespective of age group. Chemotherapy recommendations were also found to be similar irrespective of age group at various ODx RS.

Given the high-level evidence that the ODx RS provides, a key question that arises as we translate these data into our clinical practice is which patients require the test to make a decision regarding adjuvant chemotherapy in ER+ node-negative breast cancer. While clinical factors such as eligibility for chemotherapy (which may be determined by age, performance status, comorbidities) are an important factor to consider, pathological factors can also provide data. Indeed, in the MINDACT study, which validated another gene expression panel, showed those patients with clinical low-risk disease, as defined by standard pathology and clinical stage, did not benefit from chemotherapy irrespective of their genomic risk; suggesting these patients may not require

**Table 1** Patient characteristics in overall cohort, and younger versus older cohorts

Characteristics	All patients <i>n</i> = 344	Younger <i>n</i> = 133	Older <i>n</i> = 211	<i>p</i> -values
<b>Age</b>				
Median (range)	53 (29–78)	45 (29–49)	60 (50–78)	< 0.001
<b>Race</b>				
Caucasian	240 (69.8)	84 (63.2)	156 (73.9)	0.45
Black/African American	28 (8.1)	10 (7.5)	18 (8.5)	
Asian and others	47 (13.7)	21 (15.8)	26 (12.3)	
<b>Ethnicity</b>				
Hispanic	21 (6.1)	7 (5.3)	14 (6.6)	0.74
Non-Hispanic	290 (84.3)	107(80.5)	183 (86.7)	
<b>ODx RS</b>				
Mean ( $\pm$ SD)	18.80 (9.1)	17.89 (8.1)	19.37 (9.7)	0.13
Median	18	17	18	
Range	0–59	3–48	0–59	
<b>ODx risk group</b>				
Low (0–10)	57 (16.6)	24 (18.0)	33 (15.6)	0.19
Intermediate (11–25)	224 (65.1)	91 (68.4)	133 (63.0)	
High (26–100)	63 (18.3)	18 (13.5)	45 (21.3)	
<b>Breast cancer histology</b>				
Invasive ductal carcinoma	264 (76.7)	110 (82.7)	154 (73.0)	0.06
Invasive lobular carcinoma	45 (13.1)	11 (8.3)	34 (16.1)	
Mixed	26 (7.6)	7 (5.3)	19 (9.0)	
Other	9 (2.6)	5 (3.8)	4 (1.9)	
<b>Tumor size</b>				
T1	242 (70.3)	108 (81.2)	134 (63.5)	0.002
T2	93 (27.0)	24 (18.0)	69 (32.7)	
T3	9 (2.6)	1 (0.8)	8 (3.8)	
<b>Breast cancer histological grades</b>				
1	90 (26.2)	41 (30.8)	49 (23.2)	0.29
2	208 (60.5)	76 (57.1)	132 (62.6)	
3	46 (13.4)	16 (12.0)	30 (14.2)	
<b>Ki-67 status</b>				
Low	52 (15.1)	20 (15.0)	32 (15.2)	0.53
Intermediate	16 (4.7)	8 (6.0)	8 (3.8)	
High	19 (5.5)	6 (4.5)	13 (6.2)	
<b>Progesterone receptor status</b>				
Positive	303 (88.1)	125 (94.0)	178 (84.4)	0.007
Negative	41 (11.9)	8 (6.0)	33 (15.6)	
<b>Type of breast surgery</b>				
Mastectomy	102 (29.7)	45 (33.8)	57 (27.0)	0.18
Partial mastectomy	242 (70.3)	88 (66.2)	154 (73.0)	
<b>Endocrine therapy</b>				
Adjuvant chemotherapy	314 (91.3)	123 (92.5)	191 (90.5)	0.75
Adjuvant chemotherapy	111 (32.3)	40 (30.1)	71 (33.6)	0.47
Radiation	217 (63.1)	74 (55.6)	143 (67.8)	0.02

genomic testing [22]. Furthermore, as aforementioned, the ODx RS is closely associated with standard pathological markers; and a recent study demonstrated that high ( $> 25$ ) and low ( $\leq 25$ ) ODx RS can be predicted using percent ER, PR, Ki-67, and Elston grade categories [15, 16]. Data from our study suggest that this may be applicable in younger

patients as well as older, since the relationship of tumor pathology with ODx RS is the same irrespective of age.

This study has numerous strengths and limitations which should be considered when interpreting these data. While younger breast cancer patients in our study made up a larger proportion (38.7%) relative to other studies, our study is

**Table 2** Comparing ODx scores between younger (age 29–49) and older (age 50–78) patients with similar pathological characteristics

Categories	Younger subjects (age < 50) <i>n</i> = 133	Older subjects (age ≥ 50) <i>n</i> = 211	Difference (95% CI)	<i>p</i> -values
	Mean RS (SD, <i>n</i> )	Mean RS (SD, <i>n</i> )		
PR+, grade 1	14.4 (5.0, 40)	14.3 (5.7, 40)	0.13 (– 0.27 to 2.51)	0.92
PR+, grade 2 or 3	18.3 (8.0, 85)	19.5 (9.6, 138)	– 1.16 (– 3.50 to 1.18)	0.33
PR–, grade 1	22.0 (n/a, 1)	18.67 (6.6, 9)	3.33 (– 12.7 to 19.4)	0.64
PR–, grade 2 or 3	32.0 (10, 7)	27.58 (10.7, 24)	4.42 (– 4.89 to 13.72)	0.34

PR progesterone, Grade histological grade

**Table 3** Patterns in chemotherapy recommendation in younger versus older patients

Oncotype RS	Age 29–49		Age 50–78		<i>p</i> -values (OR, 95% CI)
	Chemotherapy recommended	Chemotherapy not recommended	Chemotherapy recommended	Chemotherapy not recommended	
Low ODx RS (0–10)					
% (Number recommended/total number)	0 (0/24)	100 (24/24)	0 (0/33)	100 (33/33)	NA (0% vs. 0%)
Intermediate ODx RS (11–25)					
% (Number recommended/total number)	38.7 (29/75)	61.3 (46/75)	40.3 (48/119)	59.3 (71/119)	0.82 (0.96, 0.56–1.65)
High ODx RS (26–100)					
% (Number recommended/total number)	100 (18/18)	0 (0/18)	97.7 (42/43)	2.3 (1/43)	0.51 (1.02, 0.47–2.23)

smaller than other analyses and represents patients treated at a single institution. Determination of cancer clinico-pathological characteristics during the study period was performed by multiple pathologists; however, this may be in part be abrogated as this was a single academic institution study, with standardized protocols. Additionally, we only compared two age groups (age 29–49 vs. 50–78) in our analysis, and the extremes of age may not be fully assessed. While only less than 1% (3/344) of patients were ≥ 75 years old, another limitation of the analysis regarding chemotherapy recommendation is that we are unable to distinguish recommendations between elderly versus postmenopausal subjects. This study was designed with the new RS risk categories (low ≤ 10, intermediate 11–25, high ≥ 26) making our study findings ideal for comparison with future RS studies. This study aimed to test the correlation of RS with pathological factors in different age groups and not recurrence outcomes—which were not performed given a very modest recurrence rate (4.4%). As ODx has emerged as the most validated gene expression platform to predict benefit from chemotherapy, a remaining question is when it is necessary to order given its cost, and if we can predict the RS using standard pathology across various age groups. Future studies with larger cohorts will be required to further define this relationship.

Interestingly, despite RS being similar in the younger and older age groups, a larger proportion of younger subjects had smaller tumors ( $p = 0.002$ ) and PR+ breast cancer ( $p = 0.007$ ). Given this analysis only included subjects

with node-negative breast cancer, this may reflect providers' threshold for chemotherapy in larger PR– tumors in younger woman is lower and ODx RS may not have been felt necessary to come to this clinical decision. Indeed, while some studies have shown that younger patients are more likely to have a higher RS, we found a similar distribution of RS, which may reflect a biased cohort [11]. However, once RS is available, we demonstrate no significant differences in physician chemotherapy recommendation in younger versus older patients across all ODx RS risk groups in our institution.

In summary, this study demonstrates an association between RS and standard pathology independent of age. In the clinic, oncologists may have a lower threshold to recommend adjuvant chemotherapy for a younger patient; these results suggest that standard pathology may be relied on irrespective of age. While RS can provide us with a high level of evidence to make chemotherapy decisions, ordering the test should be done so when it may influence clinical decision, and in this light standard pathology should be considered.

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## Compliance with ethical standards

**Conflict of interest** Cesar A. Santa-Maria has received Research Grants from Medimmune, Pfizer, and Tesaro as well as served on an Advisory Board for Polyphor and Genomic Health. The rest of the authors declare that they have no conflict of interest.

**Ethical approval** Chart reviewing of existing electronic health records belonging to our human participants was in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Institutional Research Committee waived the requirement for obtaining informed consents from study participants as it is a retrospective study using existing but de-identified health records.

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