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_____	_____
Zhaoli Tang	Date

The Association Between Genomic Test Use and Chemotherapy Use Among Breast Cancer Patients

By

Zhaoli Tang
Master of Science in Public Health

Health Policy and Management

_____
Dr. David H. Howard
Committee Chair

_____
Dr. Joseph Lipscomb
Committee Member

_____
Dr. Silke von Esenwein
Committee Member

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By

Zhaoli Tang

Master of Clinical Medicine
Central South University
2017

Thesis Committee Chair: David H. Howard, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Public Health
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Abstract

The Association Between Genomic Test Use and Chemotherapy Use Among Breast Cancer Patients

By Zhaoli Tang

Importance: Chemotherapy is recommended and widely used in the treatment for estrogen receptor – positive invasive breast cancer at early stages. However, tumors with similar clinical and pathological profiles have distinct responsiveness to chemotherapy. Improper chemotherapy use can result in tremendous economic and health burdens. The association between the receipt Oncotype DX 21-gene recurrence score assay (RS test) test and the receipt of chemotherapy remains to be assessed since the recommendation of the RS test by guidelines.

Objective: To identify the association between the receipt of the RS test and the receipt of chemotherapy in a nationally representative sample of early-stage breast cancer patients.

Study design: Analytic retrospective cohort study of Medicare beneficiaries with a primary diagnosis of breast cancer between 2006 and 2014 using Surveillance, Epidemiology, and End Results data set - Medicare claims linked database.

Results: Among a total sample of 45,692 patients, 8,052 received chemotherapy and 37,640 did not receive chemotherapy. The multivariable analysis showed that there was no significant association between the receipt of the RS test and the receipt of chemotherapy (marginal effects (ME, -0.0008; standard error, 0.0044). Age and clinical staging had significant effects on the receipt of chemotherapy. The impact of the RS test was most significant among subsample aged 65-70 (ME, -0.02) and 76 and above (ME, 0.04). The use for both the RS test and chemotherapy have increased between 2006 and 2014.

Conclusion and contribution of this study: The receipt of the RS test reduced the probability of receiving chemotherapy, but the association was not significant. The use of RS test and chemotherapy increased between 2006 and 2014.

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CHAPTER 1: INTRODUCTION

Breast cancer (BC) is a condition caused by uncontrol growth of breast tissue cells [1]. Globally, breast cancer is the most frequently diagnosed cancer and is among the top causes of cancer-related death [2]. In 2017, the American Cancer Society estimated that there will be 266,120 new diagnoses of invasive BC and 40,920 new deaths in the United States [3]. In the United States, BC has the highest incidence rate (accounts for approximately 30% of new cancer diagnoses) in women and is the second cause of death following lung cancer [3]. From 2005 to 2014, the incidence of BC increased 0.4% percent annually on average [3] and incidence rates are higher in women aged 40 or above [4]. About half of all new cases occurs in women aged 65 or older, who are eligible for Medicare coverage [5]. National Comprehensive Cancer Network (NCCN) recommends chemotherapy in the treatment for estrogen receptor (ER) – positive, lymph node-negative BC at early-stages [6]. However, tumors with similar clinical and pathological profiles have distinct responsiveness to chemotherapy [7]. Improper treatment decisions would lead to the over-use of chemotherapy, which can result in undesired adverse effects and great expenditure from the treatment and drug-related adverse effects [8].

The Oncotype DX 21-gene recurrence score (RS) assay is now considered a standard-of-care to guide chemotherapy decisions for the estrogen-receptor positive, human epidermal growth factor 2 (HER2)-negative, node-negative BC patients [9]. However, only 20-30% of eligible BC cancer patients receive the RS test [10]. Evaluating the impact of adoption of the RS test on chemotherapy administration can help physicians and patients make more informed decisions for whether to use

the RS test as a guidance for chemotherapy treatment.

This study will use the nationally representative sample from Surveillance, Epidemiology, and End Results data set - Medicare claims linked database (SEER-Medicare database) between 2006 and 2014 to assess the impact of the RS test adoption on the change in chemotherapy administration.

Research objectives:

I. To identify the association between the receipt of the RS test and the receipt of chemotherapy.

II. To identify the most recent trend of adopting the RS test and chemotherapy use.

Research questionss:

I. Were patients who received the RS test less likely to receive chemotherapy?

II. Has the RS test use increased between 2006 and 2014?

This study will apply descriptive analysis and a multivariate regression model to examine the association between the adoption of the RS test and chemotherapy administration, controlling for confounders.

The concept framework is an innovative combination of Anderson's Behavioral Model of Health Services Use [11] and the Ottawa Model of Research Use [12]. Andersen's model addresses that to improve access to health care, the best approach is to focus on both contextual and individual factors[13]. The two levels are distinguished from each other in that the contextual factors consist of more aggregate measures compared to the individual factors. The Ottawa Model of Research Use model introduces factors including practice environment, potential adopters of the evidence, the evidence adoption, and health-related and other outcomes.

The focal relationship of the study is the receipt of the RS test and the use of chemotherapy. The independent variable is receipt of the RS test and the outcome variable is receipt of chemotherapy.

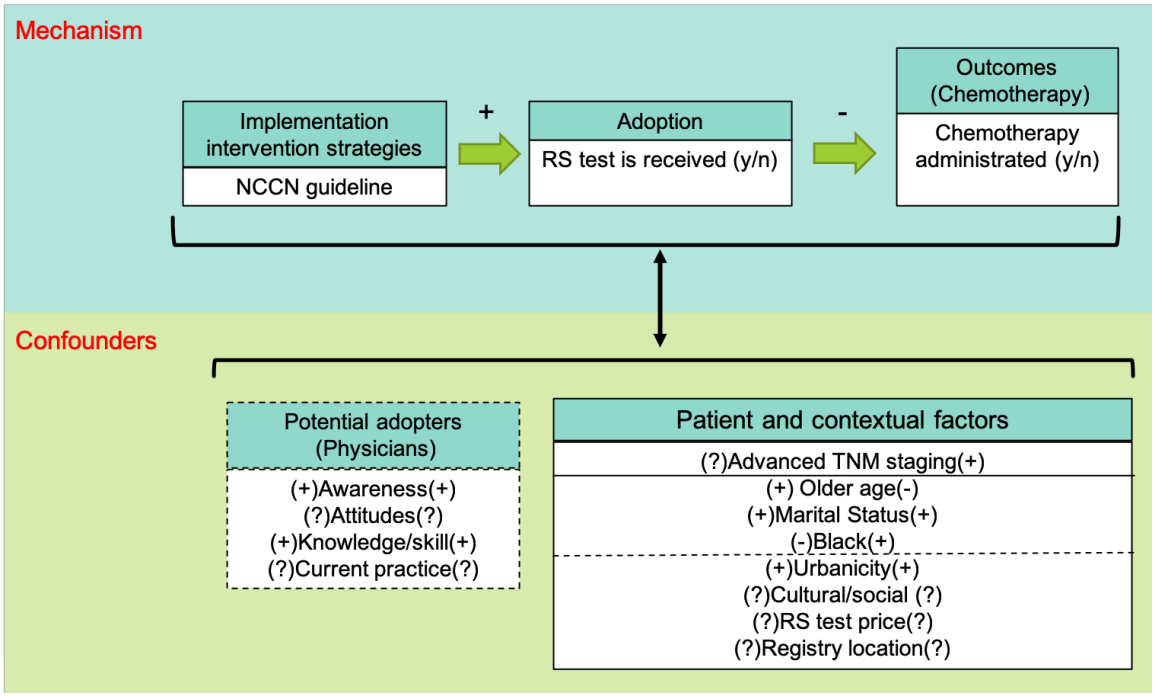

Figure 1. Conceptual Framework

CHAPTER 2: REVIEW OF THE LITERATURE

In the United States, 286,120 new cases of breast cancer are diagnosed annually [3, 10, 14]. A large proportion of breast cancer patients are elderly, who are also Medicare beneficiaries. Chemotherapy is a well-accepted treatment that is usually administrated after the surgery [6]. However, the complex factors related to prognosis and response to chemotherapy are not well reflected in the clinical or pathological manifestations [6], thus potentially leading to the improper use of chemotherapy which will result in tremendous costs and drug-related adverse effects in breast cancer patients. Evidence showed that the Oncotype DX 21-gene recurrence score assay (RS test) was validated for its ability to predict recurrence and response to chemotherapy, the RS test was included in the NCCN guidelines for breast cancer in 2008 [6]. Since then, the use of the RS test has increased but remained at a low level [10, 14]. Although the increase in the use of the RS test could be a result of natural uptake or alteration in the insurance coverage, the low overall RS test administration might be attributable to provider- or patient- related characteristics [10]. Therefore, it is of great importance to evaluate the impact of RS test adoption on chemotherapy administration to help us understand the ability of the RS test to guide proper use of chemotherapy. This literature review will address the current public health concern, define the literature gap, and state contributions of this study.

1. Breast Cancer is a Public Health Issue

Breast cancer (BC) is a condition caused by uncontrolled growth of breast tissue cells [1]. It is the most commonly seen cancer among women internationally [3, 15]. Among females in the United States,

BC has the highest incidence rate (it accounts for approximately 30% of new cancer diagnoses) and is the second highest cause of death among women following lung cancer [3]. From 2005 to 2014, the incidence of BC increased 0.4% percent annually on average [3] and the rates are higher in women aged 40 or above [4]. Among all breast cancer new cases, 50% incidence occurs in women aged 65 or older, who are eligible for Medicare coverage [5].

All BC diagnoses are accompanied by a clinical staging, which provides information about the extent of the cancer. The TNM staging system is commonly used in BC diagnosis, where T stands for the size and extent of the primary tumor; N stands for the number of lymph nodes that have been affected by the tumor; M stands for whether the cancer cells have spread to other parts of the body [16]. In addition, pathology assessments are also used to evaluate biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status (these biomarkers are measured positive (+) or negative (-)). The biomarkers provide predictive information about responsiveness to treatments, though they are not included in the staging criteria. Informed clinical staging and pathology assessment provide the foundation for treatment decisions [6].

BC is the strongest indication for chemotherapy among women in the United States [8]. Typically, chemotherapy is used after surgical interventions [6]. There are two important factors that should be evaluated before administering chemotherapy: prognostic information and predicted benefit [9]. However, since tumors sharing similar clinical and pathological features might have distinct prognoses, relying merely on the clinical and pathological information can lead to overuse of chemotherapy. Improper use of chemotherapy breaks the balance between risks and benefits for

BC patients. One of the concerns raised by researcher is that chemotherapy is the leading cause of drug-related adverse effects among BC patients [8, 17, 18], which accounts for about 6.5%-13% of total hospitalizations [19]. Another concern addresses the great individual and societal spending on chemotherapy. Total private insurance payments for BC patients who receive chemotherapy varies from $82,000 to $161,000 depending on specific regimens [20]. In addition, Medicare spending on chemotherapy is estimated to be from $16,000 to $19,000 per beneficiary [21].

2. Historical Background of the RS Test

The emergence of DNA microarray technologies in recent years allows oncologists to predict prognoses such as for disease recurrence and response to chemotherapy based on patients' gene expression profile [22]. The RS test has been validated, with strong evidence, for its value in prognosis testing and predicting the patient's response to chemotherapy [6]. It quantifies the risk of distant recurrence at 10 years by the recurrence score (RS score) from quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) analysis of RNA extracted from the breast cancer tissue [23]. Then the RS score is generated based on an algorithm and gene expression information [24]. The RS score classifies BC into three levels, namely: low (RS score 0-17), medium (18-30) and high risk (31-100), with an average risk of recurrence of 7, 14 and 31% respectively [24]. The low RS score recommends no chemotherapy while the high RS score recommends chemotherapy. The intermediated RS score leaves more discretion to physicians.

Since its commercial availability in 2004, several studies have reported the RS test's ability to predict local/distant recurrence and the ability to independently predict chemotherapy response [9,

[24-28]. In 2006, a study analyzed 2,363 patients enrolled in the NSABP Protocol B20 trial and reported that the RS test can predict the magnitude of benefit from chemotherapy [9]. In 2015, a large trial, TAILORx, which enrolled more than 11,000 patients with HR+/HER2-/LN (lymph node) - profile, revealed in preliminary results that BC patients with a low-risk score exhibited low recurrence rates after using hormonal treatment alone [29]. Later studies focused on the predictive value of the RS test on patients with affected lymph nodes. Several studies demonstrated that although node-positive BC patients exhibit higher recurrence likelihood compared to node-negative BC patients, LN+ patient with high-risk RS scores still benefit from chemotherapy [25, 28, 30]. In 2016, a clinical trial in Germany reported results in consistent with previous studies. They found that LN+ BC patient with RS score less than 12 reported a 3-year disease-free survival rate of 97.9% [30]. The NSABP B-28 trial published its results in 2018, suggesting that the RS test's ability to predict benefit might rely on the type of regimens [31].

In 2008, the NCCN guideline started to include the RS test in the recommendation for early-stage BC [32]. In the same year, Medicare began to cover the RS test in 2008 [33]. In 2015, the NCCN guideline expanded the recommendation of the RS test to BC patients with up to three affected lymph nodes [34].

Many studies find that there has been an increase in the utilization of the RS test over time, accompanied by a decrease in chemotherapy administration [7, 14, 35]. However, only 20-30% of eligible BC patients take the RS test [10, 14, 36]. Given that the RS test has been validated for its use as a predictor for BC recurrence and chemotherapy response, low utilization of the RS test indicates that among BC patients who received chemotherapy, there could be a high rate of misuse or overuse.

This overuse of chemotherapy can cause tremendous economic and health burden.

Cost-effectiveness studies suggested that the RS test could mitigate the economic burden stemmed from chemotherapy. Hornberger's analysis in 2011 reported that the RS test reduced spending on chemotherapy drugs, supportive care, and adverse events [37]. Another study reported consistent findings and further suggested that the treatments guided by the RS test showed greater cost-effectiveness compared that without the RS test among Medicare beneficiaries [38]. Later, a study by Lamond et al. found the RS test to be cost-effective in both node-negative and node-positive samples [39]. Lyman et al. reported that the RS test-guided treatment decision was associated with lower costs and similar clinical outcomes compared to treatment without the RS test [40].

Therefore, it is crucial that studies evaluate the impact of the receipt of the RS test on the chemotherapy use to help healthcare providers and patients better understand how they can utilize the RS test to make better-informed decisions on chemotherapy administration. In addition, the evaluation can also help policymakers assess the need for further advocacy to promote the use of the RS test in clinical settings.

3. Current Empirical Literature Relevant to Research

Since the first report of the RS test, studies have assessed the association between the RS test and receipt of chemotherapy. Chart review studies were among the first to analyze the impact of the RS test adoption on chemotherapy administration [41-43]. In a retrospective chart review of 85 BC patients, Asad et al. found that the RS test influenced the treatment strategy of nearly half of the patients [41]. Later studies adopted secondary data and survey methods. They also found that the RS test could

alter the clinical decision, even among physicians in different specialties [42-44]. Shelly et al. found the RS test had a notable impact on shifting from chemotherapy to hormone therapy. Besides health professionals, the RS test also influenced patients' treatment choice [45]. In addition, the impact of patients not having access to the RS test has also been studied. Joh et al. in 2011 found that without information provided by the RS test, an estimated 82% of BC patients would receive overtreatment [46].

Later studies observed the impact of the RS test depending on breast cancer subtype. De Boer et al. found that the RS test had a great impact on the treatment recommendation for hormonal receptor-positive BC patients [47]. Eiermann and colleagues reported that the RS test had an impact on the treatment for both node-negative and node-positive BC patients[48]. Enewold et al. reported an increase in the use of the RS test both in concordance with the NCCN guideline and exceeding the guideline's recommendation among ER-positive/node-negative patients [10].

In more recent years, along with the increase in the availability of larger secondary data related to the RS test use, there emerged a series of studies using large, secondary data. Since then, more inconsistent results have been reported, depending on factors including sample population characteristics, insurance coverage, and facility types [49, 50]. Dinan et al. used the SEER-Medicare database in 2015 to analyze the trend of RS test adoption and reported that adoption increased since 2006 [14]. The authors then analyzed the association between the RS test adoption and chemotherapy use using the SEER-Medicare database [7]. However, they found no significant association overall but discovered that the RS test only decreased the probability of chemotherapy use within the clinically high-risk patient sample. Epstein et al. in 2015 reported that the RS test was associated

with decreased chemotherapy use and lower health care spending among BC patients aged 65 and below, while the RS test was associated with increased chemotherapy use and higher health care spending among patients aged 75 and above [51]. Afghahi et al. analyzed patient electronic medical data and reported no significant association between RS test and chemotherapy use [36].

In addition, more recent studies started to observe more detailed outcomes. In 2016, Dzimitrowicz et al reported that RS test was associated with decreased time duration to make treatment decisions [52]. In 2017, Henry et al. reported the RS test had a disproportional impact on the use of different types of chemotherapy regimens [53]. Some recent studies also assessed the RS test's impact on radiotherapy use [54] and neoadjuvant therapy [55].

4. Summary

Among existing studies, the majority of the literature assessed the association between the RS test and chemotherapy administration. The rest provided findings in terms of the value of assessment combining the RS test and clinical/pathology profile, the disparities in clinical decision making on chemotherapy based on the RS test result, or the cost-effectiveness of the RS test. Most studies are consistent in that the adoption of the RS test has been increasing; however, findings about whether the increase RS test use has reduced chemotherapy use remains inconsistent across studies. Notably, studies that observed an association between the RS test use and reduced chemotherapy use were relatively small-scale chart review studies or survey studies, whereas studies that observed no significant association mostly used large secondary databases. Therefore, the inconsistent findings should be interpreted with caution in terms of the potential bias in both internal and external validity

introduced by certain characteristics of the sample population and the assumptions underlying the conceptual frameworks. Importantly, existing studies were constrained by the sample size and the ability of the data to fully reflect the adoption of the RS test and more importantly, the shift in the clinical practice of BC treatment. Therefore, we expect a study to more accurately evaluate the association between the RS test and chemotherapy administration. This study will use the nationally representative SEER-Medicare database from 2006 to 2014 to assess the impact of the RS test adoption on the chemotherapy administration.

CHAPTER 3: METHODS

This study used the data from the SEER-Medicare database to analyze the association between receipt of the RS test based on the NCCN guideline' recommendation and the use of chemotherapy among eligible BC patients, controlling for confounders.

1. Database

This study has been approved as exempted by the Emory IRB. This study used data from SEER and Medicare linked data set, which combines two population-based data sources from National Cancer Institute and the Centers for Medicare & Medicaid Services [7, 56]. SEER contains incidence and survival information that includes approximately 34.6% of the US population [7, 57]. SEER collects information on patient demographics, tumor characteristics, stage of diagnosis, treatment and outcome. Furthermore, SEER contains mortality data collected by the National Center for Health Statistics [57]. SEER data were collected at different cancer registries by cancer registrars who are highly trained data management experts collect and process cancer data at those registries[58]. Medicare outpatient, inpatient, and carrier (physician) claim files and enrollment files contain 100% of Medicare beneficiaries with claims for breast cancer from the Medicare Chronic Conditions Data Warehouse[59] for the period 2006 to 2014. Claim files include diagnosis codes, procedure codes, and HCPCS codes. Enrollment records include beneficiaries' months of enrollment in Medicare parts A and B. Altogether, SEER-Medicare database contains information about Medicare beneficiaries with cancer, including clinical, demographic, health outcomes and

Medicare claims[56]; therefore, it provides the most suitable information to answer to research questions in this study.

The data include exact dates of services and patients' age in years (including ages for patients older than 89) but do not include other identifiers (e.g., Medicare beneficiaries' zip codes, names).

The data were stored on the S drive of the Rollins School of Public Health data server in a password-protected folder and will be retained until the Data Use Agreement with the Department of Health and Human Services expires.

2. Study Sample

This study included only female patients with the diagnosis of breast cancer and received medical services at SEER registries between 2006 to 2014. To ensure that patients had a maximum possibility of generating breast cancer-related Medicare claims, I applied the first inclusion criterion that patients must have breast cancer as the primary diagnosis from the Patient Entitlement and Diagnosis Summary File (PEDSF) [7], except for patients who were diagnosed through autopsy. Additionally, I applied the first exclusion criteria to delete patients whose Medicare Part A and Part B coverage were discontinuous, or patients enrolled in Medicare Part C, starting from one year before their diagnosis and lasting to the end of the study or death of patients[7]. This ensured that all patients in the study sample survived at least one year after the initial breast cancer diagnosis. The second exclusion criterium was to delete patients with in situ breast cancer or beyond clinical stage IIIa for the reason that the RS test is not recommended for this population. The third criterion was to exclude patients who are not ER-positive because the RS test is recommended for this type. This

study did not exclude node-positive patients because a previous study reported that the RS test might predict health outcomes among this population[28].

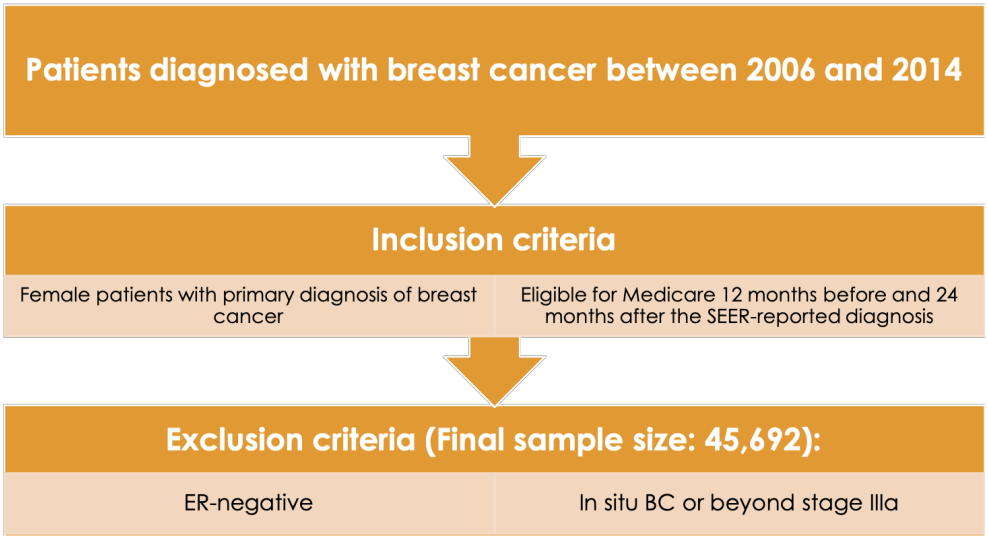

Figure 2. Flow Chart of Sample Selection

3. Research Design

This study applied descriptive analyses and a multivariable regression model to examine the association between the receipt of the RS test and chemotherapy administration, controlling for demographic and clinicopathological confounders.

Variables

The primary study outcome was the receipt of chemotherapy reported on any of the claims data in a time window between 2 months before and 12 months after the diagnosis of breast cancer[7]. The major independent factor was the adoption of the RS test reported in any of the claims data in a time window 2 months before and 6 months after the diagnosis date. Using National Claims History (NCH) and outpatient files, I identified the claims code for chemotherapy through the Current Procedural Terminology (CPT) code, which included Q0083-Q0085, G0355- G0363, J8510-J9999,

or 96400-96549. RS test information exists only in the NCH files. Because the provider name variable was encrypted, I adapted a mixed method to identify the RS test based on the year [7]. For years prior to 2013, I identified the claims code for the RS test by first identifying claims containing CPT code 84999 and determining whether they were recorded in the widow from 2 months before to 6 months after the diagnosis date. Then I ranked cost (variable name linepmt descending order) and time (variable name diagnosis date, ascending order). I identified RS based on the highest payment for each patient. The mechanism under the identification method is based on existing literature that the RS test (Oncotype DX) provided by Genomic Health was considered the most expensive claim reimbursed by Medicare compared to other items billed concurrently [7]. For year 2013 and 2014, I identified the RS test through the combination of CPT code 81479 and the count of total units associated with service as 1 (mtuscnt = 1) [60].

Other variables were selected based on the 2018 NCCN guideline. Covariates included TNM staging, age at diagnosis, sex, race/ethnicity, marital status, and urbanicity were extracted from PEDSF files. [14].

Conceptual framework

As shown in Figure 1, the focal relationship is the association between the adoption of the RS test and receipt of chemotherapy. Confounders listed in the “Patient and contextual factor” box have correlations with both dependent and independent variables, thus introducing bias into the model. However, given that not every correlation effect can be determined and that some of the confounders cannot be measured, the direction the bias is unclear. Confounders in the “Potential adopters” box are unmeasurable thus could not be included in the regression analysis.

4. Measures

The measure for the outcome variable was the receipt of chemotherapy. Previous studies suggest that the adoption of the RS test might decrease physicians' recommendation of the chemotherapy, though the evidence is inconsistent[61]. Patients at high risk (measured by ER status, more advanced node status, tumor size and histological features) are more likely to receive chemotherapy[7]. However, there is little evidence for the clinical profiles' correlations with the receipt of the RS test. As suggested by previous studies, older age at diagnosis is associated with decrease receipt of chemotherapy and is associated with a greater likelihood of receiving the RS test [7, 61]. The African-American group's likelihood to receive the RS test and chemotherapy compared to other racial/ethnic groups has been reported inconsistently by studies [7, 62]. People with fewer comorbidities are less likely to receive RS essay and are more likely to receive chemotherapy[7]. Being married is correlated with increased use of the RS test and increased use of chemotherapy[7]. Existing literature does not provide evidence that gender, rurality of the residence, and geographic region are correlated with either the RS test or the receipt of chemotherapy[7].

5. Data Analysis

This study analyzed the association between the receipt of the RS test and the receipt of chemotherapy. For the research question of whether receiving the RS test will reduce the probability of receiving chemotherapy, it is hypothesized that patients who received the RS test had a lower probability of receiving chemotherapy, and there was an increasing trend in the RS test use between 2006 and 2014. The descriptive analysis examined the demographic characteristics and

clinical profiles of patients who received chemotherapy and patients who did not receive chemotherapy. A descriptive table summarized and comparted the characteristics between the two groups and reported frequency and percentages. Chi-square tests were applied to determine the differences between the two groups. Multivariable regressions were conducted to determine the association between the RS test use and receipt of chemotherapy, controlling for demographic and clinicopathologic confounders [7]. The significance level was set at alpha=0.05. Below is the regression equation used in the analytic model.

$$\ln\left(P/_{[1-P]}\right) = \beta 1\text{RS} + \beta 2\text{TMN} + \beta 3\text{Confounders} + \varepsilon$$

Where *"P"* refers to the probability that a BC patient will receive chemotherapy. *"RS"* refers to whether the patients received the RS test, *"TMN"* refers to the clinicopathologic characteristics. "β1"- "β3" refer to coefficients for *"RS", " TMN"* and other confounders respectively. "ε" refers to error term.

For the research question whether the use of the RS test has increased, a line graph is created to demonstrate the trend in the use rate of the RS test between 2006 and 2014.

CHAPTER 4: RESULTS

I identified 45,692 female Medicare beneficiaries diagnosed with ER-positive, early stage (stage I to stage IIIa), node negative or up to three positive nodes breast cancer through SEER registries between year 2006 and 2014. Two descriptive analyses were conducted to demonstrate the sample characteristics. The overall sample was first divided into two subsamples, those that received chemotherapy (chemo-sample) and those that did not (non-chemo sample) and then divided into RS and non-RS sample. Table 1 summarized the baseline characteristics of the overall study sample, chemo sample and non-chemo sample.

Table 1. *Characteristics of the Overall Sample, Chemo Sample and Non-chemo Sample*

Variables	**Overall**	**Chemo**	**Non-chemo**	**P-value**
	Percentage/ Mean (SD)	**Percentage/ Mean (SD)**	**Percentage/ Mean (SD)**	
	N=45,692	**N= 8,052**	**N= 37,640**	
RS test				
Received	15.31	18.83	14.55	
Not received	84.69	81.17	85.45	
Age	75 (6.38)	72 (5.08)	76 (6.46)	< 0.01
Race/ethnicity				< 0.01
Black	6.26	7.59	5.98	
White	88.18	86.29	88.59	
Asian	2.37	2.33	2.37	
Hispanic	1.01	1.15	0.98	
Other	2.18	2.64	2.08	
Marital status				< 0.01
Married	50.14	55.90	48.90	
Single	49.86	44.10	51.10	
Urbanicity				0.385
Urban vs. rural	90.09	89.83	90.15	

Variables	Overall	Chemo	Non-chemo	P-value
	Percentage/ Mean (SD)	Percentage/ Mean (SD)	Percentage/ Mean (SD)	
	N=45,692	N= 8,052	N= 37,640	
Number of positive nodes	0.3 (0.65)	0.7 (0.93)	0.2 (0.54)	< 0.01
Clinical stage				< 0.01
I	63.31	34.07	69.56	
II	35.45	62.23	29.72	
IIIa	1.25	3.70	0.72	
Tumor stage				< 0.01
Tmicro	1.36	0.38	1.56	
TIa	7.80	2.99	8.83	
TIb	23.78	11.60	26.38	
TIc	39.73	38.43	40.01	
T2	24.30	40.16	20.91	
T3	2.76	6.04	2.05	
T Other	0.27	0.40	0.24	
Node status				< 0.01
N0	37.30	26.39	39.64	
N1	19.19	43.89	13.90	
N2	0.07	0.26	0.03	
N Other	43.44	29.46	46.43	
Histologic grade				< 0.01
G1	32.11	14.98	35.79	
G2	50.47	48.06	50.99	
G3	17.12	36.35	12.99	
Anaplastic	0.29	0.60	0.23	
PR status				< 0.01
PR positive	85.47	77.12	87.25	
PR negative	14.11	22.35	12.35	
PR borderline	0.42	0.52	0.40	
Tumor size				< 0.01
0 - 0.5	8.44	3.38	9.53	
0.5 - 1	23.58	11.55	26.15	
1 -2	39.73	38.43	40.01	
>2	28.22	46.58	24.30	

Variables	Overall	Chemo	Non-chemo	P-value
	Percentage/ Mean (SD)	Percentage/ Mean (SD)	Percentage/ Mean (SD)	
	N=45,692	N= 8,052	N= 37,640	
Other	0.02	0.05	0.01	
Diagnosis year				0.044
2006	11.94	11.03	12.14	
2007	12.34	12.16	12.38	
2008	12.55	12.94	12.46	
2009	12.64	12.32	12.71	
2010	12.76	12.59	12.80	
2011	12.83	12.95	12.81	
2012	12.84	13.57	12.68	
2013	12.09	12.43	12.02	

Note: Percentage is displayed for categorical variables. Mean and standard deviation is displayed for continuous variables.

The overall study sample had an average age of 75 years (SD 6.38). Most patients were non-Hispanic White (88.18%), living in the urban area (90.09%), within clinical stage I (63.31%), within tumor stage of T1c (39.73%), within a node stage between N0-N1 (37.30%), with a histologic grade of G2 (50.47%), PR-positive (85.47%), with the size of the tumor between 1-2 cm (39.73%). The proportion of patients who were married and who were single were similar. The proportion of patients diagnosed each year between 2006 to 2014 was similar as well.

Compared with the non-chemo sample, the chemo sample had a younger average age compared to the non-chemo sample (72 vs. 76 years). Non-Hispanic White had the highest percentage in both chemo sample (86.29%) and non-chemo sample (88.59%) and Hispanic patients had the least percentage in both chemo sample (1.15%) and non-chemo sample (0.98%). More patients were married in the chemo sample (55.90%) compared to the non-chemo sample (48.90%). The average

numbers of positive nodes in the chemo sample (0.7, SD=0.93) was higher than that in the non-chemo sample (0.2, SD=0.54). There were more patients with tumor stage of Tmicro in the non-chemo sample (1.56%) compared to the chemo sample (0.38%) and less patients with tumor stage of T3 in the non-chemo sample (2.06%) compared to the chemo sample (5.96%). The most common tumor stage was stage T2 among the chemo sample (40.16 %) and T1c among the non-chemo sample (40.01%). The most common node stage for the chemo sample was N1 (44.05 %) and other node stages for non-chemo sample (46.38 %). About 48.10% of patients in the chemo sample had a histology grade of G2, while about 51.06% of patients in the non-chemo sample had the same histology grade, which has the highest frequencies in both chemo and non-chemo samples. Most patients in both chemo and non-chemo samples were PR positive (77.12% and 87.25%). Tumor size of 2 cm and greater had the highest frequency (46.58%) in the chemo sample while tumor size of 1 -2 cm had the highest frequency (40.01%) in the non-chemo sample. There were no significant differences between the chemo and non-chemo sample in terms of urbanicity and year of diagnosis. Both groups had about 90% of urban sample and the percentage of diagnoses were quite evenly distributed between 2006 and 2014.

Table 2. *Characteristics of the RS Sample and Non-RS Sample*

Variables	**RS**	**Non-RS**	**P-value**
	Percentage/Mean (SD)	**Percentage/Mean (SD)**	
	N= 6,994	**N=38,698**	
Chemo			< 0.01
Received	21.68	16.89	
Not received	78.32	83.11	
Age	72 (4.72)	76 (6.48)	< 0.01
Race/ethnicity			< 0.01

Variables	RS	Non-RS	P-value
	Percentage/Mean (SD)	Percentage/Mean (SD)	
	N= 6,994	N=38,698	
Black	6.20	6.27	
White	89.06	88.02	
Asian	1.78	2.47	
Hispanic	0.85	1.04	
Other	2.11	2.19	
Marital status			< 0.01
Married	58.02	48.72	
Single	41.98	51.28	
Urbanicity			0.295
Urban vs. rural	89.75	90.15	
Number of positive nodes	0.52	0.68	
Clinical stage			< 0.01
I	60.29	63.85	
II	39.13	34.78	
IIIa	0.57	1.37	
Tumor stage			< 0.01
Tmicro	0.11	1.58	
TIa	2.50	8.76	
TIb	17.94	24.83	
TIc	48.63	38.12	
T2	28.54	23.54	
T3	2.03	2.89	
T Other	0.24	0.28	
Node status			< 0.01
N0	43.92	36.11	
N1	15.04	19.94	
N2	0.06	0.07	
N Other	40.98	43.88	
Histologic grade			< 0.01
G1	26.04	33.22	
G2	54.71	49.7	
G3	19.10	16.76	
Anaplastic	0.16	0.32	
PR status			0.344

Variables	RS	Non-RS	P-value
	Percentage/Mean (SD)	Percentage/Mean (SD)	
	N= 6,994	N=38,698	
PR positive	85.57	85.45	
PR negative	14.11	14.11	
PR borderline	0.31	0.44	
Tumor size			< 0.01
0 - 0.5	2.59	9.50	
0.5 - 1	17.79	24.63	
1 -2	48.63	38.13	
>2	31.00	27.72	
Other	0.00	0.02	
Diagnosis year			< 0.01
2006	4.18	13.34	
2007	7.45	13.23	
2008	11.50	12.74	
2009	15.57	12.11	
2010	18.52	11.72	
2011	21.46	11.27	
2012	19.27	11.68	
2013	2.06	13.91	

Table 2 shows that compared to the non-RS sample, the RS sample was more likely to be younger, non-Hispanic White, married. In addition, the RS sample tend to have the clinical profile with less lymph node involvement, more advanced clinical stages, tumor stages, histological grades, less advanced node status, larger tumor size, and more recent diagnosis years. However, there were no significant differences in urbanicity or PR status. Interestingly, the RS sample had more proportion of patients receiving chemotherapy (21.68% vs. 16.89%).

To identify the trend of the RS test uptake and chemotherapy use, a line graph (Figure 3) was created to show the change in the rate of administration of both the RS test and chemotherapy

between 2006 and 2014. The rate of RS test use had an upward trend, except for a 2 percent decrease around year 2017. Although fluctuations were observed between year 2009 and year 2012, the overall rate of chemotherapy use also demonstrated an upward trend among the study sample.

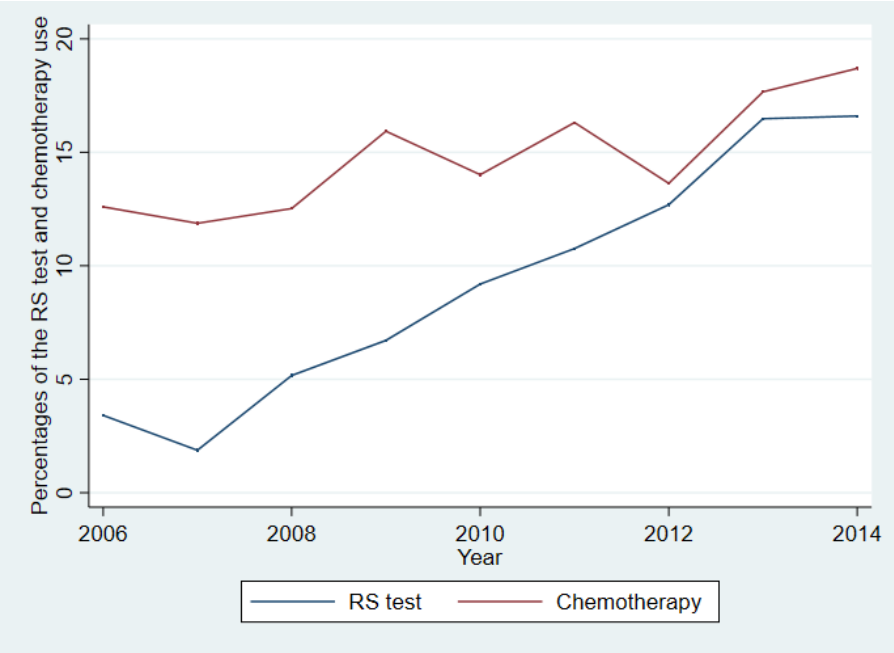

Figure 3. Trend of the RS Test and Chemotherapy Use

The year was plotted along the x-axis. The RS test use the chemotherapy use (in percentage) were plotted along the y-axis denotes the rate of. The blue line represents the RS test and the red line represents chemotherapy.

Table 3 shows the results of the multivariable regression analysis to assess whether the receipt of the RS test reduced the probability of the receipt of chemotherapy. There was no association between the receipt of the RS test and the receipt of chemotherapy (Marginal effects, -0.0008). However, compared to age group 65-70, age groups 71-75, 76-80, and above 80 had lower probabilities of receiving chemotherapy. Race categorized as “other” increased the probability of receiving chemotherapy, while White, Asian, and Hispanic were not significantly associated with receipt of chemotherapy compared to African-American. Compared to being married, the

probability of receiving chemotherapy was lower for patients who were single. In addition, the clinical profile had an impact on chemotherapy receipt. The probability of receiving chemotherapy was higher with the increase in the number positive nodes. Compared with clinical stage I, the probability of receiving chemotherapy was higher for clinical stage II and III. There was an observed increased probability of receiving chemotherapy with progressed tumor stage and node stage. Compared with histologic grade G1, histologic grade G2 G3 and G anaplastic were associated with increased probability of receiving chemotherapy. Compared with tumor size of 0.5 cm or less, tumor size of 2 cm and above decreased the probability of receiving chemotherapy. More recent diagnosis years increased the probability of receiving chemotherapy. Nevertheless, Urbanicity was not associated with receipt of chemotherapy.

Table 3. *Multivariable Regression Analysis of the Association between Receipt of RS Test and Receipt of Chemotherapy*

Variables	Marginal effects	Standard error
Received RS		
Yes	-0.0008	0.0044
No	1[Ref]	
Age		
65 - 70	1[Ref]	
71 - 75	-0.0501*	0.0039
76 - 80	-0.1220*	0.0046
> 80	-0.2437*	0.0057
Race/ethnicity		
Black	1[Ref]	
White	0.0019	0.0065
Asian	-0.0041	0.0124
Hispanic	0.0226	0.0169
Other	0.0240*	0.0120

Variables	Marginal effects	Standard error
Marital status		
Married	1[Ref]	
Single	-0.0194*	0.0034
Urbanicity		
Urban	0.0014	0.0054
Rural	1[Ref]	
Number of positive nodes	0.0435*	0.0040
Clinical stage		
I	1[Ref]	
II	0.0623*	0.0074
III	0.0453*	0.0198
Tumor stage		
Tmicro	1[Ref]	
TIa	0.0478	0.0339
TIb	0.0290	0.0766
TIc	0.1318*	0.0329
T2	0.1893*	0.0372
T3	0.2502*	0.0389
T Other	0.1353*	0.0497
Node stage		
N0	1[Ref]	
N1	0.0593*	0.0087
N2	0.1292*	0.0506
N Other	-0.0037	0.0040
Histologic grade		
G1	1[Ref]	
G2	0.0659*	0.0044
G3	0.1786*	0.0047
Anaplastic	0.1869*	0.0238
PR status		
PR positive	-0.0753*	0.0042
PR borderline	-0.0329	0.0254
Tumor size		
0 - 0.5	1[Ref]	
0.5 - 1	0.0480	0.0821
>2	-0.0455*	0.0469

Variables	Marginal effects	Standard error
Other	-0.0912	0.1304
Diagnosis year		
2006	1[Ref]	
2007	0.0100*	0.0068
2008	0.0184*	0.0067
2009	0.0175*	0.0068
2010	0.0150*	0.0068
2011	0.0162*	0.0068
2012	0.0218*	0.0067
2013	0.0161*	0.0067

Note: * P < 0.05

Based on the primary regression analysis, age has a strong association with the receipt of chemotherapy. Therefore, an additional multivariable regression analysis was conducted to assess the impact of age on the focal relationship. This was achieved with stratifying of age into 65-70, 71-75, 76-80, and 81 and above (Table 4). The finding shows that among patients aged from 65-70, the receipt of the RS test decreased the probability of receiving chemotherapy; while among patients aged 76 years old and above, receiving the RS test increased the probability of receiving chemotherapy.

Table 4. *Age-Stratified Regression on the Association of Receipt of Chemotherapy and Receipt of the RS Test*

Age group	Marginal effects of the RS test	P-value
65-70	-0.02	0.03
71-75	-0.01	0.54
76-80	0.04	0.00
81+	0.04	0.00

*This analysis included the same covariates in Table 2 (only the marginal effects of the RS test are shown in this table).

CHAPTER 5: DISCUSSION

1. Summary

Based on the literature search, this is to my knowledge the first study using the most recent SEER-Medicare data that assessed the association between the receipt of the RS test and the receipt of chemotherapy. For the research question whether BC patients who received the RS test were less likely to receive chemotherapy, the result showed that the receipt of the receipt RS test is associated with a lower rate of the chemotherapy use; nevertheless, the association was not statistically significant. Therefore, there is no evidence in support of the hypothesis that patients who received the RS test were less likely to receive chemotherapy. For the second research question of whether there was an increased trend of the RS test, the result showed the use of both the RS test and chemotherapy, though with fluctuations, demonstrated an increasing trend between 2006 and 2014. This result is consistent with the hypothesis that the RS test use has increased. This chapter will first discussion the association between the receipt the RS test and the receipt of chemotherapy, which is the main research question, and then discussion the trend of the RS test use and chemotherapy use.

2. Conclusions

This study concludes that The receipt of the RS test reduced the probability of receiving chemotherapy, but the association was not significant. There was an increasing trend of the RS test use between 2006 and 2014, accompanied by an increasing trend in the chemotherapy use.

Although literature research showed that reports on the association between the receipt of the RS test and the receipt of chemotherapy have been inconsistent, the results of this study is consistent with the most recent study based on the SEER- Medicare data by Dinan et al., who also reported no association between the receipt of the RS test and the receipt of chemotherapy [7]. In addition, by classifying patients into three risk groups based on the recommendation in the NCCN guideline, they found that age and risk groups were major predictors for the receipt of chemotherapy. The currently study did not apply the risk group categorization, instead, we included each factor (ER status, node status, and tumor size) used to classify the risk groups in order to provide more information. Dinan et al. reported that patients were more likely to receive chemotherapy if they fell into intermediate or high-risk group. which is consistent with the result of the current study that advanced clinical stages, tumor stages, node stages, and histologic grades increased the probability of receiving chemotherapy. Their findings are also consistent with the study by Enewold et al. who reported that the receipt of the RS test was not associated with the receipt of chemotherapy even taking into the account the effects of the RS score [10]. The study by Epstein et al. in 2015 could provide a partial explanation for the main result of the current study in that they found that the use of the RS test lowered that use of chemotherapy among patients aged 65 and younger while increased the use of chemotherapy among patients aged 75 and older [51]. The current study conducted an additional analysis with age stratification (65-70, 71-75, 76-80, and 81+) also discovered similar findings that the RS test decreased the probability of receiving chemotherapy among patients aged between 65 and 70 and increased the probability of receiving chemotherapy in patients aged 76 and older (Table 3). The study by Afghahi et al. reported the negative association

between the receipt of the RS test and the receipt of chemotherapy but with an insignificant p-value [36]. Notably, the findings on the associations between the receipt of the RS test and the receipt of chemotherapy varies across the literature. Though the findings of this study is consistent with a number of previous researches, there are also many studies that reported significant associations between the receipt of the RS test and the receipt of chemotherapy [50]. However, the comparison between those studies and this study should be conducted with caution. The inconsistency in the results might be attributable to several factors such as differences in geographic location or health system [48, 63-65], method of data collection [48, 63, 66, 67], and sample size [41]. In addition, findings from exiting studies should also be interpreted based on certain underlying assumptions and limitations on internal and external validity. Interestingly, most of the findings that supported the significant associations between the receipt of the RS test and decreased chemotherapy use were reported by studies conducted outside the U.S., which suggest that the health care environment might be an important factor influencing the ability of the RS test to reduce unnecessary chemotherapy use.

Notably, though the current study observed no association between the receipt of the RS test and the receipt of chemotherapy, the RS test was expected to be associated with decreased chemotherapy use in that the RS test has been validated to provide a more accurate prediction for the responsiveness to chemotherapy. Therefore, after receiving the RS test, the use of chemotherapy was expected to decrease due to the omission of those predicted as unbeneficial by the RS test. Lacking the availability of the RS score, the current study could have included in the model those whose RS score recommended receiving chemotherapy when assessing RS test's impact on the reducing unnecessary chemotherapy use. This could partially explain the insignificancy. More will

be discussed in the limitations section.

The demographic characteristics of the study sample was similar with a previous study by Dinan et al [7]. Records were similarly distributed in all age groups, about half of the patients were married, and most patients were from urban areas. The clinical profiles were consistent with their study, except for the node stage consisted of more stage N0 in their study. Another study in 2017 using National Cancer Database (NCDB) reported N1 to be most frequent node stage in their study sample between 2010 to 2013. Therefore, the different in the node stage might be partial resulted from a shift of breast cancer epidemiology, but future study should continue comparing this parameter with the availability of more recent SEER-Medicare data.

In terms of the trend of RS test use, the finding of this study is consistent with previous studies [7, 36]. Dinan et al. reported that the RS test use rate decreased slightly between 2005 and 2009, which was also manifested in the results of the current study. They also reported that the chemotherapy use rate remained stable in the same period. The results from the current study, although had some fluctuations, also remain relatively stable in that period. A study by Henry et al. reported that chemotherapy administration rate has decreased over the years [53]. Possible explanation is that this study used hospital records collected during the Michigan Breast Oncology Quality Initiative (MiBOQI). Given the geographic restriction, it is possible that chemotherapy was prescribed at a lower rate where data was collected. Therefore, the findings of their study also have a limited generalizability.

3. Strengths and Limitations

The current study has several strengths. First, this study used an up-to-date SEER-Medicare data, which was capable of capturing the most recent trend of both the RS test us and chemotherapy use. SEER-Medicare data combines data from SEER registries and Medicare claims data, which provided well-covered information about patients' demographic and clinical profile. The claims data is a proper reflection of actual treatments administrated for patients. Second, the SEER data has few missing records, which contributed to preserving the sample size. Third, the Oncotype DX® Breast Cancer Assay Billing and Coding Guidelines became available in 2012, which contributed to higher accuracy in terms of identifying the RS test in the claims data.

On the other hand, this study also has several limitations. First, this study contained some unmeasured variables such as the registry location, physicians' and patients' preferences, patients' educational level that can potentially bias the estimation. However, given the complex nature of effects of these variables might have on the focal relationship, the direction of the bias cannot be determined.

Second, the data used in this study did not include the RS test result. In order to assess the direction of bias, information about the frequency distribution of the RS score among breast cancer patients who received the RS test should be considered, together with the frequency of chemotherapy among patients who do not take the RS test, and the adherence to the RS score. More specifically, assume firstly the rate of using chemotherapy among patients without the RS test is 50%, and the expected distribution of the RS score frequency is 45% for high RS score, 30% for intermediate RS score,

and 25% for low RS score. Then assume that both the physician and the patient are 100% adherent to the RS test result so 100% patients with a high RS score, 50% of patients with an intermediate, and 0% of patients with a low RS score would score would receive chemotherapy. Then the probability of receiving the chemotherapy would be 45%, 15%, and 0% for patients with a high, intermediate, and low RS score respectively. Under the series of assumption, even if RS test does impact chemotherapy use, the difference would only be 5% (50% without and 45% with the RS test), which might not seem to be statistically significant. A large-sample study by Kizy et al. [68] provided strong scientific evidence for the frequency distribution of the RS score. They reported that in their study sample 7%, 35%, and 58% receive high, intermediate, and low RS score respectively. Under the previously stated assumptions, the probability of receiving chemotherapy should be 7%, 17.5%, and 0% for the high, intermediate, and low RS score group respectively. Given that the rate of receiving chemotherapy in the current study is much higher than the calculation based on Kizy's report, there could be some unmeasured confounders that increased the probability of chemotherapy use among the RS sample. For example, the factors could include physician and patient preferences. It could be possible that despite the fact that physicians ordered the RS test, they did not weigh the RS test result as important as other factor such as their judgment of the best treatment based on their experience or patients and their families' opinions. In addition, some of the physicians might lack the knowledge to properly interpret the RS test results. In order to evaluate and avoid this type of bias, future studies should take into account the RS score.

Third, the current study did not exclude patients who received pre-operative chemotherapy. There has been merging practice of pre-operative chemotherapy, and during the time frame of the current

study, the guideline did not recommend giving the RS test to patients who met the criteria of receiving pre-operative chemotherapy, however, some of those patients still were given the RS test. Not excluding those who received the RS test while also receive pre-operative chemotherapy would weaken the observed effect of the RS test to reduce unnecessary chemotherapy use, thus creating bias towards the null. Taken into consideration all directions for biases and the consistency with existing studies, the current study has an acceptable internal validity.

4. Implications

The current study provided the most recent assessment of the association between the receipt of the RS test and the receipt of chemotherapy, and the most recent trend the RS test use and chemotherapy use using a nationally representative data. The findings of this study supported the finding of the study by Dinan et al. The significance of this study came from the revealing of the small negative association between the RS test and chemotherapy use. Being validated as a potential mechanism to reduce the unbeneficial chemotherapy use, there might other be factors that hinder the effect of the RS test. The results of this study provide insight for health service researchers and public health practitioners into thoughts about several levels those factors might exist. If the factors involve health care environment or the health practitioner's ability to properly interpret the RS test result, then policies and regulations should be implemented to enhance the adherence to the clinical guideline to prevent wasteful use the RS test through regulatory and educational approaches. In 2015, NCCN expanded its recommendation for the RS test to up to three positive lymph node involvement, perhaps in the hope that the RS test will demonstrate its ability to avoid unnecessary

chemotherapy use with less strict indications. In addition, if the factors involve the power of the evidence on the RS test's ability to predict the responsiveness to chemotherapy, then we expect more randomized controlled trials to provide more powerful evidence.

5. Recommendations for Future Research

Future studies should continue exploring potential factors (measured and unmeasured) that influences the impact of the RS test on chemotherapy use, especially by incorporating the RS test result into the analysis. Mixed-method studies that combine quantitative and qualitative analyses can further help researchers understand how physicians interpret the RS test result and use this as a guide for their decision of chemotherapy administration. Last but not least, more clinical trials are encouraged to provide stronger evidence on the ability of the RS test to predict the responsiveness to chemotherapy for various breast cancer subtypes to help physician and patient make more informed decisions on chemotherapy treatment.

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