Chemotherapy Use for Hormone Receptor–Positive, Lymph Node–Negative Breast Cancer

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ABSTRACT

Purpose

To describe the frequency of chemotherapy use for hormone receptor (HR)–positive, lymph node (LN)–negative breast cancer from 1997 to 2004 at eight National Comprehensive Cancer Network institutions, to explore whether chemotherapy use varied over time and between institutions, and to identify factors associated with the decision to forego chemotherapy.

Patients and Methods

Among women younger than age 70 years with HR-positive, LN-negative breast cancer measuring more than 1 cm, we analyzed the frequency of chemotherapy use on a yearly basis. A multivariable logistic regression model assessed the relationship between receipt of chemotherapy and year of diagnosis, institution, tumor features, and patient characteristics. Interaction terms were added to the model, and stratified analyses were conducted to further explore the determinants of chemotherapy use.

Results

Fifty-five percent of 3,190 women received chemotherapy. Chemotherapy use was less common for patients with 1.1- to 2-cm tumors than for patients tumors greater 2 cm (47% v 87%, respectively; $P < .01$) and for women age 60 to 69 years versus women younger than age 50 years (24% v 76%, respectively; $P < .01$). On multivariable analysis, predictors independently associated with receiving chemotherapy included larger tumor size, higher grade, human epidermal growth factor receptor 2 overexpression, younger age, and institution ($P < .01$ for all). Institutions exhibited dramatically different rates of chemotherapy use (from 46% to 65%) and patterns of change in chemotherapy use over time (from a 79% relative increase to a 22% relative decrease).

Conclusion

Although institutions seemed to agree that not all women with HR-positive, LN-negative breast cancer need chemotherapy, there did not seem to be consensus regarding which women should get chemotherapy. Only prospective randomized controlled trials will conclusively establish which subtypes of HR-positive, LN-negative breast cancer benefit from chemotherapy.

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INTRODUCTION

Localized, hormone receptor (HR)–positive breast cancer represents approximately half of all invasive breast cancer in the United States.^{1,2} Studies conducted over the last 30 years, including the National Surgical Adjuvant Breast and Bowel Project B-20 trial and the Oxford Overview, have demonstrated that adjuvant chemotherapy improves survival for this type of breast cancer.³⁻⁶ A National Institutes of Health consensus panel that convened in 2000 recommended chemotherapy for the majority of women with localized breast cancer regardless of nodal, menopausal, or HR status.⁷ In 2002, the National Comprehensive Cancer Network (NCCN)

recommended chemotherapy for women younger than age 70 years with tumors more than 1 cm.^{8,9}

However, some experts argue that the decision to administer chemotherapy should be individualized because chemotherapy confers only a small absolute benefit and causes nontrivial adverse effects (eg, infections, heart failure, leukemia, and others).¹⁰ In fact, the NCCN references this position in a footnote to its recommendation. Several more recent studies have suggested that postmenopausal women and women with small, low-grade, human epidermal growth factor receptor 2 (HER-2)–negative breast cancers may not benefit from chemotherapy.^{5,7,11,12} Some practice guidelines have endorsed a risk-adapted

approach to adjuvant chemotherapy.^{7,8,13-15} For example, in 2005, the St. Gallen panel recommended chemotherapy for women younger than age 35 years or those with tumors that are larger than 2 cm, are grade 2 to 3, overexpress HER-2, or exhibit peritumoral vascular invasion.¹⁴

Patterns-of-care studies clearly demonstrate that chemotherapy use among women with breast cancer increased through the 1990s,^{16,17} but quality-of-care studies show that many women did not receive chemotherapy even when it was recommended.^{16,18-20} Unfortunately, more recent data are hard to come by. During a time when both the evidence and guidelines supported the use of chemotherapy but some experts dissented in favor of a risk-adapted approach, we wondered whether chemotherapy use continued to increase or leveled off and whether different institutions exhibited similar or variable patterns of chemotherapy administration. The goals of this study were to describe the frequency of chemotherapy use for women younger than age 70 years with HR-positive, lymph node (LN)-negative breast cancer measuring more than 1 cm treated at eight different institutions from 1997 to 2004; to explore whether chemotherapy use varied over time and between institutions; and to identify factors associated with the decision to forego chemotherapy.

PATIENTS AND METHODS

Data Source

Since 1997, the NCCN Breast Cancer Outcomes Database has collected data prospectively on patient and tumor characteristics, treatments, and outcomes for women with newly diagnosed breast cancer seen at participating member institutions.²¹⁻²⁴ The eligibility criteria and data collection procedures for the database have been described previously.^{22,25,26} Briefly, tumor characteristics and clinical/treatment information are gathered from tumor registries and medical record reviews. Patient characteristics, such as menopausal status, comorbidity, education level, race/ethnicity, income, type of insurance, and employment status, are collected from a patient-reported survey conducted when women first present to an NCCN institution. All data are subjected to rigorous quality assurance checks that include on-site audits against source documents.

The following eight institutions contributed data to this analysis: City of Hope National Medical Center, Dana-Farber Cancer Institute, Fox Chase Cancer Center, The University of Texas M. D. Anderson Cancer Center, Roswell Park Cancer Institute, University of Michigan Cancer Center, Ohio State University, and H. Lee Moffitt Cancer Center (de-identified for this analysis). Each institution is an academic cancer center; the providers who treat breast cancer at these institutions generally devote most or all of their clinical effort to breast cancer care. Institutional review boards from each center approved the data collection, transmission, and storage protocols. When institutional review boards required signed informed consent for data collection, only patients who provided consent were included in the database.

Patient Selection

Patients were included for analysis if they were diagnosed with HR-positive, LN-negative, nonmetastatic, invasive, unilateral breast cancer measuring ≥ 1 cm and presented to an NCCN institution between July 20, 1997 and December 31, 2004 ($n = 3,925$). Cancers were considered HR positive if either the estrogen or progesterone receptor was detected (quantitative receptor data were not available). Patients had to have evidence of nodal evaluation, either axillary dissection or sentinel biopsy, and all evaluated LNs had to be cancer free. In addition, patients had to have been observed for at least 180 days after their first visit to an NCCN institution. Women age 70 years or older were excluded because, as noted in the NCCN guidelines, there were insufficient data to define chemotherapy recommendations for this cohort ($n = 658$). Women with previous breast cancer were also excluded ($n = 77$).

Variables of Interest

Age at diagnosis was categorized into the following three groups: younger than age 50 years, age 50 to 59 years, and age 60 to 69 years. Comorbidity scores were derived using previously described methods.^{27,28} Women were classified as postmenopausal if they had no menses in the last 6 months, were on hormone replacement therapy, or were age 50 years or older and menstrual status was not documented in the chart or patient survey. Tumor sizes were grouped based on pathologic data (1 to 2, 2.1 to 3, and ≥ 3.1 cm). Two histologic subtypes were defined (ductal/lobular or any of the following: tubular, colloid, medullary, adenocystic, and papillary). Tumor grade was categorized as either high (if histologic or nuclear grade was high) or low-intermediate (all others), in accordance with the risk classification scheme described by the NCCN. HER-2 was considered overexpressed if the fluorescent in situ hybridization result was positive or the immunohistochemistry score was 3+ or positive. Margins were recorded for the final procedure and were considered either negative or close/positive (if < 2 mm). Type of definitive breast cancer surgery (mastectomy or breast-conserving surgery), receipt of radiation therapy (yes or no), and receipt of antiestrogen therapy (yes or no) were recorded for each patient. Women were considered to have received adjuvant chemotherapy if treatments started within 180 days of the cancer diagnosis and before any recurrence.

Data Analyses

We analyzed the relationships between receipt of chemotherapy and individual predictors using univariate logistic regression. Then, to assess the relationship between receipt of chemotherapy and selected covariates while holding all other variables constant, we constructed a multivariable logistic regression model. A covariate was included in the model if the two-tailed P value for its univariate association with receipt of chemotherapy was $P < .2$. Covariates that were significant on multivariable analysis ($P < .05$) were included in the final model; results were reported using adjusted odds ratios with 95% CIs. For year of diagnosis, 1999 was chosen as the reference group because this was the first year in which all of the centers contributed data. For institution, institution D was chosen as the reference group because it contributed data to every year of the analysis and its rate of chemotherapy use was relatively stable over time. For the other variables, reference groups were selected to optimize clinical relevance and interpretability.

To explore how chemotherapy use varied over time and between institutions, we added interaction terms to the model in a sequential manner. These analyses focused on a predetermined set of predictors, including age, tumor size, HER-2 status, tumor grade, year of diagnosis, and institution. When analyzing interaction terms, year of diagnosis was categorized into four groups (1997 to 1998, 1999 to 2000, 2001 to 2002, and 2003 to 2004) to simplify the results. When interaction terms were significant, we conducted stratified analyses of unadjusted data and explored associations and trends within each stratum using the χ^2 or Mantel-Haenszel test.

RESULTS

Patient Characteristics

The sociodemographic, tumor, and treatment characteristics of 3,190 women with HR-positive, LN-negative breast cancer measuring more than 1 cm are listed in Table 1. Although a majority of patients were age 50 years or older, a significant proportion (39.7%) was younger than age 50 years. Most were white/non-Hispanic (84.5%), were educated beyond high school (58.6%), and worked outside of the home (55.4%). Having multiple noncancer comorbid diagnoses was uncommon (6.1%). A relatively small number of patients were diagnosed in 1997 because data collection began in July of that year, but two sites (F and H) did not start collecting data until 1999. As expected, most tumors measured 1 to 2 cm (76.9%), but a substantial number were more than 2 cm ($n = 737$).

Table 1. Patient Characteristics

Characteristic	No. of Patients (N = 3,190)	%
Age at diagnosis, years		
< 50	1,266	39.7
50-59	1,107	34.7
60-69	817	25.6
Menopausal status		
Premenopausal	1,365	42.8
Postmenopausal	1,825	57.2
Race/ethnicity		
White non-Hispanic	2,695	84.5
African American non-Hispanic	171	5.4
Hispanic	198	6.2
Asian non-Hispanic	79	2.5
Other non-Hispanic	28	0.9
Unknown	19	0.6
Education		
Above high school	1,870	58.6
High school degree or less	780	24.4
Other	10	0.3
Unknown/missing	530	16.6
Health insurance		
Managed care	2,258	70.8
Indemnity	307	9.6
Medicaid/indigent	125	3.9
Medicare	395	12.4
Self-pay	81	2.5
Other	13	0.4
Unknown/missing	11	0.3
Employment		
Employed or student	1,769	55.4
Homemaker	528	16.6
Unemployed	160	5.0
Retired	417	13.1
Other	69	2.2
Unknown/missing	247	7.7
Comorbidity score		
0-1	2,994	93.9
≥ 2	196	6.1
Year of diagnosis		
1997	129	4.0
1998	300	9.4
1999	366	11.5
2000	493	15.4
2001	471	14.8
2002	541	17.0
2003	503	15.8
2004	387	12.1
Size of primary tumor, cm		
1-2	2,453	76.9
2.1-3	538	16.9
≥ 3.1	199	6.2
Hormone receptor status*		
ER and PR positive	2,584	81.0
ER positive, PR negative	488	15.3
PR positive, ER negative	102	3.2
One receptor unknown or missing	16	0.5
Histology or nuclear grade		
Low/intermediate	2,031	63.7
High	1,010	31.7
Unknown	149	4.7

(continued in next column)

Table 1. Patient Characteristics (continued)

Characteristic	No. of Patients (N = 3,190)	%
Lymphovascular invasion		
Absent	2,657	83.3
Present	450	14.1
Unknown	83	2.6
Surgical margins		
Negative	3,019	94.6
Positive/close (< 2 mm)	170	5.3
Unknown/missing	1	< 0.1
Histology type		
Invasive ductal and/or lobular	3,009	94.3
Tubular, colloid, medullary, or adenocystic	181	5.7
HER-2 status		
Not overexpressed	2,318	72.7
Overexpressed	327	10.2
Unknown	545	17.1
Type of definitive surgery		
Breast-conserving surgery	2,140	67.1
Mastectomy	1,050	32.9
Receipt of radiation therapy		
Yes	2,159	67.7
No	1,031	32.3
Receipt of hormone therapy		
Yes	2,907	91.1
No	283	8.9
Receipt of chemotherapy		
Yes	1,751	54.9
No	1,439	45.1

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

*In 16 patients, one hormone receptor was missing or unknown, and the other hormone receptor was positive.

Treatments

A majority of women (54.9%) received chemotherapy. In bivariate analysis, chemotherapy use increased as tumor size increased (46.8% for 1.0- to 2.0-cm tumors, 79.9% for 2.1- to 3.0-cm tumors, and 86.9% for > 3.0-cm tumors; Mantel-Haenszel χ^2 , $P < .01$). Chemotherapy use decreased as patient age increased (75.7% for women < age 50 years, 53.9% for women age 50 to 59 years, and 24.0% for women age 60 to 69 years; Mantel-Haenszel χ^2 , $P < .01$). There was a modest trend toward increased chemotherapy use over time (Spearman correlation, $r = 0.04$; $P = .021$). All patients had definitive surgery. A similar proportion had breast-conserving surgery (67.1%) and radiation therapy (67.7%). Almost all women received antiestrogen hormone therapy (91.1%). Those who received hormonal therapy, compared with those who did not, were more likely to have a cancer positive for both estrogen and progesterone receptor (82.3% v 67.5%, respectively; $P < .01$) and to have received chemotherapy (55.8% v 45.9%, respectively; $P < .01$).

Predictors of Chemotherapy

When controlling for other factors, women were more likely to receive chemotherapy if they were younger, premenopausal, or had fewer comorbidities (Table 2). They were also more likely to receive chemotherapy if their tumors were large, did not express either estrogen or progesterone receptor, were high grade, showed lymphovascular invasion, or overexpressed HER-2. In addition to these patient and

Table 2. Multivariable Analysis of Predictors of Receiving Chemotherapy

Variable	Odds Ratio	95% CI	P
Age at diagnosis, years			< .001
< 50	Referent		
50-59	0.50	0.38 to 0.66	
60-69	0.12	0.09 to 0.18	
Menopausal status			< .001
Postmenopausal	Referent		
Premenopausal	1.62	1.22 to 2.14	
Comorbidity score			.014
0-1	Referent		
≥ 2	0.62	0.43 to 0.91	
Year of diagnosis			.018
1997	2.42	1.40 to 4.18	
1998	1.07	0.70 to 1.62	
1999	Referent		
2000	1.17	0.84 to 1.65	
2001	1.12	0.79 to 1.58	
2002	1.27	0.91 to 1.77	
2003	1.41	1.00 to 1.99	
2004	1.46	1.01 to 2.10	
Institution			< .001
A	1.54	0.96 to 2.47	
B	0.97	0.73 to 1.27	
C	0.60	0.43 to 0.85	
D	Referent		
E	0.61	0.44 to 0.85	
F	1.72	1.14 to 2.60	
G	2.17	1.61 to 2.94	
H	1.02	0.74 to 1.40	
Size of primary tumor, cm			< .001
1-2	Referent		
2.1-3	4.81	3.68 to 6.28	
≥ 3.1	6.92	4.22 to 11.35	
Hormone receptor status			< .001
ER and PR positive	Referent		
ER positive, PR negative	1.47	1.15 to 1.89	
PR positive, ER negative	2.85	1.64 to 4.95	
One receptor unknown or missing	1.07	0.30 to 3.90	
High histologic or nuclear grade			< .001
Low/intermediate	Referent		
High	2.29	1.86 to 2.83	
Unknown	1.54	0.99 to 2.40	
Lymphovascular invasion			< .001
Absent	Referent		
Present	2.68	2.02 to 3.56	
Unknown	0.91	0.52 to 1.59	
Histologic type			< .001
Ductal and/or lobular	Referent		
Tubular, colloid, medullary, or adenocystic	0.21	0.14 to 0.32	
HER-2 status			< .001
Not overexpressed	Referent		
Overexpressed	2.15	1.53 to 3.02	
Unknown	0.65	0.47 to 0.90	
Type of definitive surgery			< .001
Breast-conserving surgery	Referent		
Mastectomy	3.03	1.89 to 4.85	
Receipt of radiation therapy			< .001
No	Referent		
Yes	2.50	1.57 to 4.00	
Receipt of antiestrogen therapy			< .001
No	Referent		
Yes	2.14	1.55 to 2.96	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

tumor characteristics, year of diagnosis and institution were significant predictors of receiving chemotherapy. Use of chemotherapy increased modestly over time; there was a 1.46 greater odds of receiving chemotherapy in 2004 versus 1999. When compared with a reference institution with an intermediate propensity to offer chemotherapy, two institutions were more likely, two were less likely, and three showed no statistically significant difference in their odds of administering chemotherapy.

Variation Across Institutions and Over Time

Across institutions, the frequency of chemotherapy use ranged from 43.5% to 60.0% in 1997 to 1998 and from 47.3% to 77.9% in 2003 to 2004. Compared with the institution that was least likely to use chemotherapy in 2003 to 2004 (institution E), the institution that was most likely to use chemotherapy (institution G) had a 1.6-fold greater likelihood of administering chemotherapy. The largest absolute increase in chemotherapy use over time occurred at institution G, where the frequency went from 46.3% in 1997 to 1998 to 77.9% in 2003 to 2004 (a 68% relative increase). The largest absolute decrease in chemotherapy use occurred at institution F, where the frequency went from 72.7% in 1999 to 2000 to 56.9% in 2003 to 2004 (a 22% relative decrease).

Interactions added to the model explored how chemotherapy use varied between institutions and over time. Only age demonstrated a significant interaction with institution. Figure 1 displays unadjusted rates of chemotherapy use for each institution across the different age subgroups. Although institutions demonstrated significant variability in their use of chemotherapy for patients age 50 years and older, the association for patients younger than age 50 years was not significant. Age, tumor size, and institution each demonstrated significant interaction with year of diagnosis on multivariable analysis. Figure 2 displays the unadjusted rates of chemotherapy use for each year of diagnosis across the different age, tumor size, and institution subgroups. Interestingly, a trend toward increasing use of chemotherapy over time only appeared among older patients. Only women with larger tumors (> 2 cm) demonstrated a significant trend toward increasing chemotherapy use over time. Some institutions demonstrated a significant trend toward increasing use of chemotherapy over time, whereas others demonstrated a significant trend toward decreased use over time. There were no significant interactions between institution and tumor size, HER-2 status, or grade or between year of diagnosis and HER-2 status or grade.

The odds of receiving chemotherapy for each institution during each 2-year period, after controlling for other covariates, are shown in Figure 3. Institution D during the 1997 to 1998 period served as the referent group. Half of the institutions demonstrated a trend toward decreased chemotherapy use over time, and half demonstrated a trend toward increased chemotherapy use over time. When each institution's performance during 2003 to 2004 was compared with itself during the first 2-year period it contributed data (Table 3), two institutions demonstrated a significant increase in their propensity to administer chemotherapy (institutions G and H), and two demonstrated a significant decrease (institutions B and F).

DISCUSSION

To better understand the patterns and predictors of chemotherapy use for women with HR-positive, LN-negative breast cancer, we analyzed

Fig 1. Percentage of patients receiving chemotherapy at each institution stratified by age at diagnosis. *P* values refer to analyses of unadjusted relationships between institution and receipt of chemotherapy for each age stratum using the χ^2 test.

data for 3,190 women treated at eight comprehensive cancer centers from 1997 to 2004. Although a majority of women received chemotherapy, almost half (45%) did not. The rate of chemotherapy use across all institutions increased only modestly over time (from 52% in 1997 to 1998 to 58% in 2003 to 2004). That older patients and women with larger tumors were significantly more likely to receive chemotherapy over time suggests that there may have been a transition away from age-based determinants toward tumor-specific determinants of chemotherapy use. On multivariable analysis, patient variables (eg, younger age, premenopausal status, and fewer comorbidities) and tumor characteristics (eg, larger primary cancer, absence of estrogen or progesterone receptor, high grade, lymphovascular invasion, and HER-2 overexpression) were associated with a higher likelihood of receiving chemotherapy. Institutions exhibited significantly different odds of chemotherapy use and divergent trends in use over time.

That almost half of the cohort did not receive chemotherapy is remarkable for several reasons. First, clinical trial data demonstrated that chemotherapy led to superior outcomes for women with HR-positive, LN-negative breast cancer before the patients we analyzed were treated.³ Second, practice guidelines recommended chemotherapy for HR-positive, LN-negative breast cancer during the time period included in our analysis.^{8,29} Third, studies questioning the benefits of chemotherapy came out largely after our analysis concluded.^{11,30} Fourth, our cohort excluded women unlikely to benefit from chemotherapy (ie, those > age 70 years or with tumors < 1 cm). Considering that no institution administered chemotherapy to more than 78% of women, there seemed to be some agreement that not all women with localized HR-positive breast cancer should receive adjuvant chemotherapy. One possible explanation for this willingness to selectively forego chemotherapy is expressed in a footnote to the NCCN guidelines, which states that chemotherapy confers only a small absolute benefit

Fig 2. Percentage of patients receiving chemotherapy by age at diagnosis, tumor size, and institution for each year of diagnosis. *P* values refer to analyses of unadjusted relationships between receipt of chemotherapy and age, tumor size, or institution using the Mantel-Haenszel χ^2 test for trend.

Fig 3. Adjusted odds of receiving chemotherapy for each institution over time. The referent group for all odds ratios is institution D during the 1997 to 1998 period.

that some may feel is not clinically significant enough to warrant the potential risks in all patients.¹⁰

However, this does not explain how providers decided when to give and when to forego chemotherapy. Our analysis showed that institutions demonstrated significant variability with regard to which women got chemotherapy, the proportion of patients who received it, and the trend in chemotherapy use over time. These interinstitutional differences were not explained by variations in established prognostic markers. Furthermore, all institutions had access to the same randomized controlled trial data and clinical practice guidelines, which, during the period analyzed in our study, did not offer clear guidance regarding which subgroups should and should not receive chemotherapy. Perhaps non-evidence-based differences in providers' opinions and preferences about chemotherapy contributed to the interinstitutional variability that we observed. One could argue that not administering chemotherapy to a significant subset of women with HR-positive, LN-negative breast cancer measuring more than 1 cm reflects poor quality care. However, we do not believe these data can be used to characterize institutions' quality of care because there is no clear expert consensus regarding what should be considered optimal care. This lack of agreement makes it all the more difficult to derive clinical practice guidelines that provide straightforward evidence and consensus-based recommendations.

Because our analysis did not include data from community-based cancer centers or office-based practices, it is not possible to address the care provided outside comprehensive cancer centers. However, the rates of chemotherapy use observed in our study were notably higher than those from previous population-based studies. During the early 1990s, a Surveillance, Epidemiology, and End Results–Medicare analysis of women age 65 to 69 years with HR-positive, LN-negative breast cancer found that 4.8% received chemotherapy,³¹ and a study of women with HR-positive or -negative breast cancer treated in Quebec found that 37% of women with stage II breast cancer received chemotherapy.³² A more recent analysis of Surveillance, Epidemiology, and End Results data found that only 26% of women with HR-positive, LN-negative breast cancer treated in 2000 received chemotherapy.³³ On the basis of these studies, community-based providers seem to be less likely to administer chemotherapy. However, some community-based providers could be more likely to administer chemotherapy if they tend to follow clinical practice guidelines or are influenced by the financial implications of administering chemotherapy. Detailed data on patterns of care in the community setting are needed but are hard to come by.

Our analysis has several limitations. First, although we did not demonstrate an association between receipt of chemotherapy and sociodemographic variables such as race/ethnicity, we had limited power to detect such a relationship because the cohort included a relatively small number of minority patients. Second, our analysis did not consider patient preferences. It is unlikely that patient preferences could account for the observed patterns of care for several reasons. First, much higher rates of chemotherapy use were observed in women with HR-negative, LN-negative breast cancer measuring more than 1 cm (91%) and in women with HR-positive, LN-positive breast cancer (92%).³⁴ Second, patient preferences are unlikely to vary significantly from institution to institution, so they could not explain the significant interinstitutional variability in chemotherapy use that we observed. Finally, we cannot assess the degree to which individual providers influenced patterns of chemotherapy use because the NCCN does not collect provider-specific data.

Deciding whether to recommend and receive adjuvant chemotherapy for HR-positive, LN-negative breast cancer is a frequent and important decision faced by many patients and nearly every oncologist in the United States. Although several studies demonstrate that

Table 3. Adjusted Odds of Receiving Chemotherapy for Each Institution in Order From Lowest to Highest Odds Ratio in 2003 to 2004

Institution	Year of Diagnosis							
	1997-1998		1999-2000		2001-2002		2003-2004	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
F	NA		Referent		0.54	0.23 to 1.27	0.27	0.11 to 0.67
A	Referent		1.22	0.29 to 5.16	0.54	0.14 to 2.07	0.37	0.10 to 1.33
B	Referent		0.85	0.44 to 1.66	0.58	0.31 to 1.11	0.39	0.20 to 0.77
E	Referent		0.66	0.26 to 1.68	0.63	0.25 to 1.56	0.56	0.22 to 1.44
D	Referent		1.20	0.69 to 2.09	1.20	0.69 to 2.07	1.70	0.99 to 2.91
C	Referent		0.46	0.17 to 1.24	0.99	0.38 to 2.58	1.83	0.72 to 4.62
G	Referent		1.31	0.53 to 3.21	2.87	1.13 to 7.30	4.00	1.42 to 11.29
H	NA		Referent		1.87	0.98 to 3.57	5.40	2.68 to 10.87

NOTE. An institution's performance during the first period it provided data served as the reference point for its performance during all subsequent periods. Abbreviation: NA, data not available.

chemotherapy improves survival,³⁻⁶ others suggest that postmenopausal women and women with lower risk breast cancer may not benefit from chemotherapy.^{5,7,11,12} Moreover, chemotherapy may confer only a small absolute benefit and can cause serious adverse events.¹⁰ Given the modest benefits and nontrivial risks of chemotherapy, together with the lack of evidence defining which subgroups actually benefit, the patterns of care that we observed are not surprising. Interestingly, these patterns of care suggest that institutions were willing to embrace risk-adapted decision making before high-quality data supported this approach.

Recent gene expression profiling studies have identified subsets of women who have a lower risk of recurrence³⁵⁻³⁷ and do not seem to benefit from chemotherapy.³⁰ These new tests help validate the concept of risk-adapted decision making endorsed by several practice guidelines^{7,8,13-15} and offer evidence-based guidance regarding who should and should not receive chemotherapy. However, the recommendations that come from these gene expression profiles do not always agree with the direction provided by clinical practice guidelines and other decision tools (eg, Adjuvant Online). However, only prospective randomized controlled trials, such as Trial Assigning Individualized Options for Treatment³⁸ and Microarray in Node-Negative Disease trial,³⁹ will conclusively establish the benefits and risks of chemotherapy within the different subgroups of HR-positive, LN-negative breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

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