Impact of Adjuvant Chemotherapy on Long-Term Employment of Survivors of Early-Stage Breast Cancer

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BACKGROUND: Many women with early-stage breast cancer are working at the time of diagnosis and survive without disease recurrence. The short-term impact of chemotherapy receipt on employment has been demonstrated, but the long-term impact merits further research. **METHODS:** The authors conducted a longitudinal multicenter cohort study of women diagnosed with nonmetastatic breast cancer between 2005 and 2007, as reported to the population-based Los Angeles and Detroit Surveillance, Epidemiology, and End Results program registries. Of 3133 individuals who were sent surveys, 2290 (73%) completed a baseline survey soon after diagnosis and of these, 1536 (67%) completed a 4-year follow-up questionnaire. **RESULTS:** Of the 1026 patients aged < 65 years at the time of diagnosis whose breast cancer did not recur and who responded to both surveys, 746 (76%) worked for pay before diagnosis. Of these, 236 (30%) were no longer working at the time of the follow-up survey. Women who received chemotherapy as part of their initial treatment were less likely to be working at the time of the follow-up survey (38% vs 27%; P = .003). Chemotherapy receipt at the time of diagnosis (odds ratio, 1.4; P = .04) was found to be independently associated with unemployment during survivorship in a multivariable model. Many women who were not employed during the survivorship period wanted to work: 50% reported that it was important for them to work and 31% were actively seeking work. **CONCLUSIONS:** Unemployment among survivors of breast cancer 4 years after diagnosis is often undesired and appears to be related to the receipt of chemotherapy during initial treatment. These findings should be considered when patients decide whether to receive adjuvant chemotherapy, particularly when the expected benefit is low. *Cancer* 2014;120:1854-62. © 2014 American Cancer Society.

KEYWORDS: employment, breast cancer, chemotherapy, survivorship, work, survey, Surveillance, Epidemiology, and End Results (SEER).

INTRODUCTION

Greater than 225,000 women are diagnosed with invasive breast cancer in the United States each year, ¹ the majority of whom are of working age and survive through the typical age for retirement. Some work loss during the treatment period is common as patients balance an arduous treatment schedule and acute side effects with work and family life. However, less is known regarding the long-term impact of cancer treatments on paid employment. Because work may be intrinsically rewarding and is also an important source of income, insurance, and social interactions, loss of work may profoundly affect quality of life in addition to causing economic losses for society, particularly when it extends beyond the treatment period. Therefore, understanding the long-term effects of treatment on employment status is a critical focus of survivorship research.²

Previous studies have primarily evaluated the employment trajectory of patients with breast cancer during treatment and soon thereafter. In a population-based study of US patients 9 months after a diagnosis of breast cancer, we previously reported that 24% had missed > 1 month of work and 32% had stopped working altogether due to breast cancer or its treatment.³ Similarly, a Dutch study found that only 70% of workers with breast cancer had even partially returned to

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Loss of paid employment after a diagnosis of breast cancer is common, often undesired, not restricted to the treatment period, and potentially related to the type of treatment administered. These findings should be considered when patients decide whether to receive adjuvant chemotherapy, particularly when the expected benefit is low.

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work 1 year after their breast cancer diagnosis. Other studies have suggested that women do eventually return to work. In a longitudinal US study conducted from 2001 through 2002, only 17% of previously employed breast cancer survivors were not working at 18 months. In a population-based study of Swedish patients with breast cancer, only 11% of those who worked before diagnosis were not working 16 months later. Thus, existing data suggest substantial effects of cancer diagnosis and treatment on employment during the first year after diagnosis but a possible waning of impact by the second year.

Less is known concerning the long-term employment outcomes of survivors of breast cancer, and specifically whether certain subgroups of patients with cancer are particularly vulnerable to loss of desired employment during the long-term survivorship period.⁸ Previous research has suggested that long-term survivors of breast cancer are, in general, less likely to be employed than their counterparts without breast cancer. 9,10 Cancer survivors may experience a change in their desire for work, prioritizing volunteerism, family, or leisure more after facing a life-threatening illness. 11 Survivors might also face discrimination from employers. 12-14 Long-term morbidity related to either treatment or disease recurrence may reduce survivors' ability to work. 15-19 Moreover, treatments may have led to periods of missed work that may have lasting consequences on survivors' subsequent ability to maintain long-term employment.

The potential impact of chemotherapy on long-term employment outcomes in particular requires further investigation. We previously found that patients who received chemotherapy were more likely to stop working in the short term,³ and in a sample of low-income survivors of breast cancer, others have found that very poor women who stop working during chemotherapy are at risk of not returning to work in the longer term.²⁰ Yet others have found no effect of chemotherapy on return to work.^{6,21} Moreover, relatively little is known regarding whether those who fail to return to work are actively seeking work.

Experts in the field have identified desirable methodologic criteria for studies of work after cancer, ²² including population-based sampling, longitudinal design, detailed measures, and adequate sample size. We developed a study that fulfilled these criteria and conducted a longitudinal study inquiring about work outcomes in the population-based sample of patients with breast cancer we had previously surveyed near the time of diagnosis, ³ seeking specifically to investigate whether chemotherapy receipt as part of the initial treatment was associated with

the employment outcomes among long-term survivors of breast cancer.

MATERIALS AND METHODS

Study Sample

We conducted a longitudinal, multicenter cohort study of women diagnosed with breast cancer in metropolitan Los Angeles and Detroit. A major prespecified objective of the current study was to examine racial/ethnic differences in disruption of paid work for patients with breast cancer into the survivorship period. Patients aged 20 years to 79 years and diagnosed with American Joint Committee on Cancer (AJCC) stage 0 to III breast cancer between June 2005 and February 2007, as reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population-based program registries in those regions, were eligible for sample selection. Using a population-based registry allows for a study sample that is generally representative of the population of incident cancer cases in the respective geographic area in terms of sex, race or ethnicity, age, and other demographic characteristics. We used the rapid case ascertainment method, which allows the SEER registries to identify patients within 1 month of their diagnosis. 23

Patients were excluded if they had stage IV breast cancer or could not complete a questionnaire in English or Spanish. Asian women in Los Angeles were excluded because of enrollment in other studies (the Los Angeles SEER protocol limits patient enrollment into multiple concurrent studies). Latina (in Los Angeles) and black (in both Los Angeles and Detroit) patients were oversampled to ensure sufficient minority representation.

Questionnaire Design and Content

We developed original questionnaires after considering the existing literature, measures previously developed to assess relevant constructs, 3,24 and theoretical models. Measures in the survey were pretested to maximize reliability and validity and were based on a priori hypotheses generated from preliminary studies, which suggested gaps in return to paid work after treatment of breast cancer. Survey content included extensive batteries of questions addressing paid work, financial issues, and other quality-of-life factors. Additional content in the 38-page initial survey questionnaire and 42-page follow-up survey questionnaire addressed other treatment and care issues relevant during the survivorship period (see online supporting information). To avoid response bias, survey recipients received survey questionnaires simply entitled

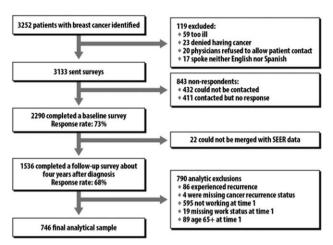


Figure 1. Flow of patients into the study from those initially identified to the final analytic sample is shown. SEER indicates Surveillance, Epidemiology, and End Results.

"A Study of Women's Experiences with Treatment for Breast Cancer" (see online supporting information).

Data Collection

After Institutional Review Board approval, eligible patients were identified and informed of all aspects and the intent of the study in the survey materials. The Institutional Review Board approved a waiver of a written signature of informed consent, with the return of a completed survey taken to indicate informed consent. After notifying physicians, we first recruited and surveyed patients at a mean of 9 months after diagnosis (mean time from diagnosis to survey response, 284 days; standard deviation, 96 days). We then contacted all respondents approximately 4 years later (mean time from diagnosis to survey response, 1524 days; standard deviation, 143 days). To encourage responses, we provided a \$10 cash incentive along with the paper survey mailing and used a modified Dillman method,²⁵ including reminders to nonrespondents. All materials were sent in English and in Spanish to those with Spanish surnames.²⁶ Responses to the baseline and follow-up surveys were combined into a single data set, into which clinical data from SEER were merged. The evolution of the sample is detailed in Figure 1.

Measures

Our primary dependent variable for analysis was defined by selecting those women who reported working (regardless of whether they were employed full time or part time) before diagnosis (as reported in the baseline questionnaire) and then determining which of these reported in the follow-up survey that they were not working at that time.

We considered several independent variables. Clinical factors included SEER-reported clinical stage of disease (AJCC stage 0, I, II, or III) and patient-reported comorbidity and treatment (chemotherapy, radiotherapy, and surgery) as measured in the baseline survey. Sociode-mographic factors were determined in the baseline questionnaire, including age, race/ethnicity, educational status, family income, marital status, work hours at the time of diagnosis (full time vs less than full time), and employment support (having a job with sick leave and/or a flexible schedule). Geographic site (Los Angeles vs Detroit) was also included in the analyses.

We measured in the follow-up survey patients' perceptions of whether, since the time of diagnosis, they were worse off with regard to health insurance, employment status, and financial status. We also evaluated, among those women not working at the time of the follow-up survey, how important it was for them to work and whether they were actively seeking employment.

Statistical Analysis

To allow statistical inferences to be more representative of the original targeted population, we applied survey weights and implemented a multiple imputation method to the calculation of percentages and regression analyses.²⁷ All percentages reported below are so weighted and reported alongside unweighted numbers. Design weights compensated for the disproportionate selection across race and SEER sites; survey unit nonresponse weights compensated for the fact that women with certain characteristics were not as likely to respond to the surveys (patients who did not respond to both surveys were more likely to be African American [35.2% vs 26.7%; P < .001], to be Latina [17.2% vs 13.3%; P = .002], to have stage II-III disease [54.9% vs 37.8%; P < .001], and to have undergone a mastectomy [37.5% vs 30.8%; P < .001). Among patients who responded to both surveys, missing data due to survey item nonresponse constituted 10% of the analytic sample when all covariates in the final model were considered simultaneously. To address missing data from nonresponse to an item, we first multiply imputed the data 5 times followed by combining the results from statistical analyses on these 5 imputed data sets using the Rubin's formula. 28,29 We limited our analytic sample to patients aged <65 years at diagnosis, whose breast cancer did not recur before the follow-up survey, who responded to both surveys, and who reported working for pay before their diagnosis in the baseline

survey. We examined patterns and correlates of paid work at the time of the follow-up survey using chi-square tests for univariate analyses and logistic regression analysis for multivariable analyses, which included the following theoretically selected independent variables: age, number of comorbidities, race, education, family income, work hours at the time of diagnosis, employment support, marital status, AJCC stage of disease, chemotherapy receipt, surgery type, radiation receipt, and geographic site. In the logistic regression analysis, we tested for interactions between chemotherapy use and other covariates in the model as well as between family income and geographic site. These interactions were not found to be significantly associated with work loss and we subsequently eliminated them from the final model. Collinearity of the covariates was assessed using variance inflation factors. 30 All analyses were conducted using SAS statistical software (version 9.2; SAS Institute Inc, Cary, NC).

RESULTS

Of the 1026 patients aged < 65 years at the time of diagnosis whose breast cancer did not recur and who responded to both surveys, 746 (76%) reported working for pay before diagnosis in the baseline survey. Of these, 236 patients (30%) were no longer working at the time of the follow-up survey.

Table 1 describes the clinical and sociodemographic characteristics of the sample, and Table 2 presents the bivariate correlates of employment at the time of the follow-up survey. As shown in Tables 1 and 2, 61% of respondents had received chemotherapy. Women who received chemotherapy as part of their initial cancer treatment were more likely to report that they were not working at the time of the follow-up survey (38% vs 27%; P = .003). There was no statistically significant difference noted by chemotherapy receipt in the percentage of respondents who considered themselves to be retired at the time of the follow-up survey (13% of patients receiving chemotherapy and 14% of those not receiving chemotherapy; P = .48).

Figure 2 depicts the pattern of employment among women who were employed at the time of their breast cancer diagnosis. Women who were employed at the time of diagnosis were substantially less likely to be employed after their initial treatment if they had received chemotherapy. Long-term survivors were also less likely to be employed 4 years after diagnosis if they had received chemotherapy as part of their initial treatment.

The excess unemployment observed for women who received chemotherapy began soon after diagnosis. Com-

TABLE 1. Characteristics of Patient Sample (n=746)

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Abbreviation: AJCC, American Joint Committee on Cancer.

pared with women who did not receive chemotherapy, women who did were more likely to report stopping work \geq 2 years before the follow-up survey (30% vs 14%; P<.001) and were more likely to have stopped work during the initial course of therapy (56% vs 13%; P<.001). Overall, 26% of patients treated with chemotherapy and 9% of others were not working both after the initial treatment and in the long-term, 22% of patients treated with chemotherapy and 7% of others were not working after

^a Percentages are weighted and missing values have been imputed.

TABLE 2. Bivariate Analyses of 4-Year Unemployment

Characteristic	% With 4-Year Unemployment ^a	P
Age at diagnosis, y		.005
<46	30.2	
46-55	28.5	
>56	43.2	
No. of comorbidities		<.001
0	17.4	
1	24.7	
≥2	48.1	
Race		<.001
White	26.4	
Black	31.0	
Latina	43.0	
Other	39.7	
Education		<.001
<high school<="" td=""><td>48.6</td><td></td></high>	48.6	
Some college	29.8	
≥College graduate	25.0	
Family income at time of baseline survey	20.0	<.001
<\$20,000	52.1	<.001
\$20,000-\$69,999	34.7	
≥\$70,000 ≥\$70,000	23.3	
Work status at time of diagnosis	20.0	.48
Employed full time	33.0	.40
Employed part time or occasional	36.7	
	30.7	<.001
Employment support Sick leave and/or flexible schedule	24.7	<.001
None		
	46.8	44
Marital status	05.7	.44
Not married or partnered	35.7	
Married or partnered	32.5	000
AJCC stage of disease	00.4	.020
0	29.4	
1	26.8	
II	39.6	
III	41.9	
Chemotherapy receipt		.003
No	26.7	
Yes	38.3	
Surgery type		.039
Lumpectomy	30.4	
Mastectomy	38.8	
Radiation receipt		.75
No	34.6	
Yes	33.4	
Geographic site		.59
Los Angeles	34.2	
Detroit	32.0	

Abbreviation: AJCC, American Joint Committee on Cancer.

their initial treatment but were working again in the long-term, 11% of patients treated with chemotherapy and 17% of others had not stopped work after their initial treatment but were not working in the long-term, and 41% of patients treated with chemotherapy and 67% of others continued working both after the initial treatment and in the long-term.

Table 3 presents a multivariable model for 4-year unemployment. Patients who reported receiving chemo-

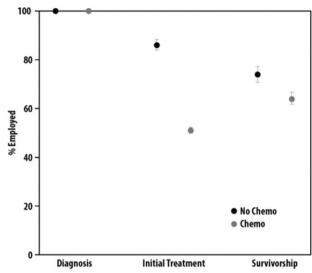


Figure 2. Employment outcomes are shown as the percentage of women working before their diagnosis, at the time of the baseline survey (approximately 9 months after diagnosis: "the initial treatment period"), and at the time of the follow-up survey (approximately 4 years later: "the survivorship period") by receipt of chemotherapy (Chemo).

therapy at the time of diagnosis were significantly more likely to report unemployment at 4 years (odds ratio [OR], 1.42; 95% confidence interval [95% CI], 1.03-1.98). Other significant correlates of 4-year unemployment were older age (OR, 1.42 for age \geq 56 years compared with age <46 years; 95% CI, 1.03-1.95), greater number of comorbidities (OR, 2.16 for \geq 2 comorbidities vs none; 95% CI, 1.59-2.94), and lack of employment support (OR, 1.33; 95% CI, 1.08-1.67).

Many women who were not employed in the survivorship period wanted to work. Of the 127 women who had not worked since diagnosis, 63 (55%) reported that it was important for them to work and 39 (39%) were actively looking for work. These figures were similar for patients who did and did not receive chemotherapy during the initial treatment period: 31% versus 32% were actively looking for work (P = .96) and 50% versus 49% reported that work remained important to them (P = .76). Moreover, those who were no longer working were significantly more likely to report that they were worse off with regard to their insurance status and financial status, as depicted in Figure 3 (P < .001 for each).

DISCUSSION

In this longitudinal survey in 2 diverse US metropolitan areas, approximately one-half of the women diagnosed with early-stage breast cancer were of working age and

^a Percentages are weighted and missing values have been imputed.

TABLE 3. Multivariable Model of Long-Term Work Loss

Characteristic	OR (95% CI)	Р
Age at diagnosis, y		.031
<46	1 (referent)	
46-55	0.76 (0.57-1.01)	
≥56	1.42 (1.03-1.95)	
No. of comorbidities		<.001
0	1 (referent)	
1	0.84 (0.61-1.17)	
≥2	2.16 (1.59-2.94)	
Race		.161
White	1 (referent)	
Black	0.86 (0.53-1.38)	
Latina	1.42 (0.87-2.33)	
Other	0.94 (0.34-2.56)	
Education		.31
≤High school	1 (referent)	
Some college	0.86 (0.65-1.15)	
≥College graduate	0.98 (0.7-1.37)	
Family income at time of baseline survey		.081
<\$20,000	1 (referent)	
\$20,000-\$69,999	1.00 (0.74-1.34)	
≥\$70,000	0.73 (0.51-1.04)	
Work status at time of diagnosis		.89
Employed full time	1 (referent)	
Employed part time or occasional	0.98 (0.75-1.28)	
Employment support		.011
Sick leave and/or flexible schedule	1 (referent)	
None	1.33 (1.08-1.67)	
Marital status		.95
Not married or partnered	1 (referent)	
Married or partnered	1.01 (0.63-1.61)	
AJCC stage of disease		.183
0	1 (referent)	
1	0.81 (0.55-1.2)	
II	1.04 (0.69-1.55)	
III	1.01 (0.48-2.12)	
Chemotherapy receipt		.038
No	1 (referent)	
Yes	1.42 (1.03-1.98)	
Surgery type		.28
Lumpectomy	1 (referent)	
Mastectomy	0.82 (0.57-1.18)	
Radiation receipt		.56
No	1 (referent)	
Yes	1.12 (0.75-1.68)	
Geographic site		.27
Los Angeles	1 (referent)	
Detroit	1.14 (0.9-1.43)	

Abbreviation: 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; OR, odds ratio.

had paid employment at time of diagnosis. We found that nearly one-third of those employed before diagnosis were no longer working 4 years later, and many of these women continued to desire employment. Patients who had received chemotherapy as part of their initial course of therapy were less likely to be working 4 years after diagnosis than patients who did not receive chemotherapy, after controlling for other factors.

To our knowledge, published studies of cancer and employment outcomes to date have provided limited in-

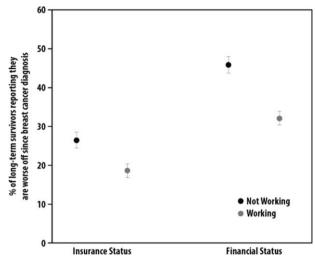


Figure 3. Perceptions of long-term survivors of breast cancer regarding their insurance status and financial status are shown based on their current employment status. Bars represent the percentage of survivors who reported being worse off at the time of the follow-up survey (approximately 4 years after diagnosis).

formation regarding the long-term impact of diagnosis and treatment on survivors of breast cancer. In analyses of the Health and Retirement Study^{10,11} and the National Health Interview Survey,³¹ cancer survivors were found to be less likely to work than controls without cancer. However, absent information concerning key clinical characteristics such as cancer stage and treatment, the mechanisms by which a cancer diagnosis affects long-term employment have remained uncertain.

Understanding which subgroups of cancer patients are most vulnerable to long-term work loss is critical for clinicians and policymakers seeking to develop appropriate interventions.³² In particular, the impact of treatments and social supports are important considerations because these are potentially modifiable. Previous studies have suggested an important influence of employment support^{3,6,7,33} or chemotherapy receipt^{21,34,35} on the short-term employment outcomes of survivors of breast cancer, including missed work, work hours, and short-term job loss. The results of the current study suggest that both of these factors may also have a long-lasting negative impact on paid employment.

We were particularly interested in chemotherapy as a risk factor for long-term unemployment because of the potential for the impact of long-term toxicities such as neuropathy or neurocognitive effects, as well as potential downstream effects of missed work during treatment due to acute toxicity. To the best of our

knowledge, few studies to date have examined the long-term impact of chemotherapy on employment outcomes. In a study of patients diagnosed with lymphoma or endometrial or prostate cancer between 1989 and 1998 in the Netherlands, chemotherapy receipt appeared to increase the risk of work loss.³⁶ In contrast, researchers who interviewed patients diagnosed with breast cancer in Quebec in 1996 and 1997 found no association between receipt of chemotherapy and employment status at the time of followup 3 years later.²¹ The contrast with the findings of the current study may be the result of changes in chemotherapy regimens and dose intensity by the time of the current study or differences in social policies and employer accommodations between the 2 countries. The timing of the current study, which spanned a period of national economic recession, may also have accentuated the adverse impact of chemotherapy on employment outcomes. In a recent study of a low-income sample of patients in the United States, chemotherapy receipt was found to be an independent predictor of long-term failure to return to work, a finding that is consistent with the current studv.20

The current study has several strengths, including its large, diverse sample; longitudinal design; and access to both clinical data and patient reports of treatment, socioeconomic characteristics, and policy-relevant outcomes. Several limitations also merit comment. First, the study was located in 2 large metropolitan areas, which may limit the generalizability of the findings, particularly to more rural areas. Second, many of our measures were drawn from patient self-report, which may have introduced bias. However, evidence supports the validity of self-report in this context.³⁷ Third, although we had access to some clinical information, we did lack information regarding the specific chemotherapy regimens used, thereby precluding our ability to differentiate whether certain approaches have a greater impact on employment outcomes. We also lacked sufficient detail regarding the nature of women's jobs to include this in the analysis, nor did we have information concerning spousal employment. Fourth, although the response rate to our surveys was high, it is possible that response bias may also have influenced the results. However, we believe it is very unlikely that correcting nonresponse bias would attenuate the association between chemotherapy and long-term employment status observed in the current study. Although we did not have valid information regarding chemotherapy receipt at time of sampling, patients who received chemotherapy may have been less likely to complete our baseline survey because it was administered during the treatment period. However, we do not believe that patients treated with chemotherapy who did not respond were less vulnerable to work loss than those who responded. In fact, the opposite may be more plausible, to the extent that those experiencing the greatest acute toxicity from chemotherapy might have been less likely to complete a survey at 9 months after diagnosis and might in fact have been those most vulnerable to employment loss related to treatment. Thus, we may actually have underestimated the negative impact of chemotherapy on paid work outcomes. Finally, we also lacked information regarding the employment outcomes of women without cancer during the time of the current study, which spanned a major recession. Although this information was not necessary to address our primary research question regarding the association between adjuvant chemotherapy and long-term employment outcomes, it might have provided potentially interesting context if available. Moreover, as noted earlier, because the recession may have accentuated any relationship between chemotherapy and subsequent unemployment, the findings of this study should not be generalized to settings in which the economic environment differs substantially from that experienced by the survivors we studied.

Similar to any observational study, challenges exist in interpreting causation. However, it appears unlikely that women with a higher risk of job loss for other reasons would have been more likely to receive chemotherapy. Indeed, we explored other potential explanatory or confounding factors for differential job loss by chemotherapy groups and did not observe an association with chemotherapy receipt, including insurance status, reasons for stopping work (eg, retirement), or less motivation to continue work (eg, less importance of work or job seeking) into the survivorship period. It is of course possible that an unmeasured factor might play a confounding role. However, the most plausible candidates for unmeasured factors associated with both chemotherapy receipt and with work loss act in a direction to strengthen rather than weaken the association observed. For example, one unmeasured factor might be the geographic microenvironment. Individuals who live in less populated areas would be expected to have less access to chemotherapy and also less access to jobs.

In conclusion, the results of the current study suggest that loss of paid employment after a diagnosis of breast cancer may be common, often undesired, not restricted to the treatment period, and potentially related to

the type of treatment administered. Many clinicians believe that although patients may miss work during treatment, they will "bounce back" in the longer term. The results of the current study suggest otherwise and highlight a possible adverse consequence of adjuvant chemotherapy. The findings reported here support current efforts to reduce the morbidity and burden of treatments for breast cancer. ³⁸ Indeed, such initiatives are actively being evaluated, including better strategies to identify those patients who might omit adjuvant chemotherapy because the marginal benefit is small. ³⁹⁻⁴¹ The results of the current study reinforce the need to advance these evaluative strategies to help physicians "first, do no harm."

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CONFLICT OF INTEREST DISCLOSURES

Dr. Jagsi was supported by a Mentored Research Scholar Grant from the American Cancer Society (MRSG-09-145-01). Dr. Jagsi has received honoraria as a medical advisory board member for eviti Inc for work outside of the current study. In addition, she is a paid employee of the University of Michigan and has provided drug and distribution only for an investigator-initiated study that was otherwise sponsored by a private philanthropic foundation (Breast Cancer Research Foundation) for AbbVie Pharmaceuticals. Dr. Katz was supported by an Established Investigator Award from the NCI (K05CA111340).

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