

Impact of Randomized Clinical Trial Results in the National Comprehensive Cancer Network on the Use of Tamoxifen After Breast Surgery for Ductal Carcinoma in Situ

Tina W.F. Yen, Henry M. Kuerer, Rebecca A. Ottesen, Layla Rouse, Joyce C. Niland, Stephen B. Edge, Richard L. Theriault, and Jane C. Weeks

ABSTRACT

Purpose

The National Surgical Adjuvant Breast and Bowel Project B-24 trial, published in June 1999, demonstrated that tamoxifen after breast-conserving surgery (BCS) and radiotherapy for ductal carcinoma in situ (DCIS) reduced the absolute occurrence of ipsilateral and contralateral breast cancer. We assessed the impact of B-24 on practice patterns at selected National Comprehensive Cancer Network (NCCN) centers.

Patients and Methods

Tamoxifen use after surgery was examined among 1,622 patients presenting for treatment of unilateral DCIS between July 1997 and December 2003 at eight NCCN centers. Associations of clinicopathologic and treatment factors with tamoxifen use were assessed in univariate and multivariable logistic regression analyses.

Results

Overall, 41% of patients (665 of 1,622) received tamoxifen. The proportion increased from 24% before July 1, 1999, to 46% on or after July 1, 1999. Factors significantly associated with receipt of tamoxifen included diagnosis on or after July 1, 1999 (odds ratio [OR], 3.85; $P < .0001$), BCS in patients younger than 70 years (OR, 3.21; $P = .0073$), no history of cerebrovascular or peripheral vascular disease (OR, 3.13; $P = .0071$), receipt of radiotherapy (OR, 1.82; $P = .0009$), and previous hysterectomy (OR, 1.34; $P = .0459$). Tamoxifen use varied significantly by center, from 34% to 74% after BCS and 17% to 53% after mastectomy ($P < .0001$).

Conclusion

Tamoxifen use after surgery for DCIS at NCCN centers increased after presentation of the B-24 results. Rates varied substantially by institution, suggesting that physicians differ in how they weigh the modest reduction in breast cancer risk with tamoxifen against its potential adverse effects in this population.

J Clin Oncol 25:3251-3258. © 2007 by American Society of Clinical Oncology

INTRODUCTION

Ductal carcinoma in situ (DCIS) accounts for approximately 20% of all screening-detected breast cancers.¹ Nearly 53,000 cases of DCIS are expected to be diagnosed in the United States in 2007.² Treatment options for DCIS include mastectomy and breast-conserving surgery (BCS) with or without radiation therapy. Compared with mastectomy, BCS with radiation therapy is associated with a higher rate of local recurrences, approximately half of which are invasive.³

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 study was designed to investigate the value of adjuvant tamoxifen therapy after BCS and radiation therapy in patients with

DCIS. In this double-blind, placebo-controlled study, 1,804 women with DCIS treated with lumpectomy and 50 Gy of whole-breast radiation therapy were randomly assigned to receive tamoxifen 20 mg daily or placebo daily for 5 years.⁴ The initial results of the B-24 trial were first presented publicly in December 1998, and the full manuscript was published in June 1999. At a median follow-up time of 74 months, tamoxifen reduced the absolute 5-year rates of ipsilateral and contralateral breast cancer events by 3.3% ($P = .04$) and 1.4% ($P = .01$), respectively.⁴ An update reported in August 2001, when median follow-up had reached 83 months, confirmed these benefits, showing that tamoxifen significantly decreased the 7-year cumulative incidence of all breast cancer events (relative risk, 0.63;

From the Departments of Surgical Oncology and Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX; Department of Information Sciences, City of Hope National Medical Center, Duarte, CA; Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY; and the Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA.

Submitted December 26, 2006; accepted April 26, 2007; published online ahead of print at www.jco.org on June 18, 2007.

Presented at the 29th Annual San Antonio Breast Cancer Symposium, December 14-17, 2006, San Antonio, TX.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Tina W.F. Yen, MD, MS, Division of General Surgery, Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI 53226; e-mail: tyen@mcw.edu.

© 2007 by American Society of Clinical Oncology

0732-183X/07/2522-3251/\$20.00

DOI: 10.1200/JCO.2006.10.2699

$P = .0003$), and of ipsilateral invasive breast cancer in particular (relative risk, 0.53; $P = .01$).⁵ However, there was no effect on survival. On the strength of these results, in July 2000, the US Food and Drug Administration approved the use of tamoxifen for the adjuvant treatment of DCIS after surgery and radiotherapy.

After the publication of the NSABP B-24 trial results, the breast cancer guidelines panel of the National Comprehensive Cancer Network (NCCN) amended the DCIS guideline in 2000 to suggest consideration of adjuvant tamoxifen in patients treated with BCS.⁶ Little is known about the impact of these emerging clinical trial data and the resulting clinical practice guideline modifications on patterns of care for DCIS. Therefore, we examined the temporal trends and determinants of tamoxifen use in the NCCN breast cancer outcomes database after surgery for DCIS.

PATIENTS AND METHODS

Patient Characteristics

The study cohort consisted of women with unilateral DCIS who received some or all of their treatment for DCIS at one of the eight institutions participating in the NCCN Breast Cancer Outcomes Database Project: Arthur G. James Cancer Hospital and Richard J. Solove Research Institute at the Ohio State University, Columbus, OH; City of Hope Cancer Center, Los Angeles, CA; Dana-Farber/Partners CancerCare, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; H. Lee Moffitt Cancer Center & Research Institute at the University of South Florida, Tampa, FL; The University of Texas M.D. Anderson Cancer Center, Houston, TX; Roswell Park Cancer Institute, Buffalo, NY; and University of Michigan Comprehensive Cancer Center, Ann Arbor, MI. Each center is an academic comprehensive cancer center with a closed, staff-model practice. The institutional review boards at each center approved the protocol, data collection processes, data transmission methods, and data repository protocols. For centers requiring project-specific informed consent, only patients who provided informed consent were included in this analysis.

All patients newly diagnosed with DCIS who presented to one of the eight participating institutions between July 1, 1997, and December 31, 2003, and who were observed for at least 365 days at the NCCN center were potentially eligible ($n = 1,707$). Patients were excluded if they had a previous breast cancer (DCIS or invasive breast cancer, $n = 48$), underwent no cancer-directed surgery ($n = 7$), received tamoxifen before the DCIS diagnosis ($n = 1$), or were participating in a tamoxifen-related protocol (Eastern Cooperative Oncology Group 13321, NSABP B-35, or Cancer and Leukemia Group B 49801; $n = 13$). In addition, patients who developed a new nonbreast cancer primary ($n = 11$) or who died ($n = 5$) within 365 days of presentation to the NCCN center were excluded, resulting in a final sample size of 1,622 women. For patients with multiple breast cancer episodes, only the first episode of breast cancer was considered in the analysis.

Data Sources

Data collected from the patients' medical records included demographics, health insurance status, tumor pathology, therapies administered, clinical trial participation, and disease recurrence. Tumor size and margin status for DCIS patients were not collected before July 1, 1999; these variables were coded as missing before that date. Collection of data on hormone receptor status for DCIS was begun in April 2003, and was therefore not available for the period under study.

Rigorous quality-assurance processes were in place to ensure the accuracy of the data used in this study, including initial and follow-up data management training; online edit checking during Web-based data entry; programmed logic checks against the pooled data repository; routine quality-assurance reports to the NCCN centers for rectification by the data managers; and annual on-site audits.

Definitions of Variables

Patients were considered to be postmenopausal if they had not experienced a menstrual period in the 6 months before diagnosis or were receiving hormone replacement therapy. Women for whom no information on menstrual status was available were classified as postmenopausal if they were age 50 or older at the time of first presentation. Comorbidities at presentation to the NCCN center, including a history of cerebrovascular or peripheral vascular disease, were classified and scored using either the Charlson Index⁷ (based on chart review) or the modified version of this index developed by Katz et al (based on a patient survey).⁸ Each institution selected one technique for collecting data about comorbidities (chart review or patient survey). Receipt of radiation therapy was defined as receipt of adjuvant radiation therapy before any recurrence and within 365 days after the first presentation to an NCCN institution. Patients were considered to have received tamoxifen if the start of tamoxifen therapy was on or after DCIS diagnosis, before any recurrence, and within 365 days after first presentation to an NCCN center.

Covariates analyzed for potential association with tamoxifen use included age at diagnosis (younger than 50, 50 to 69, or ≥ 70 years), race/ethnicity, health insurance status at presentation to an NCCN institution, menopausal status, history of hysterectomy, comorbidity score, history of cerebrovascular or peripheral vascular disease, tumor size (< 0.5 , 0.5 to < 1.0 , 1.0 to < 3.0 , ≥ 3.0 cm, or unknown), histologic grade, DCIS comedo type, definitive surgery type (BCS or mastectomy), surgical margin status, receipt of adjuvant radiation therapy, NCCN institution, and timing of receipt of tamoxifen.

Statistical Methods

The association between the receipt of tamoxifen and clinicopathologic factors was assessed in a logistic regression model. To select independent variables entered into the multivariable model, we first chose variables for which univariate associations were significant at the .20 level. The final multivariable model included predictors with overall two-sided significance of $P < .05$. Interactions of interest identified a priori were also tested in the multivariable model, and only those with statistical significance at $P < .05$ were retained. Point estimates from the multivariable model are reported as odds ratios (ORs) along with the corresponding 95% CI for each OR.

RESULTS

Median age in the study cohort was 53.4 years (range, 23.2 to 89.1 years). Eighty-five percent of the patients ($n = 1,377$) were white, 23% ($n = 378$) had undergone a hysterectomy, 48% ($n = 773$) were premenopausal, and 64% ($n = 1,030$) had been treated with BCS (Table 1).

Overall, 41% of the patients (665 of 1,622) received tamoxifen after surgery for DCIS. The proportion of patients receiving tamoxifen increased over time, from 24% (87 of 367) before July 1, 1999, to 46% (578 of 1,255) on or after July 1, 1999 (Fig 1). The increase in tamoxifen use appears to have begun around the time of the initial presentation of the NSABP B-24 results in December 1998. After the June 1999 publication of the B-24 results, the proportion of patients receiving tamoxifen reached a plateau at approximately 50%. Of patients diagnosed in 2003, 55% received tamoxifen.

The proportion of DCIS patients receiving tamoxifen according to various demographic, clinical, surgical, and pathologic factors is summarized in Table 1. In univariate analysis, patients who were younger (< 70 years), had a comorbidity score of 1 or less, had no history of cerebrovascular or peripheral vascular disease or other comorbid conditions, or had a history of a hysterectomy were significantly more likely to receive tamoxifen. There was a significant association between smaller pathologic DCIS size and tamoxifen therapy. This association remained significant when patients with missing

Tamoxifen Use After Breast Surgery for DCIS

Table 1. Demographic, Clinical, Surgical, and Pathologic Factors in Patients With DCIS by Use of Tamoxifen (N = 1,622)

Factor	Tamoxifen Use* (n = 665)		No Tamoxifen Use (n = 957)		P
	No. of Patients	%	No. of Patients	%	
Age at diagnosis, years					< .0001
Median		53.1		53.5	
Range		31.6-87.6		23.2-89.1	
< 50	246	39	386	61	
50-69	360	46	426	54	
≥ 70	59	29	145	71	
Race/ethnicity					.24
White, non-Hispanic	562	41	815	59	
Hispanic	34	47	39	53	
African American, non-Hispanic	43	39	67	61	
Asian or Pacific Islander, non-Hispanic	22	52	20	48	
Other, non-Hispanic	2	17	10	83	
Unknown	2	25	6	75	
Health insurance					.07
Managed care	456	43	600	57	
Indemnity	55	40	83	60	
Medicaid/indigent	19	47	21	53	
Medicare	117	34	232	66	
Self-pay	14	50	14	50	
Other	—	—	2	100	
Unknown	4	44	5	56	
Comorbidity score					.03
0	545	42	743	58	
1+	120	36	214	64	
History of myocardial infarction					.47
Yes	7	33	14	67	
No	658	41	943	59	
History of cerebrovascular or peripheral vascular disease					.03
Yes	10	24	31	76	
No	655	41	926	59	
Menopausal status					.85
Premenopausal	315	41	458	59	
Postmenopausal	350	41	499	59	
History of hysterectomy					.05
Yes	174	46	204	54	
No	478	39	739	61	
Unknown	13	48	14	52	
Pathologic size of DCIS, cm					.0024‡
< 0.5	80	53	71	47	
0.5- < 1.0	84	50	85	50	
1.0- < 3	119	42	164	58	
≥ 3	34	31	77	69	
Unknown	263	48	288	52	
Missing†	85	24	272	76	
Histologic grade					.96
Grade I (low)	59	41	84	59	
Grade II (intermediate)	136	41	198	59	
Grade III (high)	165	40	251	60	
Other	—	—	3	100	
Unknown	305	42	421	58	
Type of DCIS					.26
Comedo	231	42	318	58	
Noncomedo	424	40	632	60	
Unknown	10	59	7	41	

(continued on following page)

Table 1. Demographic, Clinical, Surgical, and Pathologic Factors in Patients With DCIS by Use of Tamoxifen (N = 1,622) (continued)

Factor	Tamoxifen Use* (n = 665)		No Tamoxifen Use (n = 957)		P
	No. of Patients	%	No. of Patients	%	
Margin status					< .5010‡
Positive	9	53	8	47	
Negative	547	45	658	55	
Close	16	53	14	47	
Unknown	8	62	5	38	
Missing†	85	24	272	76	
Type of breast surgery					< .0001
Breast-conserving surgery	507	49	523	51	
Total mastectomy§	158	27	434	73	
Radiation therapy after surgery					< .0001
Yes	444	53	397	47	
No	221	28	560	72	
NCCN center					< 0.0001
A	87	49	92	51	
B	83	34	162	66	
C	55	29	135	71	
D	125	32	260	68	
E	44	41	64	59	
F	78	35	144	65	
G	37	58	27	42	
H	156	68	73	32	
DCIS diagnosis date					< .0001
Before July 1, 1999	87	24	280	76	
On or after July 1, 1999	578	46	677	54	

Abbreviations: DCIS, ductal carcinoma in situ; NCCN, National Comprehensive Cancer Network.

*Tamoxifen receipt within 365 days after presentation to NCCN center.

†Tumor size and margin status were not collected in the NCCN database until July 1, 1999.

‡Analysis performed after excluding patients with missing values because tumor size and margin status were not collected in the NCCN database until July 1, 1999.

§Two percent of mastectomy patients (11 of 592) received postmastectomy radiation therapy.

values were excluded from the analysis. Twenty-two percent of patients (357 of 1,622) did not have information on tumor size and margin status, given that this information was not collected for patients presenting before July 1, 1999. Other factors associated with

receipt of tamoxifen in univariate analysis included BCS, receipt of radiation therapy after surgery, NCCN center, and diagnosis on or after July 1, 1999. Menopausal status was not found to be associated with receipt of tamoxifen.

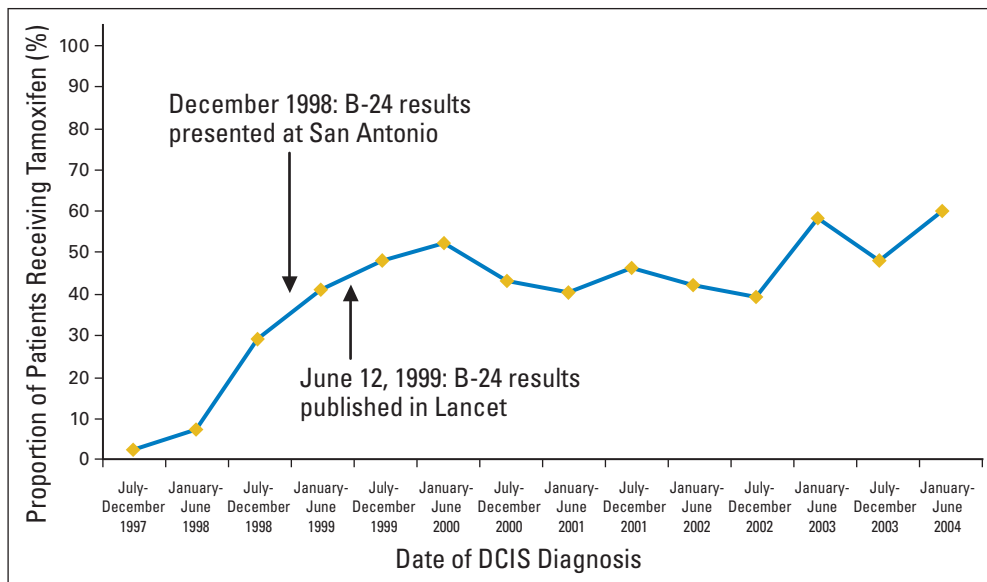


Fig 1. Rates of tamoxifen use according to date of diagnosis of ductal carcinoma in situ (DCIS).

In multivariable logistic regression analysis (Table 2), several factors were found to be associated independently with the receipt of tamoxifen. Patients who were diagnosed on or after July 1, 1999, had an almost four-fold increased odds of receiving tamoxifen. Patients who did not have a history of cerebrovascular or peripheral vascular disease had an approximately three-fold increased odds of receiving tamoxifen. Similarly, patients who underwent radiation therapy or who had undergone hysterectomy had a 1.82- and 1.34-fold increased odds of receiving tamoxifen, respectively. In addition, significant interactions were noted between type of breast surgery and age at diagnosis

and between type of breast surgery and NCCN center. As shown in Table 2 and Figure 2, BCS patients younger than age 70 years were significantly more likely to receive tamoxifen than BCS patients age 70 years and older ($P = .0073$). In contrast, there was no significant difference in tamoxifen use across age groups for mastectomy patients. Furthermore, as shown in Table 2 and Figure 3, regardless of breast surgery type, there was a wide variation in the use of tamoxifen across NCCN centers ($P = .002$). Overall, the rate of tamoxifen use was higher after BCS than after total mastectomy, with absolute rates ranging from 34% to 74% after BCS and from 17% to 53% after mastectomy.

Table 2. Factors Associated With Tamoxifen Use in Multivariable Logistic Regression Analysis (N = 1,622)

Variable	Odds Ratio	95% CI	P
Significant main terms in the model			
Date of diagnosis			< .0001
Before July 1, 1999	1.00		
On or after July 1, 1999	3.85	2.83 to 5.25	
History of CVD or PVD			.0071
Yes	1.00		
No	3.13	1.37 to 7.19	
Radiation therapy			.0009
No	1.00		
Yes	1.82	1.28 to 2.58	
History of hysterectomy			.0459
No	1.00		
Yes	1.34	1.02 to 1.76	
Unknown	1.91	0.83 to 4.42	
Interaction terms			
Age at diagnosis, in years, by breast surgery			.0073
TM			
≥ 70	1.00		
< 50	0.87	0.44 to 1.69	
50-69	1.17	0.60 to 2.27	
BCS			
≥ 70	1.00		
< 50	3.22	1.98 to 5.22	
50-69	3.21	2.03 to 5.07	
NCCN center by breast surgery			
TM			
A	1.00		
B	0.87	0.34 to 2.23	
C	1.53	0.62 to 3.79	
D	2.01	0.90 to 4.53	
E	1.35	0.47 to 3.87	
F	1.62	0.62 to 4.23	
G	3.42	1.13 to 10.36	
H	6.59	2.69 to 16.16	
BCS			
A	1.00		
B	0.20	0.12 to 0.34	
C	0.22	0.12 to 0.40	
D	0.22	0.13 to 0.37	
E	0.35	0.19 to 0.68	
F	0.36	0.21 to 0.62	
G	1.13	0.50 to 2.57	
H	1.46	0.84 to 2.53	

Abbreviations: BCS, breast-conserving surgery; CVD, cerebrovascular disease; PVD, peripheral vascular disease; TM, total mastectomy; NCCN, National Comprehensive Cancer Network.

DISCUSSION

The results of this study indicate that between July 1997 and December 2003, 41% of patients who underwent surgery for DCIS at NCCN centers received tamoxifen after surgery. There was a rapid increase in the proportion of DCIS patients treated with tamoxifen, beginning around the time of the first public presentation of the NSABP B-24 trial results in December 1998. Since the June 1999 publication of those results, the proportion of patients receiving tamoxifen has reached a plateau at approximately 50%.

A number of factors were associated with adjuvant tamoxifen therapy for DCIS in the period after the dissemination of the NSABP B-24 results. Patients with a history of cerebrovascular or peripheral vascular disease were less likely to receive tamoxifen, as were women with an intact uterus. This suggests that physicians are weighing the likelihood of tamoxifen-associated vascular and endometrial toxicity in formulating their adjuvant therapy recommendations for DCIS. Interestingly, patients who received adjuvant radiation therapy were also more likely to receive tamoxifen. The NSABP trial was restricted to women who had undergone lumpectomy and radiotherapy; there is no high-quality evidence that tamoxifen reduces recurrence risk in DCIS patients who have not received postlumpectomy radiotherapy. Therefore, physicians may be reluctant to extrapolate the results of the NSABP trial to patients who have been treated with BCS alone. It is also possible that the likelihood of receiving tamoxifen simply

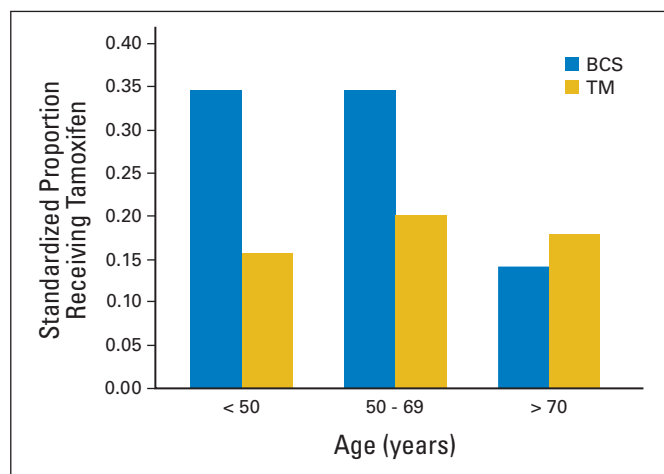


Fig 2. Rates of tamoxifen use according to type of breast surgery and age at diagnosis. Standardized proportions were adjusted for all terms in the multivariable model. BCS, breast-conserving surgery; TM, total mastectomy.

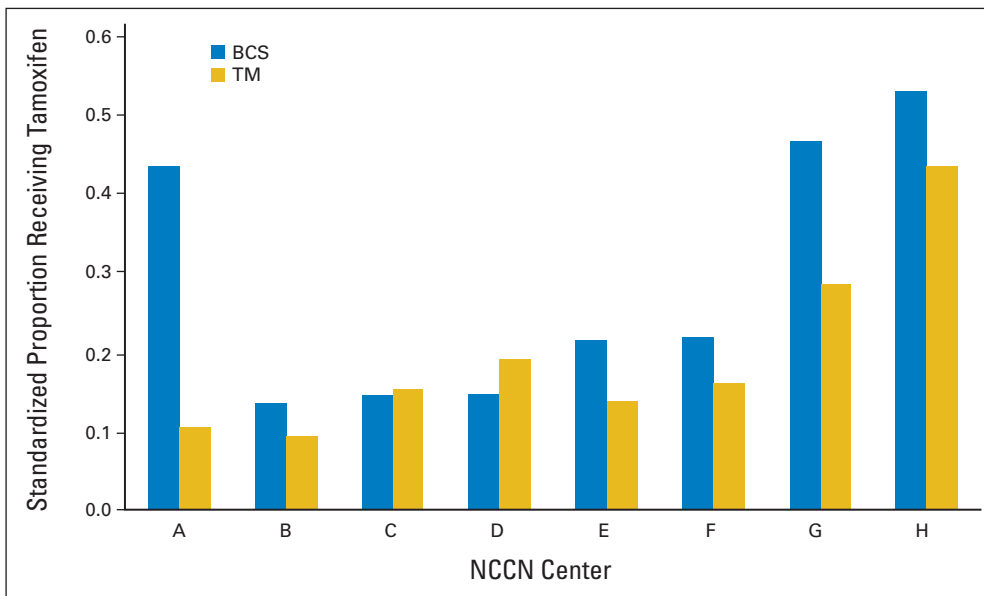


Fig 3. Rates of tamoxifen use according to type of breast surgery and National Comprehensive Cancer Network (NCCN) center. Standardized proportions were adjusted for all terms in the multivariable model. BCS, breast-conserving surgery; TM, total mastectomy.

increases with the number of breast cancer physicians involved in a patient's care. Finally, it may be that patients who were believed to be at higher risk of recurrence for reasons not captured in our model were treated more aggressively, such that they received both radiation therapy and tamoxifen.

We also found that younger age was associated with tamoxifen use, but only among women treated with BCS. This finding is consistent with three prior single-institution studies of patterns of care for DCIS, which all demonstrated that BCS was an independent predictor of tamoxifen use.⁹⁻¹¹ Thus it appears that physicians are using tamoxifen in this setting with true adjuvant intent, and not simply as chemoprevention for the contralateral breast. The fact that physicians do so selectively in women younger than age 70 years may well be explained by the fact that the risks of thromboembolic events and endometrial cancer from tamoxifen use are greater in postmenopausal women,¹² making the risk-benefit ratio for tamoxifen use in younger women more appealing.

Finally, regardless of breast surgery type, there was substantial variation in the use of tamoxifen across NCCN centers, with absolute rates ranging from 34% to 74% after BCS and from 17% to 53% after mastectomy. This suggests that in the absence of any proven survival benefit, clinical opinion leaders in these institutions differ in how they weigh the modest reduction in breast cancer events conferred by tamoxifen against its potential adverse effects.^{5,12,13} To investigate further the factors that might be associated with this striking institutional variation, we examined the association between active participation in NSABP B-24, defined by enrollment of at least 10 patients, and use of tamoxifen after the trial results were released. In the four sites that had participated actively in the trial, tamoxifen was administered to 43% of study patients versus 38% in nonparticipating centers ($P = .0214$). This suggests the possibility that physicians in centers that participated in the trial became comfortable prescribing tamoxifen for DCIS, and as a result, were likely to use it off protocol after the B-24 results were released. Alternatively, active B-24 trial participation may simply have been a marker for a pre-existing proclivity to use tamoxifen in this setting.

A strength of our study is that all of the data were entered prospectively into the database and were subject to rigorous quality assurance to ensure accuracy. However, our study also has several limitations. The NCCN database does not include information on whether patients were offered tamoxifen but declined or patients' reasons for declining. As a result, we cannot comment on the extent to which observed treatment rates reflect physician recommendations as opposed to patient preferences. In addition, we did not have information on hormone receptor status for most of the study patients. Therefore, we could not examine the impact on patterns of care of the 2002 reanalysis of NSABP B-24, suggesting that the benefits of tamoxifen are greatest in patients who have estrogen receptor (ER) –positive DCIS.¹⁴ Finally, because complete data are not available for treatment initiated after 2004, we cannot fully assess the impact on patterns of care of the United Kingdom, Australia, and New Zealand trial, published in July 2003, which concluded that the addition of tamoxifen to patients with DCIS treated with BCS with or without radiotherapy did not reduce total and ipsilateral invasive breast cancer events.¹⁵

The majority of breast cancer patients are not treated at NCCN centers. The patients who choose to receive their care at NCCN institutions, as well as the physicians who practice in these centers, may differ in systematic ways. Ideally, population-based studies should be done to determine whether our findings are generalizable. Unfortunately, currently available national data sources such as Surveillance, Epidemiology, and End Results data linked to Medicare claims have serious limitations for this kind of analysis, including incomplete capture of hormonal therapy use, insufficient clinical detail to permit a thorough analysis of factors driving physicians' treatment decisions, and inability to examine patterns of care across the full range of patient age.

The findings of our study clearly indicate the need for future prospective studies that address alternative adjuvant therapies and breast cancer chemoprevention in patients with DCIS. Among postmenopausal women with early invasive breast cancer, aromatase inhibitors are associated with better disease-free survival and greater

reduction in contralateral breast cancer risk than tamoxifen.^{16,17} Whether they offer a similar advantage among postmenopausal women with DCIS is currently being investigated in two large randomized trials. The NSABP has closed protocol B-35, in which 3,104 postmenopausal women with hormone receptor–positive DCIS treated with BCS and radiation therapy were randomly assigned to receive either tamoxifen 20 mg daily or anastrozole 1 mg daily for 5 years; results are not yet available.¹⁸ The second International Breast Cancer Intervention Study is an ongoing study with a similar design.¹⁹ These two studies will help determine whether aromatase inhibitors can be considered, in addition to tamoxifen, in the management of postmenopausal patients with DCIS. Finally, given the recent publication of the NSABP P-2 trial results,²⁰ the second-generation selective ER modulator raloxifene may be considered an alternative for lowering breast cancer risk in postmenopausal women at high risk for breast cancer, including patients with DCIS.

In conclusion, between July 1997 and December 2003, we found that 41% of patients who underwent surgery for DCIS received adjuvant tamoxifen at NCCN centers. The proportion of patients who received tamoxifen increased rapidly around the time of the initial presentation of the NSABP B-24 results in December 1998, and then reached a plateau at approximately 50%. Several patient- and treatment-related factors seem to be associated with tamoxifen use. However, given the significant variation in tamoxifen use by NCCN institution, it appears that physician beliefs and preferences regarding the reduction in breast cancer risk and potential adverse effects of tamoxifen in this patient population play a substantial role in the decision-making process regarding tamoxifen as adjuvant therapy for women with DCIS. These findings highlight the need for additional studies in DCIS patients to define clearly the role of adjuvant tamoxifen in relation to hormone receptor status, and to define subgroups of patients for whom the benefits of tamoxifen may truly outweigh its risks (perhaps younger women with ER-positive DCIS who undergo BCS). Furthermore, our findings confirm the importance of the NSABP B-35 and second International Breast Cancer Intervention Study trials,

as well as other future studies evaluating alternative adjuvant and chemopreventive strategies for patients with DCIS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment: N/A **Leadership:** N/A **Consultant:** N/A **Stock:** N/A **Honoraria:** Tina W.F. Yen, Society of Surgical Oncology and Health Science Center for Continuing Medical Education **Research Funds:** N/A **Testimony:** N/A **Other:** N/A

AUTHOR CONTRIBUTIONS

Conception and design: Tina W.F. Yen, Henry M. Kuerer, Rebecca A. Ottesen, Layla Rouse, Stephen B. Edge, Richard L. Theriault

Financial support: Henry M. Kuerer

Administrative support: Henry M. Kuerer, Rebecca A. Ottesen, Layla Rouse, Joyce C. Niland, Richard L. Theriault, Jane C. Weeks

Provision of study materials or patients: Henry M. Kuerer, Joyce C. Niland, Stephen B. Edge, Richard L. Theriault, Jane C. Weeks

Collection and assembly of data: Tina W.F. Yen, Henry M. Kuerer, Rebecca A. Ottesen, Layla Rouse, Joyce C. Niland, Stephen B. Edge, Richard L. Theriault, Jane C. Weeks

Data analysis and interpretation: Tina W.F. Yen, Henry M. Kuerer, Rebecca A. Ottesen, Layla Rouse, Joyce C. Niland, Stephen B. Edge, Jane C. Weeks

Manuscript writing: Tina W.F. Yen, Henry M. Kuerer, Rebecca A. Ottesen, Layla Rouse, Joyce C. Niland, Stephen B. Edge, Richard L. Theriault, Jane C. Weeks

Final approval of manuscript: Tina W.F. Yen, Henry M. Kuerer, Rebecca A. Ottesen, Layla Rouse, Joyce C. Niland, Stephen B. Edge, Richard L. Theriault, Jane C. Weeks

REFERENCES

1. Fentiman IS: The dilemma of in situ carcinoma of the breast. *Int J Clin Pract* 55:680-683, 2001
2. American Cancer Society: Cancer Facts & Figures 2007. <http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf>
3. Solin LJ, Recht A, Fourquet A, et al: Ten-year results of breast-conserving surgery and definitive irradiation for intraductal carcinoma (ductal carcinoma in situ) of the breast. *Cancer* 68:2337-2344, 1991
4. Fisher B, Dignam J, Wolmark N, et al: Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet* 353:1993-2000, 1999
5. Fisher B, Land S, Mamounas E, et al: Prevention of invasive breast cancer in women with ductal carcinoma in situ: An update of the National Surgical Adjuvant Breast and Bowel Project experience. *Semin Oncol* 28:400-418, 2001

6. Carlson RW, Anderson BO, Burstein HJ, et al: National Comprehensive Cancer Network Breast Cancer Clinical Practice Guidelines in Oncology, v 2.2006. http://www.nccn.org/professionals/physicians_gls/PDF/breast.pdf
7. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 40:373-383, 1987
8. Katz JN, Chang LC, Sangha O, et al: Can comorbidity be measured by questionnaire rather than medical record review? *Med Care* 34:73-84, 1996
9. Yen TW, Hunt KK, Mirza NQ, et al: Physician recommendations regarding tamoxifen and patient utilization of tamoxifen after surgery for ductal carcinoma in situ. *Cancer* 100:942-949, 2004
10. Nakhlis F, Lazarus L, Hou N, et al: Tamoxifen use in patients with ductal carcinoma in situ and T1a/b N0 invasive carcinoma. *J Am Coll Surg* 201: 688-694, 2005
11. Hird RB, Chang A, Cimmino V, et al: Impact of estrogen receptor expression and other clinicopathologic features on tamoxifen use in ductal carcinoma in situ. *Cancer* 106:2113-2118, 2006

12. Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 90:1371-1388, 1998
13. Cuzick J: Future possibilities in the prevention of breast cancer: Breast cancer prevention trials. *Breast Cancer Res* 2:258-263, 2000
14. Allred D, Bryant J, Land S, et al: Estrogen receptor expression as a predictive marker of the effective of tamoxifen in the treatment of DCIS: Findings from NSABP protocol B-24. Presented at 25th Annual San Antonio Breast Cancer Symposium, December 11-14, 2002, San Antonio, TX
15. Houghton J: Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: Randomized controlled trial. *Lancet* 362:95-102, 2003
16. Howell A, Buzdar A: Are aromatase inhibitors superior to antiestrogens? *J Steroid Biochem Mol Biol* 93:237-247, 2005
17. Howell A, Cuzick J, Baum M, et al: Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 365: 60-62, 2005

18. Vogel VG, Costantino JP, Wickerham DL, et al: National Surgical Adjuvant Breast and Bowel Project update: Prevention trials and endocrine therapy of ductal carcinoma in situ. *Clin Cancer Res* 9:495S-501S, 2003

19. Cuzick J: Aromatase inhibitors in prevention: Data from the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial and the design of IBIS-II (the second International Breast Cancer Intervention Study). *Recent Results Cancer Res* 163:96-103, 2003

20. Vogel VG, Costantino JP, Wickerham DL, et al: Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. *JAMA* 295:2727-2741, 2006
