Trends in Cancer Research
Vol. 11, 2016

Original Communication

Early-stage breast cancer treatment in the US over 20 years: Changes in therapy and short-term cancer survival

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ABSTRACT

Early-stage breast cancer adjuvant therapy and survival have changed over the last 20 years. Using the National Cancer Institute's population-based patterns of care studies, we examined adjuvant multi-agent chemotherapy and endocrine therapy utilization and cancer survival among women diagnosed with early-stage, invasive breast cancer in 1990, 1995, 2000, 2005, and 2010 who were sampled from Surveillance, Epidemiology and End Results (SEER) registries. Medical records were re-abstracted and treatment verified with physicians. Logistic regression and Cox proportional hazards regression were utilized to identify factors associated with treatment and 3-yr cancer survival. Utilization of multi-agent chemotherapy increased, regardless of nodal and estrogen receptor (ER) status but most notably among women with ER-positive tumors. There were significant changes in preferred chemotherapy regimen overtime: from cyclophosphamide, methotrexate and 5-fluorouracil (CMF) in 1990 to anthracycline, cyclophosphamide and taxane (AC-T) in 2000 to cyclophosphamide and taxane (TC) in 2010. Endocrine therapy decreased among women with ER-negative tumors and increased among women with node-negative, ER-positive tumors. Utilization of aromatase inhibitors rapidly increased. More recent diagnosis year and younger age were consistently associated with receipt of adjuvant therapy. Poorer survival was associated with earlier diagnosis year, older age, being non-Hispanic black, having more extensive disease and not receiving endocrine therapy. In conclusion, adjuvant therapy utilization and 3-year cancer survival increased over time. Whether the expanded use of genomic testing and personalize medicine influences the national trends in adjuvant therapy and survival remains to be seen.

KEYWORDS: breast neoplasm, triple negative breast cancer, breast cancer treatment, breast cancer survival, chemotherapy, endocrine therapy, disparities, population-based, trends

ABBREVIATIONS

ER	:	estrogen receptor
CMF	:	cyclophosphamide, methotrexate and 5-fluorouracil
AC-T	:	anthracycline, cyclophosphamide and taxane
TC	:	cyclophosphamide and taxane
NIH	:	National Institutes of Health
SEER	:	Surveillance, Epidemiology and End Results
NH	:	non-Hispanic
OPD	:	outpatient department
A	:	anthracycline
C	:	cyclophosphamide
F	:	5-Fluorouracil
M	:	methotrexate
T	:	taxane
OR	:	odds ratio
CI	:	confidence interval

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HR : hazards ratio
IRB : institutional review board
HMO : health maintenance organizations
FDA : US Food and Drug Administration

INTRODUCTION

In the United States the incidence of invasive breast cancer has increased from 105 per 100,000 in 1975 to 130 per 100,000 in 2013 [1]. However, during the same time period, breast cancer mortality decreased from 31 per 100,000 to 21 per 100,000. The discordance between these statistics largely reflects temporal improvements in early detection and treatment. The majority of female breast cancers in the United States are diagnosed early and have a good prognosis. Between 2006 and 2012, 61% and 31% of women diagnosed with breast cancer had localized or regional disease at diagnosis, respectively. During the same time period, the 5-year relative survival was nearly 99% for localized disease and 85.2% for regional disease.

Treatment of early-stage, invasive breast cancer has progressed over the past decades. Historically, treatment consisted of surgery, which over time has transitioned from radical to conservative procedures that may or may not be accompanied by radiation. That said, it has been estimated that between 4-35% of breast cancer patients who have mastectomies without radiotherapy will experience a locoregional recurrence and the majority of these patients will die from their disease [2]. Thus, as insights into the etiology of breast cancer have been made, new systemic agents (e.g., chemotherapeutic and endocrine) have been identified and treatment guidelines, which take into account the benefits and harms of a treatment, have been updated. Traditionally, treatment guidelines have been stratified by lymph node status, menopausal status or age, and/or estrogen receptor (ER) status, as these have long been recognized as strong prognostic predictors. In 1985, the National Institutes of Health (NIH) Consensus Development Conference recommended adjuvant multi-agent chemotherapy for premenopausal women with positive nodes, regardless of ER status, and for postmenopausal women with node-positive, ER-negative tumors [3]. In 1990 the NIH Consensus Development Conference recommended that physicians discuss the possible benefits of adjuvant therapy with all node-negative breast cancer patients [4]. By 2000, recommendations were for the use of endocrine therapy, namely tamoxifen, only among women with ER-positive tumors and multi-agent chemotherapy for "the majority" of women with localized breast cancer. It was further suggested that the chemotherapy regimen should include an anthracycline to confer an additional, albeit small, survival benefit [5]. Over the subsequent decade, anthracyclines began to fall out of favor as their cardiotoxicities came to light and utilization of new endocrine agents were identified, namely aromatase inhibitors, which have been found to be beneficial among postmenopausal women [6, 7].

During a time of rapid change in treatment guidelines, we provide the first population-based assessment of trends in the treatment of early-stage, invasive breast cancer in the United States from 1990-2010. Using population-based data collected from throughout the nation, we describe the trends in adjuvant chemotherapy and endocrine therapy and factors associated with these therapies, stratified by nodal and ER status, among women diagnosed with early-stage invasive breast cancer. We also report temporal trends in the utilization of specific agents. Finally, we investigate factors associated with three-year cancer survival, while adjusting for demographic, clinical, tumor, and treatment characteristics.

MATERIALS AND METHODS

Data source

Data were obtained from the National Cancer Institute's patterns of care studies, which are conducted annually and include a stratified random sample of cancer patients who are reported to the Surveillance, Epidemiology and End Results (SEER) cancer registries. For each reported patient, the SEER program collects demographic, diagnostic, and tumor characteristics, as well as treatment information from hospital medical records, outpatient surgical centers and pathology departments. As treatment has transitioned from the hospital to outpatient settings, registry-collected data on treatment has become less complete, especially for chemotherapy and endocrine therapy. The annual patterns of care studies provide

an opportunity to gather additional information on these treatment modalities. Briefly, each year for selected cancer sites, after obtaining institutional review board (IRB) approval, as required by the registries, hospital medical records are re-abstracted and treating physicians are contacted to verify the therapy given, including the specific agent(s) prescribed. The physicians are also asked for the names and addresses of other medical professionals who might have treated the patient and these professionals are then contacted.

Study population

Women who were reported to a SEER registry as being diagnosed in 1990, 1995, 2000, 2005, or 2010 with early-stage invasive breast cancer (T1-3, N0-2, M0) [8-10] were eligible for inclusion. Women with a previous diagnosis of cancer (other than non-melanoma skin cancers), with simultaneous cancer diagnoses (a second cancer of any site including breast), and those diagnosed at autopsy or death certificate only were also excluded. Eligible women were then stratified by age at diagnosis (less than 51 and 51 and older), race/ethnicity and registry and a random sample was selected from each stratum. Women less than age 51 were oversampled to obtain more stable estimates of the therapy provided to younger pre-menopausal breast cancer patients. Similarly, non-Hispanic black and Hispanic women were oversampled beginning in 1995 and Asian/Pacific Islanders and American Indian/Alaskan Natives were oversampled beginning in 2000.

For the current analyses, we were interested in describing temporal trends in the use of routine adjuvant therapy; therefore, women who did not undergo surgery (n = 81) and those on a clinical trial (n = 341) were excluded. One woman whose race was unknown was also excluded.

Variables of interest

Demographic factors at diagnosis included age, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and other, which included Asian/Pacific Islander/American Indians/Alaskan Natives), marital status (married/living as married, other), and insurance status (private, which include health maintenance organizations (HMO) and Military; any Medicaid; Medicare only; none/unknown). Hospital bed size (<200 beds/ treated in an outpatient setting/unknown, 200-299, 300-499, 400+, unknown) and approved residency training program status (no/unknown, yes) of the hospital where the most definitive treatment was received were also abstracted by the registry.

The clinical factors assessed included, tumor size, nodal status, ER status (not done, positive/ borderline, negative, unknown/not in chart) and comorbidities. Nodal status was determined from the pathologic findings for all regional lymph nodes and was classified as no nodes examined; no positive nodes; number of positive nodes, which were categorized into 1-3, 4-9, 10+, and number unspecified. Comorbidities abstracted from the hospital record were coded centrally by a single coder before the Charlson comorbidity score was calculated [11]. Vital status surveillance is routinely conducted on all patients reported to each registry and was categorized as living on the date of last contact or deceased with the date and cause of death recorded.

Statistical analyses

Assessments of demographic, hospital, and clinical characteristics over time were performed. Temporal trends in the receipt of chemotherapy and/or endocrine therapy, both as general categories and by specific agents, were assessed stratified by nodal and ER status. Three separate logistic regression models were created to determine whether year of diagnosis, after adjustment for age, race/ethnicity, comorbidity score and tumor characteristics, was associated with: 1) receipt of multi-agent chemotherapy plus endocrine therapy among women with node-positive, ER-positive tumors; 2) multi-agent chemotherapy among women with node-positive tumors and 3) endocrine therapy among women with ER-positive tumors. The models include all women with the tumor characteristics specified, which means women may be included in more than one model. Cox proportional hazards regression was used to determine if year of diagnosis was associated with 3-year cancer survival, after adjusting for age, race/ethnicity, tumor characteristics, comorbidity score and receipt of chemotherapy and endocrine therapy. The final date of follow-up for vital status among women in this study was December 31, 2013. Three-year survival was selected so that

the length of follow-up for each diagnosis year was similar.

All estimates were weighted to reflect the population from which the sample was drawn. The sample weights, calculated as the inverse of the sampling proportion for each sampling stratum (defined by year of diagnosis, age, race/ethnicity, and registry), were used to obtain estimates that were representative of all eligible early-stage breast cancer patients in the study areas. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina) and callable SUDAAN version 11.0.1 (Research Triangle Institute, Raleigh, NC). This software allowed for the use of sample weights and adjusted the standard errors appropriately. All tests were 2-sided and considered significant at $p \leq 0.05$.

RESULTS

A total of 6,613 women were included in these analyses. Over time the distribution of demographic and hospital characteristics varied. In comparison with 1990, the women diagnosed in 2010 were less likely to be over 70 years old, non-Hispanic white, married and have Medicare only or no/unknown insurance (Table 1). Additionally, in 2010 more women were treated in large hospitals and hospitals without a residency training program than in earlier years. Compared to 1990, women diagnosed in 2010 were more likely to have smaller tumors (<2 cm), fewer positive nodes, known ER status and a comorbidity score of at least one (Table 2).

Chemotherapy

Over the study period, use of multi-agent chemotherapy (only or in combination with endocrine therapy) increased from 48% to 75% among women with node-positive, ER-positive tumors (Figure 1a), from 78% to 83% among women with node-positive, ER-negative tumors (Figure 1b), and from 12% to 28% among women with node-negative, ER-positive tumors (Figure 1c). Among women with node-negative, ER-negative tumors, use of multi-agent chemotherapy increased from 36% in 1990 to 58% in 2000 before decreasing back to 36% in 2010 (Figure 1d).

Endocrine therapy

The use of endocrine therapy (only or in combination with multi-agent chemotherapy) over the study period increased among women with ER-positive tumors, from 63% to 68% among women with positive nodes (Figure 1a) and from 48% to 77% among women with negative nodes (Figure 1c). The use of endocrine therapy decreased among women with ER-negative tumors, from 19% to 4% among women with positive nodes (Figure 1b) and from 22% to 3% among women with negative nodes (Figure 1d).

Combination therapy

Combination therapy (multi-agent chemotherapy plus endocrine therapy) over time more than doubled among women with estrogen receptor-positive tumors (Figure 1a and 1c) and decreased almost completely among women with estrogen receptor-negative tumors (Figure 1b and 1d). Over the study period, the percentage of women who received neither modality remained relatively constant among women with node-positive tumors (Figure 1a and 1b), decreased among women with node-negative, estrogen-positive tumors (Figure 1c) and increased among women with node-negative, estrogen-negative tumors, especially between 2005 and 2010 (Figure 1d).

Chemotherapeutic agents

Regardless of nodal or hormonal status, the most frequent chemotherapy regimen used in 1990 and 1995 was the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with or without other additional agents (Table 3). However, a larger percentage of women with ER-negative tumors received this combination compared to women with ER-positive tumors. Among all women except those with node-negative, ER-positive tumors, over the course of the study period there was a shift in regimen preference to the combination of anthracycline, cyclophosphamide and taxane (AC-T) with or without additional agents. This shift in regimen preference occurred earlier and was more abrupt among women with positive nodes. The use of anthracyclines increased through 2005 with a sharp decline by 2010.

Table 1. Demographic and hospital characteristics of women diagnosed with early-stage, invasive breast cancer, by year of diagnosis; National Cancer Institute patterns of care studies (n = 6,613).

	1990		1995		2000		2005		2010	
	%[1]	N[2]	%[1]	N[2]	%[1]	N[2]	%[1]	N[2]	%[1]	N[2]
Age, years[3]										
<50	25.0	811	24.6	698	26.1	550	25.4	413	23.2	447
50-59	16.7	269	21.0	313	24.4	271	25.0	243	22.5	276
60-69	24.3	312	19.5	267	19.5	197	25.5	159	26.6	159
70+	34.0	390	34.9	327	29.9	194	24.1	152	27.8	165
Race/Ethnicity										
NH White	85.9	1525	83.2	538	74.9	403	70.1	249	71.0	247
NH Black	8.4	154	9.3	564	8.7	316	8.4	230	8.5	244
Hispanic	3.2	50	7.5	503	8.4	250	13.0	241	10.8	230
Other	2.6	53	0.0	0	8.0	243	8.4	247	9.6	326
Marital status[3]										
Married/living as	58.1	1108	54.3	819	52.2	684	60.0	551	56.9	558
Other	41.9	674	45.7	786	47.8	528	40.0	416	43.1	489
Insurance[3]										
Private	80.8	1463	78.5	1188	82.1	964	75.3	716	79.6	746
Any Medicaid	4.0	80	8.4	195	7.4	105	11.3	157	9.3	196
Medicare only	10.4	123	8.6	90	8.1	82	12.0	64	8.3	61
None/Unknown	4.9	116	4.5	132	2.4	61	1.4	30	2.8	44
Hospital bed size[4]										
<200/OPD/unknown[5]	29.3	500	26.7	407	36.0	356	25.0	237	21.8	217
200-299	27.1	457	25.1	423	21.1	284	28.4	238	20.4	213
300-399	14.9	283	15.2	206	14.2	184	17.5	184	21.7	230
400+	28.7	542	33.0	569	28.8	388	29.1	308	36.1	387
Residency program[4]										
No/unknown	50.8	902	43.6	720	53.2	535	53.7	472	53.2	456
Yes	49.2	880	56.4	885	46.8	677	46.3	495	46.8	591

NH: non-Hispanic; OPD: outpatient department.

[1]Weighted percent.

[2]Unweighted sample size.

[3]At diagnosis.

[4]Hospital where most definitive treatment was received.

[5]Less than 2.5% unknown.

Table 2. Clinical characteristics of women diagnosed with early-stage, invasive breast cancer, by year of diagnosis; National Cancer Institute patterns of care studies.

	1990 N[1] = 1,782 %[2]	1995 N[1] = 1,605 %[2]	2000 N[1] = 1,212 %[2]	2005 N[1] = 967 %[2]	2010 N[1] = 1,047 %[2]
Tumor size					
<1 cm	16.3	18.1	18.9	23.0	19.3
1-1.9 cm	35.5	39.9	34.3	33.6	40.4
2-2.9 cm	23.5	21.2	23.8	25.6	18.0
3-4.9 cm	14.2	13.2	12.9	12.4	13.5
5+ cm	5.4	5.5	8.9	5.2	8.8
Unknown[3]	5.1	2.1	1.2	0.2	0.0
Positive nodes					
0 positive	64.4	63.4	63.8	67.6	68.5
1-3 positive	17.8	17.8	18.0	21.0	19.9
4-9 positive	6.9	6.1	6.8	6.6	4.6
10+ positive	4.8	4.0	3.8	1.6	0.2
Positive, # unknown	0.8	0.3	0.1	0.6	0.4
No nodes examined	5.4	8.3	7.5	2.7	6.4
ER Status					
Not done	7.7	5.3	1.7	1.2	0.2
Positive/Borderline	61.6	59.2	61.5	71.4	76.8
Negative	17.1	18.3	24.8	22.7	19.2
Unknown/not in chart	13.7	17.3	12.0	4.7	3.8
Charlson comorbidity score					
0	89.8	82.9	83.1	78.8	74.3
1	9.2	13.9	12.6	17.7	20.4
2+	1.0	3.2	4.2	3.5	5.3

ER: estrogen receptor.

[1]Unweighted sample size; [2]Weighted percent;

[3]Includes mammography only/no size given/unknown.

By 2005, the use of CMF with or without additional agents had dropped to less than 1% among all patients, regardless of nodal or ER status. Among women with node-negative, ER-positive tumors, regimen preference shifted from CMF to anthracycline and cyclophosphamide (AC) in 2000 and then to cyclophosphamide with taxane (TC) in 2010.

Endocrine agents

Beginning in 2005, there was a clear substitution of aromatase inhibitors for tamoxifen among

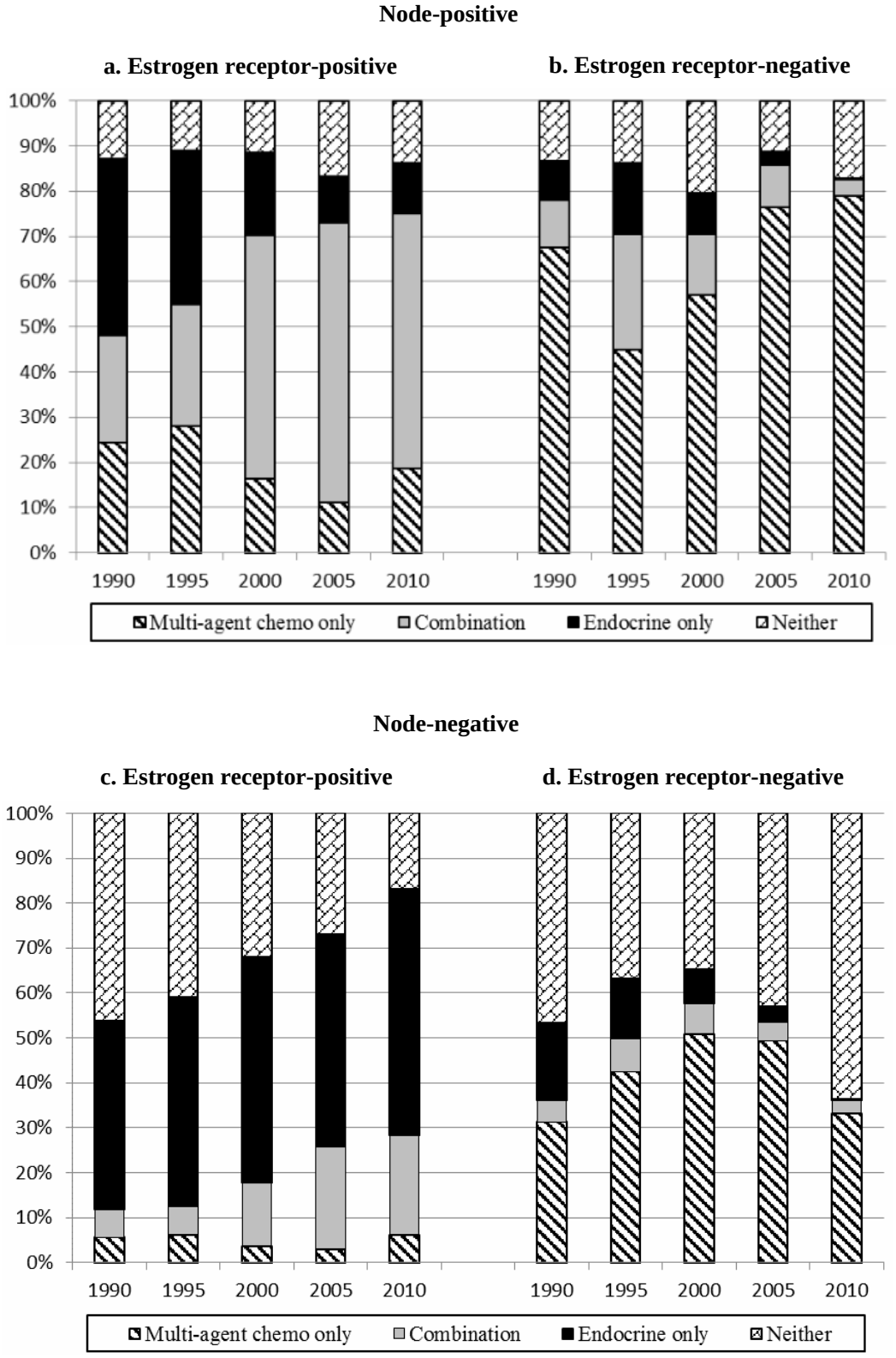

Figure 1. Treatment of early-stage, invasive female breast cancers by nodal status, estrogen receptor status and year of diagnosis; National Cancer Institute patterns of care studies.

Table 3. Weighted percentage of women diagnosed with early-stage, invasive breast cancer who received specific chemotherapeutic and endocrine therapy agents by year of diagnosis, nodal status and estrogen receptor status; National Cancer Institute patterns of care studies.

	1990	1995	2000	2005	2010
Node-positive					
Estrogen receptor-positive					
Chemotherapy					
None	51.9	45.0	29.7	27.0	24.9
AC-T +/- other	--	2.0	34.7	56.7	50.0
AC +/- other	1.9	12.1	16.5	9.7	1.4
TC +/- other	--	--	1.3	1.0	19.7
CMF +/- other	29.3	27.3	9.9	0.6	0.6
FAC/CAF +/- other	14.3	13.4	4.9	2.7	0.6
All other	2.6	0.3	3.2	2.3	2.8
Endocrine therapy[1]					
None	37.3	39.1	27.9	28.0	32.5
Tamoxifen only	59.4	60.5	71.5	17.8	31.3
Aromatase Inhibitors only	*	*	*	47.5	33.5
Other hormone only	1.6	0.2	0.2	1.3	0.1
Combinations	1.7	0.2	0.4	5.3	2.6
Estrogen receptor-negative					
Chemotherapy					
None	21.9	29.5	29.6	14.2	17.2
AC-T +/- other	--	1.7	35.9	61.2	36.9
AC +/- other	2.3	11.4	20.1	12.4	8.0
TC +/- other	--	--	0.6	4.1	22.0
CMF +/- other	45.0	38.3	9.0	--	0.6
FAC/CAF +/- other	25.8	17.0	2.6	2.6	--
All other	5.0	2.0	2.3	5.6	15.3
Node-negative					
Estrogen receptor-positive					
Chemotherapy					
None	88.1	87.4	82.1	74.2	71.6
AC-T +/- other	--	--	2.1	6.0	5.6
AC +/- other	0.5	1.1	10.3	11.4	2.9
TC +/- other	--	--	--	2.1	15.3

Table 3 continued..

	1990	1995	2000	2005	2010
CMF +/- other	10.1	9.8	4.5	5.3	0.2
FAC/CAF +/- other	0.7	1.7	0.8	0.1	--
All other	0.6	0.1	0.1	1.0	4.4
Endocrine therapy[1]					
None	51.7	47.2	35.7	29.9	22.9
Tamoxifen only	46.1	51.6	62.8	19.9	23.2
Aromatase Inhibitors only	*	*	*	47.4	49.1
Other hormones	0.7	0.1	0.0	1.0	0.2
Combinations	1.4	1.1	1.5	1.8	4.6
Estrogen receptor-negative					
Chemotherapy					
None	63.9	50.1	42.3	46.4	64.0
AC-T +/- other	--	--	13.1	35.6	20.4
AC +/- other	1.4	8.7	24.6	9.8	0.3
TC +/- other	--	--	--	--	9.4
CMF +/- other	28.3	33.2	14.2	1.1	0.8
FAC/CAF +/- other	3.9	4.1	5.5	3.6	--
All other	2.6	3.9	0.3	3.4	5.2

A: anthracycline; C: cyclophosphamide; F: 5-Fluorouracil; M: methotrexate; T: taxane.

[1]Sample sizes were insufficient to report specific agents among women with estrogen receptor negative tumors.

-- Unweighted sample size was zero; *Not specifically ascertained in 1990-2000.

women with ER-positive tumors (Table 3). However, in 2010 the preference for aromatase inhibitors to treat ER-positive tumors appeared to be greater among women with node-negative tumors. Among women with node-positive tumors, slightly more than 31% received tamoxifen and 34% received an aromatase inhibitor compared to 23% and 49%, respectively, among women with node negative tumors. Among the small percentage of women with estrogen-negative tumors who received endocrine therapy, there did not appear to be an agent preference in 2005 or 2010, regardless of nodal status (data not shown).

Determinants of therapy

In multivariate logistic models that adjusted for age, racial/ethnic, tumor characteristics and comorbidity score, year of diagnosis was associated with the increased use of multi-agent chemotherapy plus endocrine therapy among women with node-positive, ER-positive tumors, chemotherapy among women with node-positive tumors, and endocrine therapy among women with ER-positive tumors (Table 4). Older age was also associated with decreased use of chemotherapy plus endocrine therapy among women with node-positive, ER-positive tumors and chemotherapy among women with node-positive tumors; being 50-59 years vs. <50 years was associated with a higher likelihood of receiving endocrine therapy among women with ER-positive tumors. Having more advanced disease and an ER-negative tumor were also found to be associated with receipt of chemotherapy among women with node-positive tumors.

Table 4. Factors associated with receipt of chemotherapy and/or endocrine therapy among women diagnosed with early-stage invasive breast cancer; National Cancer Institute patterns of care studies.

	Chemotherapy + Endocrine				Chemotherapy				Endocrine therapy			
	N[1] = 1,811				N[1] = 2,849				N[1] = 4,138			
	OR[2]	95% CI		p	OR[3]	95% CI		p	OR[4]	95% CI		p
Diagnosis year				<0.01				<0.01				<0.01
1990	1.0	ref			1.0	ref			1.0	ref		
1995	1.3	0.8	1.9		1.8	1.2	2.7		1.1	0.9	1.5	
2000	4.5	2.8	7.1		2.0	1.3	3.2		1.8	1.3	2.5	
2005	5.9	3.7	9.5		2.9	1.8	4.4		2.1	1.4	3.3	
2010	5.2	3.0	8.9		3.6	1.8	6.9		2.4	1.7	3.6	
Age at diagnosis				<0.01				<0.01				<0.01
<50	1.0	ref			1.0	ref			1.0	ref		
50-59	1.0	0.6	1.6		0.7	0.4	1.1		1.8	1.2	2.6	
60-69	0.5	0.2	0.9		0.4	0.2	0.7		0.8	0.5	1.3	
70+	0.2	0.1	0.4		0.1	0.0	0.1		1.2	0.8	1.9	
Race/Ethnicity				0.30				0.13				0.60
NH White	1.0	ref			1.0	ref			1.0	ref		
NH Black	0.8	0.5	1.3		0.7	0.4	1.0		1.0	0.7	1.4	
Hispanic	0.6	0.4	1.1		0.6	0.4	1.0		0.9	0.6	1.4	
Other	1.1	0.6	1.9		0.9	0.5	1.7		1.3	0.8	2.1	
Tumor size				0.15				<0.01				0.04
<1 cm	1.0	ref			1.0	ref			1.0	ref		
1-1.9 cm	2.9	1.1	7.3		4.2	1.9	9.5		1.7	1.1	2.6	
2-2.9 cm	3.6	1.3	9.9		4.8	2.1	11.1		1.6	1.0	2.6	
3-4.9 cm	2.1	0.8	5.9		6.0	2.7	13.3		1.0	0.6	1.8	
5+ cm	2.9	1.0	8.3		5.0	2.1	12.1		1.4	0.6	3.2	
Unknown[5]	4.5	1.3	15.9		3.0	0.8	10.9		0.8	0.4	1.8	
Positive nodes				0.22				<0.01				0.18
0 positive									1.0	ref		
1-3 positive	1.0	ref			1.0	ref			0.9	0.6	1.3	
4-9 positive	1.5	0.9	2.6		2.0	1.3	3.2		1.4	0.9	2.3	
10+ positive	1.1	0.5	2.2		1.1	0.6	2.3		0.8	0.4	1.6	
Positive, # unknown	3.1	0.7	14.3		6.6	1.7	25.9		0.5	0.2	1.1	
No nodes examined									1.6	0.3	8.7	

Table 4 continued..

Chemotherapy + Endocrine					Chemotherapy				Endocrine therapy			
	N[1] = 1,811				N[1] = 2,849				N[1] = 4,138			
	OR[2]	95% CI		p	OR[3]	95% CI		p	OR[4]	95% CI		p
ER status								<0.01				
Positive/Borderline					1.0	ref						
Negative					1.9	1.2	3.0					
Unknown[6]					0.6	0.3	1.1					
Charlson comorbidity score				0.78				0.53				0.61
0	1.0	ref			1.0	ref			1.0	ref		
1	0.8	0.4	1.7		1.1	0.7	1.6		0.9	0.5	1.6	
2+	0.8	0.2	3.7		0.5	0.1	1.8		1.6	0.6	3.9	

CI: confidence interval; ER: estrogen receptor; NH: non-Hispanic; OR: odds ratio.

[1]Unweighted sample size.

[2]Logistic regression model includes women with node-positive, estrogen receptor-positive tumors.

[3]Logistic regression model includes women with node-positive tumors.

[4]Logistic regression model includes women with estrogen receptor-positive tumors.

[5]Includes mammography only/no size given/unknown.

[6]Includes not done/unknown/not in chart.

Cancer survival

In a Cox proportional hazards model, year of diagnosis, age, race/ethnicity, tumor size, number of positive nodes and receipt of endocrine therapy were associated with 3-year cancer survival (Table 5). There was a general improvement in cancer survival by year of diagnosis with patients diagnosed in 2010 having significantly lower mortality than women diagnosed in 1990. Women diagnosed between 50 and 59 years of age had higher mortality than women who were less than 50 at diagnosis. Women categorized as non-Hispanic white and other had significantly lower mortality compared to non-Hispanic Black women. Women with more extensive disease, based on tumor size and number of positive nodes, also experienced poorer survival. ER status and Charlson comorbidity score were not associated with mortality. Although the use of multi-agent chemotherapy was not associated with survival, receipt of endocrine therapy was associated with better survival.

DISCUSSION

This population-based study of women with early-stage, invasive breast cancer treated throughout the United States, indicates that since 1990 there has been a general increase in adjuvant therapy. Multi-agent chemotherapy particularly increased among women with ER-positive tumors. Overall, there was a significant change in preferred chemotherapy regimen from CMF in the early years to AC-T and then a remarkable decline in the use of anthracyclines between 2005 and 2010. Endocrine therapy especially increased among women with node-negative, ER-positive tumors; use of this therapy decreased substantially among women with ER-negative tumors. Utilization of aromatase inhibitors rapidly increased and became the preferred endocrine therapy among women with node-negative tumors.

Chemotherapy

Multi-agent chemotherapy was recommended for the treatment of premenopausal women with

Table 5. Factors associated with 3-year cancer-specific survival among women diagnosed with early-stage, invasive breast cancer; National Cancer Institute patterns of care studies.

	HR[1]	95% CI		p
Diagnosis year				<0.01
1990	1.0	ref		
1995	0.6	0.4	0.8	
2000	0.8	0.4	1.4	
2005	0.6	0.4	1.2	
2010	0.3	0.1	0.6	
Age at diagnosis, years				0.03
<50	1.0	ref		
50-59	2.1	1.3	3.6	
60-69	1.0	0.5	2.1	
70+	1.5	0.8	2.7	
Race/Ethnicity				0.02
NH Black	1.0	ref		
NH White	0.6	0.4	0.9	
Hispanic	0.6	0.3	1.1	
Other	0.4	0.2	0.9	
Tumor size				<0.01
<1 cm	1.0	ref		
1-1.9 cm	1.1	0.4	3.4	
2-2.9 cm	1.4	0.5	4.0	
3-4.9 cm	2.9	1.1	7.9	
5+ cm	3.8	1.3	10.8	
Unknown[2]	1.5	0.4	5.1	
Positive nodes				<0.01
0 positive	1.0	ref		
1-3 positive	1.8	0.9	3.7	
4-9 positive	2.9	1.4	6.1	
10+ positive	5.1	2.4	10.3	
Positive, # unknown	6.0	2.0	18.1	
No nodes examined	2.5	0.9	7.1	
ER status				0.06
Positive/Borderline	1.0	ref		
Negative	2.1	1.1	4.0	

Table 5 continued..

	HR[1]	95% CI		p
Unknown[3]	1.5	0.8	2.6	
Charlson comorbidity score				0.10
0	1.0	ref		
1	1.9	1.1	3.5	
2+	1.1	0.4	3.3	
Multi-agent chemotherapy				0.64
Yes	1.0	ref		
No	1.2	0.6	2.5	
Endocrine therapy				0.04
Yes	1.0	ref		
No	1.9	1.0	3.6	

CI confidence interval; ER: estrogen receptor; HR: hazard ratio; NH: non-Hispanic.

[1]Cox proportional hazards regression model - follow-up through 12/31/2013.

[2]Includes mammography only/no size given/unknown.

[3]Includes not done/unknown/not in chart.

node-positive breast cancer as early as 1985 [3] and this recommendation was expanded in 1990 to include women with node-negative breast cancer [4]. Likely because of the publication of these guidelines, in 1990 multi-agent chemotherapy was already being administered to a sizeable proportion of women with node-positive tumors; however, there was a stark contrast in utilization by ER status (ER-negative: 78%; ER-positive: 48%). In 2000, a broader recommendation established that women, regardless of nodal, menopausal or ER status, should receive chemotherapy [5]. The impact of these recommendations was observable. Between 1995 and 2000 there was a sizable increase in the use of multi-agent chemotherapy among women who had node-positive tumors. There was also an increase, albeit more limited, in multi-agent chemotherapy among women with node-negative tumors. Nevertheless, despite the 2000 Consensus Conference recommendation that the "majority" of women with breast cancer received multi-agent chemotherapy, chemotherapy utilization was always less than 30% among women with node-negative, ER-positive tumors and was only greater than 50% in 2000 and 2005 among women with node-negative, ER-negative tumors [5]. In comparison, a Swedish study reported that the use of adjuvant chemotherapy was limited until the late 1980s but by 2005 utilization was approximately 50% among women with operable breast cancer [12]. A population-based study in Quebec reported that among women with node-negative, ER-negative breast cancer the use of chemotherapy increased from about 26% in 1988 to 40% in 1993 [13], similar to the current data of 36% in 1990 and almost 50% in 1995. However, the current findings indicate that use subsequently decreased.

Endocrine therapy

The use of endocrine therapy increased over time among women with ER-positive tumors, regardless of their nodal status. The 1985 recommendation was for tamoxifen among women with node-positive, ER-positive tumors. Likely influenced by these recommendations, during the early study period the use of endocrine therapy was lower among women with node-negative, ER-positive tumors. However, by 2010 about three-quarters of women with ER-positive tumors in the current study received endocrine therapy regardless of

their nodal status. This appears to be in agreement with a Swedish study, which reported in 2005 that 60-80% of women with operable breast cancer received endocrine therapy [12].

Chemotherapeutic and endocrine agents

The most common chemotherapeutic regimen prescribed in 1990, regardless of nodal or ER status, was CMF (node-positive: 30%; node-negative: 14%; data not shown). Over the course of the study period CMF utilization decreased to less than 1% among all groups. Similar findings, albeit higher initial utilization rates, have previously been reported. A study in the Netherlands reported that about 90% of women who received chemotherapy received CMF in 2000 and by 2005 utilization had decreased to nearly zero [14]. The 2000 Consensus Conference stated that anthracyclines provided a "small benefit over other regimens which did not include anthracycline [5]". A clear shift away from CMF to regimens that included anthracyclines was observed starting in 2000. Among women with node-positive tumors the use of an anthracycline-containing regimen reached a peak in 2005; 72% among women with node-positive, ER-positive and 80% among women with node-positive, ER-negative tumors (data not shown). However, there was also a clear movement away from anthracyclines in 2010; anthracycline utilization declined by 23% among women with node-positive, ER-positive tumors and 44% among women with node-positive, ER-negative tumors (data not shown). As in the current study, a decline in anthracyclines was observed between 2005 and 2008 in the Netherlands [14]. These declines may be due, in part, to the reports of cardiotoxicity related to the use of anthracyclines [15-17].

In 1990 the NIH Consensus Conference stated that "the rate of local and distant recurrence" was decreased by adjuvant tamoxifen [4]. At around the same time, the use of tamoxifen as a chemopreventive agent for women at high risk of breast cancer became a hot topic and within the following decade was considered appropriate care [18, 19]. Thus, given tamoxifen had been viewed as a safe and effective treatment, it was not surprising that we observed high utilization during the earlier study period. The use of tamoxifen in women with ER-positive tumors reached a peak in 2000: 72% and 63% among women with node-positive and node-negative tumors, respectively. However, in 1994 the US Food and Drug Administration (FDA) added a stronger warning about the risk of uterine cancer in women treated with tamoxifen [20] and in 2002 they added a black box warning [21]. Likely as a result of these warnings, the publication of further studies examining the risk of uterine cancer [22, 23] and the approval of three aromatase inhibitors, our findings also indicate a precipitous drop in tamoxifen usage between 2000 and 2005. Endocrine therapy continued at similar or higher levels in subsequent years with tamoxifen replaced by aromatase inhibitors.

Cancer survival

Three-year cancer survival improved significantly over time, after adjusting for demographic, clinical, tumor, and treatment characteristics. This is consistent with national cancer statistics on breast cancer mortality which reported a decline from 1989 to 2012 of 36% [24]. After adjusting for multiple factors, there was no significant association between cancer survival and the receipt of chemotherapy. Of note, findings from a German population-based registry reported that the use of chemotherapy plus endocrine therapy was associated with poorer 7-year survival in pre-menopausal, but better in postmenopausal women compared to women not receiving chemotherapy [25]. Because of the observational nature of the current study this finding should be interpreted with caution. Although we adjusted for tumor characteristics, it is likely that patients who received chemotherapy had more aggressive disease, which could account for these findings. In contrast with the chemotherapy findings, women who did not receive endocrine therapy had a poorer cancer survival. Again, this should be interpreted with caution. Similarly, the same German population-based registry study found a better overall survival among hormone receptor-positive early-stage breast cancer patients who were prescribed endocrine therapy [25].

In the current study, despite no difference in the use of guideline therapy, it should be noted that there was a significantly better 3-year cancer survival

among women who were non-Hispanic white or included in the "other" racial group compared to non-Hispanic black women. Interestingly, an analysis of randomized controlled clinical trials reported poorer survival among African American women compared to white women even after controlling for multiple factors [26]. The current data are also comparable to national data on breast cancer mortality, which indicate that black women are more likely to die from breast cancer than white women [27].

Although this study had strengths, namely its population-based nature, physician-verified therapy and data collection from throughout the United States, there were limitations. First, many factors are associated with the selection of treatment and we were not able to adjust for all of these factors. For example, although Charlson comorbidity score was included as a covariate, information on severity of these comorbid conditions and performance status, which may have influenced treatment and/or survival, were unavailable. Likewise, information was not available on patient or physician preferences, barriers to healthcare access, financial concerns or social support. In order to ensure a similar length of follow-up for each diagnosis year, 3-year cancer survival was assessed. Therefore, it is unclear if observed trends in survival would be maintained or change with more follow-up. Further, genomic testing only became widely available in more recent years and we were not able to assess the impact of these tests on treatment selection and survival.

CONCLUSION

There was an increase in the use of recommended therapy and an improvement in cancer survival over time with a clear change in therapeutic agents from CMF to AC-T and a subsequent reduction in the use of anthracyclines. Further, there was a significant shift from tamoxifen to aromatase inhibitors. Whether the expanded use of genomic testing and personalized medicine influences the national trends in adjuvant therapy and survival remains to be seen.

ACKNOWLEDGMENT

This study was made possible through the efforts of the principal investigators and the cancer registry personnel at the participating Surveillance, Epidemiology and End Results registries.

CONFLICT OF INTEREST STATEMENT

This work was supported by National Cancer Institute contracts: HHSN261201000024C, HHSN261201000025C, HHSN261201000032C, HHSN261201000027C, HHSN261201000026C, HHSN261201000140C, HHSN261201000037C, HHSN261201000033C, HHSN261201000034C, HHSN261201000035C, HHSN261201000029C, HHSN261201000031C, HHSN261201000028C, and HHSN261201000030C.

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