SECTION I: MODEL INPUTS

Chapter 2:

Dissemination of Adjuvant Multiagent Chemotherapy and Tamoxifen for Breast Cancer in the United States Using Estrogen Receptor Information: 1975–1999

Angela B. Mariotto, Eric J. Feuer, Linda C. Harlan, Jeffrey Abrams

Background: **Clinical trials have shown tamoxifen to be effective only in women with estrogen receptor (ER)–positive tumors. In a previous model, trends in the utilization of adjuvant therapy were modeled only as a function of age and stage of the disease and not ER status. In this paper, we integrate this previous estimate on the use of adjuvant systemic therapy for breast cancer in the United States with information on ER status from the Patterns of Care (POC) data to estimate the dissemination of adjuvant therapy for women with different ER-status tumors. We also summarize efficacy of adjuvant systemic therapy reported in the overviews of early breast cancer clinical trials. These two inputs, dissemination and efficacy, are key pieces for models that investigate the effect of breast cancer adjuvant therapy on the decline of U.S. breast cancer mortality.** ***Methods:*** **The adjustments to the previous models are calculated using the POC data on 7116 women with breast cancer diagnosed from 1987 to 1991 and in 1995 who were randomly selected from the Surveillance, and Epidemiology, and End Results (SEER) program registries. The POC data provide more accurate information on treatment and clinical variables (e. g., ER status) than the SEER data because medical records are reabstracted and further verified with treating physicians.** ***Results:*** **Use of multiagent chemotherapy is higher for younger women (<50 years) and for women whose tumors were shown to be ER negative or borderline. The use of tamoxifen is higher among older women and women with ER-positive tumors. After 1980 the combined use of multiagent chemotherapy and tamoxifen for women diagnosed with breast cancer at ages 69 or younger increased more for women whose tumors were ER status positive or unknown than ER status negative. Older women (>69 years) seem to receive almost exclusively tamoxifen irrespective of ER status, except for a small percentage of those with more advanced stages (II- and II+/IIIA) who also receive multiagent chemotherapy.** ***Discussion:*** **The estimated dissemination trends by ER status, based on modeling the POC data, reveal that treatment strategies with demonstrated efficacy in clinical trials have been adopted into practice. The dissemination and efficacy are the two factors necessary to input into models to determine the population impact of these therapies on U.S. breast cancer mortality. The largest decline in mortality would be expected for younger women (<60 years) with ER-positive tumors or whose tumors are of unknown status because of the largest efficacy and dissemination of adjuvant therapy in this group. [J Natl Cancer Inst Monogr 2006;36:7–15]**

During the past two decades, substantial progress has been made in the treatment of invasive breast cancer. Results from clinical trials have shown that adjuvant chemotherapy and adjuvant hormonal therapy for women with early-stage breast cancer are efficacious for a larger group of women than originally hypothesized. These results have been communicated to physicians and the clinical community by using clinical announcements mechanisms, such as recommendations provided by the National Institutes of Health Consensus Development Conferences and as practice guidelines such as those provided by the National Comprehensive Cancer Network (NCCN) *(1–4)*. The dissemination of adjuvant therapy to the general population together with the benefits from these treatments are likely to translate into improvements in population-based survival and consequently into a decline in the observed breast cancer mortality.

The Cancer Intervention Surveillance Modeling Network (CISNET) (http://cisnet.cancer.gov) is a cooperative agreement funded by the National Cancer Institute that uses modeling techniques to study the impact of interventions, screening, and treatment on population-based cohorts of patients with breast, colorectal, lung, and prostate cancers. Seven mathematical modeling teams have been funded in the area of breast cancer, all of which are modeling the contribution of adjuvant treatment for breast cancer and mammography to the decline of breast cancer mortality rates. A crucial input into these models is the trends in the usage of breast cancer adjuvant systemic treatment in the general U.S. population. These estimates are combined with efficacy estimated from clinical trials to quantify the effect of adjuvant treatments at the population level.

Affiliations of authors: Division of Cancer Control and Population Sciences, National Cancer Institute, NIH, Bethesda, MD (ABM, EJF, LCH); Division of Cancer Treatment and Diagnosis, National Cancer Institute, NIH, Bethesda, MD (JA).

Correspondence to: Angela B. Mariotto, PhD, Division of Cancer Control and Population Sciences, National Cancer Institute, 6116 Executive Blvd., Ste. 504, MSC 8317, Bethesda, MD 20892-8317 (e-mail: mariotta@mail.nih.gov).

DOI: 10.1093/jncimonographs/lgj003

Table 1. History of recommendation on the use of adjuvant systemic therapy for breast cancer

Year	Population		Recommendations
1985 NIH Consensus Development Conference	**Node Negative**		
	Pre-menopausal	—	Multi-agent chemotherapy
	Postmenopausal	ER negative	Multi-agent chemotherapy
	Postmenopausal	ER positive	Tamoxifen
1988 NCI Clinical Alert	**Node Positive**		
	>3 cm	—	Multi-agent chemotherapy
	<= 3 cm	ER negative	Multi-agent chemotherapy
	<= 3 cm	ER positive	Tamoxifen
1990 NIH Consensus Development Conference	<1 cm		No adjuvant therapy
2000 NIH Consensus Development Conference*	**Positive or Negative Nodes**		
	ER negative		Multi-agent chemotherapy
	ER positive		Multi-agent chemotherapy + Tamoxifen

*Polychemotherapy should be recommended regardless of nodal, menopausal, or hormonal receptor status.

Mariotto et al. *(5)* previously modeled the trends in the usage of adjuvant multiagent chemotherapy, tamoxifen, and the combination of both among women diagnosed with invasive breast cancer in the United States from 1975 to 1999 by age group (<50, 50–69, >70) and stage (I, II node negative, and IIIA). However, these previous estimates did not use information on estrogen receptor (ER) status. Recent results from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have shown a reduction of the annual odds of death to be as large as 28% for women with ER-positive breast cancer receiving 5 years of tamoxifen *(6)*. Women with low or zero-level ER were not included in the overviews of tamoxifen clinical trials because the overall effect appeared to be small from examination of individual studies *(6)*. The 1985 NIH Consensus Development Conference recommended that postmenopausal women with breast cancer receive tamoxifen if their tumors were ER positive and they had positive lymph nodes. In 1988 the NCI Clinical Alert extended the recommendation for tamoxifen to women with negative nodes and tumors that were less than 3 cm and ER positive. The 2000 NIH Consensus Development Conference *(4)* recommended tamoxifen for nearly all women with ER-positive tumors. These recommendations are summarized in Table 1.

The objective of this paper is to update the previous estimates *(5)* by incorporating ER status information. Because of different efficacy of tamoxifen depending on ER status it is important to estimate the use of tamoxifen by ER status to correctly estimate the effect of tamoxifen at population level. Estimation of dissemination by ER status is also important in accessing the pace at which clinical trials results are being translated into clinical practice.

This paper also summarizes the efficacy of multiagent chemotherapy and tamoxifen by age and ER status on the basis of published results of meta-analyses on the early breast cancer clinical trials. These results are summarized here because they represent the other piece of information that together with dissemination of adjuvant therapy translates into the effect of adjuvant therapy at population level.

Materials and Methods

Patterns of Care Data

The Surveillance, Epidemiology, and End Results (SEER) program *(7)* collects date of diagnosis as well as other clinical and demographic information on cancer patients diagnosed in nine registries that cover approximately 10% of the U.S. population. First-course treatment in the SEER data is collected primarily from hospital medical records. Information on the use of adjuvant systemic therapy is incomplete because treatment provided in outpatient settings is not always reported in the hospital record. To obtain more accurate information on the first-course therapy, the Patterns of Care (POC) studies *(8)* were conducted by randomly sampling women in SEER, diagnosed with early breast cancer in 1987–1991 and again in 1995. Women aged 50 years and younger were oversampled and, in 1995, African Americans and Hispanics were also oversampled. Information on tumor characteristics, including ER status, as well as adjuvant therapy were abstracted from the medical records. The treating physicians were asked to verify whether chemotherapy and/or hormonal agents were administered.

Because POC data have included information on ER status since 1987 (whereas SEER has information since 1990) and more accurate information on therapy use than SEER, the adjustments to estimate the dissemination by ER status are calculated from the POC data only.

Women with a previous diagnosis of cancer, other than nonmelanoma skin cancer and women with breast cancer diagnosed at autopsy or on death certificate, were not eligible for participation in the POC studies. Women who did not undergo primary surgery *(9)* were excluded from the analysis since these patients are not eligible for adjuvant systemic therapy. Patients with unknown stage (n = 495) are also excluded. Patients with unknown information on a specific treatment were excluded from the analysis. There were on average 7.2% patients with unknown information on both multiagent chemotherapy and tamoxifen and 5.7% unknown on multiagent chemotherapy only or 5.7% unknown on tamoxifen only in the POC data. The analysis includes 7116 patients participating in the POC studies.

For the analysis, we considered four stages of disease: stage I, stage II node negative (II–), stage II node positive (II+), and stage IIIA, on the basis of the American Joint Committee on Cancer (AJCC) staging system *(10)*. Stages II+ and stage IIIA are combined into one category (II+/IIIA) to provide more stable estimates. For a more detailed description as how stage was categorized, refer to Mariotto et al. *(5)*. Age was categorized as less than 50 years, 50–69 years, and more than 70 years.

All estimates for POC were weighted to reflect the SEER population from which the sample was drawn. The weights were calculated as the inverse of the sampling proportion for

each sampling stratum, defined by each age/race/stage/registry. The standard errors of the proportions adjusted for the finite population were calculated from the SAS procedure PROC SURVEYMEANS.

ER Status

Results from ER assays on the primary tumor are coded in the POC data as follows: no test done, positive/elevated, negative/normal, borderline (undetermined whether positive or negative), ordered but results not in chart, unknown, or no information. Negative/normal, positive/elevated, and borderline categories are assigned on the basis of lab-specific determinations of ranges as noted in the laboratory report. For the purposes of this analysis ER status is classified into three categories: 1) positive, 2) negative/borderline, and 3) unknown. The unknown category includes no test performed, ordered but results not in chart, and unknown. The most recent overviews of the randomized trials of adjuvant tamoxifen among women with early breast cancer *(6)* presented results for women with ER-positive tumors (those with at least 10 fmol of ER per mg of cytosol protein), women with low or zero-level of ER protein, and women whose ER status was unknown. We have grouped ER status the same way as in the meta-analysis (positive, negative/borderline, and unknown) so that efficacy results from meta-analyses could be directly applied to the estimated proportion of women using tamoxifen, even though the 2000 NIH Consensus Development Conference suggested that women with tumors of borderline ER be treated as if they were ER positive.

Modeling Dissemination Patterns of Adjuvant Therapy by ER Status

To estimate the use of a specific adjuvant therapy by ER status we consider an adjustment to the models in Mariotto et al. *(5)* that estimated use of adjuvant therapy for women, regardless of the ER status of their tumor. Four specific adjuvant therapies are considered: multiagent chemotherapy only, tamoxifen only, combined use of multiagent chemotherapy and tamoxifen, and no adjuvant therapy.

Use of Adjuvant Therapy With No Information on ER Status

The model in Mariotto et al. *(5)* was estimated by combining SEER and POC data, taking into account strengths and limitations of the two data sources and reasonable assumptions about the dissemination process. In brief, the models reflected the dissemination trends observed in the SEER data, since SEER has more years and cases than POC, and the level of the dissemination from the POC data, because treatment verification in the POC data provided a more accurate estimate of the actual use of therapy. The probabilities of a woman diagnosed with breast cancer at calendar year y (y = 1975, …, 1999), age a, and stage k, uses the specific treatment s (multiagent chemotherapy, tamoxifen, both, none), estimated in Mariotto et al. *(5)*, is denoted as

$$P(T = s \mid Age = a, Stage = k, Year = y). \qquad [2.1]$$

For further description of the model refer to Mariotto et al. *(5)*.

Use of Adjuvant Therapy Including Information on ER Status

Using information on therapy use and ER status from the POC data, we estimate adjustments to model [2.1] to estimate the probability of receiving a specific treatment for women with a specific ER status. For each age, stage, and calendar year, the adjustments are calculated as the ratio of the probability of receiving a specific treatment s for women with a specific ER status r over the probability of receiving the same treatment s regardless of ER status, with both probabilities estimated from the POC data. The probabilities are calculated by fitting multinomial regression models on the number of women receiving each type of therapy for years 1987 and after, by ER status and for all ER status. For specific treatment s, age a, stage k, year y, and ER status r, the ratio adjustments will be denoted $A(s|a, k, y, r)$ and a detailed description of their calculation is given in the appendix. We multiply the adjustments to the dissemination models estimated in Mariotto et al. *(5)* (equation [2.1]), to obtain the probabilities of receiving treatment conditional on ER status, age, stage, and year at diagnosis,

$$P(T = s \mid Age = a, Stage = k, Year = y, ER = r) = A(s \mid a, k, y, r)\, P(T = s \mid Age = a, Stage = k, Year = y)$$

for years y = 1987, …, 1999.

The first public guideline suggesting ER status as a marker to be considered in defining breast cancer treatment is the 1985 NIH Consensus Development Conference, which recommended tamoxifen for postmenopausal women diagnosed with ER-positive tumors and positive lymph nodes. Thus, we assume that before 1985 therapy use was independent of ER status. In other words, prior to 1985, knowing a woman's ER status would not change her chance of receiving a specific therapy—meaning that the probability of receiving therapy for a woman with a given ER status is the same for any ER status and is the same in the absence of ER status information, which translates into no adjustment and ratio of 1. Thus, for years 1975–1984 we assume that the use of adjuvant therapy by ER status is the same as the use of adjuvant therapy with no ER information from Mariotto et al. *(5)*. To estimate the dissemination in 1985 and 1986, and to phase in the dissemination between the ER status therapy use–independence era and the no-independence era we fitted a logistic model through the last point year of the independence era, 1984 and 1987. A more mathematical description of the model is given in the appendix.

Duration of Tamoxifen Use

Because 5 or more years of tamoxifen is more effective than 1 or 2 years of tamoxifen, 28% versus 18% reduction in the mortality hazard ratio *(6)*, we need to estimate the proportion of women receiving 5 years of tamoxifen among all women receiving tamoxifen. To our knowledge, no population-based data contain this information. We combine information from literature and from subject matter experts (J. Abrams, personal communication) to estimate two points from the curve describing the probability of receiving 5 years or more of tamoxifen, given that the patient is receiving tamoxifen. The first point is estimated from the number of women participating in trials of 5-year tamoxifen compared with all tamoxifen trials. The 1990 review of EBCTCG *(11)* included a total of 29 892 women randomized in trials of tamoxifen around 1985. From these 4551 (15%)

women participated in trials of 5 years or more of tamoxifen. We also assumed that by 1990, 80% of the women who were recommended tamoxifen were recommended for 5 years or more (J. Abrams, personal communication). By fitting a logistic model to these two points (1985, 0.15 and 1990, 0.80), we were able to estimate the proportion of women receiving 5 years tamoxifen among all women receiving tamoxifen. This model (data not shown) implies a rapid increase in the proportion being recommended 5 years of tamoxifen from 1985 to 1991.

Efficacy of Adjuvant Multiagent Chemotherapy and Adjuvant Tamoxifen

Since efficacy and dissemination are the key inputs to calculate the effect of adjuvant therapy at population level, we summarize here the efficacy of the use multiagent chemotherapy only, tamoxifen only, and the combined use of both from the clinical trials overviews of adjuvant systemic therapy for breast cancer *(6,12)*. We have expressed the proportional reductions in deaths (all causes) reported in the overviews as the reduction in the mortality hazard ratio. The mortality reduction for women who used multiagent chemotherapy depends on age and was 27%, 14%, and 8% for women aged less than 50, 50–59, and 60–69 years, respectively *(12)*. For mortality (as for recurrence) nodal status had no significant overall effect on the proportional risk reductions after stratification by age *(12)*. Adjuvant tamoxifen substantially improved survival of women with ER-positive tumors and of women whose tumors were of unknown ER status. The proportional mortality reduction among women with ER-positive tumors was 18% and 28% in the trials of 2 and approximately 5 years of tamoxifen *(6)*. Given ER status, the effects of tamoxifen are independent of nodal status and age. Evidence from these analyses shows that chemotherapy and tamoxifen are complementary adjuvant treatments and that in some of the comparisons there were the same benefit of tamoxifen in trials of tamoxifen plus chemotherapy versus chemotherapy alone and trials of tamoxifen versus no adjuvant therapy. These results translate into the two treatments acting independently of one another. Using this independence assumption, we calculated and predicted the reduction in mortality hazard ratio due to the combined use of multiagent chemotherapy and tamoxifen by age and ER status. Thus, for women diagnosed at younger than 50 years with ER-positive breast cancer tumors, the percent reduction in mortality hazard ratio due to both treatments is

$$100 \times \{1 - (1 - 0.27) \times (1 - 0.28)\} = 47.4\%. \qquad [2.2]$$

If q represents the reduction in the mortality hazard ratio due to therapy then the effect of the therapy on survival is $S_{Therapy}(t) = S_{Base}(t)^{\{1-q\}}$, where $S_{Base}(t)$ represents the survival in the absence of adjuvant treatment.

Results

Table 2 shows the number of women with breast cancer in the POC data by stage, age at diagnosis, year of diagnosis, and ER status. Year of diagnosis is grouped as 1987–1988, 1989–1990, 1991, and 1995. The sample sizes of women diagnosed with breast cancer at age 70 or older and whose tumor is ER negative/borderline or of unknown ER status are small, so the proportions in this ER status and age group are unstable. The statistical model descried in the methods section stabilized estimates in these situations.

Table 2 displays the observed percentage of women receiving one of four modalities of adjuvant therapy (multiagent chemotherapy only, tamoxifen only, both, and none) by tumor ER status, stage, age at diagnosis, and year of diagnosis as observed in the POC data. Adjuvant therapy for women diagnosed with early-stage breast cancer increased from 1987 to 1995 irrespective of ER status, age, and stage. As would be expected on the basis of recommendations during these periods, the use of multiagent chemotherapy is higher for younger women (<50 years) and for women whose tumors are shown to be ER negative or borderline, and tamoxifen use is higher among older women and women with ER-positive tumors.

Figure 1, A–C, displays, for each age group, the estimated proportion of women using adjuvant therapy by calendar year. The height of each shaded area represents the proportion using both chemotherapy and tamoxifen (black), tamoxifen only (light gray), and chemotherapy only (dark gray). The height of the total areas represents the proportion receiving any type of adjuvant therapy. The first column of panels represents the use of adjuvant therapy among all women, regardless the ER status of their tumors and is similar to the figures in Mariotto et al. *(5)*. The new estimates (columns 2–4), including ER status information, show that tamoxifen is given more often to women with ER-positive tumors and to women whose tumors are of unknown ER status. For women with ER-negative or borderline tumors, the use of adjuvant tamoxifen was much lower than that for women whose tumors were ER positive or unknown status. The exception was for older women, especially over the age of 69 years, where tamoxifen appeared to be given instead of multiagent chemotherapy. Use of multiagent chemotherapy alone was highest among younger women (<70 years) whose tumors are ER negative or borderline.

Tables 3, A and 3, B represent published results from the meta-analysis conducted by the EBCTCG in 1998 *(6,12)*. Table 3, A shows the reduction in mortality by age resulting from the use of chemotherapy alone, and Table 3, B shows the mortality reduction by ER status with the use of tamoxifen for approximately 2 and 5 years. To estimate mortality reduction for women receiving both chemotherapy and tamoxifen compared with no treatment, we used data from Tables 3, A–B and equation [2.2] to predict reductions in mortality by age and ER status (Table 3, C). Women younger than 50 years with ER-positive tumors realize the largest benefit of the combination therapy that included the use of tamoxifen for 5 years. The mortality is nearly half of what would be expected for women without such therapy. Women aged 60–69 years receive the least benefit from the combination therapy, although they have a reduction of 34% and 27% if their tumors were ER positive or unknown, respectively. There is only an 8% reduction in mortality for the combination therapy if they have ER-negative or borderline tumors. Since tamoxifen effect for ER-negative/borderline (Table 3, B, last row) were small and inconsistent, we assumed no tamoxifen effect for this group in the calculations.

Discussion

The results show that the proportion of patients treated by multiagent chemotherapy is higher for women with ER-negative or ER-borderline tumors, whereas the proportion treated by tamoxifen is higher for women with tumors that were ER positive

Table 2. Percentage of women observed in the POC data using adjuvant therapy (MC = multiagent chemotherapy, T = Tamoxifen, both, none) by year of diagnosis, stage, age at diagnosis, and ER status and sample sizes (# of women) in each category

			ER-positive				ER-negative/borderline				Unknown			
Age	Stage	Adjuvant Therapy	1987–88	1989–90	1991	1995	1987–88	1989–90	1991	1995	1987–88	1989–90	1991	1995
<50	I	MC	11%	23%	23%	23%	37%	46%	41%	43%	14%	24%	22%	6%
<50	I	T	16%	20%	26%	28%	2%	3%	6%	1%	6%	12%	16%	11%
<50	I	Both	6%	10%	16%	6%	1%	4%	8%	2%	1%	0%	7%	1%
<50	I	None	68%	47%	35%	43%	59%	46%	46%	54%	79%	65%	54%	82%
	# Women		249	292	132	88	127	154	76	55	131	115	30	28
<50	II-	MC	33%	30%	29%	26%	47%	55%	72%	78%	34%	39%	44%	33%
<50	II-	T	12%	21%	23%	10%	3%	1%	0%	0%	2%	10%	0%	24%
<50	II-	Both	11%	19%	31%	33%	0%	6%	0%	1%	0%	3%	0%	3%
<50	II-	None	44%	30%	17%	31%	50%	38%	28%	21%	64%	48%	56%	39%
	# Women		83	122	53	32	101	123	33	35	34	36	12	22
<50	II+/IIIa	MC	61%	56%	50%	44%	82%	78%	68%	70%	69%	73%	72%	44%
<50	II+/IIIa	T	6%	2%	5%	5%	0%	0%	3%	4%	3%	2%	0%	2%
<50	II+/IIIa	Both	24%	31%	36%	45%	7%	7%	14%	17%	15%	8%	22%	41%
<50	II+/IIIa	None	9%	10%	9%	5%	11%	15%	15%	9%	12%	17%	6%	14%
	# Women		186	315	191	94	119	173	111	74	58	82	33	32
50–69	I	MC	0%	3%	4%	1%	3%	22%	15%	48%	3%	1%	3%	1%
50–69	I	T	15%	44%	51%	54%	7%	27%	22%	5%	12%	21%	35%	35%
50–69	I	Both	1%	6%	4%	3%	0%	1%	1%	10%	0%	0%	0%	0%
50–69	I	None	84%	47%	40%	42%	90%	50%	61%	37%	85%	77%	62%	64%
	# Women		83	171	93	97	33	42	27	27	66	62	31	28
50–69	II-	MC	0%	5%	0%	11%	63%	47%	45%	81%	0%	1%	40%	23%
50–69	II-	T	33%	55%	62%	24%	19%	4%	15%	8%	10%	53%	0%	4%
50–69	II-	Both	7%	9%	9%	31%	0%	3%	15%	1%	0%	0%	0%	1%
50–69	II-	None	60%	31%	29%	34%	17%	45%	24%	9%	90%	46%	60%	72%
	# Women		33	51	28	22	12	32	20	14	15	15	5	15
50–69	II+/IIIa	MC	8%	22%	11%	21%	61%	58%	61%	51%	2%	36%	24%	23%
50–69	II+/IIIa	T	45%	39%	46%	37%	9%	24%	18%	2%	56%	11%	37%	4%
50–69	II+/IIIa	Both	33%	32%	31%	31%	2%	6%	17%	38%	17%	24%	20%	49%
50–69	II+/IIIa	None	14%	7%	12%	11%	29%	12%	4%	8%	25%	29%	18%	25%
	# Women		82	217	152	101	24	72	54	37	16	48	20	15
>69	I	MC	0%	4%	0%	0%	0%	0%	0%	0%	0%	0%	7%	0%
>69	I	T	17%	45%	53%	50%	11%	28%	26%	32%	15%	18%	14%	47%
>69	I	Both	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
>69	I	None	83%	50%	47%	50%	89%	72%	74%	68%	85%	82%	79%	52%
	# Women		64	108	80	78	11	24	11	9	26	47	27	17
>69	II-	MC	0%	0%	0%	0%	0%	6%	34%	43%	0%	0%	7%	0%
>69	II-	T	20%	47%	54%	62%	14%	15%	15%	4%	66%	51%	64%	50%
>69	II-	Both	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
>69	II-	None	80%	53%	46%	38%	86%	79%	51%	53%	34%	49%	36%	50%
	# Women		33	49	20	18	7	11	6	7	6	9	8	7
>69	II+/IIIa	MC	0%	9%	5%	7%	38%	6%	16%	2%	0%	3%	0%	21%
>69	II+/IIIa	T	68%	57%	69%	66%	39%	64%	48%	35%	66%	76%	76%	30%
>69	II+/IIIa	Both	3%	4%	8%	12%	0%	9%	15%	29%	0%	1%	0%	18%
>69	II+/IIIa	None	28%	31%	19%	14%	22%	21%	22%	35%	34%	20%	24%	32%
	# Women		52	124	92	45	6	23	14	9	9	24	13	16

or tumors that were of unknown ER status. This usage pattern is consistent with recommendations from clinical trials that have shown tamoxifen to be effective in women with ER-positive tumors and in women whose tumors are of unknown status *(12,13)*. For women whose tumors have been shown to be ER negative, adjuvant tamoxifen remains a matter of research *(13)*. The results are also in keeping with recommendations of NIH Consensus Development Conference and Clinical Announcements, which are summarized in Table 1. Older women with ER-positive tumors received less multiagent chemotherapy than women with ER-negative tumors, despite results showing that the efficacy of multiagent chemotherapy is independent of ER status. This finding might be due to a combination of factors: tamoxifen being more effective in women with ER-positive tumors, the lack of data regarding the benefits of multiagent chemotherapy for older women *(7)*, the adverse side effects of multiagent chemotherapy, concerns about comorbidity, and ability to tolerate chemotherapy. Although decreasing, the proportion of women diagnosed aged 70 and older with ER-negative, stage II node-positive/IIIA breast cancer, receiving tamoxifen, is high considering the questions surrounding the benefits of tamoxifen in this group (Fig. 1, C). The combined use of both multiagent chemotherapy and tamoxifen increased more for women whose tumors were ER positive.

Our estimates of the reduction in breast cancer mortality risk by age and ER status reflect the multiplicative effect of the use of tamoxifen and multiagent chemotherapy found in data from clinical trials. They suggest an improvement in survival that is larger for younger women than for older women. However, even in

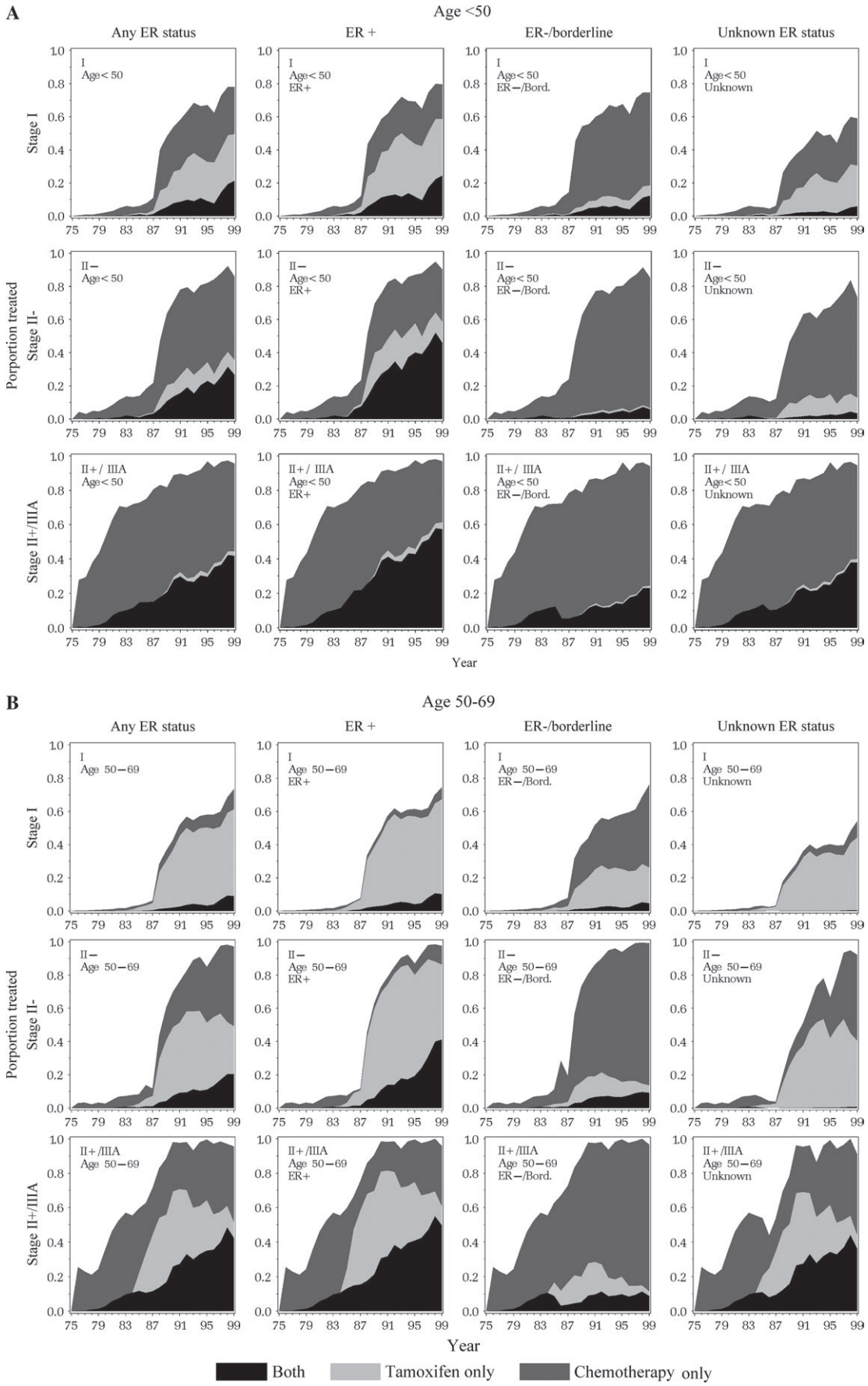

Fig. 1. Trends in the use of multi-agent chemotherapy only, tamoxifen only, and the combined use of both by age, stage, and ER status. Models estimated from SEER and POC data. Height in each shaded area represents the proportion using respective treatment. The height of the total shaded areas represents the proportion receiving any type of adjuvant therapy.

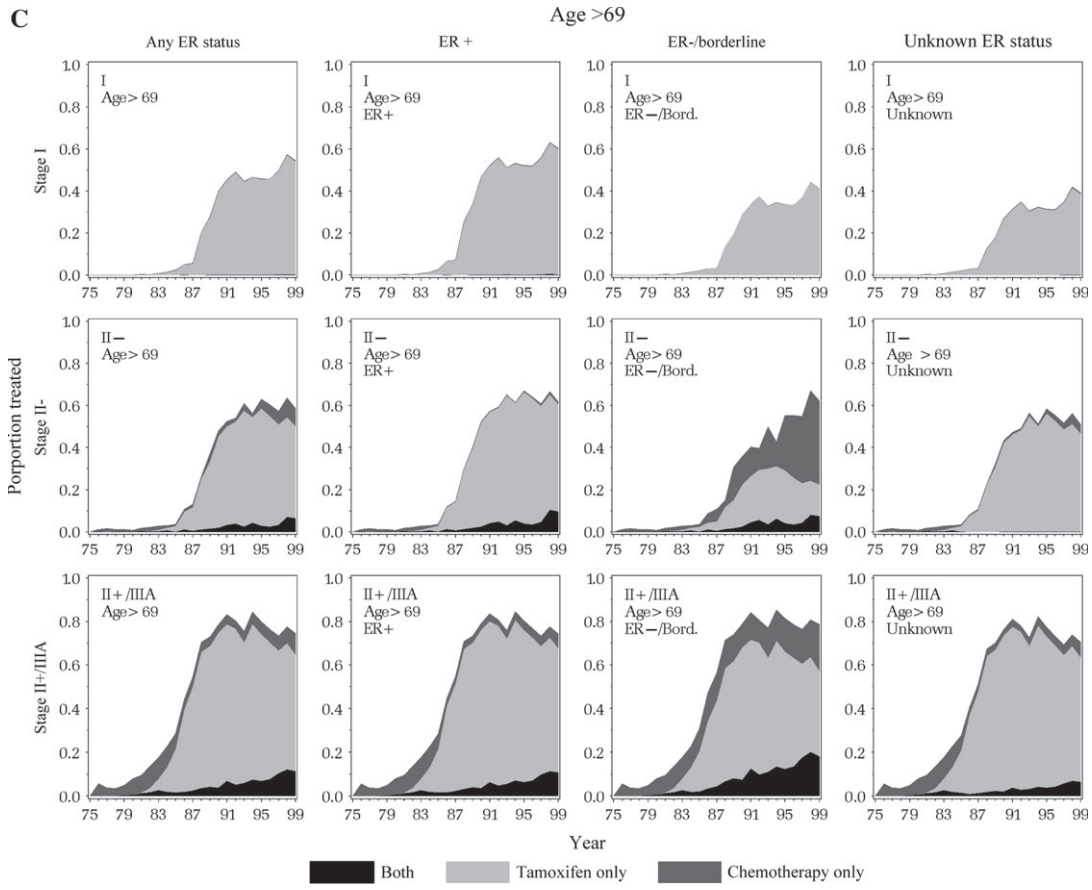

Fig. 1 (continued).

women aged more than 69 years with tumors that are ER positive, if placed on a regimen of multiagent chemotherapy and 5 years of tamoxifen, a 25% reduction in risk of mortality would be predicted.

The estimated model by ER status, which combined a previous model and adjustments estimated from the POC data, fit well the respective proportions of women using adjuvant therapies by ER status observed in the POC data. However, the dissemination curves by ER status are subject to some limitations. No information on ER status is available for before 1987. The curves before 1987 represent the assumption that treatment assignment was independent of ER status in 1984 and before. The initial NIH Consensus Development Conference was held in September 1985. On this basis we felt that a reasonable assumption was that prior to 1985, patient's treatment would not be based on the ER status of the woman. For data between 1984 and 1987 we assumed a smooth increase to the level estimated in 1987. For some combinations of age and stage, the POC data are sparse and the proportion of treatment use by ER status highly variable. Models were used to describe a general trend of the treatment use and should not be overinterpreted as describing changes at specific years.

The dissemination of duration of tamoxifen, 5 years compared to any duration, is necessary as an input into breast cancer models evaluating the contribution of adjuvant treatment and mammography to the decline of breast cancer mortality rates. Because of the lack of informative data, the estimate of duration of tamoxifen has several limitations. It is based on the number of women enrolled in clinical trials in 1985 and expert opinion on providers' recommendation of tamoxifen for 5 years. Although the duration of tamoxifen actually received in the general population interests us, the model reflected recommendations rather than adherence to 5 years of tamoxifen. Some studies *(14,15)* have shown that adherence to 5 years of tamoxifen is not optimal, for example, Partridge et al. *(15)* estimated that the overall adherence to tamoxifen decreased to 50% by year 4 of therapy, so this represents the upper bound on the use of 5-year tamoxifen therapy. The overview of the randomized trials are intent-to-treat analyses, so presumably their results are attenuated from an analysis of only women who actually completed 5 years of tamoxifen. However, the proportion of women completing 5 years of tamoxifen is probably lower in the general patient community than in trials.

The population impact represents the final phase of cancer research as new cancer control interventions move from discovery to development to delivery. The impact at the population level is the combination of the effect of the intervention at population level (effectiveness) and dissemination. Effectiveness may differ from efficacy as measured in trial settings for several reasons. One is perfect adherence to the therapy regimen, for example, not completing all cycles of chemotherapy and/or not completing all 5 years of tamoxifen. In this analysis we have provided only estimates of the dissemination of therapy, and measures of efficacy, since measures of effectiveness are not readily available. In some of the models [e.g., the M. D. Anderson Cancer Center Model in this monograph *(16)*], a rough measure of effectiveness was obtained by starting with a prior efficacy distribution and then obtaining a posterior distribution of this same parameter, which is attenuated by an amount necessary to fit population mortality trends. We also did not model the dissemination of newer

Table 3. Reduction in the mortality hazard ratio due to the use of tamoxifen only, multiagent chemotherapy only, and the combined use of both

A. Multi-agent chemotherapy only*

Age	% Reduction	
<50	27%	†
50–59	14%	†
60–69	11%	†

B. Tamoxifen only‡

	Duration			
ER status	~2 years		~5 years	
ER+	18%	§	28%	§
ER unknlown	15%	§	21%	§
ER neg/borderline	7%	§	−3%	n.s.

C. Multi-agent chemotherapy and Tamoxifen||

	ER positive		ER unknown		
Age	2 yr. Tam.	5 yr. Tam.	2 yr. Tam.	5 yr. Tam.	ER poor¶
<50	40%	47%	38%	42%	27%
50–59	29%	38%	27%	32%	14%
60–69	25%	34%	22%	27%	8%

*Data summarized from *(11)*.

†Confidence interval (CI) does not include zero.

‡Data summarized from *(6)*. n.s. = not significant (CI includes zero).

§CI does not include zero.

||Results derived from Tables 3, A and 3, B using formula [2.2].

¶Since Tamoxifen effect for ER negative/borderline (Table 3, B, last row) were small and inconsistent we assumed no tamoxifen effect for this group in the calculations.

therapies that recently have proved to be effective, such as aromatize inhibitors, luteinizing hormone–releasing hormone agonists, or newer chemotherapy agents.

In this paper, we integrate a previous estimate on the use of adjuvant systemic therapy for breast cancer in the United States with information on ER status from the POC data to estimate the dissemination of adjuvant therapy for women with different ER-status tumors. We also presented improvements in outcome reported from clinical trials. These two inputs, dissemination and efficacy, are key pieces for CISNET models that investigate the effect of breast cancer adjuvant therapy on the decline of breast cancer mortality. Estimation of dissemination of adjuvant therapy by ER status is important in accessing the pace at which clinical trials results are being translated into clinical practice, the anticipated decline in mortality that might be expected from this translation, and whether the actual decline is similar to what would be expected based on clinical trials data.

Appendix

Formally, let $P(T = s \mid Age = a, Stage = k, Year = y)$ be the probability of a woman diagnosed with breast cancer at calendar year y (y = 1975, …, 1999), age a, and stage k uses the specific treatment s. These probabilities are estimated in Mariotto et al. *(5)*. Specific treatments are multiagent chemotherapy only, tamoxifen only, combined use of multiagent and tamoxifen, and none of the previous. The new models to be estimated are $P(T = s \mid Age = a, Stage = k, Year = y, ER = r)$, the probabilities of a woman diagnosed with breast cancer at age a, stage k, year y, and ER status r uses the specific treatment s.

Using the POC data we estimate probabilities of receiving treatment s, unconditional and conditional on ER status, $\pi(T = s \mid Age = a, Stage = k, Year = y)$ and $\pi(T = s \mid Age = a, Stage = k, Year = y, ER = r)$, respectively. Symbol π is used to represent probabilities estimated from POC data. More specifically, for each age a and stage k we fit a generalized linear model, in which the probability of receiving a specific treatment follows a multinomial distribution with a logit link function *(19)*. These models are fitted to POC data using the SAS PROC LOGISTIC procedure. Explanatory variables are year of diagnosis year (y = 1987–1991 and 1995; continuous) and ER status (categorical). Dropping age a and stage k from the notation, we can write the two models for fixed age and stage as

$$\log\left\{\frac{\pi(T = s \mid Year = y, ER = r)}{\pi(T = 0 \mid Year = y, ER = r)}\right\} = \alpha_s + \beta_1 y + \beta_{2r}\,(ER = r) + \beta_3 y^2 \quad [2.3]$$

$$\log\left\{\frac{\pi(T = s \mid Year = y)}{\pi(T = 0 \mid Year = y)}\right\} = \alpha_s + \beta_1 y + \beta_2 y^2 \quad [2.4]$$

where $T = 0$ is no treatment.

Although the models allowed for a quadratic term on year of diagnosis, they were never statistically significant and were dropped out of the models. Using equations [2.3] and [2.4] without the quadratic terms, we calculate the adjustments

$$A(s \mid r, y) = \frac{\pi(T = s \mid ER = r, Year = y)}{\pi(T = s \mid Year = y)}. \quad [2.5]$$

For each age and stage we multiply the unconditional models estimated in Mariotto et al. *(5)* by the adjustment,

$$P(T = s \mid Year = y, ER = r) = P(T = s \mid Year = y)\, A(s \mid r, y), \quad [2.6]$$

for years y = 1987, …, 1999. The justification for the adjustment $A(s \mid r, y)$ is based on the fact that $P(T = s \mid Year = y)$ and $\pi(T = s \mid Year = y)$ measure the same quantity canceling out and what remains is the conditional probability of treatment given ER status and year.

To estimate the dissemination by ER before 1987, we assumed that at 1984 and before the treatment assignment was independent of ER status. In other words, knowing or not a women's ER status would not change her chance of receiving a specific therapy. In mathematical terms, the probability of receiving therapy for a woman with a given ER status is the same for any ER status and is the same in the absence of ER status information, which translates into no adjustment and a ratio of 1. Thus, for years 1975–1984 we assume that the use of adjuvant therapy by ER status is the same as the use of adjuvant therapy with no ER information from Mariotto et al. *(5)*. To estimate the dissemination in 1985 and 1986, we fit a logistic model through 1984 and 1987, {1984, $P(T = s \mid Year = 1984)$} and {1987, $P(T = s \mid Year = 1987, ER = r)$}, where the first is the model estimated in Mariotto et al. and the last is the probability given by [2.6] for y = 1987.

Because the probabilities of receiving specific treatments given ER status, $\hat{P}(T = s \mid Year = y, ER = r)$ obtained by [2.6] do not sum to 1, we normalize by

$$\hat{P}_{ky}(T = s \mid ER = r) = P(T = s \mid ER = r) \Big/ \sum_{s=1}^{4} P(T = s \mid ER = r).$$

Because the proportion of women aged older than 69 years and diagnosed with stage II– receiving both treatments is zero (Table 2, row 8 from bottom), specifically in this situation we calculate the adjustments including data of women aged 50–69 and 69 and older and stage II–. For the other age groups, younger than 50 and 50–69 years, we estimate the adjustment using women in their respective groups.

References

(1) Consensus Development Panel. National Institutes of Health Consensus Development Conference Statement: adjuvant chemotherapy for breast cancer. September 9–11, 1985. CA Cancer J Clin 1986;36:42–7.

(2) NCI alert on node-negative breast cancer. Breast Cancer Res Treat 1988;12:3–5.

(3) NIH Consensus Development Panel. Treatment of early-stage breast cancer. JAMA 1991;265:391–7.

(4) National Institutes of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1–3, 2000. J Natl Cancer Inst Monogr 2001;30:5–15.
(5) Mariotto A, Feuer EJ, Harlan LC, Wun LM, Johnson KA, Abrams J. Trends in use of adjuvant multiagent chemotherapy and tamoxifen for breast cancer in the United States: 1975–1999. J Natl Cancer Inst 2002;94:1626–34.
(6) Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998;351:1451–67.
(7) Surveillance, Epidemiology, and End Results (SEER) Program—SEER 9 Regs, Nov 2002 Sub (1973–2000). Available at http://www.seer.cancer.gov. National Cancer Institute, DCCPS, Surveillance Research Program, Cancer statistics branch, released April 2003, based on the November 2002 submission.
(8) Harlan LC, Abrams J, Warren JL, Clegg L, Stevens J, Ballard-Barbash R. Adjuvant therapy for breast cancer: practice patterns of community physicians. J Clin Oncol 2002;20:1809–17.
(9) Agresti A. Categorical data analysis. New York: John Wiley & Sons; 1990.
(10) American Joint Committee on Cancer: Manual for staging of cancer. 3rd ed. Philadelphia (PA): Lippincott; 1988.
(11) Early Breast Cancer Trialists' Collaborative Group. Systematic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31000 recurrences and 24000 deaths among 75000 women. Part 1 and part 2. Lancet 1992;339:1–15.
(12) Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998; 352:930–42.
(13) Tamoxifen for early breast cancer. Cochrane Database Syst Rev 2001(1): CD000486.
(14) Fink AK, Gurwitz J, Rakowski W, Guadagnoli E, Silliman RA. Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor-positive breast cancer. J Clin Oncol 2004;22:3309–15.
(15) Partridge AH, Wang PS, Winer EP, Avorn J. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol 2003; 21:602–6.
(16) Berry DA, Inove L, Shen Y, Venier J, Cohen D, Bondy M, et al. Modeling the impact of treatment and screening on U.S. breast cancer mortality: a Bayesian approach. J Natl Cancer Inst Monogr 2006;36:30–6.