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ORIGINAL REPORT

Two Years of Adjuvant Tamoxifen Provides a Survival Benefit Compared With No Systemic Treatment in Premenopausal Patients With Primary Breast Cancer: Long-Term Follow-Up (> 25 years) of the Phase III SBII:2pre Trial

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ABSTRACT

Purpose
The aim of this study was to evaluate the long-term effect of 2 years of adjuvant tamoxifen compared with no systemic treatment (control) in premenopausal patients with breast cancer over different time periods through long-term (> 25 years) follow-up.

Patients and Methods
Premenopausal patients with primary breast cancer (N = 564) were randomly assigned to 2 years of tamoxifen (n = 276) or no systemic treatment (n = 288). Data regarding date and cause of death were obtained from the Swedish Cause of Death Register. End points were cumulative mortality (CM) and cumulative breast cancer–related mortality (CBCM). The median follow-up for the 250 patients still alive in April 2014 was 26.3 years (range, 22.7 to 29.7 years).

Results
In patients with estrogen receptor–positive tumors (n = 362), tamoxifen was associated with a marginal reduction in CM (hazard ratio [HR], 0.77; 95% CI, 0.58 to 1.03; $P = .075$) and a significant reduction in CBCM (HR, 0.73; 95% CI, 0.53 to 0.99; $P = .046$). The effect seemed to vary over time (CM years 0 to 5: HR, 1.05; 95% CI, 0.64 to 1.73; years > 5 to 15: HR, 0.58; 95% CI, 0.37 to 0.91; and after 15 years: HR, 0.82; 95% CI, 0.48 to 1.42; CBCM years 0 to 5: HR, 1.09; 95% CI, 0.65 to 1.82; years > 5 to 15: HR, 0.53; 95% CI, 0.33 to 0.86; and after 15 years: HR, 0.72; 95% CI, 0.36 to 1.44).

Conclusion
Two years of adjuvant tamoxifen resulted in a long-term survival benefit in premenopausal patients with estrogen receptor–positive primary breast cancer.

INTRODUCTION

In the first overview from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in 1988, no obvious antitumoral effect from adjuvant tamoxifen in primary breast cancer was demonstrated for patients age younger than 50 years, but these results were challenged in the early 1990s, when the recommendation was extended to also include premenopausal women.[1,2] Before the association between estrogen receptor (ER) positivity and the effect of tamoxifen was established, the clinical benefit from adjuvant tamoxifen was proposed to be primarily related not only to ER-dependent inhibition but also to ER-independent inhibitory mechanisms.[3,4] There were also some concerns regarding the reliability of the methods used for ER testing.[5] Thus, patients without confirmed ER-positive tumors were included in early adjuvant tamoxifen trials.[2]

Between 1984 and 1991, the South Swedish and South-East Swedish Breast Cancer Groups conducted a randomized phase III trial (SBII:2pre), in which premenopausal patients with primary breast cancer were randomly assigned to 2 years of adjuvant tamoxifen or no systemic treatment (control). The first report was published in 2005 (median follow-up, 13.9 years) and demonstrated that tamoxifen significantly increased recurrence-free-survival (RFS) in patients with ER-positive and/or progesterone receptor (PR) –positive tumors (relative risk, 0.65; 95% CI, 0.48 to 0.89).[6] Regarding overall survival (OS), a nonsignificant effect of

tamoxifen was seen for patients with ER-positive and/or PR-positive tumors (relative risk, 0.79; 95% CI, 0.57 to 1.10), but a separation of the survival curves was observed toward the end of the follow-up period.

The carryover effect, indicating that the efficacy of the drug remains after cessation of treatment, has been observed in several studies with extended follow-up. In the EBCTCG overview from 2011, the absolute mortality difference after 5 years of tamoxifen versus no endocrine treatment was 3% at year 5, compared with 9% at year 15.[7] In the ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) trial, in which patients without recurrence after 5 years of tamoxifen were randomly assigned to continue tamoxifen for another 5 years or receive no further treatment, the absolute beneficial effect regarding breast cancer mortality was 0.2% at year 10 compared with 2.8% at year 15.[8] The aTTom (Adjuvant Tamoxifen—To Offer More?) trial produced similar results.[9]

We hypothesized that the carryover effect on mortality could extend beyond year 15 in premenopausal patients with breast cancer treated for 2 years with adjuvant tamoxifen. The main aim of this study was therefore to investigate the long-term effect (> 15 years) of 2 years of adjuvant tamoxifen versus no adjuvant systemic therapy in premenopausal patients, with determination of overall mortality and breast cancer–related mortality. A second aim was to investigate the effects in subgroups and over different time periods.

PATIENTS AND METHODS

Patients

Premenopausal patients (N = 564) with pathologically confirmed stage II primary breast cancer (ie, pT1pN1, pT2pN0, or pT2pN1) were included in a multicenter phase III trial between 1984 and 1991. The women were randomly assigned to 2 years of tamoxifen (n = 276) or no systemic treatment (n = 288), irrespective of hormone receptor status (Fig 1). Patients were premenopausal, defined as less than 1 year since last menstruation; follicle-stimulating hormone and luteinizing hormone levels were determined in patients with uncertain menopausal status. Details regarding surgery and radiotherapy have been reported previously.[6] Patients with metastatic disease, bilateral breast cancer, or history of other malignancies were excluded. Adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil was administered to seven patients, and one patient received goserelin. Clinical data and tumor characteristics for the two study arms are listed in Table 1.

The study included 137 patients from the South-East Healthcare Region and 427 from the South Healthcare Region in Sweden. The treatment schedule for tamoxifen was 40 mg (South-East Healthcare Region) or 20 mg (South Healthcare Region) per day orally for 2 years.

Follow-Up Data

Regular follow-up, including clinical examination, chest x-ray, and mammography, was performed for up to 10 years according to the predefined protocol, with registration of follow-up data including recurrence and death by the regional oncologic centers. For the purposes of the current study, date and cause of death were obtained from the Swedish Cause of Death Register in April 2014. The accuracy of this register regarding breast cancer has been validated.[10,11] A death was defined as breast cancer related when breast cancer was listed as a contributing cause of death. All Swedish citizens have a unique 10-digit identity code facilitating retrieval of registry information, and no patients were lost to follow-up.

Hormone Receptor Status

Hormone receptor analysis was performed using cytosol-based methods in a majority of the patients (ER, n = 457; PR, n = 449). In 2003, paraffin-embedded tumor samples were collected (n = 500) and tissue microarrays were constructed for immunohistochemical (IHC) analysis of ER and PR as previously described.[6] Levels of ER and PR were divided into categories, and the cutoff for ER or PR positivity was more than 10%. Because immunohistochemistry is now the routine method, IHC data were primarily chosen for annotation; results from the cytosol-based methods were only used in cases where IHC results were lacking. Hormone receptor data (IHC and/or cytosol based) were available for 96% of the included patients. Considering the results of the EBCTCG overview, where PR status was not predictive for tamoxifen efficacy in patients with ER-positive tumors, we chose the ER-positive subgroup (irrespective of PR status) for the time-dependent analyses of tamoxifen effect.[7]

Histologic Grade

Nottingham histologic grade was re-evaluated in 491 tumors according to the method previously described by Elston et al.[6,12]

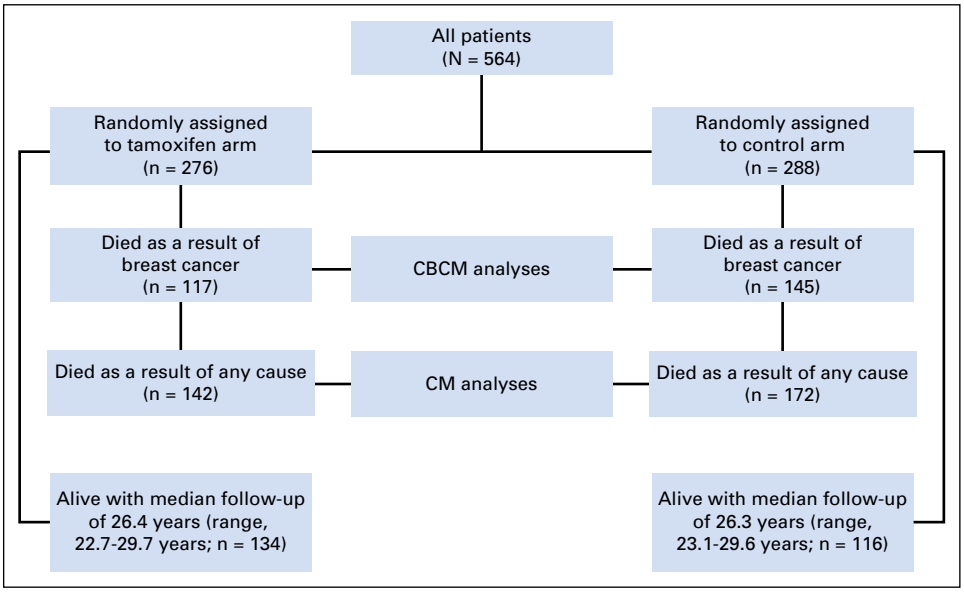

Fig 1. CONSORT diagram for the phase III SBII:2pre trial. CBCM, cumulative breast cancer–related mortality; CM, cumulative mortality.

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Tamoxifen-Treated Arm (n = 276), No. (%)	Control Arm (n = 288), No. (%)
Follow-up time, years		
Median	26.4	26.3
Range	22.7-29.7	23.1-29.6
Age, years		
Median	45	45
Range	25-57	26-58
< 40	51 (19)	61 (21)
40-49	178 (65)	184 (64)
≥ 50	47 (17)	43 (15)
Tumor size, mm		
Median	25	22
Range	5-75	2-50
≤ 20	85 (31)	122 (42)
> 20	190 (69)	166 (58)
Missing data	1	0
No. of positive nodes		
Median	2	2
Range	0-21	0-22
0	83 (30)	77 (27)
1-3	135 (49)	140 (49)
≥ 4	57 (21)	70 (24)
Missing data	1	1
NHG		
1	27 (11)	32 (12)
2	104 (42)	116 (44)
3	118 (47)	117 (44)
Missing data	27	23
ER status		
Positive	170 (65)	192 (69)
Negative	92 (35)	87 (31)
Missing data	14	9
PR status		
Positive	171 (66)	187 (67)
Negative	90 (34)	91 (33)
Missing data	15	10
Subgroup		
ER positive (any PR)	170 (62)	192 (67)
ER positive, PR positive	155 (60)	177 (64)
ER positive, PR negative	13 (5)	14 (5)
ER negative, PR positive	15 (6)	10 (4)
ER negative, PR negative	76 (29)	77 (28)
Missing data	17	10
HER2 (3+/amplified)		
Negative	197 (86)	204 (84)
Positive	31 (14)	38 (16)
Missing data	48	46
Chemotherapy (CMF × six cycles)	1 (< 1)	6 (2)
Goserelin	1 (< 1)	0

Abbreviations: CMF, cyclophosphamide, methotrexate, and fluorouracil; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NHG, Nottingham histologic grade; PR, progesterone receptor.

Ethics

The initial study was approved by the ethical committees of Lund and Linköping Universities, and oral informed consent was registered by the regional oncologic centers for all patients before random assignment. The continuation of the study in 2003 was approved by the ethical committees of Lund and Linköping Universities (Dnr LU 240-01 and Dnr Linköping 01-134, respectively).

Statistical Analyses

The primary aim of the original study was to compare the effect of adjuvant tamoxifen treatment versus control in terms of RFS (primary outcome) and OS (secondary outcome). It was planned to include at least 500 patients in a two-arm study, aiming at an absolute 15% difference in outcome regarding RFS, with 90% power and an α level of 5%.[6] Because the median follow-up time in this study exceeded 25 years for patients still alive, the risk of death not related to breast cancer was considered significant, and therefore, competing risks were taken into account. Mortality was defined as number of deaths per time unit (ie, from date of inclusion). Cumulative mortality (CM), which is equal to 1-survival, and cumulative breast cancer–related mortality (CBCM) were chosen as primary and secondary end points, respectively, and all analyses were performed using the intention-to-treat rule. CM was estimated according to the Kaplan-Meier method, whereas CBCM was estimated according to a method described by Marubini et al,[13] which, in contrast to the Kaplan-Meier method, takes deaths resulting from other causes into account in an appropriate and unbiased way. An implementation for STATA software (STATA, College Station, TX), described in the *Stata Journal*, was used to estimate CBCM.[14] To avoid uncertain estimates on the basis of a small number of patients, mortality curves were terminated when the number of patients at risk was fewer than five.[15]

Unadjusted Cox regression analyses, stratified by health care region, were used to compare survival in different subgroups. Differential effects of tamoxifen in subgroups on the basis of other prognostic factors were evaluated in a series of multivariable Cox models with main effects for tamoxifen and each factor and the corresponding interaction term. Hazard ratios (HRs) for 2 years of tamoxifen versus control for different subgroups of patients with ER-positive tumors were summarized graphically using a forest plot. In analyses of CBCM, follow-up was censored at time of death resulting from other causes.

Smoothed hazards were estimated using the hazard option of the STATA command *sts graph*. Nonproportional hazards are the rule rather than the exception in studies with long-term follow-up. Therefore, follow-up time was divided into three intervals: 0 to 5 years, more than 5 to 15 years, and more than 15 years. We chose these intervals because RFS and OS at 5 years were the primary and secondary end points in the original study and because the EBCTCG reported on follow-up at 15 years. Proportional hazards assumptions were checked using Schoenfeld's test and a two-*df* test for treatment by follow-up period interaction in a time-dependent Cox model. All statistical tests were two sided, and the corresponding *P* values should be interpreted as the degree of evidence against the null hypothesis. *P* values presented were not adjusted for multiple comparisons. All calculations were performed in STATA (version 14.0).

RESULTS

The median follow-up was 26.3 years (range, 22.7 to 29.7 years) for patients still alive in April 2014. There were 314 deaths, of which 262 were categorized as breast cancer related. Deaths unrelated to breast cancer were well balanced between the two arms, except for cardiac-related deaths (n = 8), which were all found in the tamoxifen-treated group (Appendix Table A1, online only).

Effect of Tamoxifen Therapy in Relation to Hormone Receptor Status

Table 2 lists the mortality data in the two study arms for all patients and for different subgroups according to hormone receptor status. The subgroups with ER-positive, PR-negative tumors (n = 27) and ER-negative, PR-positive tumors (n = 25) were not analyzed separately because of the small numbers of patients and events.

A trend toward a positive effect of tamoxifen was observed in CM (HR, 0.82; 95% CI, 0.66 to 1.02; *P* = .080) and CBCM (HR,

Table 2. Events Defined As Deaths in Tamoxifen-Treated and Control Arms and Different Patient Subgroups for Different Time Periods According to Hormone Receptor Status

Hormone Receptor Status	Tamoxifen-Treated Arm, No. (%)				Control Arm, No. (%)			
	0 to 5 Years	> 5 to 15 Years	> 15 Years	Total	0 to 5 Years	> 5 to 15 Years	> 15 Years	Total
All patients		(n = 276)				(n = 288)		
Death, all causes	65 (24)	44 (16)	33 (12)	142 (51)	67 (23)	65 (23)	40 (14)	172 (60)
Breast cancer–related death	63 (23)	39 (14)	15 (5)	117 (42)	62 (22)	60 (21)	23 (8)	145 (50)
ER positive (any PR)		(n = 170)				(n = 192)		
Death, all causes	30 (18)	29 (17)	24 (14)	83 (49)	32 (17)	53 (28)	28 (16)	113 (59)
Breast cancer–related death	28 (16)	25 (15)	14 (8)	67 (39)	29 (15)	50 (26)	19 (10)	98 (51)
ER positive, PR positive*		(n = 155)				(n = 177)		
Death, all causes	28 (18)	24 (15)	23 (15)	75 (48)	28 (16)	52 (29)	28 (16)	108 (61)
Breast cancer–related death	27 (17)	20 (13)	14 (9)	61 (39)	25 (14)	49 (28)	19 (11)	93 (53)
ER negative, PR negative		(n = 76)				(n = 77)		
Death, all causes	31 (41)	7 (9)	5 (7)	43 (57)	32 (42)	7 (9)	9 (12)	48 (62)
Breast cancer–related death	31 (41)	7 (9)	5 (7)	43 (57)	30 (39)	6 (8)	3 (4)	39 (51)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
*Patients with ER-positive, PR-positive tumors are also included in the ER-positive subgroup.

0.81; 95% CI, 0.64 to 1.03; $P = .090$) for all patients, irrespective of hormone receptor status (N = 564). In patients with ER-positive tumors (n = 362), tamoxifen treatment was associated with a marginal decrease in CM (HR, 0.77; 95% CI, 0.58 to 1.03; $P = .075$) and a significant decrease in CBCM (HR, 0.73; 95% CI, 0.53 to 0.99; $P = .046$). A significant beneficial effect was also seen in patients with ER-positive, PR-positive tumors (n = 332; CM: HR, 0.73; 95% CI, 0.54 to 0.98; $P = .034$ and CBCM: HR, 0.70; 95% CI, 0.51 to 0.97; $P = .030$) but not in patients with ER-negative, PR-negative tumors (n = 153; CM: HR, 0.89; 95% CI, 0.59 to 1.34 and CBCM: HR, 0.96; 95% CI, 0.61 to 1.51). All HRs and CIs are listed in Appendix Table A2 (online only). The results for CM and CBCM for ER-positive and ER-negative, PR-negative tumors are shown in Figure 2.

Subgroup Analyses in Patients With ER-Positive Tumors

The beneficial effect of tamoxifen was most evident in patients with ER-positive tumors who were younger than 40 years (CM for age < 40 years: HR, 0.45; 95% CI, 0.23 to 0.91 and age ≥ 40 years: HR, 0.89; 95% CI, 0.65 to 1.23; interaction $P = .061$; CBCM for age < 40 years: HR, 0.37; 95% CI, 0.17 to 0.82 and age ≥ 40 years: HR, 0.87; 95% CI, 0.61 to 1.22; interaction $P = .044$). Histologic grade 3 disease was also associated with a greater effect of tamoxifen (CM for grade 3 disease: HR, 0.56; 95% CI, 0.34 to 0.91 and for grade 1 to 2 disease: HR, 0.83; 95% CI, 0.58 to 1.18; interaction $P = .13$; CBCM for grade 3 disease: HR, 0.53; 95% CI, 0.31 to 0.91 and for grade 1 to 2 disease: HR, 0.78; 95% CI, 0.53 to 1.16; interaction $P = .19$). The evidence for heterogeneity of tamoxifen effect was weaker for tumor size ($> v \leq 20$ mm) and node status (N+ *v* N0; Fig 3).

Effect of Tamoxifen Therapy Over Different Follow-Up Intervals for Patients With ER-Positive Tumors

Smoothed plots of mortality and breast cancer mortality showed increasing hazards for both study arms up to a peak 6 years after random assignment, with a decline thereafter (Fig 4). The corresponding HRs for tamoxifen versus control were found to vary with time for both end points, but the assumptions of proportional hazards could not be rejected ($P = .37$ and .10 for CM and CBCM, respectively). Despite this, the effect of tamoxifen at different follow-up intervals was evaluated as preplanned (CM years 0 to 5: HR, 1.05; 95% CI, 0.64 to 1.73; $P = .84$; years > 5 to 15: HR, 0.58; 95% CI, 0.37 to 0.91; $P = .018$; and after 15 years: HR, 0.82; 95% CI, 0.48 to 1.42; $P = .49$; CBCM years 0 to 5: HR, 1.09; 95% CI, 0.65 to 1.82; $P = .76$; years > 5 to 15: HR, 0.53; 95% CI, 0.33 to 0.86; $P = .010$; and after 15 years: HR, 0.72; 95% CI, 0.36 to 1.44; $P = .35$). However, the null hypothesis of equal tamoxifen effect for the three follow-up periods could not be rejected (Schoenfeld's test $P = .33$ and .15 for CM and CBCM, respectively; two-*df* tests of treatment by time-period interaction). The effects of tamoxifen in patients with ER-positive and ER-negative, PR-negative tumors, respectively, are shown in Figure 2, and the effects for all patients and for different subgroups and follow-up periods are listed in Appendix Table A2.

DISCUSSION

The results of this long-term follow-up of a randomized phase III trial indicate that adjuvant treatment with tamoxifen for 2 years results in a long-term reduction in breast cancer–related mortality in premenopausal patients with ER-positive breast cancer, compared with a systemically untreated control group. At 25 years of follow-up, the absolute risk reduction in terms of CBCM was 12.0% (Fig 2). To our knowledge, this is the first study to present data on premenopausal patients with a median follow-up time for survivors exceeding 25 years.

Long-term follow-up is often associated with nonproportional hazards, and we therefore analyzed the carryover effect on survival during three consecutive periods: 0 to 5, more than 5 to 15, and more than 15 years. Because of the size of this study, one cannot expect statistical significance for the time-dependent analyses. However, the most pronounced effect was observed during the period of more than 5 to 15 years, where the relative reduction of CM and CBCM was almost 50% for tamoxifen versus control. The positive effect of tamoxifen was weaker for the last follow-up period (> 15 years), including fewer events and hence

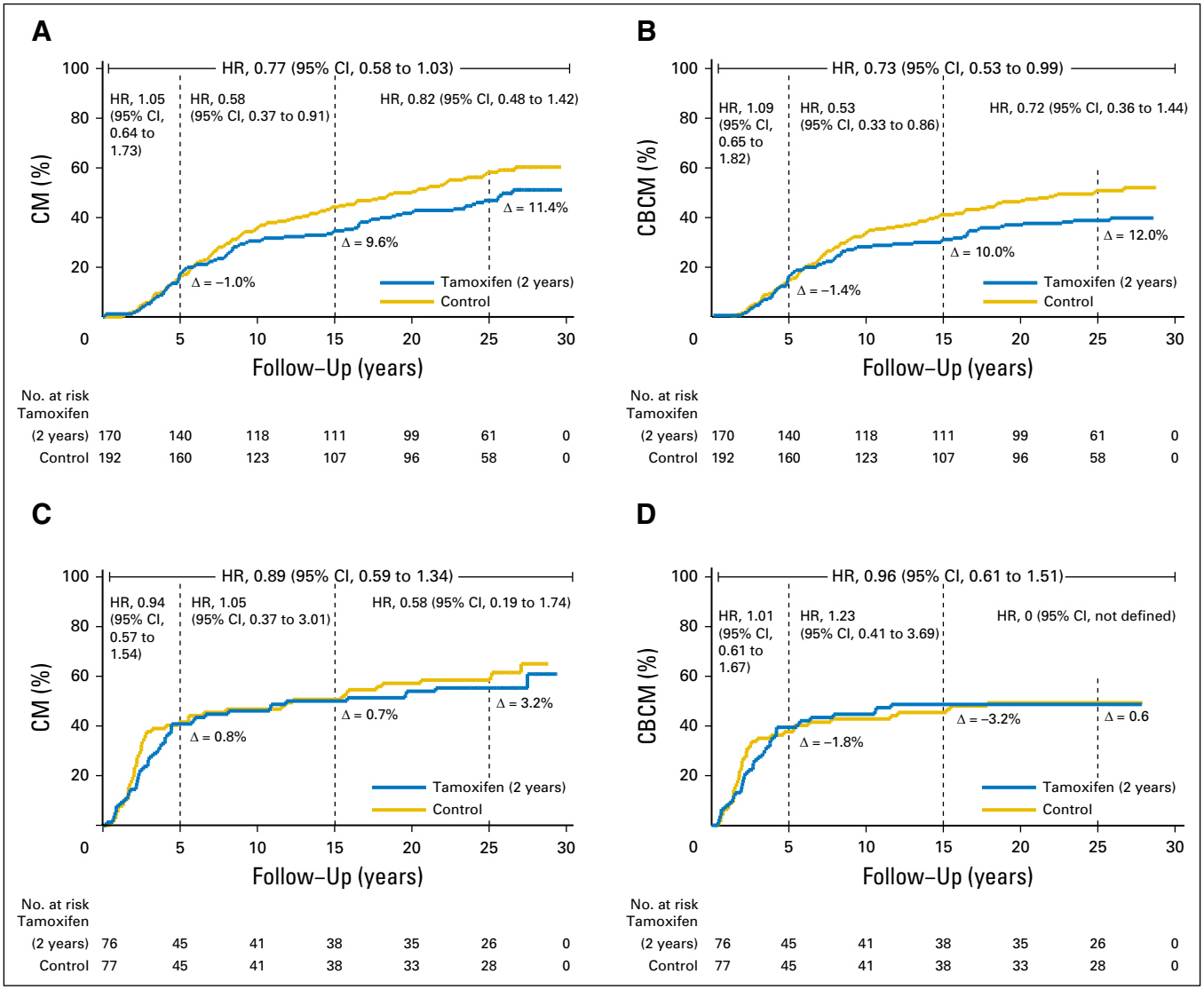

Fig 2. Cumulative mortality (CM) and cumulative breast cancer–related mortality (CBCM) according to treatment arm for patients with (A, B) estrogen receptor (ER) –positive tumors and (C, D) ER-negative, progesterone receptor–negative tumors. No patients were lost to follow-up, because Swedish Cause of Death Register comprises complete registration. Dashed vertical lines indicate the time intervals for which separate analyses of tamoxifen effect were carried out, and the follow-up times at which absolute differences in mortality were evaluated. HR, hazard ratio.

lower power, but the HRs and estimates of CM and CBCM indicate a possible carryover effect beyond 15 years. There was a high fatality rate for patients with ER-positive tumors during the first years of follow-up, without any beneficial effect of tamoxifen, as shown by the smoothed hazard plots (Fig 4). Modern adjuvant chemotherapy in addition to tamoxifen treatment would presumably have resulted in fewer early deaths.[16]

Our study shows that only 2 years of tamoxifen provides a significant decrease in breast cancer mortality in premenopausal patients with ER-positive tumors, supporting previous data on the benefit of 1 year of adjuvant tamoxifen, compared with no systemic treatment, in a trial including postmenopausal patients.[17] On the basis of the results of the ATLAS and aTTom trials, extended adjuvant treatment with tamoxifen for up to 10 years can be recommended for premenopausal patients.[8,9] As a therapeutic option for the youngest patients regaining ovarian function after chemotherapy, ovarian suppression in addition to other endocrine therapy is advocated after the publication of the SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and Exemestane Trial) trial reports.[18] According to the EBCTCG meta-analysis, tamoxifen is also effective in patients receiving chemotherapy.[16] In the EBCTCG overview, no classification according to molecular subtype was available, although it is most likely that patients with luminal A tumors benefit less from adjuvant chemotherapy than those with luminal B tumors.[19]

The HRs related to tamoxifen treatment in patients with ER-positive, PR-positive tumors were lower than those in patients with ER-positive tumors and any PR status. The predictive value of PR has been a matter of debate, and although the data are not unanimous, there have been indications that PR is predictive for adjuvant tamoxifen efficacy.[20-22] Moreover, absence or low values of PR are associated with a poorer prognosis.[23-26] In the St Gallen consensus from 2013, PR was included in the surrogate definition of molecular subtypes.[27] It was also stated that chemotherapy plus

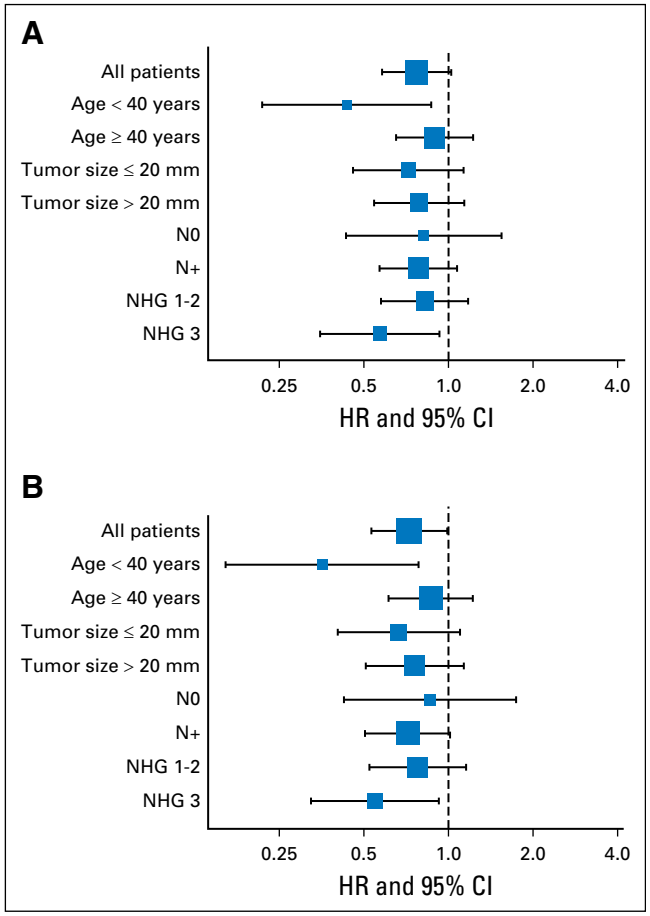

Fig 3. Forest plot showing subgroup analyses of tamoxifen versus control regarding (A) cumulative mortality and (B) cumulative breast cancer–related mortality in patients with estrogen receptor–positive tumors to end of follow-up. Boxes indicate hazard ratios (HRs); horizontal lines indicate 95% CIs. NHG, Nottingham histologic grade.

endocrine therapy should be recommended for patients with ER-positive, PR-negative tumors. Similar outcomes for patients with ER-positive, PR-positive tumors and ER-positive, PR-negative tumors in the EBCTCG meta-analysis may be associated with the benefit from chemotherapy in the ER-positive, PR-negative group. Our findings could be related to the fact that only a few patients in the study received chemotherapy, and the poor outcome related to PR negativity was therefore not masked by adjuvant chemotherapy.

A limitation of our study is that we determined hormone receptor status from retrospective IHC analyses on tissue microarrays and prospectively collected cytosol-based data to classify a majority of the tumors according to ER and PR status. However, good agreement regarding ER and PR status between these methods has been reported, and the pooling of the data would therefore have only a minor influence on the results.[28] Because ER and PR were assessed in categories with more than 10% as the cutoff, the internationally established cutoff of 1% for ER and PR positivity could thus not be applied. However, according to previous studies, patients with tumors with 1% to 9% ER-positive cells are rare, with a prognosis similar to that of patients with ER-negative tumors.[29,30] Furthermore, the daily dose of tamoxifen was 40 mg in the South-East Healthcare Region and 20 mg in the South Healthcare Region. The study was not powered to evaluate treatment by dose interaction. However, tamoxifen doses of 20 and 40 mg have been reported to have similar clinical benefit and adverse events in pre- and postmenopausal patients.[31-33] All cardiac-related deaths (n = 8) were observed in the tamoxifen-treated group (Appendix Table A1). This unbalance might partly be explained by longer median follow-up for this group (5.3 years). Another limitation is that we present deaths unrelated to breast cancer without morbidity data, because these were not prospectively collected.

The results of this study are clinically important for several reasons. First, tamoxifen is the endocrine therapy of choice for a majority of premenopausal patients with hormone receptor–positive tumors. Second, the long-term effect reported in this study is particularly important for young patients with a potentially long life expectancy who are at risk for late relapse, as is commonly seen in ER-positive breast cancer.[34]

In conclusion, these results from a prospective randomized phase III trial with a median follow-up of 26 years show that 2 years of tamoxifen treatment provides a survival benefit in premenopausal patients with ER-positive primary breast cancer. A vast majority of patients did not receive adjuvant chemotherapy, enabling a study of

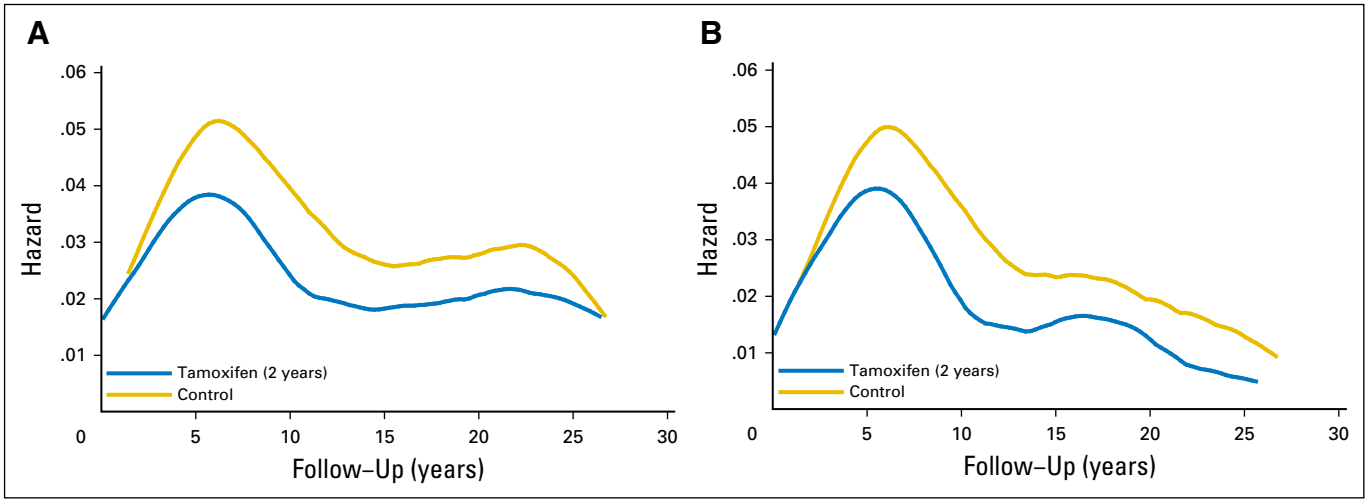

Fig 4. Smoothed hazard estimates for (A) all causes of death and (B) breast cancer–related death in patients with estrogen receptor–positive disease.

the long-term effect of tamoxifen independent of the benefit of modern chemotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: Maria Ekholm, Pär-Ola Bendahl, Lisa Rydén
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Two Years of Adjuvant Tamoxifen Provides a Survival Benefit Compared With No Systemic Treatment in Premenopausal Patients With Primary Breast Cancer: Long-Term Follow-Up (> 25 years) of the Phase III SBII:2pre Trial

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Appendix

Table A1. Causes of Death According to Treatment Arm

	Tamoxifen-Treated Arm	Control Arm
All	142	172
Nonspecified	2	5
Breast cancer related	117	145
Non–breast cancer related	23	22
Neoplastic disease		
Lung cancer	2	5
Endometrial cancer	1	1
Ovarian cancer	1	3
Esophageal cancer	2	0
Gastric cancer	1	2
Colon cancer	0	1
Rectal cancer	0	1
Renal cancer	1	0
Primary peritoneal carcinoma	1	0
Pancreatic cancer	1	1
Primary liver cancer	2	1
Parotid cancer	0	1
Cardiac disease		
Atrial fibrillation	2	0
Myocardial infarction	4	0
Chronic ischemic heart disease	1	0
Sudden cardiac death	1	0
Cerebrovascular disease		
Stroke	1	1
Pulmonary embolism	0	0
Other causes of death	2	5

Table A2. Unadjusted Cox Regression Analyses of Effect of Tamoxifen in All Patients and Different Subgroups According to Hormone Receptor Status for Different Time Periods With CM and CBCM As End Points

		Time Period (Years)							
		0 to 5		> 5 to 15		> 15		Total	
Hormone Receptor Status	No. of Patients	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
CM									
All patients	564	(n = 564)		(n = 432)		(n = 323)		(n = 564)	
Control	288	1.00		1.00		1.00		1.00	
Tamoxifen (2 years)	276	0.98 (0.70 to 1.39)	.93	0.69 (0.47 to 1.01)	.053	0.76 (0.48 to 1.21)	.25	0.82 (0.66 to 1.02)	.080
ER positive (any PR)	362	(n = 362)		(n = 300)		(n = 218)		(n = 362)	
Control	192	1.00		1.00		1.00		1.00	
Tamoxifen (2 years)	170	1.05 (0.64 to 1.73)	.84	0.58 (0.37 to 0.91)	.018	0.82 (0.48 to 1.42)	.49	0.77 (0.58 to 1.03)	.075
ER positive, PR positive	332	(n = 332)		(n = 288)		(n = 200)		(n = 332)	
Control	177	1.00		1.00		1.00		1.00	
Tamoxifen (2 years)	155	1.14 (0.67 to 1.92)	.63	0.50 (0.31 to 0.80)	.004	0.76 (0.44 to 1.32)	.33	0.73 (0.54 to 0.98)	.034
ER negative, PR negative	153	(n = 153)		(n = 90)		(n = 76)		(n = 153)	
Control	77	1.00		1.00		1.00		1.00	
Tamoxifen (2 years)	76	0.94 (0.57 to 1.54)	.80	1.05 (0.37 to 3.01)	.93	0.58 (0.19 to 1.74)	.33	0.89 (0.59 to 1.34)	.57
CBCM									
All patients	564	(n = 564)		(n = 432)		(n = 323)		(n = 564)	
Control	288	1.00		1.00		1.00		1.00	
Tamoxifen (2 years)	276	1.03 (0.73 to 1.47)	.86	0.66 (0.44 to 0.99)	.042	0.61 (0.32 to 1.18)	.14	0.81 (0.63 to 1.03)	.090
ER positive (any PR)	362	(n = 362)		(n = 300)		(n = 218)		(n = 362)	
Control	192	1.00		1.00		1.00		1.00	
Tamoxifen (2 years)	170	1.09 (0.65 to 1.82)	.76	0.53 (0.33 to 0.86)	.010	0.72 (0.36 to 1.44)	.35	0.73 (0.53 to 0.99)	.046
ER positive, PR positive	332	(n = 332)		(n = 288)		(n = 200)		(n = 332)	
Control	177	1.00		1.00		1.00		1.00	
Tamoxifen (2 years)	155	1.23 (0.71 to 2.12)	.46	0.44 (0.26 to 0.74)	.002	0.70 (0.35 to 1.39)	.31	0.70 (0.51 to 0.97)	.030
ER negative, PR negative	153	(n = 153)		(n = 90)		(n = 76)		(n = 153)	
Control	77	1.00		1.00		1.00		1.00	
Tamoxifen (2 years)	76	1.01 (0.61 to 1.67)	.98	1.2 (0.41 to 3.69)	.71	0 (not defined)		0.96 (0.61 to 1.51)	.87

Abbreviations: CBCM, cumulative breast cancer–related mortality; CM, cumulative mortality; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.