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Original Research

Effects of adjuvant tamoxifen over three decades on breast cancer–free and distant recurrence–free interval among premenopausal women with oestrogen receptor–positive breast cancer randomised in the Swedish SBII:2pre trial

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Abstract ***Aims:*** The primary aim was to compare 2 years of adjuvant tamoxifen versus no systemic treatment in premenopausal patients with oestrogen receptor (ER)–positive tumours, regarding breast cancer–free interval (BCFi) and distant recurrence–free interval (D-RFi), with 30 years of follow-up and for specified intervals. Moreover, we aimed to investigate the effects of adjuvant tamoxifen on the incidence of secondary malignancies and survival after distant recurrence.
Methods: Premenopausal patients with primary breast cancer were randomised to 2 years of tamoxifen ($n = 277$) or no systemic treatment ($n = 287$), irrespective of ER status. Information regarding events was collected by a review of medical records and from national registers.
Results: The median follow-up for all patients without events was 28 years, and only four of the patients alive had a follow-up of <20 years. With 30 years of follow-up, tamoxifen prolonged BCFi in the intention-to-treat population (hazard ratio [HR] = 0.76, 95% confidence interval

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(CI) 0.61–0.94, $p = 0.011$) compared with no treatment. In patients with ER-positive tumours ($n = 362$), tamoxifen prolonged BCFi (HR = 0.62, 95% CI 0.47–0.82, $p = 0.001$) and D-RFi (HR = 0.73, 95% CI 0.54–0.99, $p = 0.043$). The positive effect on BCFi was significant also for the interval >15–30 years (HR = 0.53, 95% CI 0.28–0.98, $p = 0.042$). For patients with ER-positive tumours who were diagnosed with distant recurrence ($n = 165$), survival after distant recurrence was shorter among tamoxifen-treated patients (median, 29 months versus 43 months). The incidence of contralateral breast cancer was 42% lower in the tamoxifen group (HR = 0.58, 95% CI 0.35–0.96, $p = 0.035$), whereas no differences were observed regarding other secondary malignancies.

Conclusions: With three decades of follow-up, 2 years of adjuvant tamoxifen reduced the incidence of breast cancer–related events and distant recurrence, and the carryover effect seems to extend beyond 15 years. Moreover, adjuvant tamoxifen seems to be associated with shorter survival after diagnosis of distant recurrence.

1. Introduction

The most recent meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), reporting long-term follow-up of patients treated with 5 years of adjuvant tamoxifen, clearly showed that there is a significant risk of late recurrences in oestrogen receptor (ER)–positive breast cancer [1]. With 20 years of follow-up, the cumulative risk of distant recurrence was 22% in node-negative patients, 31% in patients with 1–3 positive nodes and 52% for patients with 4–9 lymph node metastases. A carryover effect, i.e. continued reduction of breast cancer–related events after discontinuation of treatment, has been observed in tamoxifen studies with long-term follow-up [2,3]. In the ATLAS trial, comparing 5 and 10 years of tamoxifen, the benefit of extended therapy was not evident until after year 10 (5–9 years: rate ratio [RR] = 0.90, 95% confidence interval [CI] 0.79–1.02; ≥10 years: RR = 0.75, 95% CI 0.62–0.90) [2]. The aTTom trial provided similar results [3]. To sum up, long-term follow-up is essential to fully evaluate the effects of tamoxifen in the ER-positive subgroup.

In 2016, we reported on updated long-term survival results from the Swedish phase III trial SBII:2pre, in which premenopausal patients were randomised to 2 years of adjuvant tamoxifen or no systemic treatment, and showed that with a median follow-up of 26 years, tamoxifen significantly reduced the cumulative breast cancer–related mortality in patients with ER-positive tumours [4]. In the present study, we aimed to investigate the effects of 2 years of adjuvant tamoxifen treatment in the same cohort of patients on breast cancer–free interval (BCFi) and distant recurrence–free interval (D-RFi) with 30 years of follow-up and for specified time intervals, using reliable sources of data on breast cancer–related events. We also aimed to examine the effects of adjuvant tamoxifen on secondary malignancies, including contralateral breast cancer (CBC), and survival after distant recurrence.

2. Methods

2.1. Patients

Premenopausal patients (n = 564) with stage II breast cancer were randomised to 2 years of tamoxifen (n = 277) or no systemic treatment (n = 287; control), irrespective of the hormone receptor status (Fig. 1). A minor proportion of the patients (n = 8; <2%) received adjuvant chemotherapy and/or goserelin. According to the UICC TNM stage, third edition (1982), ≥4 lymph node metastases was classified as pN1 as long as the lymph nodes were not fixed to one another or to any other structures or as long as there was no evidence of supra/infraclavicular lymph node metastases. Details on the inclusion and exclusion criteria have been reported previously [4,5]. The patient and tumour characteristics at baseline are summarised in Table 1 (intention-to-treat [ITT] population) and Table A1 (ER-positive subgroup). The patient and tumour characteristics at the beginning of each time interval is illustrated in Table A2 (ER-positive subgroup). The two healthcare regions included 427 and 137 patients, respectively. The tamoxifen dosage was 20 mg (region 1) or 40 mg (region 2) daily for 2 years. These doses have been shown to be associated with similar benefits and risks of adverse events [6,7].

2.2. Follow-up data

Medical records from 23 hospitals were reviewed by one of the authors (M.E.), using a predefined case report form. The audit covered the period from inclusion until the last recorded healthcare contact or death and included a review of the primary diagnosis, collection of data on recurrence, CBC, distant recurrence and death. Complementary data on secondary malignancies and causes of death were obtained from the Swedish Cancer Register and the Swedish Causes of Death Register in

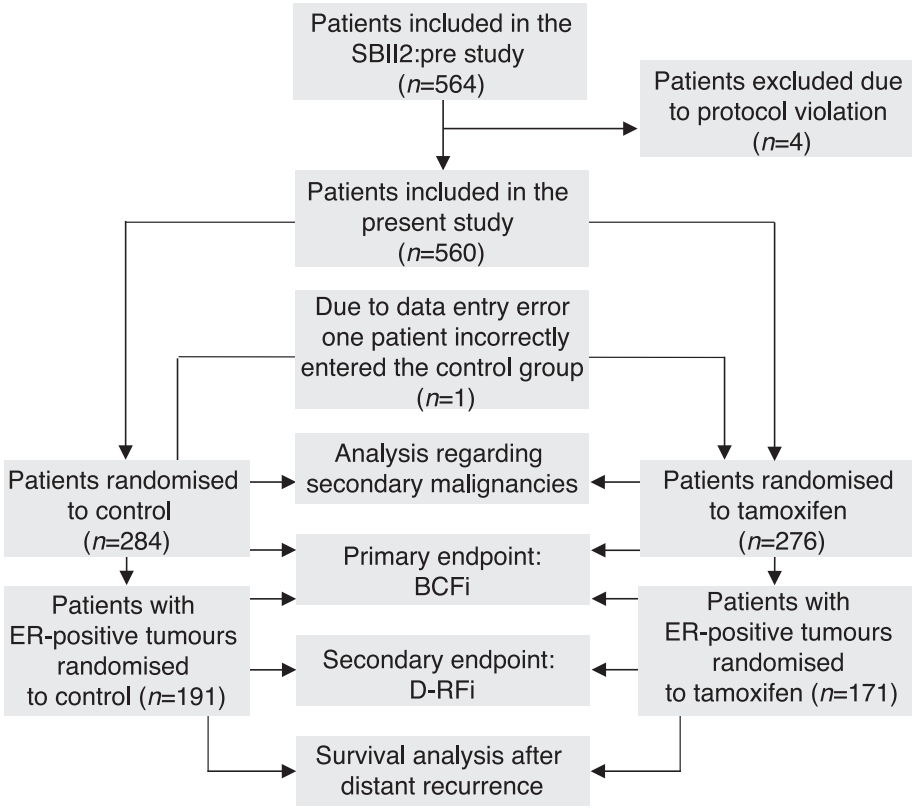

Fig. 1. CONSORT diagram for the original SBII:2pre trial and the present analyses. ER, oestrogen receptor; BCFi, breast cancer–free interval; D-RFi, distant recurrence–free interval.

January 2017. The data cut-off date for events was set at 30 November 2016. In cases with discrepancies between the register data and the data collected during the review, the latter were considered more reliable. In a few cases with uncertainties, the patients were discussed among all coauthors without revealing the allocated treatment arm.

2.3. Hormone receptor status and histological grade

Details for the analyses of the hormone receptor status and histological grade have been described previously [4,5]. In brief, data on ER status were available for 537 patients (95%). Because patients were included in the original trial, irrespective of their hormone receptor status, we present data on the ITT population, but because it is now established that patients with ER-negative tumours do not benefit from tamoxifen [6], this study focuses on the ER-positive subgroup. As ER-negative/PR-positive tumours are most likely a result from technical artefacts [8,9], they were excluded from the analyses ($n = 25$; 4%).

2.4. Statistical analysis

The end-points were chosen according to the recommendations in the DATECAN guidelines [10,11]. Considering the long-term follow-up, BCFi was chosen as the primary end-point and included any of the following first events: local, regional or distant recurrence; CBC (invasive or ductal cancer *in situ*) or breast cancer–related death. D-RFi was selected as the secondary end-point and included distant recurrence or breast cancer–related death as events. The follow-up time for patients who were alive at the data cut-off date was censored at the time of the last registered healthcare contact. For the D-RFi analyses, the follow-up time was also censored at the time when patients were diagnosed with CBC because we could not determine whether any subsequent distant recurrence was derived from the primary or the secondary breast cancer. Because patients may suffer from near-simultaneous events, we followed the recommendations outlined by Hudis *et al.* [12] and considered events within 2 months as synchronous. Near-simultaneous events were ranked according to a hierarchy of prognosis from worst to best: distant recurrence > regional recurrence > local recurrence > CBC.

All analyses were performed according to the ITT principle. To handle competing risks that commonly occur in long-term follow-up studies, i.e. deaths from causes other than breast cancer, cumulative incidence curves were estimated using a Stata implementation of a method that takes competing risks into account [13,14]. A cause-specific Cox regression analysis stratified by the

Table 1
Patient and clinical characteristics in the control group and the tamoxifen group for the intention-to-treat population (n = 560).

Characteristics	Control group (n = 284)	Tamoxifen group (n = 276)
Follow-up time for BCFi (for patients without an event)		
Median (years)	28	28
(10th and 90th percentiles)	(26 and 30)	(25 and 30)
Age (years), n (%)		
Median (range)	45 (26–58)	45 (25–57)
(10th and 90th percentiles)		
<40	59 (21)	51 (18)
40–49	183 (64)	178 (64)
≥50	42 (15)	47 (17)
Type of breast surgery		
Breast-conserving surgery	46 (16)	37 (13)
Mastectomy	238 (84)	239 (87)
Tumour size (mm), n (%)		
Median (range)	22 (2–50)	25 (5–75)
≤20	121 (43)	86 (31)
>20	163 (57)	189 (69)
Missing	0	1
Positive nodes[a], n (%)		
Median number of positive nodes (range)	1 (0–22)	1 (0–21)
0	75 (27)	83 (30)
1–3	139 (49)	136 (49)
≥4	69 (24)	56 (20)
Missing	1	1
Histological grade, n (%)		
1	32 (12)	27 (11)
2	115 (44)	105 (42)
3	116 (44)	117 (47)
Missing	21	27
ER, n (%)		
Positive	191 (69)	171 (65)
Negative	84 (31)	91 (35)
Missing	9	14
PR, n (%)		
Positive	187 (68)	171 (66)
Negative	87 (32)	90 (34)
Missing	10	15
Subgroups, n (%)		
ER+/PR+	177 (65)	155 (60)
ER+/PR−	13 (5)	14 (5)
ER−/PR+	10 (4)	15 (6)
ER−/PR−	74 (27)	75 (29)
Missing for ER and/or PR	10	17
HER2 (3+/amplified), n (%)		
Positive	38 (16)	30 (13)
Negative	203 (84)	197 (87)
Missing	43	49
Adjuvant chemotherapy and/or goserelin, n (%)		
Yes	4 (1)	4 (1)
No	275 (99)	269 (99)
Missing	5	3
Adjuvant radiotherapy		
Yes	199 (84)	186 (80)
No	37 (16)	46 (20)
Missing	48	44

BCFi, breast cancer–free interval; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.
[a] UICC TNM stage, third edition (1982).

healthcare region was used to estimate the relative effects (hazard ratios [HRs]) of tamoxifen on BCFi and D-RFi versus the control group. To examine the carryover effect of tamoxifen and handle the problem of non-proportional hazards, separate Cox regression analyses were performed for the following non-overlapping intervals: 0 to 5, >5 to 15 and >15–30 years [4,6]. The patient and tumour characteristics of the two arms are comparable by design at baseline but that is not necessarily true after 5 and 15 years, especially not if the treatment is efficient. Therefore, characteristics at baseline, 5 years and 15 years, for the patients included in the landmark analysis for BCFi, were summarised in Table A2. Homogeneity of treatment effects across subgroups of prognostic factors was evaluated in Cox models with interaction terms and illustrated in a forest plot. Cochrane's Q was used to test for homogeneity across all subgroups.

To investigate whether adjuvant tamoxifen was associated with any effect on survival after distant recurrence, survival analysis was performed after redefining time zero as the date of diagnosis of distant recurrence. Patients with CBC prior to distant recurrence were excluded from these analyses. The end-point of this analysis was death from any cause, and the estimated treatment effect was adjusted for time to distant recurrence, age and human epidermal growth factor receptor 2 (HER2) status. No data were available regarding sites of metastases. The corresponding unadjusted treatment effect on survival after distant recurrence was illustrated in a Kaplan–Meier graph.

For each of the two treatment arms (including all patients, irrespective of ER status), secondary malignancies were reported as frequency (n) and incidence (per 1000 patient-years), with the latter included because of the better survival in the tamoxifen treatment arm. For patients with several malignancies of the same type, such as skin squamous cell carcinomas, only the first malignancy was counted.

STATA 15.0, software (StataCorp LLC, College Station, TX, USA) was used for statistical calculations and graphics.

2.5. Ethics

The present study was approved by the ethical committee of Lund University (2015-350).

3. Results

Following extensive review of patient records, four patients were excluded because of protocol violations: two patients lacked invasive breast cancer, and two patients had stage IV disease at the time of diagnosis. In addition, one patient randomised to tamoxifen was found to have been entered into the study database as belonging to the control group. This data entry error was corrected. Therefore, a total of 560 patients were included in the present study, comprising 276 in the tamoxifen group and 284 in the control group (Fig. 1).

3.1. Median follow-up time and tamoxifen effect in the ITT population

The median follow-up for patients without breast cancer–related events ($n = 168$) was 28 years. Only four patients had a follow-up of <20 years for BCFi, of whom three had emigrated. At 30 years of follow-up of the ITT population, tamoxifen prolonged BCFi (HR = 0.76, 95% CI 0.61–0.94; $p = 0.011$) and D-RFi (HR = 0.85, 95% CI 0.67–1.09; $p = 0.20$), the latter not significantly. No effect of tamoxifen was seen for the 150 patients with ER-negative tumours (data not shown).

3.2. BCFi and D-RFi in patients with ER-positive tumours

Compared with no systemic treatment, tamoxifen prolonged BCFi with 30 years of follow-up (HR = 0.62, 95% CI 0.47–0.82, $p = 0.001$) ($n = 362$). Positive effects on BCFi were observed for the specified time intervals (0–5 years: HR = 0.67, 95% CI 0.47–0.96, $p = 0.029$; >5–15 years: HR = 0.60, 95% CI 0.35–1.04; $p = 0.068$; >15–30 years: HR = 0.53, 95% CI 0.28–0.98; $p = 0.042$). With 30 years of follow-up, tamoxifen also reduced the incidence of (HR = 0.73, 95% CI 0.54–0.99, $p = 0.043$) and was associated with non-significant beneficial effects for the specified time intervals (0–5 years: HR = 0.80, 95% CI 0.54–1.18, $p = 0.25$; >5–15 years: HR = 0.64, 95% CI 0.35–1.17, $p = 0.15$, >15–30 years: HR = 0.62, 95% CI 0.26–1.46, $p = 0.27$). When omitting censoring of follow-up for patients with CBC ($n = 35$), a similar effect for D-RFi was observed (HR = 0.70, 95% CI 0.52–0.94, $p = 0.017$). Fig. 2 shows the cumulative incidence curves for BCFi and D-RFi, and Table 2 displays the events and HRs by the treatment arm, for the entire follow-up period and the specified time intervals.

3.3. Subgroup analyses for BCFi in patients with ER-positive tumours

Homogeneity of treatment effects across groups defined by prognostic factors (age, nodal status, tumour size, histological grade and HER2 status) was analysed by Cox regression models with interaction terms. No significant interaction was found for any of the factors; thus, the null hypothesis of homogeneity of treatment effect across all subgroups could not be rejected; $p = 0.95$; Cochrane's Q-test. The results of the subgroup analyses are illustrated in Fig. 3.

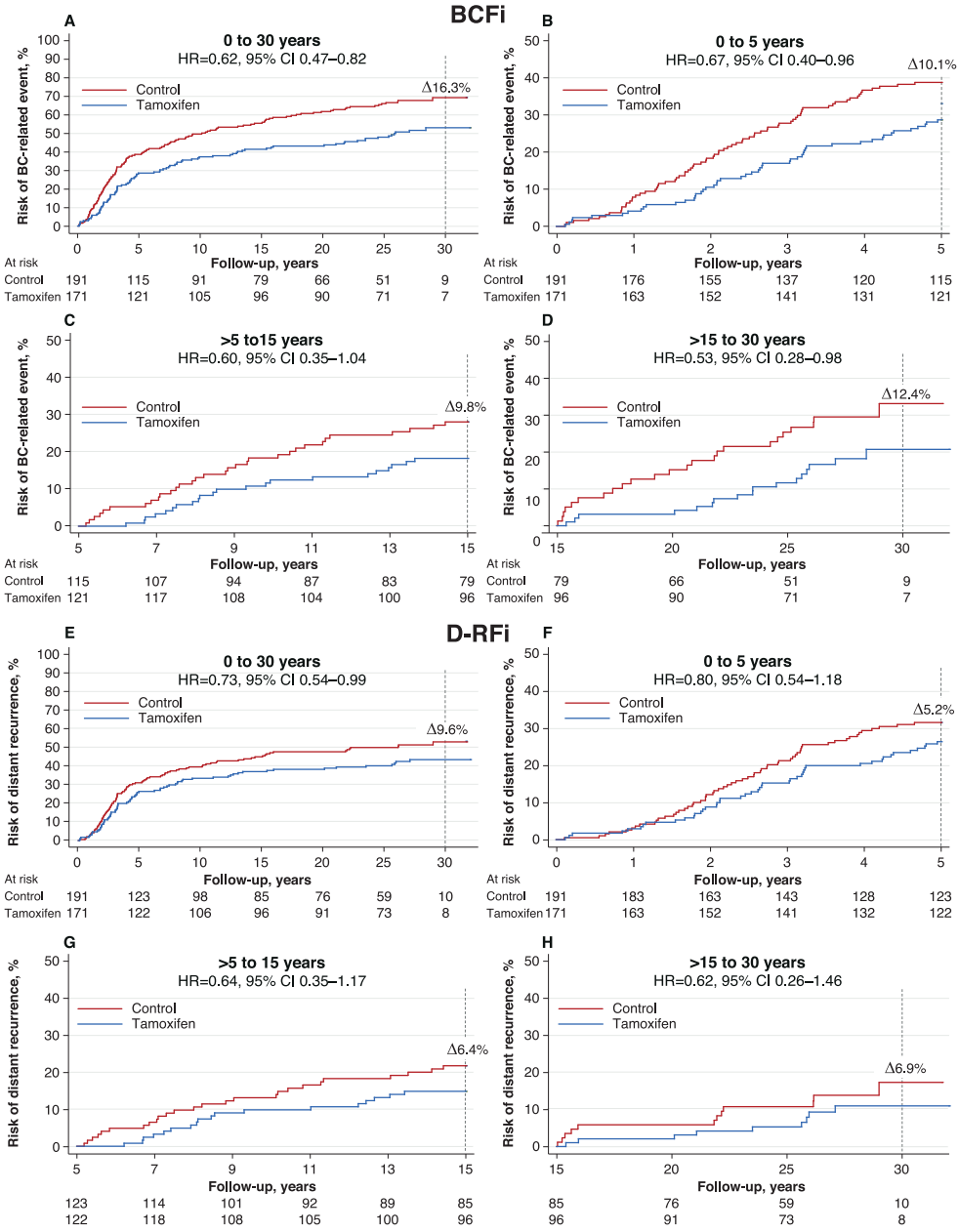

Fig. 2. Cumulative incidence curves for breast cancer–free interval (BCFi) and distant recurrence–free interval (D-RFi) according to the treatment arm for patients with oestrogen receptor–positive tumours with 30 years of follow-up (A/D) and for specified time intervals: 0–5 years (B/E), >5–15 years (C/F) and >15–30 years (D/H). Δ is defined as the absolute difference in percentage units between the two arms at 5, 15, and 30 years. BC, breast cancer; HR, hazard ratio; CI, confidence interval; BCFi, breast cancer–free interval; D-RFi, distant recurrence–free interval.

3.4. Adjuvant tamoxifen and survival after distant recurrence in patients with ER-positive tumours

Among patients with ER-positive tumours who were diagnosed with distant recurrence (n = 165), the median survival after distant recurrence was 29 months for the tamoxifen group, compared with 43 months for the control group. This corresponded to 82% higher mortality for tamoxifen-treated patients after adjustment for time to distant recurrence, age and HER2 status (HR = 1.82, 95% CI 1.26–2.63, p = 0.001). When also excluding patients with locoregional recurrence prior to distant recurrence (n = 8), a similar effect was seen (HR = 1.83, 95% CI 1.26–2.65, p = 0.001). At the data cut-off date, three patients remained alive in the tamoxifen group, compared with eight patients in the control group. Kaplan–Meier estimates of overall survival after distant recurrence are illustrated in Fig. 4.

Table 2
First breast cancer–related event, BCFi and D-RFi in patients with ER-positive tumours, according to the treatment arm for specified time intervals and the entire follow-up period.

Event	Time period (years)			
	0 to 5	>5 to 15	>15 to 30	0 to 30
Patients at risk at the start of each interval, *n*				
Control	191	115	79	191
Tamoxifen	171	121	96	171
First breast cancer–related event, *n* (%)				
All breast cancer–related events				
Control	74 (39)	32 (28)	24 (30)	130 (68)
Tamoxifen	49 (29)	22 (18)	17 (18)	88 (51)
Breast cancer–related death[a]				
Control	0 (0)	0 (0)	0 (0)	0 (0)
Tamoxifen	1[a] (1)	0 (0)	0 (0)	1 (1)
Distant recurrence				
Control	55 (29)	22 (19)	11 (14)	88 (46)
Tamoxifen	44 (26)	17 (14)	9 (9)	70 (41)
Regional recurrence				
Control	6 (3)	0 (0)	1 (1)	7 (4)
Tamoxifen	0 (0)	0 (0)	1 (1)	1 (1)
Local recurrence				
Control	6 (3)	4 (3)	3 (4)	13 (7)
Tamoxifen	1 (1)	0 (0)	2 (2)	3 (2)
Contralateral breast cancer[b]				
Control	7 (4)	6 (8)	9 (11)	22 (12)
Tamoxifen	3 (2)	5 (4)	5 (5)	13 (8)
Hazard ratio (95% confidence interval) and *p*-value				
BCFi				
Control	1.00	1.00	1.00	1.00
Tamoxifen	0.67 (0.47–0.96) $p = 0.029$	0.60 (0.35–1.04) $p = 0.068$	0.53 (0.28–0.98) $p = 0.042$	0.62 (0.47–0.82) $p = 0.001$
D-RFi				
Control	1.00	1.00	1.00	1.00
Tamoxifen	0.80 (0.54–1.18) $p = 0.25$	0.64 (0.35–1.17) $p = 0.15$	0.62 (0.26–1.46) $p = 0.27$	0.73 (0.54–0.99) $p = 0.043$

BCFi, breast cancer–free interval; D-RFi, distant recurrence–free interval; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.
[a] Death from pulmonary embolism with breast cancer as a contributing cause of death.
[b] Invasive and ductal cancer *in situ*.

3.5. Incidence of contralateral breast cancer and secondary non-breast malignancies

The incidence of CBC was 42% lower in the tamoxifen group compared with the control group (HR = 0.58, 95% CI 0.35–0.96, $p = 0.035$), whereas the incidences of secondary non-breast malignancies were similar in the two treatment groups (Table A3).

4. Discussion

In the present study, we demonstrate that 2 years of adjuvant tamoxifen reduced the incidence of breast cancer–related events and distant recurrence in premenopausal women with ER-positive breast cancer by 38% and 27%, respectively, with 30 years of follow-up, compared with no systemic treatment. BCFi was also significantly prolonged in the ITT population. For the ER-positive subgroup, this corresponded to absolute benefits of 16.3 percentage units (BCFi) and 9.6 percentage units (D-RFi) (Fig. 2). Although this trial was not powered to detect differences in outcomes for different time intervals, a significant benefit regarding BCFi was demonstrated for the interval >15–30 years, which contrasts to the findings in the EBCTCG overview [6]. Importantly, 20% of the first events were diagnosed after 15 years of follow-up and comprised mainly distant recurrences followed by CBC. The incidence of CBCs was efficiently reduced by tamoxifen therapy, whereas no association to any other second malignancy, including endometrial cancer, was found. In a contemporary cohort of patients, with a less advanced stage of disease at diagnosis and with modern adjuvant therapy, one can presume that the proportion of late first events will be even higher, emphasising the importance of long-term follow-up.

Based on register data, Kleeberg et al. found that adjuvant chemotherapy was associated with shorter survival after distant breast cancer recurrence, a phenomenon they referred to as adjuvant therapy–related shortening of survival (ATRESS) [15,16]. ATRESS

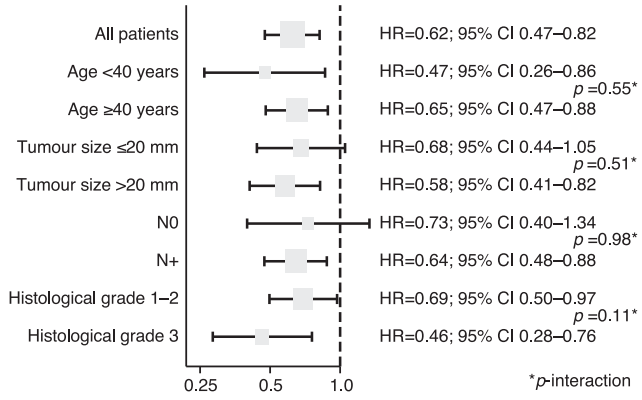

Fig. 3. A forest plot showing subgroup analyses of tamoxifen versus no systemic treatment regarding breast cancer–free interval in patients with ER–positive tumours for the entire follow-up period (0–30 years). The side of each square is inversely proportional to the standard error (SE) of the estimated HR. As a consequence of this informative scaling, estimates of treatment effects in subgroups of HER2 were omitted from the graph. No evidence for heterogeneity by the HER2 status was found ($p = 0.91$), but the SE of the treatment effect in HER2+/amplified was so large compared with the other SEs that the graph was distorted. ER, oestrogen receptor; HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2.

associated with chemotherapy has been repeatedly reported, mostly from retrospective analyses including patients with metastatic breast cancer [17–20]. Two previous studies on postmenopausal patients with recurrent disease have demonstrated an association between adjuvant tamoxifen and impaired survival in the metastatic setting [21,22]. In line with results from postmenopausal patients randomised to tamoxifen, we found that patients with ER-positive breast cancer allocated to tamoxifen had significantly shorter survival after diagnosis of distant recurrence. However, owing to the limited sample size (n = 165), our finding has to be interpreted with caution. Also, compared with those

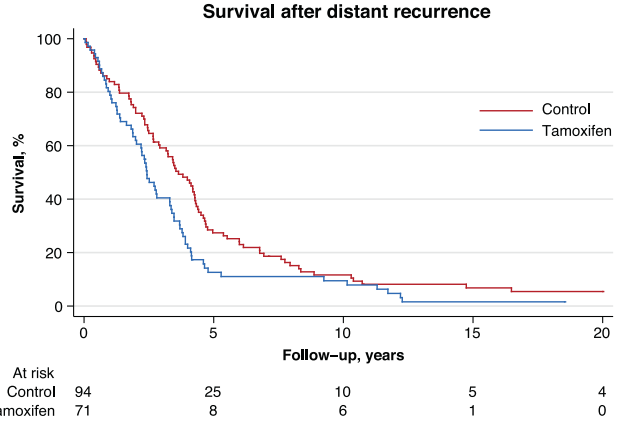

Fig. 4. Kaplan–Meier estimates of overall survival after distant recurrence in ER-positive patients, according to treatment arm. ER, oestrogen receptor.

currently available, there were less developed methods for detection and characterisation of distant metastases in the 1980s and 1990s. Therefore, important predictive factors such as the number and sites of metastases and HER2 status and ER expression in the metatstases could not be considered. However, despite the shortcomings, our findings emphasise that previous adjuvant systemic therapy may impact survival in patients with recurrent disease, and it warrants for other research groups to investigate this further.

The strengths of the present study are the long-term follow-up time of almost three decades, the careful review of medical records performed by an experienced oncologist according to a prespecified protocol and the inclusion of complementary data from national registers. This type of in-depth follow-up can be conducted in Sweden because all citizens have a personal identity number and most health care is provided by the public healthcare system, thus enabling access to individual patient files. A limitation of the study is that tamoxifen treatment was restricted to 2 years, which is shorter than currently recommended. Patients were included in the SBII:2pre trial, irrespective of ER-status. However, based on current knowledge concerning indications for tamoxifen therapy, our results are based on analyses of the ER-positive subgroup. Our data should, therefore, be interpreted with the care subgroup analyses require. Importantly, similar effects were also seen in the ITT population. We could not demonstrate increased incidence of endometrial cancer or of non-breast secondary malignancies, but this study is underpowered to detect any significant differences for this end-point.

The results presented here are important. First, they indicate that the carryover effect associated with tamoxifen remains for a long period and is not restricted to CBC but applies to all breast cancer–related events, including distant recurrence. These findings will hopefully encourage other research groups to further examine the long-term benefits of tamoxifen, especially in comparison to aromatase inhibitors. Second, although ≥5 years of endocrine therapy is superior to 2 years, our results may encourage patients experiencing difficulties in tolerating endocrine therapy to adhere to tamoxifen treatment for at least 2 years. Finally, adjuvant endocrine therapy seems to affect clinical outcomes after distant recurrence, in line with previous publications [21,22], but this has to be further investigated in additional trials.

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Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.12.034.

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