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Tamoxifen reduces the risk of contralateral breast cancer in premenopausal women: Results from a controlled randomised trial

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ABSTRACT

Background: Adjuvant treatment with tamoxifen reduces the risk of contralateral breast cancer in hormone-responsive postmenopausal patients, whereas the effect in premenopausal women has not been fully elucidated. We have therefore studied the effect of tamoxifen on contralateral breast cancer in premenopausal women in a controlled randomised trial.

Patients and methods: Premenopausal women (564) with stage II breast cancers were randomised to 2 years of tamoxifen versus control irrespective of oestrogen receptor (ER) and progesterone receptor (PgR) status. The median follow-up for patients not developing a contralateral cancer was 14 years.

Results: In the control group 35 women, and in the tamoxifen group 17 women, developed a contralateral breast cancer as a primary event. Tamoxifen significantly reduced the risk of contralateral breast cancer in all women regardless of age (hazard ratio (HR) 0.5, $p = 0.02$). In subgroup analysis the risk reduction was most pronounced in patients <40 years of age (HR 0.09, $p = 0.02$). A risk reduction was also seen in women 40–49 years of age or $\geqslant$50 years of age, although in these subgroups this did not reach statistical significance. The reduced risk of contralateral breast cancer was persistent during the whole follow-up time.

Conclusion: In this randomised trial, adjuvant treatment using tamoxifen for 2 years reduced the incidence of contralateral breast cancer by 50% in all premenopausal women, and by 90% in women <40 years of age. The effect of tamoxifen was not significantly dependent on time.

1. Introduction

Every year about 7000 women in Sweden are diagnosed with breast cancer, indicating that one woman in eight will develop the disease during her lifetime.[1] Today most women are cured and the 5-year survival rate in Sweden is about 85–90%.[2] However, apart from the risk of relapse, breast cancer patients have a 0.5–1% annual risk of developing a contralateral breast cancer, with a lifetime risk of 2–15%.[3,4] Lobular breast carcinoma, young age at diagnosis of the primary

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cancer and mutation carriers are known indicators of increased risk.[5,6] Young age is also associated with a worse prognosis once diagnosed with a secondary breast cancer.[7]

Adjuvant treatment using tamoxifen or aromatase inhibitors has been shown to reduce the risk of a second breast cancer in postmenopausal patients,[4,8–10] though data on premenopausal women are limited.[11,12] However, recent findings from a population-based study show that the effect of tamoxifen on contralateral breast cancer appears to be modified by age, with the most marked decrease in women younger than 45 years of age.[11] Contralateral breast cancer that develops following adjuvant tamoxifen treatment is to a larger percentage oestrogen receptor (ER)-negative,[4,13–15] and there are indications that second tumours diagnosed following adjuvant treatment have a worse prognosis.[7] The change in tumour biology and prognosis could indicate a treatment-escape phenomenon and development of a more aggressive phenotype where treatment has failed to prevent a contralateral cancer.

We hereby wish to further investigate the effect of tamoxifen on the development of contralateral metachronous breast cancer in premenopausal women using a controlled randomised trial of tamoxifen for 2 years versus control. Since randomisation was done independently of ER status, we also have an excellent opportunity to investigate the effect of tamoxifen on metachronous breast cancer in relation to ER status of the primary tumour.

2. Patients and methods

2.1. Study design

The study was designed to compare the effect of 2 years of adjuvant tamoxifen treatment versus no adjuvant systemic treatment in premenopausal women. From 1986 to 1991, 564 patients were enrolled and randomised from two study centres in Sweden. Randomisation was done independently of ER and progesterone receptor (PgR) status. The characteristics of this trial have previously been described in detail.[16] In brief all patients had unifocal, stage II invasive breast cancer and received surgery in the form of a modified radical mastectomy or breast-conserving surgery with axillary lymph node dissection. Radiotherapy was administered in accordance with clinical standards. Adjuvant polychemotherapy was administered in less than 2% of the patients. Verbal informed consent was registered for all patients and the study was approved by the ethical committees at the Universities of Lund and Linköping. The median duration of follow-up for patients without a breast cancer event was 14 years. Breast cancer events include local, regional, or distant recurrences, breast cancer-specific death, but not contralateral breast cancer. The term 'age' used below refers to the age at diagnosis of the first breast cancer and inclusion in the study. We define metachronous breast cancer as a second tumour developed $\geqslant 3$ months after the primary cancer, in line with some earlier studies.[6,7] The study is registered as 'SBII:2' in accordance with the criteria outlined by the International Committee of Medical Journal Editors, at the Regional Oncological Centres in Lund and Linköping, respectively. Study design and patient flow are described in greater detail in Fig. 1 and Table 1. In the present study tumour characteristics were registered for the primary tumours, but not for all second tumours making our knowledge of characteristics for the second tumour limited.

2.2. Tissue microarray (TMA) and immunohistochemical staining

TMA were available for 500 out of 564 patients included in the study. From representative areas of the invasive breast cancer tissue samples, two core biopsies were punched out and mounted into the recipient block using a tissue array machine in accordance with the manufacturer's instructions (Beecher Instruments, MD, USA). ER and PgR were analysed using the Ventana Benchmark system, using Anti-ER Clone 6F11 and Anti-PgR Clone 16 as primary antibodies.[16] In line with clinical guidelines, tumours with >10% stained nuclei were considered receptor positive.

Human epidermal growth factor receptor 2 (HER2) was measured by means of both immunohistochemistry (IHC) and fluorescence *in situ* hybridisation (FISH).[17] All patients with amplified tumours and all patients with an IHC score of 3+, where FISH could not be evaluated, were considered HER2-positive. The Nottingham histological grade (NHG) was evaluated following a written protocol, as previously described.[16]

2.3. Statistical analysis

The development of contralateral metachronous breast cancer was chosen as the primary outcome. All analyses were made using the intention to treat rule. For statistical calculations the software package Stata 10.1 (StataCorp. 2008, College Station, TX, USA) was used. A Kaplain–Meier plot was used to illustrate the development of contralateral breast cancer in a specified cohort and a log-rank test was used to evaluate the hypotheses of equality of survival curves. Hazard ratios (HR) and confidence intervals (CI) were estimated using Cox regression. Univariate Cox regression was used to compare different subgroups and multivariate Cox regression was used to adjust for effects of other prognostic markers. To assess whether the effect of tamoxifen differed with regard to ER status of the primary breast cancer, a Cox model with a term for interaction was used. Assumptions of proportional hazards were checked using Schoenfeld's test. All *p*-values correspond to two-sided tests and values of less than 0.05 were considered significant.

3. Results

Of the 564 women included in the study, 52 (9%) developed a contralateral metachronous breast cancer; 17 in the tamoxifen group and 35 in the control group (Fig. 2). The median time to development was 4 years (range 0.5–15 years). One patient diagnosed with a contralateral synchronous breast cancer in the tamoxifen treated group was excluded in the statistical analysis below.

3.1. Incidence of contralateral breast cancer without adjuvant systemic treatment

The control group was used to investigate the incidence of contralateral breast cancer when not affected by adjuvant

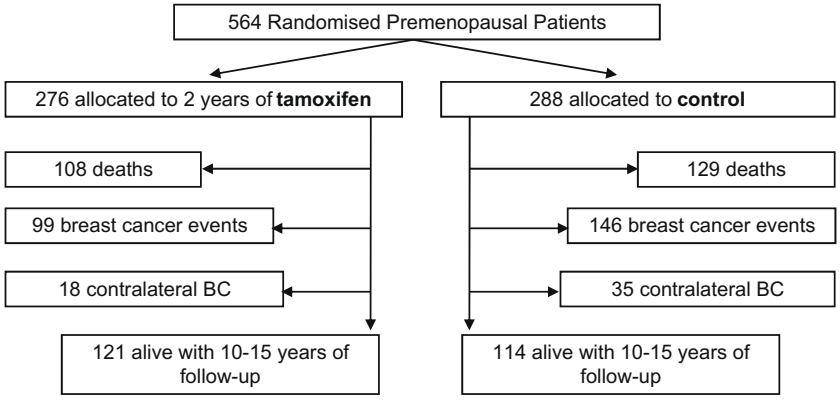

Fig. 1 – Study design.

Table 1 – Patient and tumour characteristics in relation to treatment arm.

Variable	All patients $n = 564$			Patients with contralateral breast cancer $n = 52$			
				Primary tumour		Second tumour	
	Control, $n = 288$ (%)	Tamoxifen, $n = 276$ (%)	p-Value[a]	Control, $n = 35$	Tamoxifen, $n = 17$	Control, $n = 35$	Tamoxifen, $n = 17$
Age (years)							
Median (range)	45 (26–57)	44 (25–57)		44 (27–53)	46 (39–55)	+6 (0.8–15)	+3 (0.5–12)
Node status			0.4				
N0	77 (27)	83 (30)		7 (20)	7 (41)		
N+	210 (73)	192 (70)		28 (80)	10 (58)		
Missing	1	1		0	0	35	17
Tumour size			0.005				
0–20 mm	122 (42)	85 (31)		19 (54)	6 (35)		
21+ mm	166 (58)	190 (69)		16 (46)	11 (65)		
Missing	0	1		0	0	35	17
NHG			0.5				
1	31 (12)	27 (11)		3 (9)	1 (7)		
2	118 (45)	104 (42)		17 (52)	6 (40)		
3	116 (44)	118 (47)		13 (39)	8 (53)		
Missing	23	27		2	2	35	17
ER			0.2				
Negative	72 (29)	79 (34)		8 (26)	3 (25)	10 (40)	3 (50)
Positive	173 (71)	151 (66)		23 (74)	9 (75)	15 (60)	3 (50)
Missing	43	46		4	5	10	11
PgR			0.4				
Negative	73 (30)	74 (34)		9 (29)	3 (25)	14 (56)	4 (67)
Positive	168 (70)	146 (66)		22 (71)	9 (75)	11 (44)	2 (33)
Missing	47	56		4	5	10	11
HER2			0.3				
Negative	208 (86)	203 (89)		29 (94)	11 (92)		
Positive	34 (14)	25 (11)		2 (6)	1 (8)		
Missing	46	48		4	5	35	17

Abbreviations: Control, control-arm; Tamoxifen, tamoxifen-arm; Node status, lymph node status; NHG, Nottingham histological grade; ER, oestrogen receptor; PgR, progesterone receptor; and HER2, human epidermal growth factor receptor 2.

[a] X^2-test for 2×2 tables or, where appropriate, X^2-test for trend.

treatment. The percentages of women developing contralateral metachronous breast cancer in the control group, in the various age categories, were: <40 years 20%, 40–49 years 9% and ⩾50 years 14% (Table 2). There seemed to be a trend towards a higher incidence in younger patients. Statistical analysis showed a significant difference in incidence between

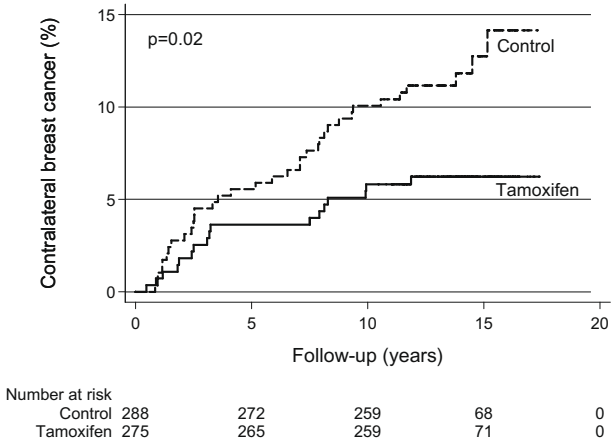

Fig. 2 – Cumulative incidence of contralateral breast cancer with regard to treatment arm.

patients <40 and 40–49 years old (HR = 0.46, $p = 0.04$, 95% CI 0.22–0.96), but not between patients <40 and ⩾50 years old (HR = 0.68, $p = 0.4$, 95% CI 0.26–1.8). A log-rank test for trend, comparing all three groups, did not show any significant difference ($p = 0.2$).

3.2. *The effect of tamoxifen on the development of contralateral breast cancer*

The percentages of contralateral metachronous breast cancers in the group treated with tamoxifen, in the various age categories, were: <40 year 2%, 40–49 years 7% and ⩾50 years 9% (Table 2). For all women, regardless of age, tamoxifen significantly reduced the risk of developing metachronous breast cancer (HR = 0.50, $p = 0.02$, 95% CI 0.28–0.88). Statistical significance remained in multivariate analysis adjusted for age (continuous variable), ER (positive versus negative), HER2 (positive versus negative), Nottingham histological grade (NHG, 2 versus 1 and 3 versus 1), tumour size (>20 versus ⩽20) and lymph node status (N0 versus N+) (HR = 0.38, $p = 0.008$, 95% CI 0.18–0.78). The effect of tamoxifen was not significantly dependent on time ($p = 0.37$; Schoenfeld's test), and the reduced risk of contralateral breast cancer seemed to be persistent during the whole follow-up time (data not shown).

Tamoxifen reduced the risk of contralateral metachronous breast cancer in both patients with ER-positive and ER-negative primary tumours (Table 3). Although this trend was similar in both groups, it only reached statistical significance in patients with ER-positive (HR = 0.43, $p = 0.03$, 95% CI 0.20–0.94) primary tumours and not in the smaller subgroup of patients with ER-negative primary tumours (HR = 0.34, $p = 0.1$, 95% CI 0.09–1.3). A test for interaction between ER status and tamoxifen effect was not significant (HR = 1.3, $p = 0.7$, 95% CI 0.28–6.1), indicating no difference in treatment effect with regard to ER status of the primary tumour. Similar results were seen when investigating the effect of tamoxifen with regard to the PgR status of the primary tumour (data not shown).

Subgroup analysis with regard to age showed that the effect of tamoxifen was highly significant in women <40 years (HR = 0.09, $p = 0.02$, 95% CI 0.01–0.68). Although a risk reduction was also seen in women 40–49 years (HR = 0.73, $p = 0.4$, 95% CI 0.35–1.5), and women ⩾50 years (HR = 0.67, $p = 0.5$, 95% CI 0.19–2.4), it did not reach statistical significance in these subgroups.

4. Discussion

This study found that 2 years of tamoxifen produced a significant risk reduction in the development of contralateral breast cancer, and this is to our knowledge the first data presented on premenopausal patients from a controlled randomised trial. We found that without adjuvant treatment 12% of all women and 20% of the women <40 years of age, developed a contralateral breast cancer within a median follow-up time of 14 years. Adjuvant tamoxifen reduced the risk by 50% in all women. Subgroup analysis showed this effect to be even more pronounced in women <40 years of age, where the risk was reduced by 90%. Risk reduction was also seen in women 40–49 or ⩾50 years of age, although in these subgroups it did not achieve statistical significance.

In line with our data, several studies have shown young age at diagnosis of the primary breast cancer to be a risk factor for contralateral breast cancer.[5,6] A recent study has also shown young age to be associated with a worse prognosis once diagnosed with a second breast cancer, especially if the time interval between the primary and the second tumour is short.[7] The reasons for increased risk in younger women are not fully understood. However, one explanation could be a higher prevalence of hereditary mutations and other genetic factors,[18] increasing the risk of breast cancer development. Another explanation might be that younger women have a smaller risk of dying from other causes, thus increasing the time at risk of developing a contralateral breast cancer. However, our study includes only premenopausal patients, with 475 out of 564 patients being <50 years old when diagnosed with their first breast cancer, and time at risk is therefore unlikely to explain the observed differences.

Table 2 – Development of contralateral breast cancer in relation to age and tamoxifen treatment.

Contralateral breast cancer	All patients, $n = 563$		Untreated arm, $n = 288$		Tamoxifen arm, $n = 275$		p-Value[a]
	No	Yes	No	Yes	No	Yes	
All ages	511 (91%)	52 (9%)	253 (88%)	35 (12%)	258 (94%)	17 (6%)	0.02
<40 years	100 (88%)	13 (12%)	49 (80%)	12 (20%)	51 (98%)	1 (2%)	0.02
40–49 years	332 (92%)	29 (8%)	167 (91%)	17 (9%)	165 (93%)	12 (7%)	0.4
⩾50 years	79 (89%)	10 (11%)	37 (86%)	6 (14%)	42 (91%)	4 (9%)	0.5

[a] Univariate Cox regression.

Table 3 – Tamoxifen effect in relation to ER status in the primary breast cancer.

	All patients, $n = 563$		Untreated arm, $n = 288$		Tamoxifen arm, $n = 275$		p-Value[a]
Contralateral breast cancer	No	Yes	No	Yes	No	Yes	
ER–	140 (93%)	11 (7%)	64 (89%)	8 (11%)	76 (96%)	3 (4%)	0.1
ER+	291 (90%)	32 (10%)	150 (87%)	23 (13%)	141 (94%)	9 (6%)	0.03
ER?	80 (90%)	9 (10%)	39 (91%)	4 (9%)	41 (89%)	5 (11%)	

Abbreviations: ER–, oestrogen receptor negative; ER+, oestrogen receptor positive; and ER?, oestrogen receptor status unknown.
[a] Univariate Cox regression.

Previous studies have shown that adjuvant treatment with tamoxifen or aromatase inhibitors reduces the risk of contralateral breast cancer in postmenopausal women.[4,8–10] Although a similar effect has been suggested in premenopausal patients,[11,12] there have also been implications of no risk reduction, or even a marginally increased risk with tamoxifen in these women.[19] In the randomised trial of adjuvant tamoxifen including only premenopausal women presented here, there was a significant risk reduction of 50% in all patients. The magnitude of reduction is similar to, or somewhat greater than that found in the data presented from randomised trials of adjuvant tamoxifen in postmenopausal women.[12,20] Interestingly, in a recent publication from a population-based study by Bertelsen and colleagues, the effect of tamoxifen on contralateral breast cancer is found to be modified by age, with the most pronounced effect being observed in women <45 years of age.[11] Age might also be significant with regard to the protective effect of chemotherapy on the development of contralateral breast cancer. In the overview by the Early Breast Cancer Trialists' Collaborative Group, chemotherapy reduced the incidence of contralateral breast cancer significantly only in women younger than 50 years of age.[21]

Using population-based register data, Hartman and colleagues found that the incidence of contralateral breast cancer in Sweden has decreased since 1972.[7] One explanation to this could be increased use of adjuvant treatment, preventing development of a second tumour. However, although fewer patients were diagnosed with a contralateral breast cancer, prognosis for those who did get a secondary tumour got worse during the same time period.[7] This might reflect a treatment-escape phenomenon and development of a more aggressive phenotype where treatment has failed to prevent a second cancer.[4] Indeed, Hartman and colleagues showed that patients with early metachronous breast cancer have a poorer survival if they had received adjuvant chemotherapy for their primary cancer, compared to those not having received prior chemotherapy.[7] Survival data for metachronous breast cancer that develops following tamoxifen treatment is not as yet available. In this study, the numbers of contralateral tumours are too few to draw any conclusions with regard to this issue.

Adjuvant tamoxifen is only effective in hormone receptor positive breast cancer.[21] Metachronous breast cancer that develops following tamoxifen treatment in postmenopausal women is also to a larger percentage ER-negative than is the case if no endocrine treatment has been given.[4,13,14] It is unclear whether the same is true for premenopausal women. In a few trials tamoxifen has been administered to women at high risk of developing breast cancer in order to study its preventive effect on the incidence of breast cancer.[15,22,23] These trials showed no reduction in the incidence of ER-negative breast cancers, while the incidence of ER-positive breast cancers was reduced almost by half.[15] Risk reduction was found to be independent of age.[15] Hence, tamoxifen seems to reduce the incidence of ER-positive tumours, while having less, if any, effect on the development of ER-negative tumours. Although it would have been interesting to explore if adjuvant tamoxifen treatment affects ER status in the contralateral breast cancer in the present randomised study, the number of contralateral breast cancer is low ($n = 52$) and ER status is unknown in 40% of them. Therefore, no robust conclusion regarding the effect by adjuvant tamoxifen treatment on ER status in the contralateral breast cancer can be drawn in the present study due to low statistical power.

The preventive effect of adjuvant tamoxifen on the development of contralateral breast cancer has been reported to be independent of ER status in the primary tumour,[12] although some studies have found the effect to be restricted to, or more pronounced in, women with an ER-positive primary tumour.[11,13,21] If so, it is unclear why tamoxifen would be effective only in women with ER-positive primary breast cancers. However, one explanation could be if ER status of the primary tumour is associated with ER status in the second tumour. Some studies do find such a correlation,[13,24] although others do not.[14] Also, even if there is such a correlation, some women with an ER-negative primary tumour will still develop an ER-positive second tumour, and tamoxifen should be effective in preventing this.[13] However, several large studies have shown that tamoxifen has no effect in patients with ER-negative primary breast cancers, and there have even been indications that tamoxifen could be detrimental for these patients.[25,26]

In our study tamoxifen reduced the development of contralateral breast cancer in patients with ER-positive as well as ER-negative primary tumours. In ER-positive patients 7% of the women in the group treated with tamoxifen and 13% in the untreated group developed a contralateral breast cancer. The corresponding numbers for ER-negative patients were 4% versus 11%. No difference in treatment effect between ER-positive and ER-negative patients could be found using a Cox model with an interaction term. Therefore, although subgroup analysis revealed a significant reduction of contralateral breast cancers only in the ER-positive subgroup, this is most likely due to the smaller number of patients with ER-negative tumours, rather than a true difference in treatment effect between the two groups.

In conclusion, in this randomised trial of premenopausal breast cancer patients, we have found that systemically untreated women, regardless of age, had a 12% risk, and women <40 years of age had a 20% risk of developing a contralateral metachronous breast cancer with a median follow-up time of 14 years. Adjuvant treatment with tamoxifen for 2 years reduced this risk by 50% in all women, and by 90% in women <40 years of age.

Conflict of interest statement

All authors of this article disclose any financial and personal relationship with people or organisations that could inappropriately influence their work. This includes employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations and grants or other funding.

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