ORIGINAL ARTICLE

Minimal impact of adjuvant exemestane or tamoxifen treatment on mammographic breast density in postmenopausal breast cancer patients: A Dutch TEAM trial analysis

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ABSTRACT

Background. Mammographic breast density is one of the strongest independent risk factors for developing breast cancer. We examined the effect of exemestane and tamoxifen on breast density in Dutch postmenopausal early breast cancer patients participating in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial.

Material and methods. Analogue mammograms of selected TEAM participants before start, and after one and two (and if available after three) years of adjuvant endocrine therapy were collected centrally and reviewed. Study endpoints were change in breast density over time, and correlations between breast density and locoregional recurrence (LRR), distance recurrence (DR), and contralateral breast cancer (CBC).

Results. Mammograms of 378 patients (181 tamoxifen, 197 exemestane) were included in the current per protocol analyses. Baseline breast density was low (breast density score <50% in 75% of patients) and not different between patients randomised to exemestane or tamoxifen (coefficient 0.16, standard error 0.17). Breast density did not change during treatment in exemestane (p = 0.25) or tamoxifen users (p = 0.59). No relation was observed between breast density and the occurrence of a LRR [hazards ratio (HR) 0.87, 95% CI 0.45–1.68, p = 0.67], a DR (HR 1.02, 95% CI 0.77–1.35, p = 0.90), or CBC (HR 1.31, 95% CI 0.63–2.72, p = 0.48).

Conclusion. The in general low breast density score in early postmenopausal breast cancer patients did not substantially change over time, and this pattern was not different between tamoxifen and exemestane users. Breast density was not a predictive marker for efficacy of adjuvant endocrine therapy.

Adjuvant endocrine therapy with tamoxifen and/or aromatase inhibitors (AIs) results in an improved relapse free and overall survival in postmenopausal hormone-sensitive early breast cancer patients. The degree of oestrogen receptor expression is predictive for the response to endocrine therapy, whereas, unfortunately, other factors cannot be used to further individualise treatment choices regarding the type and length of
endocrine treatment. Change in mammographic breast density has been suggested to be a predictive surrogate biomarker for tamoxifen efficacy [1–5].

Mammographic breast density is the result of the relative proportions of fat, epithelial and stromal tissues in the breasts [6]. It is one of the strongest independent risk factors for developing breast cancer; women with dense fibroglandular tissue in over 75% of their breasts have a 4–6 times higher risk of developing breast cancer compared to women with lower breast density percentages [7,8]. Factors associated with a higher mammographic density are hormone replacement therapy, younger age, lower body mass index, and nulliparity [9]. However, breast density decreases with age, time from menopause and with increasing number of pregnancies [10]. Additionally, treatment with tamoxifen has been associated with a decreased breast density in mainly premenopausal or early postmenopausal women, especially if the mammograms before treatment showed relatively dense fibroglandular tissue [1,11–13]. While tamoxifen blocks oestrogen binding at the oestrogen receptor, AIs inhibit the conversion from androgens to oestrogens, resulting in lowered oestrogen plasma levels in postmenopausal women. Therefore AIs, hypothetically, may also reduce mammographic density.

The effects of AIs on breast density in postmenopausal early breast cancer patients have mainly been investigated during or after treatment with the non-steroidal AIs anastrozole and letrozole [14–19]. Data on the effect of the steroidal AI exemestane on breast density are limited. In the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial, postmenopausal women with hormone-sensitive early breast cancer were randomised between sequential treatment with tamoxifen for 2–3 years followed by exemestane for 3–2 years (totalling five years) or exemestane alone for five years [20]. In the Netherlands, 2754 patients were enrolled in the TEAM trial from almost a national coverage of Dutch hospitals (76/92) offering a good framework to evaluate the effects of exemestane on mammographic breast density, and to investigate the effect on breast density in relation to treatment response.

Material and methods

Study design

The TEAM breast density study was performed within a subset of the Dutch TEAM population recruited from 13 selected hospitals (see Supplementary Appendix, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.964809) based on adequate inclusion rate, geographical distribution and availability of analogue mammograms over time. Analogue mammograms were collected at baseline (diagnosis), and after one and two years, and where available also after three years, of endocrine therapy. Ineligibility criteria for the current study were absence of analogue mammograms, having undergone a contralateral mastectomy, no mammography before start of endocrine therapy, and lack of at least one follow-up mammogram after start of endocrine therapy. The medical ethics committee of the Erasmus University Medical Centre approved the study protocol before the start of collection of mammograms.

Endpoints

The primary study aim was to examine changes in mammographic breast density in the contralateral (unaffected/untreated) breast during use of exemestane, and to compare these changes over time between patients treated with exemestane or tamoxifen. Secondary study aims included the relationship between breast density and the occurrence of a locoregional recurrence (LRR), a distance recurrence (DR) or contralateral breast cancer (CBC).

Evaluation of mammographic breast density

At the start of the TEAM trial enrolment in 2001, almost all hospitals in the Netherlands used analogue mammograms (which, in a number of hospitals, were subsequently switched to digital mammograms during the conduct of the study). As it is difficult to directly compare breast density assessed on an analogue mammogram with that of a digital mammogram, only analogue mammograms were collected and analysed for the current analyses.

Mammographic breast density was scored on the craniocaudal view of the contralateral breast by the visual estimation technique classifying the percentage of mammographic breast density into one of six categories: 0%, < 10%, 10–25%, 25–50%, 50–75%, and > 75%. Using this technique, a high intra- and inter-observer agreement can be obtained [7]. All mammograms were reviewed by three independent radiologists being very experienced in reading mammograms (AS, SL and CB). The patient’s identity, date of mammogram and randomisation arm were blinded to the radiologists. The preoperative mammogram was taken as baseline measurement. Breast density was scored on the mammogram at baseline (T0), after one year (range 6–18 months, T1) and after two years (range 18–30 months, T2) of endocrine therapy. For a number of patients, a third mammogram after three years (range 30–42 months, T3) of endocrine therapy was also available and reviewed.
Minimal impact of endocrine therapy on breast density

Clinical data

Clinical, pathological and follow-up data of the patients included in the current breast density analyses were retrieved from the main TEAM database, centralised at the datacentre in Leiden, the Netherlands.

Statistical methods

Statistical analyses were performed using the statistical package SPSS for Windows 17.0 (SPSS Inc, Chicago, IL, USA). Descriptive data are given as mean (SD) or median (range). Pearson’s χ²-test was used to compare frequencies between groups. A per-protocol analysis was performed: data of patients were analysed only if they used the allocated treatment and during the time using the allocated treatment. Data of patients randomised to upfront tamoxifen in the sequential arm were used in the analyses until the switch to exemestane. To evaluate the interrater agreement, intraclass correlations were calculated. For the longitudinal analyses of breast density, ordinal regression was used, with radiologist, year of mammogram (categorical), treatment, and treatment by time interaction as fixed effects. To account for the correlation within patients, robust estimates of variances were used [21]. Time to LRR, DR or CBC was calculated from the start of endocrine therapy up to the date of a LRR, a DR or CBC, respectively. The association between baseline breast density and LRR, DR, and/or CBC was analysed using the Cox regression method.

Results

Patients

In the 13 hospitals contributing to this TEAM sub-study (see Supplementary Appendix available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.964809), a total of 774 patients were randomised in the TEAM trial, of whom 571 (71%) were considered eligible for the current analyses (203 patients were considered ineligible because the hospital switched from analogue to digital mammography within two years after randomisation or because of a prophylactic contralateral mastectomy within 2.5 years after randomisation). Analogue mammograms of 442 (77%) patients were available (Figure 1). Of the 219 patients randomised to the sequential arm (tamoxifen as first therapy), 28 stopped therapy within one year, five had no preoperative mammogram available and two had no follow-up mammogram available, leaving 197 patients for the current analyses. Of the total group of 378 patients, 359 mammograms (171 sequential arm, 188 exemestane arm) were reviewed after one year of endocrine therapy, 292 mammograms (123 sequential arm, 169 exemestane arm) after two years, and 116 mammograms (17 of tamoxifen patients and 99 of exemestane patients) after three years of endocrine therapy.

Patients and tumour characteristics are shown in Table I A. There were no statistically significant imbalances between the patient features of both randomisation arms. Median age (range) in the sequential (tamoxifen) group was 63 years (48–91) and 62 years (45–86) in the exemestane group. The median (range) tumour sizes in the sequential and exemestane treatment cohort were 22 (4–98) and 22 (1–80) ml, respectively. The demographics tumour and treatment features of the included and excluded patients (Table IB) did not significantly differ except for distribution of hormone receptor status and adjuvant endocrine therapy regimen.

Longitudinal breast density results

The interclass correlation coefficient between the three radiologists (raters) was satisfactory: 0.74. Distribution of the mammographic breast density scores are shown in Figure 2. Overall, baseline mammographic breast density was significantly higher in patients with tamoxifen compared to patients with exemestane.
Table IA. Baseline characteristics for patient, tumour and treatment.

|                          | Tamoxifen = > exemestane | Exemestane | Total |
|--------------------------|--------------------------|------------|-------|
|                          | Number | %       | Number | %       | Number | %       |
| Total                    | 181    | 100     | 197    | 100     | 378    | 100     |
| Age (years)              |         |         |         |         |         |         |
| < 50                     | 3       | 2       | 8      | 4       | 11     | 3       |
| 50–59                    | 66      | 36      | 67     | 34      | 133    | 35      |
| 60–69                    | 69      | 38      | 66     | 34      | 135    | 36      |
| ≥ 70                     | 43      | 24      | 56     | 28      | 99     | 26      |
| BMI (kg/m²)              |         |         |         |         |         |         |
| ≤ 25                     | 61      | 36      | 79     | 42      | 140    | 39      |
| 2–30                     | 68      | 40      | 70     | 37      | 138    | 39      |
| ≥ 30                     | 39      | 23      | 38     | 20      | 77     | 22      |
| Tumour stage             |         |         |         |         |         |         |
| pT1                      | 79      | 44      | 91     | 47      | 170    | 45      |
| pT2                      | 86      | 48      | 97     | 50      | 183    | 49      |
| pT3/pT4                  | 15      | 8       | 7      | 4       | 22     | 6       |
| Pathological nodal status|         |         |         |         |         |         |
| Negative                 | 59      | 33      | 61     | 31      | 120    | 32      |
| Positive                 | 122     | 67      | 136    | 69      | 258    | 68      |
| Histological grade       |         |         |         |         |         |         |
| Grade I                  | 27      | 16      | 34     | 18      | 61     | 17      |
| Grade II                 | 77      | 45      | 91     | 49      | 168    | 47      |
| Grade III                | 66      | 39      | 59     | 32      | 125    | 35      |
| Hormone receptor         |         |         |         |         |         |         |
| OR+ PgR+                 | 119     | 66      | 146    | 74      | 265    | 70      |
| OR+ PgR−                 | 33      | 18      | 28     | 14      | 61     | 16      |
| OR+ PgR n.p.             | 24      | 13      | 20     | 10      | 44     | 12      |
| OR− PgR+                 | 5       | 3       | 3      | 2       | 8      | 2       |
| Local therapy            |         |         |         |         |         |         |
| MST, RT−                 | 66      | 36      | 67     | 34      | 133    | 35      |
| MST, RT+                 | 33      | 18      | 26     | 13      | 59     | 16      |
| BCS, RT−                 | 3       | 2       | 3      | 2       | 6      | 2       |
| BCS, RT+                 | 79      | 44      | 100    | 51      | 179    | 47      |
| Chemotherapy             |         |         |         |         |         |         |
| No                       | 119     | 66      | 142    | 72      | 261    | 69      |
| Yes                      | 62      | 34      | 55     | 28      | 117    | 31      |
| Switch to exemestane     |         |         |         |         |         |         |
| No switch                | 38      | 21      | 38     | 10      |        |         |
| Switch                   | 143     | 79      | 143    | 38      |        |         |
| Exe arm                  | 197     | 100     | 197    | 100     |        |         |

BCS, Breast conserving surgery; BMI, body mass index; Exe, exemestane; MST, mastectomy; n.p., not performed; OR, oestrogen receptor; PgR, progesterone receptor; RT, radiotherapy.

Breast density scores were low: approximately 75% of patients had a breast density score < 50% (78% of tamoxifen users, 74% of exemestane users), and only 4% of patients were categorised in the > 75% breast density group (5% of tamoxifen users, 3% of exemestane users). There were no differences in breast density classification at baseline between the treatment groups [coefficient 0.16 (standard error 0.17), trend test p = 0.28]. During treatment, no statistically significant changes in breast density over time were observed neither for patients using exemestane nor for patients using tamoxifen (p = 0.25 and p = 0.59, respectively). Furthermore, no statistically significant differences were seen in changes in breast density over time comparing patients using exemestane with those using tamoxifen (p = 0.25). The mean percentages of patients with equal, lower or higher breast densities after two years of endocrine therapy were 62%, 21% and 17%, respectively.

**Breast density and disease recurrence**

The relationship between breast density and the occurrence of a LRR, a DR and a CBC was analysed in the total group of patients as there were no differences in breast density between the two treatment regimens. Also, the baseline breast density
was used for analysis, as there were no statistically significant differences in breast density over time. At a median follow-up of six years (range 0–9 years), nine patients were diagnosed with a LRR (four in the sequential arm, five in the exemestane arm), 48 with a DR (28 in the sequential arm, 20 in the exemestane arm), and seven with a CBC (four in the sequential arm, three in the exemestane arm). There was no association between breast density score at baseline and the occurrence of a LRR (hazards ratio [HR] 0.88, 95% CI 0.45–1.68, p = 0.67), a DR (HR 1.02, 95% CI 0.77–1.35, p = 0.90), or CBC (HR 1.31, 95% CI 0.63–2.72, p = 0.48). If the changes in breast density were correlated to the occurrence of a LRR, a DR or CBC, qualitatively similar results were found: no association between change in breast density and the occurrence of an event.

**Discussion**

In the current analysis, in a large series of Dutch postmenopausal early breast cancer patients participating in the TEAM trial, we did not find a relevant change in breast density during both tamoxifen and exemestane as adjuvant endocrine treatment, nor an association between breast density and disease recurrence (LRR, DR, or CBC). Of note, the great majority of
postmenopausal women had a low breast density score at baseline, making it more difficult to find a relevant difference during our follow-up period of six years.

**AIs and breast density**

Most information on the influence of AIs on breast density in early breast cancer patients was previously only available for the non-steroidal AIs, anastrozole and letrozole, which is summarised in Table II. The effect of letrozole versus placebo has been studied in a subgroup of the NCIC CTG MA-17 trial, whereby postmenopausal breast cancer patients were randomised after five years of adjuvant tamoxifen therapy between letrozole or placebo [18]. No significant differences were found in breast density percentages over time for letrozole patients and no differences in percentage density change were observed between both groups. This was also found in patients included in the NCIC CTG MAP1 trial whereby postmenopausal women with or without prior invasive breast cancer were randomised between letrozole or placebo [14]. The effect of the other non-steroidal AI anastrozole in relation to breast density was investigated within the context of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial [16]. In the ATAC trial, early breast cancer patients were randomised between anastrozole, tamoxifen or the combination of both drugs. In the breast density side study of the ATAC trial, the percentage breast density reduction was small: 5.79% in the whole group, without significantly different patterns between the three arms. In another smaller study, including 54 postmenopausal early breast cancer patients taking anastrozole as adjuvant therapy, no significant reduction in breast density was observed after 12 months as well [17].

In the meantime, additional data on the effect of exemestane on breast density in postmenopausal early breast cancer patients has only recently been reported.
Table II. Studies of aromatase inhibitors and mammographic breast density in postmenopausal early breast cancer women.

| Study                  | Patients                | Therapy       | Mammogram | Measurement breast density | Scoring system      | Baseline PD | Change in PD | Other results                                      |
|------------------------|-------------------------|---------------|------------|----------------------------|---------------------|--------------|--------------|---------------------------------------------------|
| Cigler et al. 2010 [14]| Selected of the MaP1 trial | Letrozole n = 44, Placebo n = 23 | Digitised | Time points: 1st within 6 mo of random and density >25% of the breast | Cumulus 5 software | Letrozole vs. placebo Mean 39.6 vs. 40.0 | Letrozole vs. placebo Change at 12 mo: -1.74% vs. -0.24%, p = 0.61 | Change at 24 mo: -0.01% vs. -1.32%, p = 0.61 |
|                        |                         |               |            |                            |                     |              |              |                                                   |
|                        | 2000–2006               | Both for a year | CC-images | 2nd at 12 mo               | PD: area of dense tissue divided by the overall breast area × 100 |              |              |                                                   |
|                        |                         |               |            |                            |                     |              |              |                                                   |
|                        |                         |               |            |                            |                     |              |              |                                                   |
| Cuzick et al. 2006 [16]| Substudy of the ATAC trial | Anastrozole n = 53 | Analogue | 1st at diagnosis            | Visual assessment | 0: 6% | Reduction in breast density | Greater reduction in previous users of hormone replacement therapy |
|                        |                         |               |            |                            |                     |              |              |                                                   |
|                        |                         |               |            |                            |                     |              |              |                                                   |
|                        |                         | Tamoxifen n = 46 |            | 2nd 12 months after start ET | Ana: 5.94% (95% CI 2.74–9.15) |              |              |                                                   |
|                        |                         | Combination n = 46, MLO-images | 3rd 24 months after start ET | 26–50: 22% | Tam: 3.48% (95% CI 0.50–7.46) |              |              |                                                   |
|                        |                         | All for five years |            |                            |                     |              |              |                                                   |
| Early breast cancer    | 4th 60 months after start ET | 51–75: 30% |            |                            |                     |              |              |                                                   |
|                        |                         |               |            |                            |                     |              |              |                                                   |
| Kim et al. 2012 [2]    | Postmenopausal Single centre cohort in Korea | Tam 5 yrs n = 657 | Digital | 1st within 2 wks presurgery | PDR = prePD–postPD | >75: 6% | All groups: 35.77% | Larger PDR – Age < 50 |
|                        | Early breast cancer and DCIS, OR+ Pre- and postmenopausal | Tam 2–3 yrs → AI 3–2 yrs, n = 41 | CC-images | 2nd 13 mo (range 8–20) after start ET | Mean PDR 5.92% (–17.2–36.9) | Tam: -6.5% ± 7.1% | High baseline MD – long interval between start ET and follow-up mammogram |
|                        |                         | Tam 5yr → AI n = 192 |            |                            |                     |              |              |                                                   |
|                        |                         | AI 5 yrs n = 175 |            |                            |                     |              |              |                                                   |

(Continued)
| Study     | Patients | Therapy | Mammo- | Measurement breast density | Scoring system | Baseline PD | Change in PD | Other results |
|-----------|----------|---------|--------|---------------------------|----------------|-------------|--------------|---------------|
| Ko et al. 2013 [5] | Single centre cohort in Korea | Tam for at least 2 yr | Digital | Time points | Visual assessment | <50%: 13% | <50%: 31% | Patients with PDR ≥ 65% lower risk of recurrence that patients who did not. |
| Ko et al. 2013 [5] | n = 1066 | 1st before surgery | 50-75%: 47% | 50-75%: 44% | 2nd 19 mo (range 10–34) after start ET | PDR = downgrading of the postPD grade with the prePD as a reference | >75%: 40% | >75%: 26% | Large PDR |
| Prowell et al. 2011 [17] | Prospective single-arm single-institution | Anastrozole for 12 months | Digitised | Time points: | Cumulus software | Median: 13.4% | Median 6 mo: 13.0% | Early breast cancer, OR+ |
| Vechom et al. 2007 [18] | Substudy of the MA.17 trial | Letrozole n = 35 | Digitised | Time points | Computer-assisted thresholding programme | Letrozole vs. placebo | Letrozole vs. placebo | Early breast cancer, OR/ PgR+ |
| Vechom et al. 2007 [18] | Placebo n = 33 | 1st Before randomisation | Mean 18.5% vs. 20% | Letrozole vs. placebo | Placebo |
| Vechom et al. 2007 [18] | 1998–2003 | CC-images | 2nd Between 9 and 15 mo after randomisation | PD: dense area divided by total area × 100 | Mean 18.5% vs. 20% | Letrozole vs. placebo | Placebo |

(Continued)
from a matched case-control study including, on one hand, patients taking either anastrozole or exemestane, and on the other hand, healthy postmenopausal women from a screening cohort (Table II) [19]. A reduction in mammographic breast density of at least 5% was seen in 14% of patients after an average of 10 months of AI therapy, without differences between exemestane and anastrozole. These findings are in accordance with previous data.

Although our and the above mentioned studies on the effect of AIs on breast density are not completely comparable, the results from the current analyses in Dutch TEAM patients are consistent with observations of other AI studies on this issue finding either a small or no change in breast density over time in postmenopausal early breast cancer patients using an AI as adjuvant therapy. It is possible that AIs are not associated with a change in breast density over time, especially when the initial breast density score is low, as was the case in our patient cohort. However, it is possible that a longer follow-up is necessary. However, no significant change in breast density was observed in the ATAC study with a follow-up of five years.

Breast density and recurrence

We did not observe a correlation between breast density and LRR, DR, or CBC in both treatment groups. To date, an association between change in breast density and altered breast cancer risk, disease recurrence or survival in women using tamoxifen has been reported in four retrospective series [1–3,5]. The oldest report concerns a subsequent nested case-control study (123 breast cancer cases, 942 controls) within the first International Breast Cancer Intervention Study (IBIS-I). The IBIS-I chemoprevention study was designed to evaluate the role of tamoxifen for breast cancer risk reduction. In the nested case-control study, mammographic breast density was visually assessed at baseline and after 12–18 months by one single reader and classified in groups of 5% increments. In tamoxifen users who experienced a breast density reduction of at least 10%, a 63% reduction in breast cancer risk was observed whereas no risk reduction was observed in tamoxifen users with less than 10% reduction in mammographic breast density.

The second study concerns a cohort study including 1065 Korean hormone receptor-positive breast
cancer patients who used at least two years of adjuvant endocrine therapy (80% using tamoxifen) [2]. It was found that recurrence rates (LRR and/or DR) were more than two times lower in women with a breast density reduction of >10% compared with those without breast density reduction. A reduction in mammographic density was predominantly found in younger women (<50 years) with a higher pre-treatment breast density. Differences explaining the divergent results between this and our study are the method of breast density measurement (percentage breast density vs. density category), the different patient populations (Korean vs. Caucasian), the different age distribution (age <50 years: 64% vs. only 3%), the percentage of chemotherapy given (77% vs. 31%), and the proportion of women taking an AI (16% vs. 50%).

The third study also concerns Korean hormone receptor positive early breast cancer patients (mean age 45 years) who received at least two years of adjuvant therapy with tamoxifen [5]. Almost 70% of the patients received chemotherapy. Patients with a reduction in breast density after an average of 19 months of tamoxifen treatment had a lower risk of recurrence than patients who did not show a reduction in breast density. However, this effect was only seen in premenopausal patients.

The fourth article reports the data of a population-based case-control study performed in postmenopausal women with early breast cancer from the Swedish Cancer Register diagnosed between 1993 and 1995 [3]. Patients with available mammograms of the contralateral breast approximately one year after diagnosis and 6–36 months later were eligible. Patients with the lowest mammographic densities (the quintile with the smallest dense area) were excluded as a further reduction seemed unlikely and could not be reliably measured. Eventually, 974 patients were included in the study: 474 tamoxifen users (median time of tamoxifen treatment: 60 months) and 500 women not using endocrine therapy. Women with a relative density reduction of >20% had a reduced risk of breast cancer death of 50% (HR 0.50; 95% CI 0.27–0.93) compared with women with unchanged mammographic density. Importantly, this survival advantage was only observed in patients using tamoxifen and neither baseline nor follow-up absolute breast density was significantly associated with outcome. The same authors found that reduction of breast density during adjuvant therapy was predictive for a decreased occurrence of CBC [4].

Summarising those studies, the outcome points out to a decrease in breast densities by tamoxifen treatment in predominantly premenopausal women but also in postmenopausal women with initially ‘sufficient’ breast density. At the same time, breast density reduction during treatment coincides with a better prognosis. Of course, if initial breast density is negligible (most occurring in postmenopausal women), no further reduction may be expected with tamoxifen therapy. Second, a decreasing breast density during treatment with tamoxifen may be interpreted as an expression of compliance with the therapy or lack of a poor CYP-2D6 metaboliser status and for this reason may be a marker of effectiveness [22,23]. Finally, although different effects of tamoxifen depend in part to the endocrine status of the recipient, the net effects of this drug on breast tissue are anti-oestrogenic in both pre- and postmenopausal women [24].

In general, the effects of (non)steroidal AIs on (postmenopausal) breast density are in the same direction as for tamoxifen, i.e. decreasing breast density [14–19]. Although much less data are available about the prognostic significance of decreasing breast density by AIs as compared this data of tamoxifen. The data of Kim et al. [2] strongly suggest that AIs have a same or even stronger beneficial effect. Small differences in the degree of inhibiting aromatase by different AIs and androgenic effects of exemestane, may result in differences in the efficacy of those drugs [25,26]. No comparative data about the effects of different AIs on breast density are available.

**Strengths and limitations**

Our study has several strengths. First, the raters were blinded to treatment allocation and dates of mammograms. Second, there was a satisfactory interclass coefficient between the three independent radiologists. Third, the study included a sufficiently large sample size of postmenopausal hormone-sensitive early breast cancer patients. Moreover, the clinical, pathological and follow-up data were well documented.

There are, however, also limitations to be considered. First, the breast density was scored in one of six density categories with discrete scores and these scores were not equally distributed. Also, by using this classification method, we were not able to detect small changes in the patient cohort. Second, the breast density percentage was scored according to the visual assessment technique using analogue mammograms, which is a subjective and semi-quantitative measurement. Of note however, all other methods currently used to assess mammographic breast density on analogue mammograms also depend upon trained observers and therefore are subjective, even when digitised and provided with a fully automated user-assisted system [27]. Our analysis is a comparative study and therefore we consider these limitations of no effect on the final results. At last, due to the relatively few breast cancer events, the statistical power of this study is relatively low to find an impact on prognosis.

For future studies, alternative techniques, including the magnetic resonance imaging and ultrasound
tomography, may be more reliable in determining small changes in breast density, but these techniques are not yet validated [28]. Also, digital mammography has currently been introduced worldwide, therefore volumetric digital techniques will become available [29,30].

Conclusions

The in general low breast density scores of Dutch postmenopausal breast cancer patients participating in the TEAM trial did not significantly change over time applying for both exemestane and tamoxifen users. Also, we did not observe an association between breast density score and the risk for recurrent disease. Although the various available studies are not completely comparable, our data are consistent with the results of previously reported studies on this issue, and suggest that breast density cannot be used as a predictive factor (biomarker) for efficacy of adjuvant endocrine therapy in postmenopausal hormone-sensitive early breast cancer patients. In view of the relevance of this topic and the increased numbers of postmenopausal women using endocrine agents after early breast cancer or to prevent the development of (contralateral) breast cancer, more research into factors contributing to breast density and into more sensitive techniques to measure small differences in breast density over time are warranted.

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Supplementary material available online

Supplementary Appendix available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.964809