

RESEARCH

# Mammographic density change in a cohort of premenopausal women receiving tamoxifen for breast cancer prevention over five years: supplementary material

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## Eligibility criteria for TAM-PREV

To be eligible women were required to be: aged 33-46y; premenopausal; attending the Family History Clinic at the Nightingale & Genesis Prevention Centre, Manchester UK; and at moderate or high-risk as defined by a Tyrer-Cuzick lifetime risk of  $\geq 17\%$  (version 7, [1, 2]) as per the UK national institute of clinical excellence guidelines [3]. They also had to have a negative pregnancy test; be willing to use a non-hormonal form of contraception (Mirena coil was acceptable) and a normal mammogram no more than 12 weeks prior to joining the study. Women were ineligible if: any previous cancer in the past 5 years (except basal cell carcinoma or in situ cancer of the cervix); current or previous tamoxifen or raloxifene or other Selective Oestrogen Receptor Modulators use for more than 3 months prior to participation in study; had a prophylactic mastectomy or are planning to have this procedure; pregnancy or breastfeeding; use of hormonal contraceptives for the last 3 months (Oral Contraceptive Pill, Depo provera and Implanon/Nexplanon, Mirena coil was permitted). Women were not eligible if they had a bilateral oophorectomy; hypersensitivity to tamoxifen or any of its ingredients; personal or close family history of thromboembolism (defined as at least 2 affected relatives with 1 being a 1st degree relative); were using coumarin type anticoagulants, droperidol or bupropion; had Type 1 or 2 diabetes or symptomatic gynaecological problems requiring medication.

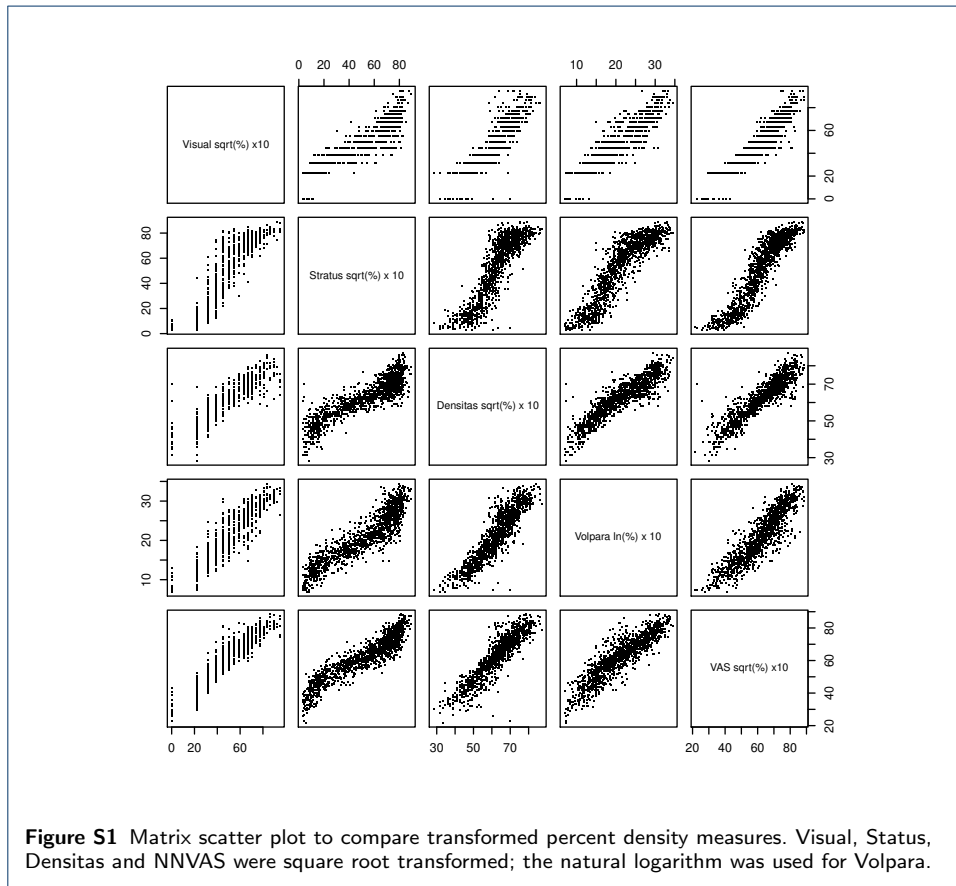
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### Supplementary material



**Table S1** Baseline characteristics of participants in analysis sample A (all women included in the study).

|                          | Tamoxifen     |                             | No tamoxifen  |                             |
|--------------------------|---------------|-----------------------------|---------------|-----------------------------|
|                          | N (% unknown) | Summary*                    | N (% unknown) | Summary*                    |
| Age (y)                  | 126 (0%)      | 42 (39-45, 33-47)           | 172 (0%)      | 41 (39-44, 31-47)           |
| BMI (kg/m <sup>2</sup> ) | 126 (0%)      | 25.8 (22.0-29.8, 18.0-51.0) | 145 (16%)     | 24.9 (22.3-29.9, 17.9-48.0) |
| Lifetime risk (%)        | 126 (0%)      | 33.3 (27.1-33.3, 17.0-80.0) | 172 (0%)      | 33.3 (25.0-33.3, 14.0-80.0) |
| Parous (n, %)            | 126 (0%)      | 103 (82%)                   | 172 (0%)      | 132 (77%)                   |
| Age first born (y)       | 95 (25%)      | 27.0 (22.0-32.0, 17.0-42.0) | 132 (23%)     | 27.0 (21.0-31.0, 15.0-40.0) |

\* summary gives median (interquartile range, range) for continuous variables and n (%) for parous.

**Table S2** Baseline characteristics of participants in analysis sample B (women with 1y density change measured). Footnote: \*summary gives median (interquartile range, range) for continuous variables and n (%) for parous; TP: Tamoxifen; FH: No Tamoxifen

|                          | Tamoxifen     |                             | No tamoxifen  |                             |
|--------------------------|---------------|-----------------------------|---------------|-----------------------------|
|                          | N (% unknown) | Summary*                    | N (% unknown) | Summary*                    |
| Age (y)                  | 94 (0%)       | 43 (40-45, 33-47)           | 112 (0%)      | 40 (38-44, 31-47)           |
| BMI (kg/m <sup>2</sup> ) | 94 (0%)       | 26.0 (22.0-29.8, 18.0-46.0) | 95 (15%)      | 24.9 (22.2-30.0, 19.2-41.2) |
| TC lifetime? (%)         | 94 (0%)       | 33.3 (33.3-33.3, 17.0-80.0) | 112 (0%)      | 33.3 (25.0-33.3, 14.0-80.0) |
| Parous (n, %)            | 94 (0%)       | 71 (76%)                    | 112 (0%)      | 88 (79%)                    |
| Age first child (y)      | 67 (29%)      | 27.0 (22.5-33.0, 18.0-39.0) | 88 (21%)      | 26.0 (20.8-30.2, 15.0-40.0) |

\* summary gives median (interquartile range, range) for continuous variables and n (%) for parous.

**Table S3** Baseline characteristics of participants excluded from analysis sample B (women with 1y density change measured). Footnote: \*summary gives median (interquartile range, range) for continuous variables and n (%) for parous; TP: Tamoxifen; FH: No Tamoxifen

|                          | Tamoxifen     |                             | No tamoxifen  |                             |
|--------------------------|---------------|-----------------------------|---------------|-----------------------------|
|                          | N (% unknown) | Summary*                    | N (% unknown) | Summary*                    |
| Age (y)                  | 32 (0%)       | 42 (38-44, 34-46)           | 60 (0%)       | 42 (40-44, 34-47)           |
| BMI (kg/m <sup>2</sup> ) | 32 (0%)       | 25.0 (22.0-29.2, 18.7-51.0) | 50 (17%)      | 24.6 (22.7-28.8, 17.9-48.0) |
| TC lifetime? (%)         | 32 (0%)       | 33.3 (25.0-40.0, 17.0-50.0) | 60 (0%)       | 33.3 (25.0-33.3, 15.0-50.0) |
| Parous (n, %)            | 32 (0%)       | 32 (100%)                   | 60 (0%)       | 44 (73%)                    |
| Age first child (y)      | 28 (12%)      | 26.0 (22.0-31.2, 17.0-42.0) | 44 (27%)      | 27.0 (22.0-31.0, 16.0-39.0) |

\* summary gives median (interquartile range, range) for continuous variables and n (%) for parous.

**Table S4** Baseline characteristics of participants in analysis sample C (women with 1y and 2y density change measured). Footnote: \*summary gives median (interquartile range, range) for continuous variables and n (%) for parous; TP: Tamoxifen; FH: No Tamoxifen

|                          | Tamoxifen     |                             | No tamoxifen  |                             |
|--------------------------|---------------|-----------------------------|---------------|-----------------------------|
|                          | N (% unknown) | Summary*                    | N (% unknown) | Summary*                    |
| Age (y)                  | 70 (0%)       | 43 (40-44, 33-47)           | 89 (0%)       | 40 (38-44, 31-47)           |
| BMI (kg/m <sup>2</sup> ) | 70 (0%)       | 26.0 (22.2-29.0, 18.0-46.0) | 76 (15%)      | 26.1 (22.6-30.0, 19.2-41.2) |
| TC lifetime? (%)         | 70 (0%)       | 33.3 (27.1-33.3, 17.0-50.0) | 89 (0%)       | 33.3 (25.0-33.3, 14.0-80.0) |
| Parous (n, %)            | 70 (0%)       | 54 (77%)                    | 89 (0%)       | 74 (83%)                    |
| Age first child (y)      | 50 (29%)      | 28.0 (23.0-33.0, 19.0-37.0) | 74 (17%)      | 27.5 (21.0-31.0, 15.0-40.0) |

\* summary gives median (interquartile range, range) for continuous variables and n (%) for parous.

**Table S5** Baseline characteristics of participants excluded from analysis sample C (women with 1y and 2y density change), out of all women included in the study (analysis sample A). Footnote: \*summary gives median (interquartile range, range) for continuous variables and n (%) for parous; TP: Tamoxifen; FH: No Tamoxifen

|                          | Tamoxifen     |                             | No tamoxifen  |                             |
|--------------------------|---------------|-----------------------------|---------------|-----------------------------|
|                          | N (% unknown) | Summary*                    | N (% unknown) | Summary*                    |
| Age (y)                  | 56 (0%)       | 42 (38-45, 33-46)           | 83 (0%)       | 42 (39-44, 32-47)           |
| BMI (kg/m <sup>2</sup> ) | 56 (0%)       | 25.0 (22.0-33.2, 18.7-51.0) | 69 (17%)      | 24.0 (21.9-29.2, 17.9-48.0) |
| TC lifetime? (%)         | 56 (0%)       | 33.3 (31.2-40.0, 17.0-80.0) | 83 (0%)       | 33.3 (33.3-33.3, 15.0-80.0) |
| Parous (n, %)            | 56 (0%)       | 49 (88%)                    | 83 (0%)       | 58 (70%)                    |
| Age first child (y)      | 45 (20%)      | 26.0 (22.0-32.0, 17.0-42.0) | 58 (30%)      | 26.5 (21.2-30.0, 16.0-39.0) |

\* summary gives median (interquartile range, range) for continuous variables and n (%) for parous.

**Table S6** Repeated measures correlation (between women) between density measures for tamoxifen group, analysis sample A (all women included in the study).

|                    | Visual % | Visual (unblind) % | Stratus % | Densitas % | Volpara % | Stratus DA | Densitas DA | Volpara DV | Densitas BA | Volpara TV |
|--------------------|----------|--------------------|-----------|------------|-----------|------------|-------------|------------|-------------|------------|
| Visual (unblind) % | 0.94     |                    |           |            |           |            |             |            |             |            |
| Stratus %          | 0.87     | 0.80               |           |            |           |            |             |            |             |            |
| Densitas %         | 0.88     | 0.85               | 0.92      |            |           |            |             |            |             |            |
| Volpara %          | 0.89     | 0.85               | 0.91      | 0.91       |           |            |             |            |             |            |
| Stratus DA         | 0.73     | 0.69               | 0.89      | 0.82       | 0.71      |            |             |            |             |            |
| Densitas DA        | 0.20     | 0.23               | 0.24      | 0.30       | 0.07      | 0.61       |             |            |             |            |
| Volpara DV         | 0.48     | 0.53               | 0.47      | 0.54       | 0.40      | 0.72       | 0.84        |            |             |            |
| Densitas BA        | -0.42    | -0.37              | -0.44     | -0.43      | -0.57     | -0.05      | 0.72        | 0.42       |             |            |
| Volpara TV         | -0.50    | -0.42              | -0.53     | -0.48      | -0.68     | -0.13      | 0.60        | 0.40       | 0.91        |            |
| NNVAS %            | 0.89     | 0.84               | 0.94      | 0.93       | 0.91      | 0.88       | 0.35        | 0.59       | -0.34       | -0.43      |

DA: dense area; DV: dense volume; BA: breast area; TV total volume

**Table S7** Linear mixed model fit, main effect estimates (95%CI)

|             | Intercept           | Age (5y)              | BMI (5kg/m <sup>2</sup> ) | Tamoxifen (Y=1, N=0) | Year 1 (Y=1, N=0)   | Time (year 2+) (y)   | (Year 1):(Tamoxifen) interaction | (Time, year 2+):(Tamoxifen) interaction |
|-------------|---------------------|-----------------------|---------------------------|----------------------|---------------------|----------------------|----------------------------------|---|
| Volpara %   | 9.0 ( 1.8 to 16.3)  | -7.2 (-43.8 to 29.3)  | -33.7 (-38.5 to -28.9)    | 7.0 (-3.8 to 17.9)   | -3.1 (-4.4 to -1.8) | 1.0 (-1.7 to 3.6)    | -17.1 (-21.4 to -12.8)           | -6.2 (-8.2 to -4.2)                     |
| Stratus %   | 7.8 ( 1.0 to 14.5)  | -14.4 (-47.3 to 18.6) | -26.8 (-31.2 to -22.3)    | 3.4 (-6.7 to 13.5)   | -1.3 (-2.4 to -0.1) | 0.2 (-2.1 to 2.5)    | -18.0 (-21.8 to -14.3)           | -2.3 (-4.2 to -0.5)                     |
| Densitas %D | 11.8 ( 2.2 to 21.3) | 2.4 (-45.7 to 50.4)   | -34.7 (-41.0 to -28.3)    | 5.0 (-9.4 to 19.3)   | -1.9 (-3.9 to 0.0)  | -1.2 (-5.5 to 3.1)   | -24.9 (-31.8 to -17.9)           | -6.9 (-10.0 to -3.9)                    |
| NNVAS %     | 7.2 (-2.1 to 16.4)  | -15.3 (-61.0 to 30.5) | -28.3 (-34.4 to -22.2)    | 4.0 (-9.8 to 17.9)   | -0.1 (-1.5 to 1.3)  | -0.8 (-4.0 to 2.4)   | -21.7 (-26.9 to -16.5)           | -5.0 (-7.2 to -2.7)                     |
| Volpara DV  | 3.0 (-7.3 to 13.2)  | 4.8 (-45.3 to 54.9)   | 7.7 ( 1.1 to 14.4)        | -6.2 (-21.7 to 9.2)  | 2.4 ( 0.5 to 4.2)   | -6.3 (-10.4 to -2.2) | -22.8 (-29.5 to -16.2)           | -6.0 (-8.8 to -3.1)                     |
| Stratus DA  | 6.2 (-3.9 to 16.3)  | -14.4 (-62.8 to 34.0) | -17.7 (-24.1 to -11.2)    | 0.8 (-14.3 to 16.0)  | -0.9 (-2.4 to 0.7)  | 0.1 (-3.1 to 3.2)    | -27.3 (-32.4 to -22.2)           | -2.6 (-5.1 to -0.1)                     |
| Densitas DA | -1.8 (-12.7 to 9.0) | 22.1 (-31.9 to 76.1)  | 24.1 ( 16.9 to 31.3)      | -8.8 (-25.1 to 7.6)  | 0.0 (-1.9 to 1.9)   | 0.3 (-4.0 to 4.6)    | -25.7 (-32.7 to -18.7)           | -4.6 (-7.7 to -1.6)                     |

DA: dense area; DV: dense volume

**Table S8** Linear mixed model fit estimated variance components (95%CI).

|             | Intercept           | Time (y)          | Intercept:Time (correlation) | Residual            | ICC                 |
|-------------|---------------------|-------------------|------------------------------|---------------------|---------------------|
| Volpara %   | 47.1 (43.5 to 51.2) | 4.3 ( 3.5 to 5.1) | -0.1 (-0.3 to 0.1)           | 14.1 (13.4 to 14.9) | 0.92 (0.90 to 0.93) |
| Stratus %   | 44.0 (40.7 to 47.8) | 4.1 ( 3.4 to 4.9) | -0.3 (-0.4 to -0.1)          | 12.2 (11.6 to 12.8) | 0.93 (0.90 to 0.94) |
| Densitas %  | 61.0 (56.2 to 66.5) | 5.2 ( 3.9 to 6.5) | 0.0 (-0.2 to 0.3)            | 23.3 (22.2 to 24.5) | 0.87 (0.83 to 0.90) |
| NNVAS %     | 60.2 (55.7 to 65.4) | 3.8 ( 2.7 to 4.8) | -0.3 (-0.5 to -0.1)          | 17.4 (16.6 to 18.4) | 0.92 (0.90 to 0.93) |
| Volpara DV  | 66.5 (61.4 to 72.2) | 5.1 ( 3.8 to 6.3) | -0.3 (-0.5 to -0.1)          | 22.3 (21.2 to 23.4) | 0.90 (0.87 to 0.91) |
| Stratus DA  | 66.4 (61.4 to 72.0) | 5.7 ( 4.7 to 6.7) | -0.4 (-0.5 to -0.2)          | 16.8 (15.9 to 17.6) | 0.94 (0.91 to 0.95) |
| Densitas DA | 70.4 (65.0 to 76.5) | 5.2 ( 3.8 to 6.5) | -0.1 (-0.3 to 0.1)           | 23.4 (22.3 to 24.6) | 0.90 (0.85 to 0.93) |

DA: dense area; DV: dense volume; ICC: intra-class correlation coefficient; CI: confidence interval

**Table S9** Linear model fit, fixed effects (95%CI), tamoxifen group only.

|             | Intercept           | Age (5y)              | BMI (5kg/m <sup>2</sup> ) | Year 1                 | Time (year 2+)       |
|-------------|---------------------|-----------------------|---------------------------|------------------------|----------------------|
| Volpara %   | 14.4 ( 5.0 to 23.6) | 18.4 (-40.6 to 77.4)  | -27.9 (-34.6 to -21.2)    | -7.0 (-10.9 to -3.0)   | -9.3 (-10.9 to -7.6) |
| Stratus %   | 9.0 ( 0.5 to 17.5)  | 0.9 (-52.5 to 54.4)   | -20.6 (-26.7 to -14.6)    | -14.2 (-17.9 to -10.6) | -3.7 ( -5.0 to -2.3) |
| Densitas %  | 15.6 ( 2.8 to 28.2) | 37.4 (-45.4 to 120.2) | -29.1 (-38.1 to -20.0)    | -17.3 (-24.0 to -10.6) | -8.9 (-11.3 to -6.4) |
| NNVAS %     | 8.9 ( -3.1 to 20.7) | 6.2 (-67.9 to 80.3)   | -21.4 (-29.7 to -13.1)    | -17.4 (-22.4 to -12.5) | -5.1 ( -6.7 to -3.4) |
| Volpara DV  | -3.0 (-15.2 to 9.3) | 56.3 (-18.3 to 130.7) | 11.2 ( 3.0 to 19.4)       | -25.6 (-31.0 to -20.2) | -3.6 ( -5.6 to -1.6) |
| Stratus DA  | 5.3 ( -6.9 to 17.4) | 9.3 (-64.1 to 82.7)   | -11.7 (-19.8 to -3.5)     | -23.8 (-28.5 to -19.2) | -3.5 ( -5.2 to -1.7) |
| Densitas DA | -9.9 (-22.6 to 2.9) | 33.5 (-46.1 to 113.3) | 23.3 ( 14.1 to 32.5)      | -20.9 (-27.6 to -14.1) | -4.7 ( -7.0 to -2.4) |

DA: dense area; DV: dense volume

**Table S10** Linear mixed model fit estimated variance components (95%CI), tamoxifen group only.

|             | Intercept           | Time (y)          | Intercept:Time (correlation) | Residual            |
|-------------|---------------------|-------------------|------------------------------|---------------------|
| Volpara %   | 47.9 (42.3 to 54.6) | 4.8 ( 3.6 to 6.2) | -0.3 (-0.6 to 0.0)           | 13.6 (12.6 to 14.7) |
| Stratus %   | 44.0 (38.9 to 50.3) | 3.5 ( 2.4 to 4.7) | -0.4 (-0.6 to 0.0)           | 12.7 (11.8 to 13.8) |
| Densitas %  | 64.5 (56.8 to 73.8) | 5.4 ( 3.2 to 7.6) | 0.0 (-0.3 to 0.4)            | 23.4 (21.7 to 25.4) |
| NNVAS %     | 61.9 (54.7 to 70.6) | 3.4 ( 1.3 to 5.2) | -0.5 (-1.0 to -0.1)          | 17.2 (15.9 to 18.7) |
| Volpara DV  | 63.5 (56.1 to 72.5) | 5.0 ( 3.4 to 6.8) | -0.6 (-0.8 to -0.3)          | 18.8 (17.5 to 20.4) |
| Stratus DA  | 63.8 (56.5 to 72.7) | 4.9 ( 3.5 to 6.5) | -0.6 (-0.8 to -0.3)          | 16.1 (14.9 to 17.4) |
| Densitas DA | 64.6 (56.8 to 74.0) | 4.6 ( 2.1 to 6.9) | -0.4 (-0.7 to 0.1)           | 23.7 (21.9 to 25.7) |

DA: dense area; DV: dense volume

**Table S11** Number of women and total number of measures that agree on breast density measure change (Volpara %, Stratus %, Densitas %, NNVAS %) above cutpoint at year 1 (T0) or year 2 (T2) compared with baseline (T0).

|                     | No change by any measure | Only one measure | Two measures | Three measures | All agree on change | Total number women |
|---------------------|--------------------------|------------------|--------------|----------------|---------------------|--------------------|
| 1y change (T0 - T1) | 6 (9%)                   | 17 (24%)         | 12 (17%)     | 16 (23%)       | 19 (27%)            | 70 (100%)          |
| 2y change (T0 - T2) | 8 (11%)                  | 8 (11%)          | 13 (19%)     | 19 (27%)       | 22 (31%)            | 70 (100%)          |

T0: entry; T1: follow-up at 1y; T2: follow-up at 2y.

**Table S12** Agreement in density change between pairs of density measures (n=70 in total from tamoxifen group, analysis sample (C)). (a) compares between baseline (T0) and first followup at one year (T1); (b) compares change between baseline and two years later (T2); and (c) considers the concordance between change measured at one year (T0 - T1) and two years (T0 - T2), including for the same measure of breast density.

| Comparison                 | Stratus %   | Densitas %  | Volpara %   | NNVAS %     |
|----------------------------|-------------|-------------|-------------|-------------|
| (a) T1 - T0                |             |             |             |             |
| Stratus %                  |             | 28/60 (47%) | 29/54 (54%) | 30/52 (58%) |
| Densitas %                 |             |             | 31/52 (60%) | 28/54 (52%) |
| Volpara %                  |             |             |             | 28/49 (57%) |
| (b) T2 - T0                |             |             |             |             |
| Stratus %                  |             | 29/58 (50%) | 36/57 (63%) | 39/54 (72%) |
| Densitas %                 |             |             | 31/55 (56%) | 31/55 (56%) |
| Volpara %                  |             |             |             | 36/56 (64%) |
| (c) (T1 - T0) vs (T2 - T0) |             |             |             |             |
| Stratus %                  | 36/55 (65%) | 25/59 (42%) | 32/58 (55%) | 32/58 (55%) |
| Densitas %                 |             | 33/51 (65%) | 32/58 (55%) | 32/58 (55%) |
| Volpara %                  |             |             | 31/54 (57%) | 31/54 (57%) |
| NNVAS %                    |             |             |             | 32/52 (62%) |