Comparison of the diagnostic workup of women referred at non-blinded or blinded double reading in a population-based screening mammography programme in the south of the Netherlands

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Background: To determine whether referred women experience differences in diagnostic workup at non-blinded or blinded double reading of screening mammograms.

Methods: We included a consecutive series of respectively 42,996 and 44,491 screens, double read either in a non-blinded or blinded manner between 2009 and 2011. This reading strategy was alternated on a monthly basis.

Results: The overall ultrasound-guided core needle biopsy (CNB) rate and stereotactic CNB (SCNB) rate per 1000 screens were higher at blinded than at non-blinded reading (7.5 vs 6.0, \( P = 0.008 \) and 8.1 vs 6.6, \( P = 0.009 \)). Among women with benign workup, these rates were higher at blinded reading (2.6 vs 1.4, \( P < 0.001 \) and 5.9 vs 4.7, \( P = 0.013 \)). The benign biopsy rates were higher at blinded double reading (\( P < 0.001 \)), whereas the positive predictive value of biopsy did not differ (\( P = 0.103 \)).

Conclusions: Blinded double-reading results in higher overall CNB and SCNB rates than non-blinded double reading, as well as a higher benign biopsy rate.

Reduction in breast cancer mortality is attributed to the combination of earlier breast cancer detection through mammography screening and substantial improvements in breast cancer treatment (Kalager et al, 2010; van Schoor et al, 2011; Mandelblatt et al, 2013). Screening mammograms can be assessed in several ways, for example, by single reading or double reading by certified screening radiologists. European guidelines consider double reading by radiologists as the gold standard for the assessment of screening mammograms, as this screening strategy significantly increases the cancer detection rate when compared with single reading (Gur et al, 2004; Duijm et al, 2009). In most programmes, including the Dutch nationwide breast cancer screening programme, independent double reading rather than blinded double

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reading is used for the assessment of screening mammograms. We recently compared these two reading strategies and found that blinded double reading increased the sensitivity of breast cancer detection, at the expense of an increased referral rate and decreased positive predictive value (PPV) of referral (Klompenhouwer et al., 2015). However, the influence of replacement of non-blinded by blinded double reading on the use of diagnostic resources at the workup of screen-positive women is unknown. We therefore compared the utilisation of breast imaging and biopsy techniques in women referred at blinded or non-blinded double reading in a population-based screening mammography programme in the south of the Netherlands.

**MATERIALS AND METHODS**

**Study population.** We used the information of respectively 42,996 and 44,491 full-field digital screens that had been double read, either in a non-blinded or blinded manner between July 2009 and July 2011 (Klompenhouwer et al., 2015).

**Screening procedure and referral.** Details of the nationwide and local breast cancer screening programme have been described previously (Fracheboud et al., 2001; Nederend et al., 2012; Klompenhouwer et al., 2015). In brief, free biennial screening mammography is offered to women aged 50–75 years. Before each screening examination, the woman completes a short questionnaire with questions about any previous breast surgery or breast malignancy and the use of hormone replacement therapy. Screening mammograms were double read in either a blinded (second reader was not informed about the first reader’s decision) or non-blinded (second reader was informed about the first reader’s decision). This reading strategy was alternated on a monthly basis. Mammograms of previous screening rounds were always available for comparison.

Women with a screening Breast Imaging Reporting and Data System (BI-RADS) category 0, 4 or 5 were referred to a dedicated breast unit (D’Orsi et al., 2003).

**Diagnostic work-up and follow-up of referred women.** A total of 15 regional and university hospitals were involved in the assessment of screen-positive women. The type of further diagnostic evaluation depended on the workup protocols of the various hospitals and could include breast tomosynthesis, (3D) breast ultrasonography, magnetic resonance imaging, ultrasound-guided fine-needle aspiration biopsy (FNAB) or core needle biopsy (CNB), stereotactic CNB (SCNB) or surgical excision biopsy. BI-RADS 0 lesions received additional imaging and biopsy if necessary. BI-RADS 4 and 5 lesions were routinely biopsied, whereas BI-RADS 3 lesions were either biopsied or followed up. Data on mammographic breast density and family history of breast cancer were extracted from the radiological and surgical records, respectively. The follow-up period of all referred women was 2 years (until the next biennial screen).

**Statistical analysis.** Descriptive statistics were performed using Statistical Package for Social Science 17.0 (SPSS Inc. Chicago, IL, USA). A Fisher’s exact test or \( \chi^2 \)-test was used to test differences in biopsy rates and workup procedures at non-blinded and blinded double reading.

**RESULTS**

**Overall workup procedures after referral.** A total of 1235/42,996 (2.9%) and 1474/44,491 (3.3%) women had been referred, respectively, at non-blinded and blinded double reading. Baseline characteristics for screened and referred women were comparable for the two reading strategies (Table 1). At both reading strategies, workup consisted of additional breast-imaging procedures only in about half of referrals, whereas the other half underwent a combination of additional breast imaging plus biopsy (\( P = 0.164 \); Table 2). The vast majority of biopsy procedures in both groups consisted of either CNB or SCNB, whereas <3% of referred women underwent FNAB and surgical biopsy was hardly used for diagnostic purposes. The distribution of various combinations of assessment at workup was also comparable, but the ultrasound-guided CNB rate and SCNB rate per 1000 screens were lower at non-blinded than at blinded double reading (6.0 vs 7.5, \( P = 0.008 \) and 6.6 vs 8.1, \( P = 0.009 \), respectively).

**Work-up in false-positive referrals.** A total of 951 (77.0% of referrals) and 1149 (80.0% of referrals) women experienced a false-positive referral at non-blinded and blinded double reading, respectively (Table 3). The distribution of type of assessment differed between both groups, with a larger proportion of women evaluated by additional imaging only at non-blinded double reading (65.0% vs 60.7%, \( P = 0.046 \)) and a larger proportion of CNB procedures at blinded double reading (9.9% vs 6.5%, \( P = 0.005 \)). Almost all diagnostic surgical biopsies following referral had been performed in false-positive cases, but the false-positive surgical biopsy rate was still very low at both reading strategies (0.37 and 0.34 per 1000 screens at non-blinded and at blinded double reading, respectively). The CNB rate (\( P < 0.001 \)) and SCNB rate (\( P = 0.013 \)) per 1000 screens were higher at blinded than at non-blinded reading.

**Overall biopsy rates and PPV of biopsy.** The two reading strategies showed comparable PPV of biopsy (46.3% vs 41.9% at non-blinded and blinded double reading, respectively, \( P = 0.103 \); Table 4). Both the overall biopsy rate and benign biopsy rate per 1000 screens were higher at blinded double reading (17.4 vs 14.3, \( P < 0.001 \) and 10.1 vs 7.7, \( P < 0.001 \), respectively), as well as the proportion of women who underwent biopsy as part of a false-positive referral (39.3% vs 34.7%, \( P = 0.032 \)).

**DISCUSSION**

We found that blinded double reading resulted in significantly higher CNB and SCNB rates than non-blinded double reading, as well as a significantly higher benign biopsy rate. A larger proportion of women at benign work-up were evaluated merely by additional imaging at non-blinded double reading, whereas a larger fraction of referrals underwent CNB procedures at blinded double reading. The PPV of biopsy was comparable for both reading strategies.

The current study included screens during the first round of digital screening in the Netherlands. We found a biopsy rate of 14.3 per 1000 screens after non-blinded double reading and 17.4 per 1000 screens after blinded double reading. To our knowledge, data of biopsy rates after blinded double reading have not been reported previously. The biopsy rates we observed after non-blinded double reading are comparable to those of a Norwegian (61/4009) and Irish (470/35204) study during the first round of digital mammography (Skaane et al., 2007; Hambly et al., 2009).

In a Dutch study, increased detection of lesions presenting as microcalcifications during the transition from screen-film to digital screening mammography resulted in an almost fourfold increase in SCNB per 1000 screened women (Nederend et al., 2012). The further intensified use of SCNB at blinded double reading may have a great impact on daily practice of regional breast clinics, as it is much more time consuming than conventional breast imaging or ultrasound-guided biopsy.

Among women with benign work-up, a larger fraction was evaluated simply by additional imaging at non-blinded double reading, whereas a larger fraction at blinded double reading also underwent CNB procedures. The higher referral rate at blinded...
double reading results in higher costs of the diagnostic procedures in the hospital, which will rise even further as a larger fraction of referrals is evaluated by CNB in addition to breast imaging at blinded double reading.

The higher biopsy rates at blinded double readings was accompanied by an increased cancer detection rate, which resulted in a comparable PPV of biopsy of >40% at both reading strategies. This PPV is within the range of those found in other European programmes and higher than those observed in the United States (Skaane et al., 2007; Vinnicombe et al., 2009; Glynn et al., 2011).

It remains a question of debate whether false-positive referrals, which received additional imaging or biopsy, have uniformly decreased odds of attending subsequent routine screening rounds (Fitzpatrick et al., 2011; Seigneurin et al., 2011; Maxwell et al., 2013).

### Table 1. Baseline characteristics of women screened and referred at non-blinded and blinded double reading

| Screened population | Non-blinded (n = 42 996) | Blinded (n = 44 491) | P-value | Referred women | Non-blinded (n = 1235) | Blinded (n = 1474) | P-value |
|---------------------|-------------------------|----------------------|---------|----------------|-----------------------|---------------------|---------|
| Age distribution, no (%) |                         |                      |         |                |                       |                     |         |
| 50–59               | 22 704 (52.8)           | 23 469 (52.7)        | 0.49    | 653 (52.9)     | 778 (52.8)            |                     | 0.91    |
| 60–69               | 14 537 (33.8)           | 14 949 (33.6)        |         | 417 (33.8)     | 491 (33.3)            |                     |         |
| 70–75               | 5755 (13.4)             | 6073 (13.6)          |         | 165 (13.3)     | 205 (13.9)            |                     |         |
| Previous breast surgery, no (%) |                     |                      | 0.58    | 129 (10.4)     | 177 (12.0)            |                     | 0.20    |
| Yes                 | 3354 (7.8)              | 3516 (7.9)           |         | 1106 (89.6)    | 1297 (88.0)           |                     |         |
| No                  | 39 642 (92.2)           | 40 975 (92.1)        |         | 39 080 (10.4)  | 44 097 (10.8)         |                     |         |
| Hormone replacement therapy, no. (%) |                     |                      | 0.74    | 55 (4.5)       | 63 (4.3)              |                     | 0.82    |
| Yes                 | 2064 (4.8)              | 2157 (4.8)           |         | 1180 (95.5)    | 1411 (95.7)           |                     |         |
| No                  | 40 932 (95.2)           | 42 334 (95.2)        |         | 39 080 (10.4)  | 44 097 (10.8)         |                     |         |
| Family history of breast cancer*, no (%) |                     |                      | 0.59    | 149 (12.1)     | 168 (11.4)            |                     |         |
| Yes                 | 1086 (87.9)             | 1306 (88.6)          |         |                |                       |                     |         |
| Screening round, no (%) |                         |                      | 0.85    | 309 (25.0)     | 334 (22.7)            |                     | 0.15    |
| Initial screen      | 4784 (11.1)             | 4968 (11.2)          |         | 926 (75.0)     | 1140 (77.3)           |                     |         |
| Subsequent screen   | 38 212 (88.9)           | 39 523 (88.8)        |         |                |                       |                     |         |
| Mammmographic breast density |                     |                      | 0.83    | 1014 (82.1)    | 1215 (82.4)           |                     |         |
| 0–50%               | 221 (17.9)              | 259 (17.6)           |         |                |                       |                     |         |
| > 50%               | 1014 (82.1)             | 1215 (82.4)          |         |                |                       |                     |         |
| Lesion abnormality at latest screen, no (%) |                     |                      | 0.34    |                  |                       |                     |         |
| Suspicious mass     | 718 (58.1)              | 827 (56.1)           |         |                |                       |                     |         |
| Suspicious microcalcifications |                     |                      |         | 334 (27.0)     | 445 (30.2)            |                     |         |
| Suspicious mass with microcalcifications |                     |                      |         | 85 (6.9)       | 95 (6.4)              |                     |         |
| Asymmetry           | 22 (1.8)                | 28 (1.9)             |         |                |                       |                     |         |
| Architectural distortion | 72 (5.8)               | 78 (5.3)             |         |                |                       |                     |         |
| Other mammographic abnormality | 4 (0.3)               | 1 (0.1)              |         |                |                       |                     |         |

*At least one first-degree relative with a diagnosis of breast cancer before the age of 50 years or at least two second-degree relatives with breast cancer.

### Table 2. Non-blinded vs blinded double reading at screening mammography: assessment following referral

| Assessment following referral | Non-blinded (n = 1235) (%) | Blinded (n = 1474) (%) | P-value | Rate (per 1000 screened women) | Non-blinded (n = 42 996) | Blinded (n = 44 491) | P-value |
|------------------------------|----------------------------|------------------------|---------|------------------------------|------------------------|----------------------|---------|
| No further assessment        | 3 (0.2%2)                 | 0 (0%)                 | —       | 0.01                         | 0                     | —                    | 0.01    |
| Additional breast imaging    | 618 (50.0%)               | 698 (47.4%)            | 0.164   | 14.4                         | 15.7                   | 0.110                |
| Additional breast imaging + FNAB | 29 (2.3)               | 36 (2.4%)              | 0.873   | 0.7                          | 0.8                    | 0.465                |
| Additional breast imaging + CNB | 259 (21.0)             | 333 (22.6%)            | 0.310   | 6.0                          | 7.5                    | 0.008                |
| Additional breast imaging + SCNB | 285 (23.1)             | 362 (24.6%)            | 0.368   | 6.6                          | 8.1                    | 0.009                |
| Additional breast imaging + FNAC + CNB/SCNB* | 16 (1.3)                | 18 (1.2%)              | 0.862   | 0.4                          | 0.4                    | 0.808                |
| Additional breast imaging + FNAC/FNAB/SCNB/SCNB* + SB | 16 (1.3)                | 14 (0.9%)              | 0.392   | 0.4                          | 0.3                    | 0.646                |
| Additional breast imaging + CNB + SCNB | 8 (0.6)                | 12 (0.8%)              | 0.614   | 0.2                          | 0.3                    | 0.413                |
| Additional breast imaging + SB | 1 (0.1)                 | 1 (0.1%)               | —       | 0.0                          | 0                     | —                    |

*Abbreviations: CNB = core needle biopsy; FNAB = fine needle aspiration biopsy; SB = surgical (open) biopsy; SCNB = stereotactic CNB.

aCNB and/or SCNB.

bCNB and/or FNAB and/or SCNB.
Many of the women with false-positive screening results experience distress (van der Steeg et al., 2011), which may last for up to 3 years after a false-positive screen and is related to the invasiveness of the assessment (Bond et al., 2013). It is therefore important to keep the number of benign biopsies as low as possible.

Our study has certain limitations. The study population consisted of women who attended the screening programme during the transition from screen-film to digital screening mammography. Therefore, the majority of subsequent screens were compared with previously obtained screen-film mammograms. Data on screening outcome after the transition to digital screening mammography are sparse and there are no studies available that compare the use of diagnostic work-up modalities during and after the transition. All screening examinations in our study comprised two-view mammography of both breasts, including a medio-lateral oblique view and a cranio-caudal view. Recent studies have shown that the addition of breast tomosynthesis to digital mammography improves the cancer detection rate in mammography screening and may reduce false-positive referrals (Friedewald et al., 2014). Breast tomosynthesis, however, has not yet been implemented in the Dutch mammography screening programme.

In summary, we conclude that blinded double reading resulted in significantly higher overall and benign biopsy rate than non-blinded double reading. Although an increased screening sensitivity at blinded double reading has been reported, the negative side effect of higher biopsy rates should be taken into account when adopting this reading strategy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Fracheboud J, de Koning HJ, Boer R, Groenewoud JH, Verbeek AL, Broeders MJ, van Ineveld BM, Hendriks JH, de Bruyn AE, Holland R, Table 3. Non-blinded vs blinded double reading at screening mammography: assessment at false positive referral

| Assessment following referral | Proportion | Rate (per 1000 screened women) |
|-------------------------------|------------|-------------------------------|
|                               | Non-blinded | Blinded |
|                               | (n = 951)   | (n = 1149) |
|                               | P-value     |       |
| No further assessment         | 3 (0.3)     | 0 (0)  |
| Additional breast imaging     | 618 (65.0)  | 698 (60.7) |
| P-value                       | 0.046       | 14.4   |
| Additional breast imaging + FNAB | 28 (2.9)  | 35 (3.0) |
| P-value                       | 0.692       | 0.7    |
| Additional breast imaging + CNB | 62 (6.5)   | 114 (9.9) |
| P-value                       | 0.005       | 1.4    |
| Additional breast imaging + SCNB | 200 (21.0) | 261 (22.7) |
| P-value                       | 0.353       | 4.7    |
| Additional breast imaging + SCNB + FNAB | 16 (1.7) | 15 (1.3) |
| P-value                       | 0.476       | 0.4    |
| Additional breast imaging + CNB + SCNB | 16 (1.7) | 14 (1.2) |
| P-value                       | 0.372       | 0.4    |
| Additional breast imaging + SCNB | 8 (0.8)   | 11 (1.0) |
| P-value                       | 0.780       | 0.2    |
| Additional breast imaging + SB | 0 (0)       | 1 (0.1) |
| P-value                       | —          | 0      |

Abbreviations: CNB = core needle biopsy; FNAB = fine needle aspiration biopsy; SB = surgical (open) biopsy; SCNB = stereotactic CNB.

Table 4. Biopsy rates and PPVs of biopsy at non-blinded and blinded double reading of screening mammograms

| Assessment at referral | Non-blinded double reading | Blinded double reading | P-value |
|------------------------|----------------------------|------------------------|---------|
| Biopsy, %              | 49.7 (614/1235)            | 52.6 (776/1474)        | 0.129   |
| False-positive referral|                           |                        |         |
| Biopsy, %              | 14.3 (614/42 996)          | 17.4 (776/44 491)      | <0.001  |
| PPV of biopsy, %       | 46.3 (284/614)             | 41.9 (325/776)         | 0.103   |
| Biopsy, %              | 34.7 (330/951)             | 39.3 (451/1149)        | 0.032   |
| Benign biopsy rate per 1000 screens | 7.7 (330/42 996) | 10.1 (451/44 491) | <0.001  |

Abbreviation: PPV = positive predictive value.

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