


# Frequency and diagnostic outcome of bilateral recall at screening mammography

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## Abstract

Our study was performed to determine the frequency of recall for bilateral breast lesions at screening mammography and compare its outcome with respect to unilateral recall. We included 329 132 screening mammograms (34 889 initial screens and 294 243 subsequent screens) from a Dutch screening mammography program between January 2013 and January 2018. During a 2-year follow-up, we collected radiological data, pathology reports and surgical reports of all recalled women. At bilateral recall, the lesion with the highest Breast Imaging Reporting and Data System score was used as the index lesion when comparing screening mammography characteristics at bilateral vs unilateral recall. A total of 9806 women were recalled at screening (recall rate, 3.0%). Bilateral recall comprised 2.8% (271/9806) of all recalls. Biopsy was more frequently performed after bilateral recall than unilateral recall (54.6% [148/271] vs 44.1% [4201/9535],  $P < .001$ ), yielding a lower positive predictive value (PPV) of biopsy after bilateral recall (42.6% vs 51.7%,  $P = .029$ ). The PPV of recall was comparable for both groups (23.2% [63/271] vs 22.8% [2173/9535],  $P = .85$ ). Invasive cancers after bilateral recall were larger than those diagnosed after unilateral recall ( $P = .02$ ), but histological subtype, histologic grading, receptor status and proportions of lymph node positive cancers were comparable. Bilateral recall infrequently occurs at screening mammography. Biopsy is more frequently performed following bilateral recall, but the PPV of recall is similar for unilateral and bilateral recall. Invasive cancers of both groups show comparable pathological features except of a larger tumor size after bilateral recall.

## KEYWORDS

epidemiology, breast cancer, screening, malignancy, bilateral recall

## 1 | INTRODUCTION

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among women, with an estimated 2.1 million

**Abbreviations:** BI-RADS, Breast Imaging Reporting and Data System; DBT, digital breast tomosynthesis; DCIS, ductal carcinoma in situ; FFDM, full-field digital mammography; MRI, magnetic resonance imaging; PPV, positive predictive value.

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new cases and 600 000 deaths in 2018 worldwide.<sup>1</sup> The proportion of bilateral breast cancer among all breast cancers is modest and ranges, for example, from 2.2% in a Dutch screening population to 4.4% in a population derived from the National University of Ireland Galway breast cancer database in Ireland.<sup>1-4</sup> A worse survival has been reported for women with bilateral breast cancer than for women diagnosed with unilateral breast cancer.<sup>5-11</sup>

The detection of bilateral breast cancer has improved as a result of the ongoing developments in breast imaging over the past years.<sup>1,2,12-14</sup> The increased detection of bilateral breast cancer is mostly attributed to the use of magnetic resonance imaging (MRI) after a diagnosis of primary breast cancer.<sup>12-14</sup> Data on bilateral recall at screening mammography are very sparse. We previously reported a screening mammography sensitivity of only 19% for bilateral breast cancer detection in women screened between 1998 and 2008.<sup>1</sup> However, in recent years, much research has been done to improve the accuracy and detection of breast cancer at screening mammography, including studies on reading strategies and implementation of breast tomosynthesis.<sup>15-18</sup> These developments may increase the number of recalls for bilateral lesions found at screening mammography and the subsequent detection of significant bilateral breast disease.<sup>15,16,18</sup> As screening mammography focuses on early breast cancer detection, it may contribute to the improvement of survival of patients with bilateral breast cancer.

Data on bilateral breast cancer in a screened population are sparse,<sup>1,2</sup> and information on overall bilateral recall is lacking. We therefore assessed the frequency and characteristics of bilateral recall at screening mammography and compared its diagnostic outcome to unilateral recall.

## 2 | METHODS

### 2.1 | Study population

This is an observational study with retrospective data collection of women aged 50 to 75 years who attended a biennial breast cancer screening program conducted in the south of the Netherlands. Details of our screening program have been described previously.<sup>19</sup> In summary, women are personally invited by letter to attend the program, which has an attendance rate of about 80%. Women being treated for breast cancer and those who still receive oncological follow-up after breast cancer treatment do not attend the screening program. A consecutive series of 329 132 full-field digital mammography (FFDM) screening mammograms (34 889 initial screening mammograms and 294 243 subsequent screening mammograms) were included between 1 January 2013 and 1 January 2018.

Women participating in the screening program are offered the option to “opt-out” of their data being used for quality assessment and scientific purposes. Ethical approval by our local Institutional Review Board was not required for this observational follow-up study, according to the Dutch Central Committee on Research involving Human Subjects.

### What's New?

Data on bilateral breast cancer in a screened population is sparse, and information on bilateral recall is lacking. Based on more than 329,000 screening mammograms, our study shows that bilateral recall occurs infrequently at screening mammography, and that the majority of these recalls are false positives. Invasive cancer has comparable pathological features in bilateral and unilateral breast cancer patients, except larger tumour size after bilateral recall. Altogether, the results highlight the need for screening radiologists to pay vigorous attention to the contralateral breast after detecting a screening mammographic abnormality in order to facilitate a timely diagnosis of bilateral breast cancer.

### 2.2 | Screening procedure and recall

The screening mammograms were obtained at four specialized screening units (three mobile units and one fixed unit at Screening Program South). All digital mammograms were acquired using a Lord Selenia FFDM system (HologicInc, Danbury, CT), with a pixel size of 70  $\mu\text{m}$  and a field of view of 232  $\times$  286 mm. The examinations were obtained by specialized screening mammography radiographers, and all screening mammograms were double read by a team of 12 certified screening radiologists. All screening radiologists read more than 10 000 screening mammograms yearly. The screening radiologists first categorized abnormal mammographic findings into one of the following categories: suspicious mass, suspicious calcifications, suspicious mass combined with calcifications, asymmetry, architectural distortion, or other abnormalities not otherwise categorized. Then, each screen was classified according to the Breast Imaging Reporting and Data System (BI-RADS) lexicon and the radiologists annotated each recalled mammographic abnormality on a drawing, which was part of the recall report.<sup>20</sup> Women with a BI-RADS 1 (normal mammogram) or 2 (benign findings) were not recalled. Women with a BI-RADS 0 (incomplete, additional imaging evaluation needed), 4 (suspicious findings) or 5 (highly suggestive of malignancy) finding were referred to a dedicated breast unit of a hospital for further analysis. The BI-RADS category 3 (probably benign finding, follow-up suggested) is not used in the Dutch screening program as this program does not provide short-term follow-up.

### 2.3 | Diagnostic workup after recall

The diagnostic workup of most recalled women (97.6%, 9567/9806) was performed in six hospitals (four large teaching hospitals and two regional hospitals) located in our screening region. After physical examination by a surgical oncologist or dedicated breast nurse, additional breast imaging was performed at a radiology department. The screening mammogram was first reassessed by a radiologist, and the

screening mammograms were routinely available for comparison and stored in the Picture Archiving and Communication System of the hospital. Additional mammographic projections were obtained at the discretion of the attending radiologist. FFDM was available in each of the seven regional hospitals. Digital breast tomosynthesis (DBT) was present in two hospitals from the beginning of the inclusion period and became available in three other hospitals in 2015. Breast ultrasonography was used for the additional characterization of mammographic abnormalities and palpable breast lesions, for biopsy guidance and for target or second look purposes following breast MRI. In accordance with the Dutch guidelines, whole breast ultrasonography was not recommended.<sup>21</sup> Breast MRI was also available in each hospital and performed if indicated, as defined by the guidelines of the European Society of Breast Imaging<sup>22</sup> and the Dutch guidelines.<sup>21</sup> Fine-needle aspiration biopsy, percutaneous core needle biopsy and stereotactic biopsy were available in each hospital, whereas the usage of MRI-guided biopsy procedures was concentrated in the larger hospitals. All biopsied recalls and women with equivocal findings after initial assessment were discussed by multidisciplinary teams that consisted of surgical oncologists, radiologists, medical oncologists, radiation oncologists, plastic surgeons, breast nurses and breast radiographers.

During 2-year follow-up, clinical data and data from diagnostic breast imaging, biopsy specimen and surgical procedures were collected of all recalled women by one of the screening radiologists (LD) and several radiology residents. Information on previous breast surgery, mammographic breast density and family history of breast cancer was retrieved from questionnaires filled in by women prior to screening mammography, radiology reports and clinical data. Breast cancers were categorized into ductal carcinoma in situ (DCIS) and invasive cancers. The TNM classification of malignant tumors was used for malignant lesions.<sup>23</sup>

## 2.4 | Definition of index lesions

In case of bilateral recall or recall for more than one ipsilateral breast lesion, the lesion with the highest BI-RADS score was used as the index lesion when comparing screening mammography characteristics at bilateral vs unilateral recall. In case of histologically proven multifocal, multicentric or bilateral breast cancer, the largest malignancy was considered the index lesion when comparing tumor characteristics.

## 2.5 | Statistical analysis

All statistical analyses were performed using Statistical Package for Social Science 23.0 (SPSS Inc., IBM Corp, Armonk, NY). The chi-square test was used to test for differences between women with unilateral or bilateral recall at screening mammography. A *P* value of less than .05 was considered to indicate a statistically significant difference. *P* values were two sided. Whenever applicable (due to small sample sizes), the Fisher's exact test was used. The independent samples

*t*-test was used for comparison of mean age between unilateral and bilateral recalls. In the case of median testing, the median test was used. Whenever applicable, Bonferroni correction was applied for multiple testing.

Data were missing in less than 0.05% of the patients and in most cases involved the lack of estrogen or progesterone receptor status due to an insufficient tissue sample. In a few cases, recalled women refrained from follow-up (*n* = 20). These cases were also excluded from analysis. In the analysis of the categorical data, we treated the missing numbers (eg, receptor status) as a separate category to allow a complete case analysis.

## 3 | RESULTS

### 3.1 | Cohort characteristics

The recall rate in our cohort was 3.0% (9806/329132). Breast cancer was diagnosed in 2236 recalled women (including 19.9% [445/2236] cases of DCIS), yielding an overall cancer detection rate of 6.8 per 1000 screening mammograms (8.1 per 1000 for initial screening mammograms (281/34899) and 6.6 per 1000 for subsequent screening mammograms (1955/294243). The overall positive predictive value (PPV) of recall was 22.8% (2236/9806) and was significantly lower for initial screening examinations than for subsequent screening examinations (11.0% [281/2566] vs 27.0% [1955/7240], *P* < .001).

### 3.2 | Baseline characteristics of recalled women

Bilateral recalls comprised 2.8% (271/9806) of all recalls and the proportion of bilateral recalls was higher among women who were screened for the first time (4.1% [105/2566] vs 2.3% [166/7240], *P* < .001). Median age, a history of previous breast surgery or a family history of breast cancer was comparable for bilateral and unilateral recalls, whereas bilateral recalls were more frequently initial screens (*P* < .001) and displayed less dense breasts at screening mammography (*P* < .001, Table 1). Table 2 shows the distribution of the mammographic abnormalities at screening mammography for unilateral and bilateral recalls. Lesion characteristics were comparable for both groups, except of a larger proportion of suspicious calcifications among bilateral recalls (*P* < .001) and fewer masses (*P* = .016).

### 3.3 | Diagnostic workup after recall

Women recalled for a unilateral mammographic abnormality more frequently underwent clinical breast imaging only, whereas a larger proportion of women with a bilateral recall received breast biopsy in addition to imaging (54.6% [148/271] vs 44.1% [4201/9535], *P* < .001, Table 3). The PPV of biopsy for breast cancer was lower for bilateral recalls (42.6% vs 51.7%, *P* = .029).

**TABLE 1** Baseline characteristics of recalled women at screening mammography

	Overall N = 9806	Bilateral recall N = 271	Unilateral recall N = 9535	P value <sup>a</sup>
Median age (range), years	58 (50-75)	58 (50-75)	58 (50-75)	.93
Screening round, No (%)				<.001
Initial	2566 (26.1)	105 (38.7)	2461 (25.8)	
Subsequent	7240 (73.9)	166 (61.3)	7074 (74.2)	
Previous breast surgery, No (%)				.99
Yes	686 (7.0)	19 (7.0)	667 (7.0)	
No	9120 (93.0)	252 (93.0)	8868 (93.0)	
Breast density, No (%)				<.001
ACR I + II (0%-50%)	6197 (63.2)	211 (77.9)	5986 (62.8)	
ACR III + IV (50%-100%)	3609 (36.8)	60 (22.1)	3549 (37.2)	
Family history of breast cancer, No (%)				.25
Yes	1189 (12.2)	39 (14.4)	1152 (12.1)	
No	8617 (87.8)	232 (85.6)	8383 (87.9)	

Abbreviation: ACR, American College of Radiology.

<sup>a</sup>Bilateral recall versus unilateral recall.**TABLE 2** Mammographic abnormality of the index lesion at screening mammography<sup>a</sup>

Mammographic abnormality, No. (%)	Bilateral recall N = 271	Unilateral recall N = 9535	P value <sup>b</sup>
Mass	151 (55.7)	5996 (62.9)	.016
Calcifications	67 (24.7)	1615 (16.9)	<.001
Mass with calcifications	14 (5.2)	348 (3.6)	.19
Asymmetry	20 (7.4)	808 (8.5)	.52
Architectural distortion	18 (6.6)	678 (7.1)	.77
Other	1 (0.4)	90 (0.9)	.33

<sup>a</sup>At bilateral recall, the lesion with the highest BI-RADS score was defined as the index lesion.<sup>b</sup>When Bonferroni correction due to multiple testing is applied, the P value should be lower than .02 for a statistically significant result.**TABLE 3** Type of additional assessment after recall and final outcome

	Bilateral recall N = 271	Unilateral recall N = 9535	P value
Type of assessment after recall, No. (%)			<.001
None or unknown	0	25 (0.3)	
Clinical breast imaging only	123 (45.4)	5309 (55.7)	
Clinical breast imaging + biopsy	148 (54.6)	4201 (44.1)	
Final outcome, No. (%)			.85
No breast cancer	208 (76.8)	7362 (77.2)	
Breast cancer	63 (23.2)	2173 (22.8)	
Positive predictive value of biopsy (%)	42.6	51.7	.029
Bilateral breast cancer, No (%)	20 (7.4)	34 (0.4)	<.001

### 3.4 | Bilateral recall in prevalent cancers

The proportion of bilateral recalls was larger among women with prevalent breast cancer (ie, women who had attended the screening program for the first time), namely 6.4% (18/281) for first screens vs 2.3% (45/1955) for subsequent screens ( $P < .001$ ).

### 3.5 | Characteristics of screen detected breast cancers and surgical treatment

The proportion of DCIS among all true positive recalls was comparable for bilaterally or unilaterally recalled women (25.4% [16/63] vs 19.7% [429/2173],  $P = .26$ ), and the distribution of the

histological subtypes of invasive index cancers was comparable for both groups, with the majority of the invasive ductal type ( $P = .54$ , Table 4).

Tumor size of invasive index cancers was larger after bilateral recall, with fewer cancers sized 20 mm or less (63.8% [30/47] vs 80.4% [1402/2173],  $P = .005$ ). The proportion of lymph node positive

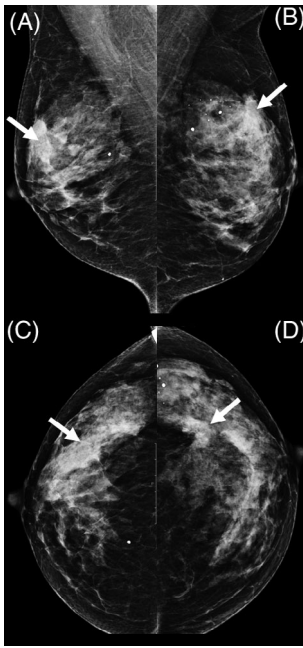
invasive cancers was higher for bilateral recalls, but this difference was not statistically significant (34.0% vs 21.4%,  $P = .06$ ). The tumors after bilateral recall tended to be of lower Bloom and Richardson grade than tumors after unilateral recall, but this difference was not statistically significant after statistical correction was performed. Tumor receptor status was comparable for both groups.

**TABLE 4** Tumor characteristics of the index breast cancers at bilateral and unilateral recall<sup>a</sup>

	Bilateral recall N = 63	Unilateral recall N = 2173	P value
Type of cancer, No. (%)			.26
Ductal carcinoma in situ (DCIS)	16 (25.4)	429 (19.7)	
Invasive	47 (74.6)	1744 (80.3)	
Histology of invasive cancers, No (%)			.54
Ductal	41 (87.2)	1375 (78.8)	
Lobular	4 (8.5)	222 (12.7)	
Ductolobular	1 (2.1)	48 (2.8)	
Other	1 (2.1)	99 (5.7)	
Tumor stage of invasive cancers, No. (%)			.005
T1 ( $\leq 20$ mm)	30 (63.8)	1402 (80.4)	
T2+ ( $> 20$ mm)	17 (36.2)	338 (19.4)	
Unknown	0	4 (0.2)	
Lymph node status of invasive cancers, No. (%)			0.06
N+	16 (34.0)	374 (21.4)	
N-	31 (66.0)	1308 (75.0)	
Unknown	0	62 (3.6)	
Bloom & Richardson grade, No. (%)			
I	13 (27.7)	743 (42.6)	.041 <sup>b</sup>
II	28 (59.6)	770 (44.2)	.040 <sup>b</sup>
III	6 (12.8)	218 (12.5)	.95
Unknown	0	13 (0.7)	
Estrogen receptor status, No. (%)			.79
Positive	43 (91.5)	1571 (90.1)	
Negative	4 (8.5)	168 (9.6)	
Unknown	0	5 (0.3)	
Progesterone receptor status, No. (%)			.81
Positive	33 (70.2)	1248 (71.6)	
Negative	14 (29.8)	491 (28.2)	
Unknown	0	5 (0.3)	
Her2/Neu receptor status, No. (%)			.15
Positive	7 (14.9)	154 (8.8)	
Negative	40 (85.1)	1581 (90.7)	
Unknown	0	9 (0.5)	
Final surgical treatment, No. (%)			<.001
Breast conserving surgery	48 (76.2)	1782 (82.0)	
Mastectomy	14 (22.2)	366 (16.8)	
No surgery	1 (1.6)	25 (1.2)	

<sup>a</sup>In case of histologically proven multifocal, multicentric or bilateral breast cancer, the largest malignancy was considered the index lesion when comparing tumor characteristics.

<sup>b</sup>Not statistically significant after Bonferroni's adjustment for multiple testing.



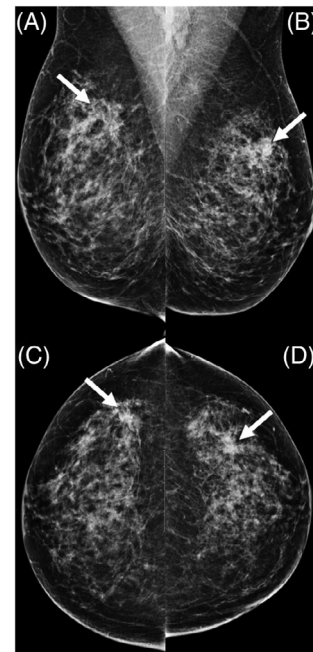
**FIGURE 1** Two-view screening mammogram (A,B, mediolateral oblique view, and C,D, craniocaudal view) shows a BI-RADS 0 mass in the right breast (A,C, upper outer quadrant), and a BI-RADS 5 spiculated mass in the left breast (B,D, upper outer quadrant). Core needle biopsy (14 gauge) revealed bilateral invasive ductal carcinoma. Tumor in the right breast: T2N1, tumor in the left breast: T1cN1. Treatment consisted of neoadjuvant chemotherapy followed by bilateral breast conserving surgery and adjuvant radiotherapy

Bilateral breast cancer was diagnosed more frequently among bilateral recalls (7.4% [20/271] vs 0.4% [34/9535],  $P < .001$ ). The 34 cancers, diagnosed in the non-recalled breast after unilateral recall, were 4 DCIS (3 intermediate grade, 1 high grade) and 30 invasive cancers. The majority of the invasive cancers were of the ductal type (76.7%, 23 cancers),  $\leq 20$  mm (86.7%, 26 cancers), lymph node negative (73.3%, 22 cancers) and Bloom and Richardson grade I (43.3%, 13 cancers) or II (46.7%, 14 cancers). The 20 non-index breast cancers in women diagnosed with bilateral breast cancer after a bilateral recall comprised 6 DCIS (all intermediate grade), 10 invasive ductal cancers and 2 invasive lobular cancers. All but one of the 12 invasive cancers were sized  $\leq 20$  mm. Figures 1 and 2 show examples of bilateral recalls with subsequently confirmed bilateral breast cancer.

A majority of breast cancer patients underwent breast conserving surgery for their index cancer (76.2% of cancers diagnosed after bilateral recall and 82.0% of cancers diagnosed after unilateral recall), whereas significantly more cancers were treated by mastectomy following bilateral recall (22.2% vs 16.8%,  $P < .001$ ).

### 3.6 | False-positive bilateral recalls

The false-positive recall rate (ie, no diagnosis of breast cancer following recall) was similar for bilateral and unilateral recalls (76.8% [208/271] vs 77.2% [7362/9535],  $P = .96$ ). False-positive recalls of non-index lesions



**FIGURE 2** Two-view screening mammogram (A,B, mediolateral oblique view, and C,D, craniocaudal view) shows a BI-RADS 4 architectural distortion in the right breast (A,C, upper outer quadrant) and an ill-defined BI-RADS 4 mass in the left breast (B,D, upper outer quadrant). Stereotactic core needle biopsy (9 gauge) revealed high-grade ductal carcinoma in situ (DCIS) in the right breast and core needle biopsy (14 gauge) yielded invasive ductal cancer in the left breast. The DCIS in the right breast had a maximum diameter of 50 mm. The invasive ductal carcinoma in the left breast was a T2N0 tumor. The patient underwent neoadjuvant chemotherapy followed by bilateral mastectomy and adjuvant antihormonal therapy

after bilateral recall mostly comprised cysts, superposition of fibroglandular tissue or fibroadenomas. One case presented as bilateral non-Hodgkin lymphoma, which was not considered a primary breast cancer.

## 4 | DISCUSSION

Our study describes the frequency and outcome of bilateral recall at screening mammography. We found that 2.7% of recalled women had their recall for a bilateral, suspicious mammographic screening abnormality. Bilateral recall was more frequently present in initial than in subsequent screening mammograms and in less dense breasts, and the distribution of mammographic abnormalities differed between unilateral and bilateral recalls. The overall proportion of true positive recalls (ie, confirmation of breast cancer after recall) was similar for women after unilateral and bilateral recalls. Although women with a bilateral recall more often underwent biopsy compared to women with a unilateral recall, a smaller proportion of these biopsies yielded cancer. The tumors after bilateral recall tended to be larger than those in women after unilateral recall, and we observed a larger mastectomy rate for breast cancers diagnosed after bilateral recall than diagnosed after unilateral recall.

Very limited data are available on the diagnosis of bilateral breast cancer in screened women. In our series, bilateral breast cancer was diagnosed in 0.4% of unilateral recalls and in 7.2% of bilateral recalls. Overall, bilateral breast cancer was confirmed in 2.4% (51/2104) of women with a screen detected cancer in our study, which is comparable to the 2.2% we previously reported in women screened by screen-film mammography between 1998 and 2008.<sup>2</sup>

Although the transition from screen-film to digital screening mammography came along with increased recall rates, the Dutch screening mammography program remains characterized by a low recall rate and we also observed a relatively low bilateral recall rate among all recalled women.<sup>24,25</sup> Bilateral recall more frequently occurred in women screened for the first time, which may be due to a higher degree of vigilance and uncertainty among screening radiologists when a woman enters the screening program, with no previous screening mammograms available for comparison. This assumption may also explain the higher frequency of bilateral recalls in women with a true positive recall after their initial (prevalent) screen.<sup>26,27</sup>

The higher biopsy rate after bilateral recall came along with a lower PPV of biopsy and a comparable overall PPV of recall for bilaterally or unilaterally recalled women. The radiologist may be more inclined to perform biopsy rather than imaging follow-up of equivocal findings at clinical breast imaging after bilateral recall. A recent study from the United Kingdom (UK) reported a reduction of 33% in the number of benign biopsies after unilateral recall because of better characterization of lesions.<sup>28</sup> However, it is not yet clear whether this may also be applicable in case of bilateral recall. Generalization of the UK findings to the Dutch screening setting may also be limited because of the higher UK recall rate and differences in clinical workup. A majority of Dutch hospitals have the availability of state-of-the-art imaging modalities such as tomosynthesis and breast MRI, which may influence the frequency and PPV of biopsy, at both unilateral and bilateral recalls.

We found a difference between unilateral and bilateral recalls with respect to mammographic abnormalities at screening mammography. To our knowledge, no literature is available on this subject. Although in both bilateral and unilateral recalls most lesions were characterized as masses, index lesions at bilateral recall were relatively more often characterized as suspicious calcifications compared to index lesions at unilateral recall. This may be due to a higher alertness among screening radiologists for calcifications than for other lesions, with a more intensified focus on calcifications in the index lesion than on the subtle abnormalities of non-index lesion in the contralateral breast, which are, for example, asymmetries or architectural distortions.

It has been shown that especially invasive lobular cancers may be difficult to detect at screening mammography as these cancers frequently present as focal asymmetries, subtle architectural distortions or no mammographic abnormality at all.<sup>1,2,29</sup> We found no significant differences in the histological types of invasive cancers when comparing unilateral and bilateral index cancers. A recent meta-analysis by Yun et al in 2018 suggests that the addition of new imaging modalities to digital screening mammography, such as DBT, may improve the

detection of invasive lobular carcinomas.<sup>30</sup> Contrast-enhanced digital mammography also increases the detection of invasive lobular carcinomas and may therefore have additional benefits, but the use of this modality in a screening setting has not yet been proven to be feasible.<sup>31</sup>

Controversy exists regarding the prognosis and survival of bilateral breast cancer, with studies reporting an equivalent or poorer survival for bilateral breast cancer than for unilateral breast cancer.<sup>3,5-10</sup> In case of bilateral breast cancer detected at screening mammography, the contralateral non-index cancer more frequently shows invasive lobular histology and less lymph node involvement, but other tumor characteristics such as tumor size, mitotic activity and receptor status are comparable to the index cancer.<sup>9</sup> Our study, performed in the era of screen-film mammography, also reported no significant differences in tumor characteristics between the index cancers of bilateral breast cancer and unilateral breast cancers. However, in our series of digital screening mammograms, we found that invasive index cancers after bilateral recall were larger than those diagnosed after unilateral recall, and they showed a tendency toward a higher rate of lymph node invasion. This is a remarkable finding as digital screening mammography has a comparable or even higher sensitivity for breast cancer detection than screen-film mammography, especially for smaller cancers and cancer detection in more dense breasts.<sup>24,32</sup> We do not have a biological explanation for the larger cancer size in women with a bilateral recall, with a tendency of these cancers for a worse Bloom & Richardson (B&R) grading and more lymph node invasion. Invasive lobular cancers are known to have a larger mean tumor size at the time of detection than invasive ductal cancers, but the breast cancers in our study showed a comparable histological distribution after unilateral or bilateral recall. Cancers after bilateral recall more frequently showed lymph node metastases and more B&R grade II tumors, but these differences were not statistically significant. Tumors in synchronous bilateral breast cancer may be considered as two biologically separate tumors, and we have previously reported similar tumor characteristics for bilateral cancers and unilateral cancers.<sup>2,33</sup>

We found that the final surgical treatment for breast cancer more frequently consisted of mastectomy rather than breast conserving surgery after bilateral recall compared to after unilateral recall. This observation can be explained by the larger tumor size of the index cancers and the higher bilateral breast cancer rate after bilateral recall. Women may be inclined to choose for bilateral mastectomy rather than breast conserving surgery in case mastectomy is already indicated for the index lesion but not necessarily for the non-index lesion. It remains, however, a question of debate whether bilateral disease should be treated by bilateral mastectomy rather than by breast conserving surgery. Guidelines for the treatment of bilateral breast cancer are not readily available and more research is needed on the efficacy of breast conserving treatment in these women, with an emphasis on the risk of cancer recurrence.

Our study has certain limitations. As mentioned previously, the recall rate in the Dutch screening program is lower than that of many other screening programs, which could limit generalization of our results to other programs.<sup>2,15,17,34,35</sup> Furthermore, small sample sizes

of certain subgroups (mainly tumor characteristics of bilateral breast cancers) limit statistical analysis and warrant careful interpretation of the results in these subgroups. Differences in imaging modalities were present among hospitals that assessed the recalled women. In several hospitals, for example, tomosynthesis was available during the major or the whole part of the inclusion period, whereas this imaging modality became available at a later stage in other hospitals. Differences in diagnostic services may influence both imaging outcome and biopsy rates, for example, when one faces equivocal findings at digital mammography without being able to perform tomosynthesis or breast MRI for problem solving.

In summary, recall for bilateral lesions occurs infrequently at screening mammography. The PPV of recall is similar for unilateral and bilateral recall, although biopsy is more frequently performed following bilateral recall. Invasive index cancers are larger after bilateral recall. Although the majority of bilateral recalls are false positive, screening radiologists should pay vigorous attention to the contralateral breast after having detected a screening mammographic abnormality in one breast in order to facilitate a timely diagnosis of bilateral breast cancer.

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#### CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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