

Trends in frequency and outcome of high-risk breast lesions at core needle biopsy in women recalled at biennial screening mammography, a multiinstitutional study

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Between January 1, 2011, and December 31, 2016, we studied the incidence, management and outcome of high-risk breast lesions in a consecutive series of 376,519 screens of women who received biennial screening mammography. During the 6-year period covered by the study, the proportion of women who underwent core needle biopsy (CNB) after recall remained fairly stable, ranging from 39.2% to 48.1% (mean: 44.2%, 5,212/11,783), whereas the proportion of high-risk lesions at CNB (i.e., flat epithelial atypia, atypical ductal hyperplasia, lobular carcinoma *in situ* and papillary lesions) gradually increased from 3.2% (25/775) in 2011 to 9.5% (86/901) in 2016 ($p < 0.001$). The mean proportion of high-risk lesions at CNB that were subsequently treated with diagnostic surgical excision was 51.4% (169/329) and varied between 41.0% and 64.3% through the years, but the excision rate for high-risk lesions per 1,000 screens and per 100 recalls increased from 0.25 (2011) to 0.70 (2016; $p < 0.001$) and from 0.81 (2011) to 2.50 (2016; $p < 0.001$), respectively. The proportion of all diagnostic surgical excisions showing *in situ* or invasive breast cancer was 29.0% (49/169) and varied from 22.2% (8/36) in 2014 to 38.5% (5/13) in 2011. In conclusion, the proportion of high-risk lesions at CNB tripled in a 6-year period, with a concomitant increased excision rate for these lesions. As the proportion of surgical excisions showing *in situ* or invasive breast cancer did not increase, a rising number of screened women underwent invasive surgical excision with benign outcome.

Key words: high-risk lesions, risk-associated lesions, surgical excision, diagnostics, mammographic screening

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What's new?

Screening mammography aims to catch breast cancer early to reduce associated morbidity and mortality. Women with suspect findings at mammography frequently are recalled for further testing with core needle biopsy (CNB). In this investigation, the proportion of high-risk lesions detected at CNB was found to have tripled among women in the Netherlands who underwent mammographic screening between 2011 and 2016. This increase was accompanied by an increase in lesion excision rates. Of excised lesions, little more than 14% proved to be malignant at two-year follow-up. The remainder of lesions exhibited benign pathology, suggesting that many women underwent potentially unnecessary surgery.

Introduction

Many countries have implemented regional or nationwide screening mammography programs with the aim to detect breast malignancy at an early stage to decrease breast cancer-related morbidity and mortality.^{1,2} Recalled women frequently have to undergo some kind of image-guided core needle biopsy in order to obtain a definite diagnosis for the abnormality detected at screening mammography. Women with benign biopsy results are usually encouraged to reattend the screening program and those diagnosed with malignant breast disease generally have an excellent prognosis after appropriate treatment. However, optimal management of so-called high-risk lesions, also known as risk-associated lesions (e.g., flat epithelial atypia, papillary lesions, radial scar and lobular carcinoma *in situ* [LCIS]), found at core needle biopsy (CNB) is controversial.^{3–6} Communication between radiologists, pathologists and surgical oncologists is crucial to determine whether a high-risk lesion should either be monitored by regular radiologic follow-up imaging or whether excision can be considered. Stereotactic core needle biopsy (SCNB) is performed more often since the introduction of digital mammography in breast cancer screening, probably because digital mammography has a higher sensitivity for the detection of small calcifications compared to screen-film mammography.⁷ It is not clear, however, to which degree high-risk lesions are more frequently diagnosed in screened women. It also remains indistinct whether these lesions have a significant impact on the diagnostic surgical excision rate to obtain a final tissue diagnosis. Therefore, we determined trends in frequency, management and pathology outcome of high-risk breast lesions found at CNB in women who were recalled at a biennial screening mammography program in the south of the Netherlands. We determined the rate of “upgrade” to ductal carcinoma *in situ* (DCIS) or invasive carcinoma to support an evidence-based approach to the management of high-risk lesions. “Upgrade” was defined as a change of diagnosis into DCIS or invasive carcinoma at final pathology after diagnostic surgical excision for lesions, which originally were classified as high-risk lesions at CNB or SCNB.

Materials and Methods**Study population and screening procedure**

We included all screening mammography examinations obtained in a southern breast cancer screening region of the Netherlands between January 1, 2011, and December 31, 2016. Women aged

50–75 years are invited to attend biennial screening mammography, which is provided free of charge. Details of our nationwide screening program have been published previously.⁸ In summary, screen-film mammography was replaced by full-field digital mammography in 2009–2010. A two-view digital mammogram (mediolateral-oblique view and craniocaudal view) of each breast is obtained by a certified radiographer, after which the examination is assessed by two screening radiologists. Previous screening mammograms are always available for comparison. Radiologists classify mammographic abnormalities in women needing further evaluation (i.e., recall) into one of the following categories: (i) suspicious mass; (ii) suspicious calcifications; (iii) suspicious mass with calcifications; (iv) asymmetry; (v) architectural distortion; (vi) other. Women with normal findings (BI-RADS 1, Breast Imaging Reporting and Data System) or benign findings (BI-RADS 2) are invited to reattend subsequent screening.^{9,10} The BI-RADS 3 classification is not used in the Dutch screening program. Women with BI-RADS 0, 4 or 5 are recalled for further analysis at a breast unit of a hospital. BI-RADS 0 lesions comprise sharply demarcated masses, architectural distortions visible at one projection only and asymmetries visible at either one or both views. Masses with indistinct margins, suspicious microcalcifications and architectural distortions visible at both views are categorized as BI-RADS 4 lesions whereas BI-RADS 5 lesions consist of spiculated masses and suspicious masses showing calcifications.

Assessment after recall and follow-up

Twenty-five hospitals were involved in the workup of the recalled women. The majority of these women (98.8%, 11,640/11,783) were analyzed in one of the seven hospitals centrally located in our screening region. Each of these seven hospitals has a dedicated surgical breast unit and state-of-the-art breast imaging equipment, whereas a total of four pathology departments deliver their services to these hospitals. At the hospital, additional imaging and biopsy procedures may be performed to establish a final diagnosis for the abnormality detected at screening mammography. We used the term CNB to cover all percutaneous histologic biopsy methods; ultrasound-guided CNB (CNB, 14–18G) as well as stereotactic CNB (SCNB, 9–11G). High-risk lesions at CNB were categorized as follows: (i) papillary lesion (consisting of papillary lesions, papillomas and papillomatosis); (ii) columnar cell lesion, flat epithelial atypia; (iii) atypical ductal hyperplasia; (iv) radial scar, complex sclerosing lesion; (v) LCIS, atypical lobular

hyperplasia; (vi) combination of high-risk lesions; (vii) other (e.g., granular cell tumor, atypia without further specification at biopsy). In addition to the feedback that the hospitals gave to the screening organization with respect to final outcome, one of the screening radiologists obtained the reports of the radiologic examinations, the biopsy reports and surgical reports of all recalled women through regular visits at these hospitals. The follow-up period of the recalled women was 2 years, which is the period until the next biennial screening round.

Only women who gave written informed consent to use their data for quality assurance of the screening program and for scientific purposes were included in this analysis. Our study was performed under the national permit for breast cancer screening, which is issued by the Ministry of Health, Welfare and Sports after advice of the Dutch Health Council and did not require an additional ethical approval.

Statistical analysis

Trends over time and variations between subgroups were expressed using proportions. The chi-square test was used to compare proportional differences, or the Fischer's Exact Test when expected values were too small. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS, version 24.0 (SPSS, Inc., Chicago, IL).

Results

Overall screening outcome

A total of 376,519 screens (41,204 initial screens and 335,315 subsequent screens) were obtained between January 1, 2011, and December 31, 2016 (Table 1). Invasive breast cancer or DCIS was diagnosed in 2,586 of the 11,783 recalled women (recall rate, 3.1%), resulting in 6.9 cancers detected per 1,000 screens and a positive predictive value of recall of 21.9%. Of

the 2,586 screen-detected malignancies, 535 (20.7%) were ductal *in situ* carcinomas and 2051 (79.3%) were invasive cancers.

Trends in frequency and outcome of high-risk lesions at CNB

Of the recalled women 64.8% (7,634/11,783) had been recalled for a suspicious mass and 18.3% for suspicious calcifications (Table 2). Over time these percentages varied between 56.4% (2016) and 72.1% (2013) and between 14.0% (2014) and 24.3% (2011), respectively (Table 2). A significant increase in the number of asymmetries as mammographic abnormality was observed during the last 3 years of the study period, from 5.2% in 2014 to 12.4% in 2016 ($p < 0.001$). This increase came along with a significant decrease in masses as mammographic abnormality, from 68.7% in 2014 to 56.4% in 2016 ($p < 0.001$; Table 2). CNB was performed in 5,212 of the 11,783 recalled women (44.2%), and varied between 39.2% (2014) and 48.1% (2011) through the years (Table 1). A majority of these biopsies comprised ultrasound guided CNB (52.1%, 2,718/5,212; 14–18 Gauge) and SCNB (35.1%, 1,832/5,212; 9–11 Gauge, Table 2). The proportions of CNB and SCNB among all percutaneous biopsy procedures were comparable for the first and last screening year (CNB: 47.2% in 2011 (366/775) vs. 50.4% in 2016 (454/901; $p = 0.449$), SCNB: 41.0% in 2011 (318/775) vs. 34.5% in 2016 (311/901; $p = 0.065$). The proportion of high-risk lesions at CNB gradually increased from 3.2% (25/775) in 2011 to 9.5% (86/901) in 2016 ($p < 0.001$; Table 1). Suspicious masses and suspicious calcifications were the dominant mammographic features at recall in women with high-risk lesions at CNB (Table 3). Of the 329 high-risk lesions, 30.4% (100/329) and 55.3% (128/329) presented as a mass or calcification at screening mammography, respectively. During the multidisciplinary meetings, at which clinical, radiologic and biopsy results were correlated with each other,

Table 1. Trends in frequency and outcome of high-risk lesions at percutaneous biopsy in women recalled at biennial screening mammography

Screening year	2011	2012	2013	2014	2015	2016	Total
Screens, <i>n</i>	51,865	61,470	65,628	65,799	64,539	67,218	376,519
Recall, <i>n</i> (%)	1,610 (3.1)	1899 (3.1)	2,398 (3.7)	2,255 (3.4)	1,740 (2.7)	1881 (2.8)	11,783 (3.1)
Core needle biopsy, <i>n</i> (%)							
Yes	775 (48.1)	856 (45.1)	973 (40.6)	885 (39.2)	822 (47.2)	901 (47.9)	5,212 (44.2)
No	835 (51.9)	1,043 (54.9)	1,425 (59.4)	1,370 (60.8)	918 (52.8)	980 (52.1)	6,571 (55.8)
High-risk lesion at percutaneous biopsy, <i>n</i> (%)	25 (3.2)	43 (5.0)	61 (6.3)	56 (6.3)	58 (7.1)	86 (9.5)	329 (6.3)
High-risk lesion at diagnostic excision, <i>n</i> (%)							
Yes	13 (52.0)	21 (48.8)	25 (41.0)	36 (64.3)	27 (46.6)	47 (54.7)	169 (51.4)
No	12 (48.0)	22 (51.2)	36 (59.0)	20 (35.7)	31 (53.4)	39 (45.3)	160 (48.6)
Excision rate for high-risk lesions							
Per 1,000 screens	0.25	0.34	0.40	0.55	0.42	0.70	0.45
Per 100 recalls	0.81	1.11	1.04	1.60	1.55	2.50	1.43
Excision outcome							
Benign, <i>n</i> (%)	8 (61.5)	16 (76.2)	17 (68.0)	28 (77.8)	18 (66.7)	33 (70.2)	120 (71.0)
Malignant, <i>n</i> (%)	5 (38.5)	5 (23.8)	8 (32.0)	8 (22.2)	9 (33.3)	14 (29.8)	49 (29.0)

Table 2. Type of mammographic abnormality at screening mammography and type of assessment after recall

Screening year	2011	2012	2013	2014	2015	2016	Total
Mammographic abnormality, n (%)							
Suspicious mass	978 (60.7)	1,256 (66.1)	1,728 (72.1)	1,550 (68.7)	1,062 (61.0)	1,060 (56.4)	7,634 (64.8)
Suspicious calcifications	390 (24.3)	371 (19.5)	406 (16.9)	315 (14.0)	299 (17.2)	381 (20.3)	2,162 (18.3)
Suspicious mass with calcifications	105 (6.5)	81 (4.3)	86 (3.6)	80 (3.5)	67 (3.9)	68 (3.6)	487 (4.1)
Asymmetry	20 (1.2)	33 (1.7)	36 (1.5)	118 (5.2)	142 (8.2)	234 (12.4)	583 (4.9)
Architectural distortion	117 (7.3)	158 (8.3)	142 (5.9)	192 (8.5)	160 (9.2)	101 (5.4)	870 (7.4)
Other	0	0	0	0	10 (0.6)	37 (2.0)	47 (0.4)
Assessment after recall, n (%)							
None or unknown	3 (0.2)	2 (0.1)	1 (0)	9 (0.4)	3 (0.2)	6 (0.3)	24 (0.2)
Imaging	831 (51.6)	1,037 (54.6)	1,422 (59.3)	1,357 (60.2)	915 (52.6)	974 (51.8)	6,536 (55.5)
Imaging + FNAC	38 (2.4)	48 (2.5)	42 (1.8)	31 (1.4)	23 (1.3)	25 (1.3)	207 (1.8)
Imaging + CNB	366 (22.7)	426 (22.4)	498 (20.8)	502 (22.3)	472 (27.1)	454 (24.1)	2,718 (23.1)
Imaging + SCNB	318 (19.8)	304 (16.0)	362 (15.1)	275 (12.2)	262 (15.1)	311 (16.5)	1,832 (15.5)
Imaging + CB + SCNB	22 (1.4)	25 (1.3)	24 (1.0)	27 (1.2)	27 (1.6)	45 (2.4)	170 (1.4)
Imaging + other combinations of percutaneous biopsy	10 (0.6)	24 (1.3)	17 (0.7)	9 (0.4)	7 (0.4)	15 (0.8)	82 (0.7)
Imaging + (S)CNB + diagnostic surgical excision	21 (1.3)	29 (1.5)	30 (1.3)	41 (1.8)	31 (1.8)	51 (2.7)	203 (1.7)
Imaging + diagnostic surgical excision	1 (0.1)	4 (0.2)	2 (0.1)	4 (0.2)	0 (0)	0 (0)	11 (0.1)

Abbreviations: FNAC, fine needle aspiration cytology; CNB, core needle biopsy (14–18 Gauge); SCNB, stereotactic core needle biopsy (9–11 Gauge).

Table 3. Mammographic abnormality of high-risk breast lesions at screening mammography

Mammographic lesion at recall	n (%)	High-risk lesions, mammographic abnormality at recall, n (%) ¹
Suspicious mass	7,634 (64.8)	100 (1.3)
Suspicious calcifications	2,162 (18.3)	182 (8.4)
Suspicious mass with calcifications	487 (4.1)	27 (5.5)
Asymmetry	583 (4.9)	4 (0.7)
Architectural distortion	870 (7.4)	11 (1.3)
Other	47 (0.4)	5 (10.6)
Total	11,783	329

¹As proportion of total number of women recalled for this specific mammographic abnormality.

Table 4. Histologic subtypes of high-risk lesions at core needle biopsy and outcome at 2-year follow-up

Histology	n (%)	Benign, n (%)	Malignant, n (%)
Papillary lesion	116 (35.3)	97 (83.6)	19 (16.4)
Columnar cell lesion, flat epithelial atypia	79 (24.0)	78 (98.7)	1 (1.3)
Atypical ductal hyperplasia	63 (19.1)	41 (65.1)	22 (34.9)
Radial scar, complex sclerosing lesion	10 (3.0)	9 (90.0)	1 (10.0)
Lobular carcinoma <i>in situ</i> , atypical lobular hyperplasia	13 (4.0)	13 (100)	0
Combination of high-risk lesions	38 (11.6)	35 (92.1)	3 (7.9)
Other	10 (3.0)	7 (70.0)	3 (30.0)
Total	329	280 (85.1)	49 (14.9)

it was decided that additional diagnostic surgical excision was needed in 169 of the 329 women in whom high-risk lesions were found. The proportion of recalled women who underwent CNB followed by additional excision for diagnostic purposes doubled from 1.3% in 2011 (21/1,610) to 2.7% in 2016 (51/1,881, $p = 0.004$, Table 2). The proportion of high-risk

lesions at CNB that was subsequently treated with diagnostic surgical excision varied between 41.0 and 64.3% through the years, with a mean of 51.4%, (169/329). Diagnostic surgical excision for high-risk lesions per 1,000 screens and per 100 recalls significantly increased from 0.25 in 2011 to 0.70 in 2016 ($p < 0.001$) and from 0.81 in 2011 to 2.50 in 2016 ($p < 0.001$; Table 1), respectively. The malignancy rate of the excisions ranged from 22.2% in 2014 (8/36) to 38.5% in 2011 (5/13; $p = 0.340$), with 29.0% (49/169) of all excisions showing DCIS or invasive breast cancer.

Histologic subtypes of high-risk breast lesions at CNB and outcome at 2-year follow-up

The most frequently diagnosed histologic subtypes among the 329 high-risk breast lesions at CNB were papillary lesions (35.3%) and columnar cell lesions/flat epithelial atypia (24.0%), followed by atypical ductal hyperplasia (19.1%) and a combination of high-risk lesions (11.6%; Table 4). Of the 329 high-risk lesions at CNB, whereof 169 were excised, 14.9% (49/329) proved to be malignant at 2-year follow-up. The rate of upgrade to DCIS or invasive carcinoma was highest for CNB yielding atypical ductal hyperplasia (34.9%, 22/63, 18 DCIS and four invasive carcinomas), followed by “other” lesions (30.0%, 3/10, all invasive carcinomas) and papillary lesions (16.4%, 19/116, 14 DCIS and five invasive carcinomas). The 41 malignancies, diagnosed in women with atypical ductal hyperplasia or papillary lesions at CNB, comprised 32 DCIS (of which 20 low grade) and nine invasive cancers (of which four low grade; Table 5). The histologic subtypes of high-risk breast lesions and year of diagnosis at CNB are presented in Table 6. No clear increase or decrease was observed in the diagnosis of the different histologic subtypes through the years, except for columnar cell lesions and flat epithelial atypia that were only diagnosed from 2012 onwards.

Tumor characteristics of breast cancers diagnosed after diagnostic surgical excision of high-risk lesions

The 49 high-risk lesions that were upgraded to malignancy at diagnostic surgical excision comprised 36 cases of DCIS and 13 invasive cancers (Table 7). The majority of these cancers were low-grade DCIS or grade I invasive cancers (61.2%,

Table 5. Type and grading of malignancy in women with high-risk lesions at core needle biopsy

Histology at percutaneous biopsy, n	Ductal carcinoma <i>in situ</i>			Invasive cancer ¹		
	Low	Intermediate	High	I	II	III
Papillary lesion	10	3	1	2	1	2
Columnar cell lesion, flat epithelial atypia	1					
Atypical ductal hyperplasia	10	8		2	2	
Radial scar, complex sclerosing lesion				1		
Combination of high-risk lesions	3					
Other				1		2
Total	24	11	1	6	3	4

¹Bloom and Richardson.

Table 6. Histologic subtypes of high-risk lesions and year of diagnosis at core needle biopsy

Histology	Screening year					
	2011	2012	2013	2014	2015	2016
Papillary lesion	17 (68.0)	19 (44.2)	12 (19.7)	22 (39.3)	17 (29.3)	29 (33.7)
Columnar cell lesion, flat epithelial atypia	0	6 (14.0)	13 (21.3)	11 (19.6)	23 (39.7)	26 (30.2)
Atypical ductal hyperplasia	5 (20.0)	6 (14.0)	16 (26.2)	8 (14.3)	11 (19.0)	17 (19.8)
Radial scar, complex sclerosing lesion	0	1 (2.3)	3 (4.9)	3 (5.4)	2 (3.4)	1 (1.2)
Lobular carcinoma <i>in situ</i> , atypical lobular hyperplasia	3 (12.0)	4 (9.3)	0	1 (1.8)	2 (3.4)	3 (3.5)
Combination of high-risk lesions	0	7 (16.3)	14 (23.0)	7 (12.5)	3 (5.2)	7 (8.1)
Other	0	0	3 (4.9)	4 (7.1)	0	3 (3.5)
Total	25	43	61	56	58	86

30/49, Table 5). The proportion of DCIS was significantly higher in this group than in women whose CNB had yielded an unequivocal malignant diagnosis (73.5% [36/49] vs. 19.7% [500/2,537], $p < 0.001$) and DCIS grading was more favorable in the first group ($p < 0.001$). Invasive cancers were more frequently of the ductal type and more frequently showed axillary lymph node metastasis in women with proven breast cancer at CNB ($p < 0.001$) compared to women with high-risk lesions at CNB (Table 7). Estrogen and progesterone receptor status of invasive cancers, tumor size and type of surgical treatment (breast-conserving surgery vs. mastectomy) were comparable for both groups.

In one woman, who underwent radiologic follow up of a columnar cell lesion, an invasive ductal cancer (18 mm, B&R grade II, no lymph node metastasis) was diagnosed at the previous biopsy site 2 years after recall. At 2-year follow-up, no breast cancer was diagnosed in the remaining 159 women without surgical intervention for their high-risk lesions.

Discussion

In a 6-year screening period, we observed a threefold increase in the proportion of high-risk lesions diagnosed at CNB. The excision rate for these lesions per 1,000 screens and per 100 recalls also tripled. The overall upgrade rates of high-risk breast lesions to (*in situ*) malignancy after excision was 29.0%. Tumor characteristics were distinctively different for cancers diagnosed after upgrading of a high-risk lesion compared to cancers with an unequivocal malignant outcome at CNB.

A Dutch study, performed shortly after the implementation of full-field digital screening mammography, reported that microcalcifications were more often diagnosed, compared to screen-film mammography. This resulted in more CNB, which was associated with an increase in the absolute number of columnar cell lesions during the digital screening period.¹¹ We found that the incidence of high-risk lesions at CNB continued to increase, even many years after the transition from screen-film to digital screening mammography. Weber *et al.* also found that the recall rate for suspicious calcifications remained significantly higher at digital screening, resulting in a permanently higher CNB rate for these lesions per 1,000 screens, compared to the period of screen-film

mammography.⁷ We observed a significant increase in the number of asymmetries as mammographic abnormality during the last 3 years of inclusion, as well as a significant decrease in the number of suspicious masses as reason for recall. This finding, however, does not explain the gradual increase in the proportion of high-risk lesions, as the vast majority of these lesions presented as a suspicious mass or suspicious calcifications at screening mammography. The type of radiologic assessment at recall showed no significant changes through the years, therefore this parameter cannot explain the increase in the proportion of high-risk lesions. A possible explanation might be the increased awareness for both the detection and report of high-risk lesions at CNB among pathologists.¹² The four departments of pathology from which data were derived for this study did not change their scoring protocol during the study period. In 2016, a protocol for structured reporting for surgical breast specimen was introduced in the Netherlands. However, the increase of high-risk lesion already started several years before the introduction of this protocol.

The optimal management of high-risk lesions remains a subject of debate. Falomo *et al.* reported serious inconsistencies in the management of these lesions at academic institutions across the United States, with surgical excision rates ranging from 39% to 95% between centers.⁵ Several studies advocate radiologic imaging follow-up for nonatypical papillomas as the malignancy rate of these lesions may be less than 2.5%,^{13,14} whereas others have found that up to 33% of these lesions may prove malignant and therefore recommend complete surgical excision.¹⁵ Considerable variation in the upgrading of flat epithelial atypia, atypical ductal hyperplasia, LCIS/atypical lobular hyperplasia and radial scar to malignancy has been reported (flat epithelial atypia: 0–15%, atypical ductal hyperplasia: 22%–32%, LCIS/atypical lobular hyperplasia: 2%–29%, radial scar: 0%–23%), resulting in mixed recommendations that range from radiologic surveillance to diagnostic surgical excision of every high-risk lesion.^{16–26} In our series, 29% of excised high-risk lesions proved to be malignant; 20.7% DCIS and 8.3% invasive breast cancer, respectively. Other studies report a somewhat lower likelihood of upgrading to malignancy of 20%–22%.^{18,19} However, comparisons between studies may be hampered by the use of different biopsy techniques and differences in the distribution of the subtypes of high-risk lesions found at biopsy.

Table 7. Comparison of tumor characteristics and type of surgery among women with a high-risk lesion vs. malignancy at percutaneous biopsy

	High-risk lesion at biopsy	Cancer at biopsy	<i>p</i>
Cancers, <i>n</i>	49	2,537	
Tumor type, <i>n</i> (%)			<0.001
DCIS	36 (73.5)	500 (19.7)	
Invasive	13 (26.5)	2037 (80.3)	
Unknown	0 (0)	0 (0)	
DCIS grading, <i>n</i> (%)			<0.001
Low grade	24 (66.7)	79 (15.8)	
Intermediate grade	11 (30.6)	181 (36.2)	
High grade	1 (2.7)	240 (48.0)	
Type of invasive cancer, <i>n</i> (%)			<0.001
Ductal	9 (69.2)	1,597 (78.4)	
Lobular	0 (0)	261 (12.8)	
Mixed ductal/lobular	0 (0)	65 (3.2)	
Other	4 (30.7)	114 (5.6)	
Unknown	0 (0)	0 (0)	
Tumor size of invasive cancers, <i>n</i> (%)			0.498
T1a–c	12 (92.3)	1,622 (79.6)	
T2+	1 (7.7)	411 (20.2)	
Unknown	0 (0)	4 (0.2)	
Lymph-node status of invasive cancers, <i>n</i> (%)			<0.001
N+	0 (0)	447 (21.9)	
NO	9 (69.2)	1,543 (75.7)	
Unknown	4 (30.8)	47 (2.3)	
Grade, <i>n</i> (%)			0.172
B&R I	6 (46.2)	889 (43.6)	
B&R II	3 (23.1)	889 (43.6)	
B&R III	4 (20.7)	238 (11.7)	
Unknown	0 (0)	21 (1.0)	
Estrogen receptor, <i>n</i> (%)			0.065
Positive	9 (69.2)	1838 (90.2)	
Negative	4 (30.8)	189 (9.3)	
Unknown	0 (0)	10 (0.5)	
Progesterone receptor, <i>n</i> (%)			0.114
Positive	6 (38.5)	1,469 (72.1)	
Negative	7 (61.5)	558 (27.4)	
Unknown	0 (0)	10 (0.5)	
Her2/Neu receptor, <i>n</i> (%)			0.166
Positive	3 (23.1)	185 (9.1)	
Negative	10 (76.9)	1842 (90.4)	
Unknown	0 (0)	10 (0.5)	
Triple receptor–negative, <i>n</i> (%)	3 (21.4)	129 (6.3)	0.739

(Continues)

Table 7. Comparison of tumor characteristics and type of surgery among women with a high-risk lesion vs. malignancy at percutaneous biopsy (Continued)

	High-risk lesion at biopsy	Cancer at biopsy	<i>p</i>
Type of final surgical treatment, <i>n</i> (%)			0.207
Breast conserving surgery	41 (83.7)	2067 (81.5)	
Mastectomy	6 (12.2)	437 (17.2)	
No surgery performed ¹	2 (4.1)	28 (1.1)	
Unknown	0 (0)	5 (0.2)	

¹Upgraded after follow-up with repeated stereotactic biopsy. Abbreviations: B&R, Bloom & Richardson; DCIS, ductal carcinoma *in situ*.

As the proportion of high-risk lesions being upgraded to malignancy remained stable over the years, the increased excision rate of these lesions resulted in an increasing number of women with a benign outcome after diagnostic surgical excision. Although a recent US study found that reattendance to a screening mammography program is not lower in women with benign surgical excision after recall,⁶ the use of this type of excision for diagnostic purposes should be kept to a minimum as it lowers the sensitivity of future screening mammography for cancer detection.²⁷

Tumor characteristics were generally more favorable for high-risk lesions upstaged to breast cancer than for cancers with an unequivocal diagnosis of malignancy at CNB, with a higher proportion of DCIS and the absence of lymph node positive invasive cancers in the first group in case of simultaneous sentinel lymph node biopsy. Tumor stage and grading of invasive cancers, as well as type of final surgical treatment, were comparable for both groups. Although almost half of the upstaged high-risk lesions comprised low-grade DCIS, the presence of intermediate-grade and high-grade invasive cancers on the other hand may lead surgical oncologists to decide for lesion excision rather than radiologic and clinical surveillance. With the changing opinion of surgical excision for low-grade DCIS towards close surveillance in the near future, low-grade DCIS could have been included as a high-risk lesion in our study. However, the clinical trials comparing surgery with active surveillance of DCIS^{28,29} are still ongoing and none have reported any results yet confirming the safety of active surveillance. As a consequence, surgical excision was and still is the most widely accepted treatment for low-grade DCIS. Taking all of the aforementioned into account we felt that considering low-grade DCIS as high-risk lesions is not justified yet.

However, considering the fact that close follow up of low-grade DCIS currently is subject of several prospective studies,^{28,29} our study shows that when a diagnostic surgical excision of high-risk lesions at CNB is performed, more than 85% of all excisions (71% [120/169] benign pathology and 14.2% [24/169] low-grade DCIS) may be preventable in the near future. In order to decrease

this number of potentially unnecessary surgical excisions, one may opt for vacuum-assisted excision of high-risk lesions as an alternative to surgical excision.^{30–32}

Our study has certain strengths and limitations. To the best of our knowledge, it is the first study that describes trends in the detection of high-risk lesions in a screened population. Furthermore, 2-year follow-up was virtually complete for all recalled women. On the other hand, comparison of the management and outcome of these lesions with other studies is limited as they show considerable heterogeneity in the type of biopsy procedures and subtyping of high-risk lesions.

Although we included a large consecutive series of screening mammograms, no more than 329 high-risk lesions were diagnosed

leaving some of the subgroups too small for a proper analysis. Moreover, only multiple (more than one) papillomas in the same breast are associated with a higher risk of developing breast cancer. Unfortunately, we were not able to fully discriminate solitary papilloma from multiple papillomas in all cases, which is a limitation for the papillary lesion group.

In conclusion, a significant increase in the proportion of high-risk lesions detected at CNB was observed, with a concomitant increased excision rate for these lesions resulting in an increasing number of screened women who underwent invasive diagnostic surgical excision with benign outcome at final pathology. Larger studies are needed to define evidence-based practice recommendations for the management of high-risk lesions detected at CNB.

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