Mammographic, US, and MR Imaging Phenotypes of Familial Breast Cancer[1]

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Purpose: To prospectively investigate the imaging (mammographic, ultrasonographic [US], magnetic resonance [MR] imaging) features of invasive and intraductal breast cancers in women at familial risk.

Materials and Methods: Ethics committee approval and informed consent were obtained. Breast cancers were identified in women at moderately increased risk, in women at high familial risk, and in documented *BRCA1* and *BRCA2* mutation carriers. All cancers were investigated with mammography, US, and bilateral dynamic breast MR imaging. Imaging findings of breast cancer in women in the different risk categories were prospectively collected and compared. With the two-sample Wilcoxon signed rank test, imaging features of cancers were compared.

Results: Seventy-six breast cancers were identified in 68 women (mean age, 41.3 years). Mammographic breast density had no influence on detectability of cancers. Imaging phenotypes differed among risk categories: 15 (23%) of 64 invasive cancers appeared as fibroadenoma-like masses without calcifications but without fibroadenoma-like internal enhancement or enhancement kinetics at breast MR imaging. Of those, 12 (80%) occurred in women at high risk and documented *BRCA1* mutation carriers. A posterior (immediately prepectoral) location was observed in 67% (32 of 48) of all breast cancers in women at high risk and mutation carriers ($P < .009$). None of the remaining *BRCA1*-associated invasive cancers exhibited calcifications; intraductal cancers were not observed. In 28 cancers in *BRCA2* carriers or women at moderately increased risk, imaging features seemed equivalent to those reported for sporadic cancers; cases of ductal carcinoma in situ were observed, and there was no preference for a posterior location in the breast. At MR imaging, a high percentage (20% [13 of 64]) of invasive cancers appeared as non-masslike enhancement; benign kinetic features were observed in 33% (25 of 76).

Conclusion: Imaging phenotypes of cancers differ among risk categories. If MR imaging is used for screening, high sensitivity rates are achievable only if morphologic and kinetic features are assessed and if non-masslike enhancement is considered. Lesion location is important in regard to malignancy.

Supplemental material: *http://radiology.rsnajnls.org/cgi/content/full/246/1/58/DC1*

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Reports (1,2) from screening programs in women at increased familial risk indicate that if mammography alone is used for surveillance, up to two-thirds of breast cancers are diagnosed as interval cancers between screening rounds. Not infrequently, these interval cancers are already large and exhibit positive axillary lymph node metastases. The limited sensitivity of mammography in women at increased familial risk has been attributed to several factors. One is "host related" (ie, caused by the on-average higher breast density of the young women who undergo screening for familial breast cancer). Other factors seem to be "tumor related" (ie, caused by specific features of familial breast cancers): Hereditary breast cancers tend to exhibit fast growth rates such that the lead time is short (3–6).

In addition, in particular, *BRCA1*-associated breast cancers have been shown to exhibit benign morphologic features (oval shape, smooth or "pushing" margins) that can make them indistinguishable from, for example, fibroadenomas (7,8). The results of all trials published so far are concordant in that breast magnetic resonance (MR) imaging offers a significantly higher sensitivity compared with the sensitivity of mammography (9–15). However, the sensitivity levels achieved with MR imaging vary in a wide range (71%–92%), and this finding indicates that a substantial number of breast cancers may go undetected at breast MR imaging as well (9–15). One reason may be that familial breast cancer may exhibit atypical or seemingly benign features not only at mammography but also at MR imaging and breast ultrasonography (US) (11).

Thus, the purpose of our study was to prospectively investigate the imaging (mammography, US, MR imaging) features of invasive and intraductal breast cancers that arise in women at familial risk.

Advances in Knowledge

- Mammographic breast density is not the main reason for nondetectability of familial breast cancer.
- Familial breast cancer may exhibit atypical imaging findings at all imaging modalities, including MR imaging.
- At MR imaging, familial breast cancer may appear as non-mass-like enhancement and may exhibit benign kinetic features or benign morphologic features.
- Among women with familial breast cancer, the imaging phenotypes vary with the different risk categories.

Materials and Methods

Our study had ethics committee approval, and informed consent was obtained from all participants.

Patient Cohort

Between February 1996 and February 2006, 629 women from 467 families with a personal and/or family history suggestive of familial breast cancer were included in a dedicated surveillance program. All women had a proved mutation in one of the breast cancer susceptibility genes (*BRCA1* or *BRCA2*) or fulfilled the criteria of increased familial risk, as established by the Consortium on Familial Breast and Ovarian Cancer of the German Cancer Aid Society. Women who tested negative for the *BRCA1* or *BRCA2* mutation were categorized on the basis of their family history into one of the following risk categories: moderate-risk group or high-risk group.

Moderate-risk group.—This group included women with at least two relatives with breast and/or ovarian cancer, one of whom received a diagnosis before the age of 50 years; a history of a relative with breast cancer diagnosed before the age of 35 years and/or a relative with ovarian cancer diagnosed at or before the age of 40 years and/or with a male relative with breast cancer and/or with a relative with bilateral breast cancer.

High-risk group.—This group included women with both breast and ovarian cancers and/or with two relatives with breast cancer before the age of 50 years and/or with three or more first- or second-degree relatives with breast cancer on the same side of the family.

All study participants underwent half-yearly clinical breast examination and breast US, annual two-view mammography, and annual breast MR imaging (12).

Imaging Technique

Mammography.—Mammography was performed in craniocaudal and mediolateral

Implications for Patient Care

- Fibroadenomas or even cystlike masses in young patients with a strong family history for breast cancer and/or with a documented *BRCA1* or *BRCA2* mutation can represent familial breast cancer, and a biopsy should be performed to confirm the diagnosis.
- Familial breast cancer may exhibit an atypical, benign-appearing morphology and/or atypical (benign) enhancement kinetics at MR imaging.
- Special attention should be paid to any lesion in the posterior part of the breast, particularly the immediate prepectoral region, because familial breast cancer resides in this location in up to two-thirds of instances.

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Abbreviations:
BI-RADS = Breast Imaging Reporting and Data System
DCIS = ductal carcinoma in situ

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Guarantor of integrity of entire study, C.K.K.; study concepts/study design or data acquisition or data analysis /interpretation, S.S., C.K.K.; manuscript drafting or manuscript revision for important intellectual content, S.S., C.K.K.; manuscript final version approval, S.S., C.K.K.; literature research, S.S., C.K.K.; clinical studies, S.S., C.K.K.; statistical analysis, S.S., C.K.K.; and manuscript editing, S.S., C.K.K.

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oblique projections. Spot compression, magnification, and additional views were obtained as needed. Independent double reading was performed. All mammograms were interpreted in compliance with the German Radiological Practice Guidelines, and mammographic findings were described and prospectively classified according to the Breast Imaging Reporting and Data System (BI-RADS) categories (16). A BI-RADS category of 0 was not assigned because a complete diagnostic assessment was performed at every visit of the screening participant, and possible additional mammographic views were obtained during that same visit.

Breast US.—Breast US was performed with high-frequency (7.5–13-MHz) probes (Elegra, Siemens, Erlangen, Germany; Logic 500, GE Medical Systems, Milwaukee, Wis; and ATL HDI 5000, Philips Medical Systems, Best, the Netherlands). Lesions were classified and described according to the BI-RADS categories (16).

Dynamic breast MR imaging.—Dynamic bilateral breast MR imaging was performed with a standard 1.5-T system (Gyroscan ACS II; Philips Medical Systems) by using a double-breast surface coil. The imaging protocol consisted of two-dimensional, gradient-echo, contrast material–enhanced dynamic imaging (repetition time msec/echo time msec, 290/4.6; flip angle, 90°) before and nine times (from 1996 to 1999) or four times (from 2000 to 2006) after bolus injection of 0.1 mmol of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) per kilogram of body weight. A section thickness of 3 mm, a full 256 × 256 (between 1996 and 1999) or 512 × 512 (between 2000 and 2006) imaging matrix, and a field of view adjusted to include both breasts (260–320 mm) was used. Each of the five or 10 dynamic image acquisitions consisted of a stack of 21–31 sections that were carefully positioned to include the entire parenchymal volume. If contrast-enhancing lesions were identified on the subtraction images, region-of-interest–based time–signal intensity curves were plotted to show the enhancement behavior during the dynamic study.

Data Collection and Analysis

For each breast cancer identified during the study period in at least one of the three imaging studies, its imaging features at each modality were documented and entered into a database. In case of multifocal or multicentric disease, only the main tumor, not each single lesion, was analyzed to avoid data clustering.

The imaging characteristics of lesions were described by using terminology according to the American College of Radiology BI-RADS (16). All examinations were read prospectively and independently by one radiologist who offered the same level of experience with the respective imaging modalities (C.K.K., with 15 years of experience).

Features were recorded separately for invasive and intraductal cancers (17). Furthermore, the location of the cancer within the breast was recorded, regarding both the quadrant (outer upper, outer lower, inner upper, inner lower, and central) and the location of the mass along the long axis of the breast (anterior, middle, or posterior portion of the quadrant).

All cancer diagnoses were validated with histologic diagnosis. Histopathological confirmation was obtained at vacuum-assisted core-needle biopsy with mammographic, US, or MR imaging guidance. All patients underwent definitive surgery; in all nonpalpable cancers, preoperative wire localization was performed with mammographic, US, or breast MR imaging guidance. The final histologic diagnosis was based on the surgical specimen and was the standard of reference.

Statistical Analysis

Differences in cancer stage and histologic type for lesions in women in the different risk groups were analyzed by using the χ^2 test. Breast density patterns in women with positive versus those with negative mammograms were compared by using the χ^2 and the Wilcoxon signed rank tests. The location of the main breast cancer mass in *BRCA1* carriers versus that of the mass in women of other risk groups was compared with the Wilcoxon signed rank test for two samples. A difference with a P value of .05 was considered statistically significant. A software package (SPSS 12.0; SPSS, Chicago Ill) was used.

Results

During the 10-year study period, 76 breast cancers were diagnosed in 68 women. This includes 17 patients who had not been in the surveillance program primarily but who developed breast cancer that, on assessment of the patients' family history and/or mutational analysis, had been categorized as familial breast cancer. Two patients had synchronous bilateral breast cancers, five women developed second primary breast cancers, and one patient experienced an ipsilateral invasive recurrence after a previous case of ductal carcinoma in situ (DCIS). Of the 68 women who received a diagnosis of breast cancer (Table 1), 20 (29%) had a moderate risk, 31 (46%) had a high risk, and 17 (25%) had tested positive for *BRCA1* or *BRCA2* mutation.

Of 76 breast cancers (Table 2), 64 were invasive and 12 were pure intraductal cancers. The most common histologic type of all invasive cancers was invasive ductal cancer, not otherwise specified (44 [69%] of 64). The cancer stage and histologic type did not differ significantly among women in the different risk groups ($P > .05$).

Imaging Findings in 64 Invasive Cancers

Mammography.—Twenty-seven (42%) invasive breast cancers occurred in women with normal or benign mammographic findings (Table E1 [*http://radiology.rsnajnls.org/cgi/content/full/246/1/58/DC1*]). Thirty-seven (58%) invasive cancers occurred in women with a nonnegative mammogram (BI-RADS category 3, 4, or 5).

Nineteen (30%) cancers appeared as a mass, 12 (19%) cancers appeared as microcalcifications without an accompanying mass, and six (9%) cancers appeared as an architectural distortion.

If a mass was present, most commonly it had typical malignant morphologic features (irregular shape, ill-defined margins) but no associated calcifications. This kind of lesion was observed

in 10 invasive cancers (30% of 64 invasive cancers, 51% of 37 nonnegative mammograms). Five invasive cancers (8% of 64 invasive cancers, 14% of 37 nonnegative mammograms) had the same malignant-appearing morphology plus calcifications. Four invasive cancers (6% of 64 invasive cancers, 11% of 37 nonnegative mammograms) had a fibroadenoma-like appearance (ie, the lesion was round or oval with smooth borders and no associated calcifications).

In the 12 invasive breast cancers that appeared as calcifications without an accompanying mass, a clustered distribution was observed in four (33%), a segmental distribution was observed in three (25%), a regional distribution was observed in three (25%), and a linear distribution was observed in two (17%).

The distribution of mammographic breast density patterns in women with invasive or intraductal breast cancer and false-negative findings on a mammogram (BI-RADS category 1 or 2) was not significantly different ($P = .6$, two-sample Wilcoxon signed rank test) from that in women with true-positive findings on a mammogram (BI-RADS category 3, 4, or 5) (Table 3).

Breast US.—Twenty-four (38%) of 64 invasive breast cancers (Table E2 [*http://radiology.rsnajnls.org/cgi/content/full/246/1/58/DC1*]) occurred in women with normal or benign findings at US at the time of diagnosis. In 40 (62%) patients

Table 1

Patient Demographics

Characteristic	All Women	Women with Moderate Risk	Women with High Risk	Mutation Carriers	
				BRCA1	*BRCA2*
No. of patients	68	20	31	11	6
No. of breast cancers*	76	22	34	14	6
Age at diagnosis (y)					
Mean	41.3	45.1	41.9	35.9	37.0
Median	40	48	40	36	37.5
Standard deviation	8.9	9.3	9.1	5.2	6.7
Range	20–60	28–60	20–60	29–45	28–46

* Two patients had synchronous bilateral cancers; six patients developed a second primary breast cancer.

Table 2

Histologic Characteristics of Breast Cancers

Characteristic	All ($n = 76$)	Women with Moderate Risk ($n = 22$)	Women with High Risk ($n = 34$)	Mutation Carriers	
				BRCA1 ($n = 14$)	*BRCA2* ($n = 6$)
Histologic type of invasive cancers ($n = 64$)					
Ductal NOS	69 (44/64)	67 (12/18)	63 (17/27)	79 (11/14)	80 (4/5)
Lobular	12 (8/64)	22 (4/18)	11 (3/27)	. . .	20 (1/5)
Medullary	8 (5/64)	. . .	11 (3/27)	14 (2/14)	. . .
Mixed ductal and lobular	8 (5/64)	6 (1/18)	11 (3/27)	7 (1/14)	. . .
Other	3 (2/64)	6 (1/18)	4 (1/27)	. . .	. . .
Stage					
Intraductal, DCIS	16 (12/76)	18 (4/22)	21 (7/34)	0 (0/14)	17 (1/6)
Invasive, all sizes	84 (64/76)	82 (18/22)	79 (27/34)	100 (14/14)	83 (5/6)
Invasive, T1	78 (50/64)	67 (12/18)	78 (21/27)	89 (17/19)*	. . .
Invasive, T2	16 (10/64)	22 (4/18)	19 (5/27)	5 (1/19)*	. . .
Invasive, T3	2 (1/64)	. . .	. . .	5 (1/19)*	. . .
Invasive, T4	5 (3/64)	11 (2/18)	4 (1/27)	. . .	. . .
Classification†					
Grade 1					
Invasive	9 (6/64)	11 (2/18)	11 (3/27)	0 (0/14)	20 (1/5)
DCIS	25 (3/12)	50 (2/4)	14 (1/7)	. . .	0 (0/1)
Grade 2					
Invasive	38 (24/64)	61 (11/18)	33 (9/27)	7 (1/14)	60 (3/5)
DCIS	8 (1/12)	0 (0/4)	14 (1/7)	. . .	0 (0/1)
Grade 3					
Invasive	53 (34/64)	28 (5/18)	56 (15/27)	93 (13/14)	20 (1/5)
DCIS	67 (8/12)	50 (2/4)	71 (5/7)	. . .	100 (1/1)

Note.—Data are percentages, and numbers in parentheses were used to calculate the percentages. NOS = not otherwise specified.

* Data are for *BRCA1* and *BRCA2* mutation carriers combined.

† Grade 1 = low grade, grade 2 = intermediate grade, grade 3 = high grade.

with breast cancer, a finding was classified as BI-RADS category 3, 4, or 5. The most frequent finding was a solid mass with irregular shape and margins, and this finding was present in 26 breast cancers (41% of 64 invasive cancers, 65% of 40 invasive cancers in women with nonnegative screening US images). Fourteen cancers (22% of 64 invasive cancers, 35% of 40 cancers in women with nonnegative screening US images) appeared as fibroadenoma-like lesions that were round or oval, that had posterior acoustic enhancement, or that had an indifferent posterior acoustic pattern. Four of these fibroadenoma-like tumors appeared almost anechoic, such that they could be mistaken for a cyst.

MR imaging.—One (2%) of 64 invasive breast cancers, a 3-mm microinvasive ductal cancer, occurred in a woman with a benign MR imaging finding (Table E3 [*http://radiology.rsnajnls.org/cgi/content/full/246/1/58/DC1*]). Sixty-three of 64 cancers had a suspicious MR imaging correlate; 50 (78%) appeared as enhancing masses, whereas 13 (21%) appeared as non-masslike enhancement.

The most frequent finding in women with invasive cancers was an enhancing mass that exhibited typical malignant features both in terms of mass morphology (ie, irregular shape, nonsmooth margins, heterogeneous or rim internal enhancement) and in terms of enhancement kinetics (fast early enhancement followed by washout or plateau of the signal intensity–time course). This finding was determined in 23 invasive breast cancers (36% [23 of 64] of all invasive cancers, 46% [23 of 50] of all cancers that were associated with masslike enhancement).

An enhancing mass with benign morphologic features (round or oval shape, smooth margins, homogeneous internal enhancement) but with suspicious kinetic features (fast initial rise followed by a strong washout of signal intensity in the delayed phase) was found in 15 invasive breast cancers (23% [15 of 64] of all invasive cancers, 30% [15 of 50] of the cancers with masslike enhancement). Of note, internal nonenhancing (dark) septations were not identified.

Table 3

Mammographic Breast Density

Findings	ACR 1	ACR 2	ACR 3	ACR 4
False-negative	22 (6/27)	33 (9/27)	26 (7/27)	19 (5/27)
True-positive	24 (9/37)	41 (15/37)	19 (7/37)	16 (6/37)

Note.—The differences among breast density codes were not significant with the χ^2 and Wilcoxon signed rank tests ($P = .98$ and .6, respectively). Data are percentages, and numbers in parentheses were used to calculate the percentages. ACR = American College of Radiology. ACR 1 = fatty breast, ACR 2 = scattered fibroglandular tissue, ACR 3 = heterogeneously dense breast, and ACR 4 = dense breast.

An enhancing mass with benign kinetic features (slow or intermediate initial rise, steady delayed phase enhancement) but with suspicious morphologic features (irregular shape, nonsmooth margins, or heterogeneous internal enhancement, or all three) was found in 12 invasive cancers (19% [12 of 64] of all invasive cancers, 24% [12 of 50] of the cancers with masslike enhancement).

Among the 13 invasive breast cancers that appeared as non-masslike enhancement, eight manifested as a focus or a focal area of enhancement and four exhibited a regional or segmental distribution. Suspicious enhancement kinetics (fast initial rise, followed by washout or plateau) was observed in seven (54%).

Imaging Findings in 12 Intraductal Cancers

Mammography.—Eight (67%) of 12 pure intraductal cancers occurred in women with normal or benign mammographic findings (BI-RADS category 1 or 2). In three of these eight patients with mammograms rated as normal or mammograms with benign findings, diffuse, monomorphic calcifications were present that had been stable over a follow-up of several years; one of these three patients had undergone excisional biopsy for calcifications, and the biopsy revealed nonproliferative mastopathic changes with calcifications (Table E4 [*http://radiology.rsnajnls.org/cgi/content/full/246/1/58/DC1*]). Calcifications classified as BI-RADS category 3, 4, or 5 were detected in four patients (33% of 12 cases of DCIS in the cohort, 100% of four mammographically detected cases of DCIS). Of those, two exhibited clustered fine pleomorphic calcifications and two exhibited coarse heterogeneous calcifications in a regional or segmental distribution.

Breast US.—In 12 (100%) of 12 pure intraductal cancers, US findings were normal or benign at the time of diagnosis. In other words, none of the cases of pure DCIS were prospectively suspected or diagnosed with US.

MR imaging.—Eleven (92%) of 12 intraductal cancers appeared as non-masslike asymmetric enhancement. One (8%) case of DCIS, a 5-mm low-grade in situ cancer, did not exhibit any enhancement and did not exhibit calcifications, but a diagnosis was determined at preventive mastectomy. Of the 11 MR imaging–visible cases of DCIS, seven (64%) exhibited a segmental or ductal distribution; the other four (36%) cases appeared as asymmetric focal areas of enhancement. The kinetic pattern was suggestive of a benign lesion with intermediate or slow initial rise and/or steady enhancement in seven (58%) of 12 cases.

Location of Cancers

The location of the main cancer mass (in the case of multicentric or multifocal disease, the main cancer manifestation was considered) for the 75 cancers that were visible with at least one imaging modality was the upper outer quadrant in 52% (39 of 75), the upper inner quadrant in 13% (10 of 75), the lower outer quadrant in 9% (seven of 75), the lower inner quadrant in 4% (three of 75), and the central quadrant in 7% (five of 75). Fifteen percent (11 of 75) of cancers showed a growth pattern in more than one quadrant.

More than half (42 [56%] of 75) of all cancers were located in the posterior portion of the breast, and within the posterior part, most frequently (40 of

42 cancers) the immediate prepectoral region was the cancer-bearing part (Table E5 [*http://radiology.rsnajnls.org/cgi/content/full/246/1/58/DC1*]). The skewed distribution of cancer location in women at high familial risk and in *BRCA1* carriers proved to show a highly statistically significant difference ($P < .009$).

Imaging Features according to Risk Category

The percentage of invasive or intraductal cancers that exhibited calcifications was low for women across all risk categories (16 [23%] of 70). Findings are indicated in Tables E1–E4 (*http://radiology.rsnajnls.org/cgi/content/full/246/1/58/DC1*). The lowest prevalence of calcifications was observed in breast cancers that arose in patients

Figure 1

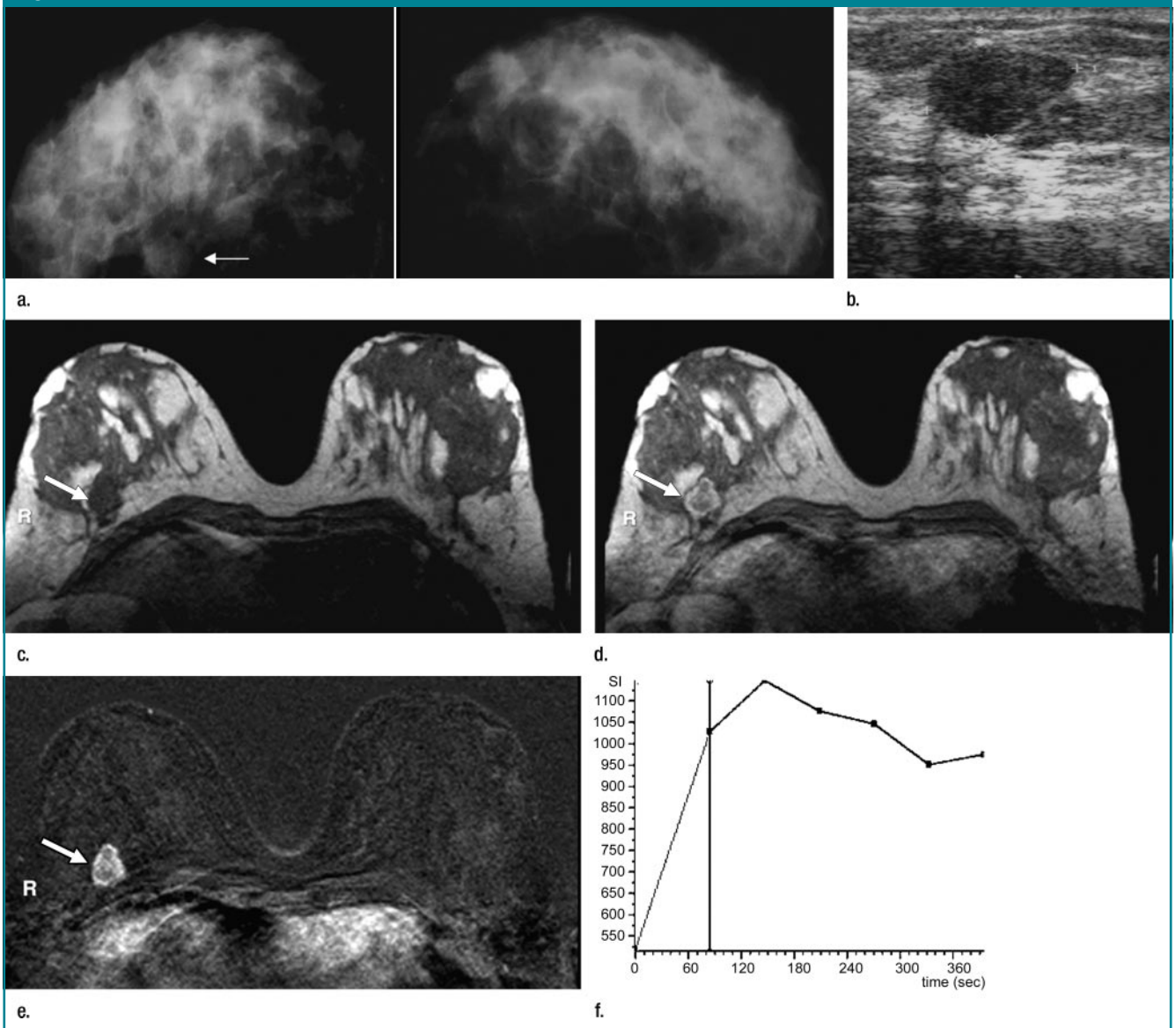

Figure 1: *BRCA1* mutation and grade 3 nonpalpable invasive ductal cancer, not otherwise specified (arrow), in 32-year-old woman. **(a)** Craniocaudal mammograms of right and left breasts reveal partly obscured mass without calcifications in immediate prepectoral region of right breast. **(b)** High-frequency (10-MHz) breast US image reveals pear-shaped oval mass with smooth borders, homogeneous echogenicity, and no posterior acoustic shadowing, all suggestive of fibroadenoma. **(c–e)** Transverse dynamic bilateral breast MR images (290/4.6; flip angle, 90°). **(c)** Nonenhanced nonsubtracted image. **(d)** First contrast-enhanced image. **(e)** Subtracted image (**c** subtracted from **d**). On MR images, mass is oval with smooth borders but has strong rim enhancement and strong washout at delayed phase. This is a typical fibroadenoma-like appearance of a *BRCA1*-associated breast cancer. **(f)** Graph shows signal intensity *(SI)*–time course of the enhancing mass.

Figure 2

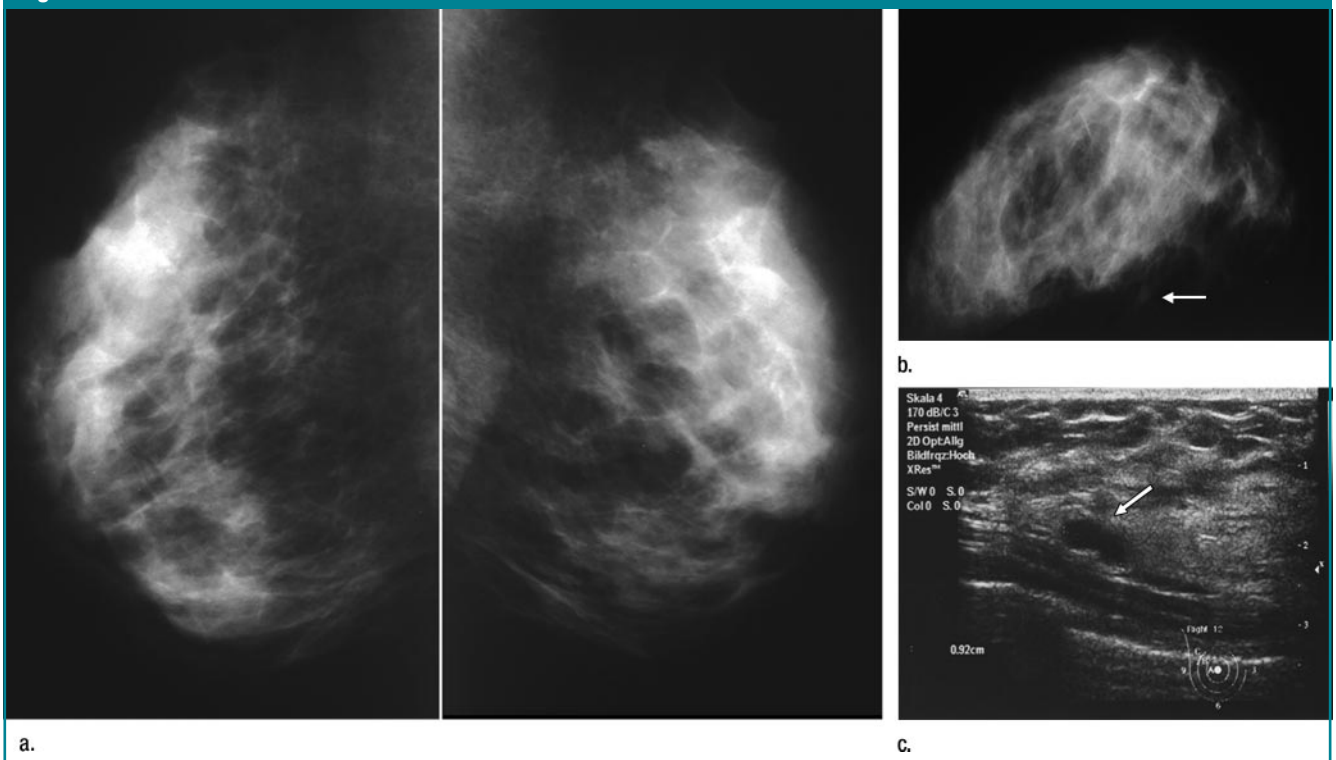

Figure 2: Lesion in 28-year-old asymptomatic woman with family history suggestive of hereditary breast cancer. **(a)** Mediolateral oblique mammograms of left and right breasts. **(b)** Craniocaudal view of right breast shows oval mass (arrow) with smooth border and no calcifications in immediate prepectoral region. **(c)** High-frequency (12-MHz) breast US image reveals oval well-defined mass (arrow) with anechoic echo pattern and posterior acoustic enhancement suggestive of a cyst. The lesion was rated as US–BI-RADS category 2 (suggestive of a cyst). *(Fig 2 continues.)*

with *BRCA1* mutation: None of the 14 *BRCA1*-associated invasive breast cancers exhibited calcifications; intraductal cancers were not observed in *BRCA1* carriers at all. As opposed to *BRCA1*-associated cancers, calcifications were observed in *BRCA2*-associated breast cancers: Two (40%) of five invasive breast cancers and one case of DCIS that were diagnosed in *BRCA2* mutation carriers exhibited calcifications.

Among the 64 invasive cancers of the entire study cohort, 15 exhibited a benign imaging phenotype (Figs 1, 2). Of those, seven appeared in documented carriers of a *BRCA1* mutation, another five appeared in women who were suspected of being, but were not yet proved to be, carriers of a *BRCA1* mutation and who belonged to the high-risk group. One of the 15 cancers occurred in a *BRCA2* mutation carrier, and two occurred in women in the moderate-risk group. Hereditary breast cancers with such a benign fibroadenoma-like morphology were predominantly high grade (13 [87%] of 15) (Fig 1).

Of 13 invasive breast cancers that appeared as non-masslike enhancement on MR images, two (15%) were observed in women at moderate risk and the remaining 11 (85%) were observed in women at high risk or in mutation carriers (Figs 3, 4).

No cases of DCIS arose in *BRCA1* mutation carriers, whereas all other groups showed an equal percentage of cases of DCIS among all cancers: Cases of DCIS represented 18% (four of 22) of cancers for the moderate risk group, 21% (seven of 34) of cancers for the high risk group, and 17% (one of six) of cancers for the *BRCA2* mutation carriers.

Although the location of the breast cancers in women at moderate risk was uniformly distributed in the anterior, middle, and posterior parts of the affected breasts, two-thirds of breast cancers that arose in women at high risk and in *BRCA1* carriers were located in the posterior part of the breast, mostly in the immediate prepectoral region (Table E5 [*http://radiology.rsnajnls.org/cgi/content/full/246/1/58/DC1*]).

Discussion

Our results suggest that the imaging phenotype of breast cancers that arose in women at increased familial risk differs from that of cancers found in women at average risk and that it also differs in cancers found among women in each of the different risk categories (moderately increased risk, high risk, and *BRCA1* or *BRCA2* mutation carriers).

It has already been suggested that familial breast cancer can exhibit benign morphologic features (oval or round shape, smooth or pushing margins)

Figure 2 (continued)

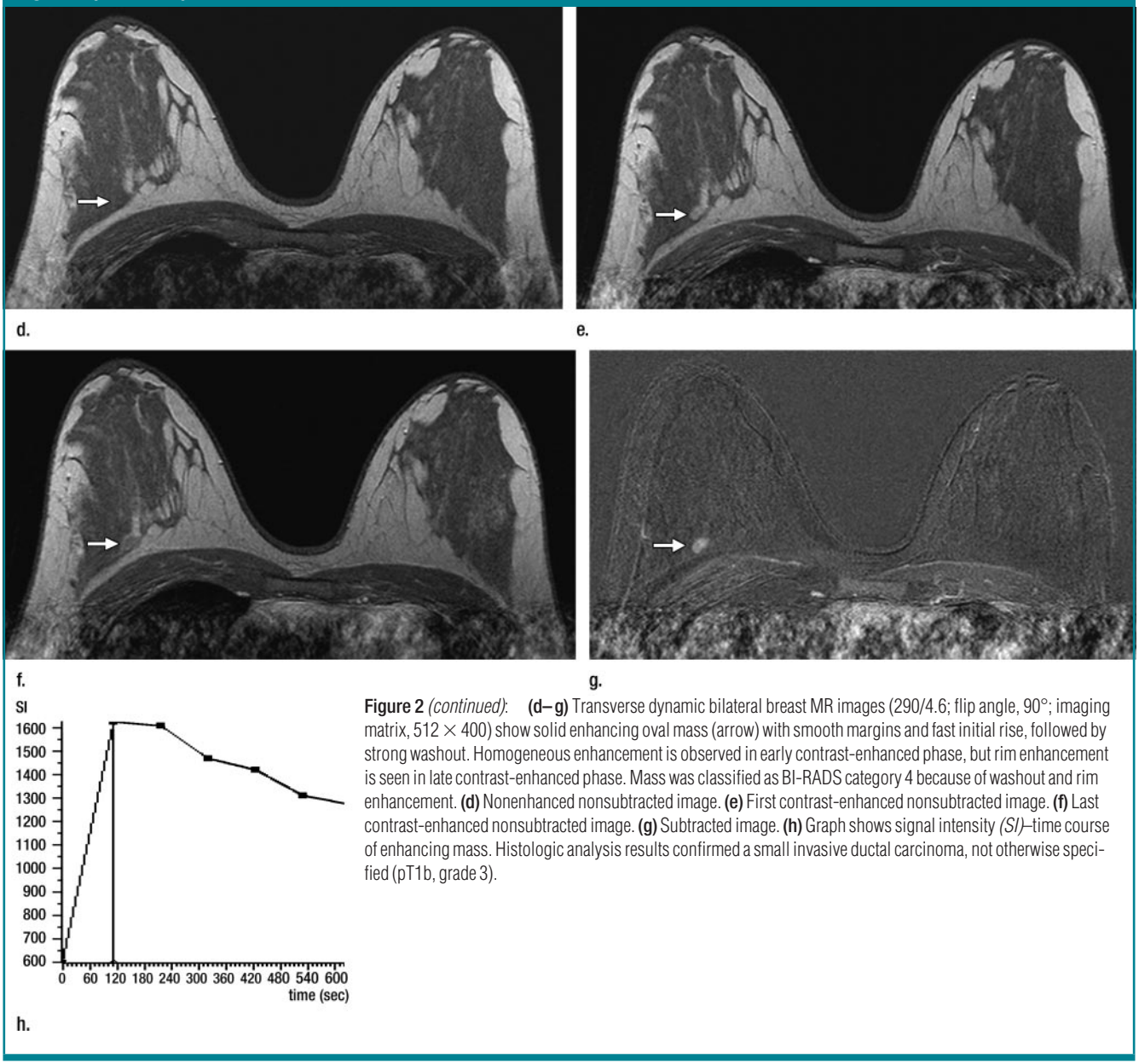

Figure 2 *(continued)*: **(d–g)** Transverse dynamic bilateral breast MR images (290/4.6; flip angle, 90°; imaging matrix, 512 × 400) show solid enhancing oval mass (arrow) with smooth margins and fast initial rise, followed by strong washout. Homogeneous enhancement is observed in early contrast-enhanced phase, but rim enhancement is seen in late contrast-enhanced phase. Mass was classified as BI-RADS category 4 because of washout and rim enhancement. **(d)** Nonenhanced nonsubtracted image. **(e)** First contrast-enhanced nonsubtracted image. **(f)** Last contrast-enhanced nonsubtracted image. **(g)** Subtracted image. **(h)** Graph shows signal intensity *(SI)*–time course of enhancing mass. Histologic analysis results confirmed a small invasive ductal carcinoma, not otherwise specified (pT1b, grade 3).

more often than sporadic breast cancer. In this series, 23% (15 of 64) of invasive cancers had this fibroadenoma-like appearance. This is in agreement with previously published results by Kaas et al (18), Tilanus-Linthorst et al (7), and Kuhl et al (11) who reported benign morphologic features in 23%–38% of familial breast cancers. Especially *BRCA1*-associated breast cancers tend to imitate fibroadenomas or even cysts.

Among the total of 15 breast cancers that exhibited benign morphologic features, 87% (13 of 15) were associated with a *BRCA1* mutation or occurred in women who, based on their family history, were suspected to carry the mutation. About half of the *BRCA1*-associated breast cancers in our cohort revealed this appearance. In the average nonselected screening cohort, the prevalence of breast cancers with benign morphologic features is low and has been reported to range between 1.4% and 4.7% (19,20); in young women without familial clustering of breast cancers, it rises to 7%—still substantially lower than the prevalence in the high-risk cohort.

The high prevalence of tumors with benign morphologic features is probably due to two reasons: First, it is well established that hereditary breast cancer tends to exhibit a medullar (or atypical medullar) differentiation (3,8,21–23)—a tumor type that is frequently associated

with benign morphologic features (pushing margins). Second, breast cancers that arise in women at high genetic risk tend to exhibit a high nuclear grade (24,25). It is well established that there is a correlation between tumor grade and morphologic appearance of the tumor: High-grade tumors are more likely to manifest mammographically and sonographically as well-defined masses, whereas intermediate- and low-grade tumors are more likely to provoke a desmoplastic reaction within surrounding tissue, giving rise to spiculated borders (19). Indeed, 13 (87%) of the 15 cancers that exhibited benign morphologic features in our cohort were high grade. Because more high-grade cancers were observable in women at high risk and in mutation carriers compared with those at moderately increased risk or in *BRCA2* carriers, this finding may also explain the higher prevalence of cancers with benign morphology in women at high familial risk.

Another feature of familial cancer observed in our cohort was the low prevalence of mammographic calcifications: Calcifications were identified in 12 (19%) of 64 invasive cancers and in

Figure 3

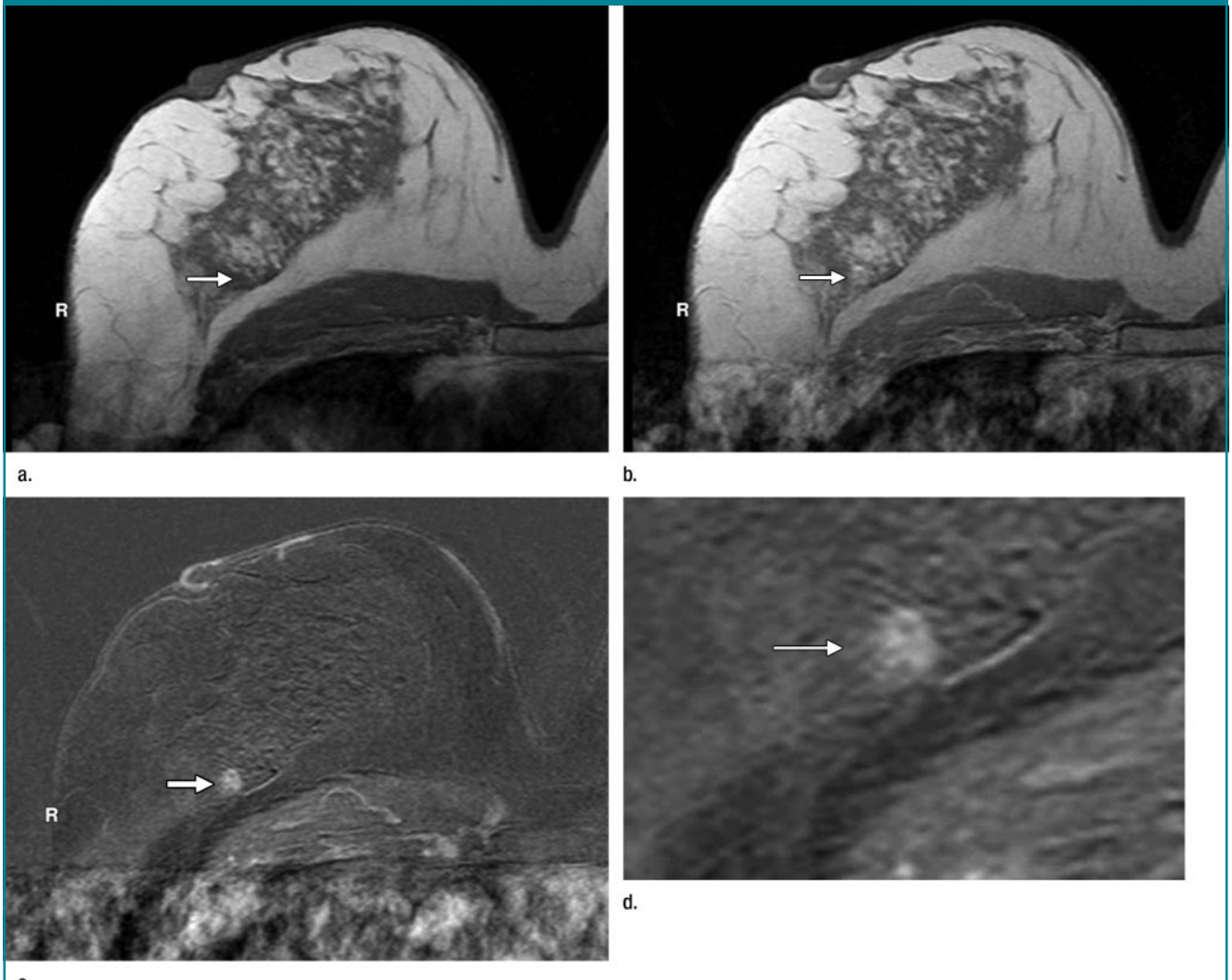

Figure 3: Small invasive breast cancer (arrow) of right breast in prepectoral region in 43-year-old asymptomatic woman suspected of being a *BRCA1* mutation carrier. **(a–c)** Transverse bilateral dynamic breast MR images, with right breast zoomed out (290/4.6; flip angle, 90°), show 6-mm area of hazy focal non-masslike enhancement. Note heterogeneous internal enhancement in immediate prepectoral region. **(a)** Nonenhanced nonsubtracted image of right breast. **(b)** Early contrast-enhanced nonsubtracted image of same breast. **(c)** Subtracted image of same breast. **(d)** Close-up view of lesion on **c**. Mammogram and breast US image (not shown) were normal (BI-RADS category 1). Excisional biopsy was performed after MR imaging–guided wire localization; results confirmed invasive ductal cancer, not otherwise specified (pT1b, grade 2).

Figure 4

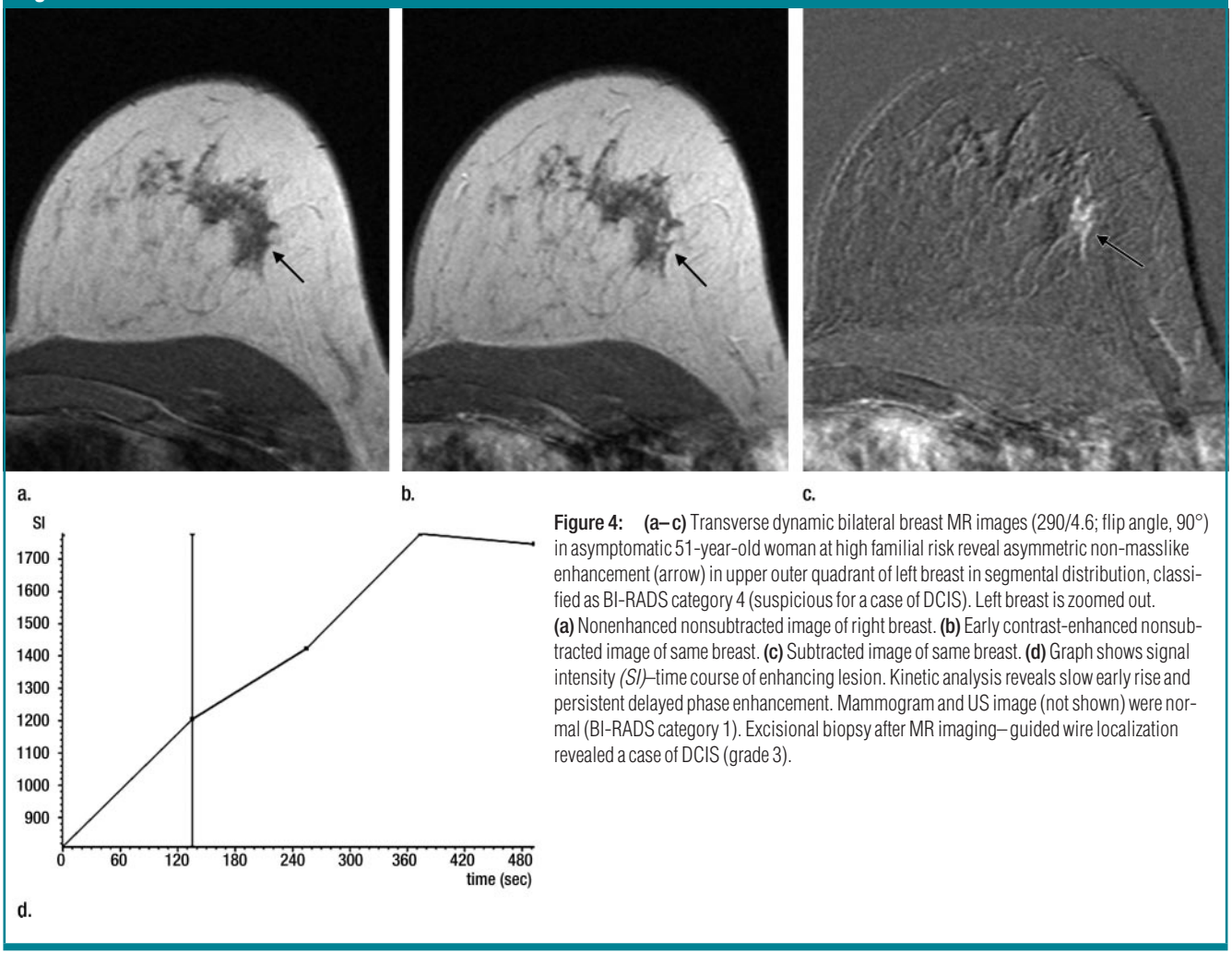

Figure 4: **(a–c)** Transverse dynamic bilateral breast MR images (290/4.6; flip angle, 90°) in asymptomatic 51-year-old woman at high familial risk reveal asymmetric non-masslike enhancement (arrow) in upper outer quadrant of left breast in segmental distribution, classified as BI-RADS category 4 (suspicious for a case of DCIS). Left breast is zoomed out. **(a)** Nonenhanced nonsubtracted image of right breast. **(b)** Early contrast-enhanced nonsubtracted image of same breast. **(c)** Subtracted image of same breast. **(d)** Graph shows signal intensity *(SI)*–time course of enhancing lesion. Kinetic analysis reveals slow early rise and persistent delayed phase enhancement. Mammogram and US image (not shown) were normal (BI-RADS category 1). Excisional biopsy after MR imaging–guided wire localization revealed a case of DCIS (grade 3).

four (33%) of 12 intraductal cancers. Stratified according to risk category, we found that *BRCA1* mutation carriers were least likely to exhibit breast cancers with calcifications: None of the invasive breast cancers associated with *BRCA1* exhibited microcalcifications; intraductal cancers were not observed in *BRCA1* mutation carriers at all. In women without documented mutation, the prevalence of calcifications was 17% (three of 18) and 26% (seven of 27) in the moderate- and the high-risk groups, respectively. This is a substantially lower percentage than that reported for the average screening cohort, in whom 50%–75% of malignant lesions seem to be associated with microcalcifications (26–28).

Interestingly, this finding matches with the prevalence of calcifications observed in women with *BRCA2*-associated breast cancers: *BRCA2* mutations are relatively rare (29,30). Accordingly, the overall number of *BRCA2*-associated breast cancers in our cohort was low, such that our findings in *BRCA2*-associated cancers may not be representative. However, it is noteworthy that in our cohort, which was small, half of the *BRCA2*-associated breast cancers (three of six) did exhibit mammographically visible calcifications, suggesting that this breast cancer may be more likely to be depicted with mammography than that occurring in *BRCA1* mutation carriers.

It is well established that mammographic sensitivity decreases with increasing breast density. Because screening for familial breast cancer involves very young women (screening starts at age 30 years or earlier), it seems natural to assume that the reduced mammographic sensitivity is caused by the dense breast tissue of women younger than 40 years of age (31,32). However, this assumption has not been confirmed with findings in our study. Mammographic fibroglandular tissue densities (as assessed according to the American College of Radiology categories) was similar among women in the different risk groups; in addition, the distribution of breast densities observed in our cohort did not differ from the breast density patterns that are

present in the average population. Moreover, in our cohort, breast densities in women with a positive (true-positive findings) mammogram did not differ significantly from those in women with a negative (false-negative findings) mammogram. We assume, therefore, that it is not, or not mainly, breast density that causes the low sensitivity of mammography in women with familial breast cancer.

All studies that have been published so far on screening women at increased familial risk for breast cancer were concordant in that MR imaging was consistently superior to mammography (and breast US). However, the sensitivity rates that were achieved with MR imaging in the different cohorts differed substantially. In the study published by Kriege and co-workers (13), breast MR imaging had a sensitivity of 71%—which is in fact low compared with sensitivity in publications from other groups; moreover, this (limited) sensitivity was achieved only if studies with findings rated as BI-RADS category 3 were taken as a positive test. If only the studies with findings rated as BI-RADS categories 4 and 5 were taken as a positive test, the sensitivity of breast MR imaging would have been 47%. This value was still higher than the corresponding mammographic sensitivity in the same cohort (40%), but it does suggest that, in this study, findings in a high number of breast MR imaging studies performed for cancers were rated as benign or probably benign.

Based on the results obtained in our cohort, we propose that this relatively low sensitivity of MR imaging in women at increased familial risk is due to the fact that these cancers may exhibit unusual imaging features also in breast MR imaging. These unusual features are *(a)* a high percentage of cancers that exhibit benign kinetic features and *(b)* a high percentage of cancers that appear as non-masslike enhancement.

Regarding kinetic features, in our cohort, 25 (33%) of 76 cancers exhibited benign kinetic features (slow or intermediate early rise, persistent enhancement in the delayed phase). This number includes 18 (28%) of 64 invasive cancers and seven (58%) of 12 intraductal cancers. Compared with the kinetic features of breast cancers in a series of consecutive women without a specific family history that was published previously (17), this proportion is substantially higher than expected. If the criteria that are used for image interpretation overemphasize enhancement kinetics, these lesions will go undetected by using breast MR imaging.

Regarding non-masslike enhancement, 20% of all 64 invasive cancers and 26% of invasive cancers arising in women at high familial risk appeared as non-masslike enhancement. In fact, the second most frequent MR imaging phenotype of women at high familial risk or with proved *BRCA1* mutation was a focus or a focal area of non-masslike enhancement. These lesions do not exhibit a correlate on nonenhanced T1- or T2-weighted MR images, they do not cause distortions of the normal fibroglandular tissue architecture, and they do not exhibit space-occupying effects but are merely visible because of their contrast enhancement. It is conceivable that this represents another reason for the nondetectability of familial breast cancer with nonenhanced imaging modalities such as mammography and breast US.

In addition to 20% (13 of 64) of invasive breast cancers, all MR imaging–visible cases of DCIS (ie, 11 of 12 intraductal cancers) appeared as non-masslike enhancement. This adds up to 24 invasive or intraductal cancers with non-masslike enhancement (32% of all cancers). Because the concept of non-masslike enhancement is relatively new (it has been propagated by the first edition of the breast MR imaging BI-RADS lexicon), the use of this concept will vary among screening sites. It is conceivable that the differences between the published sensitivity rates for cases of DCIS and invasive cancers are caused by the sets of diagnostic criteria that have been used. This is supported by the fact that, in the study published by Kriege et al (13), the very low sensitivity of MR imaging for diagnosing cases of DCIS of 17% contributed most to the overall limited sensitivity of MR imaging.

Of note, the analysis of enhancement kinetics may be misleading in non-masslike enhancement: Of 12 cases of DCIS in our cohort, seven exhibited an intermediate or slow early rise and six had a persistent type of delayed phase enhancement. DCIS lesions, just as diffusely infiltrating invasive cancers, tend to exhibit only a weak angiogenic activity and may exhibit benign kinetic features. In the article published by Kriege et al (13), it is not mentioned on which criteria the diagnosis and differential diagnosis were based, but based on a publication from the same group that appeared previously, it seems that the interpretation was mainly based on enhancement kinetics and that non-masslike enhancement was not considered (33).

Because hormonally induced enhancement will also appear as non-masslike enhancement and hormonal enhancement is frequently observed in young women undergoing breast MR imaging (34–36), the distinction between hormonally induced enhancement and non–mass-related enhancement caused by breast cancer can be difficult. In our cohort, transverse bilateral MR imaging was used; consequently, a direct side-by-side comparison of the enhancement pattern of the fibroglandular tissue was feasible. This factor facilitated the assessment of symmetry of non-masslike enhancement. If non-masslike enhancement was seen and its distribution rated equivocal, it was followed up after 3 months in order to evaluate whether it would persist over several menstrual cycles; in that case, biopsy was recommended.

The fibroadenoma-like appearance of *BRCA1*-associated breast cancer was less problematic for MR imaging than it was for mammography and breast US. The reason for this finding was that breast MR imaging offers additional diagnostic information that is independent of mass shape and margins, namely, mass internal enhancement (ie, the internal architecture) and enhancement kinetics. None of the 15 cancers with fibroadenoma-like appearance exhibited inter-

nal low-signal-intensity septations (a finding that is considered typical for fibroadenomas); moreover, a rim enhancement or a washout type of delayed enhancement was observed in all 15 of these fibroadenoma-like breast cancers. Because a plateau or washout time course is rarely seen in fibroadenomas (with the acquisition used herein, ie, two-dimensional gradient-echo MR imaging [17]) and rim internal enhancement is even less compatible with the diagnosis of fibroadenoma, these findings helped in the correct classification of these 15 lesions as BI-RADS category 4.

Independent of the morphologic features of breast cancers in our cohort, it appears that the location of lesions within the breast is an important predictor of malignancy: Women with documented *BRCA1* mutation and women at high familial risk tend to develop breast cancer in the posterior part of the breast. In this group of women, breast cancers showed a clear predilection for the posterior part of the breast, specifically for the immediate prepectoral region—more than two-thirds of breast cancers occurred in this region. This result was in contrast to the situation in women at moderately increased risk, in whom the location was evenly distributed in all three parts (posterior, middle, and anterior third) of the quadrants.

Our study had a number of limitations. First and most important, the small number of *BRCA2* mutation carriers and, accordingly, the small number of cancers in women with documented *BRCA2* mutation impaired the validity of our results. The same holds true for the overall low number of breast cancers that were observed in women at moderately increased risk. Further studies in larger groups of patients will have to be performed to corroborate (or refute) our conclusions. Second, the group of women at high risk was relatively heterogeneous; because not all women underwent mutation analysis, it is possible that this group also includes *BRCA* mutation carriers, such that the two risk groups overlap. Third, we did not include a comparison with aged-matched control subjects with breast cancer but without increased familial risk. Accordingly, it is conceivable that the findings we report were not caused by, or associated with, the specific high familial risk but may be associated with a young patient age. However, onset of breast cancer at a young age is, per se, associated with familial breast cancer (age at diagnosis has about the same predictive value as has the number of affected family members). Accordingly, a comparison with age-matched control subjects would, in turn, be biased in that a cohort with early-onset breast cancer would include a relatively high proportion of women with familial breast cancers—even in the absence of a family history of the disease. Last, a generalized estimating equation analysis was not performed for data clustering. However, we dealt with second primary tumors that arose in the opposite breasts, not with recurrences. In addition, those second primary tumors accounted for only eight of 76 cancers.

In conclusion, our results indicate that the imaging phenotype of familial breast cancer differs from that of sporadic breast cancer and also differs among women in the different risk categories, and this finding relates to all imaging modalities that were investigated (mammography, breast US, and MR imaging).

Our results imply that surveillance strategies for women at increased risk for breast cancer may have to be tailored to the type of risk category. In *BRCA1* mutation carriers, mammography will probably be of limited usefulness: None of the *BRCA1*-associated breast cancers exhibited mammographic calcifications. The absence of calcifications in *BRCA1*-associated cancers is probably the most important reason for the very low sensitivity of mammography in these women. In addition, there is growing evidence to suggest that *BRCA1* mutation carriers are more vulnerable to ionizing radiation (37–40); therefore, we propose to discontinue systematic mammographic screening in young women with *BRCA1* mutation and instead to use MR imaging (with or without US) for screening. In women with *BRCA2* mutation and in women without documented mutation, particularly those with moderately increased risk, mammography may yield additional diagnostic information (particularly microcalcifications) that may be useful for the further classification of enhancement identified with breast MR imaging.

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