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EPIDEMIOLOGY

Breast cancer detection and tumor characteristics in BRCA1 and BRCA2 mutation carriers

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Abstract
Purpose To describe imaging findings, detection rates, and tumor characteristics of breast cancers in a large series of patients with BRCA1 and BRCA2 mutations to potentially streamline screening strategies.
Methods An IRB-approved, HIPAA-compliant retrospective analysis of 496 BRCA mutation carriers diagnosed with breast carcinoma from 1999 to 2013 was performed. Institutional database and electronic medical records were reviewed for mammography and MRI imaging. Patient and tumor characteristics including age at diagnosis, tumor histology, grade, receptor, and nodal status were recorded.
Results Tumors in BRCA1 mutation carriers were associated exhibited significantly higher nuclear and histological grade compared to BRCA2 ($p < 0.001$). Triple-negative tumors were more frequent in BRCA1 mutation carriers, whereas hormone receptor-positive tumors were more frequent in BRCA2 mutation carriers ($p < 0.001$). BRCA2 mutation carriers more frequently presented with ductal carcinoma in situ (DCIS) alone 14% (35/246) and cancers more frequently exhibiting calcifications ($p < 0.001$). Mammography detected fewer cancers in BRCA1 mutation carriers compared to BRCA2 ($p = 0.04$): 81% (186/231) BRCA1 versus 89% (212/237) BRCA2. MRI detected 99% cancers in each group. Mammography detected cancer in two patients with false-negative MRI (1 invasive cancer, 1 DCIS). Detection rates on both mammography and MRI did not significantly differ for women over 40 years and women below 40 years.
Conclusions Breast cancers in BRCA1 mutation carriers are associated with more aggressive tumor characteristics compared to BRCA2 and are less well seen on mammography. Mammography rarely identified cancers not visible on MRI. Thus, the omission of mammography in BRCA1 mutation carriers screened with MRI can be considered.

Keywords BRCA mutation · Breast MRI · Mammogram · Breast cancer

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Introduction

Patients with BRCA1 and BRCA2 mutations are genetically predisposed for developing breast cancer. Previous reports have estimated that they have a lifetime risk of

breast cancer between 45 and 87% [1–4]. Tumor characteristics such as morphology, grade, and hormone receptor status will differ according to the BRCA mutation type [5, 6]. Imaging characteristics will also differ, often reflecting different tumor characteristics [7, 8].

Multiple studies demonstrate significantly higher sensitivity of breast magnetic resonance imaging (MRI) compared to mammography for detecting breast cancer, particularly in women at high risk [9, 10]. The American Cancer Society and the American College of Radiology recommend yearly mammography and MRI with MRI beginning at age 25 years and mammography at 30 for women at high risk. These two examinations can be performed either simultaneously or alternating at 6-month intervals [9–15]. However, data from several studies suggest that mammography may be of limited additional value particularly in young BRCA1 carriers [16, 17].

BRCA1 carriers often present with more aggressive tumors, which are harder to detect and characterize on mammography (e.g., triple-negative cancers). In contrast, BRCA2 carriers are more likely to present with ductal carcinoma in situ (DCIS), which often develops microcalcifications and is more likely to be detected on mammography [10, 18, 19]. In light of the limited sensitivity of mammography in mutation carriers particularly for those with the BRCA1 mutation and concern for potential radiation carcinogenesis, the possibility of eliminating mammography, particularly in younger women, has been suggested but not yet implemented.

The purpose of this study was to describe the imaging findings, detection rates, and tumor characteristics of breast cancers in a large series of patients with BRCA1 and BRCA2 mutations to potentially streamline screening strategies.

Methods

Our institutional review board approved this single-institution retrospective study, which was HIPAA compliant. The need for informed patient consent was waived.

Patients

A search of a prospectively populated database from 1999 to 2013 yielded 663 consecutive BRCA and high-risk mutation carriers diagnosed with breast carcinoma at our tertiary cancer institution. 145 patients were excluded due to suboptimal image quality or post biopsy imaging, incomplete medical or imaging reports, and 22 were excluded as they had other high-risk mutations. The study population therefore comprised 496 patients: 250 BRCA1 and 246 BRCA2 mutation carriers.

Patient and tumor characteristics

The following patient and tumor characteristics were recorded: age at diagnosis, presence or absence of clinical findings, mutation type, tumor histology, nuclear grade, receptor status, tumor size, and axillary node status.

Imaging analysis

All images were retrospectively reviewed by expert breast imagers with at least 3 years experience in breast imaging interpretation. Mammography and MRI images were reviewed blinded to patient history as well as to the images and reports of the other imaging modality. We recorded the presence or absence of mammographic findings: microcalcifications, architectural distortion, asymmetries, or masses. MRI findings were recorded including type of enhancement (mass vs. non-mass lesion).

Reference standard

Histopathology served as the reference standard in all patients.

Statistical analysis

Frequencies and percentages were used to summarize the distribution of histology, tumor receptor status, nuclear grade, and histological grade. Fisher's exact test was used to compare the distribution of these variables across mutational subgroups (BRCA1 or BRCA2). Mean was used to summarize the tumor size and the Wilcoxon test was used to compare the distribution of tumor size between BRCA1 and 2 mutation carriers.

For analysis by age group (patients aged 40 years or younger vs. patients above 40 years), detection rates between age groups were compared using Fisher's exact test.

All statistical analyses were performed using R version 3.1 (www.r-project.org) and SAS version 9.3 (Cary, North Carolina, USA). A p value of <0.05 was considered to be statistically significant.

Results

Patients and tumor findings

The population was evenly divided between BRCA1 50.4% (250/496) and BRCA2 mutation carriers 49.6% (246/496). Age at diagnosis ranged from 24 to 82 years with a mean of 44.1 years in BRCA1 mutation carriers and 45.1 years in BRCA2 mutation carriers. Invasive

carcinoma was present in 89% (440/496) of patients, and the remaining 11% (56/496) had pure DCIS. Detailed tumor characteristics are displayed in Table 1.

BRCA1 and BRCA2 mutation carriers showed statistically significant differences in tumor histology and hormone receptor status. BRCA1 mutation carriers more often had invasive ductal carcinomas and triple-negative tumors compared to BRCA2 mutation carriers who more often had hormone receptor-positive tumors including invasive lobular carcinomas ($p < 0.001$ for each comparison). Tumors in BRCA1 mutation carriers were also associated with a significantly higher nuclear and histological grade ($p < 0.001$). BRCA2 mutation carriers more frequently presented with DCIS alone, 15% (36/246), whereas BRCA1 mutation carriers presented with DCIS alone in 9% (23/250) ($p = 0.0026$).

On the other hand, tumor size did not significantly differ between the subgroups ($p < 0.001$). Lymph node status was determined in 229 BRCA1 and 211 BRCA2 carriers. There was no statistically significant difference in the number of patients with positive axillary lymph nodes at time of diagnosis: 27% (59/218) BRCA1 mutation carriers versus 35% (70/200) BRCA2 mutation carriers ($p = 0.08$).

Imaging findings

In our study which involved 496 patients, we found that 48% (240/496) of patients presented with clinical symptoms. We also found that 43/496 (9%) had interval cancers within 12 months of negative imaging. Of the patients who developed interval cancers, 28/43 (65%) were BRCA1 mutation carriers and 15/43 (35%) were BRCA2 mutation

Table 1 Patient and tumor characteristics of BRCA1 and BRCA2 mutation carriers

	Number of BRCA1 carriers (%)	Number of BRCA2 carriers (%)	Total
Histology			
Invasive ductal carcinoma	203 (81)	160 (65)	363
Invasive lobular carcinoma	2 (0.8)	18 (7.3)	20
Mixed invasive ductal and lobular carcinoma	9 (3.6)	20 (8.1)	29
Other	13 (5.2)	12 (4.9)	25
Unknown	2 (0.8)	1 (0.4)	3
Invasive carcinoma + DCIS[a]	132 (53)	150 (61)	282
Pure DCIS	21 (8.4)	35 (14)	56
Total	250	246	496
Invasive carcinoma			
Tumor receptor status			
Luminal	92 (40)	176 (83)	268
Basal	128 (56)	26 (12)	154
ER/PR neg Her2pos	3 (1.3)	5 (2.4)	8
Unknown	6 (2.6)	4 (1.9)	10
Total	229	211	440
Nuclear Grade			
1	2 (0.8)	8 (3.3)	10
2	63 (25)	102 (42)	165
3	160 (64)	105 (43)	265
Unknown	24 (9.6)	31 (13)	55
Total	249	246	495
Histological Grade			
1	2 (0.9)	4 (1.9)	6
2	32 (14)	52 (25)	84
3	180 (79)	128 (61)	308
Unknown	14 (6.1)	27 (13)	41
Total	228	211	439
Mean tumor size (cm)	1.12	1.3	

[a] Ductal carcinoma in situ

carriers. Cancers in 52% (256/496) patients were detected on screening without clinical symptoms. Of these, 10% (26/256) were diagnosed on their first screening exam; 87% (223/256) had undergone screening at regular intervals and had a negative prior screening exam; and 3% (7/256) did not comply with annual screening and the cancer was either detected at a longer interval ($n = 6$) or incidentally during the work-up of a different disease ($n = 1$).

Of the entire patient population, 76% (379/496) of patients were not originally aware they were mutation carriers and were tested at the time of diagnosis. Therefore, these patients had not undergone high-risk MRI screening and depending on age and/or compliance either underwent mammography or no screening.

At the time of their diagnosis, 94% (468/496) patients had mammograms and 60% (299/496) had MRI. Mammography and MRI were obtained simultaneously in 55% (274/496) of patients, whereas 39% (194/496) underwent only mammography and 5% (25/496) only MRI. In patients with available mammography, 86% (401/468) showed suspicious findings. However, MRI was positive in 99% (297/299) of patients.

Mammography detected significantly fewer cancers in BRCA1 mutation carriers compared to BRCA2 mutation carriers ($p = 0.011$): 81% (186/231) BRCA1 versus 89% (212/237) BRCA2. Mammography detection rates according to breast density in each mutation subgroup are displayed in Table 2. We found that 77% (41/53) of patients with positive MRI and negative mammography had dense breasts.

The detection of cancers by mammography in women with BRCA1 under 40 years was not significantly different from those over 40:81% (64/79) versus 82% (125/152) ($p = 0.41$). Detection of cancers by mammography in BRCA2 mutation patients was also not significantly different by age: 92% (73/79) of the cancers were detected on mammography in patients aged 40 years or younger and 88% (139/158) of the cancers in women over 40 years ($p = 0.04$).

Of the 2 BRCA1 carriers with a false-negative MRI, one patient had an invasive carcinoma and the other had pure DCIS. Both patients had positive findings on corresponding mammography (Table 3).

Imaging characteristics

Imaging findings on mammography and MRI are illustrated in Table 4. Cancers in BRCA2 carriers exhibited calcifications on mammography more frequently compared to BRCA1 carriers ($p < 0.001$). There was no statistically significant difference in the presence of mass or architectural distortion between the subgroups ($p > 0.05$). Enhancement patterns on MRI did not significantly differ between BRCA1 and BRCA2 mutation carriers ($p > 0.05$).

Discussion

Five to 10% of all breast cancers are hereditary and a subgroup of these patients with hereditary cancers carries a gene mutation. The most commonly recognized gene mutations are BRCA1 and BRCA2. Distinct differences in tumor and imaging characteristics between the two have been previously described [5, 6]. Nevertheless, current screening recommendations are identical for BRCA1 and BRCA2 carriers and include yearly mammography and MRI: MRI beginning at 25 years of age and mammography at 30. Both MRI and mammography are well-accepted

Table 2 Detection rates on mammography by breast density

Breast density	Detection rate in BRCA1	Detection rate in BRCA2
ACR1	100% (6/6)	71% (5/7)
ACR2	85% (51/60)	92% (54/59)
ACR3	84% (105/125)	90% (122/136)
ACR4	68% (27/40)	87% (27/31)
Total	231	233

Table 3 Imaging and tumor findings in two patients with false-negative MRI

Patient	Age at diagnosis (years)	Mutation type	MRI	Mammography	Ultrasound	Histology	Histological size (mm)
3	49	BRCA 1	Negative	Mass	Negative	Invasive carcinoma, NST[a]	2
5	35	BRCA 1	Negative	Microcalcification	Negative	High grade DCIS[b]	n.a.

[a] No special type

[b] Ductal carcinoma in situ

Table 4 Imaging findings on mammography and MRI in BRCA1 and BRCA2 mutation carriers

	Number of BRCA1 carriers (%)	Number of BRCA2 carriers (%)	Total
Mammography	$n = 231$	$n = 237$	$n = 468$
Microcalcification	77 (37)	129 (32)	206(51)
Mass and/or architectural distortion	127 (55)	102 (43.0)	229(57)
MRI	$n = 154$	$n = 143$	$n = 299$
Mass	111 (47)	93 (39)	204(86)
Mass and non-mass enhancement	15 (6)	17 (7)	32 (14)
Non-mass enhancement	28 (9)	33 (11)	61(21)
Total	154	143	297

examinations for the detection breast cancer; however, MRI is well known to be more sensitive for breast cancer detection than mammography with reported sensitivities of up to 97% [9–13].

In our study, BRCA1 carriers were more likely to develop invasive ductal carcinomas with high nuclear and histological grade, and particularly triple-negative cancers. These more aggressive tumors are more difficult to detect on mammography due to benign appearance and were therefore also more likely to present as interval cancers. This may in part be an effect of rapid growth rate especially in triple-negative cancers [20]. Hormone receptor-positive tumors with a lower histological and nuclear grade were more frequently seen in BRCA2 mutation carriers [5, 6]. BRCA2 carriers were also more likely to present with pure DCIS or DCIS adjacent to their invasive cancers [21] and more likely to have calcifications on mammography.

This study of 496 breast cancer patients carrying BRCA1 or BRCA2 mutations is, to our knowledge, the largest study describing the imaging and tumor characteristics in these patients. Our results are consistent with previous studies: MRI was equally sensitive in BRCA1 as well as BRCA2 mutation carriers with cancer detection of 99% [11, 22–25]. On the other hand, mammography detected significantly fewer cancers in patients with BRCA1 mutation than in patients with BRCA2 mutation (81 vs. 89%) again likely due to lack of calcifications and higher incidence of aggressive tumors, which often present with benign mammographic features. Hamilton et al[19] found microcalcifications in 73% of BRCA2-associated cancers compared to 12% in BRCA1 carriers, while in our larger study population, the trend in the difference was similar albeit smaller: 54 versus 33%.

To assess potential differences in cancer detection by age, we divided the study population into patients aged 40 years or younger and those above 40 years. Detection on both mammography and MRI did not significantly differ between the two age groups. This was consistent with results by Riedl et al. [26] who showed that age did not significantly affect the sensitivities of MRI and mammography in screened BRCA subgroups. Despite lack of differences in sensitivity by age, we did demonstrate that mammography added little diagnostic benefit to MRI. In the BRCA1 subgroup, we found only 2 patients with false-negative MRI and false-positive mammograms (1 invasive carcinoma and 1 pure DCIS); only one of them was younger than 40. This is in keeping with reports by Obdeijn et al. [27], Heijnsdijk et al. [28], and Narayan et al. [29]. Obdeijn focused on BRCA1 mutation carriers and found only 2 of 94 tumors detected by mammography alone, and both were patients with DCIS over 40. Heijnsdijk assessed a screening population of 1275 mutation carriers and found only one invasive tumor in the BRCA1 subgroup below the age of 40 detected by mammography alone. Narayan investigated whether adding mammography to breast MRI in women below 40 increased cancer detection rates. In this cohort, the cancer detection rate for mammography was 0%, suggesting that MRI alone may be useful in screening high-risk women under 40.

Phi et al. have recently published a meta-analysis evaluating the contribution of mammography to MRI screening based on BRCA status and age [30]. They demonstrated that addition of mammography to MRI did not significantly increase the sensitivity of MRI alone in either group. However, among BRCA2 patients under 40 years, one-third of breast cancers were detected by mammography alone. Heijnsdijk also found more tumors detected by mammography only in the below age 40 BRCA2 group (3 invasive, 4 DCIS) [28]. Rijnsburger [13] demonstrated significantly better sensitivity of mammography in BRCA2 mutation carriers than BRCA1, due to the higher proportion of DCIS in that population. In this study, we did not demonstrate any cancers in BRCA2 patients under 40 detected by mammography alone perhaps because of improved detection of DCIS on MRI.

Overall, in our study, mammography identified only two cancers that were not visible on MRI. Our findings in this hitherto unparalleled large series of high-risk patients with breast cancer add to and support prior evidence that

mammography in BRCA1 mutation carriers adds minimal benefit to MRI. This indicates that mammography can be eliminated from screening BRCA1 patients without negatively affecting patient outcome. In patients undergoing alternating screening at 6-month intervals, consideration could be given to performing another vascular-enhancing imaging study such as a second MRI or contrast-enhanced mammography rather than the less sensitive mammography [31]. In BRCA2 mutation carriers, despite our results which did not demonstrate additional benefit of mammography in patients screened with MRI, the preponderance of available data suggests that mammography may still be of value and therefore yearly screening with mammography and MRI must remain the recommendation.

Our study has several limitations. This is a single-institution retrospective analysis of a prospectively populated database with missing data in several patients. Not all patients underwent both mammography and MRI, which could potentially lead to selection bias. 76% (379/496) of patients were not aware of their mutational carrier status and were tested at diagnosis. Therefore, these patients had not undergone high-risk MRI screening and depending on age and compliance either underwent mammography or no screening at all. In addition, the database started in 1999 when MRI was not yet recommended for high-risk patients, which in part explains why known high-risk patients did not undergo MRI screening. Since the examinations were performed over a long period, results may be somewhat different due to the use of less technologically advanced imaging in the more remote patients.

In conclusion, this study of breast imaging in 496 BRCA mutation carriers with breast cancer overall confirms data from multiple smaller studies: Breast cancers in BRCA1 mutation carriers are associated with more aggressive tumor characteristics compared to BRCA2 mutation carriers and BRCA2 mutation carriers are more likely to present with DCIS alone or DCIS adjacent to the invasive cancer. MRI is very sensitive in both BRCA subgroups, whereas mammography detects more cancers in BRCA2 mutation carriers. Similar to other studies, we demonstrated minimal benefit of mammography in BRCA1 mutation carriers, and we believe that mammography could be omitted in those having screening MRI. In this study, mammography was also of limited additional value in BRCA2 mutation carriers suggesting possible omission as well; however, in light of conflicting evidence, yearly screening of BRCA2 carriers with mammography and MRI remains the recommendation. Eliminating mammograms in BRCA1 mutation carriers would reduce radiation exposure in these potentially radiosensitive patients, spare additional potential anxiety from mammography examinations, and reduce costs without negatively affecting patient outcome.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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