HHS Public Access

Author manuscript

Breast Cancer Res Treat. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Breast Cancer Res Treat. 2017 June ; 163(3): 565–571. doi:10.1007/s10549-017-4198-4.

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 1999-2013 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.

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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.

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

Results—Tumors in BRCA1 mutation carriers 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 vs. 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

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 [9,11,10,12-15]. 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 [18,19,10]. 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 vs. 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 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) didn't 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 vs. 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) vs. 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 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% [9,11,10,12,13].

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% [22-24,11,25]. 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% vs. 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 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 was 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.

Acknowledgments

This research was funded in part through the National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748.

References

1. Miki Y. Cellular functions of BRCA genes - from basic science to therapeutics. Gan to kagaku ryoho Cancer & chemotherapy. 2012; 39(4):498–501. [PubMed: 22504671]
2. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Micklem G. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995; 378(6559):789–792. DOI: 10.1038/378789a0 [PubMed: 8524414]
3. Evans DG, Shenton A, Woodward E, Lalloo F, Howell A, Maher ER. Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. BMC Cancer. 2008; 8:155.doi: 10.1186/1471-2407-8-155 [PubMed: 18513387]
4. van der Kolk DM, de Bock GH, Leegte BK, Schaapveld M, Mourits MJ, de Vries J, van der Hout AH, Oosterwijk JC. Penetrance of breast cancer, ovarian cancer and contralateral breast cancer in BRCA1 and BRCA2 families: high cancer incidence at older age. Breast Cancer Res Treat. 2010; 124(3):643–651. DOI: 10.1007/s10549-010-0805-3 [PubMed: 20204502]
5. Atchley DP, Albarracin CT, Lopez A, Valero V, Amos CI, Gonzalez-Angulo AM, Hortobagyi GN, Arun BK. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol. 2008; 26(26):4282–4288. DOI: 10.1200/JCO.2008.16.6231 [PubMed: 18779615]
6. Rakha EA, Reis-Filho JS, Ellis IO. Basal-like breast cancer: a critical review. J Clin Oncol. 2008; 26(15):2568–2581. DOI: 10.1200/JCO.2007.13.1748 [PubMed: 18487574]
7. Causer PA, Jong RA, Warner E, Hill K, Wong JW, Curpen BN, Plewes DB. Breast cancers detected with imaging screening in the BRCA population: emphasis on MR imaging with histopathologic correlation. Radiographics. 2007; 27(Suppl 1):S165–182. DOI: 10.1148/rg.27si075503 [PubMed: 18180225]
8. Gilbert FJ, Warren RM, Kwan-Lim G, Thompson DJ, Eeles RA, Evans DG, Leach MO. United Kingdom Magnetic Resonance Imaging in Breast Screening Study G. Cancers in BRCA1 and BRCA2 carriers and in women at high risk for breast cancer: MR imaging and mammographic features. Radiology. 2009; 252(2):358–368. DOI: 10.1148/radiol.2522081032 [PubMed: 19703879]
9. Kuhl C, Weigel S, Schrading S, Arand B, Bieling H, Konig R, Tombach B, Leutner C, Rieber-Brambs A, Nordhoff D, Heindel W, Reiser M, Schild HH. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol. 2010; 28(9):1450–1457. DOI: 10.1200/JCO.2009.23.0839 [PubMed: 20177029]
10. Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, Cutrara MR, DeBoer G, Yaffe MJ, Messner SJ, Meschino WS, Piron CA, Narod SA. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA : the journal of the American Medical Association. 2004; 292(11):1317–1325. DOI: 10.1001/jama.292.11.1317292/11/1317 [PubMed: 15367553]
11. Kriege M, Brekelmans CT, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM, Manoliu RA, Kok T, Peterse H, Tilanus-Linthorst MM, Muller SH, Meijer S, Oosterwijk JC, Beex LV, Tollenaar RA, de Koning HJ, Rutgers EJ, Klijn JG. Magnetic Resonance Imaging Screening Study G. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med. 2004; 351(5):427–437. DOI: 10.1056/NEJMoa031759 [PubMed: 15282350]
12. Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, Gilbert FJ, Griebsch I, Hoff RJ, Kessar P, Lakhani SR, Moss SM, Nerurkar A, Padhani AR, Pointon LJ, Thompson D, Warren RM. group Ms. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet. 2005; 365(9473):1769–1778. DOI: 10.1016/S0140-6736(05)66481-1 [PubMed: 15910949]
13. Rijnsburger AJ, Obdeijn IM, Kaas R, Tilanus-Linthorst MM, Boetes C, Loo CE, Wasser MN, Bergers E, Kok T, Muller SH, Peterse H, Tollenaar RA, Hoogerbrugge N, Meijer S, Bartels CC, Seynaeve C, Hooning MJ, Kriege M, Schmitz PI, Oosterwijk JC, de Koning HJ, Rutgers EJ, Klijn JG. BRCA1-associated breast cancers present differently from BRCA2-associated and familial

cases: long-term follow-up of the Dutch MRISC Screening Study. J Clin Oncol. 2010; 28(36): 5265–5273. DOI: 10.1200/JCO.2009.27.2294 [PubMed: 21079137]

14. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, Morris E, Pisano E, Schnall M, Sener S, Smith RA, Warner E, Yaffe M, Andrews KS, Russell CA. American Cancer Society Breast Cancer Advisory G. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007; 57(2):75–89. [PubMed: 17392385]
15. Lee CH, Dershaw DD, Kopans D, Evans P, Monsees B, Monticciolo D, Brenner RJ, Bassett L, Berg W, Feig S, Hendrick E, Mendelson E, D'Orsi C, Sickles E, Burhenne LW. Breast cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. Journal of the American College of Radiology : JACR. 2010; 7(1): 18–27. DOI: 10.1016/j.jacr.2009.09.022 [PubMed: 20129267]
16. Berrington de Gonzalez A, Berg CD, Visvanathan K, Robson M. Estimated risk of radiation-induced breast cancer from mammographic screening for young BRCA mutation carriers. J Natl Cancer Inst. 2009; 101(3):205–209. DOI: 10.1093/jnci/djn440 [PubMed: 19176458]
17. Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L. Trial Management G. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. Lancet. 2006; 368(9552):2053–2060. DOI: 10.1016/S0140-6736(06)69834-6 [PubMed: 17161727]
18. Schrading S, Kuhl CK. Mammographic, US, and MR imaging phenotypes of familial breast cancer. Radiology. 2008; 246(1):58–70. DOI: 10.1148/radiol.2461062173 [PubMed: 18096529]
19. Hamilton LJ, Evans AJ, Wilson AR, Scott N, Cornford EJ, Pinder SE, Khan HN, Macmillan RD. Breast imaging findings in women with BRCA1- and BRCA2-associated breast carcinoma. Clin Radiol. 2004; 59(10):895–902. DOI: 10.1016/j.crad.2004.03.013 [PubMed: 15451348]
20. Sung JS, Jochelson MS, Brennan S, Joo S, Wen YH, Moskowitz C, Zheng J, Dershaw DD, Morris EA. MR imaging features of triple-negative breast cancers. The breast journal. 2013; 19(6):643–649. DOI: 10.1111/tbj.12182 [PubMed: 24015869]
21. Arun B, Vogel KJ, Lopez A, Hernandez M, Atchley D, Broglio KR, Amos CI, Meric-Bernstam F, Kuerer H, Hortobagyi GN, Albarracin CT. High prevalence of preinvasive lesions adjacent to BRCA1/2-associated breast cancers. Cancer prevention research (Philadelphia, Pa). 2009; 2(2): 122–127. DOI: 10.1158/1940-6207.capr-08-0050
22. Orel SG, Mendonca MH, Reynolds C, Schnall MD, Solin LJ, Sullivan DC. MR imaging of ductal carcinoma in situ. Radiology. 1997; 202(2):413–420. DOI: 10.1148/radiology.202.2.9015067 [PubMed: 9015067]
23. Zuiani C, Francescutti GE, Londero V, Zunnui I, Bazzocchi M. Ductal carcinoma in situ: is there a role for MRI? J Exp Clin Cancer Res. 2002; 21(3 Suppl):89–95. [PubMed: 12585661]
24. Menell JH, Morris EA, Dershaw DD, Abramson AF, Brogi E, Liberman L. Determination of the presence and extent of pure ductal carcinoma in situ by mammography and magnetic resonance imaging. Breast J. 2005; 11(6):382–390. DOI: 10.1111/j.1075-122X.2005.00121.x [PubMed: 16297080]
25. Boetes C, Strijk SP, Holland R, Barentsz JO, Van Der Sluis RF, Ruijs JH. False-negative MR imaging of malignant breast tumors. Eur Radiol. 1997; 7(8):1231–1234. DOI: 10.1007/s003300050281 [PubMed: 9377507]
26. Riedl CC, Luft N, Bernhart C, Weber M, Bernathova M, Tea MK, Rudas M, Singer CF, Helbich TH. Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. J Clin Oncol. 2015; 33(10):1128–1135. DOI: 10.1200/JCO.2014.56.8626 [PubMed: 25713430]
27. Obdeijn IM, Winter-Warnars GA, Mann RM, Hooning MJ, Hunink MG, Tilanus-Linthorst MM. Should we screen BRCA1 mutation carriers only with MRI? A multicenter study. Breast Cancer Res Treat. 2014; 144(3):577–582. DOI: 10.1007/s10549-014-2888-8 [PubMed: 24567197]
28. Heijnsdijk EA, Warner E, Gilbert FJ, Tilanus-Linthorst MM, Evans G, Causer PA, Eeles RA, Kaas R, Draisma G, Ramsay EA, Warren RM, Hill KA, Hoogerbrugge N, Wasser MN, Bergers E, Oosterwijk JC, Hooning MJ, Rutgers EJ, Klijn JG, Plewes DB, Leach MO, de Koning HJ. Differences in natural history between breast cancers in BRCA1 and BRCA2 mutation carriers and

effects of MRI screening-MRISC, MARIBS, and Canadian studies combined. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2012; 21(9):1458–1468. DOI: 10.1158/1055-9965.EPI-11-1196

29. Narayan AK, Visvanathan K, Harvey SC. Comparative effectiveness of breast MRI and mammography in screening young women with elevated risk of developing breast cancer: a retrospective cohort study. Breast Cancer Res Treat. 2016; 158(3):583–589. DOI: 10.1007/s10549-016-3912-y [PubMed: 27444927]
30. Phi XA, Saadatmand S, De Bock GH, Warner E, Sardanelli F, Leach MO, Riedl CC, Trop I, Hooning MJ, Mandel R, Santoro F, Kwan-Lim G, Helbich TH, Tilanus-Linthorst MM, van den Heuvel ER, Houssami N. Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis. British journal of cancer. 2016; doi: 10.1038/bjc.2016.32
31. Le-Petross HT, Whitman GJ, Atchley DP, Yuan Y, Gutierrez-Barrera A, Hortobagyi GN, Litton JK, Arun BK. Effectiveness of alternating mammography and magnetic resonance imaging for screening women with deleterious BRCA mutations at high risk of breast cancer. Cancer. 2011; 117(17):3900–3907. DOI: 10.1002/cncr.25971 [PubMed: 21365619]

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

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 2 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