Case series

Evaluation of breast screening strategies in a high risk breast and ovarian cancer clinic

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ABSTRACT

Recent data suggest that BRCA mutation carriers younger than 40 may not benefit from mammography in addition to MRI. Our objective was to evaluate screening modalities utilized in a high-risk population. Clinicopathologic data were abstracted for patients followed in a high risk clinic from 2007 to 2017. Descriptive statistics were calculated and associations between categorical variables were evaluated using chi-square tests. 631 women comprised the study population; 496 patients had no known mutation (79%), 128 (20%) had a BRCA mutation, and 7 patients had other deleterious mutations. BRCA mutation carriers were more likely to have cancers diagnosed after mammogram callbacks (p = 0.0046) and biopsies (p = 0.0026) compared to non-BRCA mutation carriers. BRCA mutation carriers were also more likely to have cancers diagnosed after biopsies following screening MRI (p = 0.045). 13 BRCA patients were diagnosed with cancer (average age 51). Of the cancers diagnosed after abnormal MRI, 3 were DCIS; all 3 patients had a normal mammogram 4–6 months prior. In those found after abnormal mammogram (n = 6), follow up MRI was performed in 4 cases; all demonstrated the lesion. Three patients were diagnosed younger than 40, 1 on mammogram and 2 on MRI. The patient diagnosed on mammogram had no prior MRI and the lesion was seen on follow-up MRI. Interval screening MRI identified DCIS in BRCA patients with a previous normal mammogram and cancers diagnosed on mammogram were all identified on follow-up MRI. These findings support further evaluation of MRI alone until age 40 in BRCA mutation carriers.

1. Introduction

Germline pathogenic variants in a variety of genes are associated with an increased lifetime risk of breast and gynecologic cancers. Patients with a pathogenic variant in BRCA1, for example, have a lifetime cumulative risk of 72% and 44% for developing breast and ovarian cancer, respectively; for BRCA2 carriers, those risks are 69% and 17% (Kuchenbaecker et al., 2017). Although pathogenic variants in BRCA1 and BRCA2 account for the majority of hereditary breast and gynecologic cancers, pathogenic variants in a number of other high and moderate penetrance genes, including DNA mismatch repair genes, TP53, PALB2, ATM, CHEK2, BARD1, BRIP1, CDH1, NBN, NF1, PTEN, RAD51C, RAD51D, and STK11 have also been implicated. Recent improvements in knowledge and accessibility of genetic testing has enhanced the detection of hereditary breast and ovarian cancer variants, leading to more widespread use of high-risk screening tools and risk-reducing surgeries.

Breast magnetic resonance imaging (MRI) has become standard of care in breast cancer screening for high risk women (those with a deleterious mutation, prior therapeutic chest radiation, or 20–25% or greater lifetime risk of breast cancer, per the American Cancer Society), due to the increased sensitivity of identifying early breast cancers compared to mammogram, albeit at the expense of an increased false positive rate, with positive predictive values ranging from 24 to 71% (Stoutjesdijk et al., 2001; Kuhl et al., 2003). The addition of breast MRI screening has been validated in high risk populations (Krieger et al., 2004; Kuhl et al., 2005). The American Cancer Society specifically recommends that patients with germline pathogenic variants in BRCA1...
or 2 begin breast cancer screening with MRIs at 25 years old and that they add surveillance mammography at 30 years old (Saslow et al., 2007). However, mammography, like MRI, is not without potential harms of both increased radiation exposure as well as the benefit-harm trade-off of overdiagnosis versus mortality reduction. Recent data from the radiology literature suggest that BRCA1 and BRCA2 carriers under 40 years old may not benefit from mammography in addition to MRI screening (van Zelst et al., 2017; Vreemann et al., 2018).

There are a number of studies that address breast cancer screening specifically in patents that carry a pathogenic variant in BRCA, but few assess broader high-risk populations. The objectives of the present study were to evaluate screening modalities utilized in a High Risk Breast and Ovarian Cancer (HBOC) clinic, to assess abnormalities found on mammogram and breast MRI screening, and to specifically compare BRCA and non-BRCA carriers with respect to callbacks, biopsies, and cancer diagnoses. A secondary objective was to analyze screen detected cancers in BRCA patients younger than 40 years old to determine outcomes of mammography use in this population.

2. Materials and methods

Following Institutional Review Board review at the University of Virginia, all patients who were seen in the HBOC clinic at the University of Virginia from January 1, 2007 through March 1, 2017 were identified using an institutional Clinical Data Repository (CDR). Patients followed in this clinic were deemed to be high risk if they carried a known genetic mutation, met clinical criteria for a potential hereditary cancer syndrome, had a first or second degree relative with ovarian cancer, or met high risk breast criteria (over 20–25% lifetime risk of breast cancer). The CDR contains patient demographics and known genetic mutations. Through electronic medical record (EMR) review, patients who were only seen once in clinic for consultation and were deemed to not be truly high risk for breast cancer were excluded. Those who elected not to pursue their high risk screening at the University of Virginia were also excluded. Patients were considered to be high risk if they were known mutation carriers or had over a 20% lifetime risk on Tyrer-Cuzick (T-C) model or if they were deemed high enough risk to have a screening breast MRI recommendation as part of their follow-up in the high risk clinic. Details on frequency and results (e.g. callbacks, biopsies, cancer diagnoses) of breast cancer screening were abstracted by EMR review. Patients with a personal history of breast cancer were not included in this screening population. Characteristics of BRCA gene mutation carriers with screening-detected cancers were then examined granularly. Univariate analyses were used to compare baseline patient characteristics and breast cancer screening outcomes by BRCA mutation carrier status. Data were compared using Chi-square tests for categorical variables and appropriate parametric and non-parametric tests for continuous variables. A p-value < 0.05 was used for statistical significance. IBM SPSS Statistics (Version 24) was used for all statistical analyses.

3. Results

The HBOC clinic saw 1348 patients over the ten-year study period. Six hundred thirty-one patients (46.8%) were deemed to be at high-risk for breast cancer; of the high-risk patients, 496 patients had no known pathogenic variant (79%), 128 (20%) had a pathogenic variant in BRCA1 or BRCA2, and 7 patients had other pathogenic variants in known breast cancer genes (1 TP53, 1 PALB2, 3 ATM, 2 CHEK2).

The differences in patient characteristics of BRCA carriers (N = 128) versus high-risk non-BRCA carriers (N = 503) are listed in Table 1. Those with a known BRCA variants were more likely to have had genetic testing at our institution versus those who are not known to have a BRCA pathogenic variant (non-BRCA carriers) (30% vs 45%; p = 0.002). Compared to non-BRCA patients, BRCA patients were on average younger (44.0 vs 46.0; p = 0.024), had higher rates of oral contraceptive use (88% vs 80%; p = 0.037), had more total screening mammograms (6.0 vs 4.0; p < 0.001), and were younger at first screening MRI (44.0 vs 47.0; p = 0.03). Additionally, BRCA mutation carriers were more likely to undergo risk-reducing mastectomy (45% vs 14%; p < 0.001) and risk-reducing bilateral salpingo-oophorectomy (56% vs 8.9%; p < 0.001) compared to non-BRCA mutation carriers. Of note, there were no statistically significant differences in body mass index, Ashkenazi Jewish ancestry, race, insurance status, level of education, known breast cancer risk factors (e.g. age at menarche, age at menopause, parity, etc.), utilization of genetic counseling services, and age at first screening mammogram between BRCA and non-BRCA high-risk patients (all p > 0.05).

Results of screening mammograms and MRIs, including callback, biopsies, cancer diagnoses) of breast cancer screening were abstracted by EMR review. Patients with a personal history of breast cancer were not included in this screening population. Characteristics of BRCA gene mutation carriers with screening-detected cancers were then examined granularly. Univariate analyses were used to compare baseline patient characteristics and breast cancer screening outcomes by BRCA mutation carrier status. Data were compared using Chi-square tests for categorical variables and appropriate parametric and non-parametric tests for continuous variables. A p-value < 0.05 was used for statistical significance. IBM SPSS Statistics (Version 24) was used for all statistical analyses.

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Results of screening mammograms and MRIs, including callback,
biopsy, and cancer rates, are shown in Tables 2 and 3, respectively. A total of 531 patients completed at least one screening mammogram and 399 patients completed at least one screening breast MRI at our institution. In sum, there were 3258 screening mammograms and 1218 screening breast MRIs performed over the study period. In the entire cohort over the ten-year course, 3.8% of non-BRCA patients were ultimately diagnosed with breast cancer compared to 10.2% of BRCA carriers \((p = 0.0061)\). Of the high-risk patients who received mammograms at UVA, 91 BRCA and 440 non-BRCA carriers, 45% and 54%, respectively, received callbacks \((p = 0.13)\). The rate of biopsies following callbacks after screening mammograms was not significantly different between BRCA and non-BRCA patients \((29\% \text{ vs } 16\%; p = 0.30)\). However, patients with a pathogenic variant in BRCA were more likely to have cancers diagnosed after mammogram callbacks \((15\% \text{ vs } 3.8\%; p = 0.0046)\) and biopsies \((50\% \text{ vs } 13\%; p = 0.0026)\) compared to non-BRCA mutation carriers. BRCA mutation carriers were also more likely to have cancers diagnosed after biopsies following screening MRI \((27\% \text{ vs } 11\%; p = 0.045)\), but rates of MRI callbacks, biopsies, and cancers diagnosed after callbacks was not statistically significantly different between the two groups \((p > 0.05)\). BRCA patients were diagnosed with cancer \((n = 13)\) at an average age of 51 (range 29–70). Characteristics of screening-detected cancers in BRCA1 and BRCA2 carriers are shown in Table 4. Of the cancers diagnosed after abnormal MRI, three were ductal carcinoma in situ (DCIS); in all three cases, there had been a normal mammogram within 4–6 months prior to the MRI that found the cancer. In those found after abnormal mammogram \((n = 6)\), follow up MRI was performed in four cases; all demonstrated the lesion identified on mammogram. Only one of these cases had a preceding MRI and it was normal one year prior to the abnormal mammogram. Three patients were diagnosed younger than 40, one on mammogram and two on MRI. The patient diagnosed on mammogram had no prior MRI and the lesion was seen on immediate follow-up diagnostic MRI.

## 4. Discussion

Women with BRCA mutations in our patient population were more likely to have breast cancers diagnosed after both MRI and mammogram compared to patients with family history alone. Despite the differences in rates of cancer diagnoses between BRCA and non-BRCA mutation groups, the present study did not find a difference in callback or biopsy rates following both MRI and mammography. Therefore, there were more false positive recalls for those without a BRCA mutation, limiting the positive predictive value of MRI in this cohort. This has been reported scantily in the literature but certainly may hold clinical relevance, as false positives add to healthcare costs by necessitating further workup and may cause emotional harm by generating breast cancer anxiety in the patient (Nelson et al., 2016). A recent study found the false positive recall rates following mammogram or MRI to be 22.2% and 26.3% in BRCA mutation carriers and others at increased risk without a mutation, respectively (Vreemann et al., 2018). A similar trend is observed in the current study.

This study aimed to look specifically at cancers diagnosed in BRCA mutation carriers under the age of 40 in light of recent literature that calls into question the added utility of screening mammography in this population (van Zelst et al., 2017; Vreemann et al., 2018; Kramer et al., 2017; De Gonzalez et al., 2009). Of the breast cancers diagnosed in BRCA patients \((n = 13)\) in our study population, three patients were younger than 40 years old, two BRCA1 carriers and one BRCA2 carrier. Of these patients, two of the cancers were diagnosed on MRI and one on mammogram (the oldest patient of the three), and the patient whose cancer was initially seen on mammography had no prior MRI and the lesion was seen on follow-up MRI. The utility of different imaging modalities in this younger age group of BRCA patients has been examined by a research group in the Netherlands over the past few years (van Zelst et al., 2017; Vreemann et al., 2018). This group found, in a population of BRCA mutation carriers, that 3 of 61 cancers were detected only on mammogram (with none in those younger than 40) and that the addition of mammogram to MRI resulted mostly in the detection of a small number of DCIS cases that were occult on MRI. A primary argument for utilizing mammography (in addition to MRI) in breast cancer screening for BRCA mutation carriers is that it is better than MRI for identifying DCIS (Sung et al., 2016; Cilotti et al., 2007). However, in the current study, the three BRCA patients with DCIS all had normal mammograms 4–6 months prior to DCIS being detected on MRI. This is supported by a prospective study that found that 48% of high-grade DCIS cases were missed on mammography but diagnosed by MRI alone; conversely, only two cases were missed by MRI and detected on mammography (Kuhl et al., 2007).

In women under 40 years old, the number of screening mammograms needed to detect an MRI occult cancer was 1829. These results are also supported by a meta-analysis of four breast cancer screening trials of high risk women that found only one invasive cancer detected by mammography alone in BRCA1 mutation carriers (Heijnsdijk et al., 2012). Besides potentially not adding much screening benefit in this cohort, mammography has a number of risks that could be reduced by

### Table 2

| No Known Variant | BRCA1 or 2 | p-value |
|------------------|------------|---------|
| Mammo callbacks  | 237 (54)   | 41 (45) | 0.13 |
| Biopsy after mammo | 68 (16) | 12 (29) | 0.30 |
| Cancer diagnosed after mammo | 9 (1.8) | 6 (6.6) | 0.017 |
| Cancer diagnosed after callback | 9/237 (3.8) | 6/41 (15) | 0.0046 |
| Cancer diagnosed after biopsy | 9/68 (13) | 6/12 (50) | 0.0026 |

### Table 3

| No Known Variant | BRCA1 or 2 | p-value |
|------------------|------------|---------|
| MRI callbacks    | 117 (38)   | 35 (37) | 0.84 |
| Biopsy after MRI | 90 (30)    | 26 (28) | 0.73 |
| Cancer diagnosed after MRI | 10 (3.3) | 7 (7.4) | 0.080 |
| Cancer diagnosed after callback | 10/117 (8.5) | 7/35 (20) | 0.059 |
| Cancer diagnosed after biopsy | 10/90 (11) | 7/26 (27) | 0.045 |

### Table 4

| BRCA | Age | Imaging | Pathology | Grade | Size (cm) | ER/PR/HER2 | pTN* | |---|---|---|---|---|---|---|---|
|-----|----|-------|-----------|------|----------|-----------|------|---|
| 1   | 38 | Mammo | IDC, DCIS | III  | 7.5      | +/- +/-   | T3N2a | |
| 1   | 58 | Mammo | IDC      | III  | 0.5      | +/- +/-   | T1N0  | |
| 1   | 51 | Mammo | IDC, DCIS | III  | 1.6      | +/- +/-   | T1N1  | |
| 2   | 50 | Mammo | IDC, DCIS | II   | 0.9      | +/- +/-   | T1N0  | |
| 2   | 46 | Mammo | DCIS     | II   | NA       | +/NA/-   | T1N0  | |
| 2   | 56 | Mammo | IDC, DCIS | II   | 1.3      | +/- +/-   | T1N0  | |
| 1   | 48 | MRI   | IDC      | III  | 1.5      | +/- +/-   | T1Nx  | |
| 1   | 59 | MRI   | DCIS     | I    | 0.2      | +/- NA/NA | T1N0  | |
| 1   | 34 | MRI   | IDC      | II   | NA       | +/- +/-   | NA    | |
| 1   | 58 | MRI   | DCIS     | II/III | NA       | +/NA/NA  | T1N0  | |
| 1   | 66 | MRI   | IDC, DCIS | III  | 1.4      | +/- +/-   | T1N0  | |
| 2   | 29 | MRI   | DCIS     | III  | 0.8      | +/- NA/NA | T1N0  | |
| 2   | 70 | MRI   | IDC, DCIS | II   | 0.4      | +/- +/-   | T1N0  | |

Mammo = mammogram; MRI = magnetic resonance imaging; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; IDC = invasive ductal carcinoma; DCIS = ductal carcinoma in situ. * pTN = pathologic staging; M0 for all cases.

## Table 4

Characteristics of screening-detected cancers in BRCA1 and BRCA2 gene mutation carriers.
delaying when this imaging modality is started in high-risk patients. Potential harms include unnecessary costs, callback procedures, and the risk of radiation-induced breast cancer (De Gonzalez et al., 2009; Phi et al., 2016). BRCA mutation carriers may be particularly susceptible to the cumulative effect of yearly mammograms, as they have impaired repair of the double-strand DNA breaks that are caused by low-dose X-rays (Powell and Kachnic, 2003). Therefore, the potential benefit of discovering an occasional MRI occult cancer in this younger age group must be balanced with the potential harms of repeated mammography.

This study has several limitations. It is a single-institution, retrospective study. This did allow for more thorough chart review and consistency, but it also resulted in a relatively small study size of patients, especially those who were diagnosed with cancer, which limits the generalizability of the results. Finally, a proportion of patients did not follow the recommended breast cancer screening schedule and a small number were lost of follow up, both of which may have affected the data.

In conclusion, patients with a pathogenic variant in BRCA 1 or 2 were more likely to be diagnosed with breast cancer following all screening modalities compared to high-risk non-BRCA carriers. In addition, MRI was able to effectively identify DCIS in the BRCA population. In BRCA mutation carriers younger than 40 years old, there were no MRI occult cancers found. These findings begin to address the question of whether MRI alone is a reasonable breast cancer screening strategy for BRCA mutation carriers under 40 years old. Larger studies are warranted to further investigate this question.

CRediT authorship contribution statement

Anne T. Knisely: Conceptualization, Data curation, Formal analysis, Investigation, Writing - original draft. Martha E. Stewart: Data curation, Methodology, Writing - review & editing. Christine Garcia: Conceptualization, Writing - review & editing. Martha H. Thomas: Data curation, Methodology, Writing - review & editing. Susan C. Modesitt: Conceptualization, Writing - review & editing. Kari L. Ring: Conceptualization, Formal analysis, Investigation, Project administration, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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