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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 *BRCA*2 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% (Stoutjeskijk et al., 2001; Kuhl et al., 2003). The addition of breast MRI screening has been validated in high risk populations (Kriege et al., 2004; Kuhl et al., 2005). The American Cancer Society specifically recommends that patients with germline pathogenic variants in *BRCA* 1

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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 *BRCA*1 or *BRCA*2, 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,

Table 1
Patient characteristics.

	No Known Variant n = 503 (%)	*BRCA1* and *BRCA2* n = 128 (%)	p-value
Patient Age (years)*	46.0 (37.0–55.0)	44.0 (33.0–53.0)	0.024
BMI (kg/m2)*	25.9 (22.7–31.9)	26.5 (22.8–32.5)	0.94
Ashkenazi Jewish	22 (4.4)	10 (7.8)	0.11
Race			0.10
White	432 (86)	111 (87)	
Black	48 (9.5)	9 (7.0)	
Hispanic	10 (2.0)	5 (3.9)	
Asian	3 (0.6)	1 (0.8)	
Other	10 (2.0)	2 (1.6)	
Education Level			0.26
< 8th grade	6 (1.2)	3 (2.3)	
Some high school	15 (3.0)	2 (1.6)	
High school diploma	46 (9.1)	9 (7.0)	
Some college	73 (15)	19 (15)	
College degree	134 (27)	39 (30)	
Graduate school/degree	183 (36)	31 (24)	
Unknown	46 (9.1)	25 (20)	
Insurance Status			0.55
Medicare	43 (8.5)	9 (7.0)	
Medicaid	18 (3.6)	7 (5.5)	
Private	407 (81)	96 (75)	
Self-pay	14 (2.8)	5 (3.9)	
Unknown	21 (4.2)	11 (8.6)	
Reproductive Factors			
Age at menarche (years)	12.0 (12.0–13.0)	12.0 (12.0–14.0)	0.45
Age at menopause (years)	49.0 (45.0–51.0)	48.0 (43.5–53.0)	0.97
Parity	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.073
Age at first birth (years)	25.0 (21.0–29.0)	23.0 (20.5–29.0)	0.86
Breastfeeding duration (mo.)	4.0 (0.0–14.0)	1.0 (0.0–13.0)	0.11
SERM (preventive) use	48 (9.5)	9 (7.0)	0.38
Oral contraceptive use	404 (80)	113 (88)	0.037
HRT (past or present)	81 (16)	16 (13)	0.31
Genetics			
Genetic counseling**	235 (47)	62 (48)	0.73
Genetic testing**	152 (30)	57 (45)	0.002
Breast Cancer Screening/Prevention			
Screening mammogram (number)	6.0 (3.0–9.0)	4.0 (2.0–7.0)	< 0.001
Age first screening mammo (yr.)	42.0 (36.0–50.0)	41.0 (32.0–51.0)	0.23
Screening breast MRI (number)	2.5 (2.0–5.0)	3.0 (1.0–4.0)	0.64
Age first screening MRI (yr.)	47.0 (40.0–54.0)	44.0 (33.0–54.0)	0.030
Risk reducing mastectomy**	14 (2.8)	45 (35)	< 0.001
Risk reducing BSO**	45 (8.9)	72 (56)	< 0.001

Categorical variables are reported as N (%) and continuous variables as median (IQR).

SERM = selective estrogen receptor modulator; HRT = hormone replacement therapy; MRI = magnetic resonance imaging; BSO = bilateral salpingo-oophorectomy.

* As reported at initial High-Risk Clinic visit.

** At the University of Virginia.

Table 2
Results of screening mammograms.

	No Known Variant n = 440 (%)	*BRCA1* or *2* n = 91 (%)	p-value
Mammogram callbacks	237 (54)	41 (45)	0.13
Biopsy after mammogram	68 (16)	12 (29)	0.30
Cancer diagnosed after mammogram	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
Results of screening MRIs.

	No Known Variant n = 305 (%)	*BRCA1* or *2* n = 94 (%)	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

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% vs 16%; $p = 0.30$). However, patients with a pathogenic variant in *BRCA* were more likely to have cancers diagnosed after mammogram callbacks (15% vs 3.8%; $p = 0.0046$) and biopsies (50% 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% 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 (all $p > 0.05$).

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 the 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,

Table 4
Characteristics of screening-detected cancers in *BRCA1* and *BRCA2* gene mutation carriers.

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	-/-/-	T1aN0
1	51	Mammo	IDC, DCIS	III	1.6	+/-/-	T1cN1
2	50	Mammo	IDC, DCIS	II	0.9	+/+/-	T1bN0
2	46	Mammo	DCIS	II	NA	+/NA/-	TisN0
2	56	Mammo	IDC, DCIS	II	1.3	+/+/-	T1cN0
1	48	MRI	IDC	III	1.5	+/-/-	T1cNx
1	59	MRI	DCIS	I	0.2	+/NA/NA	TisN0
1	34	MRI	IDC	II	NA	-/-/-	NA
1	58	MRI	DCIS	II/III	NA	+/NA/NA	TisN0
1	66	MRI	IDC, DCIS	III	1.4	-/-/-	T1cN0
2	29	MRI	DCIS	III	0.8	+/NA/NA	TisN0
2	70	MRI	IDC, DCIS	II	0.4	+/+/-	T1aN0

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.

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 scantly 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

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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