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Differences Between Screen-Detected and Interval Breast Cancers Among BRCA Mutation Carriers

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Abstract

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Disclosures and Compliance with Ethical Standards

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Conflict of Interest: First author Dr. Melissa Pilewskie declares that she has no conflict of interest. Second author Emily C. Zabor declares that she has no conflict of interest. Third author Elizabeth Gilbert declares that she has no conflict of interest. Fourth author Michelle Stempel declares that she has no conflict of interest. Fifth author Dr. Oriana Petruolo declares that she has no conflict of interest. Sixth author Dr. Debra Mangino declares that she has no conflict of interest. Seventh author Dr. Mark Robson discloses consultant/advisory roles with AstraZeneca, McKesson, and Pfizer, and research funding to his institution from AstraZeneca, AbbVie, Medication, Myriad, Invitae, Pfizer, and Tesaro. Eighth author Dr. Maxine Jochelson has received lecture remuneration from General Electric.

Compliance with Ethical Standards

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. This article does not contain any studies with animals performed by any of the authors.

Background—BRCA mutation carriers have an elevated lifetime breast cancer risk and remain at risk for interval cancer development. We sought to compare BRCA mutation carriers with screen-detected versus interval breast cancers.

Methods—Women with a known BRCA mutation prior to a breast cancer diagnosis were identified. Clinical and pathologic factors, and imaging within 18 months of diagnosis were compared among screen-detected versus interval cancers. Interval cancers were those detected by physical exam among women undergoing regular screening.

Results—Of 124 breast cancers, 92 were screen and 22 clinically detected, of which 11 were interval cancers among regular screeners, and 10 were incidentally found on prophylactic mastectomy. Women with interval cancers were younger, had lower body mass indexes, and were more likely to be Black than those with screen-detected cancers ($p<0.05$). Interval cancers were all invasive, larger, more likely to be node positive, and more likely to require axillary lymph node dissection and chemotherapy ($p<0.05$). No significant differences were seen by BRCA mutation, mammographic density, MRI background parenchymal enhancement, tumor grade, or receptor status between cohorts. Women screened with both mammogram and MRI had significantly lower proportions of interval cancers compared to women screened with only mammogram or MRI alone ($p<0.05$).

Conclusions—Interval breast cancers among BRCA mutation carriers have worse clinicopathologic features than screen-detected tumors, and require more-aggressive medical and surgical therapy. Imaging with mammogram and MRI is associated with lower interval cancer development and should be utilized among this high-risk population.

Keywords

BRCA; interval breast cancer; screen-detected breast cancer; mutation carriers

Introduction

Women with a BRCA1 or BRCA2 germline mutation have a significantly elevated breast cancer risk, with a lifetime risk ranging from approximately 50% to 80%.[1–3] Given this elevated risk, surveillance is recommended with annual screening mammogram, MRI, and clinical breast exam.[4] Although increased surveillance is endorsed by national and international societies[5–8], there remains no consensus on the optimal schedule for imaging, with both synchronous annual MRI and mammography, or alternating MRI and mammogram every 6 months utilized in practice.

Interval cancers are tumors that present with clinical symptoms between screening rounds. Despite more-aggressive screening, BRCA carriers remain at risk for interval cancer development. In the general population, women who develop interval cancers are more likely to be younger, have dense breasts, and have a family history of breast cancer.[9–21] Interval cancers in the general population have also been shown to exhibit worse prognostic factors such as larger tumor size, higher grade, triple negative phenotype, and lymph node involvement at diagnosis.[9,22,12,13,16,23–25,20,21] There are data to suggest that interval cancers have a higher rate of recurrence and worse survival compared to screen-detected

cancers. [26,27,13,28,25,20,29] However, very little is known about risk factors and outcomes of interval cancers among BRCA carriers.

Here we sought to compare screen-detected versus interval breast cancers among women with a known BRCA mutation prior to their breast cancer diagnosis to identify differences in patient demographics, clinicopathologic features, treatments, and outcomes. Screening regimens were analyzed between the cohorts to assess the association of different screening schedules and the development of interval tumors.

Methods

Women with a known BRCA1 or BRCA2 mutation prior to their breast cancer diagnosis who were treated for their cancer at Memorial Sloan Kettering Cancer Center (MSK) between 2003 and 2016 were retrospectively identified from hospital databases following institutional review board approval. Women with a prior history of breast cancer, a variant of unknown significance, or who underwent genetic testing after their breast cancer diagnosis were excluded.

Clinically detected tumors were those detected by physical exam regardless of screening history. Interval cancers were those detected by physical exam and/or symptoms within 18 months following a negative screening exam (either mammogram or MRI). Regular screening was defined as having had breast imaging with either mammogram or MRI within 18 months prior to a breast cancer diagnosis. Patient demographics, imaging history, clinical and pathologic factors, treatments, and outcomes were collected and analyzed. Many women had their pre-diagnosis screening done at outside facilities and presented to MSK for their cancer care. All available imaging, which included 94% of images (available for 116 of 124 tumors), was reviewed by a single breast radiologist (MJ).

Patient, disease, and treatment characteristics were summarized using median (range) when continuous, and number (frequency) when categorical. Between-group comparisons were made with the Kruskal-Wallis test and Fisher’s exact test for continuous and categorical variables, respectively. All outcomes were calculated from the date of surgery to date of event. Patients who were event-free were censored at their date of last follow-up. The Kaplan-Meier method was used to estimate times to event. A p-value < 0.05 was considered statistically significant. All statistical analyses were conducted in R software version 3.4.3 (R Core Development Team, Vienna, Austria).

Results

From 2003 to 2016 there were 124 cancers diagnosed in 117 women with a known BRCA mutation, including 7 women with bilateral breast cancer. Of the 124 cancers, 92 were screen detected, 22 were clinically detected, and 10 were incidentally found on prophylactic mastectomy. Of the 22 clinically detected tumors, 11 were true interval cancers (diagnosed by clinical symptoms within 18 months of negative breast screening). Median follow-up time from breast cancer diagnosis for the entire cohort was 43.1 months (range, 6.5-169 months).

Entire Population

Table 1 compares patient demographics among all clinically detected and screen-detected tumors. Women with clinically detected cancers were significantly younger at diagnosis, had a lower body mass index (BMI), and were more likely to be Black compared to women with screen-detected tumors ($p < 0.05$). While there was a higher percentage of women with a BRCA1 mutation in the clinically detected cancer group, this difference was not statistically significant. Women with clinically detected tumors were less likely to have undergone a bilateral salpingo-oophorectomy (BSO) compared to women with screen-detected tumors. Eleven patients (10%) in the cohort did have a prior history of ovarian cancer, although rates of screen-detected and interval cancers did not differ ($p = 1.0$). No difference was seen in the presence of family history of breast cancer in first- or second-degree relatives, with both groups having very high rates of a positive family history.

Regular Screeners

Among 75 women undergoing regular screening, 64 (85%) had screen-detected tumors and 11 (15%) presented with interval cancers (Table 1). Similar to the entire cohort of clinically detected tumors, women with interval cancers were younger at diagnosis, had lower BMI, and were more likely to be Black compared to regular screeners with screen-detected tumors ($p < 0.05$).

All interval cancers were invasive, whereas 20% of screen-detected tumors were ductal carcinoma in situ (DCIS) (Table 2). Interval cancers were larger, presented at higher stage, and were more likely to be node positive compared to screen-detected tumors ($p < 0.05$). There was no significant difference in estrogen receptor, progesterone receptor, or HER2 status among interval tumors and screen-detected cancers in this population. Treatment factors are summarized in Table 3. Women with interval cancers were more likely to require an axillary lymph node dissection and to receive chemotherapy compared to those with screen-detected tumors. Among this cohort of BRCA positive patients, the majority were treated with mastectomies in all groups.

Women with interval cancers were significantly more likely to have undergone screening with mammogram alone compared to women with screen-detected tumors (46% versus 11%, $p = 0.02$) (Table 4). Among the population of regular screeners, interval cancers developed in 3/34 (8.8%) screened with alternating MRI and mammogram, 2/27 (7.4%) screened with synchronous MRI and mammogram, 5/13 (38.5%) screened with mammogram alone, and 1/2 (50%) screened with MRI alone. The median time from negative screening to development of interval cancer was 8 months (range, 5-16 months). No difference in mammographic Breast Imaging Reporting and Data System (BIRADS) density or MRI background parenchymal enhancement among MRI screeners was observed between groups.

Prophylactic Mastectomies

There were 10 cancers detected in prophylactic mastectomies. The median age at diagnosis was 45 years, all 10 women were White, 4 were BRCA1 carriers, and 6 were BRCA2 carriers. All women had negative screening within 8 months of their surgery (9 women had a

negative MRI and 1 woman had a negative mammogram alone). Eight of the 10 tumors identified on prophylactic mastectomies were DCIS, 1 was a 1 mm invasive ductal carcinoma, and the last presented with LCIS in the breast and invasive lobular carcinoma in a lymph node.

Outcomes

There were very few recurrences and deaths in the entire cohort, with 1 contralateral breast cancer, 3 local recurrences, 4 regional recurrences 4 distant recurrences, and 3 breast cancer deaths. Among the 11 women with interval cancers, 1 woman developed both a contralateral cancer and local recurrence, and 1 patient developed distant metastases and died of disease.

Discussion

Interval cancers comprised 15% of breast cancers diagnosed among a cohort of women with a known BRCA gene mutation who were undergoing regular screening prior to their breast cancer diagnosis. Demographics associated with interval cancer development among this cohort of BRCA mutation carriers included younger age and Black race, factors reported to be associated with interval cancers among the general population.[11,13,16,23,20] Women with interval cancers were less likely to have undergone a BSO, which may be a reflection of the younger age of this cohort. A lower BMI was also significantly associated with interval cancers. It is known that BMI imparts contrasting breast cancer risk among premenopausal and postmenopausal women, with a lower BMI associated with a higher breast cancer risk among premenopausal women.[30,31] While our cohort represents a relatively young population of breast cancer patients, we are unaware of other data showing that a lower BMI is associated with an increased risk of interval breast cancer development.

Mirroring reports on interval cancers among the general breast cancer population, we found that interval cancers had higher-risk features.[22,13,16,23–25,20,21] The interval cancers in this population were all invasive, larger, and more likely to be node positive at presentation compared to screen-detected tumors. While the literature demonstrates that interval cancers in the general population are more likely to be triple negative or estrogen receptor negative/progesterone negative/HER2 positive[12,13,16,25,20], we found no difference in receptor status between interval and screen-detected tumors.

In conjunction with the worse clinical features identified, women with clinically detected/interval cancers were more likely to require more extensive treatment, including axillary lymph node dissection and chemotherapy. While there were very few recurrences and deaths among this population, the morbidity and quality-of-life impact on more-aggressive breast cancer treatment are important differences among these populations. Further study to identify optimal screening strategies and mechanisms to minimize interval cancer risk are necessary.

Notably, during a period when MRI screening was available and recommended for increased surveillance in BRCA mutation carriers, only 66% of the cohort was undergoing regular screening, and among regular screeners, 17% had a mammogram alone in the 18 months prior to their breast cancer diagnosis. Komenaka et al followed 13 BRCA carriers from

1995-2002 with annual mammography alone. During the study period, 6 women (46%) developed interval cancers, 4 developed screen-detected tumors, and only 3 women did not develop breast cancer.[32] Half of all interval cancers were node positive, and all 6 women had dense breast tissue on mammogram. Although this was a small study, it highlights the high incidence of interval cancers among BRCA carriers screened with mammogram alone and the poor prognostic factors seen at presentation. Conversely, Sung et al examined high-risk women, defined as women with a personal history of breast cancer, a family history of breast cancer, a BRCA mutation, a high-risk breast lesion, or prior mantle radiation therapy, who underwent screening with both mammogram and MRI between 2005-2010. Of 222 cancers detected, only 5% were interval cancers, and, interestingly, there were no interval cancers detected among 19 women with a known BRCA mutation.[33]

MRI has been shown to detect earlier-stage cancers and has higher sensitivity in BRCA carriers than mammography, ultrasound, and clinical breast exam; therefore, it is an important screening modality among this high-risk population.[34,35] The National Comprehensive Cancer Network, American Cancer Society, and American College of Radiology[5,7,8] recommend screening with annual mammogram and MRI for BRCA carriers.[4] As noted, among a population of known BRCA carriers treated for their breast cancer at a tertiary cancer care center, there remains a cohort of women who were either not undergoing regular screening or who were receiving less-intensive screening. Data are emerging that highlight the underutilization of screening MRI among high-risk women.[36–38] It is noted that many of these women underwent pre-diagnosis screening at outside facilities. Unfortunately, we do not have data on the type of facility or screening program that women were followed in, but we are currently analyzing our own utilization of MRI screening in a dedicated high-risk screening program. Further study is necessary to investigate barriers to MRI use among high-risk women to identify possible interventions to improve appropriate screening in this cohort. Furthermore, given that interval cancers developed at a significantly younger age than screen-detected tumors, understanding barriers to screening adherence among young women at high risk are paramount.

There remain minimal data examining whether alternating MRI and mammogram every 6 months is superior to annual synchronous MRI and mammogram. In theory, if both imaging modalities were sensitive for breast cancer, then alternating imaging every 6 months would decrease interval cancer development. In our study, we found no difference in interval cancer rates among regular screeners who had alternating mammogram and MRI compared to those undergoing synchronous mammogram and MRI; however, there were relatively low numbers of women in each category for comparison. Overall, women imaged with both MRI and mammogram in any screening pattern had a lower proportion of interval cancers than women screened with mammogram alone. Lowry et al performed a comparative effectiveness analysis comparing 6 screening strategies among BRCA carriers and concluded that alternating digital mammography and MRI at 6-month intervals was the most effective screening strategy.[39]

This study is limited by the limitations inherent to a single-institution retrospective review. Furthermore, while this is the largest report on interval cancers among a population of

BRCA carriers, this remains a small cohort of women, limiting the ability to detect statistical differences between the groups.

Conclusion

Similar to reports of sporadic interval breast cancers, clinically detected/interval breast cancers among BRCA mutation carriers have worse clinicopathologic features than screen-detected tumors and require more-aggressive medical and surgical therapy. Imaging with mammogram and MRI is associated with lower interval cancer development and should be utilized among this high-risk population.

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Table 1.

Patient Demographics

BSO bilateral salpingo-oophorectomy

	Clinically detected (n = 22)	Screen-detected (n = 92)	P-value	Interval cancers (n = 11)	Screen-detected (n = 64)	P-value
	All Women			Regular Screeners		
Age at diagnosis, median (range)	42 (28, 65)	49 (27, 72)	0.01	41 (28, 65)	51 (30, 72)	0.02
Age at genetic testing, median (range)	36 (23, 60)	45 (23, 71)	0.01	36 (26, 60)	48 (23, 71)	0.07
Race			< .01			0.03
Caucasian	17 (77%)	86 (94%)		9 (82%)	59 (92%)	
Black	4 (18%)	0 (0%)		2 (18%)	0 (0%)	
Asian	0 (0%)	4 (4%)		0 (0%)	4 (6%)	
Other	1 (5%)	0 (0%)		0 (0%)	0 (0%)	
Unknown	0 (0%)	2 (2%)		0 (0%)	1 (2%)	0.03
Body mass index, median (range)	24 (19, 32)	27 (18, 46)	0.01	24 (19, 29)	27 (18, 46)	0.02
BRCA mutation			0.13			0.22
BRCA1	16 (73%)	54 (59%)		7 (64%)	35 (55%)	
BRCA2	5 (23%)	37 (40%)		3 (27%)	28 (44%)	
Both	1 (5%)	1 (1%)		1 (9%)	1 (2%)	
BSO	6 (27%)	50 (49%)	0.03	4 (36%)	41 (64%)	0.10
Family history of breast cancer	22 (100%)	83 (90%)	0.2	11 (100%)	58 (91%)	0.6

Table 2.

Pathology at Diagnosis

DCIS ductal carcinoma in situ, *ER* estrogen receptor, *PR* progesterone receptor

	Clinically detected (n = 22)	Screen-detected (n = 92)	P-value	Interval cancers (n = 11)	Screen-detected (n = 64)	P-value
	All Women			Regular Screeners		
Tumor histology			< .01			0.01
DCIS	0 (0%)	20 (22%)		0 (0%)	13 (20%)	
Invasive ductal	18 (82%)	70 (76%)		9 (82%)	50 (78%)	
Invasive lobular	0 (0%)	2 (2%)		0 (0%)	1 (2%)	
Other	4 (18%)	0 (0)		2 (18%)	0 (0%)	
Tumor size, median (range) *	1.6 (0.1, 4.3)	0.6 (0.1, 8)	< .01	1.4 (0.1, 3.5)	0.7 (0.1, 2.6)	0.03
ER positive	12 (55%)	48 (52%)	0.81	5 (46%)	35 (55%)	0.51
PR positive	8 (36%)	34 (37%)	0.47	4 (36%)	23 (36%)	0.75
HER2 positive	0 (0%)	3 (3.3%) **	1	0 (0%)	3 (5%) †	1
Nuclear grade *			0.31			0.32
Low	0 (0%)	1 (1%)		0 (0%)	0 (0%)	
Intermediate	1 (5%)	18 (25%)		0 (0%)	13 (26%)	
High	12 (55%)	48 (67%)		5 (46%)	36 (71%)	
Unknown	9 (41%)	5 (7%)		6 (55%)	2 (4%)	
Pathologic T stage			< .01			< .01
Tis	0 (0%)	21 (23%)		0 (0%)	13 (20%)	
T1	8 (36%)	65 (71%)		5 (46%)	49 (77%)	
T2	12 (55%)	4 (4%)		5 (46%)	2 (3%)	
T3	0 (0%)	2 (2%)		0 (0%)	0 (0%)	
T4	1 (5%)	0 (0%)		0 (0%)	0 (0%)	
Tx	1 (5%)	0 (0%)		1 (9%)	0 (0%)	
Node positive *	9 (41%)	10 (14%)	0.01	5 (46%)	6 (12%)	0.02
Lymphovascular invasion present	8 (36%)	12 (13%)	0.01	4 (36%)	9 (14%)	0.07

* Among invasive cancers only

** 21 screen-detected patients (23%) had unknown HER2 status

† 13 screen-detected regular screener patients (20%) had unknown HER2 status

Table 3.

Treatment Factors

SLNB sentinel lymph node biopsy, *ALND* axillary lymph node dissection

	Clinically detected (n = 22)	Screen-detected (n = 92)	P-value	Interval cancers (n = 11)	Screen-detected (n = 64)	P-value
	All Women			Regular Screeners		
Breast surgery			0.11			0.14
Unilateral mastectomy	0 (0%)	1 (1%)		0 (0%)	1 (2%)	
Bilateral mastectomy	20 (91%)	74 (80%)		9 (82%)	48 (75%)	
Lumpectomy	1 (5%)	17 (19%)		1 (9%)	15 (23%)	
None	1 (5%)	0 (0%)		1 (9%)	0 (0%)	
Axillary surgery *			0.01			0.03
SLNB only	14 (64%)	65 (90%)		7 (64%)	47 (92%)	
SLNB+ALND or ALND	8 (36%)	7 (10%)		4 (36%)	4 (8%)	
Chemotherapy *			< .01			< .01
Adjuvant	14 (64%)	37 (51%)		7 (64%)	31 (61%)	
Neoadjuvant	7 (32%)	3 (4%)		4 (36%)	1 (2%)	
None	1 (5%)	32 (44%)		0 (0%)	19 (37%)	
Endocrine therapy **	11 (92%)	32 (87%)	1	5 (100%)	24 (86%)	1
Postmastectomy radiation therapy †	6 (30%)	7 (12%)	0.08	1 (11%)	5 (12%)	1

* Among invasive cancers only

** Among invasive estrogen receptor positive cancers only

† Among patients undergoing mastectomy for invasive cancer

Table 4.

Imaging

mammo mammogram, *BIRADS* Breast Imaging Reporting and Data System, *NA* not available

	Clinically detected (n = 22)	Screen-detected (n = 92)	P-value	Interval cancers (n = 11)	Screen-detected (n = 64)	P-value
	All Women			Regular Screeners		
Regularity of screening			0.13			NA
Regular	11 (50%)	64 (70%)		11 (100%)	64 (100%)	
Irregular/no prior screening	11 (50%)	28 (30%)		0 (0%)	0 (0%)	
Type of screening			< .01			0.02
Alternating q6 month mammo/MRI	4 (18%)	33 (36%)		3 (27%)	31 (48%)	
Synchronous mammo/MRI	4 (18%)	38 (41%)		2 (18%)	25 (39%)	
Mammo only	13 (59%)	18 (20%)		5 (46%)	7 (11%)	
MRI only	1 (5%)	3 (3%)		1 (9%)	1 (2%)	
Mammogram BIRADS density *			0.67			0.45
Predominantly fatty	1 (5%)	2 (2%)		1 (10%)	2 (3%)	
Scattered fibroglandular	5 (24%)	29 (33%)		3 (30%)	23 (37%)	
Heterogeneously dense	9 (43%)	43 (48%)		4 (40%)	33 (52%)	
Extremely dense	4 (19%)	14 (16%)		1 (10%)	4 (6%)	
Unknown	2 (10%)	1 (1%)		1 (10%)	1 (2%)	
MRI background parenchymal enhancement **			0.7			1
Minimal	3 (33%)	21 (28%)		2 (33%)	17 (30%)	
Mild	2 (22%)	31 (42%)		2 (33%)	25 (44%)	
Moderate	2 (22%)	18 (24%)		1 (17%)	12 (21%)	
NA	2 (22%)	4 (5%)		1 (17%)	3 (5%)	

* Among women who had a mammogram

** Among women who had an MRI