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Research Report

Breast cancer risk in *BRCA* mutation carriers after diagnosis of epithelial ovarian cancer is lower than in carriers without ovarian cancer

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ABSTRACT

Objective: Evaluate the incidence and characteristics of breast cancers (BC) diagnosed following an epithelial ovarian cancer (EOC) diagnosis in women with pathogenic *BRCA* mutations.
Methods: Retrospective cohort study of all women in an integrated healthcare system with *BRCA* mutations diagnosed with EOC from 1/1/1997–12/31/2018. Primary outcome was rate of subsequent BC diagnosis. Secondary outcomes included risk factors associated with development of BC, median time to detection following EOC, and method of detection.
Results: There were 284 women with *BRCA*-associated EOC identified. Fifty-two women had risk-reducing mastectomy and were excluded. Of the 232 eligible women with a median follow-up of 5.6 years, 33 (14%) women were diagnosed with BC following EOC: 27 (11%) new cases and 6 (3%) recurrences. Twelve (36%) cases of BC were detected on screening mammogram, 4 (12%) on screening MRI, and 9 (27%) on work-up after presenting with a palpable lump. Twenty-nine (87%) were early stage (0-II) disease. Median interval from EOC to BC diagnosis was 80 months (IQR 32, 134) for new and 63 months (IQR 21, 94) for recurrent BCs. There was one death from breast cancer while 12 women died of ovarian cancer.
Conclusions: Most BC following *BRCA*-associated EOC is early stage and not associated with mortality. Given BC rate similar to general population and median diagnosis at 6.6 years following ovarian cancer, increased BC screening may not be warranted in the early years after EOC diagnosis.

1. Introduction

Approximately 1 in 300 to 1 in 800 individuals in the general population carry a mutation in *BRCA1* or *BRCA2* (Practice Bulletin No 182). Patients with *BRCA1* or *BRCA2* mutations are at increased risk of breast cancer, with an estimated risk of 45–85% by age 70 years. Women with *BRCA1* or *BRCA2* are also at increased risk of ovarian cancer, with an estimated risk of 39–46% for *BRCA1* carriers and 10–27% for *BRCA2* carriers by age 70 years (Practice Bulletin No 182). Currently, most women learn of their *BRCA* mutation status after a personal cancer diagnosis. A woman with a high-grade serous ovarian cancer has a 9–18% chance of carrying a germline *BRCA1* or *BRCA2* mutation (Walsh et al., 2011). While the National Comprehensive Cancer Network (NCCN) has guidelines for managing cancer risks in women with deleterious *BRCA* mutations, women who have already had a cancer diagnosis represent a population with different risks and needs for which these standard guidelines may not apply. For unaffected *BRCA* carriers, breast cancer screening includes clinical breast exam every 6–12 months starting at age 25 years, annual breast MRI from age 25–29 years, and annual mammogram from age 30–75 years. The option of risk-reducing mastectomy should be discussed, including counseling on the degree of protections, reconstruction options and risks. Consideration should also be given to risk reducing agents, such as selective estrogen receptor modulators (ie. tamoxifen, raloxifene) (Daly et al., 2020).

However, for women with *BRCA* who have had an ovarian cancer, evidence suggests that their breast cancer risk approaches population level risk. The few studies that have examined this question have reported that the risk of breast cancer after epithelial ovarian cancer (EOC) is low, 8.9–11%, near population level risk, and that survival is dominated by ovarian cancer-related mortality (Domchek et al., 2013; Gangi

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et al., 2014). Guidelines for management of breast cancer risk do not take into account the impact of an EOC diagnosis and the reported low rate of new diagnoses of breast cancer may not warrant the same risk reduction strategies.

The purpose of this study was to describe the incidence of breast cancer diagnosis in *BRCA* mutation carriers previously diagnosed with EOC in a large population-based Northern California health care system. Given the lack of clear guidelines for management of these patients, a secondary objective was to describe the method of detection of these breast cancers, the interval from ovarian cancer diagnosis, and the characteristics of these breast cancers. In addition, we explored potential factors associated with development of breast cancer after EOC among women with *BRCA* mutations.

2. Methods

Kaiser Permanente Northern California (KPNC) is a community-based integrated health system that serves 4.4 million members, with a network of 21 hospitals and many local facilities where women receive comprehensive healthcare. There are integrated medical services, access to follow-up tests and outcomes that are comprehensively captured in the electronic medical record. Women who test positive for a BRCA pathogenic mutation are referred to the Hereditary Cancer Program where they are followed by experts in hereditary cancer syndromes. All women with a BRCA 1 or 2 mutation are recommended to begin annual MRI screening at age 25 years with annual mammogram added beginning at age 30 years, alternating these studies every 6 months. Clinical breast exam is recommended every 6 months beginning at age 25 years. Currently, there is no guidance on altering this recommendation for women in our system after they have been diagnosed with an ovarian cancer and management is individualized with the treating provider and patient.

The Breast Cancer Tracking and Surveillance (BCTS) program, a database of all KPNC members with Heredity Breast and Ovarian Cancer (HBOC) germline testing who have pathogenic mutations, was used to identify female BRCA1 or BRCA2 mutation carriers with a diagnosis of EOC from 1/1/1997 to 12/31/2018. Women were excluded if they had a risk-reducing mastectomy or had incomplete medical records.

Demographic and clinic data were collected from the date of genetic testing to 5/1/19 which was the stop date for chart review. Demographic and clinical data abstracted from the electronic medical record included age, sex, date of birth, date of death, race/ethnicity, body mass index, parity, genetic test result, medical co-morbidities, cancer screening tests, family history of cancer, prior surgeries, pathology reports, cancer stage, prior chemotherapy, and use of tamoxifen or aromatase inhibitor. The method of diagnosis of breast cancer was determined by chart review, and categorized as diagnosed by palpable lump noted, screening mammogram, screening MRI, or other/unknown. Information on cancer diagnoses was also collected from the KPNC Cancer Registry.

2.1. Statistical analysis

Demographic variables and clinical characteristics were examined in bivariate analysis comparing women with *BRCA*-associated EOC who were subsequently diagnosed with breast cancer vs. those who were not. Clinical characteristics of women with a new diagnosis of breast cancer after EOC and women with recurrent breast cancer after EOC were also compared using bivariate analysis. Interval to breast cancer diagnosis, number of screening tests, and breast cancer stage was compared by method of diagnosis. Categorical variables, such as race, gene mutation, and cancer stage were compared using Fisher's exact tests and continuous variables were compared using Kruskall-Wallis tests. Proportions and Clopper-Pearson 95% confidence intervals were calculated for the levels of each categorical variable and medians and 95% confidence intervals were calculated for each continuous variable.

All analysis was conducted using SAS 9.4 and a p-value of <0.05 was considered statistically significant. The study protocol was approved by KPNC's Institutional Review Board for the protection of human subjects with waiver of consent.

3. Results

There were 290 women with *BRCA*-associated EOC (including fallopian tube or primary peritoneal cancer) identified in KPNC during the study period. Fifty-two women were excluded as they had a risk-reducing mastectomy, and 6 were excluded due to incomplete medical records. There were 232 women with *BRCA*-associated EOC included in the study, with a median follow-up of 5.6 years. Of the 232 women, 33 (14%) were diagnosed with BC following EOC and 199 did not develop BC (Table 1). Median age at genetic testing was similar between those who did and did not develop BC after EOC, 62 and 59 years respectively. There were no significant differences in proportion of *BRCA1* and *BRCA2* carriers, race or BMI. There were similar proportions of women in each cohort by timing of genetic testing in relation to ovarian cancer diagnosis, previous diagnosis of breast cancer, and use of chemotherapy for prior breast and ovarian cancer diagnoses. A notable difference was that women who developed breast cancer had a longer time from ovarian cancer diagnosis to genetic testing than those who did not develop breast cancer, 7.7 vs. 0.7 years (Table 1).

Of the 33 patients with BC after EOC, 32 (97%) received

Table 1
Clinical characteristics of all patients with BRCA associated EOC.

	Breast cancer after ovarian cancer (n = 33) Median (95% CI)		No breast cancer after ovarian cancer (n = 199) Median (95% CI)		p
Age at ovarian cancer diagnosis (years)	52.8 (48.1–57.4)		55.7 (54.1–58.0)		0.067
Age at genetic testing (years)	61.6 (56.4–72.4)		59.0 (56.0–60.5)		0.161
Follow-up time (years)	4.5 (3.7–5.2)		6.7 (3.9–9.8)		0.089
Time from EOC diagnosis to genetic testing (years)	7.7 (1.6–11.1)		0.7 (0.6–1.0)		<0.001
Median overall survival (years)	32.5 (20.0–38.3)		9.2 (7.4–14.4)		<0.001
	No.	Percent (95% CI)	No.	Percent (95% CI)	p
Gene mutation					0.704
BRCA1	21	64 (45–80)	118	59 (52–66)	
BRCA2	12	36 (20–55)	81	41 (34–48)	
Race/ethnicity					0.414
Ashkenazi Jewish	1	3 (0–16)	9	5 (2–8)	
Asian/Pacific Islander	2	6 (1–20)	28	14 (10–20)	
African American	2	6 (1–20)	16	8 (5–13)	
Hispanic/Latino	2	6 (1–20)	19	10 (6–15)	
White	24	73 (54–87)	124	62 (55–69)	
Other	2	6 (1–20)	3	2 (0–4)	
Ovarian cancer stage					<0.001
I	1	3 (0–16)	12	6 (3–10)	
II	11	33 (18–52)	16	8 (5–13)	
III	12	36 (20–55)	115	58 (51–65)	
IV	3	9 (2–24)	47	24 (18–30)	
Unknown	6	18 (7–35)	9	5 (2–8)	
Family history of breast cancer	11	33 (18–52)	93	48 (41–55)	0.133
Family history of ovarian cancer	7	21 (9–39)	32	17 (12–23)	0.618
Tamoxifen use	7	21 (9–39)	33	17 (12–23)	0.621
Aromatase inhibitor use	6	18 (7–35)	18	9 (6–14)	0.131
EOC treated with platinum-based chemotherapy	27	82 (64–93)	183	92 (87–95)	0.100
Genetic testing prior to EOC	2	6 (1–20)	18	9 (5–14)	0.747
Breast cancer prior to EOC	5	15 (5–32)	40	20 (14–26)	0.638
Breast cancer prior to EOC treated with chemotherapy	3	9 (2–24)	28	14 (10–20)	0.585

chemotherapy, 12 (38%) had stage I-II EOC and 15 (44%) had advanced stage EOC. There were more cases of breast cancer following early-stage ovarian cancer than following advanced stage diagnoses (30% vs. 8%, $p < 0.001$). There were 27 new cases of BC and 6 recurrences with a median age at diagnosis of 63 years for new and 62 years for recurrent cancers (Table 2). Twenty-four (72%) had invasive breast cancer and 5 (18%) had ductal carcinoma in situ (DCIS); 29 (87%) were early stage (0–2) disease; only one new diagnosis of BC was late stage (stage III). Thirteen (39%) were hormone receptor positive, 4 (15%) were Her2neu + and 12 (36%) were triple negative breast cancers.

Median interval from EOC to BC diagnosis was 80 months (IQR 32, 134) for new and 63 months (IQR 21, 94) for recurrent BCs; with 4 cases diagnosed within 2 years, 13 within 5 years, and 24 within 10 years (Fig. 1). There was a total person-time of follow-up for the cohort of 1521.5 person-years, and the calculated person-time incidence rate for breast cancer is 27/1521.5 = 17.8 per 1000 person years (Poisson 95% CI 11.7–25.8). Fig. 2 demonstrates the difference is overall survival among patients with and without breast cancer diagnosed after EOC. Patients with breast cancer after EOC had longer median overall survival 32.5 years vs 9.2 years for those who did not develop breast cancer ($p = 0.001$) without multivariate analysis.

Thirteen (39%) patients had at least yearly screening and 9 (27%) had screening at least every 2 years. Twenty-four (72%) women underwent screening with mammogram alone, and 7 (21%) had screening MRI in addition to mammogram. a median interval from EOC diagnosis to first imaging of 14 months for new cases and 11 months for recurrent cases. Twelve (36%) cases of BC were detected on screening mammogram, 4 (12%) on screening MRI, and 9 (27%) on work-up after presenting with a palpable lump (Table 3). Four cases (12%) of BC were diagnosed on CT or PET scan done for work-up of ovarian cancer, and four (12%) had an unknown method of detection. Those diagnosed by palpable lump seemed to have a longer median interval from ovarian cancer diagnosis and had slightly fewer average mammograms; 7 of the 9 patients diagnosed by palpable lump noticed the lump themselves and presented for evaluation of the lump. Breast cancer diagnosed by screening mammogram or MRI was earlier stage than those diagnosed by palpable lump ($p = 0.008$), though 28 (84%) of the 33 cases of breast cancer were early stage, regardless of method of detection. Mortality in patients with BC following EOC was largely driven by EOC; 12 (36%) patients died of ovarian cancer while only one (3%) patient died of breast cancer.

Table 2
Characteristics of subjects with breast cancer.

	New breast cancer after ovarian cancer ($n = 27$)		Recurrent breast cancer after ovarian cancer ($n = 6$)		
	No.	Percent (95% CI)	No.	Percent (95% CI)	*p*
Ovarian cancer stage					0.728
I	1	4 (0–19)	0	0 (0–46)	
II	9	33 (17–54)	2	33 (4–78)	
III	9	33 (17–54)	3	50 (12–88)	
IV	2	7 (1–24)	1	17 (0–64)	
Unknown	6	22 (9–42)	0	0 (0–46)	
Breast cancer stage					0.689
Stage 0	5	19 (6–38)	0	(0–46)	
Stage I	11	41 (22–61)	4	67 (22–96)	
Stage II	6	22 (9–42)	2	33 (4–78)	
Stage III	1	4 (0–19)	0	0 (0–46)	
Unknown	4	15 (4–34)	0	(0–46)	
Receptor status					
ER+	10	37 (19–58)	3	50 (12–88)	0.659
PR+	5	19 (6–38)	3	50 (12–88)	0.137
Her2neu+	4	15 (4–34)	0	0 (0–46)	1.000
Triple negative	10	37 (19–58)	2	33 (4–78)	1.000
Disease status					0.515
NED	13	48 (29–68)	2	33 (4–78)	
AWD	3	11 (2–29)	2	33 (4–78)	
DOD (OC)	10	37 (19–58)	2	33 (4–78)	
DOD (BC)	1	4 (0–19)	0	0 (0–46)	
Family history of breast cancer	7	26 (11–46)	4	67 (22–96)	0.146
Family history of ovarian cancer	5	19 (6–38)	2	33 (4–78)	0.584

4. Discussion

Women with inherited pathogenic *BRCA1* or *BRCA2* mutation have a higher lifetime risk of breast and ovarian cancer. Our study confirms that risk of developing a new breast cancer following ovarian cancer is near population level, that it tends to develop in women with earlier stage ovarian cancer and at a median of 80 months from diagnosis of ovarian cancer diagnosis. Prior studies on the risk of new breast cancer after ovarian cancer in *BRCA* mutation carriers have also reported much lower rates, in the range of 8–11%, consistent with our findings, with less described about which patients are more likely to develop disease (Daly et al., 2020; Domchek et al., 2013). These risks appear to be lower than the breast cancer risk in unaffected carriers of a similar age, with a reported risk at age 50 of 20% for BRCA 1 and 15% for BRCA 2 and 38% for *BRCA1* and 30% for *BRCA2* by age 60 (Chen and Parmigiani, 2007).

Possible reasons for the difference in breast cancer risk in the population may relate to removal of the ovaries and use of platinum-based chemotherapy. For *BRCA* mutation carriers, risk-reducing salpingo-oophorectomy has been shown in some studies to decrease breast cancer risk by approximately50%, depending on several risk factors and with younger age at time of surgery conferring a greater risk reduction (Kauff et al., 2008; Kotsopoulos et al., 2017; Heemskerk-Gerritsen et al., 2015). Prior bilateral oophorectomy has also been shown to have a favorable effect on the biological presentation of breast cancer in *BRCA* mutation carriers, with such women presenting with smaller tumors on average (Metcalfe et al., 2005). However, there is mixed data regarding this effect and given the older age of our population at RRSO, this is likely to have contributed a small degree to the difference seen in breast cancer risk. More significantly, platinum-based chemotherapy has been shown to be highly effective treatment for *BRCA*-associated ovarian cancer or breast cancer, and adjuvant chemotherapy for breast cancer has been shown to have a risk-reducing effect on the risk contralateral breast cancer in *BRCA* mutation carriers (Reding et al., 2010). It seems possible that the platinum-based chemotherapy used to treat *BRCA* carriers with EOC may reduce the risk of subsequent breast cancer by eliminating occult disease in the breast.

The typical surveillance strategy for breast cancer in BRCA carriers is intensive and costly, with mammogram and MRI every 6 months recommended. In BRCA carriers affected by ovarian cancer who subsequently develop a breast cancer, mortality is driven by ovarian cancer, with favorable breast cancer related survival (Daly et al., 2020; Domchek et al., 2013). In addition, median time to development of BC is often many years from the ovarian cancer diagnosis, ranging from 50 to 108 months. Most breast cancers were diagnosed at an early stage with very favorable long-term prognosis, and these encouraging outcomes were seen in cohorts where patients were already undergoing a reduced screening schedule, with 21–52% of women getting annual MRI and only 39% of women in our study having at least annual imaging (Daly et al., 2020; Domchek et al., 2013).

Given the lower incidence of breast cancer reported for those BRCA carriers affected by ovarian cancer, it would be ideal to define a population that could safely defer or reduce the intensive screening schedule. While there were no significant differences in family history of breast cancer, aromatase inhibitor use, or tamoxifen use among patient who did and did not develop breast cancer, we did find a higher incidence in women with early compared with late-stage ovarian cancer. There was also a longer period of time between ovarian cancer diagnosis and genetic testing in women who developed a breast cancer. The women who did not have breast cancer after EOC were higher stage and had a trend

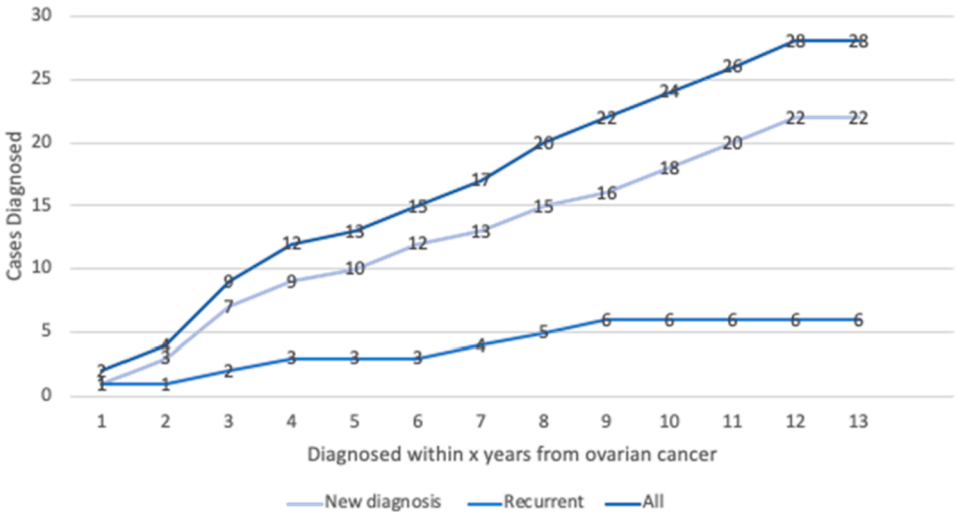

Fig. 1. Timing of diagnosis of breast cancer following diagnosis of epithelial ovarian cancer.

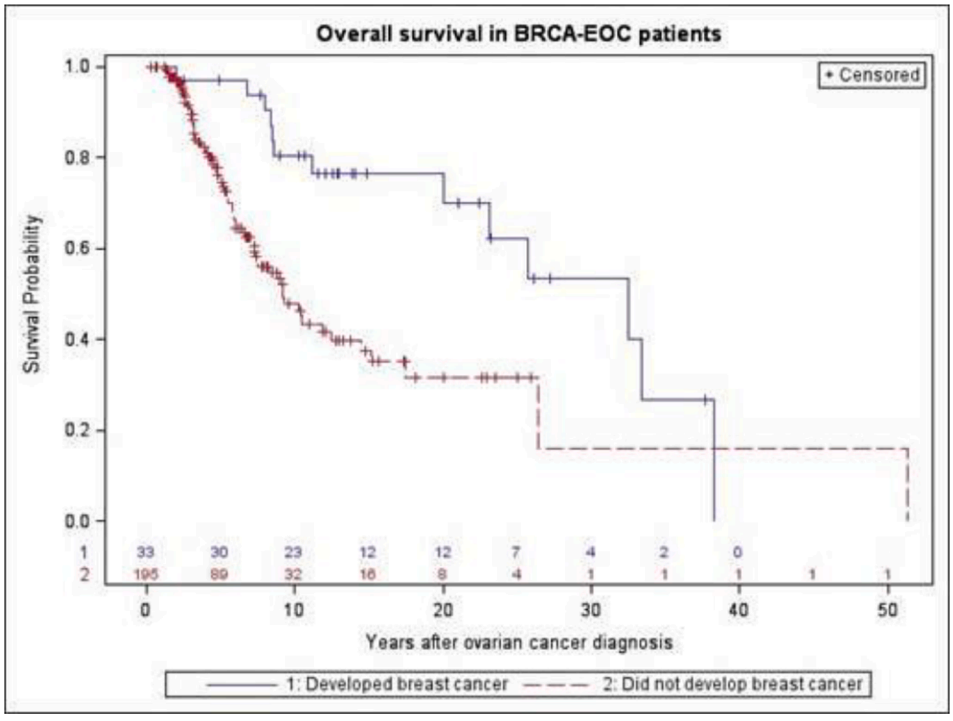

Fig. 2. Overall survival stratified breast cancer diagnosis.

towards more breast cancer prior to EOC, both factors that have historically identified ovarian cancer patients in the past and may have influenced timing of the recommendation for genetic testing.

In terms of more women with early stage EOC developing breast cancer, this could represent a survival bias, as patients who survived ovarian cancer were more likely to live long enough to develop a breast cancer, it may also delineate who would benefit most from screening. Women with advanced ovarian cancer are have a high recurrence rate in the first 5 years after diagnosis, will likely be engaged in ongoing treatment and ultimately have a five-year mortality rate of 55% from ovarian cancer (Surveillance).

Given near population risk, it is questionable what benefit addition of MRI may have for this population. Most cancers found were by mammogram or palpable lump, with very few detected by MRI. This may be a biased finding, given inconsistent use of MRI, but is worth further evaluation given the excellent breast cancer related survival. Beyond screening, RRM is another risk-reducing option available to BRCA carriers. The role after an ovarian cancer is unclear. In one study, based on a simulation using an actuarial risk of developing breast cancer at ten years post-diagnosis of BRCA-associated EOC of 7.8%, the expected benefits of RRM or screening MRI were expected to be small in terms of lives saved, particularly in women with ovarian cancer recurrence, and most likely to be of benefit among women with early stage ovarian cancer or those who survived without recurrence for ten years (McGee et al., 2017). Based on the low incidence of breast cancer, early stage at diagnosis and good long term survival outcomes seen in this and previous studies, patients and physicians should carefully consider whether the invasiveness of RRM is worth the likely limited benefits.

The strengths of this study include the large cohort of women with *BRCA* mutations followed for a median of 5.6 years. Our health care

Table 3
All breast cancers by method of diagnosis.

	Palpable lump ($n = 9$)		Screening mammogram ($n = 12$)		Screening MRI ($n = 4$)		Other/unknown ($n = 8$)		
	Median (95% CI)		Median (95% CI)		Median (95 %CI)		Median (95% CI)		p
Time from ovarian cancer to breast cancer diagnosis (months)	117.2 (80.3–362.7)		76.0 (42.7–203.3)		63.4 (26.9–140.3)		31.0 (14.7–123.8)		0.094
Number of interval mammograms	2 (1–4)		8 (2–16)		6 (3–9)		1 (0–13)		0.006
Number of interval MRIs	0 (0–1)		2.5 (0–3)		3 (1–4)		1 0–12)		0.007
	No.	Percent (95% CI)	No.	Percent (95% CI)	No.	Percent (95% CI)	No.	Percent (95% CI)	p
Ovarian cancer stage									0.216
I-II	3	33 (7–70)	7	58 (28–85)	0	0 (0–60)	2	25 (3–65)	
III-IV	4	44 (14–79)	4	33 (10–65)	4	100 (40–100)	3	38 (9–76)	
Unknown	2	22 (3–60)	1	8 (0–38)	0	0 (0–60)	3	38 (9–76)	
Breast cancer stage									0.008
0	0	0 (0–33)	2	17 (2–48)	3	75 (19–99)	0	0 (0–37)	
I	3	33 (7–70)	8	67 (35–90)	1	25 (1–81)	3	38 (9–76)	
II	5	56 (21–86)	1	8 (0–38)	0	0 (0–60)	2	25 (3–65)	
III	1	11 (0–48)	0	0 (0–26)	0	0 (0–60)	0	0 (0–37)	
Unknown	0	0 (0–33)	1	8 (0–38)	0	0 (0–60)	3	38 (9–76)	

system allows for access to information regarding all tests and services from electronic medical records with very low rates of loss to follow-up. The cohort comes from a community-based healthcare system, in a population that is unselected and thus captures current clinical practice and sheds light on how providers manage these high-risk patients who do not have clear screening recommendations. The limitations include the small number of breast cancers identified which also limits our ability to compare age-related breast cancer incidence. The sample size also prohibits a multivariate analysis of the survival curves, which could not account for confounding variables such as stage and grade. In addition, the median follow up of 5.6 years would not detect late recurrences of breast cancers or those diagnoses more remote from the ovarian cancer.

In conclusion, risks and benefits of breast cancer screening and risk-reducing surgery should be weighed carefully in this patient population, taking into account the lower incidence of breast cancer and impact of ovarian cancer on survival. Taken together, our results are in line with other cohort studies and support careful consideration of timing of initiation and inclusion of MRI for breast cancer screening.

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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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