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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ARTICLE INFO

Keywords: BRCA Breast cancer Ovarian cancer Screening Genetic testing

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.

Method: 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
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 have pathogenic mutations, was used to database of all KPNC members with Heredity Breast and Ovarian Cancer and management is individualized with the treating provider and patient.

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. |
|------------------|------------------|------------------|------------------|
| Gene mutation    | Breast cancer after ovarian cancer (n = 33) | No breast cancer after ovarian cancer (n = 199) |
| BRCA1            | 21 64 (45-80) | 118 59 (52-66) | 0.704 |
| BRCA2            | 12 36 (20-55) | 81 41 (34-48) | 0.414 |
| Race/ethnicity   | Asian/Pacific Islander 2 6 (1-20) | 28 14 (10-20) | 0.131 |
| Ashkenazi Jewish | 1 3 (0-16) | 9 5 (2-8) | 0.14 |
| African American | 2 6 (1-20) | 16 8 (5-13) | 0.133 |
| Hispanic/Latino  | 2 6 (1-20) | 19 10 (6-15) | 0.141 |
| White            | 24 73 (54-87) | 124 62 (55-69) | 0.141 |
| Other            | 2 6 (1-20) | 3 2 (0-4) | 0.141 |
| Ovarian cancer stage | 1 3 (0-16) | 12 6 (3-10) | 0.131 |
| Family history of breast cancer | 11 33 (18-52) | 93 48 (41-55) | 0.131 |
| Family history of ovarian cancer | 7 21 (9-39) | 32 17 (12-23) | 0.618 |
| Tamsoxifen use   | 7 21 (9-39) | 33 17 (12-23) | 0.621 |
| Aromatase inhibitor use | 6 18 (7-35) | 8 (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 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

| Characteristic                      | New breast cancer after ovarian cancer (n = 27) | Recurrent breast cancer after ovarian cancer (n = 6) | p     |
|-------------------------------------|-----------------------------------------------|----------------------------------------------------|-------|
| Ovarian cancer stage                |                                               |                                                    | 0.728 |
| I                                  | 1                                             | 1                                                  |       |
| II                                 | 9                                              | 2                                                  |       |
| III                                | 9                                              | 3                                                  |       |
| IV                                 | 2                                              | 1                                                  |       |
| Unknown                            | 6                                              | 0                                                  |       |
| Breast cancer stage                 |                                               |                                                    | 0.689 |
| Stage 0                            | 5                                              | 1                                                  |       |
| Stage I                            | 11                                             | 4                                                  |       |
| Stage II                           | 6                                              | 3                                                  |       |
| Stage III                          | 1                                              | 0                                                  |       |
| Unknown                            | 4                                              | 0                                                  |       |
| Receptor status                    |                                               |                                                    |       |
| ER +                               | 10                                             | 3                                                  | 0.659 |
| PR +                               | 5                                              | 3                                                  | 0.137 |
| Her2neu +                          | 4                                              | 0                                                  | 1.000 |
| Triple negative                    | 10                                             | 2                                                  | 0.515 |
| Disease status                     |                                               |                                                    |       |
| NED                                | 13                                             | 2                                                  |       |
| AWD                                | 3                                              | 2                                                  |       |
| DOD (OC)                           | 10                                             | 2                                                  |       |
| DOD (BC)                           | 1                                              | 0                                                  |       |
| Family history of breast cancer    | 7                                              | 2                                                  | 0.146 |
| Family history of ovarian cancer    | 5                                              | 2                                                  | 0.584 |
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
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.

Funding
This project has been funded in part with a grant from Kaiser Permanente Garfield Memorial Fund. All authors report no conflicts of interest.

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.

Acknowledgements
It was previously presented as an oral presentation at the 2019 Western Association of Gynecologic Oncology annual meeting and as a poster at the 2021 Society for Gynecologic Oncology Annual Meeting.

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Table 3
All breast cancers by method of diagnosis.

| No. Percent (95% CI) | Palpable lump (n – 9) | Screening mammogram (n = 12) | Screening MRI (n = 4) | Other/unknown (n = 8) |
|---------------------|----------------------|-------------------------------|----------------------|----------------------|
| 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) |
| Number of interval mammograms | 2 (1-4) | 8 (2-16) | 6 (3-9) | 1 (0-13) |
| Number of interval MRIs | 0 (0-1) | 2.5 (0-3) | 3 (1-4) | 1 (0-12) |
| Declaration of Competing Interest | Interest.

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