CME credits available for this article — www.thepermanentejournal.org

ORIGINAL RESEARCH & CONTRIBUTIONS

Survival Outcomes in *BRCA1* or *BRCA2* Mutation Carriers and the Influence of Triple-Negative Breast Cancer Subtype

Reina Haque, PhD; Jiaxiao M Shi, PhD; Claire Telford, PhD; Chantal Avila, MA; Monica Alvarado, LGC, MS; George E Tiller, MD, PhD; Tapashi Dalvi, PhD; Lia Gutierrez, MPH; Jerzy Tyczynski, PhD; James A Kaye, MD, DrPH

Perm J 2018;22:17-197

E-pub: 10/11/2018

https://doi.org/10.7812/TPP/17-197

ABSTRACT

Context: Little information exists on whether breast cancer survival differs by *BRCA1* or *BRCA2* mutation.

Objective: To determine if the risk of subsequent breast cancer or mortality differs by *BRCA1* vs *BRCA2* mutation status in women with hereditary breast cancer and whether these outcomes are modified by triple-negative biologic subtype.

Design: Retrospective cohort of 307 women with breast cancer diagnosed between 1990 and 2012 who were *BRCA1* or *BRCA2* mutation carriers identified from a managed care organization. Subjects were followed-up through 2013.

Main Outcome Measures: Subsequent breast cancer or death.

Results: In the cohort, 163 (53.0%) were *BRCA1* mutation carriers, 142 (46.3%) were *BRCA2* mutation carriers, and 2 (0.7%) had mutations in both genes. Median follow-up was 4.5 years (maximum = 24 years). The percentage of subsequent breast cancer events was similar, with 17.8% in *BRCA1* and 15.3% in *BRCA2* mutation carriers. Overall 5-year survival was similarly high, with 91.4% for *BRCA1* and 94.4% for *BRCA2* mutation carriers. In a subset of 215 *BRCA* mutation carriers, triple-negative breast cancer (TNBC) was associated with greater mortality (adjusted hazard ratio = 1.41, 95% confidence interval = 0.40-5.05) and higher risk of subsequent breast cancer (adjusted hazard ratio = 1.65, 95% confidence interval = 0.63-4.31) than non-TNBC (reference), but the confidence intervals included the null given the small sample.

Conclusion: The TNBC status was independently associated with worse outcomes regardless of *BRCA1* or *BRCA2* mutation status, suggesting that targeting treatment for TNBC may enhance survival. These results require confirmation in larger studies.

INTRODUCTION

In 2016, nearly 246,660 new cases of invasive breast cancer and 61,000 cases of noninvasive (in situ) breast cancer were diagnosed in the US; roughly 3% to 6% of these occurred in women who had a germline *BRCA1* or *BRCA2* (*BRCA1/2)* gene mutation.[1] Scarce population-based outcomes data are available for hereditary breast cancer, and most of the studies that examined clinical outcomes mainly included data on white patients collected from multiple sources, thereby potentially obscuring differences related to variable medical insurance coverage or differential treatments. Furthermore, little information exists on whether breast cancer survival differs in women who are *BRCA1* vs *BRCA2* mutation carriers, and even this evidence is conflicting.[2] *BRCA1* mutation carriers tend to have more adverse tumor characteristics than women who have wild-type *BRCA*, which complicates interpretation of survival results. For example, triple-negative breast cancer (TNBC; tumors lacking expression of the estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor-2 receptor [HER2]) is more common in *BRCA1* mutation carriers.[3] Additionally, breast cancer in *BRCA1* mutation carriers is often diagnosed at a higher grade and at earlier ages than in *BRCA2* mutation carriers.[4] Given such differences in tumor characteristics at presentation, *BRCA1* mutation carriers may be at greater risk of death or recurrence than *BRCA2* mutation carriers; however, sparse clinical data have been published to substantiate this.

Therefore, we examined 2 main goals: 1) to assess whether risks of mortality and subsequent breast cancer (ipsilateral recurrence or contralateral breast cancer) differ by *BRCA1* vs *BRCA2* mutation carrier status and 2) whether these outcomes vary by TNBC subtype in an ethnically diverse, population-based cohort of women with hereditary breast cancer who were members of a large Health Plan in California. To our knowledge, this is the only cohort of *BRCA1/2* mutation carriers in the US assembled from a single community-based Health Plan with long-term clinical follow-up data.

METHODS

Data Sources and Study Setting

This retrospective cohort study was conducted at Kaiser Permanente Southern California (KPSC), a managed care system comprising 14 hospitals and nearly 4.2 million members. The Health Plan's National Cancer Institute Surveillance, Epidemiology, and End Results (SEER)-affiliated cancer registry was used to identify patients with breast cancer. Using comprehensive KPSC electronic and paper medical records, we captured information on mutation status, tumor characteristics,

Reina Haque, PhD, is a Research Scientist III for Research and Evaluation in Pasadena, CA (reina.haque@kp.org). **Jiaxiao M Shi, PhD,** is a Biostatistician for Research and Evaluation in Pasadena, CA (jiaxiao.m.shi@kp.org). **Claire Telford, PhD,** is the Director of Health Economics and Payer Analytics for Health Economics and Outcomes for AstraZeneca Pharmaceuticals LP in Gaithersburg, MD (claire.telford@astrazeneca.com). **Chantal Avila, MA,** is a Project Manager for Research and Evaluation in Pasadena, CA (chantal.c.avila@kp.org). **Monica Alvarado, LGC, MS,** is a Genetic Counselor and Department Administrator for Kaiser Permanente Southern California Clinical Genetics Department in Pasadena (monica.x.alvarado@kp.org). **George E Tiller, MD, PhD,** is the Chief of Clinical Genetics for Kaiser Permanente Southern California in Pasadena (george.e.tiller@kp.org). **Tapashi Dalvi, PhD,** is the Director of Health Economics and Payer Analytics for Oncology Epidemiology for AstraZeneca Pharmaceuticals LP in Gaithersburg, MD (dalvit@medimmune.com). **Lia Gutierrez, MPH,** is the Director of Epidemiology for RTI Health Solutions in Barcelona, Catalunya, Spain (lgutierrez@rti.org). **Jerzy Tyczynski, PhD,** is the Senior Director of Oncology Epidemiology for Abbvie, Inc, in Chicago, IL (jerzy.tyczynski@abbvie.com). **James A Kaye, MD, DrPH,** is the Senior Director of Epidemiology for RTI Health Solutions in Waltham, MA (jkaye@rti.org).

treatments, and clinical outcomes. We also used California State and federal Social Security Administration data to ascertain deaths (via Social Security number linkage) even after disenrollment from KPSC. The KPSC institutional review board reviewed and approved this study; written and verbal informed consent was waived.

Subjects and Design

We assembled a small cohort of adult women (≥ 18 years) with a first primary breast cancer diagnosed from 1990 to 2012. Patients were initially identified from the KPSC-National Cancer Institute SEER-affiliated cancer registry (N = 55,431) and linked with the clinical genetics database to identify those tested for *BRCA1/2* mutations. Only a small fraction of the women with a breast cancer diagnosis who met the National Comprehensive Cancer Network's evidence-based guidelines for hereditary breast and ovarian cancer referral, on the basis of their personal or family history of cancer, underwent genetic counseling and testing.[4] From this linkage, we identified 685 high-risk women who were referred for genetic counseling and testing according to the guidelines. Of these, 519 women tested positive for a pathogenic or likely pathogenic variant *BRCA1/2* allele (hereafter "mutation carriers"), among whom 307 continued their treatment at KPSC and had available medical records, thereby qualifying for study inclusion. The portion of positive *BRCA1/2* results in this group was understandably high given the aforementioned referral practice. Women were followed-up for clinical outcomes through December 31, 2013.

Outcome Assessment and Definitions

Breast cancer outcomes were ascertained from medical records, pathology reports, and the SEER cancer registry. Data were extracted on recurrences (ie, local, regional, distant metastasis), second primary breast cancers (ie, contralateral breast cancer), and death (ie, breast cancer-specific and all-cause). The cause of death was identified from KPSC's membership records and State of California and national Social Security death files. We created a composite variable as a proxy for progression called subsequent breast cancer; this definition was based on recurrence, contralateral breast cancer, or breast cancer-specific death, whichever occurred first.[5-7]

We examined overall survival (OS) and disease-free survival (DFS). The OS was calculated from the date of initial breast cancer diagnosis to the date of death (even if a woman terminated her Health Plan membership) for the full cohort (N = 307). The DFS was examined separately for the subgroups of women who received adjuvant therapy (n = 248; n = 215 subset with known biologic subtype). The DFS was calculated from the date of starting the systemic treatment (ie, adjuvant hormonal or chemotherapy) to the date of recurrence, second primary breast cancer, or breast cancer death, Health Plan disenrollment, or study's end, whichever occurred first. Because *no* outcome events should happen before the systemic adjuvant therapy start date, we calculated DFS from the start date of such treatment to minimize immortal time bias.[8] We treated disenrollment and end of study as censoring events in the DFS calculation. Adjuvant radiation therapy was also treated as a time-dependent covariate.

BRCA1 or BRCA2 Status and Breast Cancer Characteristics

The main "exposure" of interest was *BRCA* mutation status (*BRCA1/2*). Germline *BRCA1/2* testing was performed on blood samples by an outside laboratory (Myriad Genetics Laboratories, Salt Lake City, UT). The main breast cancer characteristic of interest was biologic tumor subtype defined as luminal A (ER+ and/or PR+/HER2-), luminal B (ER+ and/or PR+/HER2+), HER2-enriched (ER-/PR-/HER2+), or TNBC (ER-/PR-/HER2-). Subtype classification was inferred using immunohistochemistry of the ER and PR and fluorescence in situ hybridization for HER2 status, rather than genomic signatures. Because HER2 testing commenced in the mid-2000s, the survival analyses stratified by biologic subtype are based on a subset of 215 patients with known ER, PR, and HER2 marker status. Analyses were also stratified by treatment setting (neoadjuvant or adjuvant) as appropriate.

Breast Cancer Treatments and Other Covariates

Information on first-course cancer therapy was extracted from the cancer registry. Type of chemotherapy was abstracted from the paper medical records. Use of tamoxifen and aromatase inhibitors (letrozole, anastrozole, exemestane) was identified from pharmacy records. We also extracted covariates from electronic health records, including age at diagnosis, year of breast cancer diagnosis, breast cancer stage at initial diagnosis (based on the American Joint Committee on Cancer's Tumor, Nodes, Metastasis classification system[9]), race/ethnicity, tumor characteristics, and primary cancer treatment (surgery, radiotherapy, chemotherapy). Comorbidities, captured in the year before breast cancer, were assessed using the Charlson Comorbidity Index, Elixhauser adaptation.[10] We also ascertained menopausal status at the time of the initial breast cancer diagnosis, family history of the disease, and race/ethnicity from paper medical records.

Statistical Analysis

The distributions of demographic characteristics, breast cancer characteristics, and treatments were tabulated overall and stratified by *BRCA1/2* mutation status and by biologic subtype. Because women in the study were followed-up for varying times, we calculated person-year rates of subsequent breast cancer incidence and mortality. We also estimated survival probability at defined times using the Kaplan-Meier method; log-rank tests were used to evaluate differences, and p values were 2-sided. We used Cox proportional hazards models to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between biologic subtype and outcomes; HRs are shown stratified by *BRCA1/2* mutation carrier status. In these analyses, follow-up ended on the date of the relevant study endpoint (subsequent breast cancer or death) or was censored at Health Plan membership disenrollment or the study's end (December 31, 2013), whichever occurred first. In the Cox proportional hazards models, oral adjuvant hormonal treatments (tamoxifen and aromatase inhibitors) and chemotherapy were entered as time-dependent variables. The multivariable models also accounted for

stage of breast cancer, menopausal status, surgery type, and adjuvant chemotherapy or hormonal therapy. Final models were chosen using the combination of goodness of fit, assessment of collinearity among covariates, and factors associated with both outcome and biologic subtype. The proportional hazards assumption was evaluated by examining interactions between covariates with time as well as with Schoenfeld residuals; no significant violation was found. Furthermore, we performed analyses stratifying by *BRCA1/2* status to address effect modification and potential heteroscedasticity. All analyses were performed using software (SAS Version 9.3, SAS Institute, Cary, NC).

Table 1. Breast cancer characteristics in *BRCA1* or *BRCA2* mutation carriers[a]

Characteristic	*BRCA1*, no. (%)	*BRCA2*, no. (%)	*BRCA1* and 2, no. (%)	Total, no. (%)	p value[b]
Total	163 (53.1)	142 (46.3)	2 (0.7)	307 (100)	
Stage at diagnosis					< 0.001
Stage 0	5 (3.1)	17 (12.0)	0 (0.0)	22 (7.2)	
Stage I	52 (32.1)	50 (35.2)	1 (50.0)	103 (33.6)	
Stage II	93 (57.4)	51 (35.9)	1 (50.0)	145 (47.4)	
Stage III	10 (6.2)	23 (16.2)	0 (0.0)	33 (10.8)	
Stage IV	2 (1.2)	1 (0.7)	0 (0.0)	3 (1.0)	
Missing	1 (—)	0 (—)	0 (—)	1 (—)	
Laterality					0.126
Left	81 (49.7)	83 (58.5)	1 (50.0)	165 (53.7)	
Right	82 (50.3)	59 (41.5)	1 (50.0)	142 (46.3)	
Grade					< 0.001
1	5 (3.2)	8 (5.9)	0 (0.0)	13 (4.4)	
2	24 (15.4)	58 (43.0)	0 (0.0)	82 (28.0)	
3	127 (81.4)	69 (51.1)	2 (100.0)	198 (67.6)	
Missing	7 (—)	7 (—)	0 (—)	14 (—)	
Lymph nodes					0.332
Positive	47 (31.1)	49 (36.6)	0 (0.0)	96 (33.4)	
Negative	104 (68.9)	85 (63.4)	2 (100.0)	191 (66.6)	
Missing	12 (—)	8 (—)	0 (—)	20 (—)	
Estrogen receptor					< 0.001
Positive	42 (26.1)	95 (72.0)	0 (—)	137 (46.4)	
Negative	119 (73.9)	37 (28.0)	2 (100.0)	158 (53.6)	
Test not done/missing	2 (—)	10 (—)	0 (—)	12 (—)	
Progesterone receptor					< 0.001
Positive	33 (21.2)	80 (65.6)	1 (50.0)	114 (40.7)	
Negative	123 (78.8)	42 (34.4)	1 (50.0)	166 (59.3)	
HER2/neu					0.002
Positive	6 (4.3)	17 (15.6)	0 (—)	23 (9.2)	
Negative	133 (95.7)	92 (84.4)	1 (100.0)	226 (90.8)	
Test not done/missing	24 (—)	33 (—)	1 (—)	58 (—)	
Molecular subtype					< 0.001
Luminal A	25 (20.7)	53 (56.4)	0 (—)	78 (36.1)	
Luminal B	1 (0.8)	10 (10.6)	0 (—)	11 (5.1)	
TNBC	92 (76.0)	26 (27.7)	1 (100.0)	119 (55.1)	
HER2-enriched	3 (2.5)	5 (5.3)	0 (—)	8 (3.7)	
Other/unknown/missing	42 (—)	48 (—)	1 (—)	91 (—)	

[a] Percentages within categories are based on known values. Percentages may not total to 100 because of rounding.
[b] p values indicate significant differences between *BRCA1* and *BRCA2* mutation carriers; excludes unknown/missing values.
HER2 = human epidermal growth factor-2; luminal A = estrogen receptor positive and/or progesterone receptor positive/HER2 negative; luminal B = estrogen receptor positive and/or progesterone receptor positive/HER2 negative; TNBC = triple-negative breast cancer.

RESULTS

A total of 685 patients with breast cancer were referred for genetic counseling; 519 (75.8%) of these were *BRCA1/2* mutation carriers. Among the *BRCA1/2* mutation carriers, medical records were retrievable for 307 of 519 mutation carriers (59.2%), and these patients were included in the study cohort.

Patient Characteristics

Most (88.9%) of the 307 patients in the study were younger than age 60 years at diagnosis (Supplemental Table 1). Altogether, 163 (53.0%) were *BRCA1* mutation carriers, 142 (46.3%) were *BRCA2* mutation carriers, and 2 (0.7%) were carriers of both mutations (0.7%). Nearly all women underwent genetic testing after their breast cancer diagnosis; only 3.6% were tested earlier. The age distribution of *BRCA1* mutation carriers at the time of first breast cancer diagnosis was somewhat younger than that of the *BRCA2* mutation carriers (33.1% vs 26.8% under age 40 years). A slightly higher proportion of *BRCA1* mutation carriers were premenopausal or perimenopausal (69.9% vs 64.8%), and more were smokers (34.4% vs 21.4%). Compared with *BRCA2* mutation carriers, the *BRCA1* mutation carriers had a higher proportion of Hispanic women (31.3% vs 17.6%) and a slightly higher proportion of black/African American women (11.1% vs 9.1%). Most patients (n = 245; 79.8%) had no comorbidities as defined by the Charlson Comorbidity Index, and comorbidities were similarly distributed among *BRCA1* and *BRCA2* mutation carriers. A maternal family history of breast cancer was somewhat more frequent in *BRCA1* mutation carriers than *BRCA2* mutation carriers (54.9% vs 46.3%).

Breast Cancer Characteristics and Treatments

Proportionately more *BRCA1* mutation carriers were diagnosed with early-stage breast cancer (Stages 0-II) than *BRCA2* mutation carriers (92.6% vs 83.1%; Table 1).[11] Additionally, *BRCA1* mutation carriers more often had Grade 3

tumors (81.4% vs 51.1%) and TNBC (76.0% vs 27.7%) compared with *BRCA2* mutation carriers. A larger percentage of *BRCA2* mutation carriers had HER2-enriched tumors, consistent with the fact that *BRCA1* mutation carriers were more likely to have HER2-negative tumors and thus more likely to have TNBC.

The distributions of primary breast cancer treatments were similar in *BRCA1* and *BRCA2* mutation carriers (Table 2). Altogether, 108 (35.4%) underwent breast-conserving surgery with or without adjuvant radiotherapy, whereas most (n = 190, 62.3%) chose mastectomy. In both mutation carrier subgroups, among women who underwent mastectomy, approximately half (49.5%) had a unilateral mastectomy and half (50.5%) had bilateral mastectomy.

More *BRCA1* mutation carriers (82.2%) underwent adjuvant chemotherapy than did *BRCA2* mutation carriers (69.7%; Table 2). The distribution of type of chemotherapy was similar between the 2 groups, with most receiving taxane- or anthracycline-taxane-based regimens. The median time to start chemotherapy among *BRCA1* mutation carriers was 67 days after initial breast cancer diagnosis date (interquartile range [IQR] = 51-92 days) compared with 73 days (IQR = 58-93 days) for *BRCA2* mutation carriers. Overall, about 41.4% received adjuvant hormonal therapy. Given the higher frequency of ER-positive and/or PR-positive tumors among *BRCA2* mutation carriers vs *BRCA1* carriers, oral adjuvant hormonal therapy was used approximately 2.5 times more commonly by *BRCA2* mutation carriers. Only 30 women (19 *BRCA1* and 11 *BRCA2* mutation carriers) underwent neoadjuvant chemotherapy.

Mortality

The median follow-up was 4.2 years (IQR = 2.8-6.7 years) in *BRCA1* mutation carriers and 4.9 years (IQR = 2.6-7.2

Table 2. Breast cancer treatments in *BRCA1* or *BRCA2* mutation carriers[a]

Treatment	*BRCA1*, no. (%)	*BRCA2*, no. (%)	*BRCA1* and 2, no. (%)	Total, no. (%)	p value[b]
Total	163 (53.1)	142 (46.3)	2 (0.7)	307	
Primary therapy					0.482
Breast-conserving surgery with radiation	34 (21.0)	24 (17.0)	1 (50.0)	59 (19.3)	
Breast-conserving surgery without radiation	22 (13.6)	27 (19.2)	0 (—)	49 (16.1)	
Mastectomy (with or without radiation)	103 (63.6)	86 (61.0)	1 (50.0)	190 (62.3)	
Unilateral	52 (50.5)	42 (48.8)	0 (—)	94 (49.5)	
Bilateral	51 (49.5)	44 (51.2)	1 (100.0)	96 (50.5)	
No primary therapy	3 (1.9)	4 (2.8)	0 (—)	7 (2.3)	
Other/unknown/missing	1 (—)	1 (—)	0 (—)	2 (—)	
Neoadjuvant chemotherapy response (n = 30)					0.399
Pathologic complete response (PCR) achieved	8 (5.0)	2 (1.4)	0 (—)	10 (3.3)	
PCR not achieved	9 (5.6)	7 (5)	0 (—)	16 (5.3)	
PCR unknown/missing	2 (—)	2 (—)	0 (—)	4 (—)	
Adjuvant chemotherapy (first 6 months)					0.104
Yes	134 (82.2)	99 (69.7)	2 (100.0)	235 (76.6)	
No	29 (17.8)	43 (30.3)	0 (—)	72 (23.5)	
Type of chemotherapy (n = 235)					0.629
Anthracycline based	18 (13.4)	14 (14.1)	0 (—)	32 (13.6)	
Taxane based (TC, TCH)	42 (31.4)	29 (29.3)	0 (—)	71 (30.2)	
Anthracycline + taxane (AC + paclitaxel/docetaxel; AT; AC + TH)	61 (45.5)	49 (49.5)	1 (50.0)	111 (47.2)	
Cyclophosphamide + methotrexate + fluorouracil	8 (6.0)	2 (2.0)	1 (50.0)	11 (4.7)	
Other combinations	5 (3.7)	5 (5.1)	— (—)	10 (4.3)	
Days to first chemotherapy after initial breast cancer diagnosis					
Mean (standard deviation)	70 (30)	78 (36)	77 (18)		
Median (interquartile range)	67 (51-92)	73 (58-93)	78 (65-90)		0.194
Range	8-183	7-293	65-90		
Tamoxifen/aromatase inhibitor (AI)					< 0.001
AI only	11 (6.7)	26 (18.3)	0 (—)	37 (12.0)	
Tamoxifen only	15 (9.2)	26 (18.3)	0 (—)	41 (13.4)	
Both tamoxifen and AI	14 (8.6)	35 (24.7)	0 (—)	49 (16.0)	
None	123 (75.5)	55 (38.7)	2 (100.0)	180 (58.6)	

[a] Percentages within categories are based on known values. Percentages may not total to 100 because of rounding.
[b] p values indicate significant differences between *BRCA1* and *BRCA2* mutation carriers; excludes unknown/missing values.
AC = Doxorubicin+Cyclophosphamide; AT = Doxorubicin+Docetaxel; TC = Docetaxel+Cyclophosphamide; TCH = Docetaxel+Carboplatin+Trastuzumab; TH = Docetaxel+Trastuzumab.

years) in *BRCA2* mutation carriers. During the total 1144 person-years of follow-up through December 31, 2013, we observed 33 deaths (6 caused by breast cancer). The prevalence of breast-cancer specific deaths (6/33, 18.8%) is consistent with other reports that determined that *BRCA1/2* carriership is not related to a greater risk of death compared with noncarriers.[2,12-13]

The overall 1-, 3-, and 5-year survival rates were 98.8%, 93.9%, and 91.4% for the *BRCA1* mutation carriers and was similarly high at 100%, 96.5%, and 94.3% for *BRCA2* mutation carriers. Table 3 presents the median OS by biologic subtypes among *BRCA1/2* carriers. Because of the small number of deaths, we compared mortality among patients with TNBC vs non-TNBC (the combined categories luminal A, luminal B, and HER-2 enriched). The overall mortality rate for patients with TNBC was 19.1/1000 person-years vs 15.1/1000 person-years in women with non-TNBC, corresponding to an adjusted HR of 1.41 (95% CI = 0.40-5.05); however, the CIs were broad and included the null (Table 4). Kaplan-Meier survival estimates for the TNBC vs non-TNBC subgroups are shown in Figure 1. Although women with TNBC had worse survival in the first 4 years after their initial breast cancer diagnosis than those with non-TNBC, the curves overlapped after this point (p log rank = 0.74).

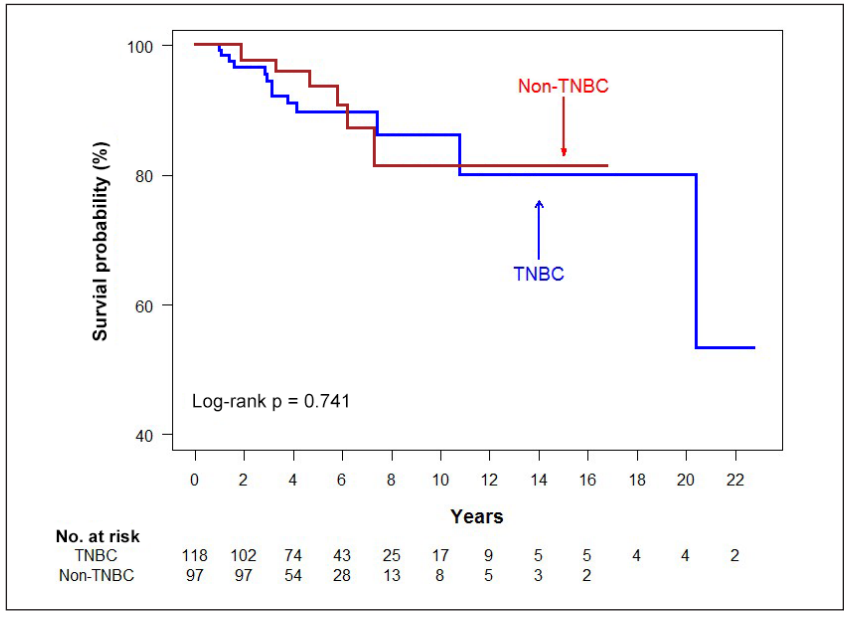

Figure 1. Overall mortality in *BRCA1* or *BRCA2* mutation carriers by triple-negative breast cancer (TNBC) status (n = 215 with known subtype).

Among patients with TNBC, there was no difference in the mortality rates

Table 3. Mortality in all *BRCA1* or *BRCA2* mutation carriers, (N = 307)[a]

Survival status	Died (any cause)		Alive/censored[b]		Total	
	BRCA1, no. (%)	*BRCA2*, no. (%)	*BRCA1*, no. (%)	*BRCA2*, no. (%)	Died (any cause), no. (%)	Alive/censored, no. (%)
1-year	2 (1.22)	0 (0)	161 (98.77)	142 (100.0)	2 (0.66)	303 (99.34)
3-year	10 (6.13)	5 (3.52)	153 (93.87)	137 (96.48)	15 (4.92)	290 (95.08)
5-year	14 (8.59)	8 (5.63)	149 (91.41)	134 (94.37)	22 (7.21)	283 (92.79)

[a] Two patients with both *BRCA1* and *BRCA2* mutations were excluded.
[b] Index date was the date of diagnosis of initial breast cancer.

Table 4. Mortality in all *BRCA1* or *BRCA2* carriers with known molecular subtype (n = 215)[a]

BRCA status	Died (any cause)	Alive/ censored[b]	Median survival, years (IQR)	Person-years	Mortality/1000 person-years (IQR 95% CI)	Overall mortality	
						Crude HR (95% CI)	Adjusted HR (95% CI)[c]
BRCA1 or *BRCA2* (n = 215)							
TNBC	13	105	4.96 (2.90-7.03)	681	19.08 (10.16- 32.64)	1.17 (0.46-2.99)	1.41 (0.40-5.05)
Non-TNBC	7	90	4.30 (2.36-6.19)	463	15.09 (6.07- 31.09)	1.0 [Reference]	1.0 [Reference]
BRCA1 (n = 121)							
TNBC	10	82	4.77 (2.90-6.58)	518	19.32 (9.26- 35.53)	2.50 (0.32-19.75)	1.60 (0.19-13.24)
Non-TNBC	1	28	4.06 (2.05-5.92)	134	7.46 (0.19-41.54)	1.0 [Reference]	1.0 [Reference]
BRCA2 (n = 94)							
TNBC	3	23	5.92 (2.90-8.12)	164	18.34 (3.78- 53.59)	0.91 (0.23-3.69)	1.34 (0.23-7.84)
Non-TNBC	6	62	4.38 (2.53-6.26)	330	18.19 (6.68- 39.60)	1.0 [Reference]	1.0 [Reference]

[a] Two patients with both *BRCA1* and *BRCA2* mutations were excluded.
[b] Index date was the date of diagnosis of initial breast cancer.
[c] Adjusted for stage (early vs late), menopausal status, surgery type (breast conservation, unilateral/bilateral mastectomy), adjuvant radiotherapy (yes/no) time dependent, hormonal therapy (yes/no) time dependent, and chemotherapy (yes/no) time dependent.
CI = confidence interval; HR = hazard ratio; IQR = interquartile range; TNBC = triple-negative breast cancer.

comparing *BRCA1* mutation carriers (19.3/1000 person-years) with *BRCA2* mutation carriers (18.3/1000 person-years; Table 4). Adjusted HRs for TNBC vs non-TNBC stratified by *BRCA1/2* status are similar to those for the combined mutation carrier group with known biologic subtypes. However, the adjusted HRs were even less precisely estimated, particularly given that only 1 woman in the *BRCA1* group died during the available follow-up time.

Risk of Subsequent Breast Cancer

Of the 307 women, we observed 58 with subsequent breast cancer (34 *BRCA1* and 24 *BRCA2* mutation carriers); in 29 of these patients, distant metastases developed during follow-up (Supplemental Table 2). The TNBC status was an independent predictor of mortality regardless of *BRCA1* or *BRCA2* mutation status. The 58 patients with subsequent breast cancer included 41 in whom contralateral primary breast cancers developed (17 *BRCA1* mutation carriers, 23 *BRCA2* mutation carriers, and 1 with both mutations).

Among the 248 women who underwent adjuvant hormonal therapy and/or chemotherapy, the recurrence risk was 11.9% in *BRCA1* and 8.1% in *BRCA2* mutation carriers (median observation time until event or censoring was 3.0 years and 3.6 years, respectively; Supplemental Table 2). Overall, the percentage of subsequent breast cancer events was 17.8% in *BRCA1* and 15.3% in *BRCA2* mutation carriers. The overall 1-, 3-, and 5-year DFS were 96.0%, 91.1%, and 87.5%, respectively, for the *BRCA1/2* combined group. The person-year rate of subsequent breast cancer was 35.2/1000 PY for TNBC vs 33.2/1000 person-years for non-TNBC (Table 4), which corresponded to an adjusted HR of 1.65 (95% CI = 0.63-4.31). This association was almost 4-fold greater in *BRCA1* mutation carriers with TNBC (adjusted HR = 3.89, 95% CI = 0.56-27.12). Kaplan-Meier DFS estimates according to TNBC and non-TNBC status largely overlapped (p log rank = 0.82; Figure 2).

Other Clinical Outcomes

A total of 30 women underwent neoadjuvant chemotherapy. The median follow-up length was 1.72 years in *BRCA1* and 4.30 years *BRCA2* mutation carriers

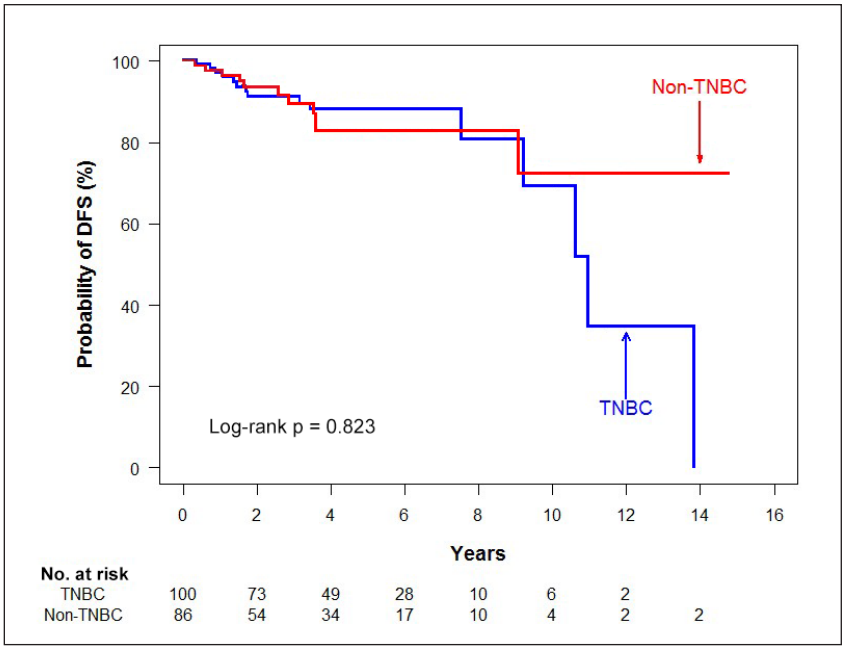

Figure 2. Disease-free survival (DFS) in *BRCA1* or *BRCA2* mutation carriers by triple-negative breast cancer (TNBC) status in those treated with adjuvant hormonal therapy and/or chemotherapy (n = 248).

in those with retrievable paper medical records. The follow-up was shorter in *BRCA1* mutation carriers because they had worse tumor characteristics and were more likely to have TNBC than *BRCA2* mutation carriers. Of these 30 women, 11 women were found to have subsequent breast cancer (8 with *BRCA1* and 3 with *BRCA2* mutations). Ten women achieved pathologic complete response, defined as the absence of residual invasive disease in the breast and axillary lymph nodes (8 *BRCA1* and 2 *BRCA2* mutation carriers; Table 2). Among the 54 women with new second primary cancers, 7 had ovarian cancer (6 with *BRCA1* and 1 with *BRCA2* mutations). Of note, none of these 7 women in whom ovarian cancer developed underwent prophylactic oophorectomy.

DISCUSSION

In this small cohort of 307 insured women with hereditary breast cancer cared for in a single institute, the 5-year OS proportions were 91.4% for the *BRCA1* mutation carriers and 94.3% for *BRCA2* mutation carriers; this finding is consistent with the literature that demonstrates that *BRCA1/2* mutation carriership is not associated with increased mortality.[2,12,13] The 5-year OS in our cohort is similar to those reported in a meta-analysis of other *BRCA1/2* populations.[3,14-15] Additionally, our results are similar to the OS in the adjuvant breast cancer trials that had up to 5 years of follow-up (Austrian Breast and Colorectal Cancer Study Group 8 trial, Arimidex-Nolvadex 95 trial, National Surgical Adjuvant Breast and Bowel Project B-33 trial).[16-18] Regarding TNBC in *BRCA1/2* mutation carriers, the 5-year OS (approximately 90%) in our study was higher than in other observational studies that included women with nonhereditary TNBC (ie, without *BRCA1/2* mutations), in which OS ranged from 70% to 75%.[19-21] This difference is probably because of the younger age of our cohort, high breast cancer screening compliance, and longer follow-up in this managed care plan. Furthermore, our results suggest that the overall mortality rate was greater in *BRCA1/2* mutation carriers who had TNBC than in those with non-TNBC. These findings must be replicated in other, larger cohorts because our results were not statistically significant, possibly because of the small sample size; however, we provided the 95% CIs to partially address this issue.

Interestingly, the risk of subsequent breast cancer and mortality were also greater in *BRCA1* mutation carriers (vs *BRCA2* mutation carriers), but again the results were based on a small number of events. Additionally, our conservative definitions for DFS included subsequent breast cancer or breast cancer deaths as the endpoints; however, if we had expanded the definition to include deaths unrelated to breast cancer, the person-year rates of DFS would have been higher than we calculated (Table 5).

A few studies found a higher prevalence of TNBC among women with *BRCA1* mutations than with *BRCA2* mutation carriers, suggesting that practice guidelines should include recommendations that all women with TNBC regardless of age at breast cancer diagnosis or family history be referred for genetic counseling and testing.[3,4] However, a paucity of data has been published indicating whether biologic subtype (ie, TNBC vs non-TNBC tumors) among *BRCA1/2* mutation carriers affects survival or the risk of subsequent breast cancer, as has been witnessed here.

Our study has a number of strengths. Subjects were identified from a single community-based Health Plan whereby women received all their health care within this organization; thus, differences in treatments resulting from variable medical insurance are minimized. Furthermore, this cohort of *BRCA1/2* mutation carriers is unique given the racial/ethnic diversity of the study population; 44% were of minority backgrounds (25% were Hispanic, 10% African American, and 9% Asian/Pacific Islander), enhancing the generalizability of our findings to other communities with similarly diverse populations. Additionally, we captured patients' vital status up to the study's end in 2013 by linking their Social Security numbers to the computerized state and national death records even if they disenrolled from the Health Plan. Moreover, access to patients' cancer registry, genetic counseling, and medical records enabled us to comprehensively and accurately capture diagnostic information, pharmacy data, surgical and adjuvant treatments, clinical outcomes, and other potentially confounding information.

The study also has limitations. We acknowledge our sample size was small, which might have contributed to the statistically nonsignificant results; however, statistical significance is *not* equal to scientific or clinical significance, and larger p values do not imply a lack of importance or even lack of an association.[22,23] Although there might be some survivor bias, the effect of this was minimal because the 5-year OS was high in both *BRCA1* and *BRCA2* mutation carriers (91.4% in *BRCA1* and 94.4% in *BRCA2* mutation carriers). Our classification of biologic subtypes was based on immunohistochemical markers, introducing some potential for misclassification. However, use of such markers is common in community hospitals, and prior studies have shown a relatively high concordance of immunohistochemical markers with gene expression patterns.[24-26] Breast cancers were not commonly tested for HER2 overexpression in our institution until the mid-2000s, thereby decreasing the number of patients available for survival analysis stratified by biologic subtype. The relatively low number of events in analyses of deaths and subsequent breast cancer occurrence precluded further analyses stratified by treatment regimen. Few women received neoadjuvant chemotherapy in our cohort, reflecting the relatively favorable stage distribution at diagnosis but limiting analyses of pathologic complete response and subsequent outcomes. Additionally, we did not have data to compare outcomes against a general population of breast cancer survivors who did not have the gene mutation. Although the maximum

Table 5. Disease-free survival by molecular subtype in *BRCA1 or BRCA2* carriers treated with systemic adjuvant chemotherapy or hormonal therapy

	Endpoints						Disease-free survival	
***BRCA* status**	**Subsequent breast cancer, no. (%)**	**Died of breast cancer**	**Died of other causes**	**Alive/ censored[a]**	**Person-years**	**Person-year rate/1000 (IQR 95% CI)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)[b]**
BRCA1 or 2 (n = 248)[c]								
1-year survival	10 (4.0)	0	1	237	—	—	—	—
3-year survival	22 (8.9)	0	1	225	—	—	—	—
5-year survival	31 (12.5)	0	2	215	—	—	—	—
BRCA1 or 2 with known molecular subtype (n = 186)								
TNBC	14	1	1	84	427	35.15 (19.67-57.97)	1.10 (0.51-2.41)	1.65 (0.63-4.31)
Non-TNBC	11	0	1	74	331	33.23 (16.59-59.45)	1.0 [Reference]	1.0 [Reference]
BRCA1 (n = 100)								
TNBC	11	1	0	63	306	39.28 (20.29-68.61)	2.23 (0.49-10.14)	3.89 (0.56-27.12)
Non-TNBC	2	0	0	23	86	23.36 (2.83-84.37)	1.0 [Reference]	1.00 [Reference]
BRCA2 (n = 86)								
TNBC	3	0	1	21	121	24.74 (5.10-72.31)	0.49 (0.11-2.25)	0.62 (0.12-3.30)
Non-TNBC	9	0	1	51	245	36.67 (16.77-69.61)	1.0 [Reference]	1.00 [Reference]

[a] Index date was the date of start of adjuvant chemotherapy or hormonal therapy.

[b] Adjusted for stage (early vs late), menopausal status, surgery type (breast conservation, unilateral/bilateral mastectomy), adjuvant radiotherapy (yes/no) time dependent, hormonal therapy (yes/no) time dependent, and chemotherapy (yes/no) time dependent.

[c] Two patients with both *BRCA1* and *BRCA2* mutations were excluded.

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; TNBC = triple-negative breast cancer.

study follow-up was 24 years, nearly two-thirds of the outcomes occurred in the first 10 years; however, our study's follow-up duration is one of the longest published to our knowledge. Furthermore, we conducted rigorous checking of proportional HR assumption, so the HRs would apply beyond 10 years, although the absolute risk itself will have smaller variance if we had a larger cohort.

CONCLUSION

Our results suggest that the risk of mortality and subsequent breast cancer was higher in *BRCA1/2* mutation carriers with TNBC than those with non-TNBC. The risk of TNBC was considerably higher among *BRCA1* than *BRCA2* mutation carriers. However, the results are based on small numbers of events and require confirmation in larger studies. If these findings are confirmed, practice guidelines should include recommendations that all women with TNBC, regardless of age at breast cancer diagnosis or family history, be referred for genetic counseling and testing. ❖

Disclosure Statement

Kaiser Permanente Southern California (KPSC) and Research Triangle Institute, Research Triangle Park, NC, received research funding for the study from AstraZeneca, Cambridge, UK. Drs Telford and Dolvi are employees of AstraZeneca US, Wilmington, DE. Dr Ty Czynski is an employee of AbbVie Inc, North Chicago, IL. The authors have no other conflicts of interest to disclose. The study was reviewed and approved by the KPSC institutional review board. For this retrospective study, formal consent was waived by the review board.

Acknowledgments

This study and article charges were supported by AstraZeneca to Kaiser Permanente and Research Triangle Institute. Data analysis was completed by the Kaiser Permanente Southern California authors. We thank Joanne Schottinger, MD, for her critical evaluation of the manuscript and Joanie Chung for her assistance with data programming.

Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

How to Cite this Article

Haque R, Shi JM, Telford C, et al. Survival outcomes in *BRCA1* or *BRCA2* mutation carriers and the influence of triple-negative breast cancer subtype. Perm J 2018;22:17-197. DOI: https://doi.org/10.7812/TPP/17-197

References

1. BRCA-related cancer: Risk assessment, genetic counseling, and genetic testing [Internet]. Rockville, MD: US Preventive Services Task Force; 2013 Dec [cited 2017 Jan 4]. Available from: www.uspreventiveservicestaskforce.org/uspstf12/brcatest/brcatestfinalrs.htm.
2. van den Broek AJ, Schmidt MK, van 't Veer LJ, Tollenaar RA, van Leeuwen FE. Worse breast cancer prognosis of BRCA1/BRCA2 mutation carriers: What's the evidence? A systematic review with meta-analysis. PLoS One 2015 Mar 27;10(3):e0120189. DOI: https://doi.org/10.1371/journal.pone.0120189.
3. Bayraktar S, Gutierrez-Barrera AM, Liu D, et al. Outcome of triple-negative breast cancer in patients with or without deleterious BRCA mutations. Breast Cancer Res Treat 2011 Nov;130(1):145-53. DOI: https://doi.org/10.1007/s10549-011-1711-z.
4. NCCN Guidelines Version 2.2016. Genetic/Familial high-risk assessment: Breast and ovarian [Internet]. Fort Washington, PA: National Comprehensive Cancer Network; 2016 [cited 2017 Jun 7]. Available from: www.tri-kobe.org/nccn/guideline/gynecological/english/genetic_familial.pdf.
5. Haque R, Shi J, Schottinger JE, et al. A hybrid approach to identify subsequent breast cancer using pathology and automated health information data. Med Care 2015 Apr;53(4):380-5. DOI: https://doi.org/10.1097/mlr.0000000000000327.
6. Haque R, Shi J, Schottinger JE, et al. Tamoxifen and antidepressant drug interaction in a cohort of 16,887 breast cancer survivors. J Natl Cancer Inst 2015 Dec 1;108(3). DOI: https://doi.org/10.1093/jnci/djv337.
7. Kwan ML, Shi JM, Habel LA, et al. Effectiveness of bisphosphonate use and risk of contralateral breast cancer and recurrence in women with early-stage breast cancer treated with tamoxifen. Breast Cancer Res Treat 2016 Apr;156(2):379-89. DOI: https://doi.org/10.1007/s10549-016-3763-6.
8. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008 Feb 15;167(4):492-9. DOI: https://doi.org/10.1093/aje/kwm324.
9. Cancer staging system: What is cancer staging? [Internet]. Chicago, IL: American Joint Committee on Cancer; c2018 [cited 2018 May 15]. Available from: https://cancerstaging.org/references-tools/Pages/What-is-Cancer-Staging.aspx.
10. Cleves MA, Sanchez N, Draheim M. Evaluation of two competing methods for calculating Charlson's comorbidity index when analyzing short-term mortality using administrative data. J Clin Epidemiol 1997 Aug;50(8):903-8. DOI: https://doi.org/10.1016/s0895-4356(97)00091-7.
11. Huzarski T, Byrski T, Gronwald J, et al. Ten-year survival in patients with BRCA1-negative and BRCA1-positive breast cancer. J Clin Oncol 2013 Sep 10;31(26):3191-6. DOI: https://doi.org/10.1200/jco.2012.45.3571.
12. El-Tamer M, Russo D, Troxel A, et al. Survival and recurrence after breast cancer in BRCA1/2 mutation carriers. Ann Surg Oncol 2004 Feb;11(2):157-64. DOI: https://doi.org/10.1245/aso.2004.05.018.
13. Cortesi L, Masini C, Cirilli C, et al. Favourable ten-year overall survival in a Caucasian population with high probability of hereditary breast cancer. BMC Cancer 2010 Mar 10;10:90. DOI: https://doi.org/10.1186/1471-2407-10-90.
14. Bonadona V, Dussart-Moser S, Voirin N, et al. Prognosis of early-onset breast cancer based on BRCA1/2 mutation status in a French population-based cohort and review. Breast Cancer Res Treat 2007 Jan;101(2):233-45. DOI: https://doi.org/10.1007/s10549-006-9288-7.
15. Kirova YM, Stoppa-Lyonnet D, Savignoni A, Sigal-Zafrani B, Fabre N, Fourquet A; Institut Curie Breast Cancer Study Group. Risk of breast cancer recurrence and contralateral breast cancer in relation to BRCA1 and BRCA2 mutation status following breast-conserving surgery and radiotherapy. Eur J Cancer 2005 Oct;41(15):2304-11. DOI: https://doi.org/10.1016/j.ejca.2005.02.037.
16. Dubsky PC, Jakesz R, Mlineritsch B, et al. Tamoxifen and anastrozole as a sequencing strategy: A randomized controlled trial in postmenopausal patients with endocrine-responsive early breast cancer from the Austrian Breast and Colorectal Cancer Study Group. J Clin Oncol 2012 Mar 1;30(7):722-8. DOI: https://doi.org/10.1200/jco.2011.36.8993.
17. Kaufmann M, Jonat W, Hilfrich J, et al. Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: The ARNO 95 Study. J Clin Oncol 2007 Jul 1;25(19):2664-70. DOI: https://doi.org/10.1200/jco.2006.08.8054.
18. Mamounas EP, Jeong JH, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: Intention-to-treat analysis of the National Surgical Adjuvant Breast and Bowel Project B-33 trial. J Clin Oncol 2008 Apr 20;26(12):1965-71. DOI: https://doi.org/10.1200/jco.2007.14.0228.
19. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: Clinical features and patterns of recurrence. Clin Cancer Res 2007 Aug 1;13(15 Pt 1):4429-34. DOI: https://doi.org/10.1158/1078-0432.ccr-06-3045.
20. Ovcaricek T, Frkovic SG, Matos E, Mozina B, Borstnar S. Triple negative breast cancer—prognostic factors and survival. Radiol Oncol 2011 Mar;45(1):46-52. DOI: https://doi.org/10.2478/v10019-010-0054-4.
21. Muendlein A, Rohde BH, Gasser K, et al. Evaluation of BRCA1/2 mutational status among German and Austrian women with triple-negative breast cancer. J Cancer Res Clin Oncol 2015 Nov;141(11):2005-12. DOI: https://doi.org/10.1007/s00432-015-1986-2.
22. Wasserstein RL, Lazar NA. The ASA's statement on p-values: Context, process, and purpose. The American Statistician 2016;70(2):129-33. DOI: https://doi.org/10.1080/00031305.2016.1154108.
23. Greenland S, Senn SJ, Rothman KJ, et al. Statistical tests, p values, confidence intervals, and power: A guide to misinterpretations. Eur J Epidemiol 2016 Apr;31(4):337-50. DOI: https://doi.org/10.1007/s10654-016-0149-3.
24. Blows FM, Driver KE, Schmidt MK, et al. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: A collaborative analysis of data for 10,159 cases from 12 studies. PLoS Med 2010;7:e1000279. DOI: https://doi.org/10.1371/journal.pmed.1000279.
25. Carey LA, Dees EC, Sawyer L, et al. The triple negative paradox: Primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 2007 Apr 15;13(8):2329-34. DOI: https://doi.org/10.1158/1078-0432.ccr-06-1109.
26. Griggs JJ, Hamilton AS, Schwartz KL, et al. Discordance between original and central laboratories in ER and HER2 results in a diverse, population-based sample. Breast Cancer Res Treat 2017 Jan;161(2):375-84. DOI: https://doi.org/10.1007/s10549-016-4061-z.

Supplemental Table 1. Demographic and clinical characteristics[a]					
Characteristic	***BRCA1*, no. (%)**	***BRCA2*, no. (%)**	***BRCA1* and *2*, no. (%)**	**Total, no. (%)**	**p value[b]**
Total	163 (53.1)	142 (46.3)	2 (0.7)	307 (100.0)	
Age at diagnosis					0.099
< 40	54 (33.1)	38 (26.8)	0 (0)	92 (30.0)	
40-49	55 (33.8)	52 (36.6)	2 (100.0)	109 (35.5)	
50-59	42 (25.8)	30 (21.1)	0 (0)	72 (23.4)	
60-69	9 (5.5)	21 (14.8)	0 (0)	30 (9.8)	
≥ 70	3 (1.8)	1 (0.7)	0 (0)	4 (1.3)	
Year of diagnosis					0.009
1990-1995	6 (3.7)	5 (3.5)	0 (0)	11 (3.6)	
1996-2001	12 (7.4)	9 (6.5)	1 (50.0)	22 (7.2)	
2002-2007	37 (22.7)	38 (26.7)	0 (0)	75 (24.4)	
2008-2012	108 (66.2)	90 (63.3)	1 (50.0)	199 (64.8)	
Race/ethnicity					0.067
Non-Hispanic white	84 (51.5)	87 (61.3)	2 (100.0)	173 (56.3)	
Hispanic	51 (31.3)	25 (17.6)	0 (0)	76 (24.8)	
Black	18 (11.1)	13 (9.1)	0 (0)	31 (10.1)	
Asian/Pacific Islander	10 (6.1)	17 (12.0)	0 (0)	27 (8.8)	
Charlson Comorbidity Index (1 year before breast cancer diagnosis)					0.695
0	130 (79.7)	114 (80.3)	1 (50.0)	245 (79.8)	
1-2	27 (16.6)	25 (17.6)	1 (50.0)	53 (17.3)	
≥ 3	6 (3.7)	3 (2.1)	0 (0)	9 (2.9)	
Year of *BRCA1/2* test					0.777
1996-1998	0 (0)	1 (0.7)	0 (0)	1 (0.3)	
1999-2001	4 (2.5)	0 (0)	0 (0)	4 (1.3)	
2002-2004	7 (4.3)	12 (8.5)	0 (0)	19 (6.2)	
2005-2007	18 (11.0)	19 (13.4)	0 (0)	37 (12.0)	
2008-2010	55 (33.7)	45 (31.7)	1 (50.0)	101 (32.9)	
2011-2013	74 (45.4)	60 (42.2)	1 (50.0)	135 (44.0)	
2014-2015	5 (3.1)	5 (3.5)	0 (0)	10 (3.3)	
Menopausal status at diagnosis					0.391
Pre-/perimenopausal	114 (69.9)	92 (64.8)	2 (100.0)	208 (67.8)	
Postmenopausal	49 (30.1)	50 (35.2)	0 (0)	99 (32.2)	
Smoking history at diagnosis					0.013
Yes	56 (34.4)	30 (21.4)	1 (50.0)	87 (28.5)	
No	107 (65.6)	110 (78.6)	1 (50.0)	218 (71.5)	
Unknown/missing	0 (—)	2 (—)	0 (—)	2 (—)	
Body Mass Index at diagnosis, kg/m^2					0.140
Underweight (< 18.5)	2 (1.3)	2 (1.4)	0 (0)	4 (1.3)	
Healthy (18.5-24.9)	50 (31.2)	53 (37.9)	0 (0)	103 (34.1)	
Overweight (25.0-29.9)	46 (28.7)	48 (34.3)	1 (50.0)	95 (31.4)	
Obesity (≥ 30.0-34.9)	28 (17.5)	22 (15.7)	0 (0.0)	50 (16.6)	
Extreme obesity (> 35.0)	34 (21.3)	15 (10.7)	1 (50.0)	50 (16.6)	
Unknown/missing	3 (—)	2 (—)	0 (—)	5 (—)	
Maternal family history of breast cancer					0.145
Yes	84 (54.9)	63 (46.3)	0 (0)	147 (50.5)	
No	69 (45.1)	73 (53.7)	2 (100.0)	144 (49.5)	
Unknown/missing	10 (—)	6 (—)	0 (—)	16 (—)	
Paternal family history of breast cancer					0.002
Yes	51 (33.8)	36 (26.9)	0 (0)	87 (30.3)	
No	100 (66.2)	98 (73.1)	2 (100.0)	200 (69.7)	
Unknown/missing	12 (—)	8 (—)	0 (—)	20 (—)	
Maternal family history of ovarian cancer					0.019
Yes	30 (19.5)	13 (9.6)	0 (0)	43 (14.8)	
No	124 (80.5)	122 (90.4)	2 (100.0)	248 (85.2)	
Unknown/missing	9 (—)	7 (—)	0 (—)	16 (—)	
Paternal family history of ovarian cancer					0.061
Yes	20 (13.5)	9 (6.7)	0 (0)	29 (10.2)	
No	128 (86.5)	125 (93.3)	2 (100.0)	255 (89.8)	
Unknown/missing	15 (—)	8 (—)	0 (—)	23 (—)	

[a] Percentages within categories are based on known values. Percentages may not total to 100 because of rounding.

[b] p values indicate significant differences between *BRCA1* and *BRCA2* mutation carriers; excludes unknown/missing values.

Supplemental Table 2. Clinical outcomes in *BRCA1* or *BRCA2* mutation carriers					
Outcome	***BRCA1*, no. (%)**	***BRCA2*, no. (%)**	***BRCA1* and *2*, no. (%)**	**Total, no. (%)**	**p value[a]**
All women (N = 307)	163(53.1)	142 (46.3)	2 (0.7)	307 (100.0)	
Deaths					
Any cause	18 (11.0)	15 (10.6)	0 (0)	33 (10.7)	
Breast cancer	4 (2.5)	2 (1.4)	0 (0)	6 (2.0)	
All other causes	14 (8.6)	13 (9.2)	0 (0)	27 (8.8)	
Alive	127 (77.9)	112 (78.9)	2 (100.0)	241 (78.5)	
Follow-up, y					0.332
Median (IQR)	4.2 (2.8-6.7)	4.9 (2.6-7.2)	9.2 (2.7-7.2)	4.5 (2.5-6.8)	
Any subsequent primary cancer					0.688
Yes	27 (16.6)	26 (18.3)	1 (50.0)	54 (17.6)	
No	136 (83.4)	116 (81.7)	1 (50.0)	253 (82.4)	
Site of subsequent primary cancers (not mutually exclusive)					0.277[b]
Breast	17 (10.4)	23 (16.2)	1 (50.0)	41 (13.4)	
Ovarian	6 (3.7)	1 (0.7)	0 (0)	7 (2.3)	
Fallopian tube	0 (0)	0 (0)	0 (0)	0 (0)	
Peritoneal	0 (0)	1 (0.7)	0 (0)	1 (0.3)	
Pancreatic	1 (0.6)	1 (0.7)	0 (0)	2 (0.7)	
Gastric	0 (0)	0 (0)	0 (0)	0 (0)	
All other	5 (3.1)	6 (4.2)	0 (0)	11 (3.6)	
Recurrences (at any time after initial breast cancer)					0.468
Yes	34 (21.0)	24 (17.6)	0 (0)	58 (19.3)	
No	128 (79.0)	112 (82.4)	2 (100.0)	242 (80.7)	
Unknown/missing	1 (—)	6 (—)	0 (—)	7 (—)	
Extent of recurrence					0.278
Local	9 (26.4)	4 (16.7)	0 (0)	13 (22.4)	
Regional	11 (32.4)	5 (20.8)	0 (0)	16 (27.6)	
Distant	14 (41.2)	15 (62.5)	0 (0)	29 (50.0)	
Adjuvant therapy (n = 248)	135 (54.4)	111 (44.8)	2 (0.8)	248 (100.0)	
Endpoints (whichever occurred first)					0.775
Recurrence	16 (11.9)	9 (8.1)	0 (0)	25 (10.1)	
Second breast primary	8 (3.0)	8 (7.2)	1 (50.0)	13 (5.2)	
Death	3 (2.2)	2 (1.8)	0 (0)	5 (2.0)	
End of follow-up	108 (80.0)	92 (82.9)	1 (50.0)	205 (82.7)	
Median follow-up, y	3.0	3.6	2.8	3.2	0.801

[a] p values indicate significant differences between *BRCA1* and *BRCA2* mutation carriers; excludes unknown/missing values.
[b] Breast cancer vs other sites.