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Article

Association of Genetic Testing Results With Mortality Among Women With Breast Cancer or Ovarian Cancer

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Abstract

Background: Breast cancer and ovarian cancer patients increasingly undergo germline genetic testing. However, little is known about cancer-specific mortality among carriers of a pathogenic variant (PV) in *BRCA1/2* or other genes in a population-based setting. **Methods:** Georgia and California Surveillance Epidemiology and End Results (SEER) registry records were linked to clinical genetic testing results. Women were included who had stages I-IV breast cancer or ovarian cancer diagnosed in 2013-2017, received chemotherapy, and were linked to genetic testing results. Multivariable Cox proportional hazard models were used to examine the association of genetic results with cancer-specific mortality. **Results:** 22 495 breast cancer and 4320 ovarian cancer patients were analyzed, with a median follow-up of 41 months. PVs were present in 12.7% of breast cancer patients with estrogen and/or progesterone receptor-positive, HER2-negative cancer, 9.8% with HER2-positive cancer, 16.8% with triple-negative breast cancer, and 17.2% with ovarian cancer. Among triple-negative breast cancer patients, cancer-specific mortality was lower with *BRCA1* (hazard ratio [HR] = 0.49, 95% confidence interval [CI] = 0.35 to 0.69) and *BRCA2* PVs (HR = 0.60, 95% CI = 0.41 to 0.89), and equivalent with PVs in other genes (HR = 0.65, 95% CI = 0.37 to 1.13), vs noncarriers. Among ovarian cancer patients, cancer-specific mortality was lower with PVs in *BRCA2* (HR = 0.35, 95% CI = 0.25 to 0.49) and genes other than *BRCA1/2* (HR = 0.47, 95% CI = 0.32 to 0.69). No PV was associated with higher cancer-specific mortality. **Conclusions:** Among breast cancer and ovarian cancer patients treated with chemotherapy in the community, *BRCA1/2* and other gene PV carriers had equivalent or lower short-term cancer-specific mortality than noncarriers. These results may reassure newly diagnosed patients, and longer follow-up is ongoing.

Genetic testing for inherited pathogenic variants (PVs) in cancer susceptibility genes has an established role in cancer treatment (1) and is relevant for secondary cancer risk reduction and testing of relatives (2). We and others reported that patients diagnosed with breast and/or ovarian cancer increasingly undergo germline sequencing of many genes (3-6). In this context, patients may experience a positive genetic test result as a worrisome second diagnosis (7,8) and wonder whether having a PV increases their chance of dying from their cancer. It is important to know whether cancer mortality is associated with germline PVs to inform treatment decision-making and how clinicians counsel patients about prognosis.

Prior studies have investigated breast and ovarian cancer-specific mortality among carriers of PVs in *BRCA1* and/or *BRCA2* (*BRCA1/2*), with mixed results. Some showed lower cancer-specific mortality in *BRCA1/2* PV carriers, particularly among cohorts treated with chemotherapy, which may reflect a greater chemosensitivity of *BRCA1/2* PV carriers vs noncarriers due to

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dysfunctional DNA repair (9-12). Additional studies showed higher cancer-specific mortality in *BRCA1/2* PV carriers (13-16), whereas others showed no difference from patients who tested negative (17-23). Several prior studies were from single institutions or academic networks, which may introduce selection bias. Few studies analyzed results according to breast cancer subtypes or looked beyond *BRCA1/2* to consider the many other genes now evaluated in clinical practice.

We studied cancer-specific mortality among a population-based cohort comprising all women diagnosed with breast cancer or ovarian cancer in Georgia or California and reported to statewide Surveillance Epidemiology and End Results (SEER) cancer registries from 2013 to 2017, together with their results of clinical germline genetic sequencing provided by testing laboratories. Given concerns that SEER underreports chemotherapy (24), we excluded patients with no chemotherapy reported, because of uncertainty about their actual treatment history; thus, we limited the study to patients with documented chemotherapy receipt. Based on studies suggesting high chemosensitivity in *BRCA1/2* PV carriers (9-11,13,22,25), our hypothesis was that patients with a PV in *BRCA1/2* or another cancer susceptibility gene would have lower cancer-specific mortality than patients having negative or uncertain genetic testing results.

Methods

Study Cohort and Dataset

All women diagnosed with breast cancer or ovarian cancer from January 1, 2013, to December 31, 2017, in California and Georgia and reported to SEER registries in California (the Los Angeles Cancer Surveillance Program, the Greater Bay Area Cancer Registry, and the Cancer Registry of Greater California) and in Georgia (the Georgia Cancer Registry) were linked to clinical germline genetic testing results from 4 laboratories (Ambry Genetics, Aliso Viejo, CA; GeneDx, Gaithersburg, MD; Invitae, San Francisco, CA; Myriad Genetics, Salt Lake City, UT) that performed the substantial majority of such testing as determined by genetic counselor and patient surveys (3,4,6). Probabilistic methods were used to optimize ascertainment and linkage accuracy, as previously reported (3,6). The analytic dataset combined genetic results from the 4 laboratories, from reports dated 2012 through the first quarter of 2019, with SEER variables.

Patients were included in the analytic cohort if they linked to a genetic result, had stages I-IV breast cancer or epithelial ovarian cancer, and received chemotherapy. Exclusion criteria included those ages younger than 20 years, more than 1 primary tumor, and diagnosed only on death certificate. Missingness was less than 5% for all variables except grade for ovarian cancer (20.6% missing). All observations with missing values were excluded except for ovarian cancer missing grade. Patients with nonepithelial ovarian cancer (eg, germ cell, sarcoma, and other histologies) were excluded because of their different epidemiology, genetics, and clinical course (Supplementary Figure 1, available online). The analytic file included both registry and laboratory information and was stripped of protected health information [as defined by the Health Information Portability and Accountability Act Privacy Rule (26)]. The study was approved by institutional review boards associated with the SEER registries.

Test Results from Laboratories

Germline genetic testing results were provided by laboratories at the level of the affected gene and consisted of the interpretation according to American College of Medical Genetics criteria that was returned to the ordering clinician: PV or likely PV (analyzed together as PV), variant of uncertain significance (VUS), and benign or likely benign (analyzed together as negative). Results from all laboratories were combined to ensure anonymity, and gene-specific results were analyzed only for those genes tested by 2 or more laboratories (n = 86).

Measures

Demographic and clinical measures were selected that were conceptually appropriate based on previously demonstrated relationships to cancer-related mortality, including social determinants of health (eg, race and ethnicity, poverty), tumor biologic features (eg, grade, subtype), and treatments (Tables 1 and 2). SEER registries provided diagnosis age, race and ethnicity (non-Hispanic White, Black, Asian, Native American and Alaskan Native, Hispanic), percent poverty at the census tract level (<10%, 10%-19%, ≥20%), marital status, tumor stage and grade, breast cancer subtype defined by expression of estrogen and/or progesterone receptors (ER/PR) and HER2 [ER/PR-positive, HER2-negative; HER2-positive with any ER/PR status, defined hereafter as HER2-positive; and ER/PR-negative and HER2-negative, defined hereafter as triple-negative breast cancer (TNBC)], and ovarian cancer histology (serous, mucinous, endometrioid, clear cell, or other adenocarcinoma). SEER registries provided information on breast cancer first-course treatment including surgery (breast-conserving surgery, unilateral or bilateral mastectomy), chemotherapy, radiotherapy, endocrine therapy, or HER2-directed therapy. First-course ovarian cancer treatment information included type of surgery, specifically debulking surgery; other surgery (SEER codes 17, 25-28, 35-37, 50-52, 55-57); or no surgery and radiotherapy. SEER registries provided date and cause of death. Overall, cancer-specific and other-cause mortality data were available through December 31, 2019, and patients alive then were coded as censored. Patients who died of other cancers or noncancer were coded as censored at date of death.

Statistical Analysis

Our question was whether PVs were associated with risk beyond that accounted for by known risk factors: thus, the base model included known correlates of breast and ovarian cancer-specific mortality (described in Measures). As covariates were selected based on known mortality associations, we did not refine the model further by excluding covariates based on *P* values or effect size. Genetic test results were then added, with the primary result being the magnitude and precision of resulting coefficients.

Separate models were specified for patients with each breast cancer subtype and ovarian cancer, because treatments and relationships of predictor variables to outcomes likely differ between these groups. We used multivariable Cox proportional hazard survival models to examine the association between genetic results, demographic and clinical factors with breast, and ovarian cancer-specific mortality. Competing risks of noncancer deaths were treated as censored. Date of chemotherapy initiation was used as the starting point for survival, and treatments

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Table 1. Characteristics of tested breast cancer patients and ovarian cancer patients who received chemotherapy

Characteristic	Breast cancer No. (%)[a]	Ovarian cancer No. (%)[a]
State		
California	15 390 (68.4)	3129 (72.4)
Georgia	7105 (31.6)	1191 (27.6)
Age at cancer diagnosis, y		
20-29	588 (2.6)	47 (1.1)
30-39	3549 (15.8)	184 (4.3)
40-49	8086 (35.9)	642 (14.9)
50-59	5641 (25.1)	1189 (27.5)
60-69	3475 (15.4)	1287 (29,8)
70-79	1059 (4.7)	765 (17.7)
80 and older	97 (<1)	206 (4.8)
Race and ethnicity		
Non-Hispanic White	13 043 (58.0)	2916 (67.5)
Black	3324 (14.8)	319 (7.4)
Native American or Alaskan Native	71 (<1)	10 (<1)
Asian or Pacific Islander	2406 (10.7)	464 (10.7)
Hispanic	3651 (16.2)	611 (14.1)
Poverty level		
High (poverty ≥20%)	4970 (22.1)	894 (20.7)
Medium (10%-19%)	7248 (32.2)	1403 (32.5)
Low (poverty <10%)	10 277 (45.7)	2023 (46.8)
Marital status		
Married	14 123 (62.8)	2433 (56.3)
Not married	8372 (37.2)	1887 (43.7)
Stage		
I	5530 (24.6)	667 (15.4)
II	11 188 (49.7)	392 (9.1)
III	4563 (20.3)	2046 (47.4)
IV	1214 (5.4)	1215 (28.1)
Grade[b]		
1	1474 (6.6)	199 (5.8)
2	8125 (36.1)	398 (11.6)
3	12 896 (57.3)	1370 (39.9)
4 (ovarian cancer only)	NA	1465 (42.7)
Subtype (breast cancer only)		
ER/PR-positive, HER2-negative	10,956 (48.7)	NA
HER2-positive, any hormone receptor status	6078 (27.0)	NA
ER/PR-negative and HER2-negative (triple-negative)	5461 (24.3)	NA
Histology (ovarian cancer only)		
Serous	NA	3099 (71.7)
Mucinous	NA	104 (2.4)
Endometrioid	NA	438 (10.1)
Clear cell	NA	310 (7.2)
Other adenocarcinoma	NA	369 (8.6)

[a]Percentages may not sum to 100 because of rounding. ER = estrogen receptor; PR = progesterone receptor; NA = not applicable.
[b]Grade was missing for 888 ovarian cancer patients.

that occurred after chemotherapy were coded as time-varying covariates to account for immortal time bias. Ovarian cancer grade was imputed using multiple imputation techniques.

Sensitivity Analysis

Proportional hazards assumptions were tested by including time-dependent covariates of all independent variables and testing for significance. All interactions between key covariates were tested. To assess generalizability to the nontested population, we examined a model with weights for test receipt. Weights were generated from a logistic regression model of genetic testing receipt across all patients (tested and not tested), using clinical and demographic measures as covariates. The inverse of the predicted probabilities of test receipt were used as weights. We examined respecification of competing mortality risks using a Fine and Gray analysis. To address potential effects of test timing and treatment selection, we excluded patients tested after treatment initiation. To account for potential error in reported cause of death, we evaluated overall rather than cancer-specific mortality.

Results

Study Population

Supplementary Figure 1 (available online) shows flow of patients into the analytic cohort, and Table 1 shows characteristics of genetically tested breast (n = 22 495) and ovarian cancer

Table 2. Genetic testing results, treatment, and mortality of tested breast cancer patients and ovarian cancer patients treated with chemotherapy

Characteristic	Breast cancer, No. (%)			Ovarian cancer No. (%)
	ER/PR-positive, HER2-negative	HER2-positive, any ER/PR status	ER/PR-negative, HER2-negative (triple-negative)	
Total No.	10 946	6089	5460	4320
Genetic testing results				
Negative	7549 (69.0)	4286 (70.4)	3619 (66.3)	2737 (63.4)
BRCA1 PV	320 (2.9)	90 (1.5)	517 (9.5)	328 (7.6)
BRCA2 PV	499 (4.6)	142 (2.3)	217 (4.0)	242 (5.6)
Other gene[a] PV	567 (5.2)	363 (6.0)	182 (3.3)	174 (4.0)
VUS	2011 (18.4)	1208 (19.8)	925 (16.9)	839 (19.4)
Surgery, breast				
Breast-conserving surgery	3718 (34.0)	2148 (35.3)	2214 (40.5)	NA
Unilateral mastectomy	2866 (26.2)	1359 (22.3)	1042 (19.1)	NA
Bilateral mastectomy	2785 (25.4)	1528 (25.1)	1359 (24.9)	NA
Other surgery	894 (8.2)	496 (8.1)	376 (6.9)	NA
No surgery	683 (6.2)	558 (9.2)	469 (8.6)	NA
Surgery, ovarian				
Debulking surgery	NA	NA	NA	2287 (52.9)
Other surgery[b]	NA	NA	NA	1675 (38.8)
No surgery	NA	NA	NA	358 (8.3)
Radiation therapy	6549 (59.8)	3073 (50.5)	2920 (53.5)	47 (1.1)
Other systemic therapy				
Endocrine therapy	8117 (74.2)	3149 (51.7)	276 (5.1)	55 (1.3)
HER2-directed therapy	433 (4.0)	5090 (83.6)	141 (2.6)	209 (4.8)
Died from cancer[c]	662 (6.0)	246 (4.0)	765 (14.0)	1244 (28.8)
Average time at risk, days	1156	1158	1111	1034

[a]Other genes in which PVs were found are listed in Supplementary Table 1 (available online). ER = estrogen receptor; NA = not applicable; PR = progesterone receptor; PV = pathogenic variant; VUS = variant of uncertain significance.
[b]Other surgeries recorded by Surveillance Epidemiology and End Results (SEER) for ovarian cancer treatment include local tumor destruction not otherwise specified, total removal of tumor or single ovary, unilateral or bilateral salpingo-oophorectomy with or without hysterectomy, and unilateral or bilateral salpingo-oophorectomy with omentectomy (SEER codes 17, 25-28, 35-37, 50-52, 55-57).
[c]Median follow-up was 41 months (range = 1-85 months).

patients (n = 4320). Among breast cancer patients, 58.0% were non-Hispanic White, 14.8% Black, 16.2% Hispanic, 10.7% Asian or Pacific Islander, and less than 1% Native American or Alaskan Native, with a similar distribution in ovarian cancer patients. Approximately one-fifth of patients lived in high-poverty areas and half in low-poverty areas. Breast cancer subtype distribution was 48.7% ER/PR-positive, HER2-negative (n = 10 956), 27.0% HER2-positive (n = 6078), and 24.3% TNBC (n = 5461). Most (71.7%) ovarian cancer patients had serous histology and high (3 and 4, 81.6%) grades. The median follow-up was 41 (range = 1-85) months. For breast cancer patients, genetic testing occurred before diagnosis in 4.6% (n = 1037) and before chemotherapy initiation in 64.0% (n = 14 411); for ovarian cancer patients, these proportions were 2.9% (n = 124) and 18.9% (n = 857), respectively.

Genetic Testing Results, Treatment, and Mortality

Genetic results are summarized in Table 2. PVs were present in 12.6% (n = 1386) of patients with ER/PR-positive, HER2-negative breast cancer; 9.7% (n = 595) with HER2-positive breast cancer; 16.8% (n = 916) with TNBC; and 17.2% (n = 744) with ovarian cancer (Supplementary Table 1, available online). PVs were most common in *BRCA1/2*. Among breast cancer patients, other common PVs were, with ER/PR-positive, HER2-negative disease (n = 567 other gene PVs): *CHEK2* (n = 214), *PALB2* (n = 120), *ATM* (84), *BRIP1* (n = 32), and *TP53* (n = 22); with HER2-positive disease (n = 363 other gene PVs): *CHEK2* (n = 156), *ATM* (n = 71), *TP53* (n = 64), and *PALB2* (n = 31); and with TNBC (n = 182 other gene PVs): *PALB2* (n = 66), *RAD51C* (n = 23), *BRIP1* (n = 23), *CHEK2* (n = 23), *ATM* (n = 19), and *RAD51D* (n = 13). Among ovarian cancer patients, other common PVs (n = 174 other gene PVs) were in *BRIP1* (n = 35), *CHEK2* (n = 27), *RAD51C* (n = 24), *ATM* (n = 19), and *RAD51D* (n = 17).

Treatment receipt is shown according to breast cancer subtype (Table 2) and genetic testing results (Table 3). Death from the diagnosed cancer occurred in 6.0% of breast cancer patients with ER/PR-positive, HER2-negative disease; 4.0% with HER2-positive disease; 14.0% with TNBC; and 28.8% of ovarian cancer patients (Table 2). *BRCA1/2* PV carriers were more likely than other patients to receive bilateral mastectomy and debulking surgery (Table 3).

Breast Cancer-Specific Mortality

Multivariable model results are shown in Table 4. Among TNBC patients, those with *BRCA1* PVs had lower cancer-specific mortality (hazard ratio [HR] = 0.49, 95% confidence interval [CI] = 0.35 to 0.69) vs those testing negative, as did *BRCA2* PV carriers (HR = 0.60, 95% CI = 0.41 to 0.89). Equivalent cancer-specific mortality was observed among TNBC patients with other gene PVs (HR = 0.65, 95% CI = 0.37 to 1.13) vs those testing negative. Among patients with HER2-positive or ER/PR-positive, HER2-negative subtypes, there was no association of cancer-specific

Table 3. Treatments received by genetic test results among tested breast cancer patients and ovarian cancer patients treated with chemotherapy

Treatment	Genetic test result					
	Negative No. (%)	VUS only No. (%)	*BRCA1* PV No. (%)	*BRCA2* PV No. (%)	Other gene[a] PV No. (%)	*P*[b]
Breast cancer						
Surgery						<.001
No surgery	1151 (8.0)	330 (8.0)	74 (8.0)	73 (8.5)	87 (7.8)	
Lumpectomy	5942 (41.5)	1582 (38.2)	119 (12.8)	113 (13.2)	311 (28.0)	
Unilateral mastectomy	3631 (25.4)	990 (23.9)	170 (18.3)	200 (23.3)	265 (23.8)	
Bilateral mastectomy	3588 (25.1)	908 (21.9)	453 (48.9)	383 (44.6)	352 (31.7)	
Other surgery	1142 (8.0)	334 (8.1)	111 (12.0)	89 (10.4)	97 (8.7)	
Radiation therapy	8943 (62.5)	2406 (58.1)	304 (32.8)	369 (43.0)	524 (47.1)	<.001
Other systemic therapy						
Endocrine therapy	7930 (55.4)	2269 (54.8)	238 (25.7)	443 (51.6)	674 (60.6)	<.001
HER2-directed therapy	3921 (27.4)	1168 (28.2)	95 (10.2)	136 (15.9)	342 (30.8)	<.001
Ovarian Cancer						
Surgery						.01
No surgery	227 (1.6)	81 (2.0)	15 (1.6)	24 (2.8)	11 (1.0)	
Debulking surgery	1458 (10.2)	416 (10)	203 (21.9)	126 (14.7)	84 (7.6)	
Other surgery	1052 (7.4)	342 (8.3)	110 (11.9)	92 (10.7)	79 (7.1)	
Radiation therapy	29 (0.2)	13 (0.3)	4 (0.4)	0 (0)	1 (0.1)	.31
Other systemic therapy						
Endocrine therapy	33 (0.2)	13 (0.3)	3 (0.3)	2 (0.2)	4 (0.4)	.60
HER2-directed therapy	127 (0.9)	42 (1.0)	20 (2.2)	11 (1.3)	9 (0.8)	.83

[a]Other genes in which PVs were found are listed in Supplementary Table 1 (available online). PV = pathogenic variant; VUS = variant of uncertain significance.
[b]A 2-sided χ^2 test was used to calculate the *P* values.

mortality with genetic test results. Other factors associated with increased cancer-specific mortality included higher stage, surgical procedure other than breast-conserving surgery, higher neighborhood poverty, and Black race, whereas Asian and Pacific Islander race and ethnicity was associated with lower cancer-specific mortality.

Ovarian Cancer-Specific Mortality

Multivariable model results are shown in Table 5. Compared with patients testing negative, lower mortality was seen in patients with PVs in *BRCA2* (HR = 0.35, 95% CI = 0.25 to 0.49) and other tested genes (HR = 0.47, 95% CI = 0.32 to 0.69) but not with *BRCA1* PVs. Other factors associated with higher cancer-specific mortality included older age, Native American and Alaskan Native race and ethnicity, higher stage, and no surgery.

Sensitivity Analysis

All covariates satisfied proportional hazards assumptions except stage (for TNBC and ER/PR-positive, HER2-negative disease), surgery (for TNBC and HER2-positive disease), endocrine therapy (for HER2-positive and ER/PR-positive, HER2-negative disease), grade (for ER/PR-positive, HER2-negative disease), radiation (for TNBC), marital status (for ovarian cancer), and histology (for ovarian cancer). Models were created with interactions between these variables and time: across all models and variables, the coefficients for the primary covariate of test result did not change in statistical significance or size. Models including interactions between test result and all other covariates found no statistically significant effects.

In models weighted for probability of genetic testing (Supplementary Tables 2 and 3, available online), PVs in genes other than *BRCA1/2* were associated with lower breast cancer-specific mortality among patients with ER/PR-positive, HER2-negative disease (HR = 0.47, 95% CI = 0.30 to 0.75; Supplementary Table 2, available online). A Fine and Gray analysis accounting for competing mortality found similar results (ER/PR-positive, HER2-negative: HR = 0.63, 95% CI = 0.42 to 0.95; Supplementary Table 4, available online). Results for ovarian cancer patients did not change statistically significantly (Supplementary Tables 3 and 4, available online).

Sensitivity analyses of excluding patients tested after starting treatment (Supplementary Table 5, available online), overall mortality (Supplementary Table 6, available online), and stratifying by stage (Supplementary Table 7, available online) found no substantial difference in results. No PV was associated with higher cancer-specific or overall mortality in any analysis.

Discussion

We studied short-term cancer-specific mortality associated with germline genetic testing results among 22 495 breast cancer patients and 4320 ovarian cancer patients treated with chemotherapy in the population-based setting of 4 SEER registries comprising the statewide populations of California and Georgia. Consistent with our hypothesis, we found that compared with those testing negative for PVs, TNBC patients with PVs in *BRCA1/2* and ovarian cancer patients with PVs in *BRCA2* or other genes (notably *BRIP1*, *CHEK2*, *RAD51C*, and *ATM*) had lower cancer-specific mortality at 41 months' median follow-up time. To our knowledge, this is the first population-based study to report lower short-term cancer-specific mortality associated with germline PVs in genes other than *BRCA1/2*. These findings can inform discussions about prognosis between patients and their oncologists.

Table 4. Breast cancer-specific mortality of patients in a multivariable proportional hazards survival model, by breast cancer subtype[a]

Characteristic	ER/PR-positive, HER2-negative HR (95% CI)	HER2-positive, any ER/PR status HR (95% CI)	ER/PR-negative, HER2-negative (triple-negative) HR (95% CI)
Genetic testing results			
Negative	1 (Referent)	1 (Referent)	1 (Referent)
BRCA1 PV	1.06 (0.71 to 1.58)	0.92 (0.29 to 2.91)	0.49 (0.35 to 0.69)
BRCA2 PV	0.73 (0.50 to 1.04)	0.39 (0.12 to 1.24)	0.60 (0.41 to 0.89)
Other gene[b] PV	0.73 (0.49 to 1.10)	0.59 (0.26 to 1.32)	0.65 (0.37 to 1.13)
VUS only	0.81 (0.64 to 1.02)	0.70 (0.49 to 1.01)	0.79 (0.64 to 0.98)
Age (per 10-year difference)	1.06 (0.99 to 1.14)	1.04 (0.93 to 1.16)	0.95 (0.90 to 1.02)
Race and ethnicity			
Non-Hispanic White	1 (Referent)	1 (Referent)	1 (Referent)
Native American or Alaskan Native	2.40 (0.77 to 7.54)	–[c]	0.56 (0.14 to 2.26)
Asian or Pacific Islander	0.91 (0.68 to 1.21)	1.20 (0.80 to 1.79)	0.66 (0.47 to 0.93)
Black	1.43 (1.14 to 1.79)	2.03 (1.43 to 2.88)	1.02 (0.84 to 1.23)
Hispanic	1.07 (0.84 to 1.37)	1.16 (0.79 to 1.71)	0.94 (0.75 to 1.16)
Poverty level			
Low (poverty <10%)	1 (Referent)	1 (Referent)	1 (Referent)
Medium (10%-19%)	0.95 (0.79 to 1.14)	1.03 (0.75 to 1.43)	1.07 (0.89 to 1.28)
High (poverty ≥20%)	1.11 (0.90 to 1.36)	1.59 (1.15 to 2.20)	1.35 (1.12 to 1.62)
Married (vs not married)	0.77 (0.65 to 0.90)	0.90 (0.69 to 1.17)	0.95 (0.82 to 1.11)
Stage			
I	1 (Referent)	1 (Referent)	1 (Referent)
II	1.36 (0.96 to 1.92)	1.63 (0.99 to 2.68)	1.99 (1.51 to 2.63)
III	4.42 (3.13 to 6.23)	4.67 (2.81 to 7.78)	6.89 (5.16 to 9.20)
IV	16.59 (11.38 to 24.17)	11.38 (6.69 to 19.38)	16.58 (11.89 to 23.12)
Grade			
1	1 (Referent)	1 (Referent)	1 (Referent)
2	1.58 (1.07 to 2.31)	1.12 (0.40 to 3.10)	1.04 (0.38 to 2.83)
3	4.13 (2.84 to 6.01)	1.80 (0.66 to 4.88)	1.23 (0.46 to 3.29)
Surgery			
Breast conserving	1 (Referent)	1 (Referent)	1 (Referent)
Unilateral mastectomy	2.03 (1.58 to 2.62)	2.02 (1.32 to 3.09)	2.26 (1.80 to 2.83)
Bilateral mastectomy	1.60 (1.22 to 2.09)	1.42 (0.90 to 2.26)	1.70 (1.35 to 2.14)
No surgery	3.70 (2.68 to 5.09)	3.13 (1.95 to 5.03)	4.26 (3.24 to 5.61)
Other surgery	1.59 (1.08 to 2.34)	3.34 (1.96 to 5.69)	2.07 (1.49 to 2.88)
Radiotherapy (vs none)	1.25 (1.03 to 1.51)	1.44 (1.08 to 1.93)	1.32 (1.12 to 1.57)
Endocrine therapy (vs none)	0.79 (0.65 to 0.94)	0.47 (0.35 to 0.63)	1.08 (0.80 to 1.47)
HER2-directed therapy (vs none)	0.82 (0.60 to 1.13)	0.61 (0.44 to 0.84)	1.21 (0.86 to 1.69)
Year of diagnosis	1.05 (0.98 to 1.13)	1.15 (1.02 to 1.29)	1.04 (0.98 to 1.10)
California (vs Georgia)	0.83 (0.69 to 1.01)	0.86 (0.63 to 1.18)	0.78 (0.66 to 0.93)

[a]Results presented are from a single multivariable proportional hazards model for each breast cancer subtype. CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; PR = progesterone receptor; PV = pathogenic variant; VUS = variant of uncertain significance.
[b]Other genes in which PVs were found are listed in Supplementary Table 1 (available online).
[c]No observations for this group.

Our findings add to an extensive literature on outcomes of *BRCA1/2*-associated breast cancer (13,14). There has been little consensus, with some studies reporting higher (14-16,27-29) and others lower cancer-specific mortality (30) among *BRCA1/2* PV carriers vs noncarriers, whereas others found no difference (17,19,22,23,31). Focusing on higher-risk subtypes and chemotherapy recipients has offered more clarity: some studies found lower cancer-specific mortality among *BRCA1/2* PV carriers who had TNBC and/or received chemotherapy (9,10,18,25,32). These results are consistent with clinical trials such as GeparSixto and INFORM, which showed that *BRCA1/2* PV–associated cancers respond well to various chemotherapy regimens (33,34). Our finding of lower *BRCA1/2*-associated cancer-specific mortality with TNBC only may reflect its more aggressive biology than other subtypes, which might confer an earlier and greater benefit from chemotherapy. *BRCA1/2* PV carriers might also have received more intensive chemotherapy—with more agents and/or of longer duration—than other patients. We found that *BRCA1/2* PV carriers more often received bilateral mastectomy (and debulking surgery for ovarian cancer); however, multivariable modeling controlled for surgical procedure, so this variation does not account for the observed results. A limitation is that SEER does not report risk-reducing salpingo-oophorectomy, which may have contributed to the lower breast cancer-specific mortality observed in *BRCA1/2* PV carriers. A further consideration is the short median follow-up of this study (41 months), because TNBC is prone to early recurrence and mortality (35). Longer follow-up is needed to determine whether lower cancer-specific mortality with *BRCA1/2* PVs emerges for late-recurring subtypes, such as ER/PR-positive, HER2-negative disease (36). Future studies should also include cases diagnosed more recently, because poly (ADP-ribose) polymerase [PARP] inhibitors

Table 5. Ovarian cancer-specific mortality of patients in a multivariable proportional hazards survival model

Characteristic	Hazard ratio (95% CI)
Genetic testing results	
Negative	1 (Referent)
BRCA1 PV	0.85 (0.68 to 1.07)
BRCA2 PV	0.35 (0.25 to 0.49)
Other gene PV[a]	0.47 (0.32 to 0.69)
VUS only	0.84 (0.72 to 0.98)
Age (per 10-year difference)	1.16 (1.09 to 1.22)
Race and ethnicity	
Non-Hispanic White	1 (Referent)
Black	0.86 (0.69 to 1.07)
Native American or Alaskan Native	2.88 (1.18 to 6.99)
Asian or Pacific Islander	0.89 (0.72 to 1.10)
Hispanic	0.91 (0.75 to 1.10)
Poverty level	
Low (poverty <10%)	1 (Referent)
Medium (10%-19%)	1.08 (0.95 to 1.23)
High (poverty ≥20%)	0.97 (0.82 to 1.14)
Married (vs not married)	0.93 (0.83 to 1.04)
Stage	
I	1 (Referent)
II	1.85 (1.18 to 2.90)
III	5.88 (4.10 to 8.42)
IV	8.18 (5.69 to 11.77)
Grade[b]	
1	1 (Referent)
2	1.12 (0.76 to 1.64)
3	1.16 (0.82 to 1.65)
4	1.19 (0.83 to 1.69)
Serous (vs not serous)[c]	0.80 (0.69 to 0.94)
Surgery	
No surgery	1 (Referent)
Debulking surgery	0.61 (0.50 to 0.73)
Other surgery[d]	0.47 (0.38 to 0.57)
Year of diagnosis	1.07 (1.02 to 1.12)
California (vs Georgia)	0.82 (0.73 to 0.93)

[a]Other genes in which PVs were found are listed in Supplementary Table 1 (available online). CI = confidence interval; PV = pathogenic variant; VUS = variant of unknown significance.

[b]Multiple imputation was used for grade because 22% of patients had missing grade data.

[c]Collapsed to serous vs not serous because of smaller numbers in subgroups of nonserous histology.

[d]Other surgeries recorded by Surveillance Epidemiology and End Results (SEER) for ovarian cancer treatment include local tumor destruction not otherwise specified, total removal of tumor or single ovary, unilateral or bilateral salpingo-oophorectomy with or without hysterectomy, and unilateral or bilateral salpingo-oophorectomy with omentectomy (SEER codes 17, 25-28, 35-37, 50-52, 55-57).

were not approved for *BRCA1/2*-associated metastatic disease until 2018, and thus their effects are unlikely to be substantial in this 2013-2017 diagnosis cohort (37-39).

We found no evidence of higher short-term cancer-specific mortality among TNBC patients with PVs in genes other than *BRCA1/2*. Furthermore, in 2 sensitivity analyses, we observed statistically significantly lower cancer-specific mortality with other gene PVs (most commonly *CHEK2*, *PALB2*, and *ATM*) among patients with ER/PR-positive, HER2-negative breast cancer. A study of *CHEK2* PV carriers including all breast cancer subtypes found equivalent cancer-specific mortality to noncarriers in the first 6 years postdiagnosis, but twofold higher mortality afterward (40). Two hospital-based series found that overall mortality was higher among *PALB2* PV carriers than noncarriers (16,41). The PATTERN trial of adjuvant chemotherapy for TNBC found no difference in disease-free survival between non-*BRCA1/2* PV carriers and noncarriers (23). Although longer follow-up is essential, our early findings suggest that carriers of PVs in genes other than *BRCA1/2* are not more likely (and may be less likely) than noncarriers to die of their breast cancer.

In contrast to breast cancer, prior ovarian cancer studies including some in population-based settings more consistently reported lower short-term cancer-specific mortality associated with *BRCA1/2* PVs (11,12,14,42,43). However, longer-term studies reported attenuation or reversal of this advantage (44,45). Our finding of lower short-term ovarian cancer-specific mortality with *BRCA2* PVs is largely consistent with prior studies (42). Our results may also reflect an emerging contribution from PARP inhibitors, which were approved in 2014 (46). However, longer follow-up is necessary.

We found lower short-term ovarian cancer-specific mortality with PVs in genes other than *BRCA1/2* (notably *BRIP1*, *RAD51C*, *CHEK2*, and *ATM*), consistent with results of the Gynecologic Oncology Group 218 trial (12). To our knowledge, this has not previously been reported in community practice. High-grade, serous ovarian cancer often has a homologous recombination-deficient phenotype conferring sensitivity to chemotherapy, particularly platinum agents, and PARP inhibitors (47). However, there is greater treatment responsiveness among ovarian cancer patients who do vs who do not carry *BRCA1/2* PVs (11,48). This enhanced response might also pertain to carriers of PVs in other genes and contribute to their lower cancer-specific mortality.

Our study has limitations. The relatively few deaths and few PVs in each gene limited statistical power to analyze the association of cancer-specific mortality with specific genes; larger subsequent analyses with longer follow-up may achieve this. Although there were many patients from most racial and ethnic groups, there were fewer Native American and Alaskan Natives. Additionally, we lack information on specific chemotherapy agents received. However, because breast cancer trials such as INFORM and GeparSixto found that *BRCA1/2* PV carriers responded well regardless of specific drugs used (33,34), this limitation seems unlikely to affect our conclusions. Although we lack information on PARP inhibitor use, the study period overlaps with their Food and Drug Administration approval, and thus their impact was probably limited, especially for breast cancer (37,38). Results for patients who underwent clinical genetic testing, potentially because of family cancer history, may not be generalizable to patients who did not; however, we found that a sensitivity analysis accounting for selection into testing offered no evidence of higher cancer-specific mortality, and additional evidence of lower cancer-specific mortality, among PV carriers. We lack data on other prognostic factors including prediagnostic screening, comorbidities, extent of surgical debulking, and metastatic recurrence. As noted previously, the median follow-up time of 41 months is short, yet it encompasses a period that matters to patients as they plan for their immediate future. The study's limitations are balanced by considerable strengths, including a large, diverse, contemporary population-based sample; genetic results obtained directly from testing laboratories; and uniform ascertainment of treatment and mortality data by SEER registries that have near-total capture of all cancers statewide, minimizing selection bias.

This study's results have substantial implications for patients newly diagnosed with breast cancer or ovarian cancer. We found that no PV, whether in *BRCA1/2* or another gene, was associated with any increase in short-term cancer-specific or

overall mortality among patients treated with chemotherapy. This may help reassure cancer patients that testing positive for a PV does not mean they are more likely to die within the first several years following their cancer diagnosis.

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Data Availability

The data underlying this article cannot be shared publicly at this time due to agreements with participating testing laboratories.

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