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Outcomes After Breast Radiation Therapy in a Diverse Patient Cohort With a Germline *BRCA1/2* Mutation

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Abstract

Purpose: *BRCA1/2* pathogenic variant (PV) mutations confer radiation sensitivity preclinically, but there are limited data regarding breast cancer outcomes after radiation therapy (RT) among patients with documented *BRCA1/2* PV mutations versus no PV mutations.

Methods and Materials: This retrospective cohort study included women with clinical stage I-III breast cancer who received definitive surgery and RT and underwent *BRCA1/2* genetic evaluation at the The University of Texas MD Anderson Cancer Center. Rates of locoregional recurrence (LRR), disease-specific death (DSD), toxicities, and second cancers were compared by *BRCA1/2* PV status.

Results: Of the 2213 women who underwent *BRCA1/2* testing, 63% self-reported their race as White, 13.6% as Black/African American, 17.6% as Hispanic, and 5.8% as Asian/American Indian/Alaska Native; 124 had BRCA1 and 100 had *BRCA2* mutations; and 1394 (63%) received regional nodal RT. The median follow-up time for all patients was 7.4 years (95% confidence

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interval [CI], 7.1–7.7 years). No differences were found between the groups with and without *BRCA1/2* PV mutations in 10-year cumulative incidences of LRR (with mutations: 11.6% [95% CI, 7.0%−17.6%]; without mutations: 6.6% [95% CI, 5.3%−8.0%]; $P = .466$) and DSD (with mutations: 12.3% [95% CI, 8.0%−17.7%]; without mutations: 13.8% [95% CI, 12.0%−15.8%]; $P = .716$). On multivariable analysis, *BRCA1/2* status was not associated with LRR or DSD, but Black/African American patients ($P = .036$) and Asians/American Indians/Alaska Native patients ($P = .002$) were at higher risk of LRR compared with White patients, and Black/African American patients were at higher risk of DSD versus White patients ($P = .004$). No in-field, nonbreast second cancers were observed in the *BRCA1/2* PV group. Rates of acute and late grade ≥3 radiation-related toxicity in the *BCRA1/2* PV group were 5.4% (n = 12) and 0.4% (n = 1), respectively.

Conclusions: Oncologic outcomes in a diverse cohort of patients with breast cancer who had a germline *BRCA1/2* PV mutation and were treated with RT were similar to those of patients with no mutation, supporting the use of RT according to standard indications in patients with a germline *BRCA1/2* PV mutation.

Introduction

As knowledge about the link between germline mutations and the development of cancers has evolved, guidelines have expanded regarding which patients with breast cancer should be evaluated for pathogenic mutations.[1–5] Patients with germline *BRCA1* or *BRCA2* (*BRCA1/2*) pathogenic variant (PV) mutations may be offered alternative definitive pharmacologic and surgical treatment options, distinct from the recommendations for non-*BRCA1/2*-associated breast cancers.[4,6] Preclinical literature suggests that *BRCA1/2*-mutated tumors may be more radiosensitive,[7] although this has not been universally found[8]; whether this is relevant in patients and if this should affect clinical decisions regarding radiation therapy (RT) for patients with breast cancer and germline *BRCA1/2* mutations remains uncertain. There have been several attempts to create guidelines and reach consensus on how to best deliver RT for such patients,[4,9,10] but additional data on clinical outcomes are needed to guide decisions.

Ionizing radiation induces both single- and double-strand breaks (DSBs) in DNA, with the latter being particularly lethal via compromising the integrity of both DNA strands simultaneously.[11] DSBs may be repaired by homologous recombination, which has high fidelity, or by nonhomologous end joining, which is relatively more error-prone. Both *BRCA1* and *BRCA2* are important to the canonical homologous recombination pathway.[12] Consequently, RT-induced DSBs in tumors with a *BRCA1/2* mutation can result in increased chromosomal rearrangements, genomic instability, and eventual cell death owing to deficiency in homologous recombination.[11] Several preclinical and clinical models suggest that a *BRCA1/2* PV mutation may render a tumor more sensitive to RT.[13–16] Although this has been hypothesized to improve tumor control, concerns have been expressed that the normal tissues of patients with *BRCA1/2* germline mutations may also be more radiosensitive and thus that such patients may experience greater toxicities and secondary radiation-induced malignancies compared with patients without such mutations.

Real-world evidence is needed to support appropriate practice in this area. A recent population-based cohort study showed that women with germline pathogenic mutations in breast cancer−associated genes were less likely to receive RT after breast-conserving surgery for early-stage, hormone receptor−positive cancer.[17] Prior studies compared outcomes for patients with early-stage breast cancer who had *BRCA1/2* PV mutations with outcomes for patients thought to have sporadic breast cancer,[18–21] but the sporadic controls had not undergone genetic testing, and *BRCA1/2* pathogenic mutation status was not confirmed.[20,22,23] Reports of outcomes among patients with *BRCA1/2* mutations and locally advanced breast cancer, for whom regional nodal irradiation (RNI) is recommended, are limited. Notably, RNI delivered in the treatment of locally advanced breast cancer exposes significantly more of the thoracic contents (including the heart and lungs) to radiation than does RT targeting only the breast (ie, for early-stage disease). For this reason, any pathogenic normal-tissue effects could be more likely to appear among patients treated with RNI. Because the clinical indications for RNI have increased,[24,25] questions about the safety and efficacy of RT for women with locally advanced breast cancer and *BRCA1/2* PV mutations are particularly relevant.

The purpose of this study was to evaluate oncologic outcomes and RT-related toxicity in a group of patients with breast cancer who underwent *BRCA1/2* germline testing via a large genetic screening program that serves a diverse patient population.

Methods and Materials

Patients

With institutional review board approval, patient databases at The University of Texas MD Anderson Cancer Center Departments of Radiation Oncology and Breast Medical Oncology were retrospectively queried and cross-referenced to identify women ≥18 years old with a diagnosis of clinical stage I−III invasive breast cancer through the year 2017 who were treated with definitive surgery and adjuvant external-beam RT, underwent *BRCA1/2* germline mutation testing, were evaluated by a breast medical oncologist at our institution, and were seen in follow-up. We included patients evaluated for a second primary cancer who underwent germline mutation testing, and information about the primary breast cancer was included for analysis. *BRCA1/2* mutations were classified as either a PV or no mutation; the latter consisted of variants of unknown significance (VUS) or no identifiable *BRCA1/2* PV. Referrals for genetic testing were based on patients' personal and family medical histories, contemporaneous National Comprehensive Cancer Network guidelines, and shared decision-making between the patient and her health care providers.

Clinicopathologic features, treatment details, and follow-up information were abstracted from the electronic medical record. Disease was staged in all cases according to the American Joint Committee on Cancer seventh edition staging manual.[26] Among women with synchronous, bilateral breast cancers, the cancer with higher clinical stage was included as the index primary breast cancer. The Common Terminology Criteria for Adverse Events, version 5.0, were used to record RT-related toxicities for the *BRCA1/2 PV* cohort. Acute toxicities were those observed within 3 months of RT treatment completion, and late toxicities were those observed afterward. Evaluation of subsequent in-field nonbreast

cancers included tumors of nonbreast histology that arose in the breast/chest wall, thorax, axilla, or neck.

Statistical analysis

Patient, tumor, and treatment characteristics were compared by χ^2 or Fisher exact tests for categorical variables; *t* tests were used to compare continuous variables. All time intervals were calculated from the date of definitive surgery for the first diagnosed breast cancer. Locoregional recurrence (LRR) was defined as clinically or pathologically confirmed disease recurrence in the ipsilateral breast/chest wall or axillary, internal mammary chain, or supraclavicular fossa nodal basins. Because local recurrences could not be distinguished from new ipsilateral primary breast cancers, both were considered to be LRR events. For disease-specific death (DSD), breast cancer−related death was scored as an event, with patients otherwise censored at last follow-up; death from other causes was considered a competing risk. Only patients with at least 1 year of follow-up after breast surgery were included in the DSD and LRR analyses. Rates of LRR and DSD were estimated by the method of cumulative incidence; outcomes based on *BRCA1/2 PV* mutational status were compared by using the Gray test.[27] Death was considered a competing risk for both LRR and DSD. The actuarial probabilities of overall survival by *BRCA1/2* status were estimated with the Kaplan-Meier method; differences were assessed with log-rank tests.

Univariate and multivariable proportional hazards models described by Fine and Gray, based on the competing risk Cox proportional hazards regression model, were used to assess the effect of potential prognostic factors on LRR and DSD.[28] Corresponding hazard ratios and 95% confidence intervals (CIs) are reported. Statistical tests were based on a 2-sided significance level. A *P* value ≤.05 was considered statistically significant in all analyses. Toxicity data were summarized by descriptive statistics such as counts and percentages. Statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc, Cary, NC) and Splus, version 8.2 (TIBCO Software Inc, Palo Alto, CA) or R, version 2.15.1 (R Project for Statistical Computing).[29]

Results

Patients

Clinicopathologic features at the time of breast cancer diagnosis of the 2213 women who met the inclusion criteria and received a diagnosis between 1977 and 2017 are shown in Table 1. The population included 37% women who self-reported their race as non-White (13.6% Black/African American, 17.6% Hispanic, and 6% Asian American or American Indian). *BRCA1/2* PV mutations were identified in 224 women (10%), 124 with *BRCA1* and 100 with *BRCA2* PV mutations. A total of 73 patients (3.2% of the entire cohort) harbored a *BRCA1/2* VUS without a PV mutation (16 *BRCA1*, 54 *BRCA2*, and 3 both).

Patients in the *BRCA1/2* PV group were younger, with a median age of 41 years ($P < .001$), and were more likely to have tumors of a higher clinical stage, triple-negative phenotype, high grade, and synchronous contralateral breast cancers (all $P < .005$) than the no-mutation group, but no significant differences were found by race between groups ($P = .075$). The

BRCA1/2 PV mutation group more often received mastectomy than breast-conserving surgery, radiation to the chest wall and RNI versus other RT targets, and chemotherapy versus no chemotherapy (all $P < .05$) and underwent bilateral salpingo-oophorectomy and risk-reducing contralateral prophylactic mastectomy within 1 year of definitive breast cancer surgery.

Survival and LRR outcomes

The median follow-up time for this analysis was 7.4 years (95% CI, 7.1–7.7 years). Ten-year overall survival rates were comparable for the *BRCA1/2* PV and no-mutation groups ($P = .875$; Fig. 1). The 10-year cumulative incidence of LRR was 11.6% (95% CI, 7.0%−17.6%) in the *BRCA1/2* PV group and 6.6% (95% CI, 5.3%−8.0%) in the no-mutation group ($P = .466$). Similarly, the 10-year DSD rate was 12.3% (95% CI, 8.0%−17.7%) in the *BRCA1/2* PV group versus 13.8% (95% CI, 12.0%−15.8%) in the no-mutation group ($P = .716$). No differences were found in LRR or DSD rates by *BRCA1/2* status when analyzed by clinical disease stage (Fig. 2 and 3). Patients who received RNI had a lower risk of LRR than those who did not (10-year cumulative incidence rates of LRR, 5.9% [95% CI, 4.6%−7.5%] vs 8.9% [95% CI, 6.7%−11.5%]; $P = .004$) but higher risk of DSD (16.6% [95% CI, 14.2% −19.1%] vs 8.7% [95% CI, 6.5%−11.5%]; $P < .001$). The LRR rates also did not differ among women who underwent bilateral salpingo-oophorectomy before or within 1 year of their breast surgery compared with women who did not, with death considered a competing risk ($P > .05$). Univariate analyses of factors found to be associated with LRR and DSD are shown in Tables E1 and E2.

Multivariable analyses

On multivariable analysis, age ≤40 and higher pathologic disease stage retained significance for associations with both LRR and DSD (Table 2). In the LRR model, being Black/African American or Asian and American Indian/Alaska Native was associated with higher rates of LRR compared with being White, whereas receipt of adjuvant hormone therapy was associated with lower rates of LRR. Factors associated with higher rates of DSD were Black/African American race compared with White race, clinical stage III versus stage I, high nuclear grade, and increased nodal burden. Although mastectomy was associated with lower rates of LRR (hazard ratio [HR], 0.360 [95% CI, 0.219–0.593]; $P \leq .001$), it correlated with higher rates of DSD (HR, 1.555 [95% CI, 1.130–2.141]; $P = .007$). Notably, *BRCA1/2* status was not an independent predictor of LRR (HR, 0.873 [95% CI, 0.496–1.536]; $P = .640$). Despite inclusion of an interaction term for TNBC and *BRCA1/2* PV in the DSD multivariable analysis model, *BRCA1/2* status was not statistically significantly associated with DSD in either the non-TNBC group (HR, 0.697 [95% CI, 0.376–1.293]; $P = .250$) or the TNBC group (HR, 0.574 [95% CI, 0.308–1.073]; $P = .082$).

Second nonbreast cancers in the radiation treatment field

No in-field nonbreast secondary tumors were observed in the *BRCA1/2* PV group. Thirteen women without *BRCA1/2* PV mutations experienced a second nonbreast primary tumor within the radiation fields (median time after surgery, 4.4 years [range, 4 months to 20 years]). Six of these women developed thyroid cancer; all 6 had received RNI that included targeting of the supraclavicular fossa. The other 7 women developed a radiation-associated

sarcoma; 4 of these were spindle cell sarcomas and none were angiosarcomas in the breast, chest wall, or intrathoracic region.

Toxicity in BRCA1/2 PV group

Acute and late toxicities among the *BRCA1/2* PV cohort are shown in Table 3. Overall, grade 3 toxicities were minimal, and no grade 4–5 toxicities were noted. Twelve women (5.4%) experienced any acute grade 3 toxicities, most of which were adverse skin effects such as dermatitis, erythema, desquamation, or hyperpigmentation. One patient developed grade 3 herpetic neuralgia of the untreated, contralateral chest wall and arm during the course of RT. No acute lung or cardiac toxicities were observed. One patient developed grade 1, asymptomatic radiation pneumonitis diagnosed on follow-up computed tomography (CT) at 3 months, and no late grade ≥2 pulmonary or cardiac toxicities were noted.

Discussion

To our knowledge, this study is one of the largest to directly compare oncologic outcomes after surgery and adjuvant RT between *BRCA1/2* PV mutation carriers and testing-confirmed noncarriers. With more than 35% of patients self-identifying as non-White, our findings represent the racially diverse demographic of the United States. Other large-scale efforts to evaluate clinical outcomes after RT in patients with a *BRCA1/2* PV mutation have focused primarily on patients with Ashkenazi Jewish ancestry and founder mutations,[30–32] although reports of other ethnic groups with *BRCA 1/2* PV mutations have also been published from Korea, France, and the Netherlands.[33–35] Strikingly, in our multivariate models of outcomes of LRR and DSD, neither *BRCA 1/2* PV mutation status was significant, whereas race was.

We demonstrated that overall survival, LRR, and DSD rates were similar between patients with and without a *BRCA1/2* PV mutation. No in-field secondary nonbreast cancers were observed in the *BRCA1/2* PV mutation group. Toxicities in the *BRCA1/2* PV mutation group were low overall. Most earlier studies comparing clinical outcomes based on *BRCA1/2* PV status did not have documentation confirming which patients did not have a *BRCA1/2* mutation and instead relied primarily on a negative family history to define that cohort,[18–20,22] whereas testing was performed for every patient in our cohort, strengthening our results. Collectively, these findings do not suggest that women with germline *BRCA1/2* mutations have more radiosensitive disease or have a different clinical response to RT than do *BRCA1/2* PV noncarriers.

Preclinical studies have shown that tumors with a heterozygous *BRCA1/2* mutation are more radiosensitive and more likely to have homologous recombination deficiencies and G2/M checkpoint defects.[7] This heightened radiosensitivity has been found to affect not only tumor cells but also lymphocytes and other benign tissues.[15,36,37] Increased radiosensitivity among *BRCA1/2* PV carriers is thought to act as a double-edged sword that may increase tumor control but simultaneously increase secondary tumors and toxicity.[16,38–40]

Second primary cancers after RT have been documented in large, contemporary, population-based breast cancer data sets, albeit at low frequencies.[41–44] Low rates of second cancers

are, in part, attributable to the use of modern radiation techniques, including CT-based simulation, image guidance, and newer linear accelerators relative to historical experiences with orthovoltage and Cobalt-60 machines. Sixty-three percent of the patients in our study (1394 women) received RNI, which exposes more of the intrathoracic contents to low-dose RT relative to whole- or partial-breast RT. In contrast, many earlier studies evaluating clinical outcomes for patients with breast cancer based on *BRCA1/2* status included only patients who received whole-breast irradiation.[18–20,22] No in-field second cancers were observed in the 214 patients in the *BRCA1/2* PV mutation group, similar to the <0.5% rate of second primary in-field tumors detected in *BRCA1/2* carriers reported by Schlosser et al.[31] Given these low frequencies, we propose that the benefits of RT, when indicated, outweigh the risk of second malignancies for women with *BRCA1/2* PV mutations.

Prior studies of toxicities among *BRCA1/2* PV mutation carriers did not find significant increases in toxicities,[18,40,45] but these studies were limited largely to women with early-stage disease requiring RT to the breast alone, a treatment with a toxicity profile distinct from that of RNI. Our rates of acute and late grade 3 dermatitis of 4.9% and 0.4% are comparable to those in the randomized NCIC MA.20 trial (3.7% and 0.7%, respectively) for patients with unknown BRCA1/2 status.[25] Three studies have shown equivalent rates of RT-related toxicity among *BRCA1/2* carriers and sporadic, untested controls.[18,33,40] To our knowledge, no demonstrable evidence has been published to date of increased radiosensitivity among *BRCA1/2* carriers.

With expanding recommendations, germline mutations will undoubtedly be detected in a larger number of patients with breast cancer than before. Currently, *BRCA1* and *BRCA2* germline mutations are associated with 5% to 7% of all breast cancer cases, disproportionately affecting younger women and portending a 50% to 80% lifetime risk of developing breast cancer.[11] The clinical conundrum for many physicians is the recommendation for subsequent surgery, RT, and systemic therapy for these patients. Women with early-stage breast cancer and PVs in *BRCA1/2* and other breast cancer−associated genes are reportedly less likely to be treated with guideline-concordant modalities, including omission of standard RT, than are their counterparts without PV mutation.[17] To address this issue, the American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology evaluated the current literature and issued a consensus statement specifically for patients with germline PV mutations; that statement declared that adjuvant RT is appropriate and carries no increased risk of toxicity in *BRCA1/2* PV mutation carriers versus noncarriers.[4] The present study adds further evidence that RT can be used safely among patients with a *BRCA1/2* PV, including a racially diverse population and those requiring RNI, groups previously understudied in this context.

Although this study generated insights into the consequences of adjuvant RT for *BRCA1/2* PV mutation carriers, certain limitations must be acknowledged. First, *BRCA1/2* PV patients in our cohort had biologically higher-risk disease, with TNBC presenting at a younger age, and were more likely to undergo neoadjuvant chemotherapy and mastectomy. This skew was expected, because many *BRCA1/2* PV carriers with early-stage disease opt for mastectomy and do not require adjuvant RT and thus were not eligible for evaluation. In addition, even

with comparable pathologic stage disease, patients with a *BRCA1/2* PV were more likely to receive RNI, likely because of some of these underlying biologically aggressive features of their tumors. However, even with more aggressive stage and pathologic features, survival and locoregional control rates were comparable between groups. A second limitation is that a large majority of patients included in the study were treated before the use of Poly(ADP-ribose)polymerase-1 inhibitors was incorporated into the treatment of patients with *BRCA1/2* PV-associated breast cancer, which is now standard. A third limitation is the challenges inherent in a retrospective study of this kind, specifically in the collection of toxicity data, with indisputable selection, follow-up, and survival biases, and the difficulty discerning between an LRR and a new primary on the ipsilateral side. Toxicities were recorded only for the 224 patients with a *BRCA1/2* PV because there are data from prospective phase 3 clinical trials with long-term follow-up documenting standard toxicities seen after RT in other cohorts. Fourth, we recorded the index primary breast cancer for all included patients. However, these patients often presented to our tertiary care cancer center after diagnosis of a second breast cancer, at which time germline testing was conducted, concordant with current National Comprehensive Cancer Network guidelines.[1] We considered VUS to be in the "no mutation" comparison group. Although 3% of *BRCA1/2* gene perturbations detected are VUS, up to 20% are estimated to be pathogenic mutations,[46,47] and the implications of this for use of RT remains uncertain. We also acknowledge that follow-up time for assessing second in-field cancers remains limited, and additional long-term screening of such patients is warranted. Nonetheless, major strengths of this series include the large number and racial diversity of patients who underwent germline mutation testing and had a known *BRCA1/2* PV mutation status.

Conclusions

This single-institution study showed that among 2213 racially diverse women who underwent germline *BRCA1/2* testing, surgery, and adjuvant RT, oncologic outcomes were similar for patients with and without PV mutations. Possessing a germline *BRCA1/2* mutation does not seem to translate to increased radiosensitivity in the clinical setting. Our findings support the delivery of guideline-concordant care for patients with breast cancer and a *BRCA1/2* mutation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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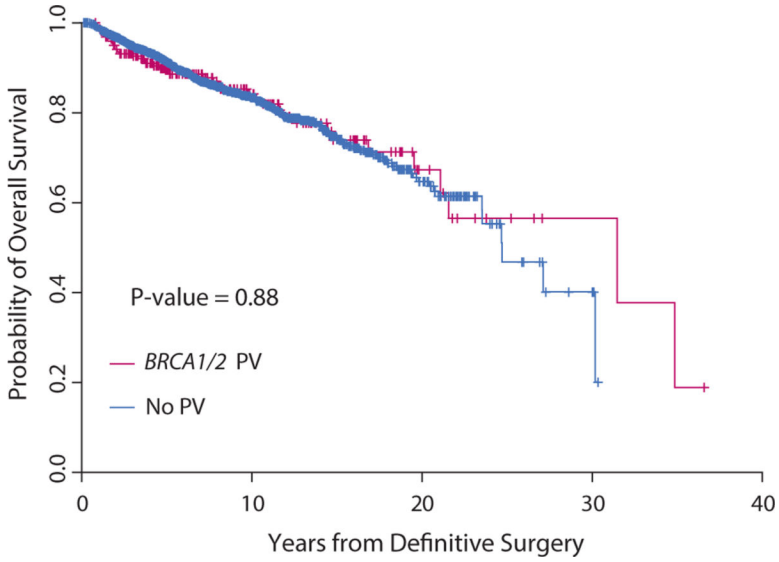

Fig. 1.
Overall survival by *BRCA1/2* status.

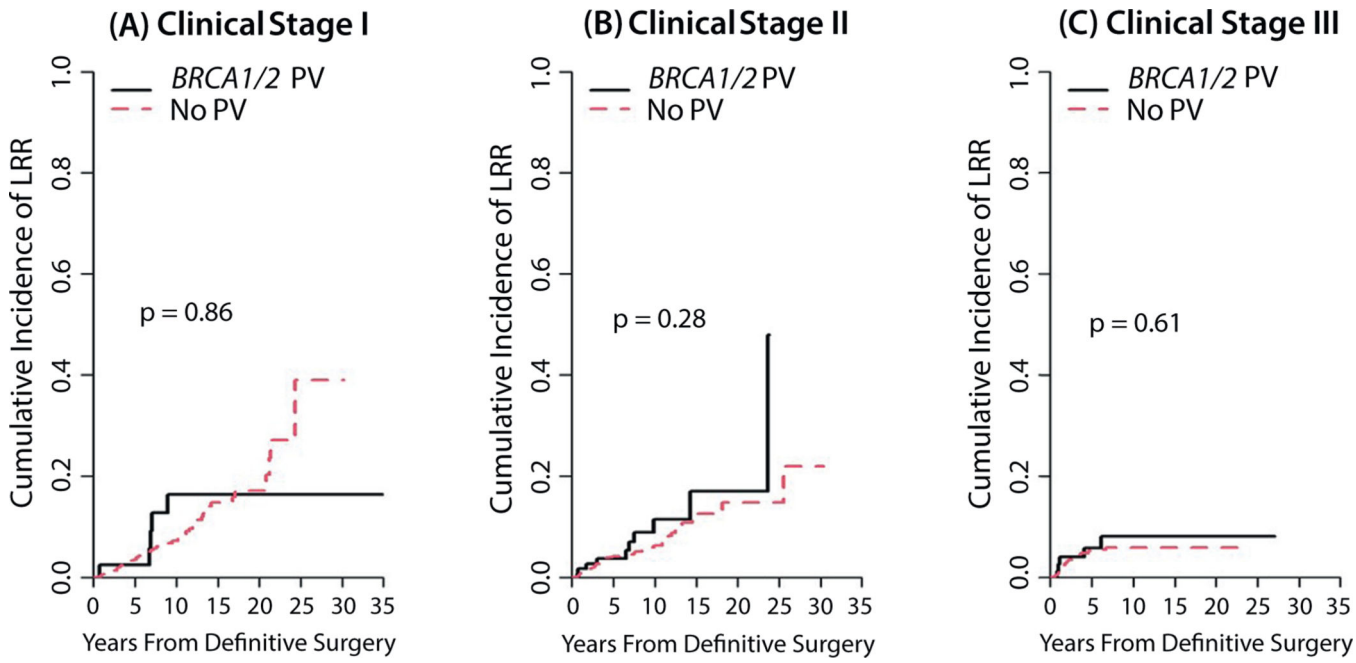

Fig. 2.

Locoregional recurrence rates by *BRCA1/2* status according to clinical disease stage I (A), II (B), or III (C).

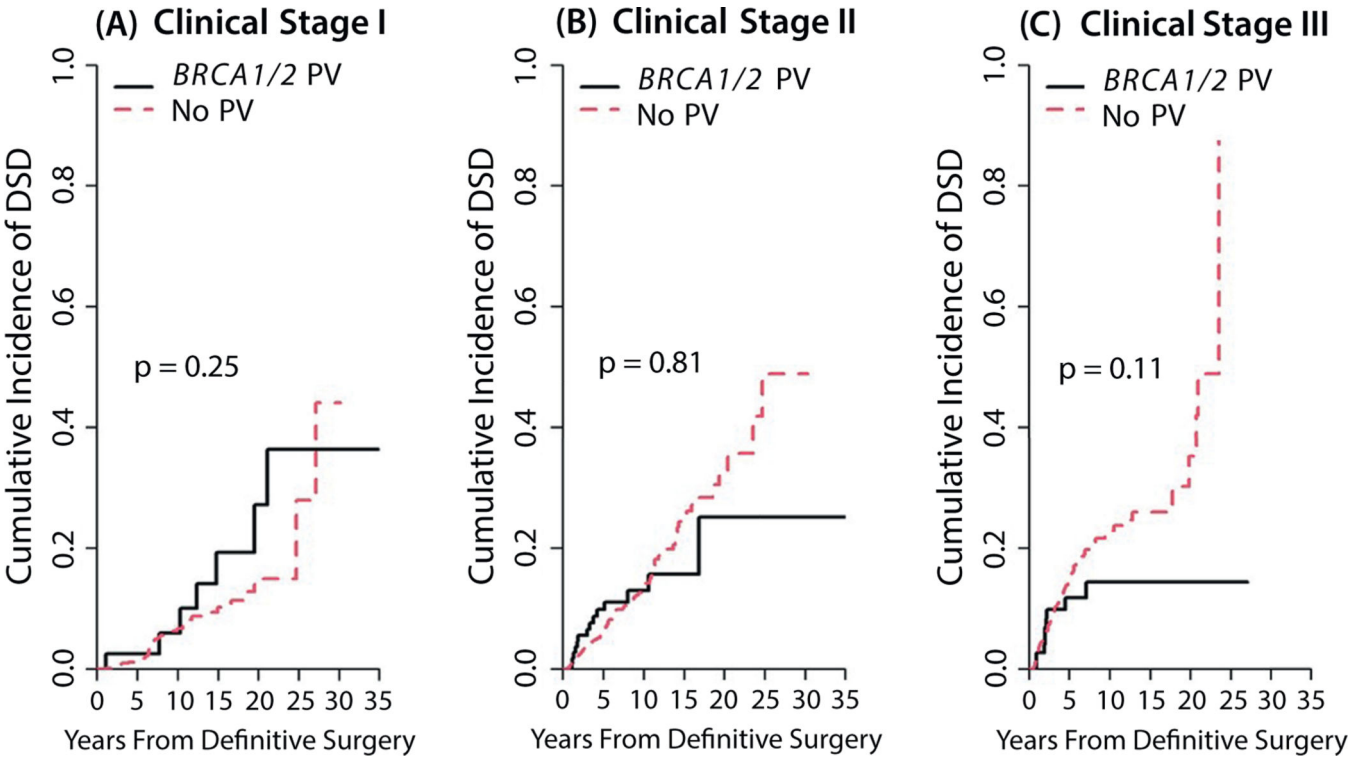

Fig. 3.

Disease-specific death rates by *BRCA1/2* status according to clinical disease stage I (A), II (B), or III (C).

Table 1

Clinicopathologic patient characteristics

Characteristic	Patients, no. (%)		*P* value
	***BRCA1/2* PV (n = 224)**	**No mutation (n = 1989)**	
Age, y			
Median (range)	41 (23–84)	46 (19–83)	<.001
≤40	108 (48.2)	577 (29)	<.001
>40	116(51.8)	1412 (71)	
Race			
Black /African American	35 (15.6)	266 (13.4)	.075
Hispanic/Latino	47 (21)	342 (17.2)	
White	124 (55.4)	1271 (63.9)	
Asian or American Indian/Alaska Native	18(8)	110 (5.5)	
Menopausal status			
Premenopausal	62 (27.7)	760 (38.2)	.002
Postmenopausal *	162 (72.3)	1229 (61.8)	
Clinical T stage			
Unknown †	4(1.8)	35 (1.8)	.036
T0/Tis	1 (0.5)	11 (0.6)	
T1	57 (25.9)	704 (36)	
T2	110(50)	807 (41.3)	
T3	35 (15.9)	266 (13.6)	
T4	17 (7.7)	166 (8.5)	
Clinical nodal status			
Unknown †	4(1.8)	35 (1.8)	<.001
N0	143(65)	993 (50.8)	
N+	77 (35)	961 (49.2)	
Overall clinical stage			
I	40 (17.9)	554 (27.9)	.005
II	110(49.1)	890 (44.7)	
III	74 (33)	545 (27.4)	

Characteristic	Patients, no. (%)		*P* value
	***BRCA1/2* PV (n = 224)**	**No mutation (n = 1989)**	
Pathologic T stage			
T0/Tis	57 (25.4)	356 (17.9)	.037
T1	86 (38.4)	866 (43.5)	
T2	60 (26.8)	504 (25.3)	
T3	17 (7.6)	227 (11.4)	
T4	4(1.8)	36 (1.8)	
Pathologic nodal status			
N0	119 (53.1)	1056 (53.1)	.993
N+	105 (46.9)	933 (46.9)	
Overall pathologic stage			
0	46 (20.5)	292 (14.7)	.063
I	55 (24.6)	605 (30.4)	
II	80 (35.7)	676 (34)	
III	43 (19.2)	416 (20.9)	
Hormone receptor status			
Unknown[†]	7(3.1)	10 (0.5)	<.001
Negative	93 (42.9)	517 (26.1)	
Positive	124 (57.1)	1462 (73.9)	
Her2-neu status			
Unknown[†]	17 (7.6)	65 (3.3)	<.001
Negative	192 (92.8)	1557 (80.9)	
Positive	15 (7.2)	367 (19.1)	
TNBC status			
Unknown[†]	13 (5.8)	22 (1.1)	<.001
Non-TNBC	126 (59.7)	1605 (81.6)	
TNBC	85 (40.3)	362 (18.4)	
Nuclear grade Unknown[†]	7 (3.1)	18 (0.9)	<.001
I-II	54 (24.9)	903 (45.8)	
III	163 (75.1)	1068 (54.2)	

Characteristic	Patients, no. (%)		*P* value
	***BRCA1/2* PV (n = 224)**	**No mutation (n = 1989)**	
LVSI			
Unknown[†]	2 (0.9)	22 (1.1)	.770
Yes	63 (28.4)	540 (27.5)	
No	159 (71.6)	1427 (72.5)	
Year of surgery ≤2000	25 11.2)	139 (7)	.038
2001–2010	89 39.7)	745 (37.5)	
2011–2017	110 (49.1)	1105 (55.6)	
Type of definitive surgery			
Breast conserving surgery	72 (32.1)	1077 (54.1)	<.001
Mastectomy	152 (67.9)	912 (45.9)	
Positive nodes, no.			
<10	211 (94.2)	1856 (93.3)	.614
≥10	13 (5.8)	133 (6.7)	
Nodes removed, no.			
Unknown[*]	1 (0.5)	3 (0.2)	.014
<10	75 (33.6)	837 (42.1)	
≥10	148 (66.4)	1149 (57.9)	
Radiation type			
Breast	54 (24.1)	748 (37.6)	<.001
Breast + RNI	18 (8.0)	329 (16.5)	
CW only	5 (2.2)	12 (0.6)	
CW + RNI	147 (65.6)	900 (45.2)	
Neoadjuvant chemotherapy			
No	72 (32.1)	930 (46.8)	<.001
Yes	152 (67.9)	1059 (53.2)	
Any chemotherapy			
Yes	202 (90.2)	1667 (83.8)	.013
No	22 (9.8)	322 (16.2)	
Adjuvant hormone therapy			

Characteristic	Patients, no. (%)		*P* value
	***BRCA1/2* PV (n = 224)**	**No mutation (n = 1989)**	
Unknown†	1 (0.5)	0	<.001
Yes	105 (47.1)	1372 (69.0)	
No	118 (52.9)	617 (31.0)	
BSO			
Yes	64 (28.6)	228 (11.5)	<.001
No or > 1 y from breast surgery	160 (71.4)	1761 (88.5)	
Synchronous contralateral breast cancer			
Yes	19 (8.5)	78 (3.9)	.002
No	205 (91.5)	1911 (96.1)	

Abbreviations: BSO = bilateral salpingo-oophorectomy; CW = chest wall; LVSI = lymphovascular space invasion; PV = pathogenic variant; RNI = regional nodal irradiation; TNBC = triple negative breast cancer.

*Patients who had a prophylactic or therapeutic BSO at the time of diagnosis were considered postmenopausal.

†Patients with unknown status were omitted from statistical analyses.

Table 2

Multivariable analyses for factors associated with locoregional recurrence and disease-specific death

Factor	HR	95% CI	*P* value
Multivariable analysis for factors associated with locoregional recurrence			
Age, y			
≤40 vs >40	1.669	1.167–2.385	.005
Race			
Black/African American vs White	1.601	1.032–2.483	.036
Hispanic/Latino vs White	1.091	0.671–1.776	.730
Asian or American Indian/Alaska Native vs White	2.329	1.353–4.009	.002
Overall pathologic stage			
I vs 0	4.447	1.734–11.406	.002
II vs 0	5.026	1.974–12.799	<.001
III vs 0	6.833	2.547–18.332	<.001
Nuclear grade			
III vs I-II	1.225	0.840–1.788	.290
LVSI			
Yes vs no	1.657	1.110–2.474	.014
Type of definitive surgery			
Mastectomy vs breast-conserving surgery	0.360	0.219–0.593	<.001
Year of surgery			
≤2000 vs 2011–2017	1.347	0.849–2.137	.210
2001–2010 vs 2011–2017	0.871	0.596–1.274	.480
Regional nodal irradiation			
Yes vs no	0.985	0.584–1.661	.950
Adjuvant hormone therapy			
Yes vs no	0.444	0.304–0.648	<.001
BRCA1/2 status			
PV vs no mutation	0.873	0.496–1.536	.640
Multivariable analysis for factors associated wtih disease-specific death			
Age, y			

Factor	HR	95% CI	*P* value
≤40 vs >40	1.532	1.179–1.991	.001
Race			
Black/African American vs White	1.679	1.195–2.360	.003
Hispanic/Latino vs White	1.064	0.751–1.506	.730
Asian, American Indian/Alaska native vs White	0.804	0.429–1.509	.500
Overall clinical stage			
II vs I	1.359	0.874–2.115	.170
III vs I	1.707	1.056–2.758	.029
Overall pathologic stage			
I vs 0	2.867	1.548–5.310	.001
II vs 0	3.363	1.894–5.972	<.001
III vs 0	5.317	2.950–9.582	<.001
Nuclear grade			
III vs I-II	1.697	1.246–2.310	.001
LVSI			
Yes vs no	1.234	0.926–1.645	.150
Type of definitive surgery			
Mastectomy vs breast-conserving surgery	1.555	1.130–2.141	.007
Year of surgery			
≤2000 vs 2011–2017	0.469	0.289–0.761	.002
2001–2010 vs 2011–2017	0.780	0.586–1.039	.090
Nodes positive, no.			
≥10 vs <10	1.512	1.015–2.253	.042
Triple-negative and *BRCA1/2* status			
Non-TNBC: PV vs no mutation	0.697	0.376–1.293	.250
TNBC: PV vs no mutation	0.574	0.308–1.073	.082
PV: TNBC vs non-TNBC	2.713	1.907–3.860	<.001
No mutation: TNBC vs non-TNBC	2.236	0.973–5.136	.058

Abbreviations: CI = confidence interval; HR = hazard ratio; LVSI = lymphovascular space invasion; PV = pathogenic variant; TNBC = triple-negative breast cancer.

Table 3

Toxicities

Toxicity	Grade	No. (%)
Acute		
Any acute*	<3	212 (94.6)
	3	12 (5.4)
Acute skin	<3	213 (95.1)
	3	11 (4.9)
Acute breast pain, atrophy, or edema	<3	224 (100)
	3	0 (0)
Acute other	<3	223 (99.6)
	3	1 (0.4)
Late		
Any late†	<3	223 (99.6)
	3	1 (0.4)
Late skin	<3	223 (99.6)
	3	1 (0.4)
Late breast pain, atrophy, or edema	<3	224 (100)
	3	0(0)
Late other	<3	224 (100)
	0	0 (0)

*No lung acute toxic effects were noted.

†One late grade-1 lung toxic effect of asymptomatic radiation pneumonitis was detected on follow-up imaging.