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Local Therapy in BRCA1 and BRCA2 Mutation Carriers with Operable Breast Cancer: Comparison of Breast Conservation and Mastectomy

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Abstract

Purpose—Women with BRCA1 and BRCA2 mutations have an elevated risk of breast cancer and ovarian cancer, but also of developing second primary breast cancer. BRCA1/2 mutation carriers with breast cancer must choose between breast conservation (BCT) and mastectomy (M) yet data on outcomes are limited. The purpose of this study is to compare BCT to M in BRCA1/2 carriers.

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Methods—655 women with BRCA1/2 mutations diagnosed with breast cancer and treated with BCT (n=302) or M (n=353) were identified and underwent follow up to assess local, regional and systemic recurrence.

Results—Local failure as first failure was significantly more likely in those treated with BCT compared to M, with a cumulative estimated risk of 23.5% vs. 5.5%, respectively, at 15 years ($p<0.0001$); 15-year estimates in carriers treated with BCT and chemotherapy was 11.9% ($p=0.08$ when compared to M). Most events appeared to be second primary cancers rather than failure to control the primary tumor. The risk of contralateral breast cancer was high in all groups, exceeding 40%, but was not statistically significantly different by use of adjuvant radiotherapy (RT) or not, suggesting no added risk from scatter RT at 10 and 15 years. There were no differences seen in regional or systemic recurrences between the BCT and M groups, and no difference in overall survival.

Conclusions—BRCA1/2 mutation carriers with breast cancer have similar survivals whether treated with M or BCT. However, women undergoing BCT have an elevated risk of a second in-breast event that is significantly reduced in the presence of chemotherapy. Contralateral breast cancer events are very common.

Keywords

hereditary breast cancer; BRCA1/2; breast conservation; mastectomy; radiotherapy

Introduction

Women with inherited germline BRCA1 or BRCA2 (BRCA1/2) mutations have an approximate 55%–85% cumulative risk of developing breast cancer by age 70 [1,2]. Thus, knowledge of expected outcomes for BRCA1/2 mutation carriers following various breast cancer treatments is needed. Breast-conserving therapy (BCT), defined as surgical excision and radiotherapy (RT), has been shown in multiple trials to result in comparable rates of tumor control and survival as mastectomy (M) in women with sporadic early stage disease [3,4]. Only limited data exist comparing outcomes following BCT versus M exclusively in women with known BRCA1/2 mutations. Estimates of local recurrence and contralateral new breast cancers following BCT compared with M could aid in surgical decision-making in a BRCA1/2 mutation carrier newly diagnosed with breast cancer. Here we compare the clinical outcomes in women with BRCA1/2 mutations treated with BCT to outcomes in similarly staged BRCA1/2 mutation carriers treated with M.

Methods

Study Design

Participants were women with a BRCA1 or BRCA2 mutation and stages I–III breast cancer treated with either BCT (breast conserving surgery and breast RT) or M and who had consented to institutional review board (IRB) approved longitudinal studies. They included women evaluated and followed in high-risk and radiation oncology clinics of 9 institutions located in the United States, Spain and Israel, and Australian and New Zealand women enrolled in the Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) [5]. All BRCA1/2 mutations were considered deleterious based on generally recognized criteria. Women with sequence variants of uncertain significance in BRCA1 or BRCA2 were excluded from the data set. Patients were included if there was detailed pathology and treatment records, with at least 6 months of clinical follow-up after breast cancer diagnosis. All patients were ascertained from kConFab or clinic databases at the time of this study regardless of recurrence or survival status. When the institutional databases were queried, 655

cases met eligibility criteria: 302 treated with BCT and 353 treated with M (241 without post-mastectomy RT, 103 with post-mastectomy RT, and 9 for which RT information was unknown). Clinical data were abstracted from medical records or (for kConFab participants) self-reported using a validated questionnaire [6]. Data from the contributing institutions was entered into a centralized database at the University of Michigan. Unique identifiers were assigned to maximize confidentiality per IRB compliance guidelines.

Statistical Methods

Patient, clinical and treatment characteristics were compared by local therapy. Statistical comparisons were made using the chi-square test statistic for categorical characteristics and Student's t-test for continuous characteristics.

Time-to-event endpoints included first failure of treatment, diagnosis of contralateral breast cancer (CBC), and overall and breast cancer-specific survival. A local failure as first failure included all breast/chest wall cancer recurrences whether locally isolated or concurrent with regional or distant failure. Regional failures consisted of a recurrence in the axillary, supraclavicular, infraclavicular, or internal mammary regions.

Overall survival estimates were calculated using the product-limit method of Kaplan and Meier [7]. Rates of first failure, CBC development, and breast cancer-specific survival were estimated using the cumulative incidence method, in order to appropriately account for competing events [8]. Asymptotic point-wise standard error estimates for the cumulative incidence estimator were calculated by the method of Pepe [9].

Cox regression models were constructed to detect significant associations between the patient, clinical, and treatment characteristics with local and distant first failure, overall and breast cancer-specific survival, and development of CBC. The time-to-event endpoints were censored at the time of competing events, if present. The following characteristics were included in analyses for local and distant first failure, and overall and breast cancer specific survival: age at diagnosis, menopausal status at diagnosis, BRCA mutation (1 or 2), breast cancer histology, T-stage, estrogen and progesterone receptor status, number of axillary lymph nodes removed, number of positive axillary nodes, use of chemotherapy, use of hormone therapy, and whether or not RT was a component of adjuvant therapy for M patients. Several clinical/treatment characteristics were modeled in a time-dependent fashion, and their inclusion depended upon the time-to-event outcome modeled. Those characteristics were development of ovarian cancer and whether patients underwent a prophylactic bilateral oophorectomy and/or a prophylactic contralateral M. For local first failure, time to prophylactic bilateral oophorectomy was modeled in a time-dependent fashion. For survival endpoints, time to bilateral oophorectomy, time to CBC, and time to ovarian cancer were modeled. For analysis of contralateral events, synchronous contralateral cases (within 180 days of the primary cases) were excluded (12 cases). Thus, the analyzable sample for CBC development was 643 cases.

P-values are reported for univariate associations and for each covariate when adjusted for all other covariates in full multivariable models. Hazard ratios are reported with 95% confidence intervals for significantly associated covariates.

Results

Study Populations

Comparisons between BCT (n=302) and M (n=353) cohorts by patient, tumor and treatment characteristics are shown in Table 1. A similar comparison was performed for the 353 M patients treated with (103) and without (250) post-mastectomy RT. Factors that differed significantly are shown in Table 2. Additional analyses by mutation status demonstrated that

when compared with BRCA2 mutation carriers, BRCA1 mutation carriers were more likely to be pre-menopausal (85.3% vs. 68.6%, $p=0.002$); have estrogen receptor (ER) negative cancers (79.9% vs. 29.5%, $p<0.0001$); and were less likely to receive hormone therapy (no hormone therapy 77.2% vs. 47.6%, $p<0.0001$). BRCA2 cancers more commonly had positive axillary nodes (BRCA2: 36.1% vs. BRCA1: 22.4%, $p=0.06$).

Patterns of Recurrence

Local and regional failures—With a median follow-up of 8.2 and 8.9 years for BCT and M patients, respectively, the cumulative incidence estimates of local failure as first failure were significantly greater following BCT than M ($p<0.0001$), Figure 1. Despite higher stage breast cancers among M patients who received post-M RT compared to those who did not (as shown in Table 2), local recurrence rates were similar due to RT treatment effect (data not shown). Median time to local failure was 7.8 years for BCT patients and 9.4 years for M.

Univariate and multivariate analyses for each patient, tumor and treatment characteristic were performed for the total sample and within BCT and M groups. The results of the multivariate analyses are shown in Table 3. Type of local therapy was the only factor significantly predicting local recurrence within the entire cohort. Multivariate analyses within treatment cohort revealed type of gene mutation and not receiving adjuvant chemotherapy (Figure 2) to be independent predictors of recurrence among patients treated with BCT. Rates of local failure were compared between the 219 patients treated with BCT who received chemotherapy and the entire cohort of 353 women treated with mastectomy. Although more local failures were observed in women treated with BCT and chemotherapy compared to mastectomy, the results did not significantly differ (ie, 8.1% vs. 3.5% at 10 years; 10.7% vs. 5.5% at 15 years, respectively; $p=0.08$). Analyses within the BRCA1 and BRCA2 BCT subgroups suggested a reduction in recurrence with use of hormonal therapy particularly in BRCA2 carriers ($p=0.08$ for BRCA2 and $p=0.13$ for BRCA1). Oophorectomy did not significantly impact rates of local failure among BCT patients (total BCT cohort: HR=0.88, $p=0.75$; BRCA1 subset: HR=1.63, $p=0.27$; BRCA2 subset: HR=0.20; $p=0.125$). Among patients treated with M, the presence of invasive lobular cancer was the only factor significantly associated with local failure.

For the 35 patients treated with BCT who experienced an in-breast tumor recurrence (IBTR), information regarding location of the lesion in the breast and histology of the initial cancer and subsequent failure was available in 23 cases. Seven of 23 recurrences (30%) were in the same quadrant and of the same histology as the initial cancer, consistent with a true recurrence. The remaining 16 (70%) cases developed recurrences either in a different quadrant from the primary, were of a different histology, or both. For the 11 patients treated with M who had a local isolated first failure, 2 of 11 (18%) failures were a different histology when compared to the initial tumor histology; the remaining 9 (82%) patients had similar histologies at diagnosis and recurrence.

The incidence estimates of regional failures as component of first failure did not vary significantly by local treatment group (data not shown).

Distant failures—The cumulative incidence estimates of distant failure as first failure did not differ significantly by type of local therapy, with 10- and 15-year rates of failure in BCT patients of 7.1% and 11.1%, and in M patients 7.4% and 9.1% ($p=0.80$). Factors significantly impacting distant failure included a BRCA2 mutation (BRCA 2 vs. BRCA 1: HR 1.9, $p=0.02$); histology (invasive lobular vs. ductal cancer: HR 3.2, $p=0.009$) and positive axillary nodes (4 or more positive vs. 0: HR 2.6, $p=0.006$). Significant factors on multivariate analysis were the presence of an invasive lobular component (HR 3.1; $p=0.01$) and a BRCA2 mutation (HR 1.9; $p=0.05$).

Contralateral Breast Cancers

Patients who presented with synchronous bilateral breast cancers were excluded from this analysis for CBC, reducing the analytical sample size to 643 of which 148 women (23.0%) developed a CBC. The cumulative incidence estimates for developing CBC were analyzed by the use of adjuvant RT; results did not demonstrate a significant difference, as shown in Figure 3 ($p=0.44$), suggesting no increase in CBC from scatter RT. Analysis by local treatment (BCT, M without RT, M with RT) also did not demonstrate significant differences (data not shown).

The presence of a BRCA1 compared to BRCA2 mutation was associated with a 1.8-fold increase in CBC ($p=0.003$). Young age at diagnosis was also associated with increased risk, with patients ≤ 35 years having a 1.8-fold increased risk relative to women 36–50 years of age ($p=0.04$); women over 50 years did not significantly differ in rates of CBC compared to women 36–50 years old ($HR=1.2$, $p=0.46$). Upon multivariate analysis, no factors emerged as independent predictors for developing a CBC.

Breast Cancer-Specific Survival and Overall Survival

No significant difference in breast-cancer specific or overall survival was observed by local treatment type. Breast cancer-specific survivals with BCT were 93.6% and 91.7% at 10 and 15 years vs. 93.5% and 92.8% with M ($p=0.85$). Overall survivals with BCT group were 92.1% and 87.3% at 10 and 15 years and 91.8% and 89.8% with M ($p=0.73$). Factors significantly associated with breast cancer-specific mortality were presence of an infiltrating lobular cancer ($HR 4.3$; $p=0.01$) and the development of a CBC ($HR 2.5$, $p=0.02$). For overall survival analyses, since mortality is known to be related to patient age, models were adjusted for patient age at time of diagnosis. The only factor significantly related to increased rates of death on multivariate analysis was the development of ovarian cancer ($HR 5.0$, $p=0.0001$).

Discussion

The overall results demonstrated a significantly increased risk of local failure in BRCA1/2 mutation carriers treated with BCT compared to carriers treated with M; however, breast cancer-specific and overall survival were comparable. The significant differences in rates of local failure by local therapy sharply contrast with the similar rates reported in multiple randomized trials comparing BCT with M [3,4,10,11]. Given the low prevalence of BRCA1/2-associated breast cancer and the older median age of women in the randomized trials, these studies included predominantly women with sporadic rather than hereditary breast cancer.

As shown by others, the different location and histology in the majority of IBTR's compared to the original cancers and the increased median time to recurrence relative to sporadic breast cancers observed in the present study, is suggestive of the development of new breast cancers rather than true recurrences [12]. Of note, in patients treated with M, our results demonstrated a prolonged median time of 9.4 years to local failure considerably longer than the average of 2–3 years reported in most surgical series [13], also suggestive of the development of new cancers. Future studies using genetic profiling of the primary and secondary lesion are needed to definitively categorize these events.

Predictors of local failure varied between BCT and M. Chemotherapy was the only independent predictor in those treated with BCT, and the reduction was consistent with that observed in many BCT studies of sporadic breast cancer [14,15]. In fact, rates of local control at 10 and 15 years in carriers treated with BCT and chemotherapy were not significantly different from rates following mastectomy although a trend in second events was observed. These results may suggest an increased chemosensitivity in BRCA1/2-associated breast cancers as recently suggested by Fourquet and colleagues [16] and should be followed over time. Given the

increasing usage of chemotherapy for invasive breast cancer, this reduction in breast events is potentially highly relevant for current practice. Our results also suggested a benefit in local control in BRCA2 carriers treated with hormonal therapy, consistent with other studies [17, 18].

Oophorectomy was not found to significantly impact rates of local failure in analyses among all patients treated with BCT or in subset analyses of those with positive estrogen or progesterone receptors or by mutation type. While the exact reason for this is uncertain, it is important to note that 73% of these women received chemotherapy, 30% received hormonal therapy and approximately 80% were premenopausal at diagnosis. Only 16% patients received no adjuvant therapy. Chemotherapy induces menopause in the majority of women over age 40 [19]. Thus, the lack of a discernable effect of oophorectomy in this study may reflect the fact that many of the patients were likely rendered post-menopausal with adjuvant therapy.

Earlier reports have shown variable rates of IBTR in BRCA1/2 mutation carriers compared to age-matched women with sporadic breast cancer treated with BCT [20–26]. In a previous paper by Pierce et al of 160 early stage BRCA1/2 carriers matched to 445 women with sporadic disease, rates of IBTR in the carriers at 10 and 15 years were 12% and 24% compared to 9% and 17% for controls ($p=.19$) [20]. The outcomes that differ between the previously published report and the current analysis are primarily the comparison groups and the rate of recurrence in these groups; the rates of IBTR are comparable between the two studies. There is some overlap of carriers between the previously published report and the current analysis; however, patient data has been updated and the overall BCT data set has expanded. Despite this, the rates of IBTR in the two papers are remarkably similar, with 10- and 15-year estimates in the current series of 10.5% and 23.5%.

Despite increased rates of local failure following BCT compared with M in the present report, no differences were observed in rates of distant failure or disease-specific or overall survival between the two cohorts. This is contradictory to recent prospective studies which strongly support a causal relationship between increased rates of local failure and subsequent distant spread [10]. While our findings may be a result of the limited sample size of the two cohorts, they may also be the result biologic differences of BRCA1/2 associated breast cancer. Local failure in women with sporadic breast cancer may generally represent a true local recurrence and a biologically more aggressive phenotype rather than the second primary cancers suggested in the current report. As mentioned above, BRCA1/2 related breast tumor may have enhanced sensitivity to chemotherapy [16]. Furthermore, close follow-up of BRCA1/2 mutation carriers may have led to early detection and treatment of new cancers thus minimizing the opportunity for distant spread. Our results will need to be followed over time and validated in prospective studies, but at present, our data at 10 and 15 years do not suggest an adverse effect of a local recurrence/new primary upon systemic failure.

We acknowledge the limitations of the current study. Although the study consists of patients followed prospectively in high risk clinics, it is a predominantly prevalent rather than incident cohort which results in survivorship and ascertainment biases. Patients attended high risk clinics or were enrolled in kConFab sometimes many years after their first breast cancer diagnosis, so patients who died early from their breast cancer are less likely to be included in this study. Therefore, our estimates for overall and breast-cancer specific survival may be higher than for a population-based incident cohort of mutation carriers. Similarly, those with more than one breast cancer diagnosis may have been more likely to have been ascertained by kConFab and the high risk clinics. Thus, the frequency of second breast cancer events and CBC seen in this study may also overestimate the true rate that would be seen in a population-based incident cohort. Likewise, biases may be hidden within treatment choice (BCT versus M) that cannot be fully adjusted for by the available patient and tumor characteristics. However, it

should be noted that patient data in both cohorts was acquired in the same manner, and that all data submitted from the collaborating institutions of patients who met the study criteria were included in the analysis. Ideally, these patient groups should be randomized to treatment (BCT versus M). However, given that the surgical decision-making process is highly personal and based upon complicated therapeutic concerns, it is doubtful whether such a study could be ethically performed.

In conclusion, our results demonstrate a significantly greater risk of local recurrence but no difference in distant failure or disease-specific or overall survival for patients with a deleterious BRCA1/2 mutation treated with BCT when compared to those treated with M. Within the BCT-treated group, use of adjuvant chemotherapy was significantly associated with reduced rates of IBTR. Among women who received adjuvant chemotherapy and BCT, local control did not significantly vary compared to control rates in women treated with mastectomy. These findings should be considered when patients with BRCA1/2-associated breast cancer are considering their local treatment options and for patients considering BCT, discussion of the role of chemotherapy not only for systemic control but also local control would be relevant. CBC was common in all patient subgroups whether treated with BCT or M. Thus, preventive strategies for the contralateral breast require strong consideration upon diagnosis of a BRCA1/2-associated breast cancer.

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Figure 1.
Cumulative incidence estimates for local failure as first failure by type of local treatment.

Figure 2.
Cumulative incidence estimates for local failure as first failure for patients choosing breast conservation by use of adjuvant chemotherapy.

Figure 3.
Cumulative incidence estimates of contralateral breast cancer by use of adjuvant radiotherapy.

Table 1

Patient, tumor and treatment characteristics by surgery type

Characteristic	Lumpectomy	Mastectomy
Frequency, <i>n</i>	302	353
Patient age at biopsy, years (<i>P</i> = 0.13)		
Mean (Std. Dev.)	41.9 (9.4)	43.0 (9.8)
Median	40.5	41.9
Minimum – Maximum	20.1 – 85.0	23.6 – 81.5
Patient age at biopsy, <i>n</i> (%) (<i>P</i> = 0.35)		
≤ 35	74 (24.5)	71 (20.1)
36 – 50	179 (59.3)	216 (61.2)
≥ 50	49 (16.2)	66 (18.7)
Race (<i>P</i> = 0.14)		
White	278 (92.1)	312 (88.4)
Black	10 (3.3)	9 (2.6)
Hispanic	9 (3.0)	17 (4.8)
Other/Unknown	5 (1.7)	15 (4.3)
Menopausal status at primary (<i>P</i> = 0.003)		
Pre-	240 (79.5)	240 (68.0)
Post-	52 (17.2)	89 (25.2)
Peri-	10 (3.3)	24 (6.8)
BRCA gene mutation (<i>P</i> = 0.01)		
1	197 (65.2)	197 (55.8)
2	105 (34.8)	156 (44.2)
Histology (<i>P</i> = 0.07)		
Infiltrating ductal	258 (85.4)	292 (82.7)
Lobular or Infiltrating ductal & lobular	10 (3.3)	26 (7.4)
Medullary or other	34 (11.2)	35 (9.9)
Clinical stage (<i>P</i> = 0.0007) ^a		
1	158 (52.3)	145 (41.1)
2	130 (43.1)	170 (48.2)
3	12 (4.0)	37 (10.5)
Unknown	2 (0.7)	1 (0.3)
Pathologic T-stage (<i>P</i> = 0.001)		
T0/T1	214 (70.8)	203 (57.5)
T2	81 (26.8)	125 (35.4)
T3	4 (1.3)	16 (4.5)
Unknown	3 (1.0)	9 (2.6)
Estrogen receptor (<i>P</i> = 0.006) ^a		
Positive	90 (29.8)	126 (35.7)

Characteristic	Lumpectomy	Mastectomy
Negative	154 (51.0)	131 (37.1)
Borderline	3 (1.0)	3 (0.9)
Unknown	54 (17.9)	93 (26.4)
Progesterone receptor ($P = 0.06$) ^a		
Positive	73 (24.2)	98 (27.8)
Negative	154 (51.0)	143 (40.5)
Borderline	3 (1.0)	0
Unknown	72 (23.8)	112 (31.7)
Final microscopic surgical margins ($P = 0.003$) ^a		
Positive	16 (5.3)	4 (1.1)
Negative	248 (82.1)	272 (77.1)
Close	0	4 (1.1)
Unknown	38 (12.6)	73 (20.7)
Nodal surgery		
Yes	292 (96.7)	350 (99.2)
Total lymph nodes removed ($P = 0.95$)		
Mean (Std. Dev.)	14.8 (8.5)	14.7 (8.5)
Median	14	14
Minimum – Maximum	1 – 48	1 – 51
Positive lymph nodes removed ($P = 0.004$)		
0	210 (71.9)	223 (63.4)
1 – 3	62 (21.2)	76 (21.6)
4+	20 (6.9)	53 (15.1)
No	10 (3.3)	1 (0.3)
Unknown	0	2 (0.6)
Radiotherapy		
No	0	241 (68.3)
Yes	302 (100)	103 (29.2)
Unknown	0	9 (2.6)
Chemotherapy ($P = 0.20$) ^a		
No	82 (27.2)	108 (30.6)
Yes	219 (72.5)	231 (65.4)
Unknown	1 (0.3)	14 (4.0)
Hormone therapy ($P = 0.09$) ^a		
No	202 (66.9)	210 (59.5)
Yes	90 (29.8)	125 (35.4)
Tamoxifen	81 (90.0)	106 (84.8)
Other	9 (10.0)	19 (15.2)
Unknown	10 (3.3)	18 (5.1)

Characteristic	Lumpectomy	Mastectomy
Adjuvant therapy ($P = 0.35$)		
Yes	254 (84.1)	287 (81.3)
No	48 (15.9)	66 (18.7)
Bilateral oophorectomy ($P = 0.28$) ^a		
No	141 (46.7)	150 (42.5)
Yes	161 (53.3)	203 (57.5)
Prior to primary diagnosis	9 (3.0)	30 (8.5)
After diagnosis, prior to failure	16 (5.3)	10 (2.8)
After diagnosis, after failure	12 (4.0)	9 (2.6)
After diagnosis, without failure	114 (38.0)	147 (41.6)
Timing unknown	10 (3.3)	7 (2.0)
Prophylactic contralateral mastectomy ($P < 0.0001$) ^a		
No	256 (84.8)	214 (60.6)
Yes	44 (14.6)	134 (38.0)
Unknown	2 (0.6)	5 (1.4)

^a Comparison between surgical groups made omitting the unknown/missing category.

Table 2

Patient, tumor and treatment characteristics for mastectomy patients with and without radiotherapy

Characteristic	(+) Radiotherapy	(-) Radiotherapy
Frequency, <i>n</i>	103	250
BRCA gene mutation ($P = 0.025$)		
1	48 (46.6)	149 (59.6)
2	66 (53.4)	101 (40.4)
Clinical stage ($P < 0.0001$) ^a		
1	16 (15.5)	129 (51.6)
2	55 (53.4)	115 (46.0)
3	31 (30.1)	6 (2.4)
Unknown	1 (1.0)	0
T-stage ($P = 0.0001$)		
T0/T1	43 (41.8)	160 (64.0)
T2	42 (40.8)	83 (33.2)
T3	15 (14.6)	1 (0.4)
T unknown	3 (2.9)	6 (2.4)
Nodal surgery		
Total lymph nodes removed ($P = 0.004$)		
Mean (Std. Dev.)	16.9 (8.9)	13.8 (8.1)
Median	15	14
Minimum-Maximum	5–51	1–40
Positive lymph nodes removed ($P < 0.0001$)		
0	33 (32.0)	190 (76.3)
1–3	30 (29.1)	46 (18.5)
4+	40 (38.8)	13 (5.2)
Chemotherapy ($P = 0.02$) ^a		
No	23 (22.3)	85 (34.0)
Yes	79 (76.7)	152 (60.8)
Unknown	1 (1.0)	13 (5.2)
Prophylactic contralateral mastectomy ($P = 0.01$) ^a		
No	71 (68.9)	143 (57.2)
Yes	28 (27.2)	106 (42.4)
Unknown	4 (3.9)	1 (0.4)

^a Comparison between surgical groups made omitting the unknown/missing category

Table 3

Significant multivariate hazard ratios for local failure as first failure

Sample/Characteristic	Hazard ratio (95% CI)	P-value
Total sample (N = 655)		
Treatment decision		
BCT	4.5 (2.3–8.9)	<0.0001
Mastectomy	1.0	
BCT sample(N = 302)		
Gene mutation		
BRCA1	1.00	0.019
BRCA2	2.9 (1.2 – 7.1)	
Adjuvant chemotherapy		
Yes	1.0	0.0001
No	5.4 (2.3 – 13.3)	
Mastectomy sample (N = 353)		
Histology		
Infiltrating ductal carcinoma (IDC)	1.0	0.003
IDC + lobular/Lobular carcinoma	9.9 (2.1 – 47.1)	
Medullary/Other	2.7 (0.4 – 17.3)	