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A randomized controlled trial of cognitive-behavioral stress management in breast cancer: survival and recurrence at 11-year follow-up

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Abstract

Non-metastatic breast cancer patients often experience psychological distress which may influence disease progression and survival. Cognitive-behavioral stress management (CBSM) improves psychological adaptation and lowers distress during breast cancer treatment and long-term follow-ups. We examined whether breast cancer patients randomized to CBSM had improved survival and recurrence 8–15 years post-enrollment. From 1998 to 2005, women ($N = 240$) 2–10 weeks post-surgery for non-metastatic Stage 0–IIIb breast cancer were randomized to a 10-week, group-based CBSM intervention ($n = 120$) or a 1-day psychoeducational seminar control ($n = 120$). In 2013, 8–15 years post-study enrollment (11-year median), recurrence and survival data were collected. Cox Proportional Hazards Models and Weibull Accelerated Failure Time tests were used to assess

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Compliance with ethical standards

Conflict of interest Dr. Antoni reports receiving publication royalties from a book he co-authored on cognitive-behavioral stress management. Dr. Glück is employed at Celgene Corporation. Other co-authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

group differences in all-cause mortality, breast cancer-specific mortality, and disease-free interval, controlling for biomedical confounders. Relative to the control, the CBSM group was found to have a reduced risk of all-cause mortality (HR = 0.21; 95 % CI [0.05, 0.93]; $p = .040$). Restricting analyses to women with invasive disease revealed significant effects of CBSM on breast cancer-related mortality ($p = .006$) and disease-free interval ($p = .011$). CBSM intervention delivered post-surgery may provide long-term clinical benefit for non-metastatic breast cancer patients in addition to previously established psychological benefits. Results should be interpreted with caution; however, the findings contribute to the limited evidence regarding physical benefits of psychosocial intervention post-surgery for non-metastatic breast cancer. Additional research is necessary to confirm these results and investigate potential explanatory mechanisms, including physiological pathways, health behaviors, and treatment adherence changes.

Keywords

Breast neoplasm; Survival; Recurrence; Cognitive therapy; Behavior therapy; Breast cancer

Introduction

Breast cancer is the most common cancer among women globally and is the second cause of cancer death in developed regions [1]. Five-year survival rates for breast cancer range from 40 % in low-income countries to 80 % in developed countries [2]. Women with breast cancer also have increased risk of psychological distress [3, 4]. A biopsychosocial model of cancer survival suggests that distress related to modifiable psychosocial factors, such as depressive symptoms, low social support, and psychological stress, may exacerbate metastatic processes, thereby influencing cancer progression and mortality [5–7]. Thus, researchers have examined whether psychological interventions aimed at modifying psychosocial factors can reduce recurrence and mortality in cancer. While one study showed such interventions could improve survival in metastatic breast cancer patients [8], efforts to replicate have had limited success, creating controversy [9]. A recent Cochrane review determined that psychological interventions were effective in improving survival at 12 months in metastatic breast cancer [9].

While most intervention studies were conducted in women with metastatic breast cancer, only one randomized controlled trial (RCT) in 2008 demonstrated beneficial effects of a psychosocial intervention on survival and recurrence in women with non-metastatic breast cancer [10]. At an 11-year median follow-up, women given a 12-month cognitive-behavioral intervention had significantly lower breast cancer-specific mortality (HR = 0.44, $p = .016$), all-cause mortality (HR = 0.51, $p = .028$), and breast cancer recurrence (HR = 0.55, $p = .034$) than control women [10].

We have found that a shorter (10-week) group-based cognitive-behavioral stress management (CBSM) program enhances physiological [11, 12] and psychological adaptation [13, 14] as women recover from surgery and undergo adjuvant treatments for non-metastatic breast cancer. The CBSM group also reported less depressive symptoms at 5- and 11-year (median) follow-ups [15, 16] and better emotional and physical well-being at

the 11-year follow-up compared to the control group [16]. This secondary analysis asked whether women from that RCT who received CBSM also had reduced mortality or breast cancer recurrence at the 11-year follow-up (range 8–15 years). It is noteworthy that this study used an intervention similar in content but briefer than that of Andersen et al. [10] and had a similar patient population, sample size, and follow-up period.

Methods

Study design and patients

Participants were women with Stage 0–IIIb breast cancer who were 2–10 weeks post-surgery and enrolled in an RCT of CBSM between 1998 and 2005. The study was a single center, single blind, randomized, parallel assignment efficacy trial approved by the University of Miami (UM) Institutional Review Board (IRB; National Institutes of Health Clinical Trial NCT01422551) in 1998. Original study design is described in previous reports [14, 17]. Women were recruited from surgical oncology practices in South Florida through advertising and private physician referrals, and at the UM/Sylvester Cancer Center. Women were excluded if not between 21 and 75 years old, not fluent in English, had stage IV breast cancer or prior serious cancer (except minor skin cancers), had begun adjuvant treatment, had a major medical condition other than cancer, were previously psychiatrically hospitalized, or currently endorsed psychosis, suicidality, major depressive disorder, or panic disorder (see CONSORT diagram Fig. 1).

Procedures

Of 502 women screened, 240 signed informed consent, were enrolled, completed baseline assessments, and were randomized to CBSM intervention or a 1-day psychoeducational control group (Fig. 1). Randomization was performed on a 1:1 basis, with each cohort averaging approximately 14 participants. Randomization and assessment were conducted by blinded study coordinators. Assessments were repeated at 6, 12 months, and 5 years post-study enrollment. Women were re-contacted in 2013, 8–15 years post-study enrollment (11-year median), for participation in a new long-term follow-up study to assess medical status, which they had previously consented to. Study personnel obtained self-report information about participants' disease status and conducted medical chart reviews to confirm recurrences and gather diagnostic- and treatment-related information. Vital statistics regarding participant death, cause, and date of death was obtained from the Florida Cancer Data System registry with approval from the Florida Department of Epidemiology and the Florida Department of Health IRB. Baseline self-reported demographic, medical, and treatment-related information was verified during medical chart reviews at the follow-up.

Intervention condition

Women randomized to CBSM [18] received a manualized intervention co-delivered by a Ph.D. level clinical psychologist and a doctoral student in clinical psychology. The group-based intervention was administered in 90-min sessions once per week for 10 weeks and aimed to improve coping and psychological adaptation as well as reduce stress and negative mood using cognitive-behavioral therapy (e.g., cognitive reframing, stress re-appraisal, effective coping skills training, assertiveness training, anger management, optimize use of

social support) and relaxation training (e.g., progressive muscle relaxation, guided visual imagery, diaphragmatic breathing). Intervention components have been discussed in detail elsewhere [13, 14, 18].

Control condition

Women randomized to the control group participated in a 1-day psychoeducational “self-help” classroom seminar within the corresponding 10-week intervention period. Participants were provided with general information about breast cancer care and health. A condensed version of select portions of the CBSM modules was provided in handouts, but women were not given opportunities to practice these techniques.

Outcomes

Three clinical outcomes of interest were examined at follow-up. Time to all-cause mortality was computed as days elapsed from date of randomization to death. Time to breast cancer-specific mortality was computed as days elapsed from date of randomization to breast cancer-related death. Disease-free interval was computed as days elapsed from date of randomization to documented breast cancer recurrence (local or distant recurrence).

Statistical analysis

Time-to-event analyses were conducted in the Statistical Package for the Social Sciences (Version 21.0) and Statistical Analysis Software (Version 9.3). Chi-square tests, Fisher’s exact test, and one-way ANOVAs were conducted to determine baseline group differences. Cox Proportional Hazards Models [19] were conducted to test group differences in time to all-cause and breast cancer mortality at 8–15 year follow-up. The Proportional Hazards Assumption was met for all regressions [20]. Estimates for hazard ratios (including 95 % confidence intervals) were declared significant based on a two-sided alpha of 0.05. Data were censored for women who did not have a death or recurrence at the time of follow-up, were lost-to follow-up, or had previously dropped out, using the date of last study contact. For seven women who had unknown breast cancer recurrence dates, data on time to recurrence was interval censored between randomization and end of study/death. Weibull accelerated failure time (AFT) models [21] using interval censoring were conducted to estimate group difference in disease-free survival time.

All models examined the effects of group assignment over and above the effects of biomedical confounders. Covariate relationships were examined to limit number of covariates and avoid model overfitting. Prognostic and treatment factors known to influence disease endpoints were chosen apriori and included in addition to variables significantly associated with outcomes [22]. The final covariates—age at diagnosis, disease stage, tumor size, Her2/neu status, and hormonal treatment received—were manually entered into the regression model (rather than automated stepwise methods [22]). Due to a high correlation between hormonal treatment and ER/PR receptor status, hormonal treatment was chosen as a covariate to limit the number of covariates. Disease stage was determined with AJCC/UICC TNM grouping [23] and was categorized as stage 0 vs. I, II, and III. The assumption of linearity was met for all continuous variables except tumor size, which was subsequently classified as a categorical variable according to AJCC/UICC TNM grouping [23]

Information on tumor grade was not available. Results were verified by independent replication analysis conducted by an NIH statistical consultant, Westat. Inclusion of appropriate study covariates and use of Weibull AFT was determined amongst authors, the NCI Network of Biobehavioral Pathways in Cancer committee, and Westat consultants.

Results

Participant characteristics

At the time of diagnosis and enrollment, women were an average of 50 ($SD = 9.03$) years old. Approximately 36 % self-reported being of a racial or ethnic minority (e.g., Black, Hispanic, Asian). See Table 1.

At the 8–15 year follow-up, 30 (12.5 %) of the 240 participants were deceased (CBSM = 15; Control = 15). The average number of years from study enrollment to death was 7.60 ($SD = 3.71$). Of these 30 deaths, 22 were breast cancer-related (CBSM = 12; Control = 10). For eight women whose death was not related to breast cancer, causes were as follows: unknown ($N = 4$), Alzheimer's disease ($N = 1$), malignant neoplasm without site specification ($N = 1$), non-traumatic subarachnoid hemorrhage ($N = 1$), and ovarian cancer ($N = 1$). There were 150 with no breast cancer recurrence, 47 had a local or distant breast cancer recurrence (CBSM = 24; Control = 23), 39 were lost-to follow-up, and 4 were deceased with unknown breast cancer status. The average disease-free interval was 5.92 ($SD = 3.91$) years. The effective sample size in specific analyses varied as a function of the cases with available covariate information (Table 1).

Adjusted Cox proportional hazards models

All-cause mortality—Cox proportional hazards models determined differences between CBSM and control groups on time to all-cause mortality adjusting for age, disease stage, tumor size, Her2/neu status, and hormonal therapy receipt. Women older at diagnosis had longer survival ($p = .025$), and those who received hormonal therapy had longer survival ($p = .045$). Over and above the effects of covariates, assignment to CBSM was associated with longer survival (CBSM HR = 0.21 (95 % CI [0.05, 0.93]; $p = .040$; see Fig. 2). See Table 2 for hazard ratios.

Breast cancer-specific mortality—Cox proportional hazards models determined differences between CBSM and control groups on time to breast cancer-specific mortality adjusting for age, tumor size, Her2/neu status, and hormonal therapy receipt. Disease stage was removed from the model due to a large standard error that led to invalid statistical inferences. Women older at time of diagnosis had longer survival ($p = .025$). Assignment to CBSM tended to be associated with breast cancer survival over and above the effects of covariates (CBSM HR = 0.25 (95 % CI [0.05, 1.11]; $p = .068$; see Fig. 3). See Table 2 for hazard ratios.

Breast cancer recurrence—Weibull AFT models were conducted to determine differences between CBSM and control groups on disease-free interval (time to breast cancer recurrence). Older age at diagnosis was associated with longer disease-free interval.

There was a tendency for assignment to CBSM to be associated with a greater disease-free interval time beyond covariate effects (CBSM HR = 0.45; 95 % CI [0.17, 1.18]; $p = .083$; Fig. 4). See Table 2 for hazard ratios.

Effects in invasive cancer subsample

Because prior psychological intervention studies of survival and recurrence effects have restricted their samples to women with invasive cancer [8, 10] we reanalyzed our data for the 197 cases with Stage I–IIIb breast cancer. Once accounting for covariates in this subsample, the only cause of death was breast cancer; therefore, all-cause mortality was not included as an outcome. The average number of years from study enrollment to breast cancer-related death was 7.56 ($SD = 3.76$), and the average disease-free interval was 5.90 ($SD = 3.96$) years. Using the covariates noted previously, we found that participating in CBSM was associated with lower odds of breast cancer mortality (CBSM HR = 0.08; 95 % CI [0.01, 0.49]; $p = .006$) and greater disease-free interval (CBSM HR = 0.24; 95 % CI [0.07, 0.82]; $p = .011$). See Table 3 for hazard ratios.

Discussion

This secondary analysis found that women with Stage 0–IIIb breast cancer who were randomly assigned to a 10-week CBSM intervention 2–10 weeks post-surgery had longer survival, up to 11-years post-enrollment, compared to those in the control group, while accounting for disease- relevant characteristics.

These findings are consistent with that of Spiegel et al. [8] and Andersen et al. [10]. Our findings are particularly relevant given the controversial evidence regarding the influence of psychosocial interventions on cancer disease outcomes [9]. It is important to note that most studies, except Andersen et al. [10] investigated these associations in metastatic breast cancer samples. Importantly, there are notable commonalities among the current study, and those of Andersen et al. [10] and Spiegel et al. [8]. These three study interventions emphasized skills around stress management, coping, and symptom management. Interestingly, when we restricted our analyses to include only those diagnosed with invasive disease (Stage I–IIIb), a sample that is more comparable to that of Spiegel et al. [8] and Andersen et al. [10] we found significant intervention effects on breast cancer mortality and disease-free interval, independent of potential confounding factors. This is the first study to replicate the Andersen et al. [10] findings suggesting that psychosocial intervention administered post-surgery for non-metastatic breast cancer is associated with improved survival.

The findings from this sample of non-metastatic breast cancer patients highlight the potential for psychosocial interventions to influence disease outcomes in a non- metastatic cancer population. They suggest there may be opportunity to modify psychosocial factors in a way that reduces the risk of metastases before they begin or slows progression. There are multiple pathways by which a psychosocial intervention may influence disease outcomes. It is possible that the short- [13, 14] and long-term [15, 16] psychological improvements from the CBSM intervention mediated the effects on survival. CBSM decreases anxiety and depressive mood the first year of primary treatment, which parallel decreases in leukocyte

pro-inflammatory and pro-metastatic gene expression over this period [12]. CBSM increases confidence in stress management skills such as relaxation and cognitive reframing in breast cancer patients [14, 24] which covary with parallel decreases in neuroendocrines, such as serum cortisol [11]. Women may continue to engage in relaxation techniques post-treatment, which could lower distress and circulating neuroendocrines mitigating inflammatory and metastatic processes via stress response pathways [5].

Skills-based aspects of the CBSM teach women cognitive restructuring to manage cancer-specific distress around fears of recurrence that persist post-treatment and cause ongoing emotional distress [4]. Components of CBSM address adaptive coping techniques and re-appraisals of harm and loss that contribute to depressive symptoms and poor QOL in breast cancer patients and survivors [25]. The effects of CBSM on depressive symptoms may be particularly important, given the strong association between depression and breast cancer survival [6, 7, 26]. Depression is an established risk factor for noncompliance with medical treatment [26]. Treatment noncompliance with long-term regimens such as endocrine therapy, and noncompliance with follow-up visits, in turn, may explain poorer clinical outcomes in breast cancer [6, 7]. Finally, group social dynamics may have influenced women's participation in behaviors that increase or decrease cancer risk, such as alcohol consumption, physical activity, and diet [27].

Strengths and limitations

Results should be interpreted with caution. Survival and recurrence were not primary endpoints in this study at the time it was planned. Other limitations include a small sample size, a low number of observed deaths, and missing data. As this was a sample of women with non-metastatic breast cancer, only 12.5 % of the sample had died by the follow-up. While generalizability is increased by the fact that approximately one-third of the sample was of an ethnic minority (i.e., Black, Hispanic, Asian), it is limited by factors such as academic study setting, geographical location, and inclusion criteria. Given the recruitment strategies and stringent inclusion criteria, the findings may be more applicable to intervention-seeking patients, and those that are relatively mentally and physically healthy.

The number of covariates used in our analyses was high in relation to the number of clinical events [22]. However, the current study used an a priori list of covariates that was theoretically based and manually entered into the model to minimize overfitting [22]. We initially chose to conduct analyses on the original full sample of 240 women, given evidence that women with Stage 0 breast cancer report similar psychological distress when compared to women with later stages of disease [3]. However, the fact that women with Stage 0 are less likely to progress and recur should be noted when interpreting the results. The fact that CBSM effects were stronger in the subsample of women diagnosed with invasive disease suggests that future research should focus on examining intervention effects on clinical outcomes in women with invasive tumors. The use of a structured, manualized intervention [18] increases feasibility, implementation, and ease of future replication.

Clinical relevance

This study provides preliminary evidence that a stress management group intervention modifying psychological adaptation early on in treatment may have lasting effects over the course of the disease for women with breast cancer. Within the context of a biopsychosocial, multidisciplinary model of care, CBSM is a group-based, manualized, feasible intervention that can be implemented in clinical oncology settings and may provide women an opportunity to reap long-term health benefits in addition to improved QOL and less depressive symptoms.

Future research directions

Additional studies should evaluate long-term effects and underlying mechanisms of cognitive-behavioral interventions on clinical disease outcomes of survival and recurrence in *non-metastatic* breast cancer patients. This is an area in need of further exploration with clinical endpoints as primary outcomes and more rigorous study designs. Research should address whether intervention-related changes in neuroendocrine, immune, inflammatory, and other tumor-promoting processes [11, 12] mediate effects of CBSM on survival [26]. Future research should also examine whether improved adherence to long-term endocrine regimens or changes in health behaviors may be explanatory mechanisms [27, 28]. Because the effects of CBSM reported here may have been diluted by including both distressed and non-distressed patients, future research could screen and pre-select patients based on clinical mood/distress symptoms [29]. Future research should also investigate the effectiveness of CBSM in venues including oncology clinics and remote platforms, in order to reach the broadest number of patients.

Conclusions

With notable limitations, women with non-metastatic breast cancer who receive CBSM intervention 2–10 weeks post-surgery showed improved survival compared to women in a 1-day group psychoeducational control condition at an 11-year median follow-up. In a subsample of women with invasive disease, breast cancer-specific survival and disease-free survival was improved for those in CBSM. This research contributes evidence for the effects of psychosocial interventions on clinical health outcomes in breast cancer patients, and may have implications for clinical practice.

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Fig. 1. CONSORT diagram. Study flow illustrated in CONSORT diagram extending from recruitment for the original trial through the present follow-up

Fig. 2. Overall survival difference in study groups. Differences between (CBSM vs. control) with Cox proportional hazards models on time to all-cause mortality controlling for covariates: age, stage of disease, HER2/neu, endocrine therapy, and tumor size

Fig. 3. Breast cancer-specific survival difference in study groups. Differences between study groups (CBSM vs. control) with Cox proportional hazards models on time to breast cancer-specific mortality controlling for covariates: age, HER2/neu, endocrine therapy, and tumor size

Fig. 4. Disease-free interval difference in study groups. Differences between study groups (CBSM vs. control) with Weibull accelerated failure time models on disease-free interval controlling for covariates: age, stage of disease, HER2/neu, endocrine therapy, and tumor size. “Cumulative Survival” indicates disease-free interval

Table 1

Means, standard deviations, and frequencies of demographic, medical, and treatment variables by study group

Variable	<i>n</i>	Control	Intervention	<i>p</i>
Age at diagnosis (years)	240	50.99 (9.06)	49.69 (8.98)	.27
Race/ethnicity	239			.64
White non-Hispanic		74 (61.7 %)	78 (65.0 %)	
Hispanic		31 (26.1 %)	30 (25.0 %)	
African American		10 (8.4 %)	11 (9.2 %)	
Asian		4 (3.4 %)	1 (.8 %)	
Employment status	240			.38
Not employed		28 (23.3 %)	34 (28.3 %)	
Employed		92 (76.7 %)	86 (71.7 %)	
Education (years)		15.47 (2.26)	15.69 (2.5)	.47
Income (thousands of dollars)	213	78.85 (68.27)	80.45 (66.11)	.86
Partnered status	240			1.00
Not partnered		45 (37.5 %)	45 (37.5 %)	
Partnered		75 (62.5 %)	75 (62.5 %)	
Menopausal status	240			.90
Premenopausal		53 (44.2 %)	54 (45.0 %)	
Postmenopausal		67 (55.8 %)	66 (55.0 %)	
Stage	239			.48
0		24 (20.0 %)	18 (15.1 %)	
I		44 (36.7 %)	39 (32.8 %)	
II		43 (35.8 %)	48 (40.3 %)	
III		9 (7.5 %)	14 (11.8 %)	
Early vs. invasive stage	239			.41
0		23 (19.2 %)	18 (15.0 %)	
I, II, III		97 (80.8 %)	101 (84.2 %)	
Positive lymph nodes		1.56 (3.60)	1.45 (2.97)	.79
Size of tumor	122	1.65 (1.14)	3.76 (12.93)	.19
Size of tumor (log-transformed)	122	0.23 (0.81)	0.55 (0.90)	.04
ER status	198			.17
Positive		78 (83.0 %)	78 (75.0 %)	
Negative		16 (17.0 %)	26 (25.0 %)	
PR status	178			.75
Positive		55 (64.7 %)	58 (62.4 %)	
Negative		30 (35.3 %)	35 (37.6 %)	
HER2/neu status	119			.24
Positive		10 (17.2 %)	16 (26.2 %)	
Negative		48 (82.8 %)	45 (73.8 %)	
Procedure type	240			.07
Lumpectomy		68 (56.7 %)	54 (45.0 %)	

Variable	<i>n</i>	Control	Intervention	<i>p</i>
Mastectomy		52 (43.3 %)	66 (55.0 %)	
Received chemotherapy	230			.06
Yes		57 (49.1 %)	70 (61.4 %)	
No		59 (50.9 %)	44 (38.6 %)	
Received radiation therapy	226			.59
Yes		69 (61.1 %)	65 (57.5 %)	
No		44 (38.9 %)	48 (42.5 %)	
Received endocrine therapy	228			.35
Yes		78 (67.8 %)	83 (73.5 %)	
No		37 (32.2 %)	30 (26.5 %)	
Body mass index (BMI)	134	26.60 (6.16)	26.63 (5.26)	.97
BMI categories	134			.30 ^a
Underweight		0 (0.0 %)	1 (1.6 %)	
Normal		33 (45.25 %)	30 (49.2 %)	
Overweight		28 (38.4 %)	16 (26.2 %)	
Obese		12 (16.4 %)	14 (23.0 %)	

ER estrogen receptor, *PR* progesterone receptor, *HER2/neu* human epidermal growth factor receptor

Intervention effects on clinical outcomes at 11-year (median) follow-up: multivariate Cox proportional hazards regressions and Weibull accelerated failure time models ($N = 240$)

Table 2

Variable	All-cause mortality ^b		Breast cancer-specific mortality ^b		Breast cancer recurrence ^c	
	HR (95 % CI)	<i>p</i>	HR (95 % CI)	<i>p</i>	HR (95 % CI)	<i>p</i>
Study condition (CBSM)	0.21 (0.05–0.93)	.040	0.25 (0.05–1.11)	.068	0.45 (0.17–1.18)	.083
Age at diagnosis	0.91 (0.84–0.99)	.025	0.91 (0.83–0.99)	.025	0.94 (0.89–1.00)	.023
Her2/neu (positive)	2.12 (0.53–8.33)	.288	1.70 (0.39–7.41)	.481	1.85 (0.70–4.91)	.199
Tumor size						
>T2	3.47 (0.40–30.13)	.259	4.81 (0.55–42.11)	.156	4.65 (0.85–25.43)	.057
T1c	1.79 (0.18–17.86)	.619	2.34 (0.23–23.89)	.474	2.89 (0.54–15.38)	.195
<T1c	–	.444	–	.306	–	–
Endocrine therapy (yes)	0.25 (0.06–0.97)	.045	0.29 (0.07–1.28)	.102	0.46 (0.16–1.29)	.121
Stage (invasive)	0.45 (0.03–7.60)	.578	– ^a	– ^a	0.64 (0.05–7.73)	.723

HR hazard ratio, 95 % CI 95 % confidence interval, *HER2/neu* human epidermal growth receptor, *CBSM* cognitive-behavioral stress management

^a Stage of disease not included in this analysis due to large standard error

^b Analyzed with Cox proportional hazards models

^c Analyzed with Weibull accelerated failure time models

Table 3

Intervention effects on clinical outcomes at 11-year (median) follow-up multivariate Cox proportional hazards regressions and Weibull accelerated failure time model: invasive tumor subsample only ($N=197$)

Variable	Breast cancer-specific mortality ^a		Breast cancer recurrence ^b	
	HR (95 % CI)	<i>p</i>	HR (95 % CI)	<i>p</i>
Study condition (CBSM)	0.08 (0.01–0.49)	.006	0.24 (0.07–0.82)	.011
Age at diagnosis	0.88 (0.79–0.97)	.010	0.94 (0.88–1.00)	.024
Her2/neu (positive)	4.33 (0.81–23.21)	.087	2.92 (0.97–8.77)	.039
Tumor size				
>T2	7.47 (0.64–87.57)	.109	4.61 (0.82–25.82)	.062
T1c	3.61 (0.29–45.71)	.321	2.89 (0.67–22.18)	.111
<T1c	–	.266	–	–
Endocrine therapy (yes)	0.28 (0.06–1.24)	.093	0.49 (0.17–1.43)	.174
Stage (III vs. I and II)	23.46 (3.65–150.62)	.001	4.03 (1.05–15.46)	.026

HR hazard ratio, 95 % CI 95 % confidence interval, *HER2/neu* human epidermal growth receptor, *CBSM* cognitive-behavioral stress management

^a Analyzed with Cox proportional hazards models

^b Analyzed with Weibull accelerated failure time models