

ORIGINAL ARTICLE

Oncofertility-related psycho-educational therapy for young adult patients with breast cancer and their partners: randomized controlled trial

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Abstract

Background: A couples' psycho-educational program called Oncofertility! Psycho-Education and Couple Enrichment (O!PEACE) therapy was created and its effect when provided before cancer treatment was examined.

Methods: This multicenter randomized controlled trial with nonmasking, parallel two-group comparison enrolled women aged 20 to 39 years with early-stage breast cancer and their partners. They were randomly assigned to receive O!PEACE (37 couples) or usual care (37 couples). Primary end points were cancer-related

posttraumatic stress symptoms, symptoms of depression, and anxiety. Secondary end points were stress-coping strategies, resilience, and marital relationship.

Results: Women receiving psycho-educational therapy had significantly reduced Impact of Event Scale-revised version for Japanese scores ($p = .011$, $\eta_p^2 = .089$). For patients with Impact of Event Scale-revised version for Japanese scores at baseline ≥ 18.27 , O!PEACE therapy improved these scores when compared with usual care ($U = 172.80$, $p = .027$, $r = 0.258$). A >5 -point reduction was present in 59.3% and 30% of women in the O!PEACE therapy and usual-care groups, respectively. For partners, O!PEACE therapy significantly improved stress-coping strategies (95% CI, -0.60 to -0.05 ; $p = .018$, $\eta_p^2 = .074$) and escape-avoidance marital communication (95% CI, -0.33 to -0.08 ; $p = .001$, $\eta_p^2 = .136$). O!PEACE therapy significantly improved the partners' support (95% CI, 0.10 – 0.50 ; $p = .001$, $\eta_p^2 = .127$), the rate of receiving fertility preservation consultations, and knowledge levels.

Conclusions: O!PEACE therapy before cancer treatment can improve posttraumatic stress symptoms, stress-coping behavior, and marital relationships. Larger sample sizes and longer term follow-up are required.

Plain Language Summary

- A psycho-educational program, the Oncofertility! Psycho-Education and Couple Enrichment (O!PEACE) therapy program was developed and evaluated for women diagnosed with breast cancer and their partners.
- A multicenter randomized controlled trial showed that the O!PEACE psycho-educational therapy, with only two precancer treatment sessions, can reduce cancer-related posttraumatic stress symptoms and improve oncofertility knowledge and marital relationships in young adult patients with breast cancer.
- The therapy could also improve stress-coping strategies in marital communications with their partners. Couples may use O!PEACE psycho-educational therapy to consider fertility preservation and improve their psychosocial aspects.

KEYWORDS

breast neoplasms, fertility preservation, mental disorders, psycho-oncology, psychotherapy

INTRODUCTION

Adolescent and young adult (AYA) patients with cancer display distress and potential psychological trauma symptoms after receiving a cancer diagnosis involving possible fertility loss. AYA patients experience conflict about fertility preservation, and many develop cancer-related posttraumatic stress symptoms (PTSS).^{1,2} Patients with cancer-related distress are more likely to refuse adjuvant chemotherapy recommended by their oncologist³ and discontinue fertility treatments than those without distress.⁴ These symptoms of posttraumatic stress disorder (PTSD) prevent childbearing after cancer treatment.⁵

Supportive psychological care for AYA patients with cancer is recommended. The American Society of Clinical Oncology Guidelines recommend that health care providers discuss oncofertility before cancer treatment and refer patients to psychological professionals if

fertility-related concerns or anxiety arise.⁶ The American Society for Reproductive Medicine Committee,⁷ Japan Society of Fertility Preservation,⁸ Japan Society for Reproductive Psychology,⁴ and Oncofertility Consortium⁹ support the need for psychosocial care and oncofertility-specialized psychological counseling for AYA patients with cancer.

Many interventional studies focusing on decisional conflicts of fertility preservation disregard cancer-related PTSS, symptoms of depression, and anxiety.^{10,11} To the best of our knowledge, no interventional studies have examined the effectiveness of post-diagnosis psychological counseling regarding fertility preservation on cancer-related PTSS and other psychosocial aspects among AYA patients with cancer.

Adding psycho-educational therapy and psychosocial interventions using decisional aids for fertility preservation may

improve psychosocial aspects. Psycho-educational therapy is a short-term, evidence-based practice that improves stress-coping strategies, self-management, and interpersonal communication skills using psychotherapeutic strategies. Systematic reviews support psycho-educational therapy as one of the most effective treatments to improve cancer-related PTSS and psychological distress for patients after diagnosis.^{12–14} Psycho-educational couple therapies after early-stage cancer diagnosis decrease cancer-related PTSS, symptoms of depression, and anxiety and improve stress management and marital relationships.^{15,16}

Coping is defined as constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of a person.¹⁷ Coping strategies are varied and include problem-focused, emotion-focused, and passive coping, such as escape-avoidance.^{17–21} Evaluating coping strategies could be helpful for couples because the cancer-related stress of the patient can have negative effects on the partner.^{22–24}

We aimed to examine the impact of Oncofertility! Psycho-Education and Couple Enrichment (O!PEACE) therapy in decreasing couples' distress. We hypothesized that O!PEACE therapy would reduce PTSS, symptoms of depression and anxiety (primary outcomes), and negative stress-coping and marital miscommunication (secondary outcomes).

METHODS

Study design and participants

This randomized controlled trial was a multicenter, nonblinded, parallel study of two groups with a pre-post design. We compared the relative impact of O!PEACE therapy with usual care in an exploratory study. From June 2015 to November 2017, outpatients were enrolled in the study during their breast surgery consultations at one of the participating hospitals in Japan.

The data were managed independently by the authors at the National Center for Child Health and Development, Japan. This study was approved by the Bio-Ethics Board of St. Marianna University School of Medicine (#2874). The study protocol was approved by the institutional review board of each participating center and was independently monitored by an external, neutral data center. The trial protocol was registered at UMIN-CTR (<https://center6.umin.ac.jp/>; ID: UMIN000017754).

Married women aged 20 to 39 years who met the criteria for early breast cancer (BC) were eligible to participate if they visited one of the participating hospitals at least twice with their partners before any cancer treatment. This study only targeted women with BC, and only married couples were included. Agreement to participate and a signed consent form were obtained from both married partners before the baseline assessments.

Randomization and masking

Participants were randomly allocated to the O!PEACE or usual-care group in a 1:1 ratio. The O!PEACE therapy group received two sessions of the brief psycho-educational couples' therapy; the usual-care group received no therapy sessions. All couples received the routine treatment regimen of their respective outpatient department.

Masking of participants and psychologists was not possible considering the nature of the psychotherapy.²⁵ To prevent any bias from the self-forecast effect, we highlighted the equal effectiveness of both courses to reduce participants' overestimation of O!PEACE therapy and to motivate both groups to complete the course.

Procedures

We created a structured, solution-focused, brief psycho-educational therapy (O!PEACE) for couples coping with anxiety and distress about oncofertility (Supplemental Material S1). It comprised two sessions. The first one included supportive therapy and relaxation and information about the risk of infertility with cancer treatments and shared decision-making regarding fertility preservation. The second session included assertive training and solution-focused approaches for couples' stress-coping and cognitive externalization for improving couples' resilience. The intervention occurred before cancer treatment and took 2 or more days.

All participants received standard care. In the usual-care group, all patients were informed of additional fertility preservation at each facility. Health care providers provided oncofertility information booklets and, on request, referred patients to fertility specialists.

The online registration and randomized allocation system were developed and managed by an outside registration center (Supplemental Material S2). The randomized block method was used to create equal-sized groups. The study staff was blinded to the randomization. Detailed methodology can be obtained from the registration center (https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000020564).

Outcomes

All primary outcome measures were collected from self-reported questionnaires in the pre- and follow-up assessments before cancer treatment began. The primary outcome was each partner's mental health (cancer-related distress, symptoms of depression, and anxiety), measured with the tools outlined here.

The Impact of Event Scale-revised version for Japanese (IES-R-J) is a self-administered questionnaire to measure cancer-related PTSS.²⁶ The cutoff point for PTSS is calculated based on the sum of all items; scores >25 indicate PTSD.²⁷

The Hospital Anxiety and Depression Scale (HADS) is widely used internationally to identify states of distress in medically ill patients.²⁸

The six-item Kessler Psychological Distress Scale (K6) is widely used for severity estimations of serious mental illness for the general population.²⁹

Secondary outcomes were evaluated using the Tri-axial Coping Scale,²² Connor-Davidson Resilience Scale,³⁰ Marital Relationships Scale,³¹ and Scale of Relationship-Focused Coping for Marital Couple Stress.³²

Statistical analyses

G*Power Statistical Software (version 3.1) (Düsseldorf, Germany) was used for the power analysis of outcome variables.³³ The final sample size was 74. Assuming a type I error level of 0.05 and a pre-post design with two measurement points without any confounders, a total sample of 74 has 0.80 power to detect around medium effect size based on previous research.³⁴

The intention-to-treat (ITT) data set included all randomized couples who consented to this study and were assigned to the groups. In data cleaning, 7.4% of all variables were missing. Thus, multiple imputation (MI) was conducted for all variables.³⁵ We analyzed the primary and secondary outcomes using five simulated data sets, obtaining five results each. The Rubin rule was applied to integrate the five results. After MI, ITT analyses were performed.

Comparisons between variables from the usual care and O!PEACE therapy at baseline and clinical outcomes were performed using χ^2 or Fisher exact test for categorical data and the Student t-test for the independent samples for continuous variables.

Primary and secondary outcomes were analyzed using analysis of covariance (ANCOVA). The pre-post design used ANCOVA when baseline differences were present, with the respective baseline scores as the covariate. ANCOVA requires two assumptions to be met: the normality and the homogeneity of the regression slopes. Normality was determined using the Shapiro–Wilk test. Nonnormally distributed variables were log-transformed. The regression slopes showed homogeneity for all primary and secondary outcomes, excluding the IES-R-J scores; for violations, the modified Johnson–Neyman procedure was conducted to calculate the crossover point as a post hoc test.³⁶ According to the crossover point, four groups were established using the two covariate score levels (high and low) of the O!PEACE and usual-care groups. The Mann–Whitney *U* test examined the impact of O!PEACE on the outcomes as a post hoc test to reduce the influence of outliers.

We assessed feasibility as the degree of knowledge of fertility preservation and BC treatment among all participants, and satisfaction with O!PEACE as the score given by the intervention group via a questionnaire.

RESULTS

The trial was completed on November 30, 2017. Seventy-four couples had consented to participate and completed baseline questionnaires (Figure 1). In total, 69 couples (34 couples in O!PEACE and 35 in usual care) completed the full trial (Supplemental Material S3).

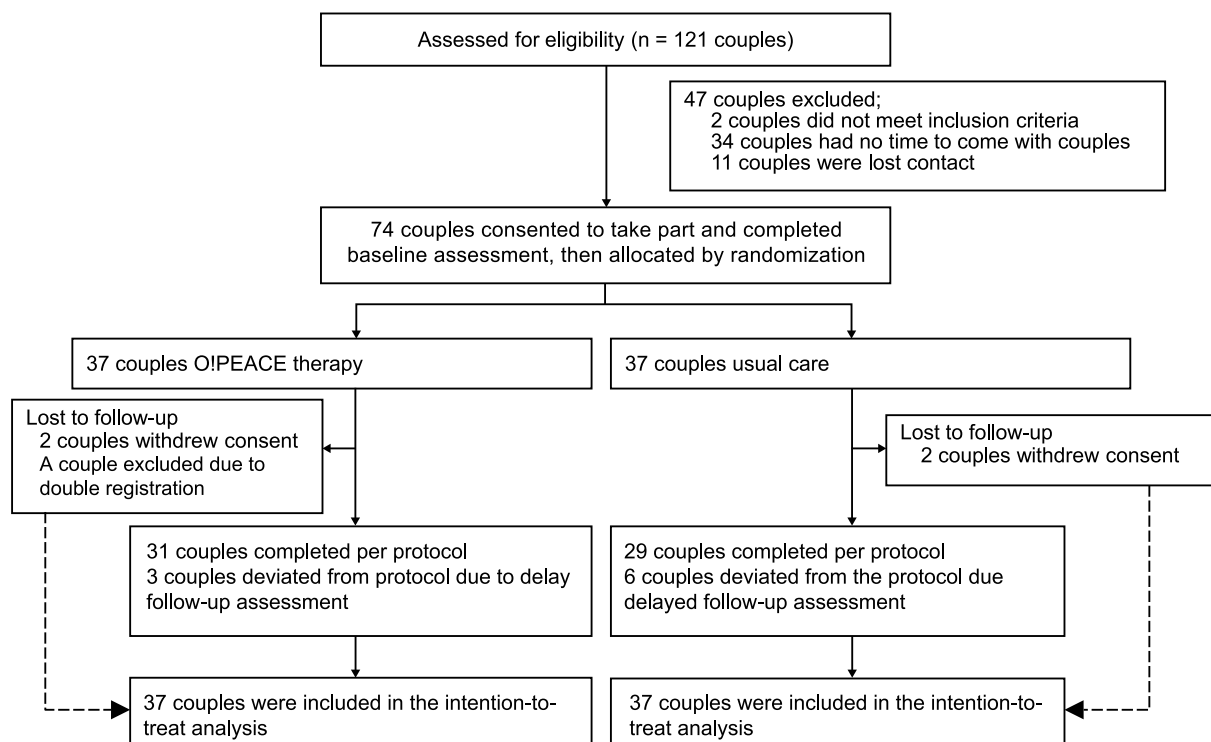


FIGURE 1 CONSORT diagram. Trial profile indicating the disposition of study participants during screening, enrollment, randomization, and participation in the trial.

TABLE 1 Demographic and baseline characteristics in the intention-to-treat population.

	Patients with breast, n = 74			Patients' partners, n = 74		
	O:PEACE therapy (n = 37)	Usual care (n = 37)	p ^a	O:PEACE therapy (n = 37)	Usual care (n = 37)	p ^a
Age (years)	35.60 (0.5)	36.20 (0.4)	.340	--	--	--
Working ratio	58.9%	64.9%	.605	94.6%	100%	.493
Marriage period (years), duration of marriage (years)	6.30 (0.8)	8.30 (1.1)	.140	--	--	--
Couples with children (ratio)			.479	--	--	--
None	40.5%	28.6%	--	--	--	--
One	38.4%	40.5%	--	--	--	--
Two or more	21.1%	30.8%	--	--	--	--
Rate of persons desirous of having more children	68.1%	51.4%	.180	64.9%	48.6%	.176
Rate of persons receiving psychiatric treatment	18.9%	18.9%	.906	6.5%	13.5%	.542
Days from pretest until posttest	16.10 (1.7)	17.00 (1.9)	.700	16.30 (1.8)	19.70 (2.7)	.290
Days from cancer diagnosis until consent ^b	25.90 (6.1)	17.50 (3.0)	.220	--	--	--
Breast cancer stage ratio			.573	--	--	--
Stage 0	26.5%	21.6%	--	--	--	--
Stage 1	45.9%	39.5%	--	--	--	--
Stage 2 or 3	27.6%	38.9%	--	--	--	--
Chemotherapy ratio	41.2%	25.7%	.205	--	--	--
Hormone therapy ratio	46.5%	39.5%	.544	--	--	--
Breast surgery ratio	91.4%	94.1%	1.000	--	--	--
Radiation therapy ratio	34.1%	33.0%	.922	--	--	--
Primary outcomes						
IES-R-J (mean [SE])	27.58 (2.9)	21.01 (2.2)	.069	16.14 (2.2)	19.04 (2.2)	.351
HADS (mean [SE])	14.79 (1.1)	12.03 (0.9)	.058	10.21 (0.9)	13.89 (1.2)	.016
K6 (mean [SE])	7.79 (0.8)	6.68 (0.6)	.289	4.03 (0.5)	6.62 (0.8)	.005
Secondary outcomes						
CD-RISC (mean [SE])	57.05 (2.9)	59.46 (2.8)	.551	63.42 (2.4)	57.06 (2.9)	.088
TAC-24						
Planning and overcoming (mean [SE])	16.71 (0.9)	16.10 (1.0)	.645	15.44 (1.1)	14.45 (0.9)	.488
Giving up and blaming (mean [SE])	2.54 (0.6)	2.52 (0.4)	.977	2.42 (0.4)	2.23 (0.4)	.730

(Continues)

TABLE 1 (Continued)

	Patients with breast, n = 74		Patients' partners, n = 74		p ^a	p ^a
	O/PEACE therapy (n = 37)	Usual care (n = 37)	O/PEACE therapy (n = 37)	Usual care (n = 37)		
Positive beliefs and distraction (mean [SE])	14.43	(0.8)	15.63	(0.9)	.318	.235
Marital relationships						
Intimacy (mean [SE])	4.50	(0.1)	4.47	(0.1)	.821	.413
Support for spouse (mean [SE])	4.04	(0.1)	3.93	(0.1)	.553	.833
Support from spouse (mean [SE])	4.31	(0.1)	4.27	(0.2)	.847	.921
Conflict (mean [SE])	2.48	(0.2)	2.71	(0.9)	.347	.682
Marital relationship-focused coping						
Active engagement (mean [SE])	2.77	(0.1)	2.44	(0.1)	.096	.577
Escape-avoidance (mean [SE])	1.90	(0.1)	1.90	(0.1)	.978	.913
Protective buffering (mean [SE])	1.61	(0.2)	1.57	(0.1)	.825	.995
Knowledge						
Oncofertility (mean [SE])	8.67	(0.4)	9.27	(0.4)	.258	.150
Breast cancer (mean [SE])	6.61	(0.3)	6.62	(0.3)	.967	.050

Note: Data are n (%) or means (SEs) for normally or skewed distributed data, respectively. Percentages may not sum to 100 because of rounding. All variables were calculated after multiple imputations.

Abbreviations: CD-RISC, Connor-Davidson Resilience Scale; HADS, The Hospital Anxiety and Depression Scale; IES-R-J, The Impact of Event Scale-revised Version for Japanese; K6, The 6-item Kessler Psychological Distress Scale; TAC-24: Tri-axial Coping Scale.

^aP values were calculated with two-tailed Student t-tests, Pearson χ^2 , or Fisher exact tests.

^bEvery couple submitted the consent documents simultaneously.

TABLE 2 Effect of intervention on primary and secondary outcomes in the intention-to-treat analyses.

	Patients with breast cancer				Patients' partners			
	OIPEACE therapy (n = 37)		Usual care (n = 37)		OIPEACE therapy (n = 37)		Usual care (n = 37)	
	Pre test	Post test	Pre test	Post test	Pre test	Post test	Pre test	Post test
	Score (95% CI)				Score (95% CI)			
Primary outcomes								
IES-R	27.6 (21.8–33.4)	21.6 (17.0–26.2)	21.5 (16.5–25.5)	19.9 (15.1–24.8)	–0.43 (–0.75 to –0.11)	.011 ^b	.089	Adjusted mean difference (95% CI)
								15.1 (11.1–19.1)
								19.0 (14.5–23.5)
								0.05 (–0.31 to 0.41)
								.245 .001
HADS	14.8 (12.5–17.1)	12.3 (10.4–14.3)	12.0 (10.2–13.9)	11.2 (9.1–13.4)	–0.86 (–2.92 to 1.20)	.406	.01	Adjusted mean difference (95% CI)
								12.4 (9.8–15.0)
								13.9 (11.5–16.3)
								0.16 (–0.10 to 0.43)
								.221 .021
K6	7.8 (6.1–9.5)	6.4 (4.6–8.2)	6.7 (5.5–7.9)	5.1 (3.8–6.4)	0.10 (–0.20 to 0.39)	.514	.007	Adjusted mean difference (95% CI)
								6.0 (4.2–7.7)
								6.6 (5.0–8.3)
								0.03 (–0.27 to 0.32)
								.854 .001
Secondary outcomes								
CD-RISC	57.0 (51.1–63.0)	58.8 (53.0–64.7)	59.5 (53.8–65.1)	57.8 (51.9–63.8)	3.11 (–1.15 to 7.38)	.146	.029	Adjusted mean difference (95% CI)
								56.9 (51.0–62.7)
								57.1 (51.3–62.9)
								–2.93 (–8.36 to 2.50)
								.283 .016
TAC-24	16.7 (15.0–18.4)	15.3 (13.3–17.2)	16.1 (14.0–18.2)	15.3 (13.6–16.9)	–0.34 (–2.44 to 1.76)	.742	.002	Adjusted mean difference (95% CI)
								13.4 (11.3–15.6)
								14.5 (12.6–16.3)
								–1.16 (–3.44 to 1.11)
								.309 .014
Giving up and blaming	2.5 (1.3–3.8)	2.3 (1.1–3.5)	2.5 (1.7–3.3)	2.3 (1.3–3.2)	0.02 (–0.28 to 0.32)	.891	.002	Adjusted mean difference (95% CI)
								2.3 (1.3–3.3)
								2.2 (1.5–3.0)
								–0.33 (–0.60 to –0.05)
								.018 .074
Positive beliefs and distraction	14.4 (12.8–16.1)	14.1 (12.3–15.8)	15.6 (13.9–17.4)	14.5 (12.7–16.3)	0.42 (–1.35 to 2.18)	.643	.003	Adjusted mean difference (95% CI)
								12.5 (10.8–14.2)
								12.5 (11.0–14.0)
								–0.07 (–2.11 to 1.97)
								.949 .001
Marital relationships scale								
Intimacy	4.5 (4.3–4.7)	4.5 (4.3–4.7)	4.5 (4.2–4.7)	4.4 (4.1–4.6)	0.12 (–0.05 to 0.30)	.155	.029	Adjusted mean difference (95% CI)
								4.3 (4.0–4.6)
								4.4 (4.2–4.6)
								–0.04 (–0.37 to 0.29)
								.81 .002
Support for spouse	4.0 (3.8–4.3)	4.0 (3.7–4.3)	3.9 (3.6–4.2)	3.8 (3.5–4.1)	0.11 (–0.19 to 0.40)	.392	.015	Adjusted mean difference (95% CI)
								4.0 (3.7–4.2)
								3.8 (3.5–4.1)
								–0.15 (–0.52 to 0.23)
								.433 .009
Support from spouse	4.3 (4.1–4.6)	4.5 (4.3–4.8)	4.3 (4.0–4.6)	4.2 (3.8–4.5)	0.30 (0.10–0.50)	.001	.127	Adjusted mean difference (95% CI)
								4.2 (3.9–4.5)
								4.2 (3.8–4.5)
								–0.19 (–0.54 to 0.16)
								.283 .017
Conflict	2.5 (2.1–2.8)	2.4 (2.1–2.8)	2.7 (2.4–3.1)	2.8 (2.4–3.2)	–0.15 (–0.44 to 0.13)	.276	.017	Adjusted mean difference (95% CI)
								3.0 (2.6–3.3)
								2.9 (2.5–3.3)
								–0.25 (–0.61 to 0.11)
								.162 .029
The Scale of Relationship-Focused Coping								
Active engagement	2.8 (2.5–3.0)	2.7 (2.4–2.9)	2.4 (2.2–2.7)	2.6 (2.3–2.9)	–0.21 (–0.62 to 0.19)	.087	.048	Adjusted mean difference (95% CI)
								2.5 (2.2–2.8)
								2.6 (2.3–2.9)
								0.003 (–0.27 to 0.27)
								.984 .002
Escape- avoidance	1.9 (1.7–2.2)	1.8 (1.5–2.0)	1.9 (1.7–2.1)	1.8 (1.6–2.1)	–0.08 (–0.38 to 0.22)	.587	.006	Adjusted mean difference (95% CI)
								2.1 (1.7–2.4)
								1.9 (1.6–2.2)
								–0.21 (–0.33 to –0.08)
								.001 .136

(Continues)

TABLE 2 (Continued)

	Patients with breast cancer						Patients' partners							
	O!PEACE therapy (n = 37)			Usual care (n = 37)			O!PEACE therapy (n = 37)			Usual care (n = 37)				
	Pre test	Post test		Pre test	Post test		Pre test	Post test		Pre test	Post test			
	Score (95% CI)			Score (95% CI)			Score (95% CI)			Score (95% CI)				
			Adjusted mean difference (95% CI)			Effect size (η_p^2)			p ^a			Adjusted mean difference (95% CI)	Effect size (η_p^2)	p ^a
Protective buffering	1.6 (1.3–1.9)	1.5 (1.3–1.8)	1.7 (1.4–1.9)	1.6 (1.4–1.8)	1.7 (1.4–1.9)	.319	1.9 (1.6–2.1)	1.7 (1.4–2.0)	1.9 (1.7–2.1)	1.9 (1.6–2.1)	1.9 (1.6–2.1)	–0.16 (–0.46 to 0.15)	.303	.016
Knowledge level														
Oncofertility	8.7 (7.9–9.4)	10.4 (9.6–11.2)	9.9 (9.1–10.8)	9.3 (8.5–10.0)	9.9 (9.1–10.8)	.006	8.3 (7.7–8.9)	9.8 (9.2–10.4)	7.6 (6.8–8.4)	9.3 (8.4–10.2)	9.3 (8.4–10.2)	0.09 (–0.82 to 0.99)	.849	.002
Breast cancer treatment	6.6 (6.1–7.1)	7.5 (7.1–7.9)	7.5 (6.9–8.0)	6.6 (6.1–7.2)	7.5 (6.9–8.0)	.769	6.4 (5.8–7.1)	7.4 (6.8–7.9)	5.5 (4.9–6.1)	7.1 (6.7–7.6)	7.1 (6.7–7.6)	–0.04 (–0.12 to 0.04)	.295	.018

Note: Data are presented as means (95% CIs) for normally distributed or skewed data, respectively. All variables were calculated after multiple imputation. The range of each score were as follows: IES-R-J was 0–88; HADS, 0–42; K6, 0–24; CD-RISC, 0–100; planning and overcoming, 0–36; giving up and blaming, 0–24; positive beliefs and distraction, 0–36; oncofertility, 4–16; breast cancer treatment, 3–12. For IES-R-J, HADS, and K6, higher scores indicated more distress. For knowledge of oncofertility and breast cancer treatment, higher scores indicated more knowledge.

Abbreviations: CD-RISC, Connor-Davidson Resilience Scale; HADS, The Hospital Anxiety and Depression Scale; IES-R-J, The Impact of Event Scale-revised Version for Japanese; K6, The 6-item Kessler Psychological Distress Scale; TAC-24, Tri-axial Coping Scale.

^aBecause of significant differences between the groups by the pretest score in analysis of covariance, two-way analysis of variance was conducted to examine the interaction effects.

^bTwo-way analysis of variance.

comes of the The IES-R-J affected by th patients with B Johnson-Ney exploratory (patients with care, O!PEACE ment IES-R-J 59.3% (16/27 compared with J-lowering e PTSS (i.e., IES- $r = 0.210$; Figure 17) of partic and usual-car and their hus improve thro

For the p stress-coping mean differer This decrease compared wi escape-avoid by the interv to -0.08 ; $p = (13.6/37)$ of respectively, communicatio O!PEACE and giving-up str their commu relationship n apy significan ference 0.30 ; $37)$ versus 1 their partners

Demographic and baseline characteristics were calculated for 74 couples using ITT analysis after MI (Table 1). All variables, including demographics, were similar in both groups in the baseline assessment scores, excluding the partners' HADS and K6 scores. Husbands in the usual-care group showed more depressive and anxiety symptoms than those in the O!PEACE therapy group, even though the psychiatric medical history was not significantly different between them. The ITT analyses of outcomes were conducted for 37 couples in each group.

Table 2 presents the results of the primary and secondary outcomes of the ITT analysis in the patients with BC and their partners. The IES-R-J score of the follow-up assessment was significantly affected by the interaction of the baseline assessment scores of patients with BC: $F(1, 70) = 6.80$; $p = .011$; $\eta_p^2 = .089$. From the Johnson–Neyman procedure, the crossover point was calculated as exploratory (18.26/18.27 of the baseline IES-R-J score; Figure 2). For patients with a baseline IES-R-J score ≥ 18.27 , compared with usual care, O!PEACE therapy significantly reduced the follow-up assessment IES-R-J score ($U = 172.80$; $p = .027$; $r = 0.258$, Figure 3). Overall, 59.3% (16/27) O!PEACE participants showed a >5 -point reduction, compared with 30.0% (6/20) of the usual-care participants. The IES-R-J-lowering effect of O!PEACE was not influenced by low baseline PTSS (i.e., IES-R-J baseline was lower than 18.27) ($U = 122.80$, $p = .078$, $r = 0.210$; Figure 3). For low PTSS at baseline, 10% (1/10) and 17.6% (3/17) of participants improved 5 points or more in the O!PEACE and usual-care groups, respectively. The patients' HADS and K6 scores and their husbands' IES-R-J, HADS, and K6 scores did not significantly improve through the intervention, as determined by ANCOVA.

For the partners, O!PEACE therapy significantly improved the stress-coping strategies of giving up and blaming others (adjusted mean difference -0.33 ; 95% CI, -0.60 to -0.05 ; $p = .018$; $\eta_p^2 = .074$). This decreased significantly in the O!PEACE (58.9% [21.8/37]) compared with the usual-care (31.4% [11.6/37]) group. The use of escape-avoidance coping among partners was significantly improved by the intervention (adjusted mean difference, -0.21 ; 95% CI, -0.33 to -0.08 ; $p = .001$; $\eta_p^2 = .136$). Overall, 54.1% (20/37) and 36.8% (13.6/37) of the O!PEACE and usual-care group participants, respectively, declined to use escape-avoidance coping in marital communication. A total of 58.9% (21.8/37) and 31.4% (11.6/37) of the O!PEACE and usual-care participants, respectively, did not use the giving-up strategy. Only partners in the O!PEACE group changed their communication style (e.g., from partner avoidance to marital relationship maintenance). For patients with BC, the O!PEACE therapy significantly improved their spousal support (adjusted mean difference 0.30; 95% CI, 0.10–0.50; $p = .001$, $\eta_p^2 = .127$); 41.6% (15.4/37) versus 17.3% (6.4/37) of patients received more support from their partners in the O!PEACE and usual-care groups, respectively.

Feasibility

Knowledge of fertility preservation significantly improved in patients (70.3% [26/37]) in the O!PEACE group, whereas the partner's

Demographic and baseline characteristics were calculated for 74 couples using ITT analysis after MI (Table 1). All variables, including demographics, were similar in both groups in the baseline assessment scores, excluding the partners' HADS and K6 scores. Husbands in the usual-care group showed more depressive and anxiety symptoms than those in the O!PEACE therapy group, even though the psychiatric medical history was not significantly different between them. The ITT analyses of outcomes were conducted for 37 couples in each group.

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knowledge levels (53.5% [19.8/37]) did not improve (adjusted mean difference, 0.30; 95% CI, 0.10–0.50; $p = .001$; $\eta_p^2 = .127$). Knowledge of BC treatment did not improve for patients or their partners in either group (Table 2). Attending fertility preservation consultations and knowledge levels significantly improved for patients but not for their partners in the O!PEACE group. A higher consultation ratio for fertility preservation was found in the O!PEACE group than in the usual care group ($\chi^2 (1) = 5.29$, $p = .029$; Cramer's $v = 5.12$, $p = .030$). Overall, 45.4% and 20.5% of patients in the O!PEACE and usual-care groups, respectively, received fertility preservation consultations by fertility specialists. The success rate of fertility preservation was not significant ($\chi^2 (1) = 1.07$, $p = .342$, Cramer's $v = 1.06$, $p = .344$), with fertility preservation ratios of 24.3% and 15.1% for O!PEACE and usual care, respectively.

Satisfaction with O!PEACE was high; the therapy helped participants feel calm (patients, 59.5%; partners, 74.1%), positive (patients, 66.5%; partners, 68.6%), and cope with the stress from treatments and plan for the future (patients, 59.5%; partners, 66.5%).

The therapy was monitored by supervisors, who randomly chose and assessed the treatment outcomes of each psychologist. The

feasibility of O!PEACE therapy was also demonstrated. There were no harmful or unintended effects for either group.

DISCUSSION

This is the first randomized controlled trial to evaluate the effect of O!PEACE exploratory therapy, which was effective for couples with mild to severe levels of cancer-related PTSS. A cancer diagnosis is a life-threatening event that may induce PTSS (in 17%–34% of patients)³⁷ and PTSD. Particularly, 29.1% and 44% of AYA patients with cancer report PTSD symptoms and cancer-related PTSS, respectively, 12 months after a cancer diagnosis.¹ For AYA patients with cancer, the possibility of fertility loss because of cancer treatment is a serious concern and the Practice Committee of the Oncofertility Consortium describes fertility preservation options available such as various freezing options, a random-start protocol for controlled ovarian stimulation, and the use of letrozole or tamoxifen to avoid high BC estradiol levels.³⁸ Many medical and psychosocial barriers to fertility preservation remain, such as a lack of information and knowledge, costs, uncertainty about the future, overwhelmingness of

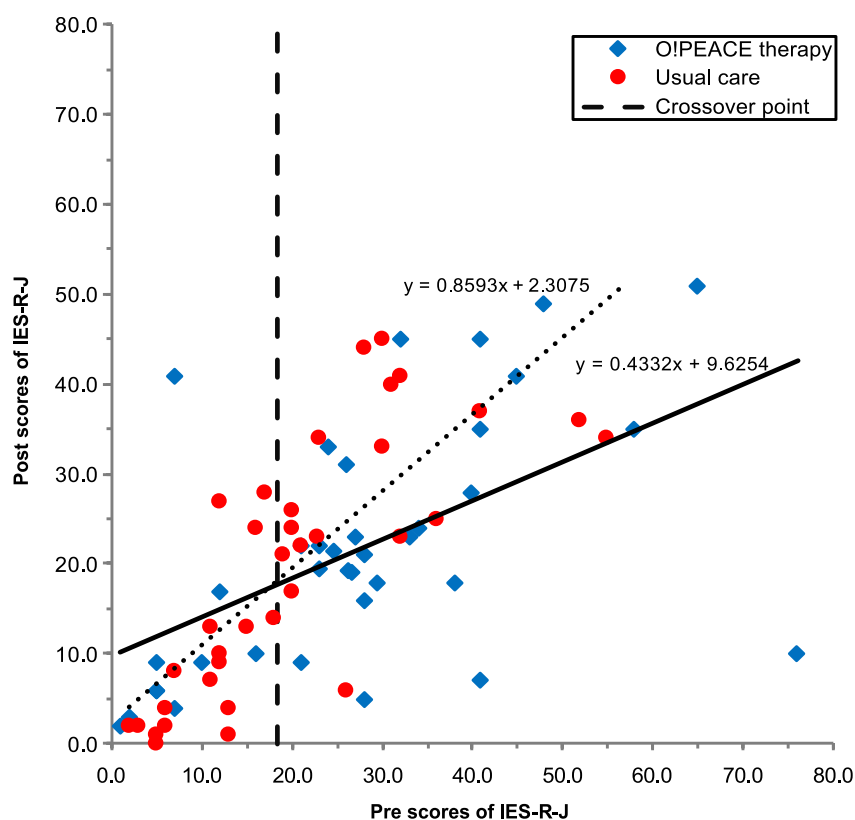


FIGURE 2 Pre-post IES-R-J score scatterplot by intervention with SROS and crossover point noted. Effects of O!PEACE therapy and usual care on the IES-R-J based on levels at baseline (individual data, logarithmically transformed). For baseline IES-R-J levels >18.27 (large dotted line), patients treated with O!PEACE therapy had significantly lower IES-R-J at postintervention ($p < .05$ vs. usual care). Level of magnification in insets: 1.0. IES-R-J indicates The Impact of Event Scale-revised version for Japanese; O!PEACE, Oncofertility! Psycho-Education and Couple Enrichment; SROS, simultaneous regions of significance.

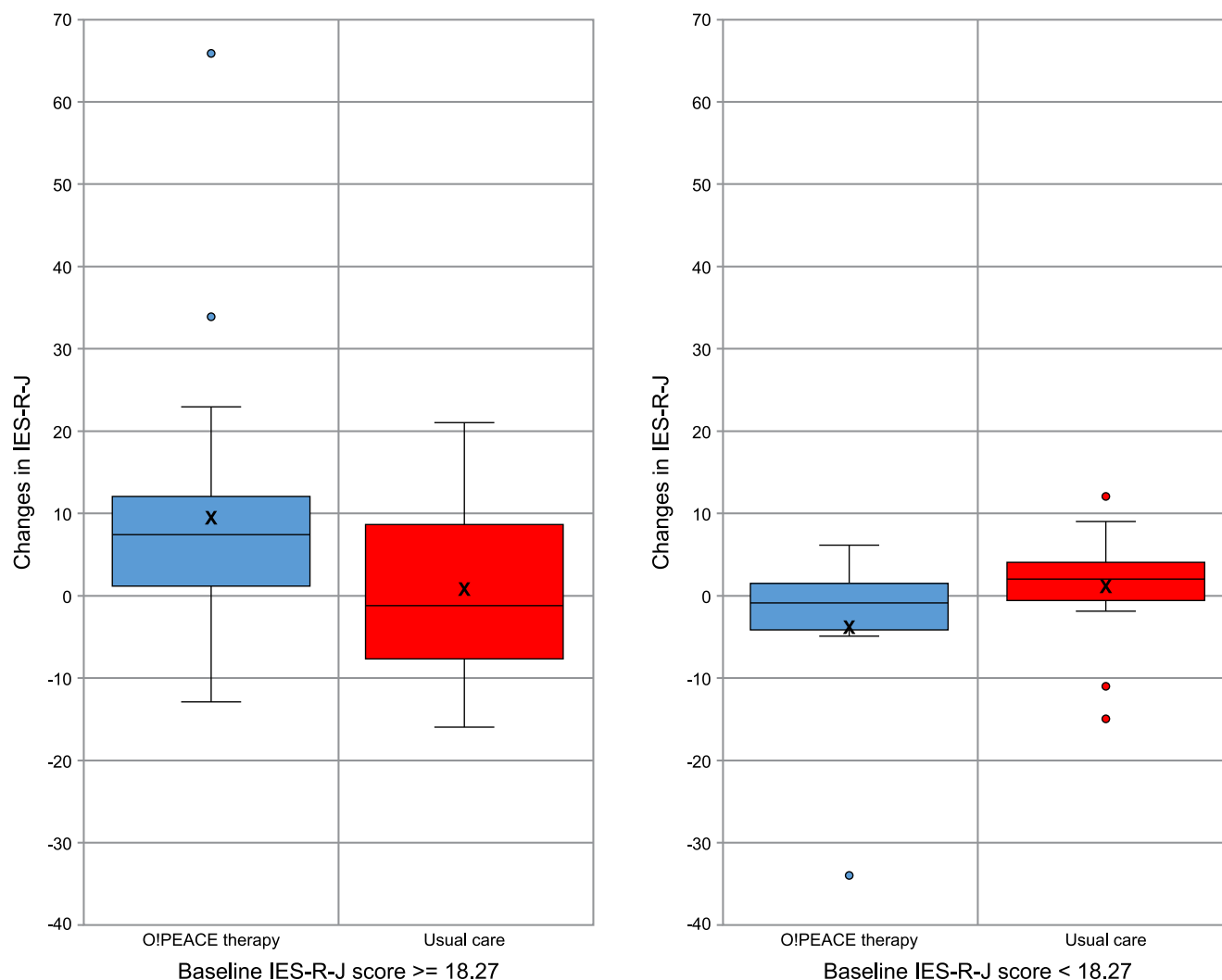


FIGURE 3 Change in upper IES-R-J scored baseline and lower IES-R-J scored baseline of the IES-R-J from pre- to postintervention. Determination of upper/lower is 18.27. Level of magnification in insets: 1.0. IES-R-J indicates The Impact of Event Scale-revised version for Japanese.

cancer diagnosis, and disagreements among partners. AYA patients may require psycho-educational therapy to reduce their PTSS and stress-coping strategies as well as supportive marital communication regarding fertility. Psycho-educational therapy appears to increase personal medical awareness, improve general psychological well-being, and decrease anxiety.^{12,13} Psycho-educational therapy using decision aids concerning fertility preservation can reduce conflict and decision regret among patients with cancer.^{39,40}

Regarding the stress-coping strategies of patients' partners, such as giving up, blaming others, and escape-avoidance, Japanese male partners are likely to have no other coping strategies when BC is diagnosed. A survey showed that 50% to 60% of Japanese men with wives with BC did not understand their partners' feelings, did not know how to support them, and worried about the limits of what they could do for their wives when diagnosed BC.⁴¹ Most Japanese partners are likely to feel helpless about supporting their wives with BC, and avoidance can worsen marital communication and cancer-related distress.⁴² When partners know how to accept and respond

supportively to their partners' cancer-related concerns through couples therapy, it can improve their stress-coping strategies, decrease patients' psychological distress, and increase relationship intimacy.^{42,43}

The reason husbands did not improve their mental health is not directly explained in this study. However, we speculate that long working hours may have influenced these results. The ratio of Japanese male workers who work 49 hours or more a week was approximately twice that of their American and European counterparts.⁴⁴ That is, patients' partners may have had severe work stress from before the BC diagnosis. When scheduling appointments for this study, many husbands complained that it was difficult to accompany their partners with BC to hospitals because of their long working hours and they were likely to prioritize work over family even after their partners' BC diagnosis.

This study had some limitations. First, it did not assess the long-term effect of the intervention because the study was designed to avoid contamination from the impact of cancer treatment itself on

mental health. Second, there is a possibility of sampling bias because there were no entry criteria for cancer-related distress, although the maximum level was clarified as one of the exclusion criteria. Given the focus on stress management, it is plausible that the effects would have been larger in a more distressed sample; future work should target such a population using cancer distress screening measures. Third, the sample size was small. We calculated the sample size before starting this study. However, the effect size of the outcome variables may be smaller than previously thought. Together, these factors may limit the generalizability of the findings. Fourth, the results of crossover points, the 18.27 IES-R-J score, may not be generalizable because of the exploratory statistics after meeting the assumption of homogeneity of the regression slopes. Fifth, the improvements in the patients' partners coping strategies may only reflect traditional sociocultural marital relationships in East Asia. O!PEACE therapy may be more helpful for couples with a more supportive and equal marital cultural background.

In conclusion, O!PEACE psycho-educational therapy with only two precancer treatment sessions can reduce cancer-related PTSS and improve oncofertility knowledge and marital relationships for young adult patients with BC. It can also reduce the stress-coping strategies of giving up and blaming others and escape-avoidance in their partners. Couples may consider and decide on fertility preservation and cope with cancer-related PTSS using supportive marital communication through O!PEACE psycho-educational therapy.

AUTHOR CONTRIBUTIONS

Tomoe Koizumi: Conceptualization, investigation, methodology, project administration, data analysis, writing—original draft, and writing—review and editing. **Yodo Sugishita:** Investigation, methodology, project administration, and writing—review and editing. **Yuki Suzuki-Takahashi:** Investigation, methodology, project administration, and writing—review and editing. **Kazuko Nara:** Investigation, methodology, project administration, and writing—review and editing. **Tomoko Miyagawa:** Investigation, methodology, project administration, and writing—review and editing. **Misako Nakajima:** Investigation, methodology, project administration, and writing—review and editing. **Kouhei Sugimoto:** Investigation, project administration, and writing—review and editing. **Manabu Futamura:** Investigation, project administration, and writing—review and editing. **Tatsuro Furui:** Investigation, project administration, and writing—review and editing. **Yasushi Takai:** Investigation, project administration, and writing—review and editing. **Hiroshi Matsumoto:** Investigation, project administration, and writing—review and editing. **Hideko Yamauchi:** Investigation, project administration, and writing—review and editing. **Shinji Ohno:** Investigation, project administration, and writing—review and editing. **Akemi Kataoka:** Investigation, project administration, and writing—review and editing. **Kiyotaka Kawai:** Investigation, project administration, and writing—review and editing. **Eisuke Fukuma:** Investigation, project administration, and writing—review and editing. **Hiroko Nogi:** Investigation, project administration, and writing—review and editing. **Koichiro Tsugawa:** Investigation, project administration, and writing—review and editing. **Nao Suzuki:**

Supervision, conceptualization, methodology, project administration, data analysis, and writing—original draft, and writing—review and editing.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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