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Full-length Article

Peri-operative individually tailored psychological intervention in breast cancer patients improves psychological indices and molecular biomarkers of metastasis in excised tumors

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ABSTRACT

Perioperative stress and inflammatory signaling can invigorate pro-metastatic molecular processes in patients' tumors, potentially worsening long-term survival. Yet, it is unknown whether pre-operative psychotherapeutic interventions can attenuate such effects. Herein, three weeks before surgery, forty women diagnosed with stage I-III invasive ductal/lobular breast carcinoma were randomized to a 6-week one-on-one psychological intervention (6 meetings with a medical psychologist and bi-weekly phone calls) versus standard nursing-staff-attention. The intervention protocol was individually tailored based on evaluation of patients' emotional, cognitive, physiological, and behavioral stress response-patterns, and also included psychoeducation regarding medical treatments and recruitment of social support. Resected primary tumors were subjected to whole-genome RNA sequencing and bioinformatic analyses, assessing a priori hypothesized cancer-relevant molecular signatures. Self-report questionnaires (BSI-18, Hope-18, MSPSS, and a stress-scale) were collected three (T1) and one (T2) week before surgery, a day before (T3) and after (T4) surgery, and three weeks (T5) and 3-months (T6) following surgery. The intervention reduced distress (GSI), depression, and somatization scores (BSI-18: $p < 0.01$, $p < 0.05$, $p < 0.05$; T5 vs. T1). Additionally, tumors from treated patients (vs. controls) showed: (i) decreased activity of transcription control pathways involved in adrenergic and glucocorticoid signaling (CREB, GR) ($p < 0.001$), pro-inflammatory signaling (NFkB) ($p < 0.01$), and pro-malignant signaling (ETS1, STAT and GATA families) ($p < 0.001$, $p < 0.01$, $p < 0.005$); (ii) increased M1 macrophage polarization ($p < 0.05$), and $CD4^+$ T cell activity ($p < 0.01$); and an unexpected increase in epithelial-to-mesenchymal-transition (EMT) signature ($p < 0.005$). This is the first randomized controlled trial to show beneficial effects of a psychological perioperative intervention on tumor pro-metastatic molecular biomarkers.

1. Introduction

The perioperative period, days to weeks before and after surgery, can exert a profound impact on long-term cancer outcomes, despite its short duration (Matzner et al., 2020; Hiller et al., 2018; Horowitz et al., 2015). This perioperative period entails heightened risks for cancer progression, but also provides unexploited opportunities to improve resistance to cancer metastasis (Horowitz et al., 2015; Ben-Eliyahu, 2003; Glasner et al., 2010; Chambers et al., 2002; Riggi et al., 2018), the leading cause of cancer mortality.

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Stress and inflammatory signaling, prevalent during the perioperative period, were shown to promote multiple pro-metastatic molecular pathways (Eckerling et al., 2021; Ricon et al., 2019; Haldar and Ben-Eliyahu, 2018; Manou-Stathopoulou et al., 2019; Shaashua et al., 2017; Haldar et al., 2020). Both psychological (e.g., fear, anxiety, depression, distress) and physiological (e.g., tissue damage, anesthetic agents) factors can induce stress-inflammatory signaling through excess secretion of epinephrine (Epi) and norepinephrine (NE), corticosteroids, opioids, prostaglandins (PGs), and other inflammatory and immune modulating factors (Horowitz et al., 2015).

Importantly, recent Pharmacological randomized clinical trials (RCTs) in breast and colorectal cancer patients showed that the blockade of adrenergic- and/or COX2 signaling can beneficially affect pro-metastatic gene expression in the excised tumors (e.g., NFkB, STAT, and GATA, transcriptional activity, EMT and M1-M2 polarization) (Shaashua et al., 2017; Haldar et al., 2020), and can improve 5-year disease-free-survival in colorectal cancer patients (Hiller et al., 2018; Horowitz et al., 2015; Eckerling et al., 2021; Ricon-Becker et al., 2023). Notably, drug beneficial impacts on pro-metastatic transcription pathways were observed following 5–7 days of pre-operative treatment.

In breast cancer patients, heightened distress may emanate from multiple stressors. These include fears related to diagnosis, adjuvant treatments, surgical procedures, medical uncertainties, anticipated post-operative disabilities, strain on relationships, and changes in physical appearance (Levett et al., 2016; Garssen et al., 2010; Katsohiraki et al., 2020). Importantly, multiple cancer related psychological stressors were shown to be effectively targeted by several psychological interventions (Antoni et al., 2006; Andersen et al., 2007; Andersen et al., 2008; Antoni et al., 2009; Gudenkauf et al., 2015). Within the domain of psychotherapeutic interventions for stress, several studies suggest that in certain circumstances, individually-tailored treatment protocols may be more feasible and effective than one-size-fits-all interventions (Hanalis-Miller et al., 2022), especially during the short but critical perioperative period. In cancer patients, most psychological interventions have been initiated a few weeks postoperatively through group sessions (Hanalis-Miller et al., 2022). Thus, these approaches may not be optimal in targeting individually diverse sources of stress, unique to the perioperative period, nor exploiting this short but critical period to improve prominent pro-metastatic biological processes. Here we present a novel perioperative individually-tailored stress-management intervention in breast cancer patients, which we have constructed based on existing treatment modules. We employed standard and new questionnaires to identify individual sources of perioperative stress, and to characterize stress responses and psychological states along the perioperative period. In a RCT of 40 breast cancer patients from a single medical center in Israel, we examined the efficacy of this intervention on (i) excised tumor molecular biomarkers known to reflect neuroendocrine, inflammatory, and pro-metastatic activity, as primary outcomes of the study, and on (ii) psychological measures of distress and resilience, as secondary outcomes. We hypothesize that the intervention will decrease (i) transcription activity related to stress-signaling (GR, CREB), (ii) pro-inflammatory signaling, and pro-metastatic signaling (NFkB, AP1, STAT family, GATA family, and ETS1), (iii) M2/M1-polarization, and (iv) Epithelial-to-mesenchymal transition (EMT). Regarding secondary outcomes, we hypothesize that the intervention will reduce psychological distress (perceived stress, somatization, depression, anxiety) and fatigue, and will increase hope and perceived social support.

2. Material and methods

2.1. Participants

Forty women, ages 40–80 (M = 61, SD = 10.42), scheduled for curative surgery as a first line treatment to remove a single stage I-III invasive ductal or lobular carcinoma tumor were recruited to the study. Recruitment was conducted at a single medical center in Israel (Beilinson Medical Center) between April 2018 and November 2021 (see CONSORT flowchart, Fig. 1). One-hundred-and-ninety patients were screened, 58 met inclusion criteria, and 40 provided informed consent. The study was approved by the Tel-Aviv University Institutional Ethics Board and by the Beilinson Medical Center Helsinki Committee (Israeli Clinical Trial Registry number: MOH_2017-08-10_000705).

Inclusion Criteria: (1) Women scheduled to undergo surgery of a single, stage I-III, invasive ductal or lobular carcinoma tumor with curative intent; (2) Age between 20 and 80 years-old.

Exclusion Criteria: (1) Patients with metastatic disease, known prior to surgery; (2) Patients who have undergone neoadjuvant treatment; (3) Patients with history or concomitant malignant disease of any type other than breast cancer; (4) Patients who were treated with chemotherapy in the last 10 years. (5) Any known immune system failure; (6) Current endorsement of psychosis, suicidality, major depressive disorder, or panic disorder.

2.2. Procedure

Women were randomized in blocks of 4, with a 1:1 ratio, to psychological intervention (n = 20) versus standard nursing staff attention (n = 20) (control condition). All women participated in a first diagnostic meeting (T1), with a licensed medical psychologist with 10 years of experience in preparing breast cancer women for surgery (Tsipi Hanalis-Miller; T.H.M.). In this first meeting dominant stress-response profiles were assessed in all participants (intervention and control). Psychological measures were collected at (T1) 2–3 weeks before surgery upon initial admission to the surgical unit (Baseline), (T2) 1-week before surgery, (T3) a day before surgery, (T4) the morning after surgery, (T5) 3–4 weeks after surgery, preparing with the patient to receive the pathology report, and (T6) ~ 3 months following the surgery. Data was collected and de-identified stored. Tumor samples of both groups were collected following surgery for whole genome RNA profiling (see below).

2.3. The intervention

A more comprehensive description of the protocol (Hanalis-Miller et al., 2024) and its perioperative implementation is provided in the Supplementary. The protocol included 6 face-to-face/remote (Zoom/-phone) meetings with the study psychologist (T.H.M) (15–90 min each meeting), as well as additional bi-weekly phone calls (Fig. 2). Tailoring to each patients' needs was based on an interview at T1, assessing previous personal/familial experience with surgery and cancer, and identifying dominant stress-response profiles using the stress response questionnaire (SRQ) (Jacoby et al., 2021). According to this assessment, the intervention mainly targeted cognitive, physiological, emotional, or behavioral response-patterns. Additionally, the intervention provided tools to address medical treatment-related sources of stress (e.g., effective communication with medical staff), and addressed the importance of social support and ways to enhance it. During the first session, the goal of the intervention was described to each woman in the intervention group as guiding her towards achieving a balanced sympathetic activation pattern, thus arriving to surgery better prepared, both physically and mentally.

Dominant stress-response patterns were addressed as follows: (i) Emotional distress by emotional disclosure (Chaikin et al., 1975; Ignatius and Kokkonen, 2007; Farber, 2006; Sloan, 2010; Zhang et al., 2019; Zhang et al., 2021; Smyth et al., 2012); (ii) Cognitive stress responses by using self-talk (Miechenbaum, 1977; Meichenbaum, 1995; Kross et al., 2014; Hamilton et al., 2011; Babakhanloo et al., 2017); (iii) Physiological arousal by diaphragmatic breathing (Garssen et al., 2010; Brown et al., 2013; Chen et al., 2017; Haase et al., 2005) and Progressive Muscle Relaxation (PMR) (Bernstein et al., 2000; Loh et al., 2021; Metin et al., 2019; Ravindra and Patel, 2021; Jacobsen, 1929); and (iv) Behavioral responses (e.g., anger) by employing behavioral

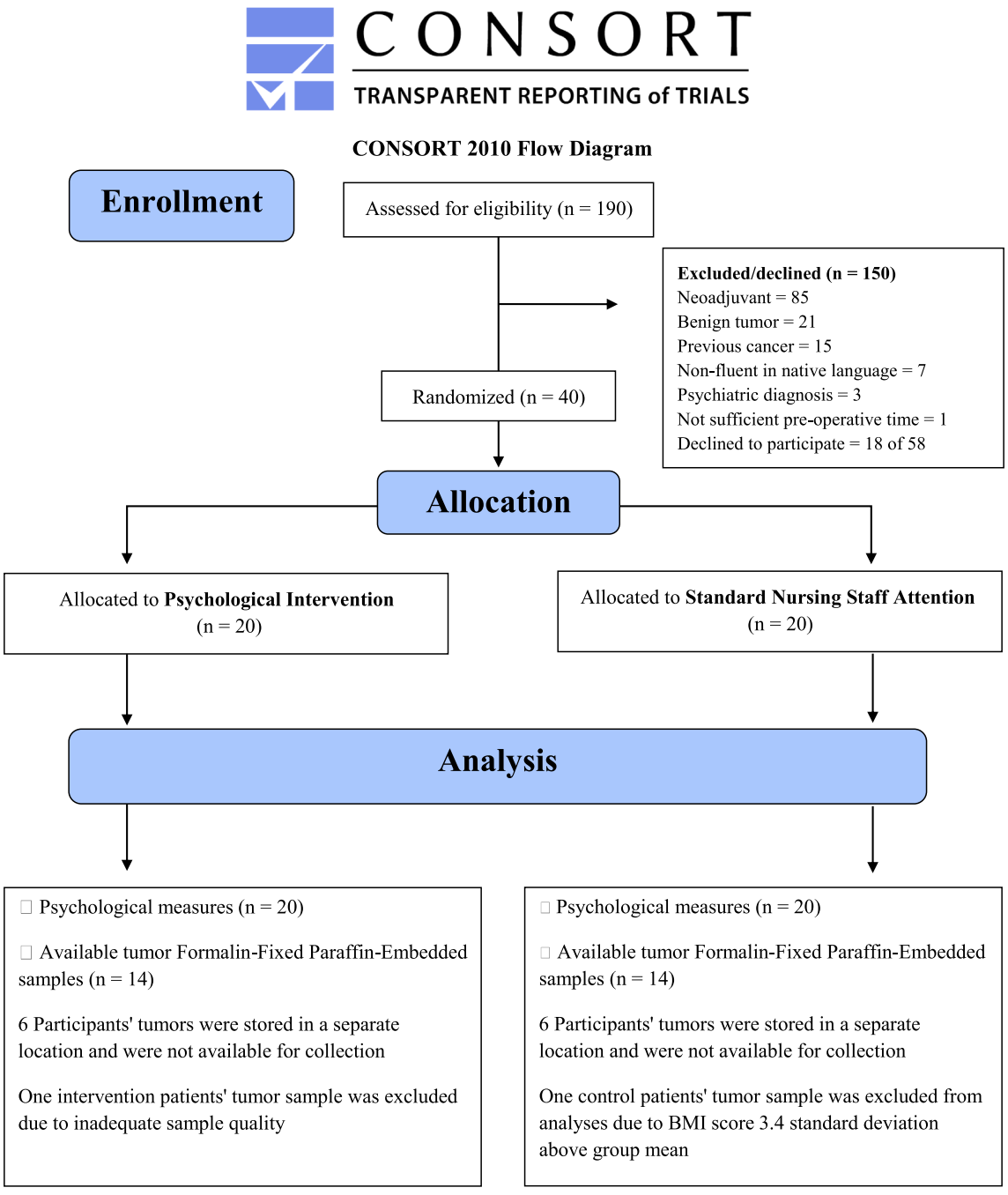

Fig. 1. CONSORT diagram.

regulation strategies in response to stress (Chapman and Gratz, 2015; Mauss et al., 2007; Tang et al., 2020).

Sessions 2&3 focused on encouraging home-training and fine-tuning of the intervention to each patient's needs. Guided imagery was offered to all patients (with 50 % patients interested in it). Guided imagery was designed to allow planning and preparing for the day of surgery, and any additional issue brought up by patients. Sessions 4 (day after surgery) was dedicated to planning and dealing with post-operative near-term challenges (e.g., pain, resuming roles at home and at work), and session 5 was dedicated to conclusion and to preparation for receiving pathology report results. At the end of session 5, participants need for additional psychological assistance was assessed. Information regarding additional resources for support and mental and emotional care were provided when warranted. 3-months after surgery, session 6 included a follow-up phone and debrief phone call.

Adherence rates were high with 16/20 patients participating in all 6 sessions. The median time for sessions was 90, 60, 30, 20, 20, and 20 min respectively for sessions 1 through 6. Also, for sessions 1, and 3–6, participants preferred meeting in-person with 100 %, 70.5 %, 77 %, 64.7 %, and 93.75 % of meetings conducted face-to-face (respectively). The remaining of the meetings were conducted via Zoom/phone. Meeting number 2 was not imbedded in the routine treatment schedule, and required arriving to the hospital especially for that meeting. For that meeting only 31.5 % of participants chose to meet in person. Additionally, participants in the intervention group utilized the option for phone calls between sessions with a median of 6 phone calls per patients (range 1–11).

Control: Control group patients received the standard nursing staff attention (treatment-as-usual) and adhered to the same psychological assessment schedule as the intervention group.

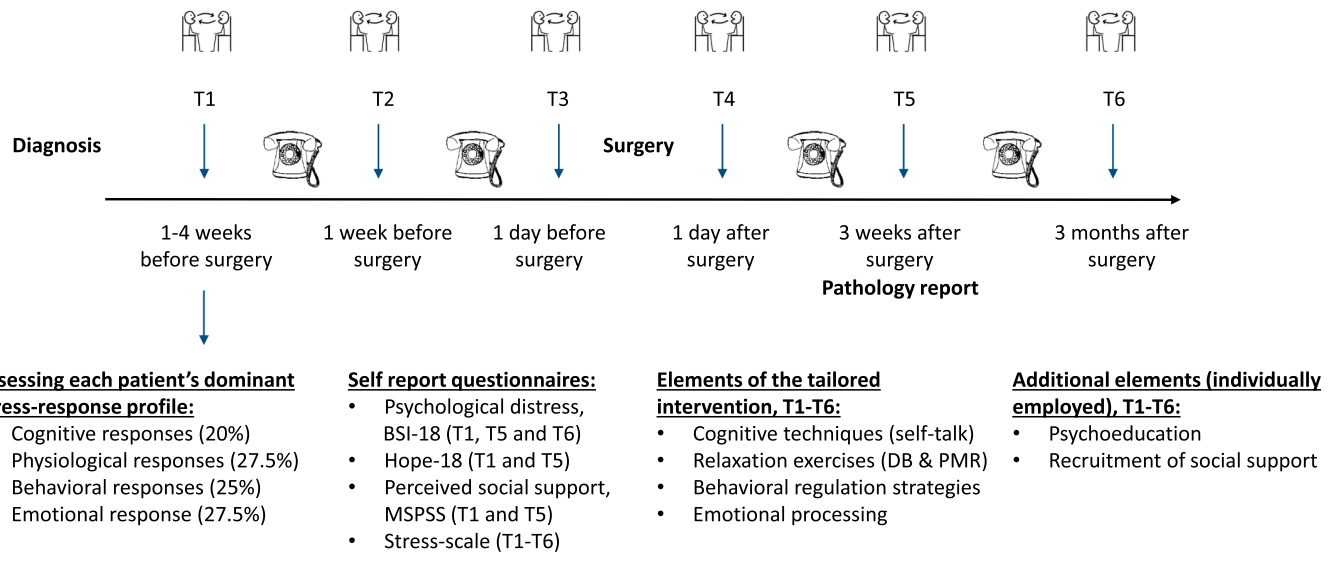

Fig. 2. The intervention timepoints of interest.

3. Measures

3.1. Self-report questionnaires:

3.1.1. Demographic Information (assessed at T1)

Participants were asked to complete a demographic questionnaire (see Table 1). Patients self-report demographics were verified in patients' medical files.

3.1.2. Psychological measurers

3.1.2.1. Stress level scale (assessed at all time points T1-T6). All participants were asked to rank their stress level during the last 24 h on a 1–100 scale (1 indicating very low stress levels and 100 indicating extreme stress). This scale was used specifically for this study as an adaptation of the visual analogue scale of stress (Monk, 1989). The control group was not assessed at T2, to reduce burden.

3.1.2.2. Hope (assessed at T1 and T5). To assess hope we used the Hope-18 questionnaire (Jacoby and Goldzweig, 2014). In addition to a global assessment of hope, this questionnaire included three subscales indicating different sources of hope: (a) intrapersonal (nine items; i.e., "At difficult times in my life, I trust myself that I will be able to get out of the difficult situation"), (b) Interpersonal (five items; i.e., "I draw strength from the relationships in my life"), and (c) Transpersonal (four items; i.e.," I have a belief that gives me a sense of comfort").

Scores were calculated based on mean of each of the 3 subscales, and for the entire set of questions (overall score). The Cronbach's alpha coefficient for the overall hope score was $\alpha = 0.87$ for session 1 (T1) and $\alpha = 0.88$ for session 5 (T5). For the intrapersonal scale it was $\alpha = 0.83$ (T1) and $\alpha = 0.76$ (T5). For the interpersonal scale it was $\alpha = 0.82$ (T1) and $\alpha = 0.90$ (T5). For the Transpersonal subscale it was $\alpha = 0.84$ (T1) and $\alpha = 0.86$ (T5).

3.1.2.3. Psychological distress BSI-18 (assessed at T1, T5, and T6). We used the short version of the Brief Symptom Inventory to measure psychological distress (BSI-18) (Derogatis and Melisaratos, 1983). In addition to a general scale of BSI (GSI – global severity index), this questionnaire examines three subscales of psychological and psychiatric problems: (a) Somatization (six items; i.e., "To what extent have you felt faint or experienced dizziness?"), (b) Anxiety (six items; i.e., "To what extent have you suffered from a feeling of stress?"), and (c) Depression (six items; i.e., "To what extent have you suffered from a feeling of depression?"). In the present study, the mean of the relevant items was computed for each subscale, and for the GSI. Cronbach's alpha coefficient for GSI was $\alpha = 0.92$, 0.94, and 0.95 for sessions 1, 5, and 6 (T1, T5, and T6), respectively. For the Somatization scale Cronbach's α were = 0.75, 0.73, and 0.88. For the Depression Cronbach's α were 0.75, 0.91, and 0.85 (T6). For the Anxiety scale Cronbach's α were 0.87, 0.88, and 0.90.

3.1.2.4. Perceived Social Support (assessed at T1 and T5). We used The Multidimensional Scale of Perceived Social Support (MSPSS) to examine subjective perception of the degree of social support (Zimet et al., 1990). The questionnaire consists of 12 statements divided into three subscales, each addressing a different source of support – (a) Family (four items; i.e.," My family is really trying to help me"), (b) Friends (four items; i.e., "I can trust my friends when problems arise"), and (c) Significant others (four items; i.e., "There is a person close to my heart who is near me when I need him"). The social support score is obtained by calculating the mean of the items for each of the scales, and a general score from the mean of all items. In the present study, the Cronbach's alpha coefficient for Total support was $\alpha = 0.88$ for session 1 (T1) and $\alpha = 0.93$ for session 5 (T5). For the Family scale $\alpha = 0.89$ (T1) and $\alpha = 0.92$ (T5). For the Friends scale $\alpha = 0.93$ (T1) and $\alpha = 0.91$ (T5). For the Significant other scale, $\alpha = 0.79$ (T1) and $\alpha = 0.94$ (T5). Support10 was deleted to increase T1 alpha.

3.1.2.5. Fatigue (assessed at T1 and T5). The fatigue-subscale (four items) from the Short Form Health Survey (SF-36) (Ware and Sherbourne, 1992) was used. In the current study the Cronbach's alpha coefficient was $\alpha = 0.74$ for session 1 (T1) and $\alpha = 0.80$ for session 5 (T5).

3.2. Molecular analysis of tumor samples

3.2.1. RNA extraction

Excised tumors are routinely stored as formalin-fixed paraffin-embedded (FFPE) blocks. FFPE blocks were available at the hospital pathological facility for 14 of the 20 patients in each group (6 participants tumors were stored in a separate location and were not available for collection). Five 5 μm sections from each block was used for gene expression profiling. RNA was extracted from suitable samples (Qiagen RNeasy following TissueLyser dissociation; excluding one sample due to insufficient RNA quality), reversed transcribed to complementary DNA (Lexogen QuantSeq 3′ FWD), and subjected to genome-wide transcriptional profiling on an Illumina NextSeq instrument (Lexogen Services

GmbH), targeting 5 million single-stranded reads per sample (achieved median 8.1 million). Reads were mapped to the GRCh38 human transcriptome using the STAR aligner (achieved average mapping rate = 98 %), quantified as gene transcripts per million mapped reads (TPM), floored at 1 TPM to suppress spurious variability, and log2 transformed for linear statistical model analysis as described below.

3.3. Data analysis and hypotheses

Baseline differences between groups on background variables and outcomes were examined via independent samples t-tests for continuous variables, and χ^2 tests for independence or Fisher's exact tests were used for categorical variables.

3.3.1. Self-report questionnaires

The analytic methods were aimed to test the a priori hypotheses that the psychological intervention would significantly reduce stress, psychological distress (somatization, depression, anxiety), and fatigue, and increase hope and perceived social support. Specifically, we hypothesize that the aforementioned psychological indices will improve relative to baseline levels (T1), in each of the later time points studied. We did not have a priori hypothesis regarding a main effect for time or for group, neither specific group differences in time-dependent trajectories. For each index (e.g., GSI) we analyzed data from all time points assessed. Prior to all analyses, the pattern of missing data was examined via a number of Little's Missing Completely At Random tests (MCAR) (Little, 1998). Treatment effects were first analyzed using a Linear Mixed Models (LMM) approach, with time and groups as fixed factors, and participant as a random factor, assessing Time × Group interactions. Following the recommendations of Hox and McNeish (Hox and McNeish, 2020:) for small samples, estimation was made via Restricted Maximum Likelihood (REML), and degrees of freedom were estimated with the Kenward-Roger approximation.

Given that the primary hypothesis was to examine the differences between the groups in the changes between T1 (baseline) and the later time points, significant LMM Time × Group interactions were followed by assessing the contrasts: Intervention (Ti-T1) – Control (Ti-T1), for each relevant Ti (i.e., for GSI, T5 and T6), employing Tukey correction for multiple comparisons. Within-group effect sizes were computed as the modeled mean difference between baseline and each post assessment (Post – T1) divided by the full sample baseline standard deviation. According to Cohen's conventions, effect sizes (*d*) of 0.20, 0.50 and 0.80 were deemed small, medium and large, respectively (Cohen, 1988).

Psychological outcomes data was analyzed based on the intent-to-treat (ITT) principle, which included all the participants in the analyses. Analyses were performed using JASP (version 0.18.3) with an alpha set at 0.05 for all statistical tests.

3.3.2. Tumor RNAseq analysis

Gene expression analyses were conducted in R (R version 4.1.1), implementing the same algorithms employed previously (Haldar et al., 2020), with standard least squares linear statistical model analyses quantifying differences in average expression (log2 TPM) between the intervention and control groups. As no demographic or disease related variable was significantly different between the groups, and given the modest sample size, we did not include any additional covariates in analyses. Differentially expressed genes (DEGs) showing > 2 fold-difference in average abundance between groups, and individual gene $p < 0.05$ (to screen out transcripts including outliners and low signal-to-noise ratios) were used as input into higher order level Transcript Origin Analysis (TOA (Cole et al., 2011), using established reference gene profiles assessing EMT (Gene Expression Omnibus GSE13915 (Choi et al., 2010), leukocyte subsets (GSE1133 (Su et al., 2004), and M1-M2 macrophage polarization (GSE5099 (Martinez et al., 2006). Additionally, bioinformatic analysis of transcription factor-binding motifs in promoters of the same differentially expressed genes were analyzed by the Transcription Element Listening System (TELiS, using TRANSFAC position-specific weight matrices (as described in Cole, 2005), as described previously (Cole et al., 2005; Lutgendorf et al., 2009). TELiS was used to assess the activity of transcription factors (TFs) previously shown to (i) be affected by β-blockade with/without COX2 inhibition, or (ii) involved in glucocorticoid and/or adrenergic signaling. Specifically, we tested the a priori hypotheses that the intervention would significantly reduce activity of pro-inflammatory TF: NFkB, AP-1; GATA1-GATA3, STAT1-STAT3, adrenergic responsive cAMP Response Element Binding Protein (CREB), and the neuroendocrine response factor GR).

3.3.3. Power

Sample size was assessed regarding our primary outcomes (molecular analyses of excised tumors), based on previous studies employing pharmacological interventions aimed at blocking β-receptors alone or together with NSAID (Shaashua et al., 2017; Hiller et al., 2020). Based on these studies and similar size effects, 12 valid samples per group will suffice to study the impact of the intervention on transcription pathways in tumor samples, with power of 0.8 and alpha of 0.05.

4. Results

4.1. Participants

There were no differences in baseline psychological, demographic and disease related indices between the two groups (see Table 1), both in the psychological measures analyses (n = 40), and for gene expression analysis (n = 26). For the whole-genome gene expression profiling analysis (n = 26; 13 in each group), two participants were excluded: 1 control patient due to BMI > 3-standard deviations above group mean, and 1 intervention patient due to insufficient RNA quality. Conducting the analyses without excluding the control patient strengthened the observed beneficial effects of the intervention on gene expression.

4.2. Psychological outcomes

For each psychological outcome we first present results of Little's MCAR test (Little, 1998) followed by the LMM analyses results, and Tukey contrasts corrected for multiple comparisons.

4.2.1. BSI-18

BSI-18 data was assessed at T1, T5 and T6, where missing data was 17.5 % of all values (Intervention and control respectively, T1, 0 %, 0 %; T5, 20 %, 35 %; T6, 30 %, 20 %). Results of Little's MCAR test (Little, 1998) were non-significant ($\chi^2(23) = 29.91$, $p = 0.466$). Therefore, data was deemed missing completely at random.

LMM analyses For GSI revealed a significant Time x Group interaction ($F(2, 57.19) = 4.18$, $p = 0.020$), without significant main effects of time or group. Tukey contrasts corrected for multiple comparisons indicated a significant group difference for T5-T1 ($z = 2.89$, $p = 0.008$), but not for T6-T1 (Fig. 3).

For the three subscales of the BSI-18, Somatization, Depression, and Anxiety, the Time x Group interactions were ($F(2, 59.08) = 2.89$, $p = 0.06$), ($F(2, 58.37) = 5.02$, $p = 0.01$), ($F(2, 56.31) = 1.75$, $p = 0.18$), respectively, and Tukey contrasts corrected for multiple comparisons indicated a significant group difference at T5-T1 for Somatization and Depression, but not Anxiety ($z = 2.36$, $p = 0.04$; $z = 3.17$, $p = 0.03$; $z = 1.87$, $p = 0.12$). No significant group differences for T6-T1 were evident in any of the subscales, as with GSI. Overall, whereas GSI and Depression showed significant Time by Group interactions and significant T5-T1 group differences, the other two subscales showed marginal or no significant effects, especially the Anxiety subscale (Fig. 3).

Examining the within-group effect sizes of (T5-T1) revealed small to medium reductions in all measures in the intervention group (Table 2). In the control group, on the other hand, medium to large increases in GSI, somatization, and depression were evident, and low increase in

Table 1
Clinical and demographic characteristics of the study groups at baseline.

Variable	RNA Seq participants			Entire sample		
	C (n = 13)	I (n = 13)	p	C (n = 20)	I (n = 20)	P
Age (Average (SD)	65.2 (10.8)	58.7 (9.9)	0.12	62.2 (11.3)	59.8 (9.5)	0.48
Weight (kg)	73.7 (13.2)	69.61 (9.2)	0.36	75.5 (20.5)	72.5 (12.9)	0.57
Height (cm)	159.08 (7.9)	163.7 (6.9)	0.13	160 (0.06)	1.63 (0.06)	0.12
BMI	29 (3.7)	26 (3.9)	0.06	29.3 (7.3)	27.1 (4.4)	0.24
Histological grade						
Grade 1	1	1	0.59	2	1	0.83
Grade 2	9	6		11	10	
Grade 3	2	5		3	5	
NA	1	1		4	4	
Tumor Diameter (Maximal cm (SD))	2.2 (1.5)	1.6 (0.7)	0.21	1.8 (1.4)	2.2 (1.9)[1]	0.58
ER Positive (average Score)	2.5 (0.8)	2.5 (0.9)	0.89	2.3 (0.9)	2.7 (0.7) [1]	0.19
PR Positive (average score)	1.8 (1.3)	1.8 (0.9)	0.95	1.6 (1.2)	1.5 (1.1) [1]	0.81
HER2/NEU (average score)	0.7 (0.9)	0.3 (0.7)	0.31	0.75 (0.9)	0.4 (0.7) [1]	0.19
Smoking						
No	13	12	0.99	18	17	0.49
Yes	0	1		2	2	
NA	0	0		0	1	
Alcohol Use						
No	13	13	0.99	20	18	0.237
Yes	0	0		0	1	
NA	0	0		0	1	
Sports						
None	4	4	0.89	5	8	0.59
Moderate	6	5		10	8	
Intensive	3	4		5	4	
Menopause						
Menopausal	10	9	0.82	13	14	0.91
Pre- Menopausal	1	2		4	3	
NA	2	2		4	3	
Tumor Location						
Bilateral	2	1	0.63	4	2	0.48
Left	8	7		11	10	
Right	3	5		5	7	
NA	0	0		0	1	
Surgical Resection						
Lumpectomy	10	13	0.22	15	15	0.47
Mastectomy	3	0		5	4	
NA	0	0		0	1	
Carcinoma Type						
DCIS	4	1	0.30	6	3	0.25
IDC	8	11		11	15	
Other	1	1		3	1	
NA	0	0		0	1	
Surgical Margin						
Free	12	12	0.76	18	17	0.83
Superior margin Involved	1	1		1	1	
NA	0	0		1	2	
Experience with surgeries in the past?						
No	4	6	0.42	4	6	0.52
Yes	9	7		15	14	
NA	0	0		1	0	
Physical Exercise						
No	6	6	0.84	7	8	0.84
Yes	6	7		12	12	

(*continued on next page*)

Table 1 (*continued*)

Variable	RNA Seq participants			Entire sample		
	C (n = 13)	I (n = 13)	p	C (n = 20)	I (n = 20)	P
NA	1	0		1	0	
Family status						
Married	8	8	1	12	15	0.31
Other	5	5		8	5	
Children						
No	1	2	0.593	1	2	0.6
Yes	12	10		19	17	
Religiousness						
Secular	8	6	0.12	12	11	0.76
Traditional	4	4		6	5	
Religious	0	3		1	3	
Very religious	1	0		1	1	
Religion						
Jewish	12	13	0.999	18	20	0.48
Other	1	0		2	0	
Working (Yes/No)						
No	5	4	0.999	8	5	0.31
Yes	8	9		12	15	
Surgery during the COVID pandemic (Pre/During)						
Pre-Covid	8	7	0.999	14	11	0.33
During Covid	5	6		6	9	

One patient's data is missing (surgery cancelled after completing baseline questionnaires).

anxiety. A difference of 0.5–1 SD between the two groups in these measures was evident at T5, and is considered a clinically significant difference (see Table 2).

4.2.2. Stress (assessed at T1, T3, T4, T5, and T6)

At T2, perceived stress scores were collected only from intervention patients (minimize patient's burden), and thus T2 data is not included in this analysis. Missing data was 20 % of all values (Intervention and control respectively T1, 5 %, 0 %; T2, 0 %, 0 %; T3, 10 %, 30 %; T4, 10 %, 25 %; T5, 15 %, 35 %; T6, 35 %, 30 %). Little's MCAR test (Little, 1998) yielded non-significant results, $\chi^2(59) = 60.61$, $p = 0.417$, indicating that data were missing completely at random.

LMM Analysis revealed a significant interaction between Time and Group (F (4, 111.43 = 3.32, $p = 0.013$), and a significant main effect of time ($F(4, 111.43) = 9.01$, $p < 0.001$), indicating reductions in stress scores from T1 to T4 ($p < 0.001$) and T1 to T6 ($p = 0.004$). Group did not exhibit a significant main effect. None of the Tukey contrasts corrected for multiple comparisons yielded significant group differences in any of the (Ti-T1) (Fig. 4).

This one-item questionnaire was significantly correlated at T1 with BSI-18 scores (Correlation with: Depression scale, $r = 0.64$, $p < 0.001$; Anxiety scale, $r = 0.72$, $p < 0.001$; Somatization, $r = 0.32$, $p = 0.043$; GSI, $r = 0.648$, $p < 0.001$).

4.2.3. Fatigue, hope, and perceived social support (assessed at T1 and T5)

For fatigue, hope and perceived social support, there were no statistically significant effects of the LMM model (See Supplementary, Figs. 6–8). Interestingly, all 9 indices suggest a descriptive difference at T5 between the intervention and control groups. These differences are of small effect sizes, yet the pattern across all 9 indices may indicate that another assessment with a larger sample is warranted.

4.3. Outcomes of whole-genome gene expression analyses

4.3.1. Primary analyses

Whole genome transcription profiling, using a cutoff of > 2-fold difference in transcript levels between treatment and control individuals, and $p < 0.05$, identified 450 differentially expressed gene transcripts (DEGs; 287 up-regulated and 163 down-regulated). DEGs were used only as input for higher level bioinformatics analyses of a-priori hypotheses reported below.

4.4. Effects of the psychological intervention versus control on adrenergic, glucocorticoid, pro-inflammatory, and pro-metastatic signaling

4.4.1. Adrenergic and glucocorticoid signaling

TELiS promoter-based bioinformatic analysis of intervention-associated DEGs indicated reduced activity of the CREB transcription control pathway, which mediates adrenergic signaling-induced gene expression (mean = −0.519 ± 0.121 standard error, P < 0.001; see Fig. 5A), as well as the glucocorticoid receptor (GR) transcription control pathway mediating HPA signaling (mean = −0.198 ± 0.039, P < 0.001).

4.4.2. Pro-inflammatory signaling

TELiS indicated decreased activity of the pro-inflammatory NFkB transcription control pathway (mean = −0.73 ± 0.255, P = 0.004; see Fig. 5A).

4.4.3. Pro-metastatic signaling

TELiS indicated reduced activity of the ETS1 transcription control pathway (mean = −0.59 ± 0.166, P < 0.001; see Fig. 5A), GATA1 and GATA2 activity (GATA1, mean = −0.23 ± 0.078, P = 0.002; GATA2,

Table 2
The effects of the psychological intervention versus control on measures of Brief Symptom Inventory (BSI-18).

BSI-18 Variable	T5-T1:			T6-T1:		
	Group contrast *p* value	Within-group *d*		Group contrast *p* value	Within-group *d*	
		Control	Interven		Control	Interven
GSI	0.008	0.56	−0.47	n.s.	0.59	0.19
Somatization	0.04	0.56	−0.34	n.s.	0.48	0.25
Depression	0.03	0.88	−0.49	n.s.	0.72	0.20
Anxiety*	n.s. 0.12	0.12	−0.44	n.s.	0.39	0.09

Results of group comparisons of (T5-T1) and (T6-T1) following LMM analyses. Within-group *d* is an effect size: According to Cohen's conventions, *d* of 0.20, 0.50 and 0.80 are deemed small, medium and large, respectively. GSI = Global Severity Index. Interven = Intervention. * LMM interaction for Anxiety was n.s., $p = 0.18$.

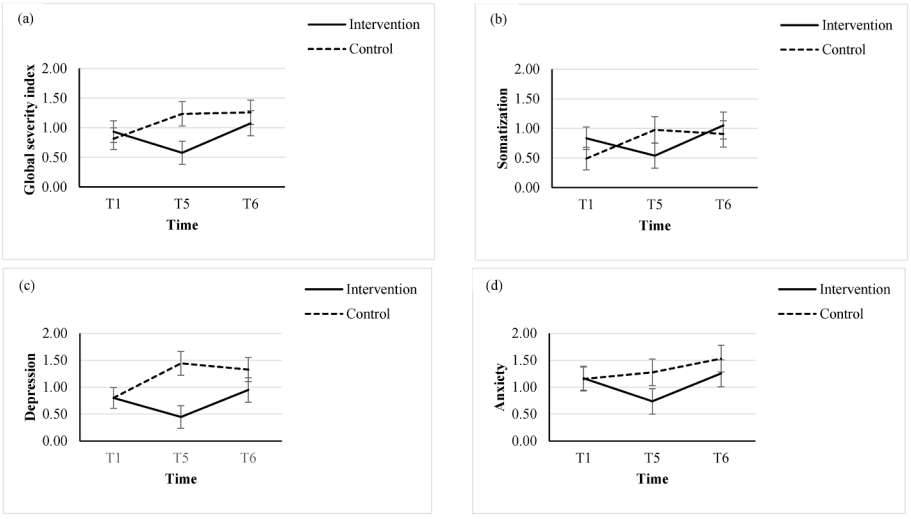

Fig. 3. The effects of the psychological intervention versus control on measures of brief symptom inventory (BSI). The effects of perioperative stress-management on: (a) Global severity index (GSI), (b) Somatization, (c) Depression, and (d) Anxiety. Measures were taken only on T1, T5, and T6, and outcomes are presented as Z-score ± SEM.

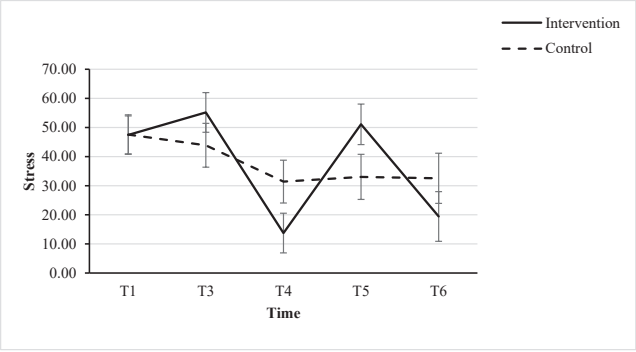

Fig. 4. The effects of the psychological intervention versus control on self-reported stress levels. The effects of perioperative stress-management on self-reported stress score (1–100, lowest to highest stress). Measures were taken in both groups on all time points except for T2. Outcomes are presented as Means ± SEM.

mean = −0.27 ± 0.091, P = 0.002), reduced activity of the STAT family control pathway (STAT1, STAT3-STAT6; mean = −0.092 ± 0.027, P < 0.01), and increased activity of AP1 transcription control pathway (mean = 0.3 ± 0.1, P = 0.002).

4.5. M1-M2 polarization

TOA analyses mapped DEGs to previously derived gene sets derived from M1 vs. M2 macrophage samples (GSE5099 (Martinez et al., 2006). Tumors from patients in the intervention group showed upregulation of M1-related gene-expression (Up-regulated genes: M1 diagnosticity score: mean = 0.5172 ± 0.16; P = 0.015; see Fig. 5B).

4.6. Epithelial-mesenchymal transition

In parallel TOA analyses, tumors from intervention group participants showed greater expression of genes characteristic of mesenchymal differentiation (GSE13915 (Choi et al., 2010) (diagnosticity z-score: mean = 0.117 ± 0.04, P = 0.003; see Fig. 5D).

4.7. Tumor-associated leukocyte activity

In parallel TOA analyses involving isolated leukocyte subpopulations (GSE1133 (Su et al., 2004), results indicated up-regulated transcriptional activity of $CD4^+$ T-cells (diagnosticity z-score: mean = 0.09 + 0.035, P = 0.0071; see Fig. 5C), and down-regulation of genes derived from dendritic cells (diagnosticity z-score: mean = 0.066 + 0.03, P = 0.0276).

5. Discussion

This is the first study to show that a pre-operative psychological intervention in cancer patients can favorably impact the molecular profile of excised primary tumors. Results of tumor transcriptional profiling indicated reduced activity of pro-metastatic transcription control pathways (ETS1, GATA1 and GATA2, STAT family), reduced M1-M2 polarization, increased $CD4^+$T cells activity, reduced pro-inflammatory transcription activity (NFkB), and decreased GR and

CREB control pathways, which mediate glucocorticoid and adrenergic signaling. These results can be considered broadly favorable, as all these changes are associated or causally linked with reduced malignant potential and reduced recurrence in breast cancer (Shaashua et al., 2017; Haldar et al., 2020; Hiller et al., 2020). Unexpectedly, an elevation in mesenchymal gene expression was also observed, contrary to previous effects observed in pharmacological studies (Shaashua et al., 2017; Hiller et al., 2020). Consistent with the intended psychological objectives of this intervention, analyses of psychological measures showed reduced distress, depression, and somatization from baseline to 3 weeks post-surgery.

Currently, there is a paucity of randomized controlled perioperative psychological intervention trials assessing gene expression in excised tumors from breast cancer patients. In recent pharmacological studies in breast and in colorectal cancer patients, a β-adrenergic blocker starting 5–7 days before surgery, alone (Hiller et al., 2020) or in combination with a COX2 inhibitor (Shaashua et al., 2017; Haldar et al., 2020), caused similar impacts to those observed herein on excised tumors. Moreover, in colorectal cancer patients, the combined drug treatment also improved 5-year DFS (although the study was not powered to assess long-term outcomes) (Ricon-Becker et al., 2023). Notably, the pre-operative part of the psychological intervention used herein has significantly reduced tumor molecular signaling directly related to adrenergic, HPA, and inflammatory responses, in addition to decreasing pro-metastatic signaling. These outcomes suggest the pre-operative physiological efficacy of the psychological intervention, as well as its potential

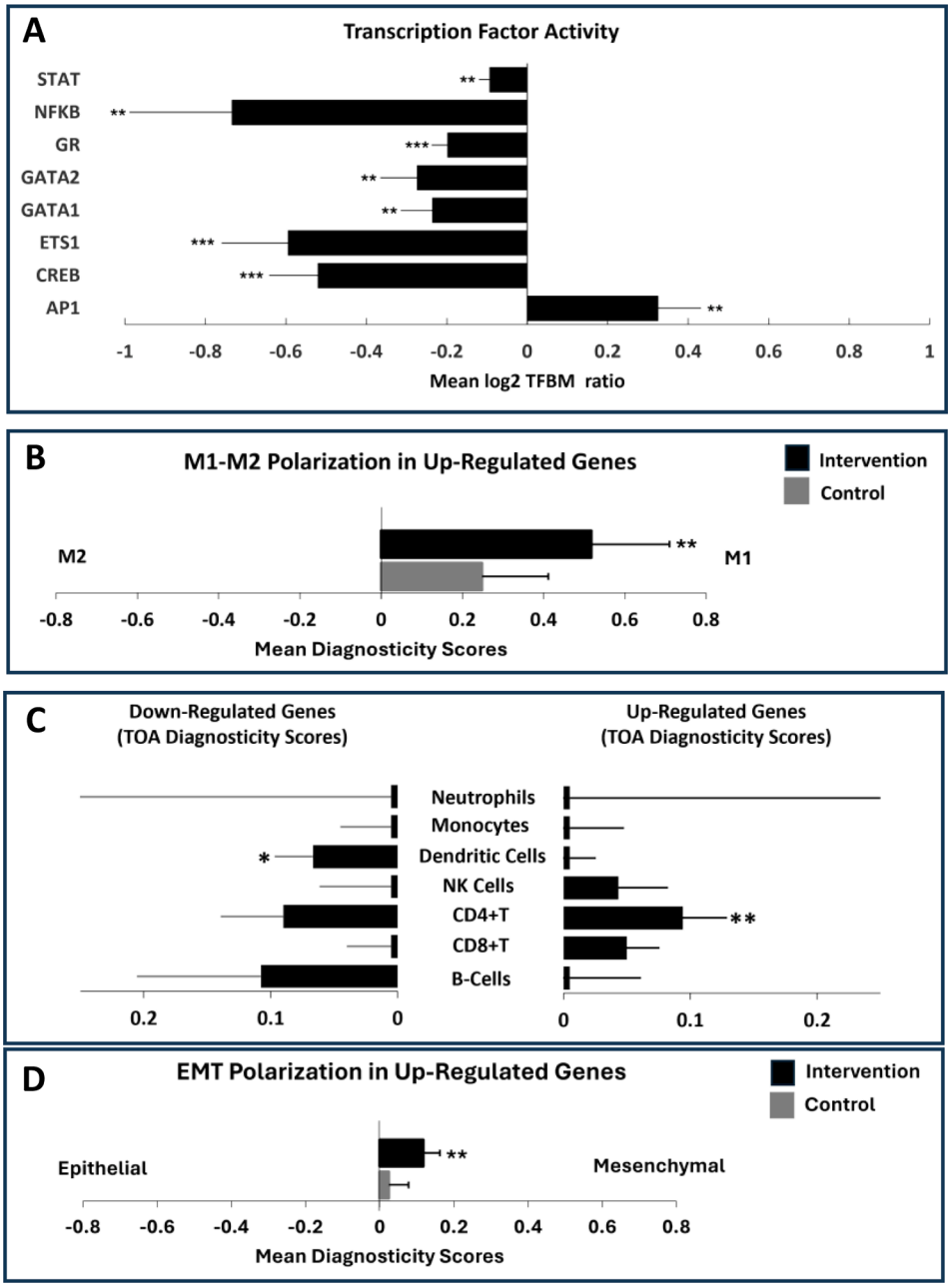

Fig. 5. Differences in the molecular characteristics of primary tumors between the psychological intervention and control groups. The effects of pre-operative stress-management on molecular characteristics of primary tumors. (A) Activity of transcription control pathways, based on analyses of transcription factor binding motifs (TFBMs) in promotors of differentially expressed genes. (B-D) Transcript origin analysis (TOA) was used to assess the effects of the intervention on: (B) M1-M2 polarization, (C) expression of genes indicative of presence of neutrophils, monocytes, dendritic cells, NK cell, T cell, and B cell, and (D) epithelial-to-mesenchymal transition (EMT). *$p < 0.05$, **$p < 0.01$, ***$p < 0.005$, ****$p < 0.0001$.

clinical significance.

In view of the impact of the psychological intervention on gene expression, the effects on GR and CREB TFs activity are intriguing. The reduced CREB activity, indicating reduced adrenergic signaling within the tumor and/or its microenvironment, could emanate from local sympathetic innervation (through nor-adrenaline), or systemic SNS signaling (through adrenaline). The effects on GR TF activity would likely originate from systemic HPA signaling, and was not evident in the pharmacological studies based on β-adrenergic blockade (Shaashua et al., 2017; Hiller et al., 2020). These findings provide molecular evidence for top-down efficacy of the treatment, through psychological regulation of HPA and SNS activity, and indicate a potential unique advantage for this psychological treatment through reducing HPA signaling.

Contrary to our hypotheses, gene expression analysis indicated an increase in EMT polarization in tumor samples from the intervention group (i.e., up-regulated gene expression associated with a mesenchymal cell phenotype). Also, higher level analysis indicated upregulated activity of the AP-1 pathway. Both outcomes are associated with negative prognosis (Liu et al., 2002; Shen et al., 2008; Zanconato et al., 2015). These findings are unexpected, as three previous pharmacological studies indicated that β-blockade, with or without a COX2 inhibition, reduced EMT gene expression (Shaashua et al., 2017; Haldar et al., 2020; Hiller et al., 2020), and one of these also reported down-regulation of the AP-1 pathway (Hiller et al., 2020). Interestingly, exploratory higher-level TFs analysis indicated that the activity of the three TFs which are considered prominent drivers of EMT were either reduced (ZEB1), as a priori expected, or unchanged (SLUG, TWIST1, TWIST2).

The 6-week, ~12-hour, psychological intervention employed herein was designed to specifically target perioperative stress responses of breast cancer patients. The intervention did not significantly affect perceived social support, fatigue, and hope, although the sample size is not sufficient to negate moderate impacts in these indices. Notably, similar psychological indices were positively affected by psychological group interventions which were initiated 2–10 weeks following surgery, and conducted throughout several months (Antoni et al., 2006; Andersen et al., 2008; Andersen et al., 2004; Bower et al., 2015; Stagl et al., 2015; Boyle et al., 2017; Bower et al., 2021). These group interventions were also effective in improving breast cancer patients' immune status (Andersen et al., 2004; McGregor and Antoni, 2009; Antoni et al., 2012; Boyle et al., 2019), and some even suggested beneficial effects on survival (Eckerling et al., 2021; Andersen et al., 2008; Andersen et al., 2010; Stagl et al., 2015) (for extensive review see: Eckerling et al. (2021). Importantly, in the current study statistically and clinically significant group differences (0.5–1 SD) in the BSI-18 scales were evident three weeks postoperatively. However, these differences were not evident two months following treatment ending (T6, three months postoperatively), suggesting a short-term reported (perceived) effects of the intervention. Thus, we suggest that future studies should consider integration of psychological short perioperative intervention with post-operative longer interventions, and in addition employ shorter perioperative pharmacological interventions, leveraging the specific advantages of each approach. Specifically, psychological interventions address stressors of multiple psychological origins, a variety of stress responses, and additional important psychological factors (e.g., fatigue) that are not targeted by the specific pharmacological intervention discussed above (Shaashua et al., 2017; Hiller et al., 2020). Additionally, psychological interventions, unlike pharmacological ones, can be employed in the great majority of patients, and for a prolonged duration, with few contraindications or adverse effects. On the other hand, pharmacological interventions can reduce adrenergic and prostanoid responses that are directly induced by the surgical procedures and tissue damage. Such responses are directly related to the impact of anesthetic agents, hypothermia, tissue injury, nociception, and some aspects of inflammatory responses, which we believe are less likely to be tempered by psychological interventions alone but occur during the critical perioperative period. These hypotheses should be tested in future studies.

The small sample size merits caution in interpreting our results. Notably, the sample size did not allow for including additional covariates in our statistical analyses, which could have enabled us to account for differential effects of the intervention based on different disease stages, tumor characteristics (e.g., triple negative), or demographic and psychological baseline characteristics of the patients. Additionally, as different intervention modules were tailored for specific patients' needs, it is difficult to assess the effectiveness of each treatment module. Future larger studies could implement the standardized tailoring process to replicate this study, and to potentially assess which treatment module is most effective for different types of patients.

In sum, this randomized-controlled trial is the first to show significant beneficial effects of a talk-intervention on molecular characteristics of excised breast tumors. Our results provide an impetus for larger studies to test the effects of this approach on short- and long-term cancer outcomes, in breast cancer patients and in other cancer types.

CRediT authorship contribution statement

Tsipi Hanalis-Miller: Conceptualization, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Itay Ricon-Becker:** Conceptualization, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Nahida Sakis:** Investigation, Writing – original draft, Writing – review & editing. **Estherina Trachtenberg:** Investigation. **Frida Ohayon:** Resources. **Sonya Wadhawker:** Resources. **Yehudit Birnboim:** Resources. **Ada Magen:** Investigation. **Eran Sharon:** Resources. **Ricardo Tarrasch:** Data curation, Formal analysis. **Gil Goldzweig:** Conceptualization. **Steve W. Cole:** Formal analysis, Resources, Software. **Rebecca Jacoby:** Conceptualization, Methodology, Project administration. **Shamgar Ben-Eliyahu:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be available upon request.

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Appendix A. Supplementary data

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