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Effects of BEAT Cancer randomized physical activity trial on subjective memory impairments in breast cancer survivors

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Background

Cancer Related Cognitive Impairment (CRCI) has been reported in up to 83% of breast cancer survivors (BCS) and for durations up to 20 years after treatment ends.[1] Changes in cognition can be slight or intense, short- or long-term, and fixed or progressive.[2] Although cancer and its treatments may impair cognitive functioning across multiple domains (e.g., executive function, attention, processing speed),[2] memory deficits may be particularly prevalent.[1] BCS have exhibited decrements in visual and verbal working memory and reported more memory complaints after treatment.[3] BCS have also performed more poorly on memory recall tasks when compared with non-cancer, age-matched controls.[4]

Rodent studies have suggested a protective effect of aerobic physical activity (PA) on cognitive impairment after chemotherapy.[5] Within the few studies to examine relationships in human models, significant associations between PA and memory have been observed.[4] This evidence suggests PA may represent an effective treatment for CRCI. The purpose of the present study was to examine the effects of a PA intervention on frequency of self-reported memory impairments in BCS at post-intervention (month 3) and follow-up (month 6) compared to BCS assigned to Usual Care (UC).

Methods

Details of the trial are described elsewhere.[6] Low-active BCS were randomized to Better Exercise Adherence after Treatment for Cancer (BEAT Cancer), a 3-month social cognitive theory-based behavioral intervention, or UC. BEAT Cancer employed a tapered schedule in which participants attended twelve supervised exercise sessions over six weeks, followed by home-based exercise and biweekly face-to-face counseling sessions for six weeks. During the first nine weeks, participants also attended six group discussion sessions targeting social

Conflict of Interest

The authors declare no conflicts of interest.

Trial Registration: United States ClinicalTrials.gov identifier NCT00721565

cognitive constructs. All participants (BEAT Cancer and UC) received copies of American Cancer Society materials related to healthy eating and PA for cancer survivors. Memory outcomes were added after the trial's inception because of growing scientific evidence supporting its importance. Hence, participants included in this study represent a subsample of the BEAT Cancer trial (N=85 of 222).[6] Participants signed the Institutional Review Board approved informed consent prior to their participation (University of Alabama at Birmingham, Institutional Review Board for Human Use Protocols: X121218020 and F121114008).

Outcome data were collected at baseline, post-intervention (month 3), and 3-month follow-up (month 6). Demographic and clinical information are reported in Table 1. The 10-item Frequency of Forgetting Scale[7] was summed to assess subjective memory impairment and four memory subscales (General Memory, Frequency of Forgetting, Frequency of Forgetting when Reading, and Remembering Past Events). Lower ratings signify greater memory impairment.

Mixed effects models were used to test the effects of BEAT Cancer compared to UC on frequency of forgetting across the intervention (month 3) and follow-up (month 6). Baseline memory ratings, study site, and significant covariates identified in our previous work[6] were included in the analyses (Table 2).

Results

A summary of the results is detailed in Table 2. Adjusting for baseline memory and covariates, significant differences favoring BEAT Cancer were observed at post-intervention in relation to overall frequency of forgetting, $t(89.6)=2.33$, $p=0.02$, frequency of forgetting subscale, $t(95.8)=2.13$, $p=0.04$, and remembering past events, $t(100) = 3.18$, $p=0.002$. Group differences in remembering past events were maintained at follow-up $t(122)=2.43$, $p=0.02$. No differences in general rated memory and frequency of forgetting when reading were observed, p's>0.40.

Discussion

Compared with UC, BEAT Cancer improved select memory outcomes post-intervention; however, most group differences were not maintained at follow-up. These results parallel those observed in relation to objectively measured PA in our previous study.[6] This suggests regular PA may positively influence memory impairments in BCS, but activity must be maintained in order for improvements in memory to continue. Positive associations between BCS' PA participation and executive functioning, visual-spatial processing, attention, working memory, verbal memory, and memory recall have been observed in other studies.[4,8] Yet, few have investigated associations longitudinally or within the context of a randomized trial.[9] Exercise interventions targeting cognitive function in cancer survivors warrant further study.

Despite decreases in objectively measured PA among BEAT Cancer participants across follow-up, more BEAT Cancer participants met PA recommendations at post-intervention and follow-up compared to UC.[6] These data warrant more research investigating dose-

response relationships between PA and memory. Specifically, whether the public health guidelines for PA are sufficient to remediate cognitive dysfunction is not known. Future prospective and experimental studies that quantify PA doses associated with different levels of memory function in BCS are needed.

Group differences in subjective memory impairment were observed at post-intervention even after adjustment for chemotherapy and hormonal therapy, suggesting PA may benefit BCS' cognitive health regardless of treatments received. Similarly, Mackenzie et al.[8] reported that women with higher cardiorespiratory fitness and faster heart rate recovery performed better on a working memory task, regardless of treatment or disease status (chemotherapy versus radiation only versus healthy control). Studies have indicated that breast cancer patients undergoing chemotherapy and hormonal therapy suffer greater cognitive deterioration when compared with non-cancer controls and patients undergoing radiation therapy or surgery alone.[3,10] Given the well-documented, long-term neurotoxic effects of adjuvant therapies, treatments to ameliorate negative cognitive sequelae are needed. Research testing receipt, dosage, and type of primary and adjuvant therapies as moderators of PA's effects on memory may identify for whom PA may be most beneficial and critical.

Despite its strengths, this study is not without limitations. As memory was not the primary outcome of the BEAT Cancer trial, only self-report measures were included. Interventions assessing other cognitive processes associated with CRCI and that include neuropsychological testing and brain imaging are needed. Because BEAT Cancer included group behavioral sessions and one-on-one behavioral counseling, it is possible that improvements in psychosocial health from these components are responsible for improvements in memory observed. Finally, participants represent a small, homogeneous sample of BCS who were not blinded to group assignment, thereby limiting the generalizability of results and increasing the possibility of social desirability bias.

BEAT Cancer when compared with UC was successful in improving subjective memory impairments in BCS at post-intervention. However, most group differences were not maintained at follow-up. Declines in PA observed at follow-up in our previous study[6] suggest regular PA may attenuate CRCI in BCS. Research is needed to further test relationships between PA and cognitive health, including interactions with other health indicators (e.g., psychosocial function) known to be associated with PA and cognition. Such research may be critical to the development of evidence-based treatments for CRCI.

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Key Points

1. BEAT Cancer participants reported improved memory at post-intervention compared to Usual Care.
2. Most differences in memory were not maintained at 3-month follow-up.
3. Decreases in physical activity following the intervention may partially explain follow-up results.
4. Research testing the effects of physical activity on memory impairments in cancer survivors is needed.
5. Investigations of interactions among psychosocial health, physical activity, and cognitive function in cancer survivors are warranted.

Table 1

Participant characteristics

	BEAT Cancer (*n*=42)	Usual Care (*n*=43)
	M±SD[a] *n*(%)	M±SD *n*(%)
Age (years)	53.07 ±10.52	54.09 ±6.84
Education (years)	16.00 ±2.39	15.56 ±2.28
White	31 (73.81)	34 (79.07)
Married/living with partner	25 (59.52)	30 (69.77)
Cancer stage		
DCIS	10 (23.81)	6 (13.95)
1	17 (40.48)	17 (39.53)
2	11 (26.19)	15 (34.88)
3	4 (9.52)	5 (11.63)
Months since diagnosis	59.69 ±58.15	45.35 ±53.28
History of chemotherapy	17 (40.48)	25 (58.14)
History of radiation	27 (64.29)	26 (60.47)
Hormonal therapy		
None	24 (57.14)	19 (44.19)
Therapy ≤1 year	4 (9.52)	15 (34.88)
Therapy >1 year	14 (33.33)	9 (20.93)
Post-menopausal	35 (83.33)	35 (81.40)

[a]Mean, Standard Deviation

Table 2

Effects of BEAT Cancer on Memory

	Unadjusted Means			Between-group Differences[a]					
	Baseline	Post-Intervention	Follow-up	Post-Intervention			Follow-up		
	M±SD[b]	M±SD	M±SD	Estimate	[95% CI][c]	*d*[d]	Estimate	[95% CI]	*d*
Frequency of Forgetting (Total; range 10–70)				**3.6**	**[0.5, 6.6]**[e]	0.49	1.9	[−1.5, 5.2]	0.21
BEAT[f]	48.9 ±8.9	50.0 ±9.1	49.8 ±8.9						
UC[f]	46.0 ±9.1	44.9 ±9.5	43.9 ±7.7						
General Memory (range 1–7)				0.2	[−0.3, 0.8]	0.17	−0.1	[−0.7, 0.6]	−0.03
BEAT	4.9 ±1.3	4.9 ±1.6	4.9 ±1.3						
UC	4.6 ±1.2	4.5 ±1.4	4.6 ±1.3						
Frequency of Forgetting (Subscale; range 5–35)				**2.0**	**[0.1, 3.8]**	0.44	0.9	[−1.1, 2.9]	0.16
BEAT	23.5 ±4.6	24.0 ±5.4	24.0 ±4.6						
UC	21.4 ±4.9	20.9 ±4.5	20.8 ±5.2						
Reading (range 2–14)				0.3	[−0.6, 1.2]	0.11	0.1	[−1.0, 1.1]	0.02
BEAT	11.1 ±2.7	11.0 ±2.6	11.0 ±2.5						
UC	10.5 ±2.6	10.3 ±2.8	10.4 ±2.0						
Past Events (range 2–14)				**1.5**	**[0.5, 2.4]**	0.64	**1.3**	**[0.2, 2.3]**	0.44
BEAT	9.6 ±2.8	10.5 ±2.2	10.1 ±2.5						
UC	9.5 ±2.4	9.0 ±3.1	8.5 ±2.7						

[a] Adjusted for baseline memory, marital status, diagnosis stage, chemotherapy history, radiation therapy history, adjuvent hormonal therapy history, comorbidities

[b] Standard Deviation

[c] Estimated Least Square Mean [95% Confidence Interval]

[d] Cohen's *d*

[e] Bold denotes p<0.05

[f] BEAT Cancer; Usual Care