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Cognitive problems among breast cancer survivors: loneliness enhances risk

Lisa M. Jaremka[1], Juan Peng[1,2], Robert Bornstein[3], Catherine M. Alfano[4], Rebecca R. Andridge[2], Stephen P. Povoski[5,6], Adele M. Lipari[5,6], Doreen M. Agnese[5,6], William B. Farrar[5,6], Lisa D. Yee[5,6], William E. Carson III[5,6] and Janice K. Kiecolt-Glaser[1,3,5]*

[1]*Institute for Behavioral Medicine Research, The Ohio State University College of Medicine, Columbus, OH, USA*
[2]*College of Public Health, The Ohio State University College of Medicine, Columbus, OH, USA*
[3]*Department of Psychiatry, The Ohio State University College of Medicine, Columbus, OH, USA*
[4]*National Cancer Institute, Bethesda, MD, USA*
[5]*Comprehensive Cancer Center, The Ohio State University College of Medicine, Columbus, OH, USA*
[6]*Department of Surgery, The Ohio State University College of Medicine, Columbus, OH, USA*

**Correspondence to: Institute for Behavioral Medicine Research, Ohio State University College of Medicine, 460 Medical Center Drive, Columbus, OH 43210, USA. E-mail: Janice.Kiecolt-Glaser@osumc.edu*

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Abstract

***Background*: Cancer survivors often experience cognitive difficulties after treatment completion. Although chemotherapy enhances risk for cognitive problems, it is likely only one piece of a complex puzzle that explains survivors' cognitive functioning. Loneliness may be one psychosocial risk factor. The current studies included both subjective and objective cognitive measures and tested whether lonelier breast cancer survivors would have more concentration and memory complaints and experience more concentration difficulties than their less lonely counterparts.**

***Methods*: The relationship between loneliness and cognitive function was tested among three samples of breast cancer survivors. Study 1 was a sample of breast cancer survivors ($n = 200$) who reported their concentration and memory problems. Study 2a was a sample of breast cancer survivors ($n = 185$) and noncancer controls ($n = 93$) who reported their concentration and memory problems. Study 2b was a subsample of Study 2a breast cancer survivors ($n = 22$) and noncancer controls ($n = 21$) who completed a standardized neuropsychological test assessing concentration.**

***Results*: Studies 1 and 2a revealed that lonelier women reported more concentration and memory problems than less lonely women. Study 2b utilized a standardized neuropsychological continuous performance test and demonstrated that lonelier women experienced more concentration problems than their less lonely counterparts.**

***Conclusions*: These studies demonstrated that loneliness is linked to concentration and memory complaints and the experience of concentration problems among breast cancer survivors. The results were also highly consistent across three samples of breast cancer survivors. These data suggest that loneliness may be a risk factor for cognitive difficulties among cancer survivors.**

Survival rates for breast cancer, the second most common cancer among American women, are on the rise [1,2]. However, survivors often experience longer-term complications after treatment completion, including cognitive difficulties [3,4]. For example, breast cancer survivors had poorer executive function, working memory, and general cognitive function than women without a history of cancer [5]. Furthermore, up to 67% of breast cancer survivors reported concentration and/or memory problems after treatment completion [3,4].

A growing body of work has focused on treatment-related factors, such as treatment type, and their relationships to survivors' cognitive functioning. Multiple meta-analyses have demonstrated that survivors who received chemotherapy are at risk for cognitive problems [6–9], although these findings are not without controversy [10]. For example, 5 years after treatment completion, cancer survivors who received standard-dose chemotherapy performed more poorly on a battery of neuropsychological tests than survivors treated with surgery or radiation [11]. In addition, memory problems increased from before to after treatment among chemotherapy-treated survivors, whereas memory difficulties declined among those who did not receive chemotherapy [12]. Although chemotherapy enhances risk for cognitive difficulties, chemotherapy-related effect sizes are small to moderate in size [7,8], suggesting that additional factors may contribute to survivors' cognitive function.

Psychosocial risk factors have received much less attention than treatment-related factors, perhaps because psychosocial factors have not been consistently linked to objective measures of cognitive difficulties among cancer

survivors [13]. However, the identification of psychosocial risk factors garners potential benefits; if psychosocial risk factors are discovered, interventions can target those risks. On the other hand, treatment-related factors, such as prior chemotherapy exposure, are not modifiable.

Loneliness, an interpersonally stressful state of perceived social isolation, may be one psychosocial risk factor for poorer cognitive function. Research using noncancer populations supports this possibility. For instance, lonelier older adults had larger cognitive declines, as measured by the Mini-Mental State Examination, over a 10-year period than their less lonely counterparts [14]. In addition, lonelier adults had larger declines in verbal episodic memory over a 4-year period compared with those who were less lonely [15]. Because cognitive difficulties are particularly prevalent among cancer survivors [3,5], it is important to determine whether loneliness also enhances risk for cognitive problems within this population, independent of treatment-related effects.

Overview of current research

The current studies addressed the relationship between loneliness and cognitive function among breast cancer survivors. We utilized three samples: (a) posttreatment breast cancer survivors who reported their concentration and memory problems, (b) posttreatment breast cancer survivors and noncancer controls who reported their concentration and memory problems, and (c) posttreatment breast cancer survivors and noncancer controls who completed a neuropsychological test measuring concentration. The third sample was a subsample of the second. We used self-report measures of memory and concentration and an objective test of concentration problems because cancer survivors report particular difficulties in these areas [4]. We hypothesized that lonelier women would have more concentration and memory complaints and experience more concentration problems than their less lonely counterparts, independent of the type of cancer treatment they received. Although cancer survivors often experience more cognitive difficulties than people without a history of cancer [5], we expected that the *relationship* between loneliness and cognitive function would be the same across these two populations. We had different cognitive assessments available in each study, consisting of both self-report and objective measures, allowing us to provide converging evidence for our hypothesis across a variety of indices. This research was approved by The Ohio State University Institutional Review Board; participants provided written informed consent before participating. All analyses were conducted using SPSS 19.0 (IBM, New York). Tables 1–3 report detailed sample characteristics, and online supporting information Tables e1–6 provide complete statistical output for all of the primary analyses.

Study 1

The first sample was selected on the basis of health. Only female breast cancer survivors who met strict health-related eligibility criteria were allowed to participate, allowing us to examine our hypothesis in a relatively homogeneous sample.

Methods

Participants and procedure

Participants were stage 0–IIIA female breast cancer survivors ($N = 200$) from the prerandomization sample of a clinical trial addressing yoga and cancer-related fatigue [16]. Survivors

Table 1. Study 1 sample characteristics

Characteristic	Category	Number (%)	Mean (SD)
Race	White	177 (88.5)	—
	Black	18 (9.0)	—
	Other	5 (2.5)	—
Education	High school or below	12 (6.0)	—
	Some college/college graduate	111 (55.5)	—
	Graduate/professional training	77 (38.5)	—
Marital status	Single	26 (13.0)	—
	Married/domestic partner	140 (70.0)	—
	Separated/divorced/widowed	34 (17.0)	—
Stage	0	18 (9.0)	—
	I	89 (44.5)	—
	II	75 (37.5)	—
	III	18 (9.0)	—
Cancer treatment	Surgery only	26 (13.0)	—
	Surgery and radiation	52 (26.0)	—
	Surgery and chemotherapy	46 (23.0)	—
	Surgery, chemotherapy, and radiation	76 (38.0)	—
Days since treatment	N/A	—	348 (235.39)
Age	N/A	—	51.58 (9.24)

N/A, not applicable; SD, standard deviation.

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Table 2. Study 2 sample characteristics

		Cancer survivors		Benign controls	
Characteristic	**Category**	**Number (%)**	**Mean (SD)**	**Number (%)**	**Mean (SD)**
Race	White	147 (79.5)	—	76 (81.7)	—
	Black	27 (14.6)	—	14 (15.1)	—
	Other	11 (5.9)	—	3 (3.3)	—
Education	High school or below	50 (27.2)	—	21 (22.6)	—
	Some college/college graduate	82 (44.3)	—	49 (52.7)	—
	Graduate/professional training	48 (25.9)	—	20 (21.5)	—
	Unknown	5 (2.7)	—	3 (3.2)	—
Marital status	Single	15 (8.1)	—	5 (5.4)	—
	Married/domestic partner	122 (65.9)	—	65 (69.9)	—
	Separated/divorced/widowed	43 (23.3)	—	20 (21.5)	—
	Unknown	5 (2.7)	—	3 (3.2)	—
Cancer stage	0	33 (17.8)	—	—	—
	I	85 (45.9)	—	—	—
	II	45 (24.3)	—	—	—
	III	20 (10.8)	—	—	—
	Unknown	2 (1.1)	—	—	—
Cancer treatment	Surgery only	55 (29.7)	—	—	—
	Surgery and radiation	49 (26.5)	—	—	—
	Surgery and chemotherapy	30 (16.2)	—	—	—
	Surgery, chemotherapy, and radiation	49 (26.5)	—	—	—
	Unknown	2 (1.1)	—	—	—
Days since treatment at T1	N/A	—	247.81 (134.10)	—	—
Days since treatment at T2	N/A	—	617.90 (157.28)	—	—
Age	N/A	—	56.64 (11.27)	—	56.93 (10.77)

Percentages reflect the proportion of participants within their respective group (cancer survivor vs. benign control). Unless otherwise specified, the reported data reflect information obtained at the study's first visit.
N/A, not applicable; SD, standard deviation.

Table 3. Study 3 sample characteristics

		Cancer survivors		Benign controls	
Characteristic	**Category**	**Number (%)**	**Mean (SD)**	**Number (%)**	**Mean (SD)**
Race	White	17 (77.3)	—	17 (81.0)	—
	Black	4 (18.2)	—	4 (19.0)	—
	Other	1 (4.5)	—	0 (0.0)	—
Education	High school or below	2 (9.1)	—	3 (14.3)	—
	Some college/college graduate	16 (72.7)	—	14 (66.7)	—
	Graduate/professional training	4 (18.2)	—	4 (19.0)	—
Marital status	Single	4 (18.2)	—	2 (9.5)	—
	Married/domestic partner	13 (59.0)	—	14 (66.7)	—
	Separated/divorced/widowed	5 (22.7)	—	5 (23.9)	—
Cancer stage	0	6 (27.3)	—	—	—
	I	7 (31.8)	—	—	—
	II	7 (31.8)	—	—	—
	III	2 (9.1)	—	—	—
Cancer treatment	Surgery only	3 (13.6)	—	—	—
	Surgery and radiation	8 (36.4)	—	—	—
	Surgery and chemotherapy	6 (27.3)	—	—	—
	Surgery, chemotherapy, and radiation	5 (22.7)	—	—	—
Days since treatment	N/A	—	364.48 (126.58)	—	—
Age	N/A	—	51.95 (7.80)	—	54.43 (10.26)

Percentages reflect the proportion of participants within their respective group (cancer survivor vs. benign control).
N/A, not applicable; SD, standard deviation.

were recruited through cancer clinics and media announcements if they had completed cancer treatment (except selective estrogen receptor modulators/aromatase inhibitors) between 2 and 36 months prior to enrolling. Individuals were ineligible if they engaged in over 5 h of vigorous activity per week, or if they had symptomatic ischemic heart disease, uncontrolled

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hypertension, liver or kidney failure, a prior history of any other cancer (except basal or squamous cell skin carcinomas), or significant visual, auditory, or cognitive impairments. Women's average age was 51.58 years ($SD = 9.24$, range 27–76), and they were primarily White (89%). Participants completed the questionnaires and interviews described in the following section.

Questionnaires

Loneliness was measured with the UCLA Loneliness Scale, which assesses perceptions of social isolation and loneliness [17]. The scale is highly reliable, demonstrates construct and convergent validity [17], and is one of the most commonly used loneliness measures.

The three-item cognitive problems scale from the Breast Cancer Prevention Trial symptom checklist provided information about survivors' concentration and memory complaints [18]. Survivors were asked how much they were bothered by forgetfulness, difficulty concentrating, and being easily distracted within the past 4 weeks. The scale has good internal consistency and discriminant validity [18]. Furthermore, factor analytic studies from four samples demonstrated that the cognitive problems scale is psychometrically and conceptually appropriate for evaluating cognitive problems [18]. In order to be consistent with prior research and scale validation, we computed a total score reflecting cognitive problems [18]. We also investigated the concentration and memory items separately, as described in detail later.

The Pittsburgh Sleep Quality Index measured sleep quality over the past month (PSQI) [19]. The PSQI can distinguish between people with and without sleep disturbances, indicating acceptable discriminant validity. The PSQI provided a way to disentangle the links among sleep quality, loneliness, and cognitive function [20,21].

The mood disorders module of the Structured Clinical Interview for DSM-IV Axis I disorders, nonpatient version (SCID-NP), measured current syndromal depression. The SCID-NP is designed for rapid and valid DSM-IV diagnoses by clinically trained interviewers [22]. The SCID-NP was included to account for potential relationships between syndromal depression and cognitive function [23].

Participants answered questions about their age, menopausal status, and highest level of education. Education level was used as a socioeconomic status index because some women in our sample did not work outside of the home.

Data analytic strategy

We performed a series of linear regressions, selecting potential confounds *a priori* on the basis of their empirical relationships to loneliness and cognitive function. Every model had the following covariates: age, education level, menopausal status, type of cancer treatment, time since cancer treatment ended, sleep quality, and syndromal depression diagnosis [20,21,23,24]. We included the interaction between loneliness and type of cancer treatment to test whether the loneliness effects were stronger for women who received certain types of treatments. Nonsignificant higher-order interactions were dropped from the model.

The first of two ancillary analyses centered on chemotherapy treatment [6–9], replacing the covariate that included all possible treatment combinations with one that focused on chemotherapy (yes vs. no). We also examined the interaction between loneliness and chemotherapy treatment. The second set of auxiliary analyses tested whether the patterns of results were similar for the memory versus concentration items of the Breast Cancer Prevention Trial symptom checklist.

Results

As expected, lonelier breast cancer survivors reported more cognitive difficulties than those who were less lonely, $b = 0.03$, $t(177) = 3.13$, $p = 0.002$. The interaction between loneliness and cancer treatment type was nonsignificant, indicating that the strength of the relationship between loneliness and perceived cognitive problems was the same across the different types of treatment, $t(174) = 1.29$, $p = 0.18$.

Ancillary analyses demonstrated that these effects remained the same when we controlled for chemotherapy (rather than all possible treatments). Lonelier breast cancer survivors reported more cognitive problems, $b = 0.03$, $t(179) = 3.25$, $p = 0.001$, and the loneliness-by-chemotherapy interaction was nonsignificant, $t(178) = 0.51$, $p = 0.61$.

The primary results were also identical if we analyzed the memory and concentration items separately. Lonelier breast cancer survivors reported more concentration ($b = 0.03$, $t(177) = 3.31$, $p = 0.001$) and memory ($b = 0.02$, $t(177) = 2.24$, $p = 0.026$) problems than those who were less lonely. Furthermore, the loneliness-by-treatment type interactions predicting concentration ($t(174) = 1.03$, $p = 0.366$) and memory ($t(174) = 1.51$, $p = 0.080$) complaints were nonsignificant, although this latter interaction approached significance.

Study 2a

The Study 2a sample was chosen for two primary reasons: (1) the sample was more heterogeneous in terms of overall health and thus allowed us to generalize the Study 1 findings to a more diverse sample, and (2) the sample consisted of both breast cancer survivors and noncancer (benign) controls, enabling us to test whether the relationships among loneliness, concentration, and memory were similar across these two populations.

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Methods

Participants

Women ($N = 278$) were recruited from cancer clinics at The Ohio State University as part of an ongoing prospective study of cancer-related fatigue. At the time of their recruitment, women were being tested for breast cancer because of a suspicious initial test. As the result of one or more follow-up tests (i.e., biopsy, fine-needle aspiration, MRI, ultrasound, mammogram, or a combination of these methods), participants received either a benign ($n = 93$) or malignant ($n = 185$) diagnosis. Individuals were ineligible if they had significant visual, auditory, or cognitive impairments or any prior history of cancer except basal or squamous cell skin carcinomas. Women's average age was 56.73 years ($SD = 11.09$, range 28–88), and they were primarily White (80%).

Procedure

Cancer survivors' first posttreatment appointment occurred 6 months after the completion of surgery, radiation, or chemotherapy, whichever came last. The second posttreatment visit was 12 months later. Benign controls were scheduled within a comparable time frame. Participants completed the following questionnaires and interviews during both visits.

Questionnaires

Loneliness was measured with the eight-item New York University Loneliness (NYUL) scale [25], which assessed the extent to which participants felt chronically alone and socially isolated. Individual items are measured on different metrics. Accordingly, each item was z-scored prior to creating the scale average [25]. The NYUL scale demonstrates convergent validity with other loneliness measures and has good internal consistency [17,25].

Cognitive function was measured with two items developed to assess cognitive impairments before, during, and after cancer treatment [4]. Women were asked to rate the severity of their worst concentration problem over the past 5 days and were then asked the same thing about memory problems. The scale anchors ranged from 0, 'not present', to 10, 'as bad as you can imagine'. The items were highly correlated ($r = 0.83$ at T1 and $r = 0.78$ at T2); consistent with Study 1, both items were combined into a single index of cognitive complaints. We also explored the concentration and memory items separately, as described later.

Participants answered questions about their age, menopausal status, and highest level of education. They also completed the PSQI and a SCID-NP interview.

Data analytic strategy

Mixed models were utilized to account for repeated assessments of each participant; a subject-specific random effect captured the within-subject correlation. Potential confounds were the same as Study 1 except that cancer status (cancer survivor vs. benign control) was added. Time since treatment and treatment type were only relevant to cancer survivors; both variables were included by adding the main effects of cancer status and the interactions between cancer status and either variable. The main effects of time since treatment and treatment type were omitted because their meaning would not be interpretable [26]. The interaction term without the corresponding main effect thus provided estimates of the effects of these covariates for cancer survivors only. We utilized this technique in order to retain the benign sample in our analyses; the results remained the same when examining only cancer survivors.

In the primary analyses, we controlled for all treatment types and tested whether visit, cancer status, or treatment type moderated the effects of loneliness on cognitive function. Nonsignificant higher-order interactions were dropped from the model. We also conducted two sets of ancillary analyses; the first focused on chemotherapy treatment (yes vs. no) and the second examined the memory and concentration items separately.

Results

Lonelier women had more cognitive complaints than their counterparts who felt more socially connected, $b = 0.63$, $t(402) = 5.18$, $p < 0.001$. The interactions of loneliness with visit, cancer status, and cancer treatment type were nonsignificant, indicating that the strength of the relationship between loneliness and cognitive function was the same over time, between cancer survivors and benign controls, and across treatment types, all p values > 0.225.

Ancillary analyses demonstrated that these effects remained the same when controlling for chemotherapy (rather than all possible treatments). Lonelier women reported more cognitive problems, $b = 0.64$, $t(404) = 5.27$, $p < 0.001$, and the interactions of loneliness with visit, cancer status, and chemotherapy were nonsignificant, all p values > 0.207.

The primary results also remained the same for the individual memory and concentration items. Lonelier women reported more memory ($b = 0.62$, $t(395) = 4.45$, $p < 0.001$) and concentration ($b = 0.64$, $t(398) = 5.21$, $p < 0.001$) problems than less lonely women. The interactions of loneliness with visit, cancer status, and treatment type were nonsignificant, all p values > 0.150.

Study 2b

The Study 2b sample was a subsample of participants from Study 2a. Breast cancer survivors and benign controls completed an objective measure of cognitive function, allowing us to investigate whether the self-report findings were consistent with a standardized neuropsychological test. We chose a neuropsychological measure that tapped concentration problems to be consistent across samples.

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Methods

Participants

A subset of women from Study 2a ($N = 43$) participated in a separate study about responses to a fast-food-type meal. Both breast cancer survivors ($n = 22$) and noncancer controls ($n = 21$) participated in the study. In addition to the Study 2a criteria, individuals were ineligible if they had symptomatic ischemic heart disease, chronic obstructive pulmonary disease, liver or kidney failure, or severe gastrointestinal problems. We also excluded women with major immune-mediated conditions, and anyone who abused alcohol or drugs or used medications with major immunological consequences. Women's average age was 53.16 years ($SD = 9.06$, range 31–75), and they were primarily White (77%).

Procedure

Women completed two visits approximately 2 weeks apart, which were scheduled between the first and second appointments discussed in Study 2a (i.e., 6–18 months posttreatment for cancer survivors). The questionnaires and tasks described in the following sections were completed prior to the parent study's meal challenge.

Questionnaires

Connor's Continuous Performance Test (second edition; CCPT-II) assesses both concentration and impulsivity via the controlled presentation of stimuli on a computer screen [27]. Participants see one letter on the screen at a time and are asked to press a computer key after every letter except X. Reaction time (RT) measures are collected for each trial. An 'omission' occurs when a participant does not press the computer key when she should have (i.e., for any letter but X), whereas a 'commission' occurs when she presses the keyboard key when she should not have (i.e., when an X appears). More omissions and greater RT variability (RT standard error) are related to concentration difficulties [27,28]. More commissions and faster RTs are linked to impulsivity [27,28]. Participants completed the CCPT-II at both visits.

Participants answered questions about their age, menopausal status, and highest level of education. They also completed the PSQI at their first visit. Data regarding participants' loneliness and syndromal depression were taken from the first Study 2a appointment. Participants also completed the short version of the Positive and Negative Affect Scale to assess their current mood at each visit [29].

Data analytic strategy

The analytic strategy for the primary analyses was identical to that in Study 2a. The number of omissions and the RT standard error were highly and moderately skewed, respectively, and were thus log and square root transformed. The first set of ancillary analyses focused on chemotherapy treatment (yes vs. no), and the second added current affect to the model to ensure the loneliness results were independent of current mood.

Results

Loneliness was related to poorer scores on both indices of concentration; lonelier women had more omissions and a larger RT standard error than less lonely women, $b = 0.06$, $t(27) = 2.89$, $p = 0.008$ and $b = 0.31$, $t(28) = 2.68$, $p = 0.012$. None of the loneliness-by-cancer status or loneliness-by-treatment type interactions were significant, indicating that the strength of the relationships between loneliness and concentration was the same between cancer survivors and benign controls and across treatment types, all p values > 0.374.

Loneliness was unrelated to either index of impulsivity, commissions and RT length, $b = 0.72$, $t(28) = 0.47$, $p = 0.643$ and $b = 1.31$, $t(28) = 0.64$, $p = 0.529$. In addition, none of the loneliness-by-cancer status or loneliness-by-cancer treatment type interactions were significant, all p values > 0.295.

Ancillary analyses demonstrated that these effects remained the same when controlling for chemotherapy (rather than all possible treatments). Lonelier women had more concentration difficulties, as reflected by more omissions and a larger RT standard error, than less lonely women, $b = 0.06$, $t(30) = 2.99$, $p = 0.006$ and $b = 0.37$, $t(30) = 3.21$, $p = 0.003$. None of the loneliness-by-cancer status or loneliness-by-chemotherapy interactions were significant, all p values > 0.150. Furthermore, loneliness was unrelated to either index of impulsivity, commissions and RT length, $b = 0.93$, $t(30) = 0.59$, $p = 0.557$ and $b = 1.34$, $t(30) = 0.71$, $p = 0.485$. None of the loneliness-by-cancer status or loneliness-by-chemotherapy interactions predicting impulsivity were significant, all p values 0.369, except that the loneliness-by-chemotherapy interaction predicting RT standard errors approached significance, $p = 0.068$. All of the primary results also remained identical when we added current affect as a covariate.

Discussion

The current studies demonstrated that loneliness is consistently linked to breast cancer survivors' concentration and memory. Studies 1 and 2a revealed that lonelier women had more concentration and memory complaints than less lonely women. Study 2b utilized a neuropsychological test and demonstrated that lonelier women experienced more concentration problems than their less lonely counterparts; there were no loneliness-related differences in impulsivity.

Multiple meta-analyses have demonstrated that cancer survivors who received chemotherapy are at risk for cognitive problems [6–9], although these findings are not without controversy [10]. Importantly, the loneliness-related

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concentration and memory complaints and objectively assessed concentration problems in our samples were independent of treatment effects. Furthermore, the strength of the relationship between loneliness and cognitive problems was the same across treatment types, suggesting that loneliness may be a risk factor for concentration and memory difficulties among survivors who received surgery, radiation therapy, chemotherapy, or any combination of these treatments.

Concentration and memory difficulties affect a significant portion of survivors; up to 67% of breast cancer survivors reported concentration and/or memory problems after treatment completion [3,4]. Thus, primary-care physicians, oncologists, nurses, and mental health practitioners may encounter cancer survivors with concentration and/or memory complaints on a regular basis. Demonstrating that loneliness is linked to concentration and memory complaints helps identify survivors who may be at risk for these common problems and lays the groundwork for research about their diagnosis and treatment. Accordingly, medical staff could benefit from assessing loneliness among cancer survivors who report cognitive difficulties. Furthermore, interventions that decrease loneliness may improve concentration and memory. One important avenue for loneliness research is delineating which types of interventions work and for whom. For example, interventions that directly attempt to reduce loneliness may not be effective for people who have a hard time perceiving existing or new relationships as supportive. Consistent with this argument, a recent meta-analysis concluded that the most effective loneliness intervention is cognitive behavioral therapy focused on maladaptive social cognition [30].

The present results are consistent with previous research examining loneliness-related cognitive difficulties among people without a history of cancer [14,15]. The current studies extend prior work in a new direction by demonstrating that loneliness is linked to concentration and memory complaints and objectively assessed concentration problems among breast cancer survivors, who are particularly at risk for cognitive difficulties [3,5]. Moreover, these relationships were independent of any treatment-related effects. Studies 2a and 2b demonstrated that the relationships between loneliness and cognitive function were similar for cancer survivors and noncancer controls. Taken together, prior research and the current studies suggest that cognitive risk factors among nonmedical populations, such as loneliness, may also apply to cancer survivors. Accordingly, it is important for medical professionals and research scholars to recognize the potential similarities between cancer survivors and people without a history of cancer. A noteworthy question for future research is whether people who were lonelier prior to their cancer diagnosis have poorer cognitive function during and after treatment than their less lonely counterparts.

Demographic characteristics, mental health, and health behaviors may contribute to the link between loneliness and cognitive function. For instance, lonelier people have poorer sleep quality than less lonely people [21]; poor sleep quality enhances risk for cognitive problems [20]. The current studies demonstrated that the results were independent of participants' age, education, menopausal status, type of cancer treatment, time since cancer treatment ended, sleep quality, and syndromal diagnoses. Consequently, loneliness is related to memory and concentration complaints and objectively assessed concentration problems independent of participants' demographic characteristics, health, and health behaviors.

Additional research is needed to delineate the pathways linking loneliness to memory and concentration difficulties. Elevated inflammation is one plausible mechanism. For example, naturalistic and laboratory studies demonstrated that loneliness elevates inflammatory markers, such as interleukin-6 [31,32]. In addition, people treated with interferon-α, an inflammatory cytokine, often reported concentration and memory problems [33], suggesting that elevated inflammation is linked to cognitive problems. Therefore, loneliness may be linked to memory and concentration difficulties because of its effects on inflammation. Another possibility is that elevated inflammation underlies both the experience of loneliness and cognitive problems; proinflammatory cytokines induce 'sickness behaviors', including anhedonia, social withdrawal, and negative affect [34]. Furthermore, higher levels of soluble tumor necrosis factor receptor II, an inflammatory marker, were concurrently and prospectively linked to memory complaints among breast cancer survivors [35].

Elevated subsyndromal depressive symptoms are another possible mechanism linking loneliness and cognitive complaints. Although the current results were independent of syndromal diagnoses, subsyndromal depressive symptoms may still play a role. Loneliness and depressive symptoms were highly related in the present studies; adding both variables to our analyses would have produced a high degree of multicollinearity. Prior research suggests that loneliness may lead to elevated depressive symptoms and not vice versa. For example, lonelier people experienced more concurrent depressive symptoms and larger increases in depressive symptoms over time than their counterparts who felt more socially connected [36–38]. On the other hand, depressive symptoms did not consistently predict changes in loneliness over time [36,37]. Depression enhances risk for cognitive problems [39]. Accordingly, prior research suggests that loneliness may elevate depressive symptoms, which could have downstream consequences for cognitive function.

Other unexplored psychological mechanisms may also play a role. For example, according to the loneliness model, a recent theoretical approach to understanding loneliness-related consequences, loneliness affects cognitive function

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because lonely people feel socially unsafe [40]. In turn, this lack of social safety creates a hypervigilance toward cues of rejection or other social threats, setting off a cascade of physiological stress responses, ranging from hypothalamic–pituitary–adrenal axis activation to inflammation. One key direction for future research is to determine whether the same mechanisms underlie the links between loneliness and subjective and objective indices of cognitive function.

The current samples were primarily White and female, one limitation of the present results. The study hypotheses were also designed and tested after data collection for all three samples was complete. Accordingly, additional research should design studies to *a priori* test the relationships among loneliness, memory, and concentration difficulties in more diverse samples. Two of the three samples utilized self-report measures of cognitive function, and all of the results were cross-sectional in nature, another limitation of the current studies. Further research using broader neuropsychological tests is needed to fully understand the links between loneliness and cognitive function.

Theoretically, loneliness may lead to a downward spiral whereby loneliness causes cognitive problems, which then further exacerbates loneliness. Research is needed to test whether the links between loneliness and memory/concentration difficulties are unidirectional or cyclical, another limitation of the current study. Indeed, understanding whether cognitive problems exacerbate loneliness is an intriguing question. On the one hand, socially supportive relationships may help people cope with cognitive difficulties. On the other hand, persistent distress may cause people to socially withdraw or feel alienated and lonely.

In sum, lonelier breast cancer survivors had more concentration and memory complaints and experienced more objectively assessed concentration problems than those who were less lonely. These data suggest that loneliness may be a risk factor for cognitive difficulties among cancer survivors.

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Conflict of interest

All authors declare no financial conflicts of interest.

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