



# Relationship between self-reported cognitive function and work-related outcomes in breast cancer survivors

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## Abstract

**Purpose** This study examined the relationship between perceived cognitive function including perceived cognitive impairment (PCI) and perceived cognitive ability (PCA) and work ability, work performance, work productivity, and intention to leave employment in breast cancer survivors (BCS).

**Methods** A cross-sectional study design was used in the study. Employed BCS completed questionnaires assessing PCI and PCA (Functional Assessment of Cancer Therapy–Cognitive-3); emotional work demands (Self-Focused Emotional Labor Scale); and work ability index (WAI), work performance, work productivity (Work Limitations Questionnaire (WLQ)), and intention to turnover. Separate regression models examined the relationship between PCI and PCA and work-related outcomes.

**Results** Participants were 68 employed female BCS who were on average 52 (SD = 8.6) years old and 5 (SD = 3.8) years post-treatment with majority working full time. PCI was associated with poorer work ability ( $B = -0.658$ ), work performance (time- $B = 0.647$ , physical- $B = -0.414$ , and mental- $B = 0.689$ ), and work productivity ( $B = 0.731$ ), but not intent to leave work. PCA was related to higher levels of work ability ( $B = 0.472$ ), work performance (time- $B = -0.462$  and mental- $B = -0.453$ ), and work productivity ( $\beta = -0.494$ ), but not physical demands or intent to turnover.

**Conclusions** Employed BCS with negative perceptions of cognitive function reported poorer work outcomes with the exception of the intent to leave employment. In contrast, positive views of one's cognitive abilities were related to improved ratings of work outcomes again with the exception of intent to leave employment.

**Implications for Cancer Survivors** Healthcare providers need to assess and address perceived cognitive functioning to promote work-related outcomes in BCS.

**Keywords** Breast cancer survivor · Cognitive impairment · Work ability · Work productivity · Work performance

## Introduction

There are over 32 million cancer survivors worldwide. Approximately, 40–44% of those who are diagnosed with cancer are between the ages of 15 to 69 years of age [1, 2], many of whom would be considered in their prime years of employment. Increasing evidence indicates that cancer survivors see working as beneficial. In fact, most cancer survivors regard work as a vital aspect of recovery [3, 4] and, to them, represents a return to normal life activities [5, 6]. In addition,

cancer survivors reported work as contributing to a meaningful and purpose-driven life and improved their overall sense of well-being [5, 7, 8].

Regardless of the benefits associated with working, many cancer survivors report difficulty returning to work and/or difficulties in their ability to work once they resumed their position [9]. A comprehensive review of literature found 16–30% of cancer survivors who returned to work reported disability in physical (physical effort and heavy lifting) and/or cognitive limitations (attention, concentration, and keeping up with work pace) [10]. Breast cancer survivors (BCS), who represent approximately 3.2 million survivors worldwide [11], often report ongoing symptoms, including cognitive impairment as a result of the short and/or long-term sequelae associated with the cancer diagnosis and treatment [8, 12, 13]. Perceived cognitive impairment, commonly referred to as “chemo-brain” by survivors [14], in turn, has been associated with difficulty in everyday functioning [15,

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16] and poorer quality of life [8] and can impact work-related outcomes in BCS [8, 17].

The long-term effects of perceived cognitive function on work-related outcomes in BCS are not well known. A recent integrative review found that PCI is negatively related to work performance [17]. However, most of these studies have been limited by measuring PCI using a single item and none of them measured both PCI and PCA, two distinct, potentially important and independent concepts of perceived cognitive function [18–20]. In addition, most studies to date do not examine the relationship between perceived cognitive function and a range of work-related outcomes, but rather focus primarily on return to work in contrast to measures of perceived work ability, work performance, work productivity, and intention to leave work. Additionally, the majority of previous studies are limited by failing to account for known factors that may influence work-related outcomes [17]. Therefore, the current study attempts to address these limitations by fully exploring the relationship of perceived cognitive function on work-related outcomes in BCS. Specific aims were to (1) examine the relationship between PCI and work ability, work performance, work productivity, and intent to turnover and (2) examine the relationship of PCA and work ability, work performance, work productivity, and intent to turnover. In addition, we controlled for known factors that may influence work-related outcomes including age [7, 21–25], level of education [24–27], and time post-treatment [28], as well as, emotional work demands [7]. Emotional work demands, or the amount of effort, planning, and control needed to suppress negative emotions [29, 30], is a potentially important factor and has been linked to negative outcomes such as emotional exhaustion, stress, and burnout [31, 32] which in turn can impact work performance and work productivity [7]. Findings from this work are important as it will improve our understanding of the relationship of perceived cognitive function and work-related outcomes in BCS who have returned to work.

## Methods

### Participants and procedures

This descriptive, cross-sectional study was approved by the University Institutional Review Board. A total of 68 BCS (stage I–IIIA) were recruited from a large urban National Cancer Institute-designated Cancer Center in the Midwestern United States. Inclusion criteria were female, BCS who were between 21 to 70 years of age, actively employed in part-time or full-time positions, and a minimum of 1-year post-adjuvant treatment. BCS with a history of other or secondary cancers or metastasis, or a diagnosis of dementia, depression, and stroke were excluded from study participation.

### Data collection

Clinic staff approached consecutive BCS about the study, fully explained the study requirements, and obtained informed consent from those that were eligible and interested in participating. Upon consent, questionnaire packets were either given or mailed to each participant with a self-addressed stamped return envelope. Information regarding participants' sociodemographic characteristics, medical data, employment status (full-time or part-time), perceived cognitive function including PCI and PCA, psychosocial work demands (emotional work demands), work ability, work performance, work productivity, and intent to turnover were collected. Study questionnaires took approximately 50 minutes to complete. BCS who completed and returned the questionnaires were compensated with a \$10 gift card. All questionnaires were de-identified and stored in a password-protected database.

### Measures

**Survivor characteristics** Demographic information collected included age, education, employment status, marital status, income, and medical information (stage of disease, time post-treatment, type of adjuvant therapy, and use of anti-hormonal medications including tamoxifen and aromatase inhibitors). Medical information was validated by a medical record review.

**Perceived cognitive impairment and perceived cognitive ability** The Functional Assessment of Cancer Therapy–Cognitive Version 3 (FACT-Cog3), which includes two distinct subscales that measure both PCI and PCA, was used in this study [23, 33, 34]. The PCI subscale is a 20-item self-report questionnaire that measures symptoms of perceived cognitive impairment in the last 7 days. The PCI subscale consists of 20 negatively worded questions (e.g., My thinking is slower than usual) with scores ranging from 0 = never to 4 = several times a day. Higher PCI scores indicate greater levels of cognitive impairment. The Cronbach's alpha for this subscale was 0.96. In contrast, the PCA subscale contains nine positively worded questions (e.g., I am able to keep track of what I am doing, even if I am interrupted) with the response scale ranging from 0 = never to 4 = several times a day. Higher PCA scores indicate greater levels of perceived cognitive abilities. The Cronbach's alpha for this subscale was 0.94.

**Emotional work demands** The Self-focused Emotional Labor Scale was used to assess emotional work demands. This scale assesses employee emotions when dealing with interpersonal transactions in the workplace. The instrument is a six item self-report questionnaire with scores ranging from 1 to 5 points, with higher scores reflecting a higher ability to suppress negative emotions [35]. The Cronbach's alpha for this scale was 0.84 in this study.

## Work outcomes

**Work ability** The Work Ability Index (WAI) was used to assess the BCS's perception of work ability. Work ability has been defined as having the occupational competence related to the “physical, mental, and social demands of work, work community and management, organizational culture, and work environment” [36, p. 551]. Total work ability scores range from 7 to 49, with higher scores indicating better work ability. Scores ranging from 7–27 indicate poor work ability, 28–36 moderate work ability, 37–43 good work ability, and 44–49 excellent work ability [9, 31, 37, 38]. In this study, the Cronbach's alpha for the WAI was 0.82.

**Work performance and productivity** The Work Limitations Questionnaire (WLQ) is a 25-item self-report questionnaire that assesses the degree to which health problems (e.g., breast cancer) interfere with job performance and productivity [39]. The WLQ uses four scales to assess limitations in performing specific job-related demands [39]. The Time Management Subscale, a five-item scale with a range from 5 to 25, addresses challenges with time management and scheduling demands. The Physical Demands Subscale, a six-item scale with scores ranging from 6 to 30, measures the job tasks that require physical strength, movement, endurance, coordination, and flexibility. The Mental-Interpersonal Subscale, a nine-item scale ranging from 9 to 45, assesses cognitively demanding tasks and social interactions that occur on the job. The Output Demand Subscale, a five-item scale that ranges from 5 to 25, addresses work productivity [39, 40]. Participants were asked to rate their level of difficulty of completing specific demands in the past 2 weeks. Higher scores are indicative of poorer work performance, except for the Physical Demands Subscale in which higher scores indicate better work performance [17, 41, 42]. The Cronbach's alpha for this study for time management, physical, mental, and output demands/work productivity subscales were 0.84, 0.79, 0.92, and 0.92, respectively. In this study, each subscale was evaluated as an outcome of interest.

**Intent to turnover** The definition of intent to turnover is the degree to which an employee intends to leave their job and/or organization and is positively related to actual turnover [43]. The Intent to Turnover Scale is a three-item, 7-point Likert scale ranging from 1 = strongly disagree to 7 = strongly agree and assesses the employee's intentions of quitting their job within the next year [44]. Overall scores range from 3 to 21, with higher scores indicative of intent to turnover. The Cronbach's alpha for this instrument was 0.70.

## Data analysis

The main goal of the data analysis was to determine the relationship between perceived cognitive function (PCI and PCA) and work-related outcomes while controlling for survivor

characteristics and emotional work demands. Characteristics of the sample were assessed with descriptive statistics. Separate regression analyses were ran to assess the relationship of PCI and PCA to each work-related outcome, controlling for age, education, time post-treatment, and emotional work demands. For each model, the amount of variance explained by the variables of interest on work-related outcomes was reported. The Statistical Package Social Sciences (SPSS v. 23) was used for the analysis [45].

## Results

Descriptive statistics for the study sample are shown in Table 1. BCS who participated were on average 52 (SD = 8.6) years of age and 5 (SD = 3.8) years post-treatment. The majority of survivors were white (92%), married or living with a partner (78%), and employed full time (79%). In regards to their medical history, the majority received surgery, chemotherapy, and radiation as part of their primary adjuvant therapy. Table 2 displays the means and standard deviations for the major study variables. Based on the threshold categories for the WAI, it was noted that 10.3% of BCS reported poor perceived work ability. As for work performance and productivity subscales, mental and interpersonal demands were rated highest indicating greater difficulty.

### Relationship of perceived cognitive function and work ability

Age, education, time post-treatment, emotional labor, and PCI explained 47% of the variance of work ability, with PCI related to poorer work ability ( $\beta = -0.658$ ,  $p < 0.000$ ). In the regression equation using age, education, time post-treatment, emotional labor, and PCA, 30% of the variance of work ability was observed, with PCA significantly related to higher levels of work ability ( $\beta = .472$ ,  $p < 0.000$ ). Age, education, time post-treatment, and emotional work demands were not significantly related to work ability in these regression models. Figure 1 displays a summary of the reduced model of variables significantly related to work ability.

### Perceived cognitive function, work performance, work productivity, and intent to turnover

**Time management** Age, education, time post-treatment, PCI, and emotional work demands explained 42% of the variance of time management, with perceived cognitive impairments significantly related to poorer time management (greater difficulty with job time and scheduling demands) ( $\beta = 0.647$ ,  $p < 0.000$ ). Age, education, time post-treatment, PCA, and emotional work demands explained 27% of the variance in

**Table 1** Sample Characteristics

	Breast cancer survivors ( <i>n</i> = 68) (M, SD)	Frequency/percent
Age, years	52.12 (8.16)	
Education, years	15.96 (1.87)	
Months post treatment	59.50 (46.12)	
Race		
White, non-Hispanic		64 (94%)
Non-white, non-Hispanic		4 (6%)
Marital status ( <i>n</i> = 64)		
Married/living with partner		53 (83%)
Single/divorced/widow		11 (17%)
Employment status ( <i>n</i> = 65)		
Full time		51 (79%)
Part time		14 (22%)
Stage of disease ( <i>n</i> = 66)		
In situ or stage 0		9 (13.%)
Stage I		26 (39.4%)
Stage I		24 (36.4%)
Stage IIA and IIB		7 (10.6%)
Stage IIIA and IIIB		0 (0%)
Type of adjuvant therapy ( <i>n</i> = 68)		
Surgery		67 (98.5)
Chemotherapy		42 (61.8)
Radiation		44 (64.7)
Tamoxifen user ( <i>n</i> = 66)		
No, never used		35 (53.1%)
Yes, but not in the last month		8 (12.1%)
Yes, used in the last month		23 (34.8%)
Aromatase inhibitor user ( <i>n</i> = 66)		
No, never used		42 (63.6%)
Yes, but not in the last month		7 (10.6%)
Yes, used in the last month		17 (25.8%)

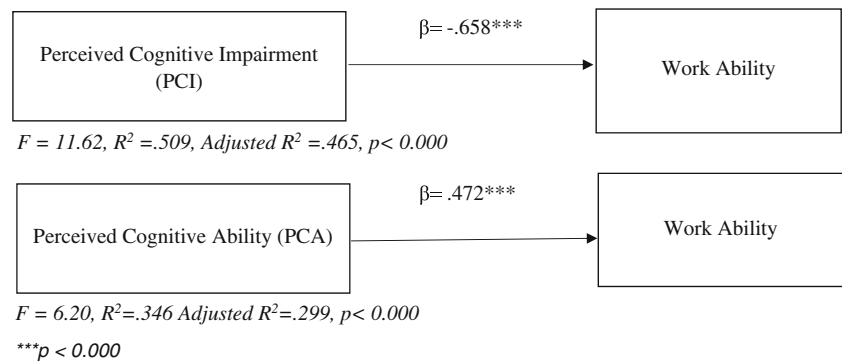
time management, with perceived cognitive abilities significantly related to better (or lower scores) time management ( $\beta = -0.462, p = 0.001$ ). None of the other variables examined

contributed significantly to time management. Figure 2 displays a summary of the reduced model of significant variables related to time management.

**Table 2** Descriptive statistics of variables of interest (*n* = 68)

Variable	Mean (SD)	Potential range	Actual range
Perceived cognitive impairment	27.3(16.5)	0–80	0–71
Perceived cognitive ability	22.8(8.2)	0–36	9–36
Emotional work demands	16.9(5.2)	6–30	6–30
Work Ability Index	38.9(7.5)	7–49	19–49
WLQ-time management	8.5(4.0)	5–23	7–25
WLQ-physical demands	26.8(4.4)	6–30	12–30
WLQ-mental/interpersonal demands	15.3(6.3)	9–45	9–41
WLQ-output demands/productivity	8.8(4.4)	5–25	5–25
Intent to turnover	9.1(4.6)	3–21	3–18

**Fig. 1** Impact of PCI and PCA on work ability



**Physical demands** Age, education, time post-treatment, perceived cognitive impairment, and emotional work demands explained 19% of the variance of physical demands, with PCI significantly related to greater difficulty completing work with higher physical demands ( $\beta = -0.414$ ,  $p = 0.009$ ). In contrast, perceived cognitive abilities nor any of the other variables of interest significantly contributed to physical demands. Figure 2 displays the reduced model indicating the significant variables related to physical demands.

**Mental/interpersonal demands** Age, education, time post-treatment, perceived cognitive impairments, and emotional work demands explained 63% of the variance of mental and interpersonal demands, with PCI significantly related to increased mental and interpersonal demands (greater difficulty in cognitive processing and social interactions at work) ( $\beta = 0.689$ ,  $p < 0.000$ ). In the regression equation, age, education, time post-treatment, PCA, and emotional demands explained 41% of the variance of mental/interpersonal demands. Higher cognitive abilities were related to less difficulty (lower scores) in mental and interpersonal demands ( $\beta = -0.453$ ,  $p < 0.000$ ). Higher levels of emotional work demands (less emotional work-related stress) were related to less difficulty in cognitive processing and social interactions ( $\beta = 0.346$ ,  $p = 0.003$ ). Figure 2 displays significant relationships with mental and interpersonal demands.

**Work output demands/productivity** Age, education, time post-treatment, PCI, and emotional work demands explained 53% of the variance in work output, with PCI significantly related to lower (poorer) work output ( $\beta = 0.731$ ,  $p < 0.000$ ). In the regression equation, age, education, time-post treatment, cognitive abilities, and emotional work demands explained 29% of the variance, with higher levels of cognitive abilities related to higher levels (lower scores) of productivity at work ( $\beta = -0.494$ ,  $p < 0.000$ ). Figure 2 displays significant relationships with work output/productivity.

**Intent to turnover** There was no significant relationship between PCI or PCA and intent to turnover in any of the regression models conducted.

## Discussion

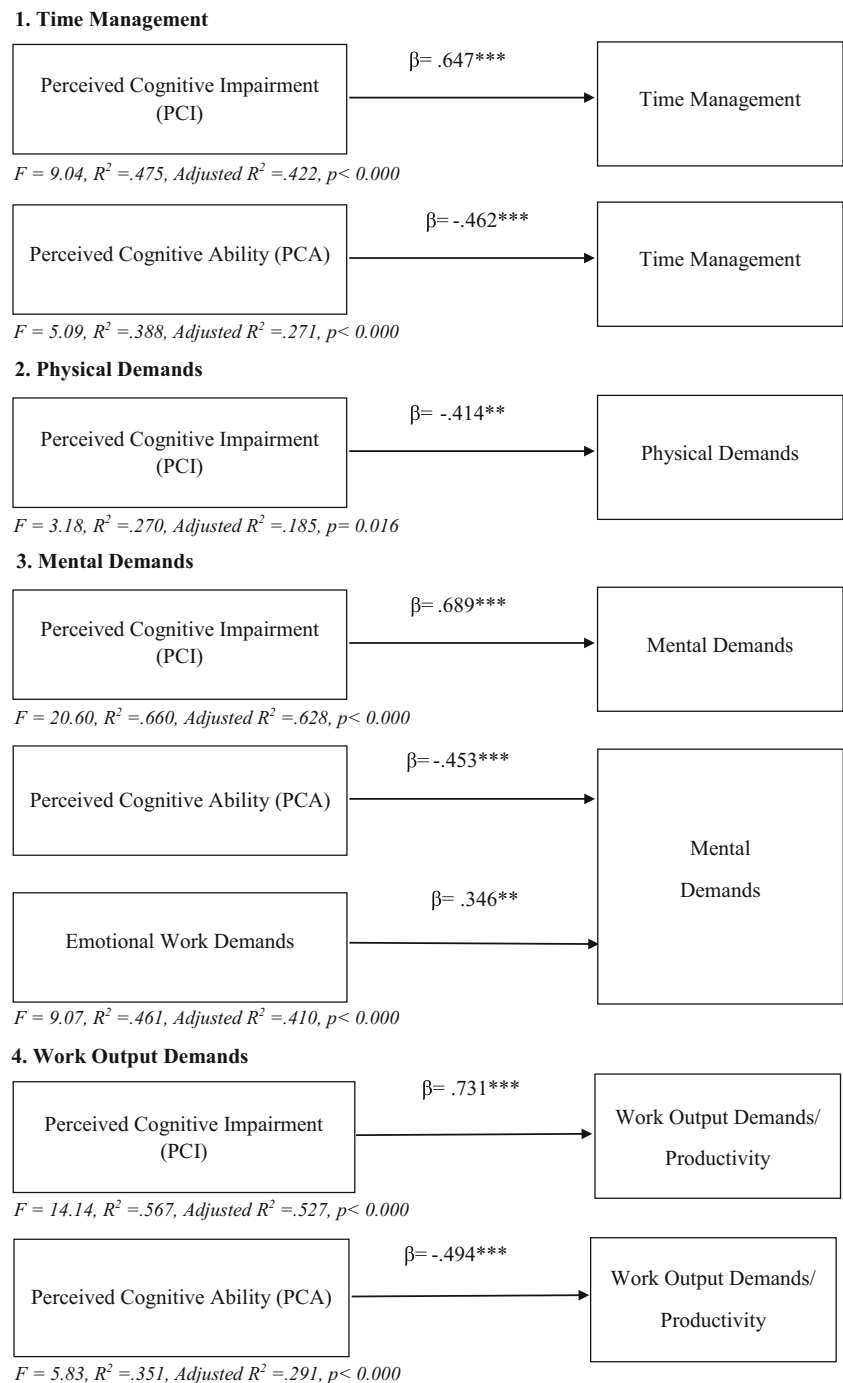
This study focused on perceived cognitive function, including both PCI and PCA and their relationships to several self-reported work outcomes in employed female BCS. To our knowledge, this is the first study to explore both positive and negative perceptions of cognitive function with the goal of gaining a more comprehensive view of perceived cognitive function on specific work outcomes. Notably, the variation in results underscores the importance of assessing both PCI and PCA as separate, independent aspects of perceived cognitive function.

### The importance of PCI on work ability, work performance, and productivity

In this study, PCI was significantly related to work performance and work productivity. Our findings are consistent with an earlier study in which perceived cognitive limitations or impairments were related to poorer work performance and productivity in a sample of 122 BCS aged 18–65 [41]. Similarly, Feuerstein et al. found that perceived cognitive limitations related to work was significantly related to poorer performance and productivity in 95 brain cancer survivors [46]. Additionally, Hansen et al. noted perceived cognitive limitations related to work was significantly associated to poorer work productivity in 100 BCS, accounting for 31% of the variance [47]. Taken together, these studies suggest that perceived cognitive impairment is significantly related to poorer work performance and productivity. Thus, interventions focusing on improving perceived cognitive impairment may ultimately modify self-ratings of work performance and productivity. Such an improvement in perceived cognitive function and positive work outcomes would have significant implications for the financial stability and quality of life of BCS [48].

The literature is less clear, however, in regards to the impact of PCI and competence related to work or work ability [18, 36]. In the present study, BCS who reported greater levels of cognitive impairment reported poorer work ability. In a related



**Fig. 2** Impact of PCI and PCA on work performance and productivity

study, of 653 cancer survivors, 23% reported that their cancer had impaired their cognition and work ability [38]. However, Taskila et al. found that perceptions of work ability did not significantly differ in 591 cancer survivors compared to 757 adults without cancer [49]. These findings suggest that most likely, a smaller subgroup of cancer survivors exists who report problems in both perceived cognitive function and work ability.

The mixed results across studies may be due to the use of different measures used to assess perceived cognitive

impairment, the time following cancer treatment in which measurement occurred, and/or the fact that each study only used a portion of the WAI rather than the entire scale. More research is needed to examine the impact of PCI on work ability, as work ability is directly related to loss of work productivity, retirement intentions, long-term absence, early retirement, need for rehabilitation, and work disability [50–57] and a consistent pattern of findings would provide greater confidence in the observed relationship of PCI and work ability.

## **The positive relationship between PCA and work ability, work performance, and productivity**

When employed BCS perceive themselves as having cognitive abilities, there is a significant and positive relationship with personal levels of ability to work, work performance and productivity. Previous studies have focused solely on PCI [17]. The role of perceived self-efficacy or a sense of competence related to a specific task or function has been positively associated with increased levels of perceived work performance [58] and may prove to be a useful clinical concept because it can be modified and has been shown to influence work outcomes in employed cancer survivors [59].

## **Intent to turnover was not easily explained**

In the present study, perceived cognitive function including PCI and PCA were not related to intention to turnover. Intent to turnover is important to understand as it has been closely linked to actually leaving employment [60] and in some cases permanently. Intent to turnover, however, is a complex concept that may be affected by multiple factors. Previous studies have identified other important factors that are related to the intent to turnover, including job resources, job satisfaction, work engagement, and personal characteristics, including levels of optimism and/or pessimism [61]. Cancer-related factors may also influence intent to turnover. In a recent study, BCS reported feeling “vulnerable” upon returning to work due to physical and mental changes [62], which, in turn, may make them less likely to leave their current position and seek new employment elsewhere. In addition, the need for financial income and continued health benefits may make it impractical for them to consider leaving their current job. Lastly, it has been reported that an employer’s positive/supportive response to a cancer diagnosis and treatment is related to prolonged employment [63]. Thus, further research is needed to better understand the complex confluence of factors related to the intent to turnover in BCS.

## **Emotional work demands may impact mental and interpersonal work demands**

In the present study, emotional work demands were significantly related to work performance requiring mental (cognitive) and interpersonal demands. We found that as emotional work demands was reduced, BCS reported less difficulty in cognitive processing and social interactions. Emotional labor or the ability to suppress negative emotions is often an under recognized aspect of a job [35]. Interpersonal relationships with customers and/or coworkers often require some type of emotional labor. The greater the demand for and monitoring of emotional labor, the greater expenditure of psychological energy and/or emotional stress [35], which in turn,

may negatively impact work performance. This supports our findings that emotional labor was an important factor in cognitive processing and demands associated with interpersonal interactions. However, emotional labor was not significantly related in any of the other regression models with PCI or PCA, suggesting that different factors may be important for different dimensions of work performance and productivity. Future research that analyzes each of the WLQ subscales as separate outcome indicators, as we have done in this study, may yield essential information to improving overall work performance and productivity.

## **Survivor characteristics were not significantly related to work-related outcomes**

Age and education were not significantly related to work outcomes in this study. BCS, in this study, were on average 52 years of age and almost 5 years post-treatment. Few studies have examined these survivor characteristics in the context of work-related outcomes. Bouknight et al. in a prospective study of 416 newly diagnosed BCS researchers found that at 12 months post diagnosis, BCS were less likely to return to work if they had less than high school education [30]. Conversely, having a college education was associated with a greater likelihood of return to work, which was sustained at 18 months post diagnosis. However, those authors did not examine work-related outcomes after return to work [30]. In addition, time post-treatment was not related to any of the work-related outcomes in the study. In our study, the failure to note a significant relationship between time post-treatment and work-related outcomes may be due the cross-sectional nature of the study design. Prospective studies that follow BCS over the trajectory from diagnosis through survivorship are needed to identify the important predictors of work-related outcomes.

## **Importance of understanding work ability, work performance, and work productivity in the context of breast cancer survivorship**

A portion of the BCS who participated in this study reported poor work-related outcomes. Over 10% of BCS reported poor work ability, indicating substantial concerns regarding perceived work performance. In addition, mean scores on the WLQ subscales were higher than previously published means for a sample of healthy adults of similar age [50]. This suggests that a subset of BCS may be at risk for poor work-related outcomes, including poor work performance and lower productivity. Lower productivity has important financial implications. Lower productivity is related to more frequent and longer absenteeism from work, which may have financial implications from foregone earnings. In a recent study, Ekwueme et al. examined productivity costs (at work and home) among

BCS and found the total annual productivity costs from missed work were \$344 million for younger women and \$1072 million for older women ( $\geq 45$  years of age) [64]. Therefore, understanding factors such as perceived cognitive function (PCI and PCA) and its role in work-related outcomes is paramount.

In the interim, there are things that cancer survivors can do to improve their work situation. Cancer survivors need to seek out information regarding their rights and responsibilities in their institution and methodically consider options [65]. Organizations have return to work policies and programs in place that are designed to support cancer survivors with concerns [66]. These programs are designed to include work adjustments and accommodations to support successful re-entry into the work place and retention including adjustment to working hours (e.g., flexible hours), adjustments at the workplace (e.g., private space to reduce distractions, remote work), and adjustments to workload (e.g., reduced demands, provision of assistance) [67–70]. Cancer survivors with cognitive concerns may also utilize published work-related guidance tools that are especially designed to help facilitate discussions and find solutions to minimize the impact their cancer diagnosis and treatment may have on their employment and work-related outcomes [71]. Information on many types of strategies are also available for cancer survivors and employers. For example, the United Kingdom Macmillan Cancer Support Organization [72] and the U.S. Job Accommodation Network [73] provide information regarding the sequela of cancer, its potential impact on work, and resources to support both cancer survivors and employers regarding returning to work and remaining at work of those with a history of cancer and its treatment.

## Strengths and limitations

An important strength of this study was the inclusion of a patient-reported measure of both cognitive impairment and cognitive abilities since this is certainly what clinicians most often rely upon. This also allowed us to examine a range (both positive and negative valence) of perceived cognitive function on a number of work-related outcomes. Results of the study must be examined with acknowledgement to its limitations. First, the cross-sectional nature of the study limits us to identifying relationships among survivor characteristics, cognitive function (PCI and PCA), emotional work demands, and work-related outcomes and not causal inferences. Prospective and longitudinal studies initiated as close as possible to cancer diagnosis or following primary cancer treatment in fully employed BCS would allow for a more thorough examination of the short- and long-term sequela of cognitive changes and their impact on work-related outcomes over time. Second, this study like most to date included only subjective self-reports of cognitive function [18]. Future studies using a combination of

both neuropsychological assessments and subjective reports (generic and work related) would allow for more comprehensive diagnostics and, ultimately, appropriate and evidence-based intervention planning [74]. The sample was limited to early stage BCS who were predominately white and married. Future studies of cancer survivors with other types of cancers and poorer prognosis should be included to increase generalizability of study findings. Future studies should also compare those with and without work problems related to BCS and cognitive problems in order to determine the specificity of these findings.

## Conclusion

PCI and PCA have broad consequences for BCS, their families, and employers if unrecognized and/or not addressed. Research is needed to determine the cognitive and workplace factors that can explain the link between cognitive function and work sustainability in order to develop improved screening, interventions, and rehabilitative strategies for health care providers.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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

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