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Feasibility Study of Adverse Childhood Experiences, Treatment-Related Sequelae, and Inflammatory Markers in Breast Cancer Survivors

Lori Ranallo, MSN, RN, APRN-BC, CBCN®, Harsh B. Pathak, PhD, Jianghua He, PhD, Jaromme Geebum Kim, MA, Karla Van Goethem, BGS, Karin Denes-Collar, LSCSW, LCSW, Julia Danielle Caldwell, RN, BSN, and Jamie S. Myers, PhD, RN, AOCNS®, FAAN

OBJECTIVES: To explore the incidence of adverse childhood experiences (ACEs) in breast cancer survivors and potential associations with long-term treatment-related sequelae.

SAMPLE & SETTING: English-speaking breast cancer survivors three or more years from diagnosis with complete treatment response (N = 120) were recruited prior to scheduled survivorship clinic visits.

METHODS & VARIABLES: Participants in this cross-sectional observational feasibility study rated anxiety, depression, fatigue, sleep disturbance, cognitive issues, resilience, and ACEs (experienced prior to age 18 years). Blood samples were analyzed for inflammatory and epigenetic biomarkers.

RESULTS: ACEs assessment was feasible. Higher ACE scores correlated with greater fatigue, anxiety, and depression, and with lower cognitive function ($p < 0.05$). Resilience was positively associated with cognitive function and negatively associated with fatigue, anxiety, and depression.

IMPLICATIONS FOR NURSING: There is evidence for the impact of ACEs on long-term treatment-related sequelae in women with breast cancer. Oncology nurses should consider incorporating ACEs assessment into the workflow for women receiving survivorship care.

KEYWORDS adverse childhood experiences; breast cancer; resilience; anxiety; depression; cognition

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The Centers for Disease Control and Prevention (CDC) and Kaiser Permanente first studied adverse childhood experiences (ACEs) in the late 1990s and found them to be associated with multiple risk factors for leading causes of death in the United States, including heart disease and cancer (Felitti et al., 1998). Of the 9,508 respondents who completed the CDC–Kaiser study questionnaire concerning ACEs, more than 50% reported at least one ACE and 25% reported two or more ACEs (Felitti et al., 1998). The CDC–Kaiser study questionnaire contained the following seven categories of ACEs: "psychological, physical, or sexual abuse; violence against mother; or living with household members who were substance abusers, mentally ill or suicidal, or ever imprisoned" (Felitti et al., 1998, p. 245). The definition of ACEs was later expanded to include child abuse (physical and mental) and neglect, as well as adversities within the home like parental or sibling violence; parental separation or divorce; or mental illness, substance misuse, or incarceration among family members (Holman et al., 2016). Exposure to peer or community violence has also been included in definitions and categories of ACEs (Finkelhor et al., 2013).

As a result of the CDC–Kaiser study (Felitti et al., 1998), research has been conducted to learn more about the potential relationship between ACEs and cancer. A systematic review by Holman et al. (2016) was conducted to further evaluate the association between ACEs and the risk of cancer in adulthood. Of the 12 studies included in the review, 5 used ACE summary scores to evaluate the risk of any cancer type, and all results were positive for associations between ACE summary scores and adult cancer risk. However,

the review included only one study evaluating the risk of breast cancer in African American women, and this study did not show an association with ACEs. Modesitt et al. (2006) investigated the impact of a history of violence at any age on risk of breast or gynecologic cancers. In a sample of 101 women, 48.5% had experienced violence; of these, 46.9% (23 of 49) had experienced violence during childhood (Modesitt et al., 2006). In this study, having a history of violence was associated with a 2.6-fold increased likelihood of having stage III–IV cancer at initial diagnosis. A potential explanation for a relationship between ACEs and an increased risk of cancer is the known association between ACEs and behaviors like tobacco use, alcohol use, and dietary choices leading to obesity. These behaviors also are noted to be associated with a chronic inflammatory response (Elisia et al., 2020; Ellulu et al., 2017; Wang et al., 2010).

Literature Review

ACEs and Anxiety, Depression, and Fatigue

Additional review of the literature yielded results from studies that found that individuals with a history of ACEs may be at risk for higher levels of short-term anxiety, depression, or fatigue prior to, during, and six weeks to nine months following diagnosis and treatment of cancer.

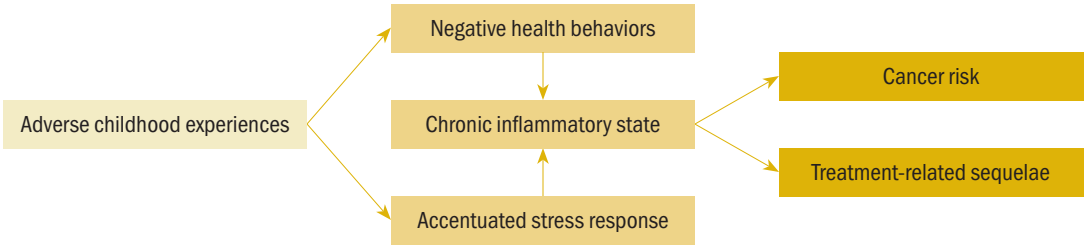
Before, during, and after treatment: Armer et al. (2018) found an association between ACEs and anxiety prior to diagnosis of ovarian cancer that was sustained for 12 months postdiagnosis. Similarly, Kuhlman et al. (2017) demonstrated that ACEs were associated with higher ratings for depression between diagnosis and initiation of adjuvant therapy for 271 women with early-stage breast cancer. Sarafim-Silva et al. (2018) demonstrated that patients with head and neck cancer who reported ACEs were 12 times more likely to experience higher levels of depression during the pretreatment period than patients with no history of ACEs. ACEs were also found to be associated with anxiety and depression during treatment for 92 patients undergoing active treatment for metastatic lung cancer (McFarland et al., 2020). Witek Janusek et al. (2013) evaluated 40 women with breast cancer during a period of nine months following surgery. The study results demonstrated a relationship between ACEs and higher ratings for depression and fatigue.

Short-term and long-term trajectory: Archer et al. (2012) assessed ACEs and recent stressful life events in 90 patients with head and neck (n = 56) and colorectal cancer (n = 34) before surgery and at 6, 12, and 24 weeks after surgery. The study results showed that ACEs and recent stressful events were associated with higher rates of depression. Han et al. (2016) found a relationship between ACEs and higher ratings of fatigue before, during, and six weeks following radiation therapy in a small sample of breast cancer survivors (BCSs) (n = 20). ACEs predicted postoperative pain severity, pain interference, and neuropathic symptoms 12 months after surgery and adjuvant therapy in patients with breast cancer (n = 44) in a secondary analysis (Kanzawa-Lee et al., 2020). Only one study has been conducted to evaluate the relationship between ACEs and long-term sequelae for anxiety and depression. A cross-sectional study of women with breast cancer who were within five years of diagnosis indicated that ACEs were associated with anxiety and emotional distress (McFarland et al., 2020). However, the time frame since diagnosis and treatment was not assessed as a factor, and no description was provided regarding variation in time since diagnosis and treatment. This feasibility study was designed to begin to address this research gap related to long-term sequelae.

Causal Mechanisms

In addition to associations between ACEs and behaviors associated with higher cancer risk (e.g., tobacco use, alcohol use, dietary choices leading to obesity), potential causal mechanisms for ACE-related adult cancer risk may be related to a predisposition for an accentuated stress response to prolonged periods of psychosocial stress. This stress may lead to dysregulation of the stress pathway (hypothalamic–pituitary–adrenal [HPA] axis), a chronic inflammatory state, and the potential for telomere shortening, which is a cellular marker of biologic aging (Lang et al., 2020; Tyrka et al., 2010). Epigenetics research indicates that ACEs are associated with DNA methylation along the *NR3C1* gene encoding for the glucocorticoid receptor (GR) on the HPA axis (Williams et al., 2016). Results from a study conducted with leukocyte GR indicate that the percentage of methylation at CpG (a DNA sequence in which cytosine and guanine bases are connected by a phosphate group following base pairing of the two nucleotides) sites 1 and 3 may be associated with ACEs (Tyrka et al., 2012). Other research indicates that being a carrier of the short allele for the serotonin transporter (SERT) gene promoter polymorphism (5-HTTLPR) may predispose individuals with ACEs to an accentuation of the stress response (Hänsel et al., 2010). Chronic inflammation is evidenced by elevated by-products of the stress response,

FIGURE 1. Conceptual Model for Potential Relationships Between Adverse Childhood Experiences, Cancer Risk, and Treatment-Related Sequelae



Note. Based on information from Centers for Disease Control and Prevention, 2021; Felitti et al., 1998.

such as C-reactive protein (CRP) and inflammatory cytokines (in particular, interleukin [IL]-6) (Flouri et al., 2020; John-Henderson et al., 2020). In a study by Steel et al. (2020), 66% of a sample of 408 patients diagnosed with cancer reported at least one ACE, and ACEs were found to be associated with poorer survival and lower levels of IL-2.

Chronic inflammatory states also may be associated with some of the symptoms that patients experience during and following cancer treatment, such as sleep disturbance, fatigue, emotional distress, and cognitive impairment (Myers, 2008). Previous studies have indicated potential relationships between these symptoms and CRP, tumor necrosis factor-alpha, interferon gamma, IL-2, IL-6, IL-8, and IL-12 (Lin et al., 2019; Oppegaard et al., 2021; Tsai, 2017; Tsai et al., 2019). One hypothesized mechanism for cancer-related cognitive impairment is acceleration of the aging process, including cognitive aging (Wang et al., 2021). Telomere shortening is a cellular marker of aging. This study included an examination of a panel of relevant inflammatory molecules, telomere length, and genetic and epigenetic biomarkers to assess their contribution to the potential relationship between ACEs and long-term treatment-related sequelae. The combination of chronic inflammation from cancer and cancer treatment, in conjunction with chronic inflammation and epigenetic changes from ACEs, may potentiate the risk of more severe long-term treatment-related sequelae.

Resilience

The concept of resilience has been studied in the context of ACE-related mental and physical health outcomes in children and adults (Hall et al., 2021). *Resilience phenomena* are defined as "patterns of positive development in the context of adversity" (Masten & Barnes, 2018. p. 2). More broadly, *resilience* is "the capacity of a system (including human individuals) to adapt successfully to challenges that threaten the function, survival, or future development of the system" (Masten & Barnes, 2018, p. 2). The characteristics and behaviors associated with resilience may be related to individuals' ability to cope with and overcome the impact of ACEs (Masten & Barnes, 2018) and may be protective against the negative impact of chronic stress (Hall et al., 2021). Resilience was of interest in this study with regard to individuals' perceptions and severity ratings for long-term treatment-related sequelae, in particular sleep disturbance, fatigue, emotional distress (anxiety and depression), and cognitive impairment.

Purpose

More research is needed to determine whether ACEs are associated with increased risk of breast cancer. No research was found in the literature review that evaluated the potential impact of ACEs on long-term treatment-related sequelae in any population, nor was any research found that investigated the potential moderating effect of resilience on the severity or duration of long-term treatment-related sequelae related to ACEs in the cancer survivor population.

The purpose of this cross-sectional observational feasibility study was to explore the incidence of ACEs in the BCS population and the potential association between ACEs and long-term breast cancer treatment outcomes. The study was designed to achieve the following aims: (a) Investigate the feasibility and acceptability of ACE assessment during standard survivorship clinic visits for female BCSs; (b) describe the incidence, type, and quantity of ACEs reported by BCSs at a survivorship clinic; (c) explore the correlation between ACEs Questionnaire scores and

TABLE 1. Sample Characteristics (N = 119)

Characteristic	$\bar{X}$	SD	Range
Age (years)	62.95	9.79	39–84
Age at diagnosis (years)	48.26	9.7	29–77
Time since diagnosis (years)	14.69	6.8	1–31[a]
Education (years)	15.83	3.06	6–24
Alcohol usage (drinks per week)	3.82	7.37	0–35
Characteristic		**n**	**%**
Race			
Asian		2	2
Black		7	6
White		110	92
Ethnicity			
Hispanic		5	4
Non-Hispanic		114	96
Employment status			
Retired		53	45
Full-time		50	42
Part-time		9	8
Not employed		7	6
Relationship status			
Married		89	75
Divorced		9	8
Widowed		9	8
In a relationship		6	5
Not in a relationship		6	5
Disease stage			
0		29	24
I		35	29
II		39	33
III		16	13
Hormone receptor status			
Positive		87	73
Negative		32	27
HER2/neu status			
Negative		103	87
Positive		16	13
Type of surgery[b]			
Mastectomy		73	61
Reconstruction		62	52
Lumpectomy		50	42
Received chemotherapy			
Yes		69	58
No		50	42

Continued in the next column

TABLE 1. Sample Characteristics (N = 119) *(Continued)*

Characteristic	n	%
Received radiation therapy		
Yes	64	54
No	55	46
Received endocrine therapy		
Yes	75	63
No	44	37
Currently receiving endocrine therapy		
No	106	89
Yes	13	11
Smoking history		
Never smoker	79	66
Former smoker	38	32
Current smoker	2	2
Alcohol user		
Yes	68	57
No	51	43
Use of drugs other than prescribed medication or alcohol in past 30 days		
No	116	97
Yes	3	3
Request/referral for emotional or psychological support in past 30 days		
No	114	96
Yes	5	4
Comorbidities[b]		
Hypertension	52	44
Diabetes	19	16
Cardiovascular disease	14	12
Other cancer	12	10
Number of comorbidities		
0	40	34
1	47	39
2	27	23
3	5	4

[a] 2 participants were less than 3 years from diagnosis.
[b] Participants could choose more than 1 response.
Note. Because of rounding, percentages may not total 100.

patient-reported outcomes (PROs) for duration and severity of long-term sequelae after treatment for breast cancer; (d) explore resilience characteristics as a potential moderator of the effect of ACEs on long-term treatment-related sequelae; and (e) explore the correlation between ACEs and inflammatory

biomarker levels, epigenetic and genetic expression, and telomere length. Expected outcomes from this study were to provide preliminary data to inform future research investigating ACEs as risk factors for adult breast cancer and as potential predictors of long-term treatment-related sequelae, and to identify associations between ACEs and the incidence and severity of long-term treatment-related sequelae, as well as potential relationships with associated biomarkers that may explain the mechanisms for these associations.

TABLE 2. ACEs Incidence, Type, and Quantity (N = 119)

Variable	n	%
Number of ACEs reported		
0	42	35
1	24	20
2	20	17
3	11	9
4	9	8
5	7	6
6	2	2
7	1	1
8	1	1
9	1	1
10	1	1
Type of ACE reported[a, b]		
Experiencing verbal abuse	35	45
Living with someone who was depressed, mentally ill, or suicidal	31	40
Loss of parent through divorce, abandonment, death, or other reason	31	40
Experiencing physical abuse	28	36
Living with someone who was misusing alcohol or drugs	23	30
Experiencing sexual abuse	19	25
Parents or adults in the home physically abusing each other	17	22
Feeling unwanted or unloved	12	16
Insufficient food, clothing, protection, or care	12	16
Living with someone who was incarcerated	6	8
Belief that ACEs negatively affected health[b]		
Not much	32	42
Some	35	45
A lot	10	13

[a] Participants could choose more than 1 response.
[b] Responses were out of 77 participants who reported at least 1 ACE.
ACE—adverse childhood experience
Note. Because of rounding, percentages may not total 100.

Methods

Conceptual Models

Felitti et al. (1998) developed the ACE Pyramid model to depict the hierarchy of relationships between ACEs; the constellation of social, emotional, and cognitive issues; and the adoption of behaviors that result in higher risk of disease, disability, social problems, and early death. The ACE Pyramid model has been updated to include societal precursors to ACEs and the underlying disruptions to neurodevelopment that contribute to the negative impact on health and well-being throughout the lifespan (CDC, 2021). Based on the ACE Pyramid and narrowing the focus to the potential relationships between ACEs, cancer risk, and long-term treatment-related sequelae, the conceptual model developed for this study is depicted in Figure 1.

Study Design

The study design, instrument selection, and data collection procedures were informed by the University of Kansas Cancer Center's Patient and Investigator Voices Working Together Rapid Reactor Team. This team consists of patient advocates (cancer survivors and co-survivors [i.e., individuals who support or supported the patient through cancer and treatment]) who work with researchers to ensure that research is patient centered and feasible from a patient perspective. Feedback from this team was implemented to reduce the number of study questionnaires to minimize participant burden and ensure that the sequence of their administration progressed from least emotionally sensitive to most sensitive. This feedback also ensured that the study questionnaires were administered in a private space so that participants felt comfortable answering honestly. All participants were provided with a list of available community resources for psychosocial care, and the services of a licensed specialist clinical social worker from the University of Kansas Cancer Center's Masonic Cancer Alliance were available if completing the study questionnaires was emotionally triggering for participants.

One adjustment to the study design was made to the genetic component of the biomarker panel. Previous research has shown that carrying the short allele of the 5-HTTLPR polymorphism is associated with reduced gene and protein expression, less efficient transporter function, and subsequent reduction in circulating serotonin (Yokoyama et al., 2015). Therefore, SERT was measured as a surrogate marker for 5-HTTLPR polymorphisms.

Recruitment and Informed Consent

University of Kansas Medical Center Institutional Review Board approval to conduct the study was obtained in October 2022. Participants were recruited between November 2022 and May 2023 from patients scheduled for follow-up surveillance and care by an advanced practice nurse (APN) at the University of Kansas Cancer Center Breast Cancer Survivorship Clinic in Kansas City. This clinic is a component of a comprehensive cancer center and located on the outskirts of an urban setting. The population served includes patients from urban, suburban, and rural neighborhoods located two to three hours from the cancer center. Most BCSs receiving care at this clinic are women aged 18 years or older who are a minimum of three years from diagnosis with breast cancer, have completed primary cancer therapy, and have achieved a complete response. This population provided a convenience sample for recruitment. For this study, only English-speaking women were recruited, and ongoing endocrine therapy was allowed. Based on medical history and assessment by the APN, women with diagnoses of Alzheimer disease, related dementias, or other conditions that would preclude their ability to understand and complete study questionnaires were excluded. Participation in other survivorship-related research was not exclusionary. The APN contacted all eligible patients about one week in advance of their scheduled appointment at the clinic to discuss the study and ascertain interest in participation. Those who expressed interest were provided a copy of the informed consent document for review via email or postal mail if preferred. At the time of the appointment, the APN answered any remaining questions and confirmed patients' interest in participation. A password-protected study tablet was used to obtain electronic consent.

PRO Measures

PROs Measurement Information System (PROMIS) item banks were used to assess PROs (Cella et al., 2010). These are psychometrically strong and have been well validated for individuals diagnosed with cancer (Cella et al., 2001, 2011). Items are ranked on a scale ranging from 1 to 5. Higher scores on these forms indicate greater severity. Scoring procedures convert total sums to T-scores and SDs for analysis. The four-item PROMIS short forms were used to measure participants' self-reported anxiety, depression, fatigue, and sleep disturbance (Cella et al., 2019). The eight-item PROMIS short form was used to measure participants' self-reported cognitive function (Cronbach's alpha ranges from 0.89 to 0.98) (Henneghan et al., 2023). Higher scores on this form indicate better cognitive function. Resilience was measured using the Brief Resilience Scale (Cronbach's alpha = 0.87), a six-item, five-point Likert-type scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree) (Masten & Barnes, 2018; Sánchez et al., 2021; Smith et al., 2008). Higher scores indicate greater resilience. The 10-item ACEs Questionnaire was used to assess the number and types of ACEs that participants reported experiencing prior to age 18 years (Cronbach's alpha = 0.88) (Murphy et al., 2014).

TABLE 3. Correlations Between ACEs and PROs

PROMIS Variable	Spearman's Rho	p
Anxiety	0.2819	0.0019*
Cognitive function	–0.19	0.0385*
Depression	0.1962	0.0325*
Fatigue	0.1899	0.0385*
Sleep disturbance	0.1656	0.0718

* $p < 0.05$
ACE—adverse childhood experience; PRO—patient-reported outcome; PROMIS—PROs Measurement Information System
Note. ACEs were measured using the ACEs Questionnaire, a 10-item survey assessing the number and types of ACEs that participants experienced prior to age 18 years. PROs were measured using the PROMIS item banks. Items are ranked on a scale ranging from 1 to 5. Scoring procedures convert total sums to T-scores and SDs for analyses. The 4-item short forms were used to measure self-reported anxiety, depression, fatigue, and sleep disturbance. Higher scores indicate greater severity. The 8-item short form was used to measure cognitive function. Higher scores indicate better cognitive function.

Data Collection

Following informed consent, the study tablet was used to administer the study questionnaires via REDCap (Harris et al., 2009, 2019) during a survivorship clinic visit. These questionnaires required about 15 minutes to complete. If participants were unable to complete the study questionnaires during their clinic visit, a link to the REDCap project was provided via email, and a procedure for providing a hard-copy format with postage-paid return was available via postal mail if preferred.

Sample Collection

During standard laboratory sampling for participants' surveillance and follow-up care appointments at the survivorship clinic, one additional tube of

ethylenediaminetetraacetic acid–treated blood was collected, processed into plasma and buffy coat, and stored by the Biospecimen Repository Core Facility team. Blood samples were labeled only with participants' study identification and stored for batch analyses.

Blood Sample Analyses

Circulating levels of CRP, interferon gamma, IL-2, IL-6, IL-8, IL-12(p70), and tumor necrosis factor-alpha were measured in patient plasma samples using magnetic bead–based immunoassays following manufacturer's protocol. The beads were read on a Bio-Rad Bio-Plex 200 system. Levels of SERT were measured using an enzyme-linked immunosorbent assay following manufacturer's protocol. The absorbance measurements from the enzyme-linked immunosorbent assay plates were made using a Tecan Infinite® M200 PRO microplate reader. Patients' genomic DNA was isolated from buffy coat samples using the QIAGEN QIAamp DNA Blood Mini Kit following manufacturer's protocol. The genomic DNA was used to measure telomere length using a quantitative polymerase chain reaction assay from ScienCell Research Laboratories following manufacturer's protocol and read on a Bio-Rad CFX96 Real-Time instrument. To assess promoter methylation status along the *NR3C1* gene, genomic DNA samples were submitted to EpigenDx to perform their ADS2386-FS assays, which covered 12 CpG sites, 10 of which overlapped with those reported by Tyrka et al. (2012) to have increased methylation associated with ACEs.

Statistical Analyses

The planned sample size of 120 participants provided 92% power of detecting a Pearson correlation coefficient of 0.3 with a two-sided Fisher's Z test at the 0.05 level of significance. For linear regression testing of a moderator effect, the study was 80% powered for detecting a 0.05 increase in R^2 (adding the interaction term between Brief Resilience Scale scores and ACEs Questionnaire scores).

Descriptive statistics (ranges and means) were used to describe the sample demographics and to calculate the percentages of eligible participants who consented and completed the study questionnaires, as well as to describe the incidence, type, and quantity of ACEs reported by participants. Nonparametric tests or measures (Wilcoxon rank sum, chi-square test, Spearman's rho) were used to measure the correlations among ACEs Questionnaire scores and the attributes of participants' breast cancer at diagnosis (age at diagnosis, stage of disease, cell type, hormone receptor status, HER2/neu status); body mass index; PROs for long-term treatment-related sequelae (sleep disturbance, fatigue, anxiety, depression, and cognitive impairment); and biomarker levels and epigenetic expression associated with DNA methylation without control for multiple testing. Linear regression modeling was used to explore the potential for a moderating effect of resilience scores (moderator variable) on the association between ACEs Questionnaire scores (independent variable) and participants' PROs (dependent variables) of sleep disturbance, fatigue, anxiety, depression, and cognitive impairment, as

TABLE 4. Correlations (Spearman's Rho) Among Resilience, ACEs, and Patient-Reported Outcomes

Variable	ACEs	Fatigue	Anxiety	Depression	Cognitive Function
Fatigue	0.1899*	–	–	–	–
Anxiety	0.2819**	0.505***	–	–	–
Depression	0.1962*	0.4292***	0.6887***	–	–
Cognitive function	–0.19*	–0.4965***	–0.5803***	–0.5815***	–
Resilience	–0.1962*	–0.4992***	–0.523***	–0.4802***	0.4246***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
ACE—adverse childhood experience; PROMIS—Patient-Reported Outcomes Measurement Information System
Note. ACEs were measured using the ACEs Questionnaire, a 10-item survey assessing the number and types of ACEs that participants experienced prior to age 18 years. Patient-reported outcomes were measured using the PROMIS item banks. Items are ranked on a scale ranging from 1 to 5. Scoring procedures convert total sums to T-scores and SDs for analyses. The 4-item short forms were used to measure self-reported anxiety, depression, and fatigue. Higher scores indicate greater severity. The 8-item short form was used to measure cognitive function. Higher scores indicate better cognitive function. Resilience was measured using the Brief Resilience Scale, a 6-item, 5-point Likert-type scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree). Higher scores indicate greater resilience.

TABLE 5. Linear Modeling for ACEs, Resilience, and Patient-Reported Outcomes

Outcome	Coefficient	Standard Error	t	95% CI	p
Anxiety					
ACEs	3.87	1.66	2.33	[0.573, 7.16]	0.022
Resilience	–4.34	1.24	–3.52	[–6.79, –1.9]	0.001
ACEs/resilience interaction	–0.824	0.464	–1.78	[–1.74, 0.094]	0.078
Constant	64.3	4.62	13.91	[55.14, 73.46]	< 0.001
Cognitive function					
ACEs	–0.17	1.75	–0.1	[–3.64, 3.3]	0.923
Resilience	5.15	1.3	3.95	[2.57, 7.73]	< 0.001
ACEs/resilience interaction	–0.117	0.489	–0.24	[–1.09, 0.851]	0.811
Constant	30.21	4.87	6.2	[20.56, 39.86]	< 0.001
Depression					
ACEs	2.85	1.71	1.66	[–0.542, 6.24]	0.099
Resilience	–3.69	1.27	–2.9	[–6.21, –1.17]	0.004
ACEs/resilience interaction	–0.595	0.477	–1.25	[–1.54, 0.35]	0.215
Constant	61.11	4.76	12.84	[51.68, 70.54]	< 0.001
Fatigue					
ACEs	0.1133	2.067	0.05	[–3.98, 4.21]	0.956
Resilience	–6.55	1.54	–4.26	[–9.59, –3.51]	< 0.001
ACEs/resilience interaction	0.1401	0.5765	0.24	[–1, 1.28]	0.81
Constant	72.39	5.75	12.59	[61, 83.77]	< 0.001

ACE—adverse childhood experience; CI—confidence interval; PROMIS—Patient-Reported Outcomes Measurement Information System
Note. ACEs were measured using the ACEs Questionnaire, a 10-item survey assessing the number and types of ACEs that participants experienced prior to age 18 years. Patient-reported outcomes were measured using the PROMIS item banks. Items are ranked on a scale ranging from 1 to 5. Scoring procedures convert total sums to T-scores and SDs for analyses. The 4-item short forms were used to measure self-reported anxiety, depression, and fatigue. Higher scores indicate greater severity. The 8-item short form was used to measure cognitive function. Higher scores indicate better cognitive function. Resilience was measured using the Brief Resilience Scale, a 6-item, 5-point Likert-type scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree). Higher scores indicate greater resilience.

measured by PROMIS scores. For each model, the interaction between Brief Resilience Scale score and ACEs Questionnaire score was tested to examine the moderation effect. Because of the small sample size and the exploratory nature of this study, no other variables were controlled in these models.

Results

All 120 patients who were approached to participate in the study provided informed consent, and full data were collected for 119 (99%). One participant did not have time to complete the study questionnaires during the clinic visit. She did not have an email address, so the hard-copy format was sent to her home address accompanied by a self-addressed stamped envelope. However, she did not complete or return the study questionnaire.

Participant demographics are listed in Table 1. The sample was primarily White (92%), non-Hispanic (96%), highly educated ($\bar{X}$ = 15.83 years, range = 6–24 years), retired (45%), and married (75%), with a mean age of 62.95 years. The mean time since cancer diagnosis was 14.69 years.

No referrals to the licensed specialist clinical social worker were required during the study. For ACE incidence, 77 participants reported one or more ACEs (65%), and 33 (28%) reported three or more (see Table 2). The most common ACEs types were verbal (n = 35, 45%) or physical abuse (n = 28, 36%); parental loss or abandonment (n = 31, 40%); and depressed, mentally ill, or suicidal family members (n = 31, 40%). For impact of ACEs, 44 participants (58%) reported that ACEs had "some" or "a lot" of negative effect on their health. No correlation was seen between ACEs Questionnaire scores and breast cancer attributes at diagnosis (age at diagnosis, stage of disease, cell type, hormone receptor status, HER2/neu status) or body mass index. Significant positive correlations ($p < 0.05$) were seen

between ACEs Questionnaire scores and PROMIS scores for fatigue, anxiety, and depression, controlled for multiple testing (see Table 3). ACEs Questionnaire scores were negatively correlated with self-reported cognitive function ($p < 0.05$). Brief Resilience Scale scores were positively associated with cognitive function and negatively associated with fatigue, anxiety, and depression (see Table 4). No evidence of a moderating effect of resilience was demonstrated for ACEs' impact on the severity of long-term treatment-related sequelae (see Table 5). Sleep disturbance was not included in the linear modeling for resilience moderation because of the lack of significant correlation with ACEs Questionnaire scores.

Blood samples were obtained from 115 of the 120 participants (96%) and included in the analyses. Missing samples were because of difficulty with venipuncture (n = 1), participant forgetting to go to the laboratory (n = 1), sample collection after business hours (n = 1), and sample discarded in error (n = 2). Of those with blood samples, telomere data were available for only 114 participants. Descriptive statistics for the biomarker data are outlined in Table 6. No correlations were found between ACEs Questionnaire scores and biomarkers associated with inflammation, SERT (as a surrogate marker for 5-HTTLPR polymorphisms), or telomere length.

Based on procedures and findings from Oberlander et al. (2008) and Tyrka et al. (2012), cytosine methylation for 12 CpG sites encompassing the Exon 1F promoter region for the *NR3C1* gene encoding for the GR on the HPA axis were analyzed. Of these, methylation was detected for only five sites (see Supplemental Table 1 online). A small but significant inverse correlation was seen between ACEs and methylation for CpG site 206 (correlation = –0.1912, $p = 0.0404$).

Research results have indicated there may be differences in individuals' responses to specific types of ACEs (Hinnen et al., 2024). Post facto Wilcoxon rank sum tests were used to examine potential relationships between individual ACEs Questionnaire items and biomarker levels. Participants who reported living with someone who had been incarcerated tended to have higher levels of methylation at CpG site 206 ($p = 0.0257$). Participants who reported experiences of sexual abuse had significantly lower levels of CRP ($p = 0.0191$)

TABLE 6. Descriptive Statistics and Correlations Among ACEs and Biomarkers (N = 114)

Variable	Minimum	Maximum	Median	$\bar{X}$	SD	Spearman's Rho	p
ACEs Questionnaire score	0	10	1	1.79	2.08	–	–
CRP (ng/ml)	402	676,094	61,720	149,524	177,697	–0.01	0.97
Interferon gamma (pg/ml)	0.94	104.03	28.94	32.53	16.45	0.09	0.33
IL-2 (pg/ml)	0.39	24.79	3.92	5.94	4.82	–0.01	0.92
IL-6 (pg/ml)	0.17	14.68	1.45	2.37	2.92	0.04	0.7
IL-8 (pg/ml)	0.25	47.95	3.4	7.01	9.55	0.07	0.47
IL-12(p70) (pg/ml)	0.27	26.7	2.64	3.94	3.64	–0.01	0.91
SERT (pg/ml)	4.83	296.8	22.67	34.67	37.74	0.01	0.91
Telomere length per diploid cell (kb)	106.9	604.5	193	241.43	130.78	–0.09	0.32
Telomere length SD per diploid cell (kb)	7.8	44.4	14.2	17.73	9.6	–0.094	0.32
TNF-alpha (pg/ml)	1.7	23.87	5.7	7.19	4.56	0.0092	0.9236

ACE—adverse childhood experience; CRP—C-reactive protein; IL—interleukin; SERT—serotonin transporter; TNF—tumor necrosis factor
Note. ACEs were measured using the ACEs Questionnaire, a 10-item survey assessing the number and types of ACEs that participants experienced prior to age 18 years. Circulating levels of CRP, interferon gamma, IL-2, IL-6, IL-8, IL-12(p70), and TNF-alpha were measured in patient plasma samples using magnetic bead–based immunoassays. Levels of SERT were measured using an enzyme-linked immunosorbent assay. Patients' genomic DNA was isolated from buffy coat samples and used to measure telomere length with a quantitative polymerase chain reaction assay.

Discussion

Results from this feasibility study were consistent with published findings that indicated correlation between ACEs and higher levels of patient-reported severity for fatigue, anxiety, and depression. As predicted, results from this study demonstrated a significant negative correlation between ACEs and patient-reported cognitive function. However, because of the lack of control for multiple testing, these significant associations must be considered exploratory, and additional research is needed for confirmation.

As anticipated from the limited literature assessing the association between ACEs and breast cancer (Holman et al., 2016), the majority of the women being seen for their annual breast cancer survivorship clinic visit reported at least one ACE (65%) and almost one-third of the participants reported three or more ACEs. More than half of these participants perceived that ACEs had a negative impact on their health. Although resilience scores correlated in the expected direction with cognitive function, fatigue, anxiety, and depression, no moderating effect was demonstrated on the severity of these PROs in individuals with ACEs.

Generalizability of findings from this study may be limited because of the cross-sectional design and because participants were recruited from a survivorship clinic. The sample included only BCSs with stage I–III disease who were adherent to survivorship care. Women with advanced and/or more aggressive disease and those who experienced barriers to follow-up care, such as lack of insurance or financial toxicity, were not included in the sample. The lack of inclusion of a population that was potentially at greater risk for severe outcomes may have diluted the study results. In addition, this dilution may have masked a moderating effect of resilience on ACEs' impact on long-term treatment-related sequelae.

The epigenetic results should be reviewed with caution. An inverse correlation between ACEs Questionnaire scores and methylation at CpG site 206, which corresponded to CpG site 9 in the Tyrka et al. (2012) publication, is the opposite of what was expected based on the reported relationship between ACEs and methylation along the *NR3C1* gene encoding for the GR on the HPA axis (Williams et al., 2016). From a biomarker perspective, the inverse correlation between CRP and the ACE for sexual abuse was unexpected. In addition, the significant correlation between the ACE of living with someone with a history of incarceration and higher levels of CRP, although in the expected direction, may not be valid because the number of participants who reported this type of ACE was quite small and unbalanced compared to the full sample. Because the sample for this study excluded women with more advanced disease or those unable to adhere to survivorship care, one unknown factor is how the mean time of 15 years since diagnosis may affect CpG methylation at specific sites and/or the serum biomarkers. These issues, combined with the lack of control for multiple testing, may indicate that these results do not present a true relationship between the variables.

KNOWLEDGE TRANSLATION

- Assessment of adverse childhood experiences (ACEs) during annual breast cancer survivorship clinic visits is feasible.
- Women with breast cancer who have experienced ACEs may be at increased risk for long-term fatigue, anxiety, depression, and cognitive issues.
- Oncology nurses should consider incorporating ACE assessment into the workflow for breast cancer survivorship visits.

Implications for Nursing

The results of this cross-sectional observational feasibility study provide preliminary evidence for the incidence of ACEs and the potential impact of ACEs on long-term treatment-related sequelae for women with breast cancer. Oncology nurses should be aware of this potential impact and consider incorporating assessment of ACEs into the workflow for women receiving survivorship care for breast cancer. Use of the ACEs Questionnaire may be appropriate in the survivorship clinic setting where access to psychosocial support is available. Likewise, nurses in primary care settings would benefit from understanding the potential relationships among ACEs, cancer risk, and long-term treatment-related sequelae. Prospective data collection and evaluation will help to advance nursing knowledge about pertinent risk factors and inform future research to determine whether effective interventions may be targeted to mitigate long-term treatment-related sequelae in BCSs with a history of ACEs. Expanding the research beyond breast cancer to other cancer types should also be considered.

Conclusion

Feasibility was demonstrated for the assessment of ACEs during an annual survivorship visit for women with breast cancer. The majority of participants receiving care at a breast cancer survivorship clinic

reported one or more ACEs. ACEs were associated with higher self-reported levels of fatigue, anxiety, and depression, as well as reduced self-reported cognitive function, in women who were three or more years past completion of primary treatment for breast cancer. Additional prospective research is needed with a more diverse sample of women, including those with stage IV and/or more aggressive disease, to describe the potential impact of ACEs on the severity and duration of treatment-related sequelae during and after the completion of primary therapy for breast cancer. A larger sample size would allow stratification by years since diagnosis and could yield important information related to CpG methylation and biomarker-level trajectories (i.e., the impact of time on biomarker levels in relationship to ACEs, cancer, treatment, and other stressors). Future prospective research with a larger sample size may also yield more informative results related to inflammatory biomarkers, genetic status, and epigenetic expression as predictors of exacerbation or prolongation of long-term treatment-related sequelae.

Lori Ranallo, MSN, RN, APRN-BC, CBCN®, is a nurse practitioner at the University of Kansas Cancer Center in Westwood; **Harsh B. Pathak, PhD,** is a research associate professor in the Department of Pathology and Laboratory Medicine, and **Jianghua He, PhD,** is a professor and **Jaromme Geebum Kim, MA,** is a graduate research assistant, both in the Department of Biostatistics and Data Science, all at the University of Kansas Medical Center in Kansas City; **Karla Van Goethem, BGS**, is a data administration program manager and **Karin Denes-Collar, LSCSW, LCSW,** is an associate director, both in the Masonic Cancer Alliance at the University of Kansas Cancer Center in Fairway; and **Julia Danielle Caldwell, RN, BSN**, was, at the time of this writing, an honors nursing student and **Jamie S. Myers, PhD, RN, AOCNS®, FAAN,** is a research associate professor, both in the School of Nursing at the University of Kansas in Kansas City. Myers can be reached at jmyers@kumc.edu, with copy to ONFEditor@ons.org. (Submitted April 2024. Accepted May 28, 2024.)

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QUESTION GUIDE FOR A JOURNAL CLUB

Journal clubs can help to increase and translate findings to clinical practice, education, administration, and research. Use the following questions to start discussion at your next journal club meeting. Then, take time to recap the discussion and make plans to proceed with suggested strategies.

1. Describe the types and severity of adverse childhood experiences (ACEs). Discuss any clinical experiences that you have related to understanding ACEs in cancer survivors.
2. What is the reported level of ACEs in the sample of breast cancer survivors discussed in this article?
3. Discuss the relationship between ACEs and psychological symptoms in breast cancer survivors.

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