Childhood Adversity and Inflammation in Breast Cancer Survivors

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Objective: Elevated inflammation predicts behavioral symptoms, disease progression, and mortality in patients with breast cancer and breast cancer survivors, although predictors of inflammation remain largely unknown. Adverse experiences in childhood have been associated with higher rates of psychological and physical illness, and elevated inflammatory activity in studies of healthy adults. However, little research has examined the association between childhood adversity and inflammation in the context of cancer, where inflammation is particularly relevant for health. **Methods:** The current study examined the association between three types of childhood adversity—abuse, neglect, and a chaotic home environment—and inflammatory markers (interleukin [IL]-6 and C-reactive protein), in breast cancer survivors who had completed primary cancer treatment 1 year earlier (n = 152). **Results:** The combined measure of childhood adversity was associated with elevations in plasma levels of IL-6 (B = 0.009, p = .027, η^2 = 0.027, after controlling for age, body mass index, ethnicity, alcohol use, and cancer treatment (surgery, radiation, and/or chemotherapy). Examination of individual types of adversity demonstrated a positive association between abuse and IL-6 (B = 0.043, p = .030, η^2 = 0.026), chaotic home environment and IL-6 (B = 0.031, p = .005, η^2 = 0.043), and chaotic home environment and soluble tumor necrosis factor receptor type II (B = 0.012, p = .009, η^2 = 0.037), after controlling for relevant confounds. **Conclusion:** Childhood adversity was associated with elevated markers of inflammation in breast cancer survivors, with potential negative implications for health and well-being. In particular, chaotic home environment showed unique links with inflammatory outcomes. **Key words:** early life stress, maltreatment, inflammation, immune dysregulation, cytokines, carcinoma.

IL = interleukin; **CRP** = C-reactive protein; **sTNF-RII** = soluble TNF receptor type II; **BMI** = body mass index.

INTRODUCTION

Chronic inflammation is a key regulator of cancer development and progression (1,2). Immune cells at the site of the tumor and malignant cells themselves secrete proinflammatory cytokines, which help create a tumor microenvironment that promotes cancer growth (3). In studies of patients with breast cancer and breast cancer survivors, elevated levels of serum inflammatory markers such as interleukin (IL)-6 and C-reactive protein (CRP) are associated with poor response to cancer therapy, increased risk of recurrence, and reduced survival, as well as elevated behavioral symptoms such as cancer-related fatigue (4–7). Although cancer treatments such as surgery, radiation, and chemotherapy lead to acute elevations in proinflammatory cytokines (8), factors associated with chronic inflammation in cancer survivors have not been determined.

One factor leading to increased levels of inflammation may be adverse experiences in childhood. Childhood adversity can be broadly defined as a stressful experience or material hardship that is not considered a normative part of development. Childhood adversity is associated with worse psychological adjustment in adulthood and vulnerability to disease (9–14). Compelling evidence also suggests that childhood adversity is associated with chronic inflammation in healthy adults (15–20), although few studies have examined these links in clinical samples.

Within the context of cancer, experimental studies in animal models have documented associations between stress, inflammation, and cancer progression (21,22). Evidence from human studies suggests that childhood stress is associated with immune dysregulation in patients with cancer and cancer survivors, including poorer immune response to basal cell carcinoma tumors in those who had also experienced a traumatic stressor within the previous year (23) and higher expression of two latent herpes virus antibody titers in breast cancer survivors (24). To our knowledge, only one previous study has examined the association between childhood adversity and inflammation in women with breast cancer. In a longitudinal study of 40 women diagnosed as having early-stage breast cancer and followed up for 9 months after tumor resection, Witek-Janusek and colleagues (25) found that childhood physical neglect (but not physical abuse or emotional/abuse neglect) was associated with a small increase in circulating IL-6 levels.

This work provides preliminary evidence that childhood experiences may lead to alterations in immune system function and potentially inflammatory activity in cancer survivors. However, a number of questions have not been addressed. First, the degree to which effects of early adversity persist in the posttreatment period and are evident among women treated with more intensive therapies (i.e., chemotherapy) has not been determined. Second, psychological factors that may mediate effects of childhood adversity on adult inflammatory activity have not been assessed. Current perceived stress and depression are potential mediators because early life stress is associated with both worse psychological adjustment and elevated inflammation in adulthood (12,15).

Finally, the possibility that different types of childhood adversity may have differential effects on inflammation has not been carefully addressed. Researchers exploring the relationship between childhood adversity and physical health commonly sum the number of adverse experiences across domains to create a cumulative index for each person (16,26). However, this approach may mask the unique effects of different types of adversity. A significant body of research in developmental psychology has shown that different types of childhood maltreatment, including abuse, neglect, and a chaotic home environment, predict specific behavioral patterns in later childhood and psychological outcomes in adulthood (27–29).

Focusing first on abuse, a recent systematic review and meta-analysis found that reports of abuse in childhood are associated with twice the likelihood of adverse mental health outcomes in adulthood (12). Of note, these effects are not limited to physical

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Received for publication July 10, 2013; revision received December 20, 2013.
DOI: 10.1097/PSY.0000000000000041

0033-3174/14/7603–0208

abuse. Emotional abuse, which involves threats of violence or other verbal aggression, belittling, blaming, and ridiculing from caregivers (adapted from Norman et al. (12)), predicts adverse outcomes even after accounting for all other forms of abuse (30,31).

Neglect is also reliably associated with negative mental health outcomes. Neglect refers to the failure to meet the adequate physical needs of the child (physical neglect; (9)) or to a relationship between the parent and child in which the parent ignores or is psychologically unresponsive to the child (emotional neglect; (32)). The consequences of neglect are distinct from and, in some cases, are more detrimental than other forms of maltreatment (9,33). For example, the Minnesota Mother-Child Project followed up 200 low-income families longitudinally and found that emotionally neglected children had the most dramatic decline in developmental achievements from 9 to 24 months in comparison with infants who were experiencing other forms of maltreatment including physical or verbal abuse (29).

In addition to overt abuse and neglect, aspects of the family climate also influence child development (34). Home environments characterized by unpredictability and lack of routines or structure have been shown to negatively influence children's cognitive and emotional development (35). This is consistent with Bronfenbrenner's (34) bioecological model of human development, which posits that predictable social environments promote competent development, whereas disruptions to continuity and predictability disrupt healthy development. Parental behaviors that contribute to a chaotic environment have been shown to impart negative health effects on their offspring; for example, parental alcoholism and violence or constant arguing in the home is associated with worse psychological and physical health of the children, even many decades later (14,36).

Based on the broader literature linking childhood adversity to heightened inflammation in epidemiological studies of healthy adults (15,16,37,38), we hypothesized that women who experienced more childhood adversity would show higher levels of circulating inflammatory markers 1 year after completing their breast cancer treatment. Furthermore, drawing from the developmental literature, we examined the association between inflammation and three distinct types of childhood adversity: abuse, neglect, and exposure to a chaotic home environment. Finally, we tested whether these relationships exist beyond the presence of psychological distress, including stress and depressive symptoms, which is associated with both experiences of past trauma and heightened inflammatory processes in adulthood (e.g., Refs. (39,40)).

METHODS

Participants

Participants for this study ($n = 152$) were drawn from a larger study of cognitive functioning after breast cancer treatment (41). Recruitment for the parent study took place in Los Angeles, primarily through tumor registry rapid case ascertainment from hospitals with collaborating physicians between June 2007 and March 2012. Oncology practices also provided direct referral. Eligibility criteria included a) originally diagnosed as having stages 0 to IIIA breast cancer, b) completed primary cancer treatment within the past 3 months and not yet started endocrine therapy, c) age 21 to 65 years, d) no neurologic or immune-related medical conditions, and e) nonsmoker. In the parent trial, participants completed questionnaires and provided blood samples at baseline (after primary treatment completion) and at 6- and 12-month follow-ups. The analyses reported here focus on self-report questionnaires and immune data collected at the 12-month time point to minimize acute treatment effects on the inflammatory markers. The research was approved by the UCLA institutional review board, and informed consent was obtained from participants.

Demographic and Medical Variables

Demographic variables included age, ethnicity, marital status, annual household income, and employment status. Medical variables included date of diagnosis, surgery type (lumpectomy or mastectomy), type of adjuvant therapy (chemotherapy and/or radiation), and whether they were currently receiving endocrine therapy, all determined from medical chart review. Women reported whether they currently smoked and how many alcoholic drinks they consumed each week.

Assessment of Childhood Adversity

Childhood adversity was assessed with the Risky Families questionnaire, which was adapted from Felitti et al. (14) by Taylor et al. (42). The 13-item scale assesses early experiences within the home from ages 5 to 15 years. Respondents rate aspects of their family environment on a 5-point scale from 1 (not at all) to 5 (very often). The validity of this scale has been demonstrated through corroboration with in-person interviews (42). The 13 items from this scale demonstrated high internal reliability, $\alpha = .89$.

To determine whether there are unique effects of specific types of adversity on inflammation, we created three subscales: abuse, neglect, and chaotic environment. See Table 1 for the specific items and Table 2 for subscale means. For all subscales, higher scores indicate higher levels of adversity.

The abuse subscale included two items that capture physical (pushed, grabbed, shoved, or slapped) and emotional abuse (swear at, insult, put down, or threaten) directed at the individual by their parents or other adults in the home. We averaged these two items to create a subscale score. The two items were highly correlated, $r = 0.68$.

The neglect subscale included three items that capture how much attention and affection the individual received from adults in the home. The three items assessed how much the individual felt loved and cared for (reverse scored), was shown physical affection (reverse scored), and was neglected or left to fend for themselves. We averaged these three items to create a subscale score, $\alpha = .81$.

The chaotic environment subscale included four items that capture the amount of chaos and conflict in the home. To assess environmental dimensions of chaos, we included the following items: amount of arguing and shouting between parents, presence of an alcoholic or drug user in the home, and amount of violence between adults (43). How individuals understand and interpret their environment is also important, and thus, one item asked how chaotic and disorganized participants believed their home was. We averaged these four items to create a subscale score, $\alpha = .77$.

Current Depressive Symptoms and Perceived Stress

Depressive symptoms in the last 2 weeks were assessed with the 21-item Beck Depression Inventory-II (44). Perceived stress in the past week was measured with the 14-item Perceived Stress Scale, a measure of perceived unpredictability and uncontrollability of current stressors (45). Higher scores on these scales indicate higher symptoms. Both scales are widely used and have strong reliability and validity (45,46).

Inflammatory Markers and Immune Cells

Blood samples for circulating inflammatory markers were collected by venipuncture into EDTA tubes, placed on ice, centrifuged for acquisition of plasma, and stored at −80°C for subsequent batch testing. All samples were collected in the morning to control for possible diurnal variations. We focused on inflammatory markers that can be detected reliably in the plasma and reflect activity of three key proinflammatory cytokines (IL-6, IL-1β, tumor necrosis factor [TNF] α). Specifically, we assessed plasma levels of IL-6, CRP, soluble TNF receptor type II (sTNF-RII), and IL-1 receptor antagonist (IL-1ra). CRP was assayed using high-sensitivity enzyme-linked immunosorbent assay (immundiagnostik; ALPCO Immunoassays, Salem, NH), with a lower limit of detection of 0.2 mg/l. Plasma levels of IL-6, IL-1ra, and sTNF-RII were determined by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN), with a lower detection limit of 0.039 pg/ml for IL-6, 31 pg/ml for IL-1ra, and 234 pg/ml for sTNF-RII. All

TABLE 1. Risky Families Questionnaire Items Within Each Subscale

Subscale	Item
Abuse	How often did a parent or other adult in the household swear at you, insult you, put you down, or act in a way that made you feel threatened?
	How often did a parent or other adult in the household push, grab, shove, or slap you?
Neglect	How often did a parent or other adult in the household make you feel that you were loved, supported, and cared for? (reverse scored)
	How often did a parent or other adult in the household express physical affection for you, such as hugging, or other physical gestures of warmth and affection? (reverse scored)
	How often would you say you were neglected while you were growing up, that is, left on your own to fend for yourself?
Chaotic environment	In your childhood, did you live with anyone who was a problem drinker or alcoholic, or who used street drugs?
	How often would you say that a parent or other adult in the household behaved violently toward a family member or visitor in your home?
	How often would you say there was quarreling, arguing, or shouting between your parents?
	Would you say the household you grew up in was chaotic and disorganized?

samples were run in duplicate. The intra-assay and interassay precision of all tests was less than or equal to 10%.

Analytic Method

Bivariate correlations between early adversity variables and inflammatory markers were estimated with the Pearson coefficient (r). To test whether these relationships were present after controlling for relevant confounds, we regressed markers of inflammation (IL-6, CRP, IL-1ra, and sTNF-RII) on Risky Families total score and on each adversity subscale while controlling for covariates. Variables that were expected to be related to the dependent variables based on empirical evidence were included as covariates including the following: age; body mass index (BMI); ethnicity; receipt of radiation, chemotherapy, and/or endocrine therapy; and number of alcoholic drinks per week (47).[1]

In follow-up analyses, we tested the influence of other biobehavioral factors on the relationship between early adversity and inflammation. We ran a set of analyses in which depressive symptoms and perceived stress were added to the model to see if these constructs accounted for some of the relationship between early adversity and inflammation. Several studies have also reported an interaction between depressive symptoms and early adversity when predicting biological outcomes (26,48); thus, we tested the interaction of depressive symptoms and Risky Families total score on inflammation.

All inflammatory markers were log transformed before any analyses because their distributions were skewed. Women with CRP levels above 10 (n = 3) were removed from the data set because CRP values above 10 are likely indicative of acute infection (49). We reported eta squared (η^2) as our effect size measure; η^2 is the portion of the total variance that is attributed to a specific predictor (50).

RESULTS

Participant Characteristics

Sample characteristics are presented in Table 2 (n = 152). Women were, on average, 52 years old and 1.6 years from initial cancer diagnosis. Most women were white (83%), were in a committed relationship (66%), had a household income above $100,000 (62%), and were employed full time (45%). Most had been treated with radiation therapy (76%) and/or chemotherapy (53%) and were currently receiving endocrine therapy (71%).

Table 2 also displays the childhood adversity and inflammatory marker means for the sample. The mean (standard deviation) Risky Families total score was 27.75 (10.5; range, 12–55). Most (61%) of women endorsed at least one form of childhood adversity, defined as rating one item on the Risky Families questionnaire as occurring often or very often. This is similar to national samples in which just more than half report having at least one early adverse experience (14).

Associations Between Childhood Adversity and Inflammation

We hypothesized that childhood adversity would be positively associated with inflammation. Results partially supported this hypothesis. Correlations between childhood adversity variables and inflammatory markers are presented in Table 3. The Risky Families total score was significantly correlated with IL-6 and marginally associated with CRP. After controlling for potential confounds (i.e., age, BMI, ethnicity, alcohol use, and cancer treatment), Risky Families total score remained positively associated with IL-6 ($B = 0.009$, $p = .027$, $\eta^2 = 0.027$), although the relationships with CRP, IL-1ra, and sTNF-RII were nonsignificant.

Our second aim was to test whether subtypes of childhood adversity had unique relationships with inflammatory markers. As shown in Table 3, the abuse subscale was significantly correlated with IL-6 and CRP and was marginally associated with sTNF-RII. After controlling for potential confounds, abuse remained positively associated with IL-6 ($B = 0.043$, $p = .030$, $\eta^2 = 0.026$). The neglect subscale was significantly correlated with IL-6, but after adding covariates to the model, the effect was not significant. Chaotic environment was significantly correlated with all inflammatory markers. After controlling for confounds, chaotic home remained significantly associated with IL-6 ($B = 0.031$, $p = .005$, $\eta^2 = 0.043$), and with sTNF-RII ($B = 0.012$, $p = .009$, $\eta^2 = 0.037$).

Influence of Depressive Symptoms and Perceived Stress on Relationship Between Childhood Adversity and Inflammation

We then examined the influence of depressive symptoms and perceived stress on the relationship between childhood adversity and inflammation. In models that included depressive symptoms

[1]Smoking was an exclusion criterion for study enrollment; however, five women reported smoking within the past week at the time of the assessment used in these analyses. We ran all analyses with and without these women. The results remained the same; thus, they were left in the sample in the analyses reported here.

TABLE 2. Characteristics of the Sample

	Total (n = 152)
Age, M (SD), y	51.7 (7.8)
Years since diagnosis, M (SD)	1.6 (0.2)
Ethnicity, *n* (%)	
White	126 (83)
Other	26 (17)
Marital status, *n* (%)	
In committed relationship	99 (65.6)
Other	52 (34.4)
Family yearly income, *n* (%)	
<Under $60,000	17 (11.5)
$60,001-$100,000	29 (26.3)
>$100,000	92 (62.2)
Employment, *n* (%)	
Employed full time	68 (45)
Employed part time	29 (19.2)
Other	54 (35.8)
Cancer treatments received, *n* (%)	
Chemotherapy	80 (52.6)
Radiation therapy	115 (75.7)
Surgery type, *n* (%)	
Lumpectomy only	104 (68.4)
Mastectomy only	48 (31.6)
Current endocrine therapy	108 (71)
Health behaviors	
Current smoker, *n* (%)	5 (3)
No. drinks in past week, M (SD)	2.8 (3.7)
Risky Families questionnaire	
Total score	27.75 (10.5)
Abuse subscale	1.91 (1.1)
Neglect subscale	1.98 (1.04)
Chaotic environment subscale	2 (0.98)
Inflammatory markers	
IL-6, pg/ml	1.44 (0.95)
CRP, mg/l	1.78 (2.27)
IL-1ra, pg/ml	251.66 (160.28)
sTNF-RII, pg/ml	2014.62 (515.44)
Beck Depression Inventory	8.69 (7.01)
Perceived Stress Scale	14.32 (6.82)

M = mean; SD = standard deviation; IL-6 = interleukin 6; CRP = C-reactive protein; IL-1ra = interleukin-1 receptor antagonist; sTNF-RII = soluble TNF receptor type II.

and perceived stress, the associations between the Risky Families total score and IL-6 and between the abuse subscale and IL-6 were attenuated (B = 0.007 [p = .087, η^2 = 0.016] for Risky Families total score and B = 0.036 [p = .078, η^2 = 0.017] for abuse subscale). However, the association between chaotic environment and IL-6 and sTNF-RII remained significant in models that controlled for these variables (B = 0.027 [p = .013, η^2 = 0.033] for IL-6, and B = 0.013 [p = .008, η^2 = 0.038] for sTNF-RII). We also tested the interaction of Risky Families total score and depressive symptoms on all inflammatory outcomes, although no significant interaction emerged (all p values >.35).

Unique Effect of Chaotic Environment After Controlling for Abuse and Neglect

The chaotic environment subscale captures experiences going on *around* but not necessarily *directed at* the individual, whereas the other two subscales capture behaviors directed at the individual (or in the case of neglect, withheld from the individual). Of course, these may be overlapping experiences. Thus, we conducted follow-up analyses to examine the unique association of the chaotic environment subscale and inflammation, controlling for experiences of abuse and neglect. Results are presented in Table 4. Chaotic environment remained significantly associated with sTNF-RII (B = 0.019, p = .002, η^2 = 0.053), after controlling for abuse and neglect, but the association with IL-6 dropped to marginally significant (B = 0.025, p = .066, η^2 = 0.018).[22] Results remained the same when we ran these analyses controlling for perceived stress and depressive symptoms.

DISCUSSION

Stress in early life is associated with poor health and increased mortality decades later. One mechanism underlying this association may be immune dysregulation and, specifically, activation of the proinflammatory cytokine network (51). Exposure to stressful experiences in early life is associated with elevations in inflammatory markers in adulthood (15–20,37,38) as well as elevated inflammatory responses to acute psychosocial stressors (48,52). Our data provide additional support for this pathway in a clinical population. In a sample of breast cancer survivors, a general measure of childhood adversity was associated with elevated levels of the proinflammatory cytokine IL-6. This association remained significant in analyses controlling for biobehavioral factors that are themselves associated with inflammation (and poor cancer outcomes), including BMI and depressive symptoms (53–55).

Elevated levels of inflammatory markers are especially relevant in cancer samples because inflammation is associated with reduced survival, greater risk of cancer recurrence, and worse behavioral symptoms (4,6,7). Of note, stressful experiences in early life have also been associated with increased risk of a cancer diagnosis (14,56) and worse quality of life, cancer-related distress, and behavioral symptoms in breast cancer survivors (57,58). Thus, childhood adversity may be one factor driving the increase in inflammation that is associated with worse cancer outcomes. Identifying childhood adversity as a risk factor for poor outcomes in survivorship will allow for the early identification of at-risk women and align them with appropriate resources. In addition, identifying heightened inflammation as a long-term effect of stress in early life may drive the development of more targeted treatments.

Our findings further extend previous research by showing that distinct types of maltreatment may have differential effects on inflammatory processes in adulthood. Most studies in this area combine across multiple types of adverse experiences to create a cumulative early adversity index (e.g., Refs. (16,26)). The current study found that disaggregating different types of early adverse experiences may provide insight into the specific effects of adversity on immune function. In particular, growing up in a chaotic

TABLE 3. Correlations Between Childhood Adversity Variables and Inflammatory Markers

	1	2	3	4	5	6	7
1. Risky Families total score	—						
2. Abuse subscale	0.750***	—					
3. Neglect subscale	0.751***	0.560***	—				
4. Chaotic home subscale	0.869***	0.584***	0.473***	—			
5. IL-6 (ln)	0.235**	0.266***	0.162*	0.265**	—		
6. IL-1ra (ln)	0.123	0.115	0.076	0.164*	0.392***	—	
7. sTNF-RII (ln)	0.132	0.148†	0.014	0.204*	0.266***	0.325***	—
8. CRP (ln)	0.143†	0.204*	0.127	0.166*	0.448***	0.451***	0.264***

IL-6 = interleukin 6; IL-1ra = interleukin-1 receptor antagonist; sTNF-RII = soluble TNF receptor type II; CRP = C-reactive protein.
† $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$.

and conflictual home environment was associated with increased levels of IL-6 and sTNF-RII. After controlling for experiences of abuse and neglect, the association between chaotic home environment and sTNF-RII remained significant, whereas the relationship with IL-6 became marginally significant. These results indicate that there may be something uniquely detrimental about growing up in a home characterized by conflict and parental strife that is independent from experiencing other forms of maltreatment. This finding is consistent with previous research showing that witnessing family violence, frequent verbal arguments between parents, and parental substance abuse are associated with worse mental and physical health (e.g., Ref. (36)). Our findings contribute to this literature by suggesting that increased inflammation may be a mechanism by which these experiences influence adult health.

Consistent with previous research in middle-aged women (59), we found that reports of physical and/or emotional abuse were positively associated with circulating concentrations of IL-6. This relationship was attenuated in models that included depressive symptoms and perceived stress, suggesting that the impact of childhood abuse on adult inflammation may be related, in part, to its detrimental effect on psychological functioning. We found no associations between neglect and any of the inflammatory markers. These findings contradict extensive animal and human literature suggesting a powerfully detrimental effect of maternal separation on biological profiles (e.g., Refs. (60,61)) and preliminary evidence that physical neglect is associated with elevated IL-6 in breast cancer survivors (25). This may be because the Risky Families questionnaire assesses a lack of affection, rather than physical neglect or separation from a parent.

There are several mechanisms by which early adverse experiences may lead to increased inflammation in adulthood. First, repeated stressful experiences in childhood may lead to neural and endocrine changes that promote dysregulated physiological responses to future stressors, or allostatic load (62). Second, the biological embedding model suggests that when stress occurs during sensitive periods of development, it calibrates how the immune system will function throughout the life course (51). In particular, stress during development may prime macrophages to overrespond to stressors in adulthood. One outcome of both allostatic load and the biological embedding of early adversity may be an increased production of proinflammatory cytokines and decreased sensitivity to inhibitory hormonal signals.

In addition, growing up in a stressful environment may undermine a child's sense of predictability and safety. Indeed, children who live in unpredictable and stressful environments develop

TABLE 4. Regression Models Examining Relationship Between Chaotic Environment and Inflammation Controlling for Abuse and Neglect

	IL-6 (ln)		sTNF-RII (ln)	
Predictor	β	SE	β	SE
BMI	0.039***	0.009	0.01**	0.004
Age	0.005	0.006	0.007**	0.002
Ethnicity	0.038*	0.019	−0.019*	0.008
Average drinks per week	−0.009	−.011	−0.017**	0.005
Endocrine therapy (yes/no)	−0.060	0.096	0.028	0.041
Radiation (yes/no)	0.148	0.100	0.004	0.042
Chemotherapy (yes/no)	−0.071	0.084	0.034	0.035
Abuse	0.020	0.027	−0.009	0.011
Neglect	−0.004	0.016	−0.008	0.007
Chaotic environment	0.025†	0.014	0.019**	0.006

BMI = body mass index; IL-6 = interleukin 6; sTNF-RII = soluble TNF receptor type II; CRP = C-reactive protein; SE = standard error.
† $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$.

maladaptive schemas about themselves and the world, including viewing the world as a threatening place and a general interpretive style characterized by suspicion of others (32). Living in such a threat-vigilant manner may result in heightened sympathetic nervous system activation, which can trigger increased production of proinflammatory cytokines, in preparation for potential injury. Although this heightened immune activation may be adaptive in an environment with frequent threats to survival, this response may have detrimental effects over the long term (63).

There are several limitations to this study. First, our measure of maltreatment does not assess all components of the construct. The Risky Families questionnaire was based on questions from a foundational study that demonstrated a dose-response relationship between early adverse experiences and disease incidence in a sample of 10,000 adults (14), and bolstered with questions developed through qualitative interviews (42). Previous work has shown associations between the Risky Families scale and biological outcomes (42,64–66); however, it does not assess all forms of childhood adversity including sexual abuse, physical neglect, and low socioeconomic status, which have been linked to increased adulthood inflammation (19,25,37,51). Chronicity and timing of adverse experiences also likely influence their impact, although these dimensions are not captured. Other aspects of the child's home environment such as crowding, frequent residential moves, caregiver changes, and lack of routines should also be assessed in future studies because they may be relevant for physical health given their association with psychological well-being and developmental outcomes (34,35,43). A second limitation is the reliance on retrospective reporting of childhood experiences. Although retrospective reporting of past experiences has been criticized, the consensus in the literature is that retrospective recall is a valid and reliable way to capture experiences that occurred decades earlier (67,68). A third limitation is the cross-sectional nature of the data, which limits our ability to evaluate potential mediators. Finally, our sample is generally representative of women with early-stage breast cancer in the Los Angeles area, but results may not be generalizable to other groups, including women of lower socioeconomic status and of different ethnicities.

Overall, our findings demonstrate that childhood adversity is associated with increased markers of inflammation in a sample of breast cancer survivors, with the most consistent effects seen for a chaotic, conflictual home environment. Future research should continue to explore the relationships between childhood adversity and inflammation in clinical samples, and the psychological and biological mechanisms by which these stressful experiences "get under the skin." Studying these relationships in patients with cancer and cancer survivors is especially important because of the known link between inflammation and poor cancer outcomes.

Source of Funding and Conflicts of Interest: This work was supported by National Institutes of Health (NIH)/National Cancer Institute RO1 CA 109650 and the Breast Cancer Research Foundation. A.D.C. was supported by the National Institute of General Medical Sciences (T32GM084903), the National Institute on Aging (T32AG033533), and the UCLA Career Development Program in Population-Based Cancer Prevention and Control Research (R25T, National Cancer Institute/NIH Cancer Education and Career Development Program). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or other funding agencies. The authors declare no conflicts of interest.

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