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Influence of stressors on breast cancer incidence in the Women's Health Initiative

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Abstract

Objective—To examine associations among life events stress, social support, and breast cancer incidence in a cohort of postmenopausal women.

Design and main outcome measure—Women's Health Initiative observational study participants, breast cancer free at entry, who provided assessment of stressful life events, social support, and breast cancer risk factors, were prospectively followed for breast cancer incidence (n=84,334).

Results—During an average of 7.6 years of follow-up, 2,481 invasive breast cancers were diagnosed. In age-adjusted proportional hazards models, one stressful life event was associated with increased risk, but risk decreased with each additional stressful life event. After adjustment for confounders the decreasing risk was not significant. Stressful life events and social support appeared to interact in relation to breast cancer risk such that women who had greater number of stressful life events and low social support had a decreased risk of breast cancer.

Conclusions—This study found no independent association between stressful life events and breast cancer risk. The results are compatible with a more complex model of psychosocial factors interacting in relation to breast cancer risk.

Introduction

Despite decades of study and plausible biologic mechanisms, the relationship between psychosocial factors and breast cancer risk is not established (for reviews, see Hilakivi-Clarke, Rowland, Clarke, & Lippman, 1993; Nielsen & Brønbdk, 2006). The most extensively studied psychosocial factors in relation to breast cancer incidence are stress and stressful life events (Geyer, 2000).

Most studies of stress and breast cancer have measured stress in terms of highly threatening or adverse life events. While a recent review of prospective studies identified limited evidence for increased risk of breast cancer incidence associated with stressful life events (Nielsen &

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Brønbdk, 2006), three recent prospective studies reported a protective association between chronic stressors and breast cancer incidence (Kroenke et al., 2004; Nielsen et al, 2005; Schernhammer et al., 2004). Much of the existing research is limited by failure to adjust for confounding factors and small study size (Nielsen & Brønbdk, 2006).

In addition to weaknesses in study design, the majority of these studies considered only the independent effects of single psychosocial risk factors, despite several theoretical models based on extensive biological data that suggest the importance of understanding and modeling interactions between the factors in relation to cancer risk. For example, Hilakivi-Clarke and colleagues (1994) propose a model in which life event stress, personality, and social support interact to influence an individual's ability to cope, which in turn mediates breast cancer risk via alterations in neuroendocrine and immune functioning. A key aspect of this model proposes that the number of stressful life-events is not an independent predictor increased risk of breast cancer; instead, the interaction between stress and available psychosocial support, and the effect of this interaction on an individual's ability to cope with stress, increases risk. In this model, women with more stressful life events who lack social support would be least able to cope with stress and thus more likely to experience negative health consequences. This is consistent with an established theory of stress that acknowledges the role of moderating variables, e.g., social supports, in determining "how individuals perceive particular stressors, how they react to those stressors, and what health consequences those reactions produce." (Tennant, Langeluddecke, & Byrne, 1985, p.113.)

Two potential mechanisms are proposed by the model to explain how these psychosocial risk factors work to increase breast cancer risk. The first is a behavioral mechanism such that the interaction between high risk psychosocial factors leads to risky health behaviors, such as alcohol consumption, physical activity, and diet, and these factors serve as mediators of cancer risk. The second mechanism is a biologic mechanism such that high risk psychosocial factors lead directly to physiological states that are associated with growth of breast cancer via endocrine or immunological factors. Hormones play an important role in the development of breast cancer. Thus, multiple stressful life events in the absence of social support may influence cancer risk through activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis resulting in an increase in endogenous estrogens (Antoni et al., 2006). Prolonged exposure to sex hormones, especially estrogen, results in an increased incidence of breast cancer (Hankinson 2005, 2006).

Standard single risk factor analyses do not take into account that psychosocial factors operate cumulatively in cancer development as proposed in the Hilakivi-Clarke model (Grossarth-Maticek et al., 2000). While social support is well accepted as important for quality of life and survival after diagnosis with breast cancer (Kroenke, Kubzansky, Schernhammer, Holmes, & Kawachi, 2006; Michael, Berkman, Colditz, Holmes, & Kawachi, 2002), an independent association between social support and breast cancer risk is not supported in the literature (Bleiker, Van der Ploeg, Hendricks, & Ader, 1996; Edwards et al., 1990; Price et al., 2001). Significant interactions between life events and support in relation to outcomes among women with breast cancer have been demonstrated (Alferi, Carver, Antoni, Weiss, & Durán, 2001; Butler, Koopman, Classen, & Spiegel, 1999). One study designed to evaluate the interaction between social support and stressful life events in relation to breast cancer incidence found that women with major stressors and low social support are at higher risk of breast cancer compared with those with low stressors and high social support (Price et al., 2001). These findings suggest that the influence of stressful life events may depend on the woman's level of social support.

We investigated the main effects of stressful life events as well as the interaction between stressful life event and social support in relation to breast cancer incidence in a cohort of 84,334

postmenopausal women enrolled in the Women's Health Initiative (WHI) observational study. We tested the hypotheses, based on the model proposed by Hilakivi-Clarke and colleagues (1993) that (1) stressful life events are not independently associated with breast cancer risk after adjustment for health behaviors, and (2) recent highly threatening stressful events in the presence of low levels of social support are associated with an increased breast cancer risk.

Method

Women's Health Initiative Observational Study

The design of the WHI observational study has been previously described (Matthews et al., 1997; Women's Health Initiative Study Group, 1998). The WHI observational study is a multi-ethnic cohort of 93,676 post-menopausal women, ages 50–79, enrolled 1993–1998 at 40 geographically diverse clinical centers throughout the United States. Eligibility criteria included 1) age 50–79, 2) postmenopausal status, 3) willingness to provide informed consent and 4) at least a three-year life expectancy. Recruitment methods are detailed elsewhere (Hays et al., 2003). At baseline, participants provided detailed information about psychosocial factors, medical history, and known or suspected risk factors for cancer through a self-administered questionnaire. Mammogram screening was not a required study component but determined by each women's interaction with their own health care providers. Medical history, including history of mammography screening, was updated annually by mail and/or telephone questionnaires. Human Subjects Review Committees at each participating institution approved the protocol. This current analysis was additionally approved by the Human Subjects Review Committee at Oregon Health and Science University.

Included in this study were women who reported no history of breast cancer at baseline ($n=87,498$). In order to exclude women with undiagnosed breast cancer at baseline, breast cancer cases diagnosed before the first follow-up visit ($n=398$) and women with less than 1 year of follow-up ($n=971$) were excluded, as were those missing information at baseline on stressful life events or social support ($n=1792$). After exclusions, 84,334 women were included in the analysis.

Measures

Stressful life events—Life events are a measure of life stressors (Rahe, 1979). The questionnaire completed by participants in the WHI contained a life events inventory developed from the Beta-Blocker Heart Attack Trial modification of the Alameda County Epidemiologic Study (Ruberman, Weinblatt, Goldberg, & Chaudhary, 1984) and further modified to ensure relevance to older women. The questionnaire was completed at baseline and again in year 3 of follow-up. Participants were asked to indicate yes or no as to whether any of eleven life changes had occurred over the past year: spouse died, spouse had serious illness, close friend died, had major problems with money, divorced or break up, close friend divorced, major conflict with children or grandchildren, lost job, physically abused, verbally abused, and pet died. Positive responses were added and number of life events ranged from zero to eleven with a higher score indicating more life events (mean = 1.7, standard deviation (SD) = 1.4). The number of life events was divided into five categories (roughly quintiles) based on the observed distribution (0, 1, 2, 3, 4 or more). Additionally, women were asked to appraise each life event that occurred based on the amount of upset that it caused on a scale of 1 (did not upset me) to 3 (upset me very much). This scale ranged from 0 to 33 with a higher score indicating a participant experienced a greater number of more stressful events. (mean = 3.3, SD=3.2). The stress-weighted number of life events was also divided into five categories (0, 1–2, 3, 4–5, 6 or more) based on the observed distribution.

Social support—Social support was assessed using nine items chosen from the Medical Outcomes Study questionnaire (Sherbourne & Stewart, 1991). Participants ranked on a 5-point scale how often specific types of support, including emotional (for example, someone you can count on to listen to you when you need to talk), affectionate (for example, someone to love you and make you feel wanted), tangible (for example, someone to take you to the doctor if you need it), and positive interaction (for example, someone to have a good time with) were available. The summary score ranged from 9 to 45 (mean = 36.0, SD = 7.8), where a higher score indicates more social support. Based on the Hilakivi-Clarke model, we hypothesized that life event stress would increase breast cancer among women with lower social support. Thus, social support was hypothesized to have a nonlinear effect whereby it would have very strong effects in lower ranges of measurement, but no progressive benefit as the absolute level of support increased as would be expected for a unidirectional linear association. No established, clinically-meaningful cut-offs exist for the MOS social support scale in the published literature (Hardy et al., 2004). To establish our categories for the interaction analysis we categorized social support into quartiles based on the distribution in this population and assessed the pattern of association between social support and breast cancer incidence. We observed similar effect estimates for social support quartiles one and two and quartiles three and four. Based on this analysis, a median split was used to classify subjects as having higher versus lower social support.

Follow-up and breast cancer ascertainment—Breast cancer cases were initially identified from annual follow-up survey information and then confirmed by medical record and pathology report review (available in 98.2% of participants) by physician adjudicators at local clinics. All cases subsequently were centrally adjudicated and characteristics coded (histology, extent of disease, receptor status) using the Surveillance, Epidemiology, and End Results coding system (Curb et al., 2003). Only invasive breast cancer cases confirmed by central review were included as cases. Information regarding mammography frequency was collected annually from all participants. The number of mammograms reported in follow-up was divided by the number of surveys completed creating a proportion representing mammography adherence during follow-up. Women who reported receiving a mammogram on most years (eg., mammogram rate 75 percent or greater) during follow-up were classified as adherent (Humphrey, Helfand, Chan, & Woolf, 2002).

Other measurements—The following classes of characteristics were assessed as potential confounders in multivariate models based on recommendations from a systematic review of the association between stress and breast cancer (Nielsen and Brønbdk, 2006) as well as previous analyses of breast cancer risk in the WHI (Chelbowksi et al., 2005).

Socio-demographic: Age, education, ethnicity, income, insurance status.

Co-morbid conditions: Lifetime history of cardiovascular disease, diabetes, cancer diagnosis other than breast cancer, and obesity measured by body mass index.

Gail model score: The Gail model, originally developed by Gail et al. (1989) and subsequently adapted for the Breast Cancer Prevention Trial, predicts the risk of invasive breast cancer using incidence rates from the Surveillance, Epidemiology, and End Results (SEER) program. The five year risk from Gail prediction was calculated from information gathered at baseline on age, age at menarche, number of previous breast biopsies, presence of atypical hyperplasia on biopsy, age at first childbirth, number of first-degree relatives with a history of breast cancer, and the interactions between biopsies and age and between age at first childbirth and number of affected first-degree relatives.

Other reproductive factors: parity, length of breast feeding, oral contraceptive use and duration of hormone therapy use.

Behavioral factors: amount of exercise, alcohol use, smoking status, fat intake, and mammography adherence.

Analyses

First we evaluated the association between levels of stressful life events and socio-demographic characteristics, breast cancer risk factors, and health behaviors using chi-square tests.

Model development focused on determining the extent to which stressors work independently or interact with social support to increase the risk of incident invasive breast cancer. Follow-up began at baseline (date psychosocial questionnaire was completed) and continued until diagnosis of breast cancer, death, or date of closeout, which ever came first. Cox proportional regression (SAS PROC PHREG) was performed to estimate the hazard ratio for breast cancer (and 95% confidence intervals) for baseline category of stressful life event adjusting for confounders. We checked the proportional hazards assumption by including an interaction with log (base-e) transformed time for each covariate and found no violations. Missing data on each potential confounder was small (<2%) with the exception of income and family history. An indicator for missing was created for each of these measures. Primary analysis was performed as a complete case analysis. Stressful life events and stress weighted life events were modeled as a categorical variable and a linear trend was assessed in additional analyses.

In the first step, the proportional hazards models to assess the association between life events and breast cancer risk were age-adjusted. To adjust for age, proportional hazards models were stratified by 5-year age groups and age was also included as a continuous variable. The next set of models examined whether the age-adjusted estimates were confounded by sociodemographic characteristics or co-morbid conditions. Models were then fitted to assess confounding by breast cancer risk factors, including five-year breast cancer risk score based on the Gail model (Gail et al., 1989) and other reproductive factors. In final models, lifestyle factors were included to evaluate the role of risky health behavior in mediating any observed association between stressful life events and breast cancer incidence. For each model fitted, variables with a p -value >0.25 (with the exception of age) that did not confound the association between life events and risk of breast cancer were removed in a stepwise fashion.

The induction time between stressful life events and breast cancer incidence is unknown. For example, perhaps the influence of stressful life events occurs many years before breast cancer detection or perhaps stressful life events accelerates the development of breast cancer lesions or otherwise influences the probability of diagnosis. To evaluate associations over varying periods of time, we conducted Cox proportional hazards regression models with stressful life events treated as a time-varying covariate, incorporating the most recent life events status into the modeling. Time-varying models predict from each assessment point, rather than assuming that prediction from baseline is sufficient. Women without a year three measure were excluded from these sub-analyses ($n=11,106$). All model development was conducted in the same steps described for the primary analysis above.

In a third set of analyses, we evaluated the influence of cumulative stressful life events hypothesizing that women with higher cumulative life events stress would be at the greatest risk of breast cancer. Cumulative life event stress was calculated by averaging life event stress score at baseline and year three and evaluated in relation to breast cancer incidence after year three. We also calculated change in stressful life events from baseline to year three to investigate whether stable increasing life events stress would be at the greatest risk of breast cancer after year three. Again, women without a year three measure were excluded from these

sub-analyses and the time to event was calculated from the date of completion of the year three psychosocial questionnaire and continued until diagnosis of breast cancer, death, or date of closeout, which ever came first. Again, all model building was conducted as described for the primary analysis above.

A final set of Cox proportional hazard models were constructed in which an interaction between social support and number of life events was fitted to test the hypothesis that increased psychosocial stress (high life event stress in the presence of lower social support) is associated with an increased breast cancer risk. Tests for statistical (multiplicative) interaction were performed with likelihood ratio tests. To further understand the interaction, models were stratified on social support. Given that the functional form of social support in relation to life events and breast cancer risk was not known, we also conducted sensitivity analyses to evaluate the interaction using social support as a continuous variable. Because social support was not measured again after baseline, we did not examine updated levels in social support.

Results

During approximately seven and a half years of follow-up (637,627 person-years), 2,481 incident, invasive breast cancers were diagnosed. The mean age at baseline was 64.5 (SD 7.3) years. In this cohort, women with fewer stressful life events tended to be better educated, report more income, and have private insurance (Table 1). Women with a higher number of stressful life events had lower five year risk from Gail prediction, were more likely to be non-White, were more likely to smoke, and less likely to engage in physical activity. During follow-up, 70.6% of all study participants adhered to current recommendations to have a mammogram every one or two years; that is 72% of those with no stressful life events compared to 65% of those with four or more stressful life events ($p < 0.0001$).

In age-adjusted analyses, women who reported one life event were 14% more likely to be diagnosed with breast cancer during follow-up compared to women with no life events (hazard ratio (HR) 1.14; 95% confidence interval (CI): 1.02 to 1.27). The risk appeared to decrease with each additional increase in the number of life events, although none of the groups differed significantly from each other ($p=0.076$). After adjustment for race/ethnicity, socioeconomic status, and co-morbid conditions at baseline, one stressful life event remained marginally associated with increased risk of breast cancer (HR 1.12, 95% CI: 1.01 to 1.25) compared to none. Further adjustment for breast cancer risk and behavioral factors (smoking, alcohol consumption, fat intake, and mammography) did not alter the elevated risk associated with one stressful life event; however, the apparent decreased risk associated with increased stress was completely attenuated after the addition of the breast cancer risk factors to the model (Table 2). Results using stress-weighted number of life events were similar; results from the life events scale are displayed for the remaining analyses.

Similar but smaller (and non-significant) effects were found when life events were modeled as a time-varying covariate (Table 2). As in the baseline analysis, the non-significant protective effect associated with more life events in the age-adjusted time varying models were attenuated by inclusion of confounders and breast cancer risk factors. No association was observed between breast cancer incidence and high levels of cumulative life events (Table 2) or three-year change (increase) in life events (data not shown).

In multivariable adjusted regression analyses, we observed a marginally significant interaction between life events and social support ($p=0.07$). Table 3 shows estimated hazard ratios in relation to life events for women above and below the median for social support. Compared with women with no life events and lower social support, women with lower social support who reported one life event experienced increased risk of breast cancer (HR 1.20, 95% CI 1.00

to 1.43), while an increasing number of life events (above one) were significantly protective against breast cancer ($p=0.04$). In contrast, we observed no association between life events and breast cancer among women with high social support, although the direction of the effect estimates was consistent with increasing risk as life events increased ($p=0.323$). Analyses evaluating the interaction using continuous social support qualitatively confirmed the non-significant negative association between life events and breast cancer risk among women at the lowest levels of social support (e.g., women at the fifth and twenty-fifth percentile of social support) and no association between life events and breast cancer among women in the highest levels of social support (e.g., women at the 75th and 90th percentile), although the interaction using continuous social support was highly non-significant ($p=0.75$).

Discussion

Overall in this prospective cohort study, we did not observe a significant association of breast cancer with life events and we found limited evidence of an interaction between life events and social support.

While the effect of stress and social support has been convincingly demonstrated in relation to breast cancer progression and outcomes (for reviews see Nielsen & Brønbdk, 2006 and Spiegel 1997), the evidence for these factors as predictors of breast cancer is weak. Other prospective studies evaluating the influence of stress on breast cancer incidence have provided mixed and inconsistent results. Two cohort studies recently reported elevated breast cancer incidence associated with increased self-reported stress (Lillberg et al., 2003; Metcalfe, Davey Smith, Macleod, & Hart, 2007); however, these studies had relatively small sample sizes (108 and 62 breast cancer cases, respectively). Additionally, neither study reported a simple 'dose-response' relationship between increasing stress and breast cancer risk.

An independent association between stress and reduced risk of breast cancer was reported in several recent prospective studies. The Copenhagen City Heart Study reported a statistically significant association between stress and reduced risk of breast cancer (Nielsen et al., 2005). In the Nurses' Health Study, a weak reduction in breast cancer risk associated with caregiving (Kroenke et al., 2004) and job strain (Schernhammer et al., 2004). Since increased psychosocial risk factors have been associated with decreased mammography use (Messina et al., 2004), results suggesting decreased risk could reflect detection bias such that women with high psychosocial stress only appeared to have lower breast cancer incidence. Our current analysis was controlled for mammography during follow-up and the significant association between increasing life events and low breast cancer risk in women was abrogated when the model was fully adjusted for sociodemographic characteristics and breast cancer risk factors.

It is established that the risk of breast cancer increases with increasing circulating estrogen levels (Hankinson, 2005, 2006). In the Nurses' Health Study, women with high levels of caregiving stress had significantly lower levels of estradiol and bioavailable estradiol compared to women providing no care; suggesting that increased stress may protect against breast cancer via reductions in endogenous estrogen levels (Kroenke et al., 2004). However, the weak and inconsistent association between life events and incident breast cancer in this large cohort of women does not provide strong support for hormonal or other biologic mechanisms linking stress and breast cancer. The attenuation of an apparent protective effect of life events with control for breast cancer risk suggests confounding may be a possible explanation for the observed results. Additionally, the limited attenuation of the effect of life events after adjustment for behavioral factors associated with breast cancer is not consistent with a mediating effect.

Only two published studies reported they evaluated an interaction between stress and social support. One report showed a higher risk of breast cancer in women with high stress and low social support (Price et al., 2001); while another reported no significant interaction (Kroenke et al., 2004). While not statistically significant, our results suggest an association between stress and breast cancer incidence in the absence of social support but no association in the presence of social support contrary to our hypothesized interaction effect.

These findings from the current study may be consistent with hypotheses that social support primarily works at the highest levels to influence health by buffering the influence of stress (Thoits, 1982). Prior studies among patients with health conditions (e.g., diabetes, lung disease, cardiac disease, arthritis) found support for buffer effects for social support (Littlefield, Rodin, Murray, & Craven, 1990; Pennix et al., 1998). In studies conducted with cancer patients, results are mixed. Ringdal and colleagues (2007) reported that high social support worked to buffer against reactions to an external stressful event (in that study, diagnosis with terminal cancer). However, Pennix (1998) and Kornblith (2001) did not find evidence that high social support buffered stress in relation to health outcomes. In a sample of women with breast cancer, Kornblith et al. (2001) found that low social support worked additively with life event stress to influence outcomes rather than acting as a buffer.

Unlike the cohorts in which similar studies have been conducted, the WHI cohort is ethnically diverse (15% minority, including 7.8% African-American, 3.6% Latina, 3.0% Asian/Pacific Islander, 0.5% American Indian/Alaskan Native). Prior analysis of the WHI cohort found age-adjusted differences in breast cancer incidence rates between racial/ethnic groups such that all minority groups had lower incidence than white women, however adjustment for breast cancer risk factors accounted for the differences for all but African American women (Chlebowski et al., 2005). We investigated an interaction between race/ethnicity and stress in relation to breast cancer incidence in this population and found no significant interaction. In addition, we conducted stratified analyses in order to further examine the role of race/ethnicity; for white women, the results from the stratified model were unchanged from the entire population. Among groups of non-white women, the direction of the results were similar to the results from the entire population except that among African American women increasing life events after one life event was associated with a non-significant increase in breast cancer risk. Future research should further evaluate the role of psychosocial factors in breast cancer prevention and control in diverse populations (e.g., Soler-Vila et al., 2003).

Our findings, which ran contrary to our hypotheses, may reflect flaws in the underlying theory, inadequate statistical power, or measures that are unreliable or do not capture the theoretical construct. The theory may not be correct, although the study was designed to test a theory that was developed based on a significant body of human, as well as animal research (Hilakivi-Clarke et al., 1993). Limited statistical power was not an issue in the primary analyses; however, within strata of social support, power was more limited to evaluate the association of stressful life events with breast cancer risk.

Measurement problems are possible. While the prospective design of WHI ensured that psychosocial characteristics were assessed prior to breast cancer diagnosis, we operationalized stress using a brief self-report measure of how many life events occurred for women over the past year. While results for the simple count of life events were similar to results for life events weighted by the women's appraisal of how stressful these events were, self-report measures have been shown to be less reliable over time and do not take into account contextual factors when deriving a stress score (Klein & Rubovits, 1987). An additional limitation of the self-report instrument used in this study is that while it was adapted for use with older adults, some stressors relevant to older people were not included, such as death of a parent or caregiving. The gold standard for stress assessment is a structured interview such as the LEDS (Life Events

and Difficulty Scale). However, the structured interview in WHI was not practical. The self-report measures of life events stress and social support selected for inclusion was based on input from leading behavioral sciences investigators to ensure the scales met the following criteria: (1) research findings suggesting that the concept was important to women's health; (2) scale had adequate reliability and validity and, when available, normative data in samples of elderly persons; (3) brevity of the measure or its ability to be reduced in length on the basis of analytic strategies (e.g. factor analysis); and (4) absence of redundancy with other constructs in the questionnaire. All measures were pre-tested and the questionnaire revised to improve reliability (Matthews et al., 1997). Further, recent research suggests that the incremental value of conducting an interview to assess stressful life events over the self-report questionnaire approach may be limited (Lewinsohn, Rohde, & Gau, 2003).

A repeated measure of life events stress three years after baseline allowed us to consider recent levels of stress, as well as the influence of "chronic" or increasing stress over a three-year period, rather than a single baseline value to test associations with breast cancer incidence over varying periods of time. This type of analysis is important with a parameter likely to be variable, in contrast to other breast cancer risk markers, such as race/ethnicity or Gail score, and takes advantage of the longitudinal design of the WHI with a repeated measure of stressful life events. The results from these additional analyses were compatible with no association between stressful life events and breast cancer. Thirteen percent ($n=11,106$) of women who were part of the follow-up cohort did not complete the stressful life events questionnaire in year three and thus were not included in the time-varying or cumulative/change models. To evaluate the influence of excluding these women from the time-varying analyses, we compared our baseline results from the entire cohort to the results after excluding women without year three stressful life events. The results were unchanged, supporting that the loss to follow-up doesn't explain the findings in the time-varying analyses.

Categorizing social support to test the interaction may have led to spurious findings. A considerable body of social support research is based on the assumption that each unit increment in perceived social support is associated with a corresponding increase in adjustment through the entire range of the continuum. However, some evidence suggests problems with a unidirectional linear assumption and our preliminary analysis with social support did not support a linear association between social support and breast cancer risk. In breast cancer patients, poor support and/or negative interactions with intimate partners reduced emotional adjustment while positive interactions were not associated with better adjustment or well-being (Coyne and Anderson, 1999; Manne, Taylor, Dougherty, & Kemeny, 1997). When we modeled the interaction with social support as a continuous variable, the results supported the findings from the analysis of interaction with dichotomized social support, whereby social support has stronger effects in the lower ranges of measurement, but the effect was attenuated possibly because the linear assumption was not met. However, future research focused on those with the lowest levels of social support is warranted to elucidate the nature of the association.

The strengths of the current study include the prospective design with a large number of breast cancer cases, comprehensive breast cancer risk assessment, definitive breast cancer endpoint assessment based on central pathology report adjudication, repeated measurement of stressful life events, and inclusion of a validated measure of social support at baseline.

This study provides an opportunity to evaluate a question of long-standing interest in the field of health psychology, that of the association between stress and breast cancer, within a large, well-characterized cohort of women (Tomatis, 2001). Further, it examines this association with multiple measures of stressful life events and considers behavioral mediators and the moderating influence of social support. It appears unlikely that stressful life events are independently associated with breast cancer risk or that an association is mediated through

risky health behavior; however, social support and stressful life events may interact in relation to breast cancer risk. More research is needed to establish whether increased psychosocial stress (e.g., stressful life events in the absence of protective psychosocial factors, such as social support) is prospectively associated with decreases in the level of endogenous estrogen. In future research, additional repeated measurements of factors related to stress, social support, health habits, and endogenous estrogen may help to clarify the association, if any, and identify mechanisms. Additionally, factors such as depression or coping that could potentially predict onset of breast cancer were not examined in this research and should be the focus of future research. Clinicians may reassure patients that stressful life events alone or in the presence of poor social support are unlikely associated with increased breast cancer risk.

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Appendix

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Table 1
 Characteristics of 84,443 study participants, by level of stressful life events, Women's Health Initiative Observational Study

	Total n=84,334	0 (n=18,570)	1 (n=26,385)	2 (n=19,625)	3 (n=11,044)	4+ (n=8710)
Mean age (years)	63.5 (7.3)§	64.3 (7.3)	64.1 (7.3)	63.2 (7.3)	62.6 (7.3)	61.6 (7.2)
Social support (continuous)	36.0 (7.8)	37.5 (7.3)	36.9 (7.4)	35.8 (7.7)	34.6 (8.0)	32.3 (8.5)
Five Year Risk from Gail prediction *	1.8 (1.0)§	1.9 (1.0)	1.9 (1.0)	1.8 (1.0)	1.7 (1.0)	1.6 (1.0)
Race/ethnicity (%)						
White	83.9	87.1	86.5	83.6	80.7	74.0
African American	7.8	5.0	6.3	8.5	10.3	13.1
Hispanic	3.6	3.1	2.7	3.4	4.4	7.1
Asian/Pacific Islander	3.0	3.5	3.0	2.7	2.4	2.8
Alaskan Native/American Indian	0.42	0.26	0.33	0.41	0.56	0.93
Other	1.1	0.8	1.0	1.1	1.3	1.9
Education level (%)						
Less than high school education	4.9	4.3	4.2	4.8	5.5	7.8
High school/GED	16.2	16.4	16.4	16.2	15.9	15.2
School after high school	36.3	33.0	34.8	37.3	39.5	41.8
College degree or higher	41.9	45.6	44.0	41.0	38.3	34.1
Income level (%)						
< \$20,000	14.4	10.6	11.8	14.6	18.5	25.0
\$20,000 – \$49,999	40.3	39.2	40.7	40.2	40.9	41.2
\$50,000 – \$99,999	27.8	30.2	29.0	28.0	25.7	21.5
>\$100,000	10.2	12.2	11.3	10.0	8.2	5.8
Insurance (%)						
No insurance	2.7	1.6	1.85	2.8	3.7	5.9
Public insurance	9.1	8.9	8.9	8.8	9.5	10.3

	Total n=84,334	0 (n=18,570)	1 (n=26,385)	2 (n=19,625)	3 (n=11,044)	4+ (n=8710)
Private insurance	87.3	88.5	88.4	87.5	85.8	82.4
Alcohol use						
Doesn't drink	41.5	39.1	39.6	42.0	43.5	48.7
>0 to 2 drinks per day	54.0	56.5	55.6	53.3	52.5	47.4
> 2 alcoholic drinks per day	4.3	4.3	4.6	4.5	3.9	3.8
Current smoker	6.2	4.8	5.3	6.5	7.5	9.5
Physical activity $\geq$ 4 episodes moderate/ strenuous activity (exceeding 20 min)/week (%)	29.5	32.8	30.6	29.2	26.8	23.1
BMI $\geq$ 30, kg/m ² (%)	24.6	19.8	22.4	25.6	28.5	34.6
Mammography during follow-up (%) [§]	70.6	71.5	71.9	71.2	69.0	65.4

Note: All comparisons are significant at $p < 0.001$.

* Gail model: Computed from age, age at menarche, number of previous breast biopsies, presence of atypical hyperplasia on biopsy, age at first childbirth, number of first-degree relatives with a history of breast cancer, and the interactions between biopsies and age and between age at first childbirth and number of affected first-degree relatives

[§] Mammography during follow-up: Computed as percent of annual visits reporting mammogram since last visit and dichotomized as adherent ($\geq 75\%$) or non-adherent ($< 75\%$)

Table 2

Hazard Ratios and 95% confidence interval (CI) for association between stressful life events and breast cancer in the Women's Health Initiative Observational Study

	Cases	Person-years	Age-adjusted		+ Socio-demographic and health factors ^a		+ Gail model score and other breast cancer risk factors ^b		+ Behavioral factors ^c	
			Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Baseline Life Events N=84,334										
0	519	140,456	reference		reference		reference		reference	
1	838	199,225	1.14	(1.02,1.27)	1.12	(1.01,1.25)	1.12	(1.01,1.25)	1.12	(1.01,1.26)
2	585	148,657	1.08	(0.96,1.22)	1.08	(0.96,1.21)	1.08	(0.96,1.22)	1.08	(0.95,1.22)
3	316	83,821	1.05	(0.91,1.21)	1.06	(0.92,1.22)	1.08	(0.94,1.24)	1.08	(0.93,1.24)
4+	223	65,468	0.97	(0.82,1.13)	0.98	(0.83,1.15)	1.02	(0.86,1.19)	1.02	(0.87,1.21)
p-value (total/trend)			0.076/0.53			0.20/0.86		0.30/0.82		0.33/0.85
Baseline Life Events Weighted by Participant's Appraisal of Stress N=84,334										
0	519	140,456	reference		reference		reference		reference	
1	838	199,225	1.16	(1.04,1.3)	1.15	(1.02,1.28)	1.14	(1.02,1.28)	1.145	(1.02,1.29)
3	585	148,657	1.06	(0.93,1.21)	1.043	(0.91,1.19)	1.050	(0.92,1.20)	1.056	(0.92,1.21)
4+	316	83,821	1.056	(0.93,1.20)	1.062	(0.93,1.21)	1.070	(0.94,1.22)	1.055	(0.92,1.21)
>5	223	65,468	1.023	(0.90,1.16)	1.039	(0.91,1.18)	1.065	(0.94,1.21)	1.063	(0.93,1.21)
p-value (total/trend)			0.08/0.64		0.19/0.93		0.23/0.76		0.24/0.85	
Time-varying stressful life events N=84,334										
0	625	172,152	reference		reference		reference		reference	
1	862	210,637	1.09	(0.98,1.21)	1.09	(0.99,1.21)	1.09	(0.98,1.21)	1.09	(0.98,1.22)
2	535	137,611	1.01	(0.90,1.13)	1.01	(0.90,1.13)	1.02	(0.91,1.15)	1.01	(0.90,1.14)
3	281	68,733	1.04	(0.90,1.19)	1.06	(0.92,1.22)	1.07	(0.93,1.24)	1.08	(0.93,1.25)

	Cases	Person-years	Age-adjusted		+ Socio-demographic and health factors ^a		+ Gail model score and other breast cancer risk factors ^b		+ Behavioral factors ^c	
			Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
4+	178	48,494	0.91	(0.77,1.08)	0.93	(0.79,1.11)	0.96	(0.81,1.14)	0.97	(0.81,1.16)
p-value (total/trend)			0.18/0.35		0.24/0.58		0.38/0.87		0.36/0.91	
Cumulative stressful life events N=73,228										
0	147	132,487	reference		reference		reference		reference	
0-1	652	133,645	1.09	(0.91,1.30)	1.08	(0.90,1.29)	1.08	(0.90,1.29)	1.037	(0.86,1.25)
1-2	477	103,623	1.04	(0.86,1.25)	1.04	(0.86,1.25)	1.04	(0.86,1.26)	1.032	(0.85,1.25)
2-3	207	47,047	1.01	(0.82,1.25)	0.99	(0.80,1.23)	1.01	(0.82,1.26)	0.987	(0.79,1.23)
3-5	105	25,509	0.96	(0.75,1.24)	0.99	(0.77,1.28)	1.04	(0.80,1.34)	1.027	(0.79,1.33)
p-value (total/trend)			0.67/0.38		0.74/0.44		0.90/0.76		0.98/0.87	

Note: The first p-value is the chi-square test of the overall association between classifications, i.e. between breast cancer incidence and stressful life events. We also show the p-value for a chi-squared test of linear trend which evaluates whether breast cancer risk increases with number of stressful life events.

^a Adjusted for age plus education (<high school, high school or equivalent, some college, >=college degree), ethnicity (AI/AN, Asian/Pi, Caucasian, Black/AA, Hispanic, Other), diagnosis with diabetes (yes/no), and BMI (linear). Additional factors considered: income (don't know/missing, <20K, 20K to < 50K, 50K to <100K, 100K+), insurance status (none, public, or private), cardiovascular disease (yes/no), previous other cancer diagnosis (yes/no), and hypertension (no, yes-untreated, yes-treated).

^b Adjusted for those on the left plus five-year breast cancer risk from Gail prediction (age, age at menarche, number of previous breast biopsies, presence of atypical hyperplasia on biopsy, age at first childbirth, number of first-degree relatives with a history of breast cancer, and the interactions between biopsies and age and between age at first childbirth and number of affected first-degree relatives) plus (no births, 1,2,3,4,5+), history of hysterectomy/bilateral oophorectomy, OC use (never, >0 to <5 years, 5 to <10 years, and 10+ years), HRT use (never, >0 to <5 years, 5 to <10 years, 10+ years). Additional factors considered: number of months breast feeding (never, 1-8 mo, >8 mo).

^c Adjusted for those on the left plus alcohol consumption (none, 0-1/day, 1-2/day, 2-3/day, >3/day), smoking (never, past, current), fat intake (<30% vs. >=30%), and annual mammography rate during follow-up. Additional factors considered: current physical activity (vigorous exercise 2+ days/week)

Hazard Ratios and 95% confidence interval (CI) for association between baseline stressful life events and breast cancer by social support in the Women’s Health Initiative Observational Study

Stressful life events	Social Support	
	Low Social Support Hazard Ratio (CI)	High Social Support Hazard Ratio (CI)
0	Reference	Reference
1	1.20 (1.00,1.43)	1.08 (0.93,1.25)
2	1.07 (0.88,1.29)	1.09 (0.92,1.28)
3	0.98 (0.79,1.22)	1.17 (0.96,1.43)
4+	0.89 (0.70,1.13)	1.26 (0.99,1.61)

Note: Hazard ratio adjusted for age, education (<high school, high school or equivalent, some college, >=college degree), ethnicity (AI/AN, Asian/PI, Caucasian, Black/AA, Hispanic, Other), diagnosis with diabetes (yes/no), BMI (linear), five-year breast cancer risk from Gail prediction (age, age at menarche, number of previous breast biopsies, presence of atypical hyperplasia on biopsy, age at first childbirth, number of first-degree relatives with a history of breast cancer, and the interactions between biopsies and age and between age at first childbirth and number of affected first-degree relatives) parity (no births, 1, 2, 3, 4, 5+), history of hysterectomy/bilateral oophorectomy, OC use (never, >0 to <5 years, 5 to <10 years, and 10+ years), HRT use (never, >0 to <5 years, 5 to <10 years, 10+ years), alcohol consumption (none, 0–1/day, 1–2/day, 2–3/day, >3/day), smoking (never, past, current), fat intake (<30% vs. >=30%), and annual mammography rate during follow-up..

p-value for interaction (p=0.074)

p-value for overall association between breast cancer incidence and stressful life events: High social support (p=0.323); Low social support (p=0.043)