ISSN: 2321-8819 (Online) 2348-7186 (Print) Impact Factor: 1.498 Vol. 6, Issue 1, January, 2018

Social Support, Inflammation, and Depressive Symptoms among Cancer Survivors and Older Adults: Testing Direct and Mediation Effects

Danish Imtiaz[1], Farjad Ikram[2] and Aemen Sultan[3]
[1]University of Health Sciences, Lahore, Pakistan
Email: danishimtiaz17@yahoo.com
[2]University of Health Sciences, Lahore, Pakistan
Email: fudgefury@gmail.com
[3]University of Health Sciences, Lahore, Pakistan
Email: amy_sultan16@hotmail.com

Abstract

Background: There are two leading hypotheses that explain how social networks influence chronic diseases, such as depression. The "main effects hypothesis" describes a direct relationship between social support and depressive symptoms. The "stress- buffering hypothesis" posits that inadequate social support and life events increase the risk of disease outcomes. Insufficient social support is believed to be expressed through physiological changes (e.g., inflammation) that lead to the development of depression and other chronic conditions. The objective of this study was to empirically test these two leading hypotheses among cancer survivors and older adults without cancer and to explore the intermediate pathways between social support, chronic inflammation, and depressive symptoms.

Method: A secondary analysis of two waves of data (2005-2011) from the National Social Life, Health, and Aging Project (NSHAP) was used to test the hypotheses of interest (n=698). Depressive symptoms were measured with the 11-item Iowa version of the CES-D. Inflammation was measured by C-reactive protein (CRP), Tumor necrosis factor-alpha (TNF-α), and Vascular Endothelial Growth Factor (VEGF). Social support was assessed with six items measuring emotional and tangible support. Structural equation models were used to assess direct and indirect paths between social support, inflammation, and depressive symptoms.

Results: Cancer survivors and older adults without a history of cancer were similar in terms of their depressive symptoms, inflammatory levels and social support over time. A significant negative direct effect was observed between the total amount of social support in Wave 2 (W2) and depressive symptoms in W2 (p=0.01). No differences between cancer survivors and older adults without cancer were observed in path models and no indirect paths between social support, inflammation, and depressive symptoms were statistically significant in either group.

Discussion: The results support the main effects hypothesis, whereby social networks directly influence depressive symptoms. Clinicians should consider screening for social support to prevent or reduce depressive symptomatology.

Keywords: social support, inflammation, depressive symptoms, cancer survivors

Background

Cancer survivors are at risk for depressive symptoms in the United States. Approximately 14% of cancer survivors in 2010 self-reported current depression compared to 9% of those without a history of cancer (61). The prevalence of depression varies by primary cancer site with lung, gynecological, and hematological cancer survivors reporting the highest levels of depression at the time of cancer diagnosis (62). Variation in the prevalence estimates also exists between studies. For example, studies among breast cancer survivors report prevalence estimates ranging from 1% to as high as 56% (63). Despite this variation, the consistently high occurrence of depressive symptoms in this population underscores the need to understand the potential pathways that place cancer survivors at risk for poor mental health outcomes.

1. Social Networks and Depression

Two prominent frameworks, the "main effects hypothesis" and the "stress- buffering hypothesis," have emerged to describe how social support gets "under the skin" (64–66). The "main effects" hypothesis posits that social support directly contributes to health via the perception of help from peers and social influence on health behaviors, ideas, and emotions, irrespective of existing levels of support or experiencing stressful life events, such as cancer (64, 66). The perception of adequate social support from the network members may directly improve health outcomes, while inadequate support may lead to poor to health outcomes (7). Among cancer survivors, low social support is associated with higher depressive symptomatology (67,68) and is predictive of the development of depression (10–12). However, few studies have considered how alterations in social support from life events, such as cancer, directly impact psychosocial well-being.

Disparities in social structures (e.g., policies, norms, etc.), interpersonal relations, including negative social interactions, and individual risk factors (e.g., economic position, demographics, etc.) are expressed through biological pathways. The "stress- buffering hypothesis" posits that socially supported individuals are safeguarded against physiological responses to acute and chronic stressors, ultimately protecting them from the development of disease downstream (64,65). Stressors activate the immune response in ways that elevate systemic levels of inflammation (e.g., pro-inflammatory cytokines such as, tumor necrosis factor-alpha (TNF-α) (72). Instable or low social support over time may be perceived as a continuously stressful situation and may result in sustained levels of chronic, low-grade inflammation (65). Chronic inflammation can create an ideal tumor promoting environment (13,73) where tumor initiation, progression, angiogenesis, and metastasis can occur (13). This is especially important for cancer survivors, as deleterious physiological changes may lead to inequities in cancer recurrence (74). Moreover, inflammation is related to aging (75), the development of depressive symptoms, and atherosclerosis (72). Therefore, cancer survivors may be at an increased risk of inflammation-related comorbidities, including depression (55), compared to the general older adult population.

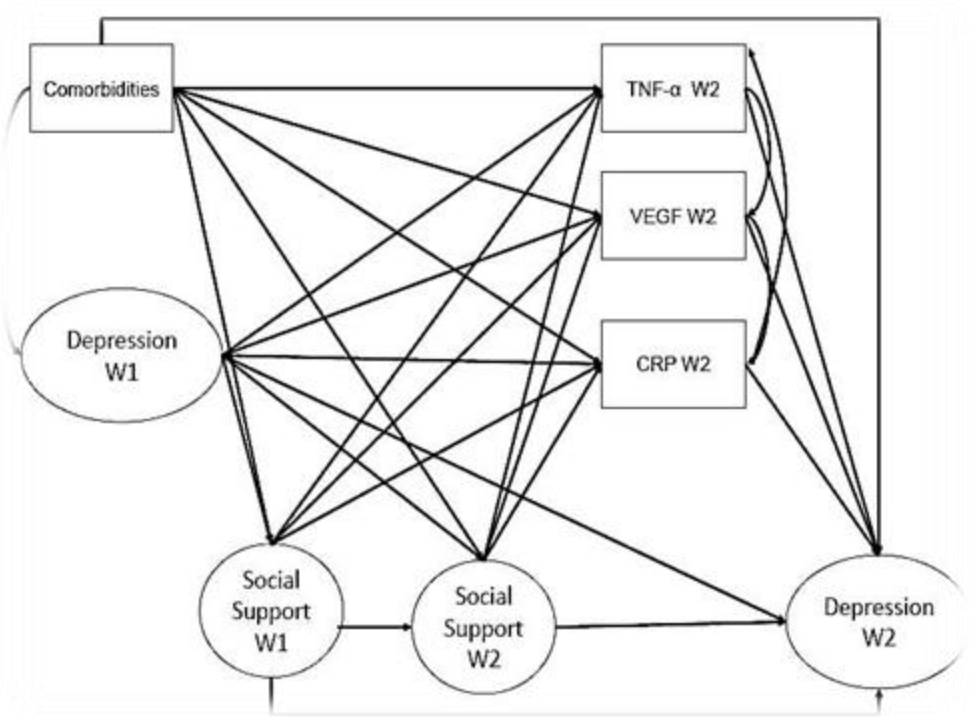
Previous studies have established a robust link between elevated inflammation and depression in both clinically depressed (76) and community samples (77). The relationship between inflammation and depression is bi-directional (78), as depressed individuals exhibit a larger inflammatory response to stressors (76,79) and medication- induced inflammation can result in the manifestation of depressive symptoms (77).

Previous studies provide mixed evidence for an association between immune functioning and social network components in the general adult population (25, 54,31–34,80), and among cancer survivors (47, 69,35–39). However, several studies demonstrate beneficial effects when social networks are adequate and elevated levels of inflammation when they are inadequate. For example, an experimental study demonstrated that participants who perceived negative social situations with their partner, friends, and family had higher Interleukin-6 (IL-6) and TNF-α responses over time and demonstrated worse stress tolerance (81). In a longitudinal population-based study, Yang et al., (2014) observed that social strain was positively associated with C-reactive protein (CRP) and

IL-6 and that social support were negatively associated with CRP and IL-6 (48). Glei et al. (2012) found that higher social support was associated with higher CRP (34) and Ford et al. (2006) showed that higher social network index scores were associated with elevated CRP in older men (aged >60) (32). Similarly, in a qualitative review of cancer survivors, Penwell and Larkin (2010) noted that the majority of studies (5/7) supported a positive association between social support and inflammation (25).

Collectively, the literature provides evidence for direct relationships between social support and inflammation, social networks and depressive symptoms, and depressive symptoms and inflammation. However, no studies have formally tested inflammation as an intermediate pathway. The objective of this study was to empirically test the main effects and stress-buffering model in a population of older adults, who either did or did not report a history of cancer (Figure 1). Specifically, our aims are threefold: 1) to assess the main affects hypothesis by directly testing the role of social support and depressive symptomatology; 2) to test the stress-buffering hypothesis by assessing the relationship between social support and depressive symptoms; and 3) to investigate three markers of inflammation (TNF-α, CRP, and Vascular Endothelial Growth Factor (VEGF)) as potential intermediate pathways to elucidate the mechanisms by which social support influences depressive symptoms. Support for a main effects hypothesis would be indicated by no group differences between cancer survivors and older adults without cancer. More pronounced relationships between social support and depressive symptoms, as well as significant intermediate paths between social support, inflammation, and depressive symptoms among cancer survivors would provide evidence for the stress-buffering hypothesis.

Figure 1. Hypothesized relations between social support, inflammation, and depression



Methods

2. Study Population

A sample of 2,261 older adults between the ages of 57-85 participated in two waves of data collection (Wave 1 (W1): 2005-2006, Wave 2 (W2): 2010-2011) by the National Social Life, Health, and Aging Project (NSHAP) (12, 57). Cancer survivorship was defined by individuals who self-reported a diagnosis of cancer (excluding skin cancers such as, melanoma, basal cell carcinoma, and squamous cell carcinoma) on the W1 questionnaire. Participants who self-reported a history of cancer for the first time in W2 were excluded, since their social support networks would not reflect their cancer diagnosis in W1 (n=148). In accordance with the American Heart Association and the CDC guidelines, participants with CRP levels greater than 10 (an indication of acute infection) were excluded from the analysis because the present study is focused on chronic, low-grade inflammation (n=160) (49). We conducted a complete case analysis and excluded individuals with out of range biomarker data or who were missing at least one inflammatory marker (n=1,226). Missing data on social support (n=1) and covariates (n=28) was also excluded. There was no missing data for depressive symptoms. Our final sample consisted of 698 individuals, of whom 90 reported a history of cancer.

3. Measures

Depressive symptoms

Depressive symptoms was measured during the W1 and W2 home interview and was assessed using the 11-item Iowa short-form version of the Center for Epidemiologic Studies Depression (CES-D) Scale (82). The Iowa version of the CES-D has been previously validated and shown to exhibit the same dimensions as the 20-item CES-D, while losing little precision (83). Each respondent was asked to report how often in the past week they felt depressed, like everything was an effort, sad, etc... Response options included 0= "rarely or none of the time", 1= "some of the time", 2= "occasionally", and 3= "most of the time." Two items 'felt happy' and 'enjoyed life' were reverse coded to be consistent with the other items. The Iowa short form does not diagnose clinical depression, but rather, is a scale of depressive symptomatology. For the path analysis, all items were summed with higher scores indicating higher levels of depressive symptoms. For the latent variable model each scale item was used to measure the underlying construct of

depression. The Cronbach's alpha for the NSHAP sample was 0.80 in W1 and 0.79 in W2.

Social Support

Social support questions were adapted from Schuster et al. (1990) (184).

Participants were asked in each wave of data collection to report how often they could 1) open up to, and 2) rely on their spouse/partner, family, and friends, for a total of six questions. Responses were measured on a three-point scale ranging from 0= "hardly ever or never" to 2= "often." The six social support questions were summed to calculate the total amount of support received, with higher scores indicating more perceived social support for path models. For the latent variable model each scale item was used to measure the underlying construct of social support.

Inflammation

Three inflammatory markers previously associated angiogenesis and tumor progression, were chosen to estimate chronic, low-grade inflammation: CRP, TNF-α, and VEGF (13, 14). CRP was measured in both waves, while the other two biomarkers were only collected in W2 (58). Biospecimen collection, storage and processing have been previously described (58, 59,48). The coefficients of variation were considered within an acceptable range for all inflammatory markers (9.5% for CRP, 7.2% for TNF-α and 8.5% for VEGF). All inflammatory markers were natural log transformed to normalize their distributions.

Covariates

Confounders were selected from the literature and were measured in W1: age (continuous), gender (0=male (reference) vs. 1=female), education (1=high school education or less vs. 0=some college or more (reference), marital status (0=married/cohabitating partner (reference) vs. 1=unmarried), race (0=non-Hispanic (reference), 1=other), smoking (1=smoker vs. 0=non-smoker (reference), and CRP (continuous). Physical activity was classified as: low activity (e.g., exercise less than once a month), some activity (exercise at least once a month to less than twice a week), or frequent activity (exercise three or more times per week). Obesity was assessed with body mass index (BMI). Trained NSHAP interviewers objectively measured height and weight. Body mass index was derived from measured height and weight and was calculated as [(weight (lbs)/ height (in)^2)*703] (77). Comorbid conditions were defined by a modified version of the Charlson Comorbidity Index (7). Individuals who reported any of the following conditions were assigned one point for each condition: hypertension, heart condition (including: heart attack/myocardial infarction, congestive heart failure, stroke, or any procedure for coronary artery disease), diabetes, COPD/asthma, arthritis, Alzheimer's disease or dementia, and sensorimotor conditions (e.g., urinary or stool incontinence, or other urinary problems). Scores of the 11 questions were summed, for a total of 11 possible points. Functional impairment was measured using the Activities of Daily Living Scale (77) Scores were summed to represent higher levels of impairment in the path analysis. For the latent variable model each scale item was used to measure the underlying construct of physical disability.

4. Statistical Analysis

Means and standard deviations for continuous variables and proportions for categorical variables were calculated to compare cancer survivors to older adults without cancer on socio demographic, social support, mediator, and outcome variables. Simple linear regression was conducted to test differences between continuous variables and cancer survivors and older adults. Chi-square tests were used to test for differences in the proportions of categorical variables for cancer survivors and older adults. Pearson correlations were used to test preliminary correlations between depressive symptoms, social support, and inflammatory markers.

Path analyses were used to test for group invariance because convergence problems were experienced with the latent variable model for the cancer group. First, each group was tested separately to determine if the model fit well for both groups using Hu & Bentler (1999)'s criteria for satisfactory model fit: RMSEA $\leq$ 0.06, CFI $\geq$ 0.95, and SRMR $\leq$ 0.08 (85). Improvements in model fit often take many forms, but the present study only focused on adding a residual covariance if it was theoretically plausible and substantial enough that over-fitting (and possibly chance covariation) did not occur.

We additionally conducted a latent variable model with the total sample because latent models have the ability to parcel out measurement error (68). SEM testing proceeded in two phases: a measurement phase and a structural phase (68). In the measurement phase, we estimated the construct reliability using coefficient H (68), which was

considered acceptable for all factors (Social Support W1= 0.95, Social support W2= 0.95, Functional Impairment W1= 0.85, Depressive symptoms W1= 0.81, Depressive symptoms W2= 0.80). In the initial measurement phase, a confirmatory factor analysis (CFA) model was imposed on the variance-covariance matrix in which all latent variables and standalone manifest variables were allowed to covary. This method ensures that any badness of fit in the model is the result of measurement model misspecification, rather than structural relations among the latent variables. Similar to the path model, the measurement model was evaluated to determine if improvements in model fit could be made. Modification indices were used to determine if meaningful improvements from residual covariances could be added to improve the initial model fit. Theoretically plausible modifications were made in a sequential fashion starting with the modification that would provide the largest drop in chi-square value. Once a modification was incorporated, the model was re-estimated and new modifications were reviewed. Direct and indirect effects were estimated for the structural model and are reported in SAS version 9.3 (SAS Inc., Cary, NC) was used to test distributional assumptions and calculate descriptive statistics and Mplus version 7 (Muthén & Muthén, Los Angeles, CA) was used to conduct SEM.

Results

Correlations between social support, inflammation, and depressive symptoms are reported in Table 1. Depressive symptoms were moderately correlated across waves

(r=0.55, p<0.05). Depressive symptoms in W2 was weakly correlated with social support in W1 (r=-0.21, p<0.05), social support in W2 (r=-0.25, p<0.05), CRP in W1 (r=0.14, p<0.05), CRP in W2 (r=0.12, p<0.05), and TNF-α in W2 (r=0.13, p<0.05). Social support in W2 was weakly, but positively correlated with TNF-α in W2 (r=0.14, p<0.05), CRP W1 (r=0.10, p<0.05), and CRP in W2 (r=0.08, p<0.05).

The hypothesized path model fit well for each group, albeit a low CFI for the cancer survivors (Cancer survivors: RMSEA= 0.05, CFI=0.93, SRMR=0.04; Older adults: RMSEA=0.03, CFI=0.98, SRMR=0.02). No theoretically plausible misspecifications were identified for each group. Configural invariance was estimated by testing the model for both groups simultaneously. The model fit well and the modification indices did not indicate significant misspecification (RMSEA= 0.03, CFI=0.98, SRMR=0.02). More social support in W2 was directly associated with less depressive symptoms in W2 for older adults (estimate= -0.12, p<0.01). Social support in W1 was associated with VEGF in W2 among older adults (estimate=-0.10, p=0.04).

TNF-α was positively associated with depressive symptoms among cancer survivors (estimate=0.18, p=0.02).

Table 1. Correlations among depressive symptoms and inflammation in Wave 2 (n=698)

Items	1	2	3	4	5	6	7
1. Depressive Symptoms W2	-						
2. Depressive Symptoms W1	**0.55***	-					
3. Social Support W2	**0.25***	**-0.30***	-				
4. Social Support W1	**0.21***	**-0.30***	**0.61***	-			
5. CRP W2	**0.12***	**0.08***	**-0.10***	-0.07	-		
6. CRP W1	**0.14***	**0.10***	0.00	-0.01	**0.51***	-	
7. TNF-α	**0.13***	**0.14***	-0.05	-0.06	**0.09***	**0.09***	-
8. VEGF	0.00	-0.05	-0.03	**-0.08***	**0.11***	**0.09***	**0.20***

Finally, path invariance was tested by constraining all paths to be equal across groups. The p-value was not statistically significant, indicating that a significant amount of badness of fit was not introduced into the model when constraining the parameters to be equal across groups (scaled χ^2=66.81, *df*= 54, p=0.1132), indicating that these groups did not differ and was considered the final model. The final path model fit well (RMSEA= 0.03, CFI= 0.97, SRMR=0.03) and is presented in Figure 3. No mediation effects were observed between social support, inflammation and depression Social support in W2 was significantly associated with depressive symptoms (estimate= - 0.11, p=0.01).

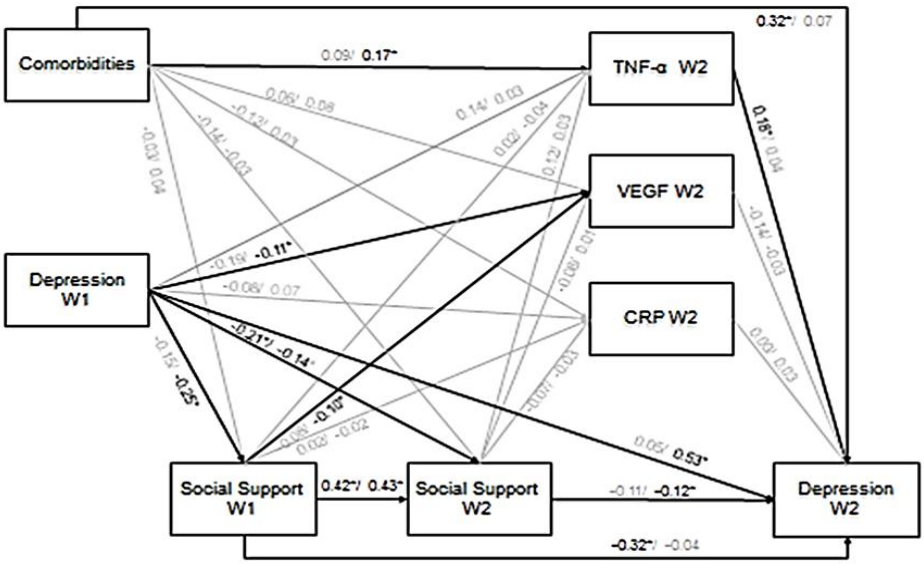


Figure 2. Standardized results from the path analysis for cancer survivors and older adults prior to constraining paths to be equal

Final path model for cancer survivors and older adults. All parameters are free to vary across groups. Controlling for BMI, CRP, age, race, gender, education level, marital status, smoking status, physical activity, and functional impairment in Wave 1. Estimates are standardized and presented as cancer survivor/ older adults.

*denotes $p<0.05$

For the latent variable model, the initial measurement model fit well despite a low CFI, (RMSEA=0.03, CFI=0.92, SRMR=0.05) but the modification indices suggested three plausible modifications: a covariance between the indicator for social support "rely on spouse" and the CES-D indicator "felt lonely" in W1 and W2, and a covariance between the CES-D indicator "could not get going" and the functional impairment indicator "getting dressed" in W1. After incorporating the final modifications we assessed the model fit. The model fit well (RMSEA $\leq$ 0.06 and SRMR $\leq$ 0.08), except in terms of the CFI (O). Next, items measured at two time points were constrained to be equal to each other. The scaled chi-square indicated that constraining the items to be equal across time points did not introduce a significant amount of badness of fit (scaled χ^2=21.71, *df*= 15, p=0.1156) and was considered our final measurement model (RMSEA=0.03, CFI=0.92, and SRMR=0.05).

Table 2. Standardized estimated direct and indirect effects for the path models

From Social Support W2 to Depression W2									
		-0.07	0.61	**-0.12**	**<0.01**	**-0.11**	**0.01**	**-0.24**	**0.03**
Total effect Total indirect effect		0.03	0.36	0.00	0.99	0.00	0.82	0.00	0.64
Direct Effect Social Support W2 → Depression W2		0.11	0.42	**0.12**	**<0.01**	**-0.11**	**0.01**	**-0.25**	**0.03**
Social Support W2 → CRP W2 →	Depression W2	0.00	0.99	0.00	0.66	0.00	0.58	0.00	0.82
Social Support W2 → TNF-α	Depression W2	0.02	0.35	0.00	0.70	0.00	0.57	0.00	0.99
Social Support W2 → VEGF	Depression W2	0.01	0.59	0.00	0.80	0.00	0.97	0.00	0.56

*Bold indicates $p<0.05$

Next, the hypothesized structural model was estimated using the modifications from the final measurement model. Specifically, hypothesized direct and indirect paths were

modeled from social support in W1 and W2 to each inflammatory marker in W2, and depressive symptoms in W2. The final structural model fit well, except in terms of CFI (RMSEA=0.03, CFI=0.92, and SRMR=0.05). The results of the latent variable model for the total sample were similar to the constrained path analysis, and supported a direct path from the factor social support in W2 to the factor depressive symptoms in W2 (estimate= -0.25, p=0.03) (Figure 4). No evidence of an indirect effect between social support, inflammation, and depressive symptoms was observed.

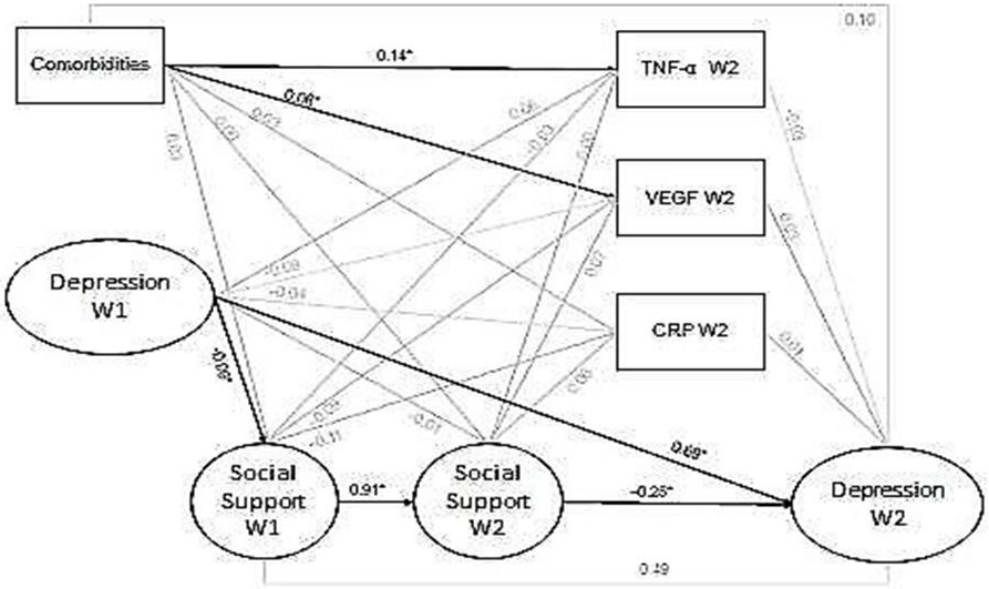
Discussion

The current study is one of few to investigate intermediate inflammatory pathways using two social support frameworks. Our study provides support for a main effects hypothesis, whereby social support directly influences depressive symptoms, and provides little evidence for the stress buffering hypothesis.

Consistent with other studies that support a direct relationship between social support and depressive symptomatology (66,77), our study demonstrated that a constrained path model fit the data well, indicating no group differences between cancer survivors and older adults. Additionally, we observed an inverse relationship, meaning that higher total support was associated with lower depressive symptoms, while controlling for a number of known confounding factors, such as sociodemographic factors, smoking status, physical activity, functional impairment, and multiple comorbidities.

Although social science researchers hypothesize that chronic inflammation is a key pathway by which social support influences chronic disease outcomes, we found no empirical evidence for an intermediate link, whereby higher levels of social support lead to lower levels of chronic inflammation, which in turn leads to a lower occurrence of depressive symptoms. Moreover, these relationships were similar across groups, suggesting that social support directly influences depressive outcomes, regardless of facing a major stressful life experience, like cancer.

Figure 4. Structural model depicting relationships between factors and observed variables



Controlling for BMI, CRP, age, race, gender, education level, marital status, smoking status, physical activity, and functional impairment in Wave 1. Estimates are standardized. Covariances and residuals are not depicted for simplicity.

*denotes p<0.05

We only identified one study that tested inflammation as a mediator among cancer survivors. Hughes et al. (2014) showed that breast cancer patients with lower pre- treatment social support had higher IL-6 concentrations over time, and that higher levels of IL-6 predicted marginally larger increases in depressive symptoms (35). The differences in the results may be due to the use of

clinical samples versus population based samples and the inflammatory measures used. Additionally, we simultaneously tested these interrelationships using robust a SEM framework. Support for a main effects model may suggest that interactions with network members directly influence emotional states (86,87) and that the perception of lower support is detrimental to psychosocial functioning, regardless of experiencing a stressful event. In a meta-analysis, Mitchell and colleagues demonstrated that the pooled risk of depressive symptoms in long-term survivors was similar to their spouses, which may suggest transmission of depressive symptoms between partners (prevalence in cancer survivors= 26.7% versus 26.3%, RR=1.01 (95% CI: 0.86–1.20; p=0.88) through shared maladaptive behaviors or coping strategies, and/or lower resources that contribute to poor psychosocial outcomes (88).

However, not all stressful events are perceived equally and may be individual and context specific. Therefore, some cancer survivors may be more resilient to life stress (89). It should also be noted that socially supported individuals may be able to buffer stress by attenuating or preventing a stress response in the first place. The perception that others will help them and provide resources in times of need may prevent a situation from being interpreted as highly stressful (64); however we had no way of measuring perception of the stress response. Additionally, we only tested depressive symptoms as the main outcome and other chronic or acute diseases may show more pronounced relationships that support the stress-buffering hypothesis. For example, Kielcott-Glaser et al. (2005) showed that socially supportive interactions were associated with a stronger immune response and faster wound healing compared to those who reported conflict interactions (90).

Our results, in accordance with other studies, highlight that increased social support can reduce depressive symptomatology for cancer survivors and the older adult population, in general (77). Both groups may benefit from network interventions that enhance perceived feelings of emotional and tangible support. Providers should screen older adults and cancer survivors for adequate social support in order to prevent the negative cascade of symptoms associated with depressive symptoms and other chronic diseases. Given the health relevance of inflammation and depressive symptoms, social support interventions may improve long-term health and quality of life.

The goal of this study was to empirically test two leading social network hypotheses over a five-year period using a two-group SEM framework with a large sample of older adults and multiple markers of inflammation. Despite these strengths, our study is not without limitations. First, the 11-item Iowa short-form CES-D measures depressive symptoms, rather than a clinical diagnosis of depression and some researchers have argued that this scale measures psychological distress, rather than depressive symptoms (91,92). Second, the results may be due to reverse causality, given that individuals with depressive symptoms may have higher levels of circulating inflammation (90). However, other studies support a unidirectional, rather than bidirectional relationship between social support, inflammation, and depressive symptoms (35). Third, TNF-α and VEGF were only measured in W2 and failure to control for these variables at baseline may have caused residual confounding. Fourth, our cancer survivor sample was small and the model (or portions of the model) may have been underpowered. Fifth, the cancer survivors and older adults were similar in terms of network support and depressive symptoms, which may be attributed to the time since cancer diagnosis, since the majority of cancer survivors had been diagnosed more than 10 years prior to the start of the NSHAP study. Therefore, a better proxy for stressful life events should be considered. Future large-scale studies should investigate the interrelationships among recent cancer survivors (e.g., < five years from diagnosis) to determine if differences exist. Finally, our analytic sample had large amounts of missing data due to assay-related problems with the inflammatory markers.

Sensitivity analyses demonstrated that those who were missing were healthier than those included in the analytic sample on factors such as smoking and physical activity, which are both associated with inflammatory levels (59,60). Therefore, the inclusion of unhealthier older adults in the analytic sample may have overestimated the true associations of interest. Future longitudinal studies with repeated biomarker measures are needed to verify our findings. Additionally, because of the strict exclusion criteria, our study may have limited generalizability outside of this population.

5. Conclusion

In conclusion, our analysis supports a main effects hypothesis whereby social support is associated with lower levels of depressive symptoms, irrespective of life events. The results do not support an intermediate mechanism whereby inflammation mediated the relationship

between social support and depressive symptoms. A better understanding of the physiological mechanisms underlying social influences on depressive symptomatology and cancer survival is needed to elucidate meaningful biomarkers for therapeutic agents, as well as psychosocial interventions to improve well-being in late life. Public health interventions should consider the direct benefits of enhancing network support for cancer survivors and older adults at risk for depressive symptoms.

REFERENCES

1. Antoni MH, Lutgendorf SK, Cole SW, Dhabhar FS, Sephton SE, McDonald PG, et al. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nat Rev Cancer. 2006;6(3):240–248.
2. Candido J, Hagemann T. Cancer-Related Inflammation. J Clin Immunol. 2012 Dec 9;33(1):79–84.
3. Karin M. Nuclear factor-κB in cancer development and progression. Nature. 2006;441(7092):431–436.
4. Scott J. Social network analysis. Sage; 2012.
5. Valente TW. Social network influences on adolescent substance use: An introduction. Connections. 2003;25(2):11–16.
6. Smith KP, Christakis NA. Social networks and health. Annu Rev Sociol. 2008;34:405–429.
7. Christakis NA, Fowler JH. The spread of obesity in a large social network over 32 years. N Engl J Med. 2007;357(4):370–379.
8. Prell C. Social network analysis: History, theory and methodology. Sage; 2012.
9. Valente TW. Social networks and health: Models, methods, and applications. Oxford University Press; 2010.
10. Burt RS. Structural holes: The social structure of competition. Harvard university press; 2009.
11. Berkman LF, Glass T. Social integration, social networks, social support, and health. Soc Epidemiol. 2000;1:137–173.
12. Berkman LF, Breslow L. Health and ways of living: the Alameda County study. 1983 [cited 2017 Feb 13]; Available from: http://www.popline.org/node/633420
13. Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. J Behav Med. 2006;29(4):377– 387.
14. Feld SL, Suitor JJ, Hoegh JG. Describing changes in personal networks over time. Field Methods. 2007;19(2):218–236.
15. Cornwell B. Social disadvantage and network turnover. J Gerontol B Psychol Sci Soc Sci. 2015;70(1):132–142.
16. Cornwell B, Schumm LP, Laumann EO, Kim J, Kim Y-J. Assessment of social network change in a national longitudinal survey. J Gerontol B Psychol Sci Soc Sci.
17. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol. 1989;129(1):125–137.
18. Newsom J, Jones RN, Hofer SM. Longitudinal data analysis: A practical guide for researchers in aging, health, and social sciences. Routledge; 2013.
19. Juster R-P, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev. 2010;35(1):2–16.
20. Pierce BL, Neuhouser ML, Wener MH, Bernstein L, Baumgartner RN, Ballard-Barbash R, et al. Correlates of circulating C-reactive protein and serum amyloid A concentrations in breast cancer survivors. Breast Cancer Res Treat. 2009;114(1):155–167.
21. Ledermann T, Macho S, Kenny DA. Assessing mediation in dyadic data using the actor-partner interdependence model. Struct Equ Model Multidiscip J. 2011;18(4):595–612.
22. Hancock GR, Mueller RO. Structural equation modeling: A second course. Iap; 2013.
23. Costanzo ES, Lutgendorf SK, Sood AK, Anderson B, Sorosky J, Lubaroff DM. Psychosocial factors and interleukin-6 among women with advanced ovarian cancer. Cancer. 2005;104(2):305–313.
24. Muthén LK, Muthén BO. Mplus Version 7 user's guide. Los Angel CA Muthén Muthén. 2006;
25. Smith S, Jaszczak A, Graber J, Lundeen K, Leitsch S, Wargo E, et al. Instrument development, study design implementation, and survey conduct for the National Social Life, Health, and Aging Project. J

Gerontol B Psychol Sci Soc Sci. 2009;64(suppl 1):i20–i29.
26. Hawkley LC, Kocherginsky M, Wong J, Kim J, Cagney KA. Missing data in Wave 2 of NSHAP: Prevalence, predictors, and recommended treatment. J Gerontol B Psychol Sci Soc Sci. 2014;gbu044.
27. Berg JW, Downing A, Lukes RJ. Prevalence of undiagnosed cancer of the large bowel found at autopsy in different races. Cancer. 1970;25(5):1076–1080.
28. Jahn JL, Giovannucci EL, Stampfer MJ. The high prevalence of undiagnosed prostate cancer at autopsy: implications for epidemiology and treatment of prostate cancer in the Prostate-specific Antigen-era: High prostate cancer prevalence: Research implications in the PSA-ERA. Int J Cancer. 2015 Dec 15;137(12):2795– 802.
29. Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. Clin Chem. 1997;43(1):52–58.
30. McDade TW, Burhop J, Dohnal J. High-sensitivity enzyme immunoassay for C- reactive protein in dried blood spots. Clin Chem. 2004;50(3):652–654.
31. Cappiello M, Cunningham RS, Knobf MT, Erdos D. Breast cancer survivors information and support after treatment. Clin Nurs Res. 2007;16(4):278–293.
32. Hayward MD, Wallace RB. Wave 2 of the National Social Life, Health, and Aging Project: An Overview. J Gerontol B Psychol Sci Soc Sci. 2014;69(Suppl 2):S1–S3.
33. Cornwell B, Schumm LP, Laumann EO, Graber J. Social Networks in the NSHAP Study: rationale, measurement, and preliminary findings. J Gerontol B Psychol Sci Soc Sci. 2009;64(suppl 1):i47–i55.
34. Ruan D. The content of the General Social Survey discussion networks: an exploration of General Social Survey discussion name generator in a Chinese context. Soc Netw. 1998;20(3):247–264.
35. Jette AM, Branch LG. The Framingham disability study: II. Physical disability among the aging. Am J Public Health. 1981;71(11):1211–1216.
36. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
37. Kleinbaum DG, Klein M. Statistics for Biology and Health. Logistics regresion. A Self-Learning Text. 3-rd ed. Springer New York Dordrecht Heidelberg London; 2010.
38. Hung WW, Ross JS, Boockvar KS, Siu AL. Recent trends in chronic disease, impairment and disability among older adults in the United States. BMC Geriatr. 2011;11:47.
39. Gewandter JS, Fan L, Magnuson A, Mustian K, Peppone L, Heckler C, et al. Falls and functional impairments in cancer survivors with chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study. Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2013 Jul;21(7):2059–66.
40. Goodwin JS, Hunt WC, Samet JM. A population-based study of functional status and social support networks of elderly patients newly diagnosed with cancer. Arch Intern Med. 1991;151(2):366–370.
41. Avlund K, Lund R, Holstein BE, Due P, Sakari-Rantala R, Heikkinen R-L. The impact of structural and functional characteristics of social relations as determinants of functional decline. J Gerontol B Psychol Sci Soc Sci. 2004;59(1):S44–S51.
42. Antonucci TC, Akiyama H. Social networks in adult life and a preliminary examination of the convoy model. J Gerontol. 1987;42(5):519–527.
43. Carstensen LL, Isaacowitz DM, Charles ST. Taking time seriously: A theory of socioemotional selectivity. Am Psychol. 1999;54(3):165.
44. Van Tilburg T. Losing and gaining in old age: Changes in personal network size and social support in a four-year longitudinal study. J Gerontol B Psychol Sci Soc Sci. 1998;53(6):S313–S323.
45. Southwick SM, Litz BT, Charney D, Friedman MJ. Resilience and Mental Health: Challenges Across the Lifespan. Cambridge University Press; 2011. 383 p.
46. Helgeson VS, Snyder P, Seltman H. Psychological and physical adjustment to breast cancer over 4 years: identifying distinct trajectories of change. Health Psychol. 2004;23(1):3.
47. Heller T, Gibbons HM, Fisher D. Caregiving and family support interventions: Crossing networks of aging and developmental disabilities. Intellect Dev Disabil. 2015;53(5):329–345.
48. Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta- analysis of cytokines in Alzheimer's disease. Biol Psychiatry. 2010;68(10):930– 941.
49. Albert MA, Glynn RJ, Ridker PM. Effect of physical activity on serum C-reactive protein. Am J Cardiol.

2004;93(2):221–225.
50. Autenrieth C, Schneider A, Döring A, Meisinger C, Herder C, Koenig W, et al. Association between different domains of physical activity and markers of inflammation. Med Sci Sports Exerc. 2009;41(9):1706–1713.
51. Zhao G, Okoro CA, Li J, White A, Dhingra S, Li C. Current depression among adult cancer survivors: findings from the 2010 Behavioral Risk Factor Surveillance System. Cancer Epidemiol. 2014;38(6):757–764.
52. Linden W, Vodermaier A, MacKenzie R, Greig D. Anxiety and depression after cancer diagnosis: Prevalence rates by cancer type, gender, and age. J Affect Disord. 2012;141(2):343–351.
53. Zainal NZ, Nik-Jaafar NR, Baharudin A, Sabki ZA, Ng CG. Prevalence of depression in breast cancer survivors: a systematic review of observational studies. Asian Pac J Cancer Prev. 2013;14(4):2649–2656.
54. Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. Psychol Bull. 1985;98(2):310.
55. Hinzey A, Gaudier-Diaz MM, Lustberg MB, DeVries AC. Breast cancer and social environment: getting by with a little help from our friends. Breast Cancer Res. 2016;18:54.
56. Kawachi I, Berkman LF. Social ties and mental health. J Urban Health. 2001;78(3):458–467.
57. Gagliardi C, Vespa A, Papa R, Mariotti C, Cascinu S, Rossini S. Social support networks and depression of women suffering from early-stage breast cancer: a case control study. J Psychosoc Oncol. 2009;27(2):216–229.
58. Nausheen B, Gidron Y, Peveler R, Moss-Morris R. Social support and cancer progression: A systematic review. J Psychosom Res. 2009 Nov;67(5):403–15.
59. Hipkins J, Whitworth M, Tarrier N, Jayson G. Social support, anxiety and depression after chemotherapy for ovarian cancer: a prospective study. Br J Health Psychol. 2004;9(4):569–581.
60. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. Bmj. 2005;330(7493):702.
61. De Leeuw JRJ, De Graeff A, Ros WJG, Hordijk GJ, Blijham GH, Winnubst JAM. Negative and positive influences of social support on depression in patients with head and neck cancer: a prospective study. Psychooncology. 2000;9(1):20–28.
62. Miller GE, Blackwell E. Turning up the heat: Inflammation as a mechanism linking chronic stress, depression, and heart disease. Curr Dir Psychol Sci. 2006;15(6):269– 272.
63. Reiche EMV, Nunes SOV, Morimoto HK. Stress, depression, the immune system, and cancer. Lancet Oncol. 2004;5(10):617–625.
64. Schmitz KH, Neuhouser ML, Agurs-Collins T, Zanetti KA, Cadmus-Bertram L, Dean LT, et al. Impact of Obesity on Cancer Survivorship and the Potential Relevance of Race and Ethnicity. JNCI J Natl Cancer Inst. 2013 Sep 18;105(18):1344–54.
65. Stuck AE, Walthert JM, Nikolaus T, Büla CJ, Hohmann C, Beck JC. Risk factors for functional status decline in community-living elderly people: a systematic literature review. Soc Sci Med. 1999 Feb;48(4):445–69.
66. Sogaard M, Thomsen RW, Bossen KS, Sorensen HT, Norgaard M. The impact of comorbidity on cancer survival: a review. Clin Epidemiol. 2013;5(Suppl 1):3–29.
67. Deimling GT, Arendt JA, Kypriotakis G, Bowman KF. Functioning of Older, Long - Term Cancer Survivors: The Role of Cancer and Comorbidities. J Am Geriatr Soc. 2009;57(s2):S289–S292.
68. Rottenberg Y, Litwin H, Manor O, Paltiel A, Barchana M, Paltiel O. Prediagnostic self-assessed health and extent of social networks predict survival in older individuals with cancer: A population based cohort study. J Geriatr Oncol. 2014 Oct;5(4):400–7.
69. Unger JB, McAvay G, Bruce ML, Berkman L, Seeman T. Variation in the impact of social network characteristics on physical functioning in elderly persons: MacArthur Studies of Successful Aging. J Gerontol B Psychol Sci Soc Sci. 1999;54(5):S245– S251.
70. Seeman TE, Crimmins E. Social environment effects on health and aging. Ann N Y Acad Sci. 2001;954(1):88–117.
71. de Leon CFM, Gold DT, Glass TA, Kaplan L, George LK. Disability as a function of social networks and support in elderly African Americans and Whites The Duke EPESE 1986–1992. J Gerontol B Psychol Sci Soc Sci. 2001;56(3):S179–S190.
72. Seeman TE, Bruce ML, McAvay GJ. Social network characteristics and onset of ADL disability:

MacArthur studies of successful aging. J Gerontol B Psychol Sci Soc Sci. 1996;51(4):S191–S200.
73. Green AF, Rebok G, Lyketsos CG. Influence of social network characteristics on cognition and functional status with aging. Int J Geriatr Psychiatry. 2008;23(9):972–978.
74. Leung J, Pachana NA, McLaughlin D. Social support and health-related quality of life in women with breast cancer: a longitudinal study: Social support, quality of life, and breast cancer. Psychooncology. 2014 Sep;23(9):1014–20.
75. Bloom JR, Stewart SL, Chang S, Banks PJ. Then and now: quality of life of young breast cancer survivors. Psychooncology. 2004;13(3):147–160.
76. Bellury L, Pett MA, Ellington L, Beck SL, Clark JC, Stein KD. The effect of aging and cancer on the symptom experience and physical function of elderly breast cancer survivors. Cancer. 2012 Dec 15;118(24):6171–8.
77. Soares A, Biasoli I, Scheliga A, Baptista RL, Brabo EP, Morais JC, et al. Association of social network and social support with health-related quality of life and fatigue in long-term survivors of Hodgkin lymphoma. Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2013 Aug;21(8):2153–9.
78. Sapp AL, Trentham-Dietz A, Newcomb PA, Hampton JM, Moinpour CM, Remington PL. Social networks and quality of life among female long-term colorectal cancer survivors. Cancer. 2003 Oct 15;98(8):1749–58.
79. Kanamori S, Kai Y, Aida J, Kondo K, Kawachi I, Hirai H, et al. Social participation and the prevention of functional disability in older Japanese: the JAGES cohort study. PloS One. 2014;9(6):e99638.
80. Thompson T, Rodebaugh TL, Pérez M, Schootman M, Jeffe DB. Perceived social support change in patients with early stage breast cancer and controls. Health Psychol. 2013;32(8):886.
81. Howard AF, De Bibiana JT, Smillie K, Goddard K, Pritchard S, Olson R, et al. Trajectories of social isolation in adult survivors of childhood cancer. J Cancer Surviv. 2014;8(1):80–93.
82. Cornwell B, Laumann EO. The health benefits of network growth: New evidence from a national survey of older adults. Soc Sci Med. 2015;125:94–106.
83. Seeman TE. Social ties and health: The benefits of social integration. Ann Epidemiol. 1996;6(5):442–451.
84. Cappiello M, Cunningham RS, Knobf MT, Erdos D. Breast cancer survivors information and support after treatment. Clin Nurs Res. 2007;16(4):278–293.
85. Hayward MD, Wallace RB. Wave 2 of the National Social Life, Health, and Aging Project: An Overview. J Gerontol B Psychol Sci Soc Sci. 2014;69(Suppl 2):S1–S3.
86. Cornwell B, Schumm LP, Laumann EO, Graber J. Social Networks in the NSHAP Study: rationale, measurement, and preliminary findings. J Gerontol B Psychol Sci Soc Sci. 2009;64(suppl 1):i47–i55.
87. Ruan D. The content of the General Social Survey discussion networks: an exploration of General Social Survey discussion name generator in a Chinese context. Soc Netw. 1998;20(3):247–264.
88. Jette AM, Branch LG. The Framingham disability study: II. Physical disability among the aging. Am J Public Health. 1981;71(11):1211–1216.
89. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
90. Kleinbaum DG, Klein M. Statistics for Biology and Health. Logistics regresion. A Self-Learning Text. 3-rd ed. Springer New York Dordrecht Heidelberg London; 2010.
91. Hung WW, Ross JS, Boockvar KS, Siu AL. Recent trends in chronic disease, impairment and disability among older adults in the United States. BMC Geriatr. 2011;11:47.
92. Gewandter JS, Fan L, Magnuson A, Mustian K, Peppone L, Heckler C, et al. Falls and functional impairments in cancer survivors with chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study. Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2013 Jul;21(7):2059–66.
93. Goodwin JS, Hunt WC, Samet JM. A population-based study of functional status and social support networks of elderly patients newly diagnosed with cancer. Arch Intern Med. 1991;151(2):366–370.
94. Avlund K, Lund R, Holstein BE, Due P, Sakari-Rantala R, Heikkinen R-L. The impact of structural and functional characteristics of social relations as determinants of functional decline. J Gerontol B Psychol Sci Soc Sci. 2004;59(1):S44–S51.
95. Antonucci TC, Akiyama H. Social networks in adult life and a preliminary examination of the convoy model. J Gerontol. 1987;42(5):519–527.
96. Carstensen LL, Isaacowitz DM, Charles ST. Taking time seriously: A theory of socioemotional selectivity. Am Psychol. 1999;54(3):165.
97. Van Tilburg T. Losing and gaining in old age: Changes in personal network size and social support in a four-year longitudinal study. J Gerontol B Psychol Sci Soc Sci. 1998;53(6):S313–S323.