

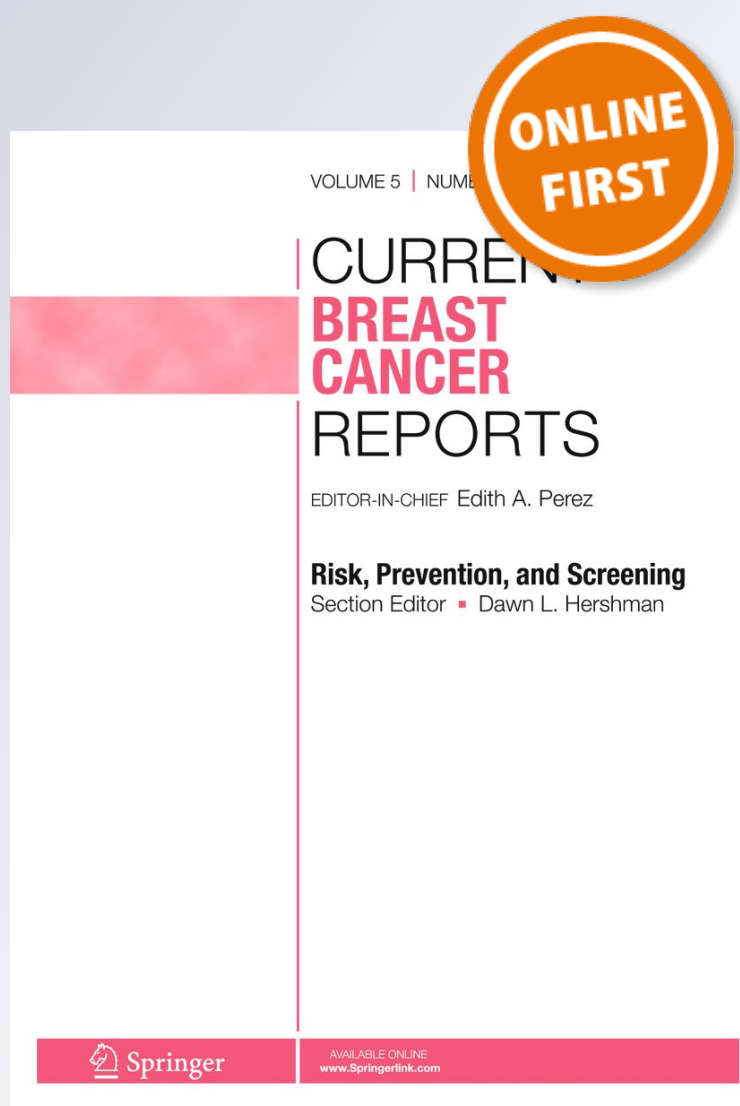
# Caregiving Stress and Its Toll on Health From a Psychoneuroimmunological Perspective

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# Caregiving Stress and Its Toll on Health From a Psychoneuroimmunological Perspective

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## Abstract

**Purpose of Review** The purpose of this review was to discuss the psychological and physiological effects of caregiving stress in the general population as well as among cancer caregivers.

**Recent Findings** Although caregiving for a loved one with cancer may be shorter in duration (i.e., number of months), it is often more intense (i.e., number hours per day) than caring for individuals with other chronic illnesses because cancer treatment has shifted toward outpatient therapy and placed a significant burden of informal caregiving on families, especially spouses/partners.

**Summary** Informal caregiving psychologically and physiologically taxes the caregiver and may negatively influence the caregiver's health and well-being, regardless of chronic disease population. Unique to breast cancer and other female cancer populations, males often find themselves in the caregiving role. In addition, a paucity of research examining the role of caregiving among the cancer survivorship population exists, despite it being a very real possibility that survivors may find themselves in this position, given advancements in cancer treatment.

**Keywords** Caregiving stress · Breast cancer · Psychoneuroimmunological perspective · Cancer treatment · Psycho-oncology · Review

## Introduction

By its broad definition, caregiving is the provision of support for another person in activities of daily living, and in the case of chronic illness, often medical care tasks. Caregivers must help with management of symptoms and care tasks, while also providing emotional and occasionally financial support to the patient. This care is crucial to maintaining the independence of adults with chronic medical conditions [1]. In the USA, the estimated prevalence of an adult caring for another adult is 16.6% (or almost 40 million Americans in 2015). Data from an American Association of Retired Persons (AARP) and National Caregiving Alliance survey found that among all caregivers, 7% reported cancer as the main reason their care receiver needed their care [2]. Cancer was also cited as one of the most common conditions where caregivers reported 21 or more hours of weekly care provided and high care burden [2]. Another study found that in fact cancer caregivers provided almost 32 h a week of care, nearly a full-time job, with 39% providing this care for a year or more [3]. Based on 2016 estimates, more than 15.5 million Americans with a cancer history (patients and survivors) were alive on January 1, with this number expected to grow to more than 20 million over the next 10 years [4]. With this growth, an increasing number of informal, family caregivers will be needed to support the health needs of cancer patients.

Cancer may provide unique challenges to family caregivers relative to other illness conditions, including the very swift health deterioration in patients, more daily hours of intense care, concerns about disease recurrence and progression, and

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a diverse range of toxicities and symptom management. These challenges may require technical skills and frequent monitoring from caregivers [5••]. Additionally, in comparison with other caregivers whose care receiver was on hospice, cancer caregivers were more likely to be younger, a spouse, live with their care receiver, and report “out of pocket” expenses [6]. The role of informal caregivers in cancer has risen with a shortage of health care providers and the provision of chemotherapy in outpatient settings [7]. In contrast with formal caregivers, however, informal caregivers do not receive training (half have never provided medical/nursing tasks prior to their current care for their relative) and do not have time to prepare themselves for their care role [8••]. Ultimately, with advancing treatments for cancer and individuals surviving longer following a cancer diagnosis (either with the disease or in remission), patient’s health care utilization and medical costs are increasing and caregivers are serving in their role for longer periods of time [5••, 9]. Another cost, however, is the psychological and physiological toll taken on relatives and friends who provide this instrumental care to individuals with chronic illness.

### Caregiving Stress Associated With Well-Being and Mental Health

The caregiving context has long been associated with chronic stress and burden. Caregiver burden reflects the strains (physiological, emotional, psychological, social, and economic) experienced by a caregiver who is providing consistent care to a family or friend. Though positive outcomes of care have been reported, caregiving has been associated with increased risk for negative outcomes such as depression and even earlier mortality [1, 10–13]. The predominant models that have been applied or developed to examine caregiver stress and burden in a variety of illness contexts including cancer focus on the role of stress appraisal and coping. For example, the stress and coping model developed by Lazarus and Folkman [14] has guided caregiving research and suggests that stress occurs when a situation is appraised as stressful and exceeding one’s resources to manage the stressor. Consequently, individuals employ emotion-based or problem-solving coping techniques to manage resulting stress. In applying this model to cancer caregivers, Fitzell and Pakenham [15] found that caregivers’ stress appraisal was the strongest predictor of their adjustment (e.g., positive affect, life satisfaction).

Stemming from research on caregivers for individuals with dementia, the Stress Process Model [16] describes a pathway to the emotional and psychological outcomes of extended informal care through primary and secondary stressors. Primary stressors result from the care recipient’s disease such as the severity of disease and functional impairments, as well as a caregiver’s emotional response to those stressors such as role overload. Primary stressors then can proliferate into secondary

stressors such as family disagreements, financial strain, or missed workdays. Gaugler and colleagues [17] found empirical support for this model as applied to cancer caregiving. Further, the level of psychological distress, financial strain, and physical burden reported by cancer caregivers has been found to be similar to that of dementia caregivers [3] and equivalent even to that of cancer patients [7, 18].

Cancer caregivers have been found to report high levels of caregiver burden, stress, and negative health effects [8••] as well as work productivity loss among employed caregivers for adults with advanced stage cancer [19]. Further, one study found that cancer caregivers who reported high levels of caregiving stress were significantly more likely to have arthritis, chronic back pain, and heart-related diseases 2 years after their care receiver’s cancer diagnosis [20]. Recent research has found that the number of comorbidities a patient with cancer *and* their caregiver have can negatively impact how a caregiver copes with their caregiving responsibilities and their quality of life [21]. Thus, it is important to keep in mind that given the commonality of multimorbidity and the likelihood that caregivers themselves may have health concerns, the context of cancer caregiving may be multifaceted in how it affects caregiver stress. Across chronic conditions, caregiver burden tends to be associated with being female, having low levels of education, having no choice in accepting the caregiving role, residing with the care recipient, spending a greater number of hours caring, social isolation, financial strain, and depression [13]. Given a recognition of the risk factors for caregiver burden and stress, a number of interventions have aimed to improve caregiver mental health and well-being.

While few interventions have considered the needs of family caregivers for cancer patients in addition to improving patient outcomes (such as patient well-being or symptom management), a number of patient interventions incorporate caregivers and some studies have been focused on cancer caregivers alone [7]. The most common type of cancer caregiving intervention in the literature is psychoeducational, followed by skills training and therapeutic counseling [7]. Psychoeducational programs offer education on physical care and symptom management for patients, as well as emotional care for patients and caregivers themselves. Skills training aims to develop communication, coping, problem-solving, and behavioral change skills. Therapeutic counseling builds a therapeutic relationship to address cancer or caregiving-specific concerns. Content of these interventions can include skills to address patient care tasks such as emptying an ostomy bag, marital or family care such as improving communication and intimacy, and a focus on care for the physical and emotional needs of the caregiver [7].

A recent meta-analysis of skills training, counseling, and psychoeducational interventions aimed at cancer caregivers showed modest improvements in caregiver burden (effect size 0.22 at 3 months) and anxiety (0.20 at 3 months) but a

reduction in effect over time (burden = 0.10 after 6 months; anxiety = 0.16). However, the interventions did not significantly reduce caregiver's depressive symptoms [7]. A majority (63%) of interventions were targeting the care dyad (both caregiver and care receiver), yet the meta-analysis showed that interventions which targeted the caregiver alone resulted in a better caregiver appraisal of a benefit from caregiving (e.g., seeing caregiving as an opportunity for personal growth, enhancing self-esteem) [7]. Following the meta-analysis, some more recent intervention innovations have included examining the characteristics that may define the success of interventions.

For example, Dione-Odomm and colleagues [22] examined the timing of a palliative care telehealth intervention for caregivers and found that whether caregivers received the intervention immediately following their care receivers' advanced cancer diagnosis or 12 weeks later did not make a difference on depression and grief scores 8 to 12 weeks following the death of the patient. Depression and grief did not improve with the intervention, but it is unclear whether scores might have been worse without receipt of the intervention. One study by Holm and colleagues [23] examined characteristics of caregivers of palliative care cancer patients who did not improve from participating in a psychoeducational intervention and found that these caregivers had more favorable scores on measures of stress and burden at baseline, suggesting that they were a less vulnerable group with less room for improvement. Further, given the demands of participating in a research study, it may be that more adjusted caregivers are more likely to volunteer to participate resulting in modest intervention effects. Researchers should take into account how to design interventions that can reach those caregivers who may need the support most. A recent intervention also considered physiological impacts resulting from a tailored psychoeducation intervention focused on caregivers of hospitalized cancer patients. Close to the patient's death, caregivers who had received the intervention were better able to calm themselves as reflected in their heart rate variability [24].

### Caregiving Stress Associated With Physiological Dysregulation

The chronic psychological stress and burden associated with caregiving can cascade into poor functioning and unregulated physiological systems. Consequently, caregivers are at risk and have a greater likelihood of suffering with chronic diseases [8•, 20]. For example, caregivers develop heart disease including coronary heart disease and report more arthritis and chronic back pain at a greater rate than controls [20, 25, 26]. Caregivers also have greater inflammation than non-caregivers [27–31], a major predictor for frailty, cognitive decline, and all-cause mortality [32–34]. We have begun to

elucidate the mechanisms of how psychological stress can result in physiological dysregulation that precedes chronic disease development and poorer quality of life [35].

The brain internalizes psychological and environmental stress via activation of the arousal systems, the sympathetic nervous system, and hypothalamic-pituitary-adrenal axis [36]. The hormones released have pervasive, wide-ranging effects on the body [35]. Epinephrine supports the fight-or-flight response and is relatively short acting [37], whereas cortisol remains in circulation longer and can interact with almost all cells, including lymphocytes [38, 39]. Acute stress results in an adaptive integrated multi-system response; however, unremitting and chronic stress such as caregiving can shift functioning toward sympathetic dominance and excessive exposure to cortisol that can drive immune cells into an unregulated pro-inflammatory state [40–43]. This shift toward a pro-inflammatory state [44, 45] has cascading effects on numerous facets of immune function. Researchers have examined how caregiving stress and burden appear to drive immune dysregulation and mechanisms underlying the poor immune functioning [46•]. Using a psychoneuroimmunological lens, we review work linking caregiving stress to physiological dysfunction.

Caregiving stress appears to have differential cascading effects on systemic inflammation. In a landmark study, dementia caregivers' interleukin-6 (IL-6) increased at fourfold greater rate than matched controls during a 6-year longitudinal study [27]; the difference could not be explained by common confounding variables (e.g., chronic health conditions, medication use, sleep, obesity, or smoking). Specific to cancer caregiving, at baseline, those providing care for a relative recently diagnosed with brain cancer had similar C-reactive protein (CRP) levels, a marker of systemic inflammation, compared to controls. However, at the 4-month follow-up, caregivers' CRP was higher than controls' CRP levels and this increase was associated with a reduction in the expression of inhibitory-kappa B (I- $\kappa$ B), a transcription factor that produces anti-inflammatory effects [30]. In a later report providing a snapshot comparing baseline to an 8-month assessment, stress associated with caregiving for these brain cancer patients was linked to upregulation of several pro-inflammatory gene factors such as nuclear factor-kappa B (NF- $\kappa$ B), but the difference in systemic CRP levels observed at 4 months was no longer present [47]. Furthermore, individual differences among caregivers of neuro-oncology patients can influence systemic inflammation, with obesity, anxiety, and lower self-esteem enhancing the impact of caregiver burden on cytokine levels [48]. Despite appearing inconsistent (caregiving for loved ones with dementia vs. cancer), it is important to note that these cancer caregiving populations are often recruited quickly after the cancer diagnosis. Thus, the length of time cancer caregivers have been exposed to caregiving stress may not have pushed the body into chronic stress activation,

meaning cancer caregiving studies may capture the immediate or acute stress associated with an earlier phase of caregiving compared to the often extended chronic caregiving context associated with dementia patients.

Caregiver stress can also promote reactivation of latent herpesviruses that are widespread within the US adult population [49, 50]. Following the primary exposure, herpesviruses remain in a dormant state or latent while being controlled by cellular immunity. Under distress, the cellular immune response becomes compromised and the virus reactivates [51]. Humoral immunity responds by producing antibodies to the latent virus, suggesting that elevated herpesvirus antibody titers serve as a proxy for poorer cell-mediated immunity. Familial dementia caregivers had higher herpesviruses antibody titers compared to matched controls [52, 53]. Furthermore, this poorer function appears linked to reduced lymphocyte proliferation, not the antibodies' ability to neutralize the herpesviruses [52, 53]. Herpesvirus reactivation is often asymptomatic, but has been associated with elevated systemic inflammation [54]. Taken together, caregivers appear to have reduced lymphocyte activity and heightened herpesvirus antibody production that may fuel a greater pro-inflammatory systemic environment.

The chronic stress associated with caregiving also hastens telomere shortening [31, 55–57]. Telomeres protect the integrity of the cell's genetic material and once a telomere reaches a critically short length, it can no longer proliferate and the cell dies or undergoes apoptosis, programmed cell death [58, 59]. Among caregivers, telomere length was shorter than in the controls [31]. Additional work has begun to uncover the mechanism. The length of caregiving for a chronically ill child was associated with shorter telomeres and linked to higher oxidative stress as well as reduced activity of telomerase, which lengthens the telomere [55]. In addition, caregivers had greater systemic inflammation [31]. Higher levels of inflammation activate lymphocyte proliferation, further shortening telomeres due to increased replication and oxidative stress enhancing telomere erosion [60]. This evidence linking chronic stress and telomere shortening provides additional biological pathways connecting stress and chronic disease [59, 61–63].

In summary, caregiving stress and burden can wreak havoc on normal physiological functioning. Several different immune outcomes are associated with systemic inflammation. Not only does systemic inflammation reduce physical health [32–34] but it also fuels changes in mood [64] and sickness behavior [65], resulting in a cyclical negative pattern. Thus, dysregulation of the arousal systems and the natural spillover to the immune system appears to be one pathway that caregiving stress leads to poorer physical and mental health. However, to date, the majority of the literature examining the psychoneuroimmunological effects of caregiving has focused on caregivers for dementia patients. Cancer caregiving

has many unique characteristics as compared to caregiving for dementia patients. Thus, as health professionals, we must cautiously apply the physical health detriments and mechanisms observed in dementia caregivers and conduct additional research focused on cancer caregivers.

## Uniqueness of Caregiving for Cancer Patients

A cancer diagnosis is stressful. Both the patient and partner/spouse often receive a lot of information with multiple options, yet some basic questions about how their lives will change cannot be answered [66••]. Cancer stage at diagnosis drives the treatment regime; early detection of some cancers has greatly reduced the distress surrounding diagnosis and prognosis [67]. However, more advanced cancer stages that include metastasis from the primary site to another organ beyond the lymphatic system dramatically changes the treatment plan and may even immediately lead to implementation of palliative care [67]. Thus, even within the literature of cancer caregiving, attention to type of cancer and stage at diagnosis must be carefully considered or at a minimum, both should be included statistically to determine if there are significant relationships to be explored.

Furthermore, a cancer diagnosis often occurs unexpectedly and can happen at any age; hence, there is little mental preparation and lifestyle adjustment prior to shifting into the caregiving role. Cancer caregiving in regard to sociodemographic characteristics is similar to other caregiving populations. Typically, they are females (55–75%) and range in age from 18 to 90 years (average 48–59 years depending on study) [3, 5••, 20, 68–71, 72••]. Cancer caregiving, however, tends to require more hours of care per week (31.3 vs. 26.3 h) for a shorter duration of time (less than 1 vs. 4–9 years) [3]. Depending on the type of cancer, stage at diagnosis, and treatment regime, cancer patients experience pain, immobility, fatigue, appetite loss, cognitive decline, and treatment complications/side effects that can all significantly influence their ability to complete activities associated with daily functioning [73, 74]. Cancer caregivers must assist with these decrements in activities of daily living, while often maintaining full-time employment [3, 72••, 75•].

The effects of cancer caregiving on the physiology of caregivers are not yet well understood; however, specific psychoneuroimmunological mechanisms have been assessed. Two separate research teams followed caregivers of newly diagnosed brain cancer patients; one in Canada with reports at 4 and 8 months [30, 47] and one in the USA that lasted 12 months [48]. Caregiving for neuro-oncology patients appears to upregulate a pro-inflammatory state in lymphocytes that may be modulated by the caregiver's physical and mental health levels [30, 47, 48]. In addition, during this early phase of caregiving stress (i.e., acute stress due to cancer diagnosis

and patient treatment demands), neuroendocrine dysregulation does not appear to be the culprit [47]. Thus, the chronic stress paradigm may not be the best lens to investigate all stages of caregiving stress on physical health and that caregiving stress varies depending on care receiver's cancer population.

Caregiving for a loved one is stressful at the time of cancer diagnosis and the immediate following 1–2 year(s) [3, 72•, 75•]; however, much less is known about the long-term psychological and physical well-being of caregivers following cancer recurrence in their loved one or during the bereavement process. In a 5-year follow-up study, current and bereaved caregivers reported the greatest distress while former caregivers had stress levels similar to age-matched population norms [76]. In addition, caregivers had similar physical health levels as compared to their non-caregiving counterparts [76]. More recently, at 8-year post-cancer diagnosis, 85% of the caregivers were no longer actively caregiving as the cancer patient was in remission or deceased [71]. Similar to the 5-year follow-up, current and bereaved caregivers reported greater psychological distress and poorer mental health as compared to former caregivers whose loved one was in remission [71]. Even though there is limited data, health professionals must attend to the caregivers' needs in the event of cancer recurrence as well as following the death of the cancer patient.

### Caregiving for Breast Cancer Patients

Breast cancer is a sexual dimorphic disease, meaning females account for 98.9% of new incidences and mortalities [77, 78]. Consequently, in societies dominated by heterosexual relationships, males often assume the caregiving role. Given the more traditional gender-role based research, much of the previous literature reviewed stems from female caregivers, leaving a gap in understanding how males are affected by the stress and burden of caregiving [79•].

The majority of cancer caregiving studies report data with roughly 25–35% male populations [20, 66, 75•, 80, 81], but only a few have discussed outcome differences by caregiver's sex or have placed focus on males [20, 70, 75•]. Husband caregivers reported higher esteem compared to wife caregivers and greater esteem reduced their perceived stress. This lower perceived stress and higher esteem among male caregivers was linked with better psychosocial functioning in their wives (i.e., the care receiver). However, care-receiving wives with poorer psychosocial functioning appeared to increase their husband's caregiving stress, regardless of esteem [68]. In a longitudinal study, a caregiver's depressed mood at baseline influenced the cancer patient's depressive symptoms roughly 11 months later [75•]. This association was stronger

among husband caregiver-wife cancer patient dyad compared to wife caregiver-husband cancer patient dyad [75•].

Caregiver's sex appears to play a role in development of physical health impairments over an 8-year period. Stressed male caregivers were more likely to develop heart disease whereas stressed female caregivers had a greater likelihood to develop arthritis and chronic back pain [20]. Taken together, cancer caregiving can differentially affect male and female caregivers in both psychological and physical health outcomes. As research continues to examine cancer caregivers' stress, investigators and clinicians need to consider sex differences in psychological and physiological outcomes as well as test the underlying biopsychosocial mechanisms that may be driving the observed differential physical health decline.

### Caregiving as a Breast Cancer Survivor

As biomedical technology continues to advance, the cancer survivor population, especially female breast cancer survivors, continues to grow exponentially and provides opportunities for health professionals to enhance quality of life [82]. Following cancer diagnosis and successful treatment, cancer survivors often expect to return to pre-disease functioning. However, cancer survivors can continue to experience poorer cognitive functioning [83], mobility limitations, and cancer-related fatigue for years after treatment completion [73, 84–87]. The relationship between cancer survivorship and caregiving for others has yet to be thoroughly understood.

Two published studies start to describe how caregiving provided by breast cancer survivors may influence their well-being and mortality risk. Parrish and colleagues [88] discovered that caregiving for another at time of breast cancer diagnosis did not significantly influence depression risk at 3 or 12 months post-diagnosis. Only breast cancer stage at diagnosis significantly predicted depression risk at both follow-ups [88]. Together, these findings suggest that the stress of caregiving did not exacerbate the inherent depression associated with breast cancer diagnosis among older women. Rottenberg and colleagues [89] more recently found that women having an intermediate-stage breast cancer diagnosis and a living spouse for which one provides or has provided cancer caregiving had increased likelihood of survival 15 years since diagnosis. For women with an early- and late-stage breast cancer diagnoses, caregiving for a spouse with cancer, current or past, had no effect on mortality. Furthermore, being unmarried or losing a spouse that one provided cancer caregiving significantly increased one's risk of dying following her own breast cancer diagnosis [89].

Unfortunately, both studies were secondary data analyses using large public datasets not designed with the specific intent to understand the complex relationship between caregiving and breast cancer survivorship. Given the known benefits

of social relationships [90], caregiving for another with a concurrent cancer diagnosis may give the patient a sense of purpose and goal to enhance their own health and lead to protective health behaviors [10, 91•]. Breast cancer patients who have cared for a close relative with cancer may also have developed a greater skillset to navigate their treatment due to the previous experience of assisting their spouse or family member successfully manage the process from cancer diagnosis through treatment and into survivorship [89]. Being more familiar with the tools and resources available to them as they live through it will also increase their chances of surviving and having a greater quality of life. These limited data leave numerous unanswered questions into the complex issues breast cancer survivors might face as they assume the role of caregiving.

## Conclusions

Caregivers for a family member or spouse/partner with a chronic condition are an expanding population due to significant medical advancements improving survival rates as well as transitioning medical treatment to outpatient settings [72••]. Being a caregiver can be a positive experience; however, the stress and burden that often are associated with caregiving have been reliably linked to poorer mental and physical health outcomes. Initially, caregiving stress research primarily focused on caregivers of patients with dementia. However, similarities in caregiving stress have been observed across multiple types of chronic diseases, including cancer [3, 79••]. Caregiving for a loved one with cancer shares many experiences with other caregiver populations, yet there are unique qualities.

Cancer caregivers often have no warning of the diagnosis and possibility of rapid deterioration and death of their loved one, in comparison to other chronic diseases such as diabetes or dementia that have warning signs/behaviors, clinical pre-disease stages, and patients can live for a relatively extended period of time [5••]. In addition, cancer caregivers report a more intense experience that is shorter in duration (i.e., months), but a greater time demand (i.e., hours per week) compared to other chronic disease populations [3]. The stress created by this different time requirement may be compounded if the caregiver also works full-time and is responsible for other individuals (i.e., children or elderly parents).

Using a psychoneuroimmunological framework enables greater understanding into how the psychological stress of caregiving can cascade in physiological dysfunction that causes or exacerbates the mental and physical health detriments observed in burdened caregivers. In regard to the cancer caregiving knowledge, we have moderate evidence that interventions can improve mental and psychological health

[7, 72••], but there is a paucity of research in regard to physical health improvements or correcting the observed physiological dysregulation associated with caregiving. The burden of breast cancer caregiving often falls on male spouses/partners due to the majority of relationships being heterosexual [79••]. Thus, more research investigating needs and concerns of male caregivers is warranted as our current information is based primarily on female caregiving experiences. Finally, with the population of breast cancer survivors ever expanding, we need to examine as researchers and be sensitive as health professionals to the dual influence of having a history of breast cancer and fulfilling the caregiver role on mental and physical health.

## Compliance with Ethical Standards

**Conflict of Interest** Jeanette M. Bennett and Amanda N. Leggett declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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