Biological Research for Nursing
2018, Vol. 20(3) 300-311

DOI: 10.1177/1099800417740970
journals.sagepub.com/home/brn
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The Role of Biomarkers in Research on Caregivers for Cancer Patients: A Scoping Review

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Abstract

Background: Biomarkers can be used as prognostic, predictive, or monitoring indicators of an associated outcome. The purpose of this review was to provide a comprehensive summary of the research examining the use of biomarkers as surrogate end points for clinical outcomes in family caregivers for cancer patients, identify gaps, and make recommendations for future research. **Methods:** A scoping review, a process of mapping the existing literature, was conducted. Studies comparing biomarkers across caregivers and controls and/or examining relationships between biomarkers and psychological health were reviewed. **Results:** The studies ($N = 18$) of caregivers for cancer patients who were identified used biomarkers to predict outcomes ($n = 13$) and to monitor the efficacy of interventions ($n = 6$). Biomarkers were divided into two categories based on physiological systems involved: (1) neuroendocrine function (sympathetic–adrenal–medullary axis activity, hypothalamic–pituitary–adrenal axis activity) and (2) immune function. Predictive biomarkers were sensitive to differences between caregivers and controls. The biomarkers were used to evaluate outcomes frequently associated with stress, depression, and anxiety. Cortisol was the biomarker most commonly measured to monitor the efficacy of interventions. **Discussion:** Biomarkers are most commonly incorporated into caregiver studies to predict group membership and psychological health. Neuroendocrine biomarkers, specifically cortisol, are most frequently assessed. Future research should include biomarkers of other physiologic functions (e.g., cardiovascular function, cognitive dysfunction, and cell aging) and those that serve as multisystem indicators. Expanding the scientific study of biomarkers will contribute to our understanding of the mechanisms through which stress may influence caregiver health.

Keywords

biological markers, caregiver, health

More than 2.8 million family members and friends were caregivers for patients with cancer in the United States in late 2015 (National Alliance for Caregiving, 2016). Although caregivers for patients with cancer have reported positive impacts from their experiences (Bishop, Curbow, Springer, Lee, & Wingard, 2011; Mosher et al., 2017), acting as an informal caregiver has been correlated with an increase in psychological symptoms such as depression and anxiety (Kim & Schulz, 2008; Schulz & Sherwood, 2008). Furthermore, caregivers for individuals with cancer report greater emotional and practical burden compared to those caring for an elderly family member or one with Alzheimer's disease (National Alliance for Caregiving, 2016). This burden, which caregivers often perceive as stressful, may cause physiological changes in the caregiver that ultimately affect their health (Bevans & Sternberg, 2012). However, the mechanisms explaining why and how caregiving puts individuals at higher risk of developing health problems are not well understood. Once research identifies these mechanisms and provides a better understanding of how they affect caregiver health, researchers and clinicians will be better able to design effective preventive interventions that target these mechanisms (Fonareva, Amen, Zajdel, Ellingson, & Oken, 2011).

Biomarkers that reflect underlying physiological processes may provide us with a greater understanding of the mechanisms through which stress influences the health and well-being of caregivers. Various definitions of a biomarker exist (Lassere, 2008). For this review, we focus on biomarkers as defined by the National Cancer Institute (2015): A "biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or a condition or disease." Biomarkers can serve several unique purposes: (1) to identify the presence or absence of a specific disease (prognostic biomarker), for instance, increased blood glucose concentration for the

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diagnosis of diabetes mellitus; (2) to predict the psychological or pharmacological response from a specific therapy to help determine the optimal treatment (predictive biomarker), for example, blood cholesterol concentrations for determination of the risk of heart disease; and (3) to monitor side effects and efficacy of ongoing treatments or interventions (monitoring biomarker; Lassere, 2008; Prata, Mechelli, & Kapur, 2014).

Integrating biomarkers into family caregiving research provides a more comprehensive assessment of an individual's health and responses to an intervention (Corwin & Ferranti, 2016). The majority of existing studies, however, have primarily focused on caregivers for patients with dementia (Allen et al., 2017; Lovell & Wetherell, 2011). Research examining biomarkers of health outcomes in caregivers for cancer patients is less well-developed. The purpose of this review was to provide a comprehensive summary regarding the research examining biomarkers as surrogate end points for clinical outcomes in family caregivers for patients with cancer, identify gaps in the literature, and make recommendations for future research.

Method

We used a scoping review approach to effectively identify the body of literature on biomarkers in cancer caregivers. This approach comprises a process of mapping the existing literature when the research topic addressed might be broad in nature and may involve many different study designs (Arksey & O'Malley, 2005). We searched the following databases using comparable search strategies with search terms adapted for each database: PubMed, EBASE, CINAHL Plus, PsycINFO, and Scopus. Our search terms were *caregivers/caregiving* AND *neoplasm/cancer* AND *biological markers* OR *blood* OR *saliva* OR *urine* OR *physiological* OR *endocrine system* OR *immune system* OR *cardiovascular system* OR *cognitive dysfunction* OR *inflammation* OR *cortisol* OR *cytokine*. Included articles were full-text, peer-reviewed English-language reports of studies of informal caregivers for patients diagnosed with cancer. We excluded articles if they did not provide information about caregivers for patients with cancer, if they did not measure any biomarkers, or if they did not report original research.

The initial search yielded 830 articles. After removal of duplicates, 412 articles remained. We (JP and MFB) screened these articles using the titles and abstracts, excluding an additional 394 articles. Studies were excluded because they did not include information about caregivers for patients diagnosed with cancer ($n = 157$), did not measure biomarkers ($n = 195$), or were not reporting original research ($n = 42$). JP conducted the primary full-text assessment of the remaining 18 articles, while MFB examined all of the articles independently. These 18 studies met inclusion/exclusion criteria, and we included them in this review. We present a flow diagram of the selection process in Figure 1.

We categorized each study and each of its biomarkers according to guidelines established in the existing literature (Lassere, 2008; Prata et al., 2014). Specifically, we categorized each study based upon its purpose for including the biomarker

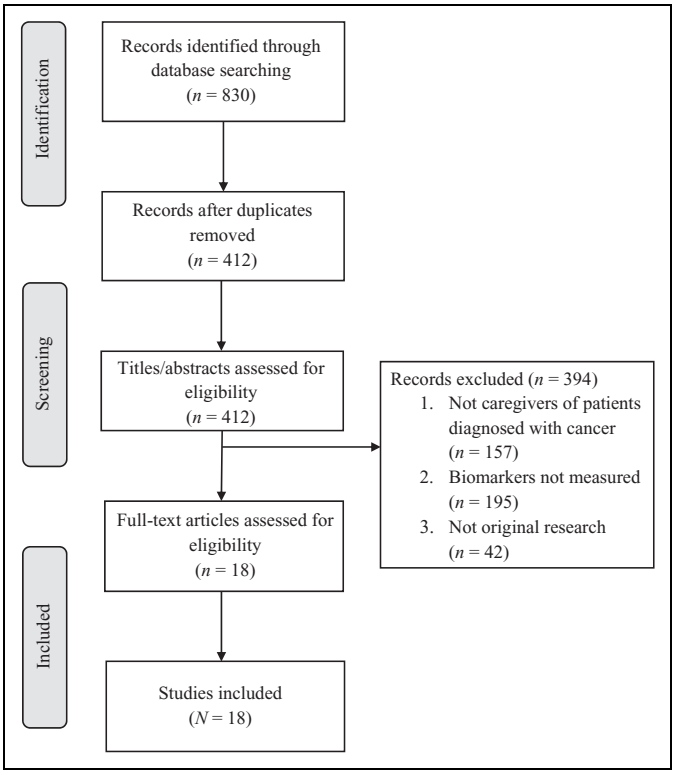

Figure 1. Flow diagram depicting the selection process for articles reporting studies of biomarkers in cancer caregivers.

(i.e., prognostic, predictive, or monitoring) and each biomarker based upon the associated physiological system: (1) neuroendocrine function (sympathetic–adrenal–medullary [SAM] axis activity, hypothalamic–pituitary–adrenal [HPA] axis activity) or (2) immune function. Table 1 provides descriptions of the biomarkers represented in this review.

Results

Table 2 includes descriptions of study design and population (sample) for each reviewed study. The researchers' purpose for collecting biomarkers in 13 of the 18 studies was to predict group membership (caregiver or control) or psychological outcomes in cancer caregivers (Bevans et al., 2016; Cohen & Pollack, 2005; Goodfellow, 2003; Khalaila, Cohen, & Zidan, 2014; Lucini et al., 2008; Lutz Stehl et al., 2008; Miller et al., 2008; Miller, Cohen, & Ritchey, 2002; Miller et al., 2014; Nightingale, Pereira, Curbow, Wingard, & Carnaby, 2017; Rohleder, Marin, Ma, & Miller, 2009; Sherwood et al., 2016; Thomas et al., 2012). These biomarkers represented neuroendocrine or immune function (Table 3). Monitoring the efficacy of an intervention was the purpose for including biomarkers in six of the studies (Table 4); the interventions included PsychoEducation, Paced Respiration and Relaxation (PEPRR; Laudenslager et al., 2015), a mindfulness-based stress reduction program (MBSR; Lengacher et al., 2012), back massage (Goodfellow, 2003; Pinar & Afsar, 2015), art-making classes (Walsh, Radcliffe, Castillo, Kumar, & Broschard, 2007), and a

Table 1. Description of Biomarkers Included in this Analysis.

Biomarker	Brief Defintion	Association With Health
Neuroendocrine function		
SAM axis activity		
CAT (EPI, NE)	A group of chemically related neurotransmitters released by the adrenal medulla following sympathetic nervous system activation	↑: ↑ CVD
Salivary pH	The level of acidity in the saliva	—
sAA	Enzyme secreted by the salivary gland in response to adrenergic activity	—
HPA axis activity		
Cortisol	Corticosteroid released by the zona fasciculata of the adrenal cortex	↑: ↑ CVD; ↓ mental health; ↓ cognitive function
DHEA-S	Steroid produced by the zona reticularis of the adrenal cortex	↓: ↑ CVD; ↓ mental health
Endorphin	Neuropeptide primarily produced by the pituitary gland in response to physiological stressors	↓: ↓ feelings of elation; ↓ stress regulation; ↓ mental health
Oxytocin	Neuropeptide produced by the paraventricular nucleus of the hypothalamus and released by the posterior pituitary gland	↓: ↓ social bonding and attachment; ↓ stress regulation; ↓ mental health
Immune function		
Cytokines (e.g., IL, TNF-α)	Proteins produced by various cell types that mainly interact with cells of the immune system	↑: ↑ age-related diseases (e.g., osteoporosis, atherosclerosis)
CRP	Plasma protein produced by the liver in response to inflammation	↑: ↑ CVD
NK cell	A type of lymphocyte critical to the innate immune system	↓: ↑ cancer; ↑ viral infection; ↑ autoimmune disease

Note. ↑ = increased; ↓ = decreased; CAT = catecholamine—norepinephrine (NE) and epinephrine (EPI); CRP = C-reactive protein; CVD = cardiovascular disease; DHEA-S = dehydroepiandrosterone sulfate; IL = interleukin; HPA = hypothalamic–pituitary–adrenal; NK = natural killer; sAA = salivary α-amylase; SAM = sympathetic–adrenal–medullary; TNF-α = tumor necrosis factor-α.

music intervention (Fancourt et al., 2016). Only one study (Goodfellow, 2003) included biomarkers both to predict health outcomes and to monitor the efficacy of an intervention.

Seven of the studies (39%) had cross-sectional designs, while 11 (61%) had longitudinal designs. The study populations varied, and there was a wide range of sample sizes, from 19 to 134. The majority of the studies included were conducted in the United States ($n = 12$), with the remaining conducted in Canada ($n = 3$), Italy ($n = 2$), and the United Kingdom ($n = 1$).

Neuroendocrine Function

The neuroendocrine system is the first line of response to a perceived stressor and coordinates the response of other physiological systems including the immune and cardiovascular systems. The fight-or-flight response (the acute stress response) initiates a series of responses with the activation of the SAM axis, which stimulates the release of catecholamines (CATs), namely, epinephrine (EPI) and norepinephrine (NE). The HPA axis mediates a more delayed hormonal response that releases glucocorticoids (Klein & Crowin, 2007; Nater, Skoluda, & Strahler, 2013).

SAM axis activity. The CATs, EPI and NE, serve as the primary biomarkers representing SAM axis activity. We found two studies that reported EPI, NE, and CAT-turnover levels (Bevans et al., 2016; Cohen & Pollack, 2005). Studies comparing EPI and NE levels between caregivers and controls or between different groups of caregivers yielded mixed results. In one study, researchers found higher EPI and NE levels in caregivers for patients with advanced cancer compared with caregivers for patients with localized cancer (Cohen & Pollack, 2005). In another, authors reported no significant difference in EPI, NE, and CAT-turnover levels between caregivers and noncaregivers (Bevans et al., 2016), although NE levels among caregivers in this study were significantly lower at the time of initial hospital discharge compared to pretransplantation (Bevans et al., 2016). In examining relationships between CAT levels and psychological health outcomes in caregivers, Bevans et al. (2016) found that higher perceived stress was associated with lower levels of EPI.

Salivary α-amylase (sAA) and salivary pH were less frequently used as markers of SAM axis activity. Rohleder, Marin, Ma, and Miller (2009) measured sAA in caregivers for patients with a brain tumor undergoing radiotherapy and achieved some puzzling results. Caregivers' diurnal rhythm of sAA secretion decreased during the first half of the follow-up (about 18 weeks after study entry). However, neither the diurnal rhythm nor the total daily output of sAA differed significantly between caregivers and noncaregivers at study entry. In another study, Khalaila, Cohen, and Zidan (2014) found that caregivers had lower salivary pH, or higher salivary acidity, than noncaregivers. In addition, lower pH levels in the caregivers were related to more depressive symptoms.

Table 2. Summary of Reviewed Studies.

First Author (Year)	Design	Sample
Bevans (2016)	Longitudinal; T1 = before HSCT, T2 = DC, T3 = 6 weeks after DC	CGs = 21; NCs = 20
Cohen (2005)	Cross-sectional	CGs (daughter, localized CA) = 39; CGs (daughter, advanced CA) = 41
Fancourt (2016)	Longitudinal; T1 = pre-INT, T2 = post-INT; saliva collection at 7:00 p.m. (pre-INT), 8:15 p.m. (post-INT)	CGs (current) = 72; CGs (bereaved) = 66; patients = 55
Goodfellow (2003)	Longitudinal; T1 = pre-INT, T2 = immediately post-INT, T3 = 20-min post-INT	CGs (INT) = 21; CGs (control) = 21
Khalaila (2014)	Cross-sectional	CGs (CA) = 68; CGs (non-CA) = 42
Laudenslager (2015)	Longitudinal; T1 = baseline, T2 = 4 weeks, T3 = 12 weeks; saliva collection upon awakening, 30-min postawakening	CGs (INT) = 74; CGs (control) = 74
Lengacher (2012)	Longitudinal; T1 = baseline, T2 = 1 week, T3 = 3 weeks, T4 = 6 weeks; saliva collection at 2 time points (pre-INT, post-INT)	CGs = 23; patients = 24
Lucini (2008)	Cross-sectional; saliva collected at 7:30 a.m., 10:30 p.m.	CGs = 58; NCs = 60
Lutz Stehl (2008)	Cross-sectional	CGs (parent) = 19
Miller (2002)	Cross-sectional; saliva collected 1,4, 9, 11, and 13 hr after awakening	CGs = 25; NCs = 25
Miller (2008)	Cross-sectional; saliva collected upon awakening and 0.5, 1, 4, 9, and 14 hr after awakening	CGs = 11; NCs = 10
Miller (2014)	Longitudinal; T1 = baseline, T2–T4 = 2, 4, and 8 months; saliva collected upon awakening and 0.5, 1, 4, 9, and 14 hr after awakening	CGs = 33; NCs = 47
Nightingale (2017)	Longitudinal; T1 = initiation of RT, T2 = 5 weeks into RT; saliva collected upon awakening and at 9:00 p.m.	CGs = 32
Pinar (2015)	Longitudinal; T1 = baseline, T2 = Day 7	CGs (INT) = 22; CGs (control) = 22
Rohleder (2009)	Longitudinal; T1 = before RT, T2 = after RT, T3 = 6 weeks after RT, T4 = 4 months after RT	CGs = 18; NCs = 19
Sherwood (2016)	Longitudinal; T1 = baseline (within 3 months of diagnosis), T2–T4 = 4, 8, and 12 months	CGs = 134
Thomas (2012)	Cross-sectional; saliva collected upon awakening, 30 min and 8-hr postawakening, and at bedtime	CGs (female) = 19; NCs (female) = 26
Walsh (2007)	Longitudinal; T1 = pre-INT, T2 = post-INT; saliva collection at 2 time points (pre-INT, post-INT)	CGs = 69

Note. CA = cancer; CG = caregiver; DC = discharge; HSCT = hematopoietic stem cell transplantation; INT = intervention; NC = noncaregiver; RT = radiotherapy; T = time point.

HPA axis activity. The biomarker researchers used most frequently to measure caregivers' neuroendocrine function was cortisol. Investigators assessed salivary or serum cortisol in eight studies as predictors of group membership or psychological outcomes (Bevans et al., 2016; Cohen & Pollack, 2005; Lucini et al., 2008; Miller et al., 2008; Miller et al., 2002; Miller et al., 2014; Nightingale et al., 2017; Thomas et al., 2012). Due to the known circadian variation in cortisol release, investigators in these studies often measured cortisol in a time series (Lucini et al., 2008; Miller et al., 2008; Miller et al., 2002; Miller et al., 2014; Nightingale et al., 2017; Thomas et al., 2012). The results regarding group comparisons are inconsistent: increased serum cortisol levels in caregivers for patients with advanced cancer compared to those for patients with localized cancer (Cohen & Pollack, 2005), lower levels of cortisol in caregivers than in noncaregivers (Bevans et al., 2016; Thomas et al., 2012), decreased levels of cortisol in caregivers for patients with late-stage cancer compared to those for patients with Stage 1 cancer (Thomas et al., 2012), and no significant difference in salivary cortisol levels between caregivers and noncaregivers (Lucini et al., 2008; Miller et al., 2008; Miller et al., 2014).

The researchers also used two or more cortisol values to create indexes: the cortisol awakening response (CAR, an increase of approximately 50% in cortisol levels within the first 30–40 min after morning awakening) and diurnal cortisol slope. Thomas and colleagues (2012) assessed CAR among spouses whose partners had prostate cancer and found that, although caregivers had a CAR of 13% compared with a CAR of 39% in control subjects, this difference was nonsignificant. In addition, diurnal cortisol slope became flatter (more dysregulation in cortisol rhythm) in caregivers in comparison to controls (Miller et al., 2002) and at 5 weeks postradiotherapy compared to the start of radiotherapy (Nightingale et al., 2017). When examining the relationships between cortisol levels and health outcomes in caregivers, Thomas et al. (2012) found that lower cortisol levels were associated with the presence of post-traumatic stress disorder symptoms. In addition, findings showed that a flattened diurnal cortisol slope was related to caregiver's

Table 3. Studies in Which Biomarkers Were Used to Predict Group Membership and Outcomes.

		Results	
Biomarker	First Author (Year)	Comparisons Between Groups or Time Points	Relationship Between Biomarkers and psychological Health Outcomes
Neuroendocrine function			
SAM axis activity			
CAT (EPI and NE)	Bevans (2016)[a]	• EPI, NE, CAT-turnover: (ns) CGs (vs. NCs) • NE:↓T2 (vs. T1) in CGs	• (−) Chronic stress and EPI
	Cohen (2005)[b]	• EPI, NE:↑CGs, advanced CA (vs. CGs, localized CA)	—
sAA	Rohleder (2009)[c]	• Diurnal rhythm at T1: (ns) CGs (vs. NCs) • Diurnal rhythm over time:↓CGs (vs. NCs) • Total daily output at T1: (ns) CGs (vs. NCs) • Total daily output over time:↑CGs (vs. NCs)	—
Salivary pH	Khalaila (2014)[c]	• ↓CGs, CA (vs. CGs, non-CA)	• (−) Chronic stress and salivary pH • (−) Depression and salivary pH
HPA axis activity			
Cortisol	Bevans (2016)[a,c]	• (ns) CGs (vs. NCs)[c] • (ns) CGs and NCs over time[c] • ↓CGs (vs. NCs) at T2, T3[a] • ↓CGs over time[a] • ↑NCs over time[a]	• (ns) Chronic stress and cortisol[a]
	Cohen (2005)[a]	• ↑CGs, advanced CA (vs. CGs, localized CA)	• (ns) Emotional distress and cortisol
	Lucini (2008)[c]	• (ns) CGs (vs. NCs)	—
	Miller (2002)[c,d]	• Diurnal cortisol slope:↓CGs (vs. NCs)	—
	Miller (2008)[c]	• (ns) CGs (vs. NCs)	—
	Miller (2014)[c]	• (ns) CGs (vs. NCs)	—
	Nightingale (2017)[c]	• Diurnal cortisol slope:↓T2 (vs. T1)	• (−) QOL at T1 and diurnal cortisol slope at T2
	Thomas (2012)[c]	• ↓CGs (vs. NCs) • ↓CGs, late stage (vs. CGs, stage 1) • Diurnal cortisol slope: (ns) CGs (vs. NCs) • CAR: (ns) CGs (vs. NCs)	• (−) PTSD and cortisol • (−) Depression and diurnal cortisol slope
Immune function			
Cytokines	Bevans (2016)[a]	• IL-6: (ns) CGs (vs. NCs) • TNF-α: (ns) CGs (vs. NCs) • TNF-α:↓T2 (vs. T1) in CGs	• (ns) Chronic stress and TNF-α
	Cohen (2005)[a]	• IL-2, IL-12:↓CGs, advanced CA (vs. CGs, localized CA)	• (−) Emotional distress and IL2, IL12
	Miller (2002)[a,d]	• TNF-α:↑CGs (vs. NCs) • IL-6:↓CGs (vs. NCs) • IL-1β: (ns) CGs (vs. NCs)	—
	Miller (2008)[a]	• IL-1 receptor antagonist:↑CGs (vs. NCs) • IL-6: (ns) CGs (vs. NCs)	—
	Rohleder (2009)[a]	• IL-6: (ns) CGs (vs. NCs) at T1	—
	Sherwood (2016)[a]	—	• (+) Anxiety and latent class membership (IL-1ra) in male • (ns) Depression and latent class membership (IL-1ra, IL-6)

(continued)

Table 3. (continued)

Biomarker	First Author (Year)	Results: Comparisons Between Groups or Time Points	Results: Relationship Between Biomarkers and psychological Health Outcomes
CRP	Miller (2008)[a]	• ↑CGs (vs. NCs)	—
	Miller (2014)	• (ns) CGs (vs. NCs)	—
	Rohleder (2009)[a]	• (ns) CGs (vs. NCs) at T1 • ↑CGs (vs. NCs) over time	—
NK cell	Goodfellow (2003)[a]	—	• (↓) Stress and NK cell activity only in females at T1 • (↓) Depression and NK cell activity at T1
	Lutz Stehl (2008)[a,d]	—	• (ns) Stress and NK cell activity

Note. ↑ = increased; ↓ = decreased; (+) = positively associated; (−) = negatively associated; (ns) = not significantly different or associated; CA = cancer; CAR = cortisol awake response; CAT = catecholamine; CG = caregiver; CRP = C-reactive protein; EPI = epinephrine; HPA = hypothalamic–pituitary–adrenal; HSCT = hematopoietic stem cell transplantation; IL = interleukin; NC = noncaregiver; NE = norepinephrine; NK = natural killer; PTSD = post-traumatic stress disorder; QOL = quality of life; ra = receptor antagonist; sAA = salivary α-amylase; SAM = sympathetic–adrenal–medullary; TNF-α = tumor necrosis factor-α.
[a]Biomarker of interest measured in serum. [b]Biomarker of interest measured in urine. [c]Biomarker of interest measured in saliva. [d]Caregivers for pediatric cancer patients.

Table 4. Studies in Which Biomarkers Were Used to Monitor Intervention Effects.

Biomarker	First Author (Year)	Intervention	Results
Neuroendocrine function			
Cortisol	Fancourt (2016)[a]	Music intervention	• ↓post-INT (vs. pre-INT) • (ns) current CGs (vs. bereaved CGs, patients)
	Laudenslager (2015)[a]	PEPRR	• CAR: (ns) post-INT (vs. pre-INT)
	Lengacher (2012)[a]	MBSR	• ↓post-INT (vs. pre-INT) at T2, T3 but not at T4
	Pinar (2015)[b]	Back massage	• CGs (INT):↓T2 (vs. T1) • CGs (control): (ns) T2 (vs. T1)
	Walsh (2007)[a]	Art-making class	• (ns) post-INT (vs. pre-INT)
DHEA-S	Laudenslager (2015)[a]	PEPRR	• (ns) post-INT (vs. pre-INT)
Endorphin	Fancourt (2016)[a]	Music intervention	• ↓post-INT (vs. pre-INT) in current CGs, bereaved CGs, patients
Oxytocin	Fancourt (2016)[a]	Music intervention	• ↓post-INT (vs. pre-INT) in current CGs, bereaved CGs, patients
Immune function			
Cytokines	Fancourt (2016)[a]	Music intervention	• GM-CSF, IFNγ, IL-2, IL-4, IL-6, IL-17, TNF-α: ↓post-INT (vs. pre-INT) in current CGs, bereaved CGs, patients
	Laudenslager (2015)[a]	PEPRR	• IL-6: (ns) post-INT (vs. pre-INT)
	Lengacher (2012)[b]	MBSR	• IL-6: ↓post-INT (vs. pre-INT) in CGs at T4 but inconsistent before and after MBSR session
CRP	Laudenslager (2015)[a]	PEPRR	• (ns) post-INT (vs. pre-INT)
Neuropeptides	Fancourt (2016)[a]	Music intervention	• β-endorphin, oxytocin:↓post-INT (vs. pre-INT) in current CGs, bereaved CGs, patients
NK cell	Goodfellow (2003)[b]	Therapeutic back massage	• (ns) CGs (INT) (vs. control) • (ns) T2, T3 (vs. T1)

Note. ↑ = increased; ↓ = decreased; (ns) = not significantly different; CAR = cortisol awakening response; CRP = C-reactive protein; DHEA-S = dehydroepiandrosterone sulfate; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFNγ = interferon γ; IL = interleukin; INT = intervention; MBSR = mindfulness-based stress reduction program; NK = natural killer; PEPRR = PsychoEducation, Paced Respiration and Relaxation; TNF-α = tumor necrosis factor-α.
[a]Biomarker of interest measured in saliva. [b]Biomarker of interest measured in serum.

quality of life (Nightingale et al., 2017) and depressive symptoms (Thomas et al., 2012).

Cortisol was used as a biomarker to monitor the efficacy of interventions in five studies (Fancourt et al., 2016; Laudenslager et al., 2015; Lengacher et al., 2012; Pinar & Afsar, 2015; Walsh et al., 2007). The results from these studies were mixed. In three studies (Fancourt et al., 2016; Lengacher et al., 2012; Pinar & Afsar, 2015), researchers reported a significant reduction of cortisol levels in caregivers for patients with cancer after interventions (i.e., music intervention, MBSR, back massage), although the change was not always sustained over time (Lengacher et al., 2012). In the remaining two studies, researchers did not observe a significant difference in either CAR (Laudenslager et al., 2015) or cortisol levels (Walsh et al., 2007) in relation to their respective interventions (i.e., PEPRR, art-making class).

Only one study involved the biomarker dehydroepiandrosterone sulfate (DHEA-S). Laudenslager et al. (2015) found that the PEPRR intervention had no significant effect on DHEA-S levels across the study.

In an additional study (Fancourt et al., 2016), researchers examined the neuropeptides β-endorphin and oxytocin as outcomes to monitor the effects of a music intervention. Caregivers who received the intervention had decreases in both neuropeptide levels. These findings are counterintuitive and require future study.

Immune Function

In addition to the SAM and HPA axes, the immune system is an essential component of the stress response. Psychological stressors activate a number of changes in the immune system that are associated with human disease (Klein & Corwin, 2007; Nater et al., 2013).

Cytokines. Cytokines are useful biomarkers of the immune response to stress since cytokines secreted by immune cells act as chemical messengers, activating and regulating immune and inflammatory responses throughout the body (Klein & Corwin, 2007; Nater et al., 2013). Researchers included a number of cytokines in the studies we reviewed such as interleukin (IL)-6, IL-2, IL-12, and tumor necrosis factor-α (TNF-α).

IL-6 was the most frequently measured of the cytokines in this body of literature (Bevans et al., 2016; Miller et al., 2008; Miller et al., 2002; Rohleder et al., 2009). Authors suggest that IL-6 is a more reliably detectable biomarker than many other cytokines because circulating levels of IL-6 in asymptomatic individuals are often higher than those of other cytokines, and the relationship between psychological stress and IL-6 appears to be relatively consistent (Hänsel, Hong, Camara, & von Känel, 2010; Nater et al., 2013). In the present review, however, we found that most studies comparing IL-6 levels between caregivers and noncaregivers (Bevans et al., 2016; Miller et al., 2008; Rohleder et al., 2009) showed no significant difference between the two groups. Bevans et al. (2016) found, in their longitudinal study, that the IL-6 levels for caregivers remained stable over time despite high levels of perceived stress. Only in one cross-sectional study (Miller et al., 2002) did authors report that IL-6 levels were significantly lower in caregivers caring for their children with cancer than in noncaregivers. In addition, three studies (Fancourt et al., 2016; Laudenslager et al., 2015; Lengacher et al., 2012) involved measuring IL-6 levels to monitor the effect of an intervention among cancer patients and caregivers. Both the music intervention (Fancourt et al., 2016) and a 6-week MBSR program (Lengacher et al., 2012) generated significant decreases in IL-6 levels, but decreases in IL-6 were inconsistent in the MBSR study, with the only significant reduction happening at Week 6 (as opposed to at Weeks 1 and 3) postintervention. In another study (Laudenslager et al., 2015), researchers reported that the PEPRR intervention had no significant effect on IL-6 levels.

Investigators studied IL-2 and IL-12 levels less frequently than IL-6. In one study investigating both IL-2 and IL-12 levels, Cohen and Pollack (2005) found that caregivers for patients with advanced cancer had significantly decreased IL-2 and IL-12 levels compared with caregivers for patients with localized cancer. Additionally, researchers assessed TNF-α in two studies (Bevans et al., 2016; Miller et al., 2002), yielding inconsistent results. Miller, Cohen, and Ritchey (2002) found higher TNF-α levels in caregivers than in controls. Bevans et al. (2016), however, found no significant difference in TNF-α levels between caregivers for allogeneic hematopoietic stem cell transplantation patients and noncaregivers, but TNF-α levels in those same caregivers were lower after initial transplantation discharge compared with before transplantation.

C-reactive protein (CRP). The acute-phase protein CRP is considered to be a potential biomarker of immune function because it is rapidly generated in the liver in response to inflammation (especially an increase in IL-6 levels) and infection (Nater et al., 2013; Pepys & Hirschfield, 2003). Three studies (Miller et al., 2008; Miller et al., 2014; Rohleder et al., 2009) examined CRP levels in caregivers. Miller et al. (2008) reported significantly increased CRP levels in caregivers compared to noncaregivers. In another study, Rohleder et al. (2009) found that caregivers and noncaregivers had similar levels of CRP at study entry, but the groups' trajectories diverged significantly over time, with caregivers' CRP levels increasing and noncaregivers' levels decreasing significantly.

Natural killer (NK) cell activity. In two studies (Goodfellow, 2003; Lutz Stehl et al., 2008), researchers examined the association between NK cell activity and psychological health outcomes in caregivers for cancer patients, yielding mixed results. Goodfellow (2003) reported a significant inverse relationship between NK cell activity and perceived stress in female caregivers, while Lutz Stehl et al. (2008) did not observe a significant association between the two. Additionally, higher levels of depression were related to lower NK cell activity (Goodfellow, 2003). Goodfellow et al. (2003) also reported on their findings regarding the use of NK cell activity as a biomarker to monitor the effects of therapeutic back massage in caregivers.

They observed no significant Group × Time interaction and no significant changes in NK cell activity in the intervention group over time, though the back massage had a significant positive effect on mood and decreased perceived stress.

Discussion

In this scoping review, we summarized current knowledge about the assessment of biomarkers in informal caregivers for patients diagnosed with cancer. The majority of the studies included in this review measured biomarkers with the aim to better characterize differences between groups of caregivers and noncaregivers and to predict psychological health outcomes (e.g., depression). Biomarkers assessing neuroendocrine and immune function received the most attention among these studies, particularly cortisol and pro-inflammatory cytokines. A few of the studies used biomarkers, primarily cortisol, in order to evaluate the effect of an intervention. Unfortunately, the evidence regarding the use of cortisol and pro-inflammatory cytokines as surrogate end points for clinical outcomes among cancer caregivers is mixed, making it difficult to draw valid and meaningful conclusions. However, a major consideration regarding an explanation for the inconsistencies across studies is the variability in the methods researchers used to collect the biomarkers, especially cortisol, a point we discuss more fully below.

Our findings from this review revealed a high level of heterogeneity across assays used, yielding scant evidence (small sample sizes and few studies per biomarker) for drawing conclusions. Based on the selection of biomarkers, we determined that the intent more often has been to assess the physiological stress response, such as changes in the HPA axis, than to assess the impact of caregiving on physical health, such as the immune system or cardiometabolic function. As a result of the emphasis on research regarding the impact of caregiving on the physiological response to stress, there is an emerging hypothesis that caregivers, especially those with more burden, demonstrate dysregulation of the HPA axis, suggesting a "burnout" phenomenon (Klein & Corwin, 2007). Although studies testing interventions to reverse the negative impact of caregiving on the HPA axis have found relatively consistent improvement in cortisol levels, these effects appear to be immediate and, perhaps, short term. Studies have not yet demonstrated the sustainability of these improvements over the long term. This observation also applies to changes in inflammatory cytokines. In addition, isolating the relationship between the changes in inflammatory biomarkers due to the stress of caregiving and cardiovascular disease is difficult, which can limit clinical application (Soeki & Sata, 2016).

Despite the growth in this field, the exploration of the use of biomarkers in cancer caregiver research is still in its early stages, and there are numerous complexities that make interpretation of the research challenging. Through the present review, we identified four major gaps in the literature that could be used to guide future research: (a) standardization of appropriate and accurate biomarker collection, (b) exploration of biomarkers of other physiologic functions beyond the stress and immune responses (e.g., cardiovascular function, cognitive dysfunction, cell aging), (c) exploration of biomarkers that can serve as multisystem indicators, and (d) identification of biomarkers that can be used to monitor the efficacy of caregiving interventions. Above all, the variability in methodological standards for collecting biomarkers is a critical barrier to interpreting this literature and likely contributed to the inconsistent results. For example, some studies described using a specific specimen collecting time to capture the peak level of biomarkers (Bevans et al., 2016; Lucini et al., 2008), whereas others (Miller et al., 2002; Nightingale et al., 2017; Thomas et al., 2012) reported using a collection time or times during which the diurnal rhythm is known to affect the biomarkers of interest. Although recommendations exist to guide cortisol sampling (Saxbe, 2008; Stalder et al., 2016), assessments varied in these studies in terms of specific sampling times throughout the day, the type of biological sample measured (saliva vs. serum), and whether a baseline measure was included. These variations inhibit consensus of findings across studies. Following a more standardized approach to biomarker collection across studies would strengthen the developing body of evidence. Until further research addresses the potential differences between salivary and serum cortisol as well as the difficulty in measuring free cortisol as opposed to cortisol that is bound to cortisol-binding globulin (CBG), the value of cortisol as a measure of the stress response in caregivers will continue to be limited (Hellhammer, Wüst, & Kudielka, 2009; Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007). Researchers also have to consider possible sources of variance (e.g., age, gender, menstrual cycle, oral contraceptives, and CBG), which may affect the measures (Hellhammer et al., 2009; Kudielka, Hellhammer, & Wüst, 2009).

There is a developing body of evidence that caregiving is a risk factor for the development of cardiovascular diseases. Interestingly, research has not focused on biomarkers of cardiovascular function among cancer caregivers. In dementia caregivers, researchers have investigated several cardiovascular biomarkers, focusing on coagulation factors, such as D-dimer, von Willebrand factor (VWF), plasminogen activator (PAI-1), and P-selectin (Aschbacher et al., 2005; Aschbacher et al., 2009; Aschbacher et al., 2006; Mausbach et al., 2006; Mills et al., 2009; von Känel, Ancoli-Israel, et al., 2010; von Känel, Mausbach, et al., 2010). Findings from these studies demonstrate that cardiovascular biomarkers are useful for understanding the links between caregiving stress and risk factors in cardiovascular disease. In particular, D-dimer levels are a good indicator of cardiovascular health and manifest statistically significant elevations in caregiving populations. D-dimer thus has the potential to be a convenient and cost-effective biomarker for clinicians dealing with chronically stressed caregivers potentially at risk of cardiovascular disease (Aschbacher et al., 2005; Aschbacher et al., 2006; von Känel, Ancoli-Israel, et al., 2010; von Känel, Mausbach, et al., 2010). In addition, in one study (von Känel, Mausbach, et al., 2010), researchers assessed the procoagulant index, a composite of standardized

z-scores of D-dimer, VWF, and PAI-1. This approach aligns with recent systems' biology research by combining complicated hemostatic processes into one biologic pathway of hypercoagulability (Lo, Denney, & Diamond, 2005). Another aspect of cardiovascular risk is related to lipid metabolism. Authors have proposed using serum lipoprotein particle profile assessed via nuclear magnetic resonance (NMR) spectroscopy as a biomarker for identifying risk of lipid-related cardiovascular disease. The NMR analysis directly measures the concentration and size of individual lipoprotein particles in addition to standard lipids (Jeyarajah, Cromwell, & Otvos, 2006). Previous studies have demonstrated that serum lipoprotein particle profile by NMR analysis is an accurate and sensitive indicator of cardiovascular risk compared to traditional measures in noncaregiver populations (Jeyarajah et al., 2006; Kontush, 2015; Otvos et al., 2011).

Although investigators have not assessed cardiometabolic biomarkers in cancer caregivers, several (Corà, Partinico, Munafò, & Palomba, 2012; Goodfellow, 2003; Lai, Li, & Lee, 2011; Lee, Yiin, & Chao, 2016) have measured clinical markers of cardiovascular function, including blood pressure, blood volume pulse, heart rate, and heart rate variability, in cancer caregivers. The results indicate that caregivers had worse cardiovascular health compared with noncaregivers. In-depth investigations of cardiovascular function among cancer caregivers, however, are limited. Therefore, further studies using cardiovascular biomarkers are needed to elucidate the risks of impaired cardiovascular health in cancer caregiver populations.

Chronic stress, such as that experienced by caregivers for cancer patients, may also contribute to a number of changes in important brain structures such as the prefrontal cortex and hippocampus, which may lead to cognitive decline and dementia (Bremner, 1999; Klein & Corwin, 2007). A growing body of literature has demonstrated that caregivers report poorer cognitive function versus control subjects (Corrêa et al., 2015; Vitaliano, Murphy, Young, Echeverria, & Borson, 2011; Vitaliano, Ustundag, & Borson, 2016). Despite evidence of cognitive impairment among cancer caregivers, no study has examined biomarkers of cognitive function in this population. One study (Corrêa et al., 2015) did examine levels of brain-derived neurotrophic factor (BDNF), one of the neurotrophins involved with synaptic plasticity and neuronal survival and repair (Bremner, 1999), in dementia caregivers. Findings indicated that the caregivers for dementia patients had lower BDNF levels than noncaregivers, but that there was a significant relationship between BDNF levels and only one cognitive domain, working memory, which investigators assessed using the backward digit span (the participant hears a sequence of digits and must repeat them in reverse order). Future studies are needed to investigate biomarkers of cognitive function in cancer caregivers.

Another potential effect of inflammation and metabolic abnormalities is the shortening of a region of repetitive nucleotide sequences at each end of a chromosome (telomere attrition), which causes cellular aging (Epel et al., 2004; Klein & Corwin, 2007). Therefore, telomere length may provide valuable information about the biological state of or increased disease risk in caregivers. Previous work (Damjanovic et al., 2007; Epel et al., 2004; Litzelman et al., 2014) has examined the association between caregiving and shortened telomere length. Researchers found significant associations between caregiving stress and shortened telomere length in long-term dementia caregivers (Damjanovic et al., 2007) and in mothers caring for chronically ill children (Epel et al., 2004), while others (Litzelman et al., 2014) did not observe any difference in telomere length between caregivers and noncaregivers. One study additionally showed that greater caregiving strain was associated with shorter telomeres (Litzelman et al., 2014). Although the evidence is conflicting, the results are suggestive of the utility of telomere length in assessing the risk of age-related disease at a cellular level among chronically stressed caregivers.

Of course, there is a recurring question relevant to much of the literature on the use of biomarkers regarding the sensitivity and specificity of any individual biomarker (Laudenslager, 2014). This ongoing issue signifies that further research is required to identify alternative, collective, multidimensional, or composite biomarkers. Authors have proposed that allostatic load, an emerging multisystem indicator, has the potential to contribute significantly to understanding the relationships between stress and health. Allostatic load typically includes a combination of neuroendocrine, immune, metabolic, cardiovascular, and anthropometric biomarkers, for example, a composite score based on 10 indicators from a number of different systems, such as EPI, NE, cortisol, and DHEA-S from the neuroendocrine system; high-density lipoprotein (HDL), the HDL–total cholesterol ratio, and total glycosylated hemoglobin from the metabolic system; systolic and diastolic blood pressure from the cardiovascular system; and the anthropometric measure of waist–hip ratio (Juster, McEween, & Lupien, 2010). Several studies in caregivers for dementia patients (Clark, Bond, & Hecker, 2007; Dich, Lange, Head, & Rod, 2015; Roepke et al., 2011) found that caregiving stress was significantly associated with allostatic load. Results from previous studies suggest that allostatic load represents a potential mechanism linking caregiving outcomes to downstream health consequences.

Finally, though the use of physiological biomarkers as an outcome in intervention research for informal caregivers is uncommon, it has the potential to support the efficacy of intervention research (Corwin & Ferranti, 2016). Relatively few studies have examined whether interventions designed to improve caregivers' health result in changes in physiological health outcomes. Furthermore, the studies we reviewed that measured biomarkers as outcomes had limited generalizability due to small sample size ranging from 42 to 158. Results from these studies, however, suggest the value of broadening the focus of studies on caregiver interventions to include their impact on biologic risk factors associated with psychological outcomes. The inclusion of physiological markers strongly linked to psychological symptoms as primary outcome

variables is particularly important, as it may capture effects of the intervention that cannot be measured adequately with self-report questionnaires (Aboulafia-Brakha, Suchecki, Gouveia-Paulino, Nitrini, & Ptak, 2014). Expanding the scientific study of biomarkers as primary or secondary outcomes of intervention research will contribute to understanding the impact of caregiving on the health of caregivers and improve our ability to develop, target, and evaluate tailored interventions.

Conclusion

In this review, we identified biomarkers that researchers have frequently measured among informal caregivers for patients with cancer. Based on our findings, we conclude that biomarkers have been useful in caregiver research, particularly when they were linked to psychological health. However, there remain a number of issues to be addressed related to their measurement, interpretation, and reliability. Further research is needed to support reliability and repeatability as well as to identify additional novel biomarkers. Expanding the scientific study of biomarkers will contribute to understanding the mechanisms underlying the effects of caregiving on caregiver health. A better understanding of these mechanisms, in turn, will guide and support the development of effective intervention strategies targeting those mechanisms.

Acknowledgment

We would like to thank Judith Welsh, National Institutes of Health Library Informationist, for developing the database search strategies and performing the literature search in support of this article.

Author Contributions

J. Park contributed to conception, design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. M. Bevans contributed to conception, design, analysis, and interpretation; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. A. Ross contributed to interpretation, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. S. Klagholz contributed to interpretation, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Intramural Research Program at the National Institutes of Health Clinical Center.

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