USE OF BIOMARKERS IN RESEARCH ON CAREGIVERS' HEALTH: A SCOPING REVIEW

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BACKGROUND

- More than 2.8 million family members provide unpaid care for cancer patients in the U.S. (1).
- Caregiving burden is perceived as stressful and may cause physiological changes in the caregivers ultimately affecting their health (2).
- Biomarkers that reflect underlying physiological processes may provide us with a greater understanding of mechanisms through which stress may influence health among caregivers (3).
- Biomarkers are defined as "biological molecules found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or a condition or disease"(4).
- Biomarkers can serve several 3 unique purposes (5,6)
  1) Prognostic biomarker: confirmation of diagnoses
  2) Predictive biomarker: prediction of clinical outcomes
  3) Monitoring biomarker: monitoring treatment effect
- The scientific search for the biomarkers of health outcomes in caregivers is in its early stages (3).

OBJECTIVE

The purpose of this review was

1) to provide a comprehensive summary of the research examining biomarkers as surrogate endpoints for clinical outcomes in family caregivers of patients with cancer;
2) to identify existing gaps; and
3) to make recommendations for future research.

METHODS

- Scoping review
- Data source (Search engine)
  - PubMed, EBASE, CINAHL Plus, PsycINFO, and Scopus
- Search strategy
  - Keywords: "caregivers/caregiving" AND "neoplasm/cancer" AND "biological markers/biomarker" 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"
  - Inclusion criteria
    - ✓ Informal caregivers of patients diagnosed with cancer
    - ✓ Full-text, peer-reviewed, English-language studies
  - Exclusion criteria
    - ✓ Not caregivers of patients diagnosed with cancer
    - ✓ Biomarkers not measured
    - ✓ Not original research
- Study selection
  - The initial search yielded 830 articles.
  - A total of 18 studies were identified.
    - ✓ Prognostic (n=0), Predictive (n=13), Monitoring (n=6)
    - ✓ Design: Cross-sectional (n=7), Longitudinal (n=11)
    - ✓ Nationality: U.S. (n=12), Canada (n=3), Others (n=3)
- Categorization of biomarkers

	Physiological categories	Biomarkers
1	Neuroendocrine function	
	1) SAM axis activity	CAT (EPI, NE), Salivary pH, sAA
	2) HPA axis activity	Cortisol, DHEA-S, Endorphin, Oxytocin
2	Immune function	Cytokines, CRP, NK cell

Note. CAT (catecholamine- norepinephrine [NE] and epinephrine [EPI]); CRP (C-reactive protein); DHEA-S (dehydroepiandrosterone sulfate); HPA (hypothalamic-pituitary-adrenal); NK (natural killer); sAA (salivary alpha-amylase); SAM (Sympathetic adrenal-medullary)

RESULTS

Table 1. Biomarkers to predict group membership and outcomes

Biomarkers	Design (study #)	Results of the review: Group comparisons	Results of the review: Relationship between biomarkers and psychosocial health outcomes
Neuroendocrine function			
1) SAM axis activity			
CAT (EPI & NE)	C (1)	• EPI, NE, CAT-turnover: ↑ CGs, advanced CA (vs CGs, localized CA)	—
	L (1)	• EPI, NE, CAT-turnover: (—) CGs (vs NCs) • NE: ↓ CGs, DC (vs CGs, before HSCT)	• (↓) Chronic stress & EPI
sAA	L (1)	• Diurnal rhythm: ↓ CGs (vs NCs) over time • Total daily output: ↑ CGs (vs NCs) over time	—
Salivary pH	C (1)	• ↓ CGs, CA (vs NCs, non-CA)	• (↓) Stress & Salivary pH • (↓) Depression & Salivary pH
2) HPA axis activity			
Cortisol	C (5)	• (ǂ) CGs (vs NCs)	• (—) Emotional distress & Cortisol • (↓) PTSD & Cortisol • (↓) Depression & Diurnal cortisol slope
	L (3)	• (ǂ) CGs (vs NCs) • (ǂ) CGs (vs NCs) over time	• (—) Chronic stress & Cortisol • (↓) QOL initiation of RT & diurnal cortisol slope 5 weeks into-RT
Immune function			
Cytokines	C (3)	• IL-6: (ǂ) CGs (vs NCs) • IL-2, IL-12: ↓ CGs, advanced CA (vs CGs, localized CA) • TNF-α: ↑ CGs (vs NCs)	• (↓) Emotional distress & IL-2, IL-12
	L (3)	• IL-6: (—) CGs (vs NCs) • TNF-α: (—) CGs (vs NCs) • TNF-α: ↓ CGs, DC (vs CGs, before HSCT)	• (—) Chronic stress & TNF-α
CRP	C (1)	• ↑ CGs (vs NCs)	—
	L (2)	• (—) CGs (vs NCs) • (—) CGs (vs NCs) over time	—
NK cell	C (2)	—	• (ǂ) Stress & NK cell activity • (↓) Depression & NK cell activity

Note. ↑ = increased; ↓ = decreased; (↑) = positively associated; (↓) = negatively associated; (—) = not significantly different or associated; (ǂ)= mixed; C (cross-sectional); CA (cancer); CAR (cortisol awake response); CAT (catecholamine- norepinephrine [NE] and epinephrine [EPI]); CG (caregiver); CRP (C-reactive protein); DC (discharge); HPA (hypothalamic-pituitary-adrenal); IL (interleukin); L (longitudinal); NC (non-caregiver); NK (natural killer); PTSD (post-traumatic stress disorder); RT (radiotherapy); SAM (Sympathetic adrenal-medullary); TNF-α (tumor necrosis factor-α)

Table 2. Biomarkers to monitor intervention effect

Biomarkers	Study #	Intervention	Results of the review
Neuroendocrine function			
Cortisol	5	• Art-making class • Back massage • MBSR • Music intervention • PEPRR	• (—) after art-making class • ↓ after back massage • ↓ after MBSR • ↓ after music intervention • CAR: (—) after PEPRR
DHEA-S	1	• PEPRR	• (—) after PEPRR
Endorphin	1	• Music intervention	• ↓ after music intervention
Oxytocin	1	• Music intervention	• ↓ after music intervention
Immune function			
Cytokines	3	• MBSR • Music intervention • PEPRR	• IL-6: ↓ after MBSR • IL-6: (—) after music intervention • GM-CSF, IL-2, IL-4, IL-6, IL-17, TNFα: ↓ after MBSR
CRP	1	• PEPRR	• (—) after PEPRR
Neuropetide	1	• Music intervention	• β-endorphin, oxytocin: ↓ after music intervention
NK cell	1	• Music intervention	• (—) CGs, intervention (vs control)

Note. ↑ = increased; ↓ = decreased; (—) = not significantly different, CAR (cortisol awake response); CRP (C-reactive protein); DHEA-S (dehydroepiandrosterone sulfate); GM-CSF (granulocyte-macrophage colony-stimulating factor); IL (interleukin); INT (intervention); MBSR (mindfulness-based stress reduction program); NK (natural killer); PEPRR (PsychoEducation, Paced Respiration and Relaxation)

DISCUSSION

- Biomarkers are most commonly incorporated into caregiver studies to predict group membership and psychological health.
- Neuroendocrine and immune biomarkers, specially cortisol and cytokines, are most frequently assessed.
- Recommendations for the future research
  - Appropriate and accurate biomarker collection
  - Biomarkers of other physiologic function (e.g., cardiovascular function, cognitive dysfunction, cell aging)
  - Biomarkers with multisystem indicators (e.g., allostatic load)
  - Biomarkers to monitor the efficacy of caregiving interventions
- Expanding the scientific study for biomarkers will contribute to our understanding of the mechanisms through which stress may influence caregiver health.
- Future direction
  - Biomarkers of cardio-metabolic risk in cancer caregivers: Lipoprotein particle profile by nuclear magnetic resonance (NMR) spectroscopy

Reference

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