Rigor and Reproducibility: A Systematic Review of Salivary Cortisol Sampling and Reporting Parameters Used in Cancer Survivorship Research

Jennifer M. Hulett, PhD, APRN, FNP-BC¹ ,
 Kristen L. Fessele, PhD, RN, ANP-BC, AOCN² ,
 Margaret F. Clayton, PhD, APRN, FNP-BC³,
 and Linda H. Eaton, PhD, RN, AOCN⁴

Abstract

Salivary cortisol is a commonly used biomarker in cancer survivorship research; however, variations in sampling protocols and parameter reporting limit comparisons across studies. Standardized practices to provide rigor and reproducibility of diurnal salivary cortisol sampling and reporting are not well established. Previous systematic reviews examining relationships between diurnal salivary cortisol and clinical outcomes have resulted in mixed findings. It remains unclear which sampling protocols and reporting parameters offer the greatest utility for clinical research. This review examines diurnal salivary cortisol sampling protocols and reporting parameters to evaluate whether a standardized approach is recommended. A comprehensive search of intervention studies among adult cancer survivors including diurnal salivary cortisol resulted in 30 articles for review. Sampling protocols ranged from 1 to 4 days with the majority of studies sampling cortisol for 2 days. Sampling instances ranged from 2 to 7 times per day, with the majority collecting at 4 time points per day. Diurnal cortisol slope and cortisol awakening response (CAR) were the most commonly reported parameters associated with clinical outcomes. Flattened cortisol slopes, blunted CARs, and elevated evening cortisol concentrations were associated with poorer psychosocial and physiological outcomes. Based on our review, we propose that a rigorous, standardized diurnal salivary cortisol sampling protocol should include sampling at key diurnal times across ≥ 3 consecutive days to report diurnal cortisol parameters (i.e., CAR and slope) and objective measures of participant protocol adherence. Diminishing budgetary resources and efforts to minimize participant burden dictate the importance of standardized cortisol sampling protocols and reporting parameters.

Keywords

best practices, cancer, cortisol measurement, review, rigor, salivary cortisol

Salivary cortisol is commonly used as a biomarker in biobehavioral research to measure the hypothalamic–pituitary–adrenal axis (HPAA) response to stress. Although salivary cortisol has been used as an outcome measure in research for over a decade, lack of standardized measurement and reporting practices has resulted in a wide variation of sampling strategies across studies that limit comparisons of findings (Ryan, Booth, Spathis, Mollart, & Clow, 2016; Subnis, Starkweather, McCain, & Brown, 2013). These issues have further limited reproducibility of study results, prompting the National Institutes of Health (2016) to call for increased transparency in rigorous experimental design description and reporting.

The specifics of the research question should guide the development of the sampling protocol, along with consideration of participant burden (Granger, Johnson, Szanton, Out, & Schumann, 2012). A review of existing literature reveals

studies with salivary cortisol collection times ranging from 1 to multiple times per day and across 1 to multiple consecutive days. Anecdotally, from our own experiences and discussions with colleagues engaged in salivary cortisol research, we have observed that there is a common struggle with the “messiness”

¹ College of Nursing, University of South Carolina, Columbia, SC, USA

² Memorial Sloan Kettering Cancer Center, New York, NY, USA

³ College of Nursing, University of Utah, Salt Lake City, UT, USA

⁴ School of Nursing & Health Studies, University of Washington, Bothell, Bothell, WA, USA

Corresponding Author:

Jennifer M. Hulett, PhD, APRN, FNP-BC, College of Nursing, University of South Carolina, 1601 Greene Street, Columbia, SC 29208, USA.

Email: hulett@sc.edu

of salivary cortisol measurement, including the difficulty of interpreting clinically relevant findings.

Granger, Johnson, Szanton, Out, and Schumann (2012) provide an overview of salivary cortisol specimen collection, including diurnal rhythm considerations and potential confounders of findings. However, standardization of sampling protocols and salivary cortisol parameter reporting is not well established. Previous systematic reviews examining relationships between salivary cortisol and clinical outcomes have reported mixed findings. Therefore, in the present systematic review, we examine salivary cortisol sampling protocols and reporting parameters in the current literature to identify which protocols and parameters might support standardized practices in salivary cortisol research. We review salivary cortisol sampling and reporting during the past 10 years, a period that coincides with the emergence of salivary cortisol as a popular biobehavioral research outcome measure, particularly in cancer survivorship literature. Due to the rapidly expanding body of literature on salivary cortisol and clinical outcomes in cancer survivorship (our area of scholarship) combined with the observed variability among sampling patterns, we focused this review on salivary cortisol sampling in cancer survivors.

Background

Diurnal Cortisol Pattern

Cortisol follows a diurnal circadian pattern, with lowest concentrations at night, a slow rise during preawakening hours, a sharp rise after waking (i.e., “eyes open”) with a peak at 30–45 min after waking (i.e., the cortisol awakening response [CAR]), and a decline that begins by 60 min after waking and continues for the remaining waking hours of the day (i.e., cortisol diurnal slope; Adam & Kumari, 2009; Stalder et al., 2016). Salivary cortisol measurement at a single time point has limited value due to variances between and within individuals (Pruessner et al., 1997). More useful protocols call for multiple measurements that provide context within the overall diurnal pattern (Segerstrom, Boggero, Smith, & Sephton, 2014).

Cortisol parameter reporting falls into three main categories: (1) mean concentrations at collection time points (e.g., waking, postwaking, and bedtime), (2) total cortisol production (reported as a mean or as the area under the curve with respect to ground [AUC_g or simply AUC]), and (3) parameters describing the cortisol response to awakening and the change in diurnal pattern over time (i.e., diurnal slope). The CAR refers to the dynamic change from the waking baseline cortisol concentration to the peak cortisol concentration that occurs within the first hour after waking (Stalder et al., 2016). Authors have also reported the CAR as the CAR increase, the area under the curve with respect to increasing (AUC_i or CAR_{auc}). Both Fekedulegn et al. (2007) and Khoury et al. (2015) have provided in-depth explanations of cortisol parameters and derived calculations.

The sharp-rising surge of the CAR is the normal expected pattern associated with HPA activation and is necessary for management of anticipated daily stress (Clow, Thorn, Evans, & Hucklebridge, 2004). Abnormal CAR and diurnal slope patterns indicate aspects of HPA dysregulation. Researchers have reported that both heightened and blunted CARs are associated with psychosocial stress and poor health outcomes, resulting in mixed conclusions regarding the predictive value of the CAR for clinical outcomes (Adam & Kumari, 2009).

Salivary Cortisol Sampling Issues

Research participant education to promote adherence to a specific protocol's collection procedures is key to enhancing reliability and reproducibility of cortisol-related results. Measurement of waking salivary cortisol requires participants to accurately adhere to collection times for the self-collection of specimens while still in bed in order to synchronize measurement of the baseline cortisol level with the moment of real awakening (Stalder et al., 2016). Salivary cortisol measurement requires cognizance of the time-sensitive nature of specimen collection and accuracy in reporting the actual sampling collection time. Because the CAR occurs within a range of 30–60 min after waking, unreported deviations from the collection protocol by participants introduce the risk of missing the CAR response as well as potentially skewing calculations of the diurnal rhythm parameters (e.g., slope) that are anchored to waking and CAR concentrations (Hulett et al., 2018). Given the existing inter- and intraindividual variability in diurnal cortisol rhythms, discrepancies in sampling times further complicate attempts to interpret diurnal patterns of sample participants. The potential for inaccuracies in salivary cortisol sampling highlights the need for greater transparency in optimal salivary cortisol sampling practices.

The variance in salivary cortisol sampling protocols historically stems from a lack of consensus on best practices. Ryan, Booth, Spathis, Mollart, and Clow (2016) describe common inconsistencies in diurnal salivary measurement across randomized controlled trials (RCTs), including issues with cortisol sampling schedules, a lack of consecutive collection days, heterogeneity in the reporting of cortisol parameters, and failure to consider the diurnal nature of cortisol for sampling and parameter reporting. Stalder et al. (2016) reported on variations in methods of CAR measurement and offered expert consensus guidelines for rigorous assessment of the CAR. Segerstrom, Boggero, Smith, and Sephton (2014) provided recommendations regarding the number of days of salivary cortisol sampling necessary to reliably assess for cortisol variability and calculate diurnal cortisol parameters. However, there remains scant literature focusing on these methods in the cancer survivorship population.

McEwen (1998) suggested that HPA hypervigilance due to chronic stress contributes to the neuroimmune dysregulation observed in chronically ill populations. Among cancer

survivors, prolonged cortisol activation may suppress tumor-fighting immune functions and has been further associated with risk of cancer recurrence (Mundy-Bosse, Thornton, Yang, Andersen, & Carson, 2011; Witek-Janusek, Gabram, & Mathews, 2007). For these reasons, salivary cortisol remains an important outcome measure in cancer survivorship and stress research.

Method

It remains unclear which cortisol sampling protocols and reporting parameters offer the most utility in clinical research. Recognizing existing limitations in salivary cortisol sampling protocols and acknowledging emerging expert consensus guidelines, we focused this review on cancer-related salivary cortisol studies that included assessment of the diurnal cortisol rhythm and utilized repeated sample collections (more than one collection time per day) to answer the following questions:

- (1) What are the common salivary cortisol sampling protocols and parameters reported?
- (2) What methods are used to monitor participant adherence to cortisol sampling protocols?
- (3) What are the relationships between salivary cortisol sampling protocols and parameters and the detection of clinical outcomes among cancer survivors?

Database Search

We systematically searched the following databases for this review: PubMed, Medline, the Cumulative Index to Nursing and Allied Health Literature, the Cochrane Central Register of Clinical Trials, EMBASE, PsycINFO, Scopus, and Google Scholar. Gray literature searches included the Conference Papers Index and ProQuest Biological Sciences database. We also performed an ancestry search of references from reviewed articles. We filtered the database searches to limit studies to those conducted in human adults and published within the period from January 2006 to June 2016.

Key Words

For the search, we combined the primary term *salivary cortisol* with the following associated terms: *best practices*, *biobehavioral intervention*, *biomarker*, *CAR*, *cortisol postawakening response*, *cortisol rhythm*, *cortisol slope*, *cortisol variability*, *diurnal cortisol*, *glucocorticoid*, *hydrocortisone*, *HPAA*, *intervention*, *meta-analysis*, *randomized control trial*, *salivary cortisol patterns*, *stress*, *stress management*, *stress reactivity*, and *systematic review*.

Inclusion and Exclusion Criteria

We focused this review on salivary cortisol measurement in studies of adults with a history of a cancer diagnosis. Because our primary objective was to examine current salivary cortisol

research sampling protocols, we included all study design types. Inclusion criteria were, thus, the following: (1) adults (≥ 18 years of age), (2) cancer diagnosis (pre- or posttreatment for cancer), and (3) salivary cortisol included as an outcome measure. We excluded studies (1) among individuals with Cushing's disease, (2) evaluating the effects of exogenous glucocorticoids, (3) focusing on endocrine-related cancers, (4) that were unpublished or abstract publications only, (5) involving salivary cortisol measurement in a laboratory setting only, (6) that sampled cortisol at one time point in a single day, (7) in which the sampling protocols did not include an awakening salivary cortisol collection, (8) testing interventions yet lacking pre- or postintervention salivary cortisol sampling, (9) not available in English, and (10) that did not undergo peer review.

Article Selection

Figure 1 illustrates the process we used to identify, screen, and select articles for review. As we searched each database, we screened titles based on the inclusion and exclusion criteria. We imported articles selected during this stage of screening into an EndNote X7 library and further examined them by abstract review and, as necessary to determine eligibility, in-depth reading of the paper. At least two coauthors reviewed each of the abstracts and selected articles to ensure that they satisfied all inclusion and exclusion criteria. We discussed results of this review as a group and resolved disagreements via consensus. We retained 30 articles for further analysis.

Results

We included studies published from January 2006 to June 2016, which corresponds to the time of the rise in popularity of cortisol measurement. Table 1 presents data extracted from the articles. Study designs were observational ($n = 9$), nonrandomized controlled trials (non-RCTs; $n = 8$), RCTs ($n = 5$), prospective matched cohorts ($n = 5$), and longitudinal observations ($n = 3$). Sample sizes ranged from 21 to 266 participants per study, with an average of 88.7 ($SD = 56.6$). Combined participants in the reviewed studies comprised 2,528 cancer survivors and 302 healthy controls. Cancer types included breast (66.2%, $n = 1,674$), ovarian (20.5%, $n = 519$), lung (4.6%, $n = 116$), prostate (5.6%, $n = 142$), and other cancers (i.e., colon, leukemia, cervical, head, and neck; 3%, $n = 77$).

Question 1: What Are the Common Salivary Cortisol Sampling Protocols and Parameters Reported?

The time period for cortisol sampling assessment ranged from 1 to 4 days (Table 2). The majority of studies assessed cortisol for 2 consecutive days, followed by 3 days, with fewer studies sampling for 1 day and a single study sampling for 4 days (see Tables 1 and 2). Number of daily sampling time points ranged from 2 to 7, with the majority of studies collecting at 4 time points per day, followed by 5 and 3 times per day. Nearly one

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart of article identification, screening, and selection process.

third of studies (28%) did not sample postawakening cortisol. Among the 22 studies that did assess postawakening cortisol, the majority sampled cortisol 30 min after waking. Some studies sampled cortisol at additional time points: 12 p.m. ($n = 11$ [38%]), 4:00–5:00 p.m. ($n = 18$ [60%]), and 9:00–10:00 p.m. ($n = 15$ [50%]). In 26 studies (86.7%), evening and bedtime cortisol sampling took place in the range of 8 p.m.–12 a.m. Common cortisol reporting parameters were cortisol diurnal

slope, CAR, mean cortisol concentrations at collection time points, and AUC (including AUCg) calculations.

Question 2: What Methods Are Used to Monitor Participant Adherence to Cortisol Sampling Protocols?

In seven studies, authors did not provide information regarding objective monitoring (e.g., external monitoring with an

Table 1. Studies Measuring Salivary Cortisol in Adult Cancer Survivors: Sampling Protocol Characteristics and Key Findings.

First Author (Year)	Study Aim	Sample Participants	Primary Outcome Measures + Salivary Cortisol	Study Design	Saliva Collection Protocol	Sampling Time Points	Sampling Collection Time Verification	Cortisol Parameters Reported	Clinical Findings Associated With Cortisol Parameters
Days of consecutive sampling in protocol = 1									
Campos (2015)	Measure effects of Tai Chi Chih on cortisol and inflammatory cytokines in women with BC	63 women with BC, Stages I–III	IL-4, IL-6, IL-10, IL-12, TNF- α	RCT: IG = Tai Chi Chih, CG = health education	Awaken (7 a.m.), 30 min postawaken, 12 p.m., 5 p.m., 10 p.m. for 1 weekend day	Baseline + postintervention (at 13 weeks)	Precollection instructions on sampling	AUC, diurnal slope, CAR	No postintervention group differences for slope or CAR. IG had lower AUC than CG ($p = .02$)
Carlson (2007)	Compare relationships among salivary cortisol, melatonin, catecholamines, sleep quality, and stress between women with BC and healthy controls	33 women with BC (majority Stage II) and 33 healthy controls	Urinary catecholamines, urinary melatonin, PSQI, SOSI, CES-D, STAI, POMS	Prospective, matched cohort	Awaken, 12 p.m., 5 p.m., and 10 p.m. for 1 day	Baseline	Presampling instructions, self-report time log	Diurnal slope, AUC _g , AUC _i	No significant associations between psychosocial measures and cortisol parameters for either group
F. H. Hsiao (2012)	Measure effects of a body-mind-spirit intervention on diurnal cortisol in women with BC	48 women with BC (Stages 0–III)	BDI-II, MLQ	RCT: IG = body-mind-spirit intervention, CG = education session	Awaken, 30-min postawaken, 45-min postawaken, 12 p.m., 5 p.m., and 9 p.m. for 1 day	Baseline, Months 2, 5, and 8	Precollection instruction, self-report time log	Diurnal slope	Lower evening cortisol and steeper slope pattern were more likely to be observed at 8 months in the IG compared to the CG
F. H. Hsiao (2013, 2015)	Examine relationships between and among cortisol and sleep, psychological well-being, and depression in women with BC	2013: 76 women with BC (Stages 0–IV) 2015: 62 women with BC (Stages 0–III)	BDI-II, MLQ, ECR-R, MOS-sleep	Longitudinal observation	Awaken, 30-min postawaken, 45-min postawaken, 12 p.m., 5 p.m., and 9 p.m. for 1 day	Baseline, months 2, 5, and 8. Additional month 14 collection in 2013 study cohort	Self-reported collection time log	Diurnal slope	2013: Increased 9 p.m. cortisol across 14 months predicted worsening depression. 2015: Flatter cortisol slope over 8 months was predictive of greater tumor sizes, and associated with increased BMI, and later times of awakening
Matchim (2011)	Measure effects of MBSR on physical and psychological outcomes in women with BC	36 women with BC (Stages 0–II)	Heart rate, respiratory rate, BP, POMS, C-SOSI, FFMQ	Quasi-experimental: IG = MBSR, CG = usual care	Awaken and 4 p.m. for 1 day	Intervention completion, 1-month follow-up	Not reported	Mean morning and afternoon cortisol levels	MBSR reduced mean morning cortisol ($p < .05$), but the change was not sustained at 1-month follow-up. Mindfulness scores were higher in IG compared to CG ($p < .05$), and the difference was sustained at 1 month ($p < .001$)
Zeitzer (2014)	Examine relationship between diurnal salivary cortisol patterns and plasma cortisol parameters in women with advanced BC	97 women with advanced BC	Cortisol (salivary, plasma)	Prospective, cross sectional	Day 1: 9 p.m. Day 2: awaken, 30-min postawaken (1 total day)	Baseline	Sleep logs, actigraphy	CAR, means at time points (awaken, 30-min postawaken, 9 p.m.) and diurnal slope (all for salivary cortisol)	Steepest of the diurnal slope for salivary cortisol correlated with amplitude of plasma cortisol ($r = -.29, p < .05$) and with the time of the postawakening spike of morning cortisol (i.e., CAR; $r = -.23; p < .05$)

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Table 1. (continued)

First Author (Year)	Study Aim	Sample Participants	Primary Outcome Measures + Salivary Cortisol	Study Design	Saliva Collection Protocol	Sampling Time Points	Sampling Collection Time Verification	Cortisol Parameters Reported	Clinical Findings Associated With Cortisol Parameters
Bower (2014)	Days of consecutive sampling in protocol = 2 Measure effects of an Iyengar yoga intervention on inflammatory biomarkers and cortisol in BC survivors with fatigue	31 women with BC (Stages 0-II)	sTNF- α , IL-1 α , IL-1 β , CRP, IL-6	RCT: IG = Iyengar yoga, CG = health education	Awaken, 30-min postawaken, 8 hr postawaken, and bedtime for 2 days	Baseline, postintervention, 3 months	Precollection instruction, self-report collection times	Diurnal slope, AUCg, means at time points	No significant changes in cortisol production after Iyengar yoga intervention
Chan (2006)	Assess psychophysiological outcomes of psychosocial interventions for BC patients	76 women with BC (Stages 0-III)	GHQ12, PSS, Chinese MAC, CECS, YSSI	RCT: IG = body-mind-spirit, IG = supportive-expressive, IG = social support self-help, CG = educational materials	Awaken, 45-min after awaken, 12 p.m., 5 p.m., and 9 p.m. for 2 days	Baseline, 4 and 8 months	Not reported	AUC, diurnal slope, mean concentrations	Compared to baseline, the body-mind-spirit IG had significantly reduced AUC at 4 months ($p = .03$, ES = .63), which was sustained at 8 months ($p = .02$, ES = .70). The social support intervention was associated with lower mean cortisol level at 8 months ($p = .03$). There were no relationships between stress and cortisol parameters for any of the groups
Couture-Lalande (2014)	Compare the stress response, circadian, and reactive profiles of salivary cortisol in BC survivors and women who have not had BC	22 female BC survivors (Stages 0-II) and 25 women with no history of BC	VAS (stress), sleep quality, BFS, TSST	Two-group, prospective, cross sectional	Prior to lab visit: awaken, 30-min postawaken, 12 p.m., 4 p.m., and 9 p.m. for 2 days. Lab visit day: same as above + 7 times during lab visit	Baseline, pre-poststress test	Sampling instructions, self-report log books	Diurnal slope	Patterns suggested BC survivors had a blunted cortisol response to an acute stressor compared to controls. Diurnal cortisol reactivity patterns, including the slope, appeared to normalize over time
Cuevas (2014)	Examine motivation, physical activity, stress, mental function, and salivary cortisol in BC survivors	94 women with BC (all stages)	AMSP, LTPA, IPAQ, SF-36, and PSS	Prospective, cross-sectional	Awaken, 45-min postawaken, 8-hr postawaken, and bedtime for 2 days	Baseline	Not reported	Diurnal slope	Cortisol was not associated with psychosocial variables including stress
Giese-Davis (2006)	Effects of depression on autonomic nervous system and HPAA function in women with MBC	90 women with MBC (Stage IV): 45 with depression and 45 without	PSS, SF-36, SCID, PTSD SCID, PANAS, ECG, HRV, BP, and aortic characteristic impedance	Non-RCT modified performed between 4 p.m. and 7 p.m.	1 week prior to TSST: Awaken, 30-min postawaken, 12 p.m., 5 p.m., and 9 p.m. for 2 days. During TSST: 10 collections	Baseline (1 week prior to TSST), day of TSST, day after TSST	MEMS bottles and caps	Diurnal slope, CAR	Prior to TSST, depressed women (those in the 50th percentile) with MBC had a blunted CAR (mean = .12, SRD = -.34) compared to nondepressed MBC women (28 %), which was sustained post-TSST, suggesting hyporesponsiveness to acute stress

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Table 1. (continued)

First Author (Year)	Study Aim	Sample Participants	Primary Outcome Measures + Salivary Cortisol	Study Design	Saliva Collection Protocol	Sampling Time Points	Sampling Collection Time Verification	Cortisol Parameters Reported	Clinical Findings Associated With Cortisol Parameters
Ho (2013)	Examine relationships between diurnal cortisol pattern and social support and sleep in women with BC	181 Chinese women with BC (stage not reported)	HADS, YSSI, self-perceived health, stress, and sleep quality	Cohort	Awaken, 12 p.m., 5 p.m., and 9 p.m. for 2 days	Baseline	Patients self-reported time of awaken	Diurnal slope	Diurnal cortisol slope associated with perceived stress ($p < .05$). Regression predicted flatter cortisol slope would be associated with later awaken ($p < .01$), negative social support ($p < .05$), poorer self-perceived health ($p < .01$), poorer self-perceived quality of sleep ($p < .05$), and total sleep hours ($p < .01$) ($\Delta R^2 = 58.7\%$, $p < .01$)
C. P. Hsiao (2011)	Examine relationships among cortisol, perceived stress, and symptom distress in men with prostate cancer	53 men with prostate cancer (Stages I–III): 24 treated with prostatectomy and 29 with radiation therapy	PSS; symptom indexes	Nonrandomized comparison	Awaken, 11:00 a.m. to 12:00 p.m., 4 p.m. to 5 p.m., and 9 p.m. to 10 p.m. for 2 days	2 consecutive weekdays, 6–8 weeks postsurgery, or start of radiation therapy	Sampling instructions	Mean cortisol concentrations, diurnal slope, AUCi, AUCg	Perceived stress positively associated with mean noon ($p < .01$) and afternoon cortisol levels ($p < .01$) and symptom distress ($p < .05$). AUCg correlated with perceived stress ($p < .01$)
Kim (2012)	Examine relationship between diurnal cortisol rhythm and cancer prognosis	37 men and 15 women with lung cancer matched to healthy controls (32 men and 24 women)	Eastern Oncology Group (ECOG) Performance Status (PS); disease stage	Nonrandomized comparison of patients with lung cancer versus healthy controls	Awaken, 30-min postawaken, 60-min postawaken, 9 p.m. for 2 days	Baseline and 3 weeks	Sampling instructions	Mean awaken cortisol, diurnal cortisol decline (slope), CARi, CARauci	Mean awaken cortisol ($rs = -.41$; $p < .01$) and diurnal cortisol decline ($rs = .36$, $p < .01$) correlated with disease stage. Either CARi or CARauci were associated with clinical disease stage, (both $p > .05$). Poorer ECOG PS negatively correlated with lower cortisol at awaken ($rs = -.77$, $p < .001$) and 30-min ($rs = -.83$, $p < .001$), and 60-min postawaken ($rs = -.83$, $p < .001$). Altered diurnal rhythm (i.e., blunted CAR and flattened cortisol diurnal slope) was more strongly associated with ECOG PS than with disease stage
Kosaka (2014)	Comparison of CAR and daily life stress between survivors of head and neck cancer with long-term and short-term dental prostheses	13 men and 8 women with head and neck cancer: 11 long-term and 10 short-term prosthesis wearers	UW-QOL v42, STAI (Japanese version)	Nonrandomized comparison of short-term versus long-term prosthesis wearers	Awaken, 30-min postawaken for 2 days	Single time	Precollection instructions; self-reported log of collection times	CAR	Mean CAR of short-term prosthesis wearers was lower than that of long-term prosthesis wearers ($p = .02$). Short-term prosthesis wearers reported lower QOL and greater daily stress than long-term prosthesis wearers ($p = .01$). Blunted CAR was associated with poorer QOL in short-term prosthesis wearers and greater daily stress

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Table 1. (continued)

First Author (Year)	Study Aim	Sample Participants	Primary Outcome Measures + Salivary Cortisol	Study Design	Saliva Collection Protocol	Sampling Time Points	Sampling Collection Time Verification	Cortisol Parameters Reported	Clinical Findings Associated With Cortisol Parameters
Palesh (2008)	Exploration of HPAA dysregulation, vagal functioning, and sleep problems in women with MBC	99 women with MBC	Sleep actigraphy, PSS, and vagal regulation	Prospective, cross-sectional	Awaken, 30-min postawaken, 12 p.m., 5 p.m., and 9 p.m. for 2 days	Baseline	Actigraphy, electronic bottles, and wrist timers	Diurnal slope, median cortisol values at time points	Disrupted sleep observed with flattened cortisol slope ($p = .04$). No associations between stress and cortisol
Scherling (2011)	Comparison of neurofunction during working-memory task between women with BC prior to chemotherapy and healthy controls	46 women with BC and 23 healthy women	Visuospatial working-memory testing, neuropsychological function via fMRI	Prospective, age-matched cohort	Awaken, 30-min postawaken, 60-min postawaken, 10 a.m., 2 p.m., 6 p.m., and 9 p.m. for 2 days	Baseline	Pre-collection instructions	Diurnal index, AUCg	No significant differences in cortisol levels between BC patients and controls. No associations between cortisol and neurocognitive function prior to chemotherapy
Septon (2013)	Determine the prognostic value of diurnal cortisol rhythm in patients with lung cancer	62 patients with non-small cell lung cancer	Survival data	Prospective, cross-sectional	Awaken, 45-min postawaken, 4 p.m., 9 p.m. for 2 days	Baseline	Sampling instructions	Diurnal slope, diurnal mean levels, CAR, and AUC	Slope predicted 3-year survival from time of diagnosis ($p = .01$). Flattened cortisol slope associated with advanced lung cancer ($p = .00$), poor performance ($p = .01$), and male gender ($p = .03$)
Cash (2015)	Examine the associations of circadian rhythm disruption, distress, and diurnal cortisol rhythm with tumor progression in women with BC	43 women with BC (pretreatment and Stages 0–IV)	Tumor progression (VEGF, MMP-9, TGF- β , IL-1 β , TNF- α , IL-6R, MCP-1, IL-6, IL-12, IFN- γ) IES, And POMS	Prospective, cross-sectional	Awaken, 30-min postawaken, 4 p.m., and bedtime for 3 days	Baseline	MEMS bottles and electronic bottle caps, actigraphy	Diurnal slope, diurnal mean, CAR, mean awoken, and mean bedtime	Greater tumor progression (VEGF, TGF- β , and MMP-9) associated with disrupted circadian rhythms ($p = .02$) and higher CAR levels ($p = .02$)
Dedert (2012)	Examine stress, coping, circadian disruption, and endocrine activation in women with BC	57 women with BC (pretreatment and Stages 0–IV)	IES, modified Brief COPE, and actigraphy	Prospective, cross-sectional	Awaken, 30-min postawaken, 4 p.m., and bedtime for 3 days	Baseline	MEMS bottles and caps, actigraphy, self-report, and PalmPlot	Diurnal slope, diurnal mean, CAR, mean awoken, and mean bedtime	Disrupted rest/activity (daytime sedentaryness) associated with abnormal (flattened) diurnal cortisol slope in presurgical BC patients. Actigraphy demonstrating more optimal rest/activity rhythm was correlated with a steeper slope ($rs = -.41$, $p = .003$)
Hoyt (2014)	Explore associations between coping strategies and diurnal cortisol rhythm in prostate cancer	66 men with localized prostate cancer	Brief COPE, Emotional Approach Coping Scale	Longitudinal observation	Awaken, 8 hr postawaken, bedtime for 3 days	Baseline and 4 months later	Self-report sampling time by text or voice mail	Diurnal slope	High avoidance-oriented coping associated with abnormal (flatter) diurnal cortisol slopes based on lower cortisol at awoken ($p = .03$) and 8-hr postawaken ($p = .02$)

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Table 1. (continued)

First Author (Year)	Study Aim	Sample Participants	Primary Outcome Measures + Salivary Cortisol	Study Design	Saliva Collection Protocol	Sampling Time Points	Sampling Collection Time Verification	Cortisol Parameters Reported	Clinical Findings Associated With Cortisol Parameters
Loizzo (2010)	Measure effects of a self-healing program on quality of life in women with cancer	68 women with breast and gynecological cancers (Stages I-III)	FACIT-G v4 2, SF-36, MACS, resting heart rate, cardiac vagal tone, IL-6, NK cells, and leukocytes	Pre-/postdesign with 20-week program	Awaken, 45-min postawaken, 8 p.m., and 11 p.m. for 3 days	Baseline and program completion at 5 months	Not reported	Cortisol circadian amplitude, wake-up change (CAR), a.m. cortisol max, and means at 8 p.m. and 11 p.m. AUC, mean cortisol values and collection times	Improved maximal a.m. cortisol ($n = 14$ cortisol samples) post-self-healing program compared to baseline
Lutgendorf (2008)	Examine IL-6 levels, diurnal cortisol rhythms, and depression in women with ovarian cancer	137 women with ovarian cancer (Stages I-IV)	IL-6, CES-D	Cross-sectional	Awaken, 30-min postawaken, 3 p.m., 6 p.m., and 8 p.m. to 12 a.m. for 3 days	Presurgery	Not reported	AUC, mean cortisol values and collection times	Higher evening cortisol associated with elevated IL-6 ($p < .01$), greater total ($p = .03$) and vegetative depression ($p = .01$). Greater AUC in invasive ovarian cancer patients ($p < .05$) compared to patients with noninvasive ovarian cancer
Matousek (2011)	Examine the effects of MBSR on CAR in women with BC	33 women with BC (Stages I-II)	CES-D, MSCL, PSS-10	Cohort study MBSR program	Awaken, 30-min postawaken, and 45-min postawaken for 3 days	Pre- and post-MBSR, 8-week program	Not reported	CAR, AUC	Increased CAR after MBSR. Higher CAR pre-MBSR was associated with reduced symptoms post-MBSR ($p < .002$). Stress and depression were not associated with CAR
Schmidt (2016)	Explore association between diurnal cortisol rhythms and fatigue during chemotherapy or radiotherapy in women with BC	265 women with BC	Fatigue Assessment Questionnaire	Secondary analysis of data from 2 RCTs	Awaken, 30-min postawaken, 12 p.m., 5 p.m., and 10 p.m. for 3 days	Baseline	Precollection instructions	Morning mean, CAR, evening mean, AUC, and diurnal slope	Greater fatigue associated with increased evening cortisol ($p = .004$) and higher AUC ($p = .04$)
Schrepf (2013)	Examine relationships between posttreatment inflammatory changes and self-reported functioning in ovarian cancer patients	163 women with ovarian cancer	POMS, CESD-D3, performance status (1-item, functional ability), sleep (1-item, hour of sleep), and plasma IL-6	Prospective, longitudinal	Awaken, 4 p.m.–6:30 p.m., and bedtime for 3 days	Baseline and 6 and 12 months	Self-reported collection time on specimens	Diurnal slope and means at time points morning, afternoon, and nocturnal	Women without recurrence by 1 year maintained normal IL-6 and cortisol levels. Decreased fatigue associated with decreased IL-6 ($p = .02$) and nocturnal cortisol ($p = .05$). Increase in steepness of diurnal slope at 1 year postsurgery ($p < .001$)
Schrepf (2015)	Examine the relationships between HPAA activity, tumor inflammation, and survival prior to treatment for ovarian cancer	113 women with ovarian cancer	Ascites fluid, IL-6	Prospective, cross-sectional	Awaken, 5 p.m., and bedtime for 3 days	Baseline	Precollection instructions and self-reported collection logs	Mean night cortisol, diurnal slope, and cortisol variability index	Reduced cortisol variability ($p = .01$), flattened diurnal slope ($p = .04$), and elevated night cortisol ($p = .02$) were associated with decreased ovarian cancer survival

(continued)

Table 1. (continued)

First Author (Year)	Study Aim	Sample Participants	Primary Outcome Measures + Salivary Cortisol	Study Design	Saliva Collection Protocol	Sampling Time Points	Sampling Collection Time Verification	Cortisol Parameters Reported	Clinical Findings Associated With Cortisol Parameters
Tell (2014)	Examine day-to-day variations in sleep behaviors, sleep disturbance, and fatigue as predictors of diurnal cortisol in women with BC	130 women with BC	MFSI-SF, PSQI, and sleep diary	Prospective, cross-sectional	Awaken, 30-min postawaken, 12 p.m., 5 p.m., and bedtime for 3 days	Baseline	Not reported	Diurnal slope, CAR	Sleep disturbance ($p = .006$) and fatigue ($p = .03$) were associated with disrupted cortisol rhythm. Greater fatigue predicted higher awaken cortisol ($p = .03$) and lower CAR ($p = .005$). Feeling less rested in the a.m. predicted higher CAR ($p = .02$) and flatter diurnal slope ($p = .04$). Longer day napping periods predicted a higher CAR ($p = .05$)
Weinrib (2010)	Examine alterations in diurnal cortisol rhythm and potential links with depression, stress, and functional disability in women with ovarian cancer	100 women with ovarian cancer; 77 with benign disease, and 33 healthy women	Performance status (0–4 scale), PSS, POMS, CES-D, modified Life Experiences Survey	Three-group, prospective, cross-sectional	Awaken, 4:30–6:30 p.m., and bedtime for 3 days	Baseline	Self-reported collection times	Morning, afternoon, and evening mean concentrations; cortisol variability (nocturnal cortisol/morning cortisol)	Dysregulated cortisol in women with ovarian cancer was associated with greater functional disability (all $p < .05$). Ovarian cancer group had diminished cortisol variability ($p = .02$) and higher afternoon and nocturnal cortisol levels than healthy controls ($p < .00$) and those with benign disease ($p = .02$). Evening cortisol in women with ovarian cancer was associated with function ($p < .05$), fatigue ($p < .01$), and depression ($p < .01$). Stress was not associated with nocturnal cortisol ($p > .05$)
Costanzo (2012)	Days of consecutive sampling in protocol = 4 Compare responses to everyday stress between cancer survivors and those without cancer history. Examine effects of daily stress on quality of life and associated cortisol patterns	111 participants with no cancer history matched with 111 cancer survivors: BC (29.7%), prostate (20.7%), colon (14.4%), and other (<10%)	DISE, PANAS, physical symptoms	Prospective, matched cohort	Awaken, 30-min after awaken, prior to lunch, and bedtime for 4 days	Baseline	Sampling instructions	Diurnal slope, AUC, and CAR	No difference in CAR or diurnal cortisol slope in either group between stressful and nonstressful days. In participants without history of cancer, AUC was increased on stressful days compared to nonstressful days ($p = .003$). Longer time since cancer diagnosis was associated with a lower AUC ($p = .04$)

Note. AMSP = Apter Motivational Style Profile; AUC = area under the curve; AUCg = area under the curve with respect to ground; AUCi = area under the curve with respect to increase; BC = breast cancer; BFS = Bidimensional Fatigue Scale; BDI-II = Beck Depression Inventory; BMI = body mass index; BP = blood pressure; C-SOSI = Calgary Symptoms of Stress Inventory; CAR = cortisol awakening response; CARI = cortisol awakening response increase; CARauci = area under the cortisol curve with respect to increase; CECs = Courtauld Emotional Control Scale; CES-D = Centers for Epidemiological Studies-Depression; CG = control group; Chinese MAC = Mental Adjustment to Cancer; COPE = Coping Orientation to Problems Experienced; CRP = C-reactive protein; DISE = Daily Inventory of Stressful Experiences; ECG = electrocardiogram; ECR-R = Experiences in Close Relationships-Revised; ES = effect size; FACIT-G = Functional Assessment of Cancer Therapy-General; FFMQ = Five Facet Mindfulness Questionnaire; fMRI = functional magnetic resonance imaging; GHQ12 = General Health Questionnaire 12; HADS = Hospital Anxiety Depression Scale; HRV = heart rate variability; IES = Impact of Events Scale; IL = interleukin; IFN- γ = interferon γ ; IG = intervention group; IPAQ = International Physical Activity Questionnaire; LTPA = Leisure Time Physical Activity; MACS = Mental Adjustment to Cancer Scale; MBC = metastatic breast cancer; MBRS = mindfulness-based stress reduction; MCP-1 = monocyte chemoattractant protein; MEMS = medication event monitoring system; MFSI-SF = Multidimensional Fatigue Symptoms Inventory-Short Form; MLQ = Meaning in Life Questionnaire; MMP-9 = metalloproteinase; MOS = Medical Outcomes Study; MSCL = Medical Symptom Checklist; NK = natural killer; PANAS = Positive and Negative Affect Scale; POMS = Profile of Mood States; PSQI = Pittsburgh Sleep Quality Index; PSS = Perceived Stress Scale; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SCID = Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV; SF-36 = Short-Form Health Survey; SOSI = Symptoms of Stress Inventory; STAI = State-Trait Anxiety Inventory; TGF- β = transforming growth factor β ; TNF- α = tumor necrosis factor α ; TSST = Trier Social Stress Test; sTNF-RII = Soluble Tumor Necrosis Factor receptor Type II; SRD = success rate difference; UW-QOL = University of Washington Quality of Life; VAS = Visual Analog Scale; VEGF = vascular endothelial growth factor; YSSI = Yale Social Support Index; HPAA = hypothalamic-pituitary-adrenal-axis.

Table 2. Descriptive Statistics for Cortisol Sampling Times and Parameters Reported in Reviewed Studies.

Study Characteristic	Studies, <i>n</i> (%)
Consecutive days of collection	
1	6 (20)
2 ^a	12 (40)
3	11 (37)
4	1 (3)
Number of collections/day	
2	2 (7)
3	6 (20)
4 ^a	10 (33)
5	8 (27)
6	3 (10)
7	1 (3)
Postawakening sampling time points (min postawakening) ^b	
0	8 (27)
30 ^a	13 (43)
45	4 (13)
30 and 45	3 (10)
30 and 60	2 (7)
Distinct cortisol parameters reported ^c	
Diurnal slope	22 (73)
CAR, CARi, CARauci	16 (53)
Means at sampling time points	15 (50)
AUC, AUCg	11 (37)
AUCi	3 (10)
Cortisol variability	2 (7)

Note. *N* = 30. AUC = area under the curve (total cortisol production); AUCg = area under the curve with respect to ground (total cortisol production); AUCi = area under the curve with respect to increase from baseline; CAR = cortisol awakening response; CARi = cortisol awakening response increase; CARauci = cortisol awakening response as the area under the curve with respect to increase from baseline.

^aMode. ^bPostawakening cortisol sampling time points defined as sampling within 30–60 min after waking for the purpose of measuring the dynamic change in cortisol from waking to the peak cortisol concentration of the day.

^cTwenty-three studies reported more than one cortisol parameter.

electronic device) to validate participants' adherence to the sampling protocol. In another seven studies (23%), authors reported that participants received precollection sampling instructions only. In five studies (17%), researchers used medication event monitoring systems (MEMS; *n* = 3), actigraphy (*n* = 1), or both MEMS and actigraphy (*n* = 1) to validate cortisol sampling times. In 11 studies (47%), researchers used a combination of providing participants with presampling instructions and asking participants to self-report collection times by journal log, telephone, or texting.

Question 3: What Are the Relationships Between Salivary Cortisol Sampling Protocols and Parameters and the Detection of Clinical Outcomes Among Cancer Survivors?

The reviewed studies used salivary cortisol measures to explore clinical outcomes related to stress (13 studies) and other psychosocial outcomes (11 studies), mindfulness meditation (7 studies), disease progression (6 studies), and sleep

Table 3. Summary of Relationships Between Cortisol Parameters and Clinical Outcomes.

Cortisol Parameter	Clinical Outcomes
Mean awoken	Reduced after MBSR intervention (Matchim, Armer, & Stewart, 2011) Negatively associated with clinical disease stage (Kim et al., 2012)
Mean bedtime/evening	Reduced after BMS intervention (F. H. Hsiao et al., 2012) Increased evening cortisol associated with worsening depression (F. H. Hsiao et al., 2013, 2015; Lutgendorf et al., 2008; Weinrib et al., 2010) Increased evening cortisol associated with decreased survival in ovarian cancer (Schrepf et al., 2015) Elevated IL-6 associated with higher evening cortisol (Lutgendorf et al., 2008) Cancer-related fatigue associated with higher evening cortisol (Schmidt et al., 2016) Perceived stress positively associated with higher afternoon cortisol and more symptom distress (C. P. Hsiao, Moore, Insel, & Merkle, 2011)
Mean midday (noon)	Perceived stress positively associated with higher noon cortisol and greater symptom distress (C. P. Hsiao et al., 2011)
CAR/CARi/CARauci	Increased CAR associated with tumor progression (Cash et al., 2015) Increased peak CAR associated with self-healing intervention (Loizzo et al., 2010) Increased CAR after MBSR intervention (Matousek, Pruessner, & Dobkin, 2011) Blunted CAR associated with depression (Giese-Davis et al., 2006) Napping associated with improved CAR (Tell, Mathews, & Janusek, 2014) Blunted CAR associated with poorer QOL in short-term prosthesis wearers and greater daily stress (Kosaka, Sumita, Otomaru, & Taniguchi, 2014)
AUC/AUCg	Reduced total cortisol after Tai Chi Chih intervention (Campo et al., 2015) Reduced total cortisol after BMS intervention (Chan et al., 2006) Cancer-related fatigue associated with greater total cortisol production (Schmidt et al., 2016) Greater time elapsed since cancer diagnosis associated with lower total cortisol production (Costanzo et al., 2012) Perceived stress associated with total cortisol production (C. P. Hsiao et al., 2011) Perceived stress associated with increased total cortisol among healthy control participants but not among cancer survivors (Costanzo, Stawski, Ryff, Coe, & Almeida, 2012) Greater AUC in invasive ovarian cancer patients compared to patients with noninvasive ovarian cancer (Lutgendorf et al., 2008). IL-6 positively associated with greater AUC (Lutgendorf et al., 2008)

(continued)

Table 3. (continued)

Cortisol Parameter	Clinical Outcomes
AUCi	MBSR associated with decrease in cortisol from baseline (Matchim et al., 2011)
Diurnal cortisol slope	Steeper slope after BMS intervention (F. H. Hsiao et al., 2012)
	Flattening associated with disrupted sleep and fatigue (Palesh et al., 2008; Tell et al., 2014)
	Flatter slope associated with greater tumor size and BMI (F. H. Hsiao et al., 2013, 2015)
	Slope correlated with clinical disease stage (Kim et al., 2012)
	Flattened slope predictive of early lung cancer death, advanced lung cancer stage, and poor Karnofsky performance score (Sephton et al., 2013)
	Flattened slope associated with decreased survival in ovarian cancer (Schrepf et al., 2015)
	Flatter slope associated with poorer sleep and perceptions of stress, health, and social support (Ho et al., 2013)
	Flatter slope associated with cancer-related avoidance coping (Hoyt et al., 2014)
	Steeper slope associated with improved fatigue (Schrepf et al., 2013)
	Normalized diurnal patterns observed in ovarian cancer survivors remaining disease free at 1 year posttreatment (Schrepf et al., 2013)
	Steeper slope associated with greater amplitude of plasma cortisol (Zeitzer, Nouriani, Neri, & Spiegel, 2014)
	Flattened slope associated with acute stress in BC survivors compared to healthy controls; slope trends toward normal over time (Couture-Lalande, Lebel, & Bielajew, 2014)
	Disrupted rest/activity cycles are associated with flattened diurnal cortisol rhythm (Dedert et al., 2012)

Note. AUC = area under the curve (total cortisol production); AUCg = area under the curve with respect to ground (total cortisol production); AUCi = area under the curve with respect to increase from baseline; BC = breast cancer; BMI = body mass index; BMS = body-mind-spirit; CAR = cortisol awakening response; CARauci = cortisol awakening response as the area under the curve with respect to increase from baseline; CARi = cortisol awakening response increase; MBSR = mindfulness-based stress reduction; IL-6 = interleukin-6; QOL = quality of life.

(5 studies). Table 3 summarizes clinical outcomes by cortisol reporting parameters.

Stress. A total of 13 studies (40%) examined stress outcomes, with consecutive days of sampling ranging from 1 to 4 and number of collections per day ranging from 2 to 5. In studies in which cortisol was sampled for 1 day, researchers observed no associations between cortisol parameters and perceived stress (Carlson, Campbell, Garland, & Grossman, 2007; Matchim, Armer, & Stewart, 2011).

In eight studies, researchers sampled cortisol across 2 days, collecting salivary specimens 2–5 times per day. In six of these studies, perceived stress was associated with higher noon and afternoon cortisol concentrations (C. P. Hsiao, Moore, Insel, & Merkle, 2011), flattening or blunting of the diurnal cortisol patterns including the cortisol slope (Couture-Lalande, Lebel, & Bielajew, 2014; Ho, Fong, Chan, & Chan, 2013), and blunting of the CAR (Giese-Davis et al., 2006; Kosaka, Sumita, Otomaru, & Taniguchi, 2014). In the remaining studies that sampled cortisol across 2 days, researchers did not observe associations between stress and cortisol parameters (Chan et al., 2006; Cuevas et al., 2014; Palesh et al., 2008).

Finally, three stress-related studies involved sampling of cortisol for 3 or 4 days, with specimens collected a minimum of 3 times each day. Researchers reported that perceived stress was not associated with the CAR, cortisol slope (Costanzo, Stawski, Ryff, Coe, & Almeida, 2012; Matousek, Pruessner, & Dobkin, 2011), or evening cortisol (Weinrib et al., 2010).

Psychosocial outcomes. In 11 studies, researchers examined relationships between cortisol and psychosocial measures using either 2- or 3-day sampling protocols. In studies with 2-day sampling, researchers reported relationships between a blunted CAR and increased depression (Giese-Davis et al., 2006) and poorer quality of life (Kosaka et al., 2014). While flatter cortisol slope was associated with poorer social support, poorer sleep, and poorer perceptions of health in one study (Ho et al., 2013), other studies indicated no associations between cortisol slope (including diurnal index measures) and psychosocial variables including stress (Cuevas et al., 2014), memory during chemotherapy, physical activity, stress (Cuevas et al., 2014), and neurocognitive function prior to chemotherapy (Scherling, Collins, Mackenzie, Bielajew, & Smith, 2011). In all studies with 3-day sampling protocols, researchers reported associations between cortisol parameters (slope, CAR, and evening cortisol) and psychosocial outcomes. Flatter cortisol slope was associated with avoidance coping (Hoyt et al., 2014). Fatigue was associated with higher awakening cortisol, flatter cortisol slope, blunted CAR, higher evening cortisol, and higher cortisol AUC (Schmidt et al., 2016; Tell, Mathews, & Janusek, 2014; Weinrib et al., 2010); and improved fatigue was associated with steeper cortisol slopes (Schrepf et al., 2013). Higher evening cortisol was also associated with depression (Lutgen-dorf et al., 2008; Weinrib et al., 2010) and poorer function (Weinrib et al., 2010).

Mindfulness meditation. The number of consecutive sampling days among the seven studies involving mindfulness meditation ranged from 1 to 3 days, and all of these repeated the baseline measures at 1–8 months. Among the studies that had 1 day of sampling, findings indicated that Tai Chi Chih practice was associated with a lower cortisol AUC (Campo et al., 2015), a body-mind-spirit intervention was associated with steeper diurnal cortisol slopes and lower evening cortisol concentrations (F. H. Hsiao et al., 2012); and a mindfulness-based stress

reduction (MBSR) program was associated with lower morning cortisol (Matchim et al., 2011).

Among the studies with 2-day sampling protocols, number of daily collection times ranged from 4 to 5. Researchers reported no changes in cortisol slope or total cortisol production with yoga (Bower et al., 2014). A body–mind–spirit intervention (Chan et al., 2006) was not associated with cortisol slope but was associated with reduced AUC. Among 3-day sampling protocols (sampling times ranged from 3 to 4 times per day), self-healing was associated with increased CAR magnitude (Loizzo et al., 2010), and a higher CAR (dynamic increase) pre-MBSR was associated with a reduction of symptoms following MBSR among participants with a greater awakening response (AUC at baseline; Matousek et al., 2011).

Disease progression. The six studies that examined associations between salivary cortisol and indicators of disease progression used sampling protocols of 1–3 days. In a study with a 1-day sampling protocol involving collection of cortisol at 6 time points throughout the day and repeated measures at 14 months, researchers reported that a flatter cortisol slope was predictive of greater tumor size among women with breast cancer (F. H. Hsiao et al., 2013, 2015). Among studies using 2-day sampling protocols (specimens collected 4 times per day), cortisol parameters (i.e., cortisol slope and CAR) were blunted or flattened with advancing cancer disease stage (Kim et al., 2012; Sephton et al., 2013).

Studies with 3-day cortisol sampling protocols (specimens collected 3–4 times per day) yielded mixed results. Researchers observed an association between a higher CAR, but not diurnal slope, and tumor progression (Cash et al., 2015). In another study, there was no association between the CAR and disease progression (Dedert et al., 2012). In two other studies, a flatter cortisol slope, higher evening cortisol, and a larger AUC were associated with poorer cancer outcomes including decreased survival (Lutgendorf et al., 2008; Schrepf et al., 2015).

Sleep. In the five sleep-related studies, researchers sampled cortisol over 1–3 consecutive days, collecting specimens 4–6 times per day. In a study in which specimens were sampled 4 times per day across 1 day, researchers reported no associations between sleep and cortisol parameters (i.e., AUCg, AUCi, and cortisol slope; Carlson et al., 2007). In studies in which researchers sampled cortisol across 2 or 3 days (with cortisol collections occurring 4 or 5 times per day), flattening of the cortisol slope was associated with disrupted sleep (Dedert et al., 2012; Ho et al., 2013; Palesh et al., 2008; Tell et al., 2014).

Discussion

In the present review, we examined which cortisol sampling protocols and parameters might inform standards to increase the reproducibility of salivary cortisol research findings. In the majority of the reviewed studies researchers collected salivary specimens across 2 consecutive days at 4 collection times per day (Tables 1 and 2), a protocol that is consistent with

previously reported recommendations (Adam & Kumari, 2009). Single-day sampling protocols appear to yield less meaningful information in terms of clinical outcomes. It is worth noting that single-day sampling might reflect the significant laboratory expenses associated with performing cortisol enzyme immunoassay testing. Additionally, diurnal cortisol parameters may not have been the primary outcomes of interest. Our findings in the present review were consistent with previous literature in that single-day cortisol assessments appeared less reliable for detecting meaningful changes in cortisol activity than sampling over multiple days, which may be due to intrapersonal cortisol variations (Ryan et al., 2016).

Nearly one third of the studies we reviewed did not measure a postawakening cortisol (i.e., 30–60 min after awakening; Carlson et al., 2007; Ho et al., 2013; Hoyt et al., 2014; C. P. Hsiao et al., 2011; Matchim et al., 2011; Schrepf et al., 2013, 2015; Weinrib et al., 2010), which may reflect research designs based on earlier cortisol research studies for which an expert consensus to guide sampling protocols did not exist (Stalder et al., 2016). Exclusion of a postawakening cortisol measure limits detection and calculation of diurnal salivary cortisol parameters. In general, however, the studies we reviewed provide further support for including postawakening collections at 30–60 min postawakening. The two most common cortisol parameters reported in these studies were the diurnal slope and CAR (Table 2), suggesting that at least one, if not both, of these parameters should be considered for future reporting to allow comparison of findings across studies.

A majority of the studies (77%) included cortisol sampling times between the cortisol peak of the day (i.e., postawakening) and 5 p.m. (Table 1). Clinical outcomes, however, were often not associated with cortisol concentrations at these time points (i.e., noon to 5 p.m.), which is consistent with previous literature. Therefore, for budgetary purposes, sampling between the cortisol peak of the day and early evening may be of less priority compared to sampling at time points necessary for calculating diurnal parameters.

Most of the studies did not include objective (i.e., external) measures to verify salivary cortisol sampling collection times by participants (e.g., MEMS). Nearly a quarter of the studies did not provide information regarding instruction of participants on the sampling protocol or how sampling times were reported (e.g., self-report journals; Chan et al., 2006; Cuevas et al., 2014; Loizzo et al., 2010; Lutgendorf et al., 2008; Matchim et al., 2011; Matousek et al., 2011; Tell et al., 2014). Although Jacobs et al. (2005) have reported consistency between self-reported times and electronic monitoring times, self-reported data are susceptible to inaccuracies because of unreported deviations from collection protocols. Without instruction on the self-collection protocol, participants might be unaware that a protocol deviation has occurred. Participants might not report protocol deviations for various other reasons as well (e.g., fear of disappointing the researcher). Accurate calculation of diurnal cortisol parameters relies on the accuracy of reported sample collection times; therefore, the inclusion of objective measures (e.g., MEMS) as supporting evidence of

protocol adherence would increase the rigor of salivary cortisol measurement.

We observed a few noteworthy trends that might offer guidance for future cortisol research. Studies with longitudinal designs with repeated measures were more likely to detect clinical findings (Campo et al., 2015; Chan et al., 2006; Hoyt et al., 2014; F. H. Hsiao et al., 2012, 2013, 2015; Kim et al., 2012; Loizzo et al., 2010; Matchim et al., 2011; Matousek et al., 2011; Schrepf et al., 2013) than studies with alternative designs. Studies sampling cortisol for 3 or more consecutive days were more likely to detect an association between a cortisol parameter and a clinical outcome (Cash et al., 2015; Costanzo et al., 2012; Dedert et al., 2012; Hoyt et al., 2014; Loizzo et al., 2010; Lutgendorf et al., 2008; Matousek et al., 2011; Schmidt et al., 2016; Schrepf et al., 2013, 2015; Tell et al., 2014; Weinrib et al., 2010). Although not surprising given previous literature, we found that the variety of sampling times per day yielded mixed results regarding associations between cortisol parameters and clinical outcomes. Our findings support previous conclusions by Segerstrom et al. (2014) who suggested that sampling salivary cortisol across a minimum of 3 consecutive days for mean cortisol, 4–8 days for AUC measures, and at least 10 days for diurnal slope increases the reliability of detecting between-person differences in these measures.

Limitations

We focused on cancer survivor populations in the present review as this is our area of scholarship; however, this focus may have excluded high-quality cortisol studies from other populations that could provide insight into the relationships between cortisol and clinical outcomes. Additionally, there may be differences among various cancer survivor populations that we did not account for in this systematic review. Potential confounding differences in the diurnal cortisol pattern may exist among heterogeneous cancer survivors (based on disease, stage, treatment type, and time since treatment) that would further limit the utility of comparing cortisol parameter findings across cancer populations. While more of the studies we reviewed reported cortisol slope and CAR parameters, some did report AUC calculations, suggesting that AUC may be emerging as a popular cortisol parameter to consider in future cortisol reporting.

We did not use traditional guidelines (e.g., Johns Hopkins Evidence-Based Model; Dearholt & Dang, 2012) to assess the quality and levels of evidence in the reviewed studies as such guidelines emphasize study design (e.g., RCT) as part of the literature appraisal process. Given the issues mentioned above regarding cortisol sampling (i.e., the heterogeneity in cortisol sampling protocols and the extent to which participants adhere to self-collection sampling times), the rigor of the study design becomes secondary to the method; that is, a study with a rigorous design such as an RCT but without a rigorous cortisol sampling method optimized to detect meaningful clinical outcomes may have reduced utility. Thus, we focused on

appraising the rigor of salivary cortisol collection protocols and parameters. Finally, a number of the studies in this review had small samples and were designed as pilot studies (Bower et al., 2014; Campo et al., 2015; Couture-Lalande et al., 2014; C. P. Hsiao et al., 2011; Kosaka et al., 2014; Matousek et al., 2011). Thus, our findings may reflect studies that were underpowered to detect clinical outcomes.

Implications and Recommendations

Our findings from the present review show that flattened cortisol slopes, blunted CARs, and elevated evening cortisol concentrations were associated with poorer psychosocial (e.g., sleep disruption, depression, and fatigue) and physiological outcomes (e.g., disease progression) in cancer patients and survivors (see Table 3). Results were mixed for CAR findings and questions remain: What constitutes an expected CAR for cancer survivors and how is this distinguished from an exaggerated CAR, given the inter- and intrapersonal variances observed with diurnal cortisol rhythms? While trends suggest a possible relationship between an exaggerated CAR response and cancer disease progression, the use of longitudinal sampling may further inform the interpretation of variations in CAR patterns among cancer populations.

Based on our findings in this review and taking into account intra- and interpersonal variability in postawakening cortisol, we propose that a more rigorous, standardized salivary cortisol sampling protocol should include the following: (1) assessments at awakening: 30-, 45-, and 60-min postawakening; and bedtime (to allow for calculation of the CAR and slope parameters); and (2) sampling across 3 or more consecutive days with longitudinal, repeated measures. Moreover, we suggest including validation of participants' adherence to collection time points for increased measurement rigor. Standardization of cortisol sampling protocols, parameter reporting, and participant protocol adherence would improve rigor and reproducibility of findings and allow comparative analyses across studies.

Any standardized cortisol sampling protocols must preserve budget resources and minimize participant burden. Protocols that use 3 or more consecutive days of sampling are more likely to detect associations with clinical outcomes than those with fewer days of sampling. Prioritizing the number of consecutive sampling days over the number of sampling time points per day (as long as diurnal calculations can be performed) may thus increase the chances of detecting relationships between salivary cortisol and clinical outcomes while minimizing use of resources and participant burden. Finally, longitudinal studies with repeated measures offer the most rigorous designs for detecting clinical outcomes associated with cortisol.

Author Contributions

Jennifer M. Hulett contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Kristen L. Fessele

contributed to conception, design, acquisition, and analysis; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. The conception of the study, study design, method, data analyses, and interpretation of findings were performed by Hulett, Fessele, Clayton, and Eaton. Article searching, extraction, and analyses were performed by Hulett, Fessele, and Eaton. The manuscript was drafted by Hulett and critically edited by Fessele, Clayton, and Eaton.

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ORCID iD

Jennifer M. Hulett <https://orcid.org/0000-0001-5833-7624>

Kristen L. Fessele <https://orcid.org/0000-0003-2336-6841>

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