

Review

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Posted Date: 13 October 2025

doi: 10.20944/preprints202510.0882.v1

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Review

A Literature Review on Hypothalamic–Pituitary–Adrenal (HPA) Axis Dysregulation in Older Adults with Cancer: A Missing Link in Predicting Treatment Toxicity?

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Abstract

Older adults with cancer face disproportionately high rates of severe treatment-related toxicities, yet current prediction tools rarely incorporate biomarkers that capture physiological resilience. The hypothalamic–pituitary–adrenal (HPA) axis—central to stress adaptation, immune regulation, and tissue repair—undergoes pronounced age-related alterations, including elevated basal cortisol, reduced dehydroepiandrosterone (DHEA) and its sulphate form DHEAS, and an increased cortisol:DHEA(S) ratio. These changes may impair immune function, delay recovery, and exacerbate vulnerability to treatment toxicity. This narrative review synthesizes mechanistic and clinical evidence linking HPA-axis dysregulation to treatment tolerance in geriatric oncology. Common patterns include blunted diurnal cortisol slopes, elevated evening cortisol, and low DHEA(S), which are associated with fatigue, functional decline, and reduced survival across cancer types. However, their predictive value for acute treatment toxicities remains underexplored due to methodological heterogeneity, lack of age-specific reference ranges, and absence from existing geriatric toxicity models. This review proposes a translational roadmap that prioritizes (1) standardization of salivary cortisol/DHEA(S) protocols; (2) prospective, age-stratified validation studies using standardized toxicity endpoints; (3) interventional testing of behavioral or pharmacological strategies to modulate HPA function; and (4) integration into oncology workflows and electronic decision-support tools. Incorporating endocrine biomarkers into risk prediction could refine treatment stratification, enable targeted supportive care, and ultimately improve outcomes for older cancer patients.

Keywords: Cortisol:DHEA(S) ratio; hypothalamic–pituitary–adrenal (HPA) axis; chemotherapy toxicity; older adults

1. Introduction

Cancer predominantly affects older adults, from fewer than 26 cases per 100,000 people in age groups under age 20, to about 350 per 100,000 at ages 45–49 and more than 1,000 per 100,000 people in age groups 60 years and older [1]. Older adults face a disproportionate risk of treatment-related toxicities, exacerbated by age-related physiological changes [2–4]. Despite this vulnerability, most current oncology risk stratification tools, such as the Cancer and Aging Research Group (CARG) score [5] and the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) [6], largely omit endocrine parameters [5,7–9], particularly those involving stress-response systems such as the hypothalamic-pituitary-adrenal (HPA) axis. This omission may limit the precision of toxicity prediction in older patients, whose endocrine function is already altered by aging.

The HPA axis is a central regulator of systemic stress responses, inflammation, and immune function [10–13]. Its principal effector hormone, cortisol, coordinates adaptive responses to physiological and psychological stressors [14–16]. In cancer populations, cortisol dysregulation is frequently observed, characterized by elevated basal secretion, blunted diurnal slopes, and impaired

reactivity to acute stress [17–26]. These alterations are found across tumor types and treatment modalities and have been associated with fatigue, cognitive impairment, and reduced physical functioning [17]. However, whether cortisol dysregulation actively contributes to poor outcomes or merely reflects disease burden remains an open question.

Older adults exhibit specific changes in HPA-axis physiology that may amplify these disruptions [27–29]. Age-related endocrine changes include elevated basal cortisol secretion, impaired negative feedback sensitivity [30,31], and a decline in dehydroepiandrosterone (DHEA) (also a steroid hormone produced in the adrenals, often measured in its active sulphated form DHEAS) which counterbalances many of the adverse effects of cortisol [32,33]. These alterations result in an elevated cortisol:DHEA(S) ratio and may compromise immune regulation [34], physical function [35], and treatment tolerance in the context of cancer [36,37]. This convergence of age-related endocrine aging and cancer-related stress burden may amplify physiological risk in this population.

To date, although some studies exist [38–40] and the field of biomarkers for toxicity prediction is developing [41,42], no large-scale prospective studies have evaluated whether pre-treatment HPA axis dysregulation features (e.g., diurnal slope, evening elevation, cortisol:DHEA(S) ratio) predict acute treatment-related toxicities—such as Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 adverse events, dose reductions, or unplanned hospitalizations—in older cancer patients. While observational studies link cortisol abnormalities to outcomes like survival and fatigue, their predictive value for treatment-specific complications remains uncharacterized.

This review argues that HPA-axis dysregulation is not merely an incidental correlate of disease burden, but a potential biomarker of impaired physiological resilience in geriatric oncology. I propose that cortisol and DHEA(S) may serve as prognostic, predictive, and monitoring biomarkers—each playing a distinct role in improving treatment decision-making and supportive care strategies. Figure 1 illustrates the hypothesized convergence of aging-related endocrine decline and cancer-related stressors in disrupting HPA function and increasing toxicity risk.

This review hypothesizes that age-related HPA-axis dysregulation is a clinically meaningful predictor of treatment-related toxicity in older adults with cancer, and that standardized biomarker assessment could enhance risk stratification in geriatric oncology. To this end, this review aims to: (1) Examine how aging and cancer interact to disrupt cortisol and DHEA(S) dynamics; (2) Differentiate the prognostic, predictive, and monitoring potential of these biomarkers; (3) Map mechanistic pathways linking HPA dysregulation to treatment toxicity phenotypes; (4) Critically appraise methodological heterogeneity in biomarker assessment; (5) Propose a translational roadmap for integrating HPA-axis biomarkers into geriatric oncology risk models.

2. HPA-Axis Dysregulation in Cancer Patients: Current Evidence

2.1. Prevalence and Patterns of HPA Axis Dysregulation

Evidence from observational studies consistently demonstrates that HPA-axis dysregulation is highly prevalent among cancer patients, irrespective of tumor type or treatment modality [17,43]. A systematic review of 17 studies reported altered HPA-axis activity in 16 cohorts compared to cancer-free controls, with 13 identifying elevated baseline cortisol levels or exaggerated responses to stress [17]. However, cortisol dysregulation in cancer can manifest as either hyper- or hypocortisolism, depending on tumor type, treatment and comorbidities [39]. Nevertheless, these findings confirm the widespread disruption of endocrine regulation in oncology populations. Typical patterns of dysregulation include elevated basal cortisol concentrations, often 20–200% higher than controls, blunted diurnal slopes, indicating impaired circadian regulation, and exaggerated or blunted responses to pharmacological or psychosocial stressors. These patterns collectively point to a state of maladaptive neuroendocrine regulation in cancer patients, marked by sustained cortisol activation without appropriate rhythmicity or stress termination.

These abnormalities suggest a failure of adaptive endocrine regulation under chronic disease stress [44–46]. Notably, the prevalence and severity of cortisol dysregulation appear largely

independent of tumor type, stage, or anticancer therapy—underscoring its potential as a *non-specific biomarker of systemic vulnerability* rather than a cancer-type-specific marker.

2.2. Associations with Clinical Outcomes

Cortisol dysregulation—whether reflected in elevated evening levels, blunted diurnal slopes, or reduced awakening responses—has been consistently associated with adverse outcomes in cancer populations. These include both patient-reported symptoms (e.g., fatigue, cognitive dysfunction, sleep disturbance [18,47,48]) and clinical endpoints (e.g., more advanced disease states [23]). Currently, there is scarce prospective evidence connection pre-treatment cortisol or cortisol:DHEA(S) to acute treatment toxicities (e.g., CTCAE ≥ 3 , dose reductions, hospitalizations). An overview of studies assessing cortisol or cortisol:DHEA(S) in relation to treatment toxicities or toxicity-related outcomes in cancer, specifically in older adults, is shown in Table 1. The following paragraphs further elaborate on associations between cortisol and DHEA(S) in cancer populations, not exclusively in older adults, to provide a rigorous overview of existing literature on topic.

In head and neck cancer patients ($n \approx 50$), elevated evening cortisol was associated with worse progression-free survival (HR=1.848, 95% CI=1.057–3.230), while elevated mean cortisol across the day was linked to significantly shorter survival (HR=2.662, 95% CI=1.115–6.355), whereas diurnal slope was not statistically significant [25]. In breast cancer survivors, a blunted diurnal cortisol slope prospectively predicted more severe fatigue and slower psychomotor recovery [24]. Other studies report similar associations in oral cancer and myeloproliferative neoplasms, where cortisol abnormalities correlate with fatigue severity, emotional distress, and poorer quality of life [39,49].

Further, patients with advanced non-small cell lung cancer post-chemotherapy showed reduced salivary DHEAS concentrations compared to age-matched controls, with lower DHEAS concentrations being associated with higher fatigue and depression scores [50].

Despite these consistent associations, the vast majority of studies conceptualize cortisol (and the cortisol:DHEA(S) ratio) as a *prognostic biomarker* of global health status or survival. Critically, few studies have examined its *predictive value* for treatment-related toxicity, such as grade ≥ 3 adverse events (per Common Terminology Criteria for Adverse Events (CTCAE) v.5.0), dose reductions, unplanned hospitalizations, or treatment discontinuations.

This represents a significant knowledge gap. No large-scale prospective studies have yet tested whether pre-treatment cortisol features (e.g., blunted slope, high cortisol:DHEA(S) ratio) are associated with acute toxicities during chemotherapy or immunotherapy. Furthermore, the temporal sequence—whether cortisol dysregulation precedes or results from treatment and disease burden—remains insufficiently studied.

Only two small longitudinal studies have explored cortisol trajectories across chemotherapy cycles [49,51]. These limitations underscore the urgent need for time-series, mechanistic studies that can differentiate cause from consequence and clarify the *monitoring potential* of HPA biomarkers.

Table 1. Studies assessing cortisol or cortisol:DHEA(S) in relation to treatment toxicities or toxicity-related outcomes in older adults with cancer.

Study	Study design	Cancer & treatment context	Biomarkers & matrix	Sampling window	Toxicities / AE endpoint	Main toxicity(-related) finding
Oh et al., 2019 [47]	Cross-sectional observational	Advanced lung cancer (mixed age; mean 64.3 \pm 9.2 \rightarrow includes ≥ 65 subset)	Salivary cortisol	Upon awakening (0, +30, +60 min) and nighttime (~21:00–22:00)	Symptom burden (MDASI), performance status (toxicity-related)	Blunted CAR and flatter diurnal slope associated with worse performance status and higher burden of multiple concurrent symptoms (incl. nausea cluster), indicating HPA

Study	Study design	Cancer & treatment context	Biomarkers & matrix	Sampling window	Toxicities / AE endpoint	Main toxicity(-related) finding
Fang et al., 2020 [50]	Case-control (post-chemotherapy patients vs age-matched controls)	NSCLC after chemotherapy (population typically older; paper notes lung cancer median diagnosis age ≈70)	Salivary DHEA, DHEA-S, and cortisol	Daytime saliva (single-timepoint per protocol)	Fatigue & depression scores after chemotherapy (toxicity-related)	dysregulation tracks toxicity-related symptomatology. Patients had reduced salivary DHEA-S vs controls; lower DHEA-S associated with higher fatigue and depression after chemo—supporting relevance of the cortisol/DHEA(S) axis to post-treatment symptom toxicity. Higher nighttime cortisol associated with worse quality of life and higher perceived stress, consistent with cortisol dysregulation mapping onto toxicity-related well-being impairments in HNC.
Cruz et al., 2022 [21]	Cross-sectional	Head & neck cancer (HNC; adult cohort with older subset)	Nighttime salivary cortisol	Nighttime (single sample per protocol)	Quality of life (UW-QOL) and perceived stress (toxicity-related)	Higher nighttime cortisol associated with worse quality of life and higher perceived stress, consistent with cortisol dysregulation mapping onto toxicity-related well-being impairments in HNC.
Morrow et al., 2002 [52]	Repeated-measures within-subject	Ovarian cancer receiving cisplatin/carboplatin (disease predominantly in older women; median diagnosis age ≈63)	Serum cortisol (total)	Serial samples pre-infusion and hourly for 6 h across two chemotherapy cycles	Acute CINV (nausea/vomiting; treatment toxicity)	Serum cortisol fell immediately after platinum infusion (vs control day), supporting a direct chemo-HPA interaction potentially relevant to CINV pathophysiology.
Hursti et al., 1993 [53]	Observational	Cisplatin-treated ovarian cancer (adults incl. 65 years or older)	Nocturnal urinary cortisol	Night prior to chemotherapy	CINV (vomiting ± nausea)	Lower pre-chemo nighttime cortisol predicted more severe cisplatin-induced nausea/vomiting in 42 patients
Fang et al., 2020 [50]	Cross-sectional case-control	Advanced NSCLC after chemotherapy (adults incl. older)	Salivary DHEA & DHEAS & cortisol	Single post-chemo sampling	Fatigue and depression scores	Lower DHEAS associated with higher fatigue and depression after chemotherapy vs. controls; patients had reduced DHEA/DHEAS post-chemo.
Toh et al., 2019 [54]	Prospective cohort	Early breast cancer receiving adjuvant chemotherapy (mixed ages;	Plasma DHEAS & DHEA	Pre-chemotherapy baseline	CRCI (FACT-Cog domains) during & after therapy	Higher pre-chemo DHEAS predicted lower odds of CRCI (verbal

Study	Study design	Cancer & treatment context	Biomarkers & matrix	Sampling window	Toxicities / AE endpoint	Main toxicity(-related) finding
Toh et al., 2022 [55]	Longitudinal cohort	includes older subset though mean ~49 Early breast cancer on anthracycline-based chemo (adults incl. older subset)	(UHPLC-MS/MS) DHEA, DHEAS, estradiol (plasma)	Pre-, during, and post-chemo	CRCI trajectories	fluency, mental acuity) over treatment; DHEA not predictive. Within-patient DHEA(S) variations tracked with cognitive symptom trajectories across treatment. Higher endogenous cortisol correlated positively with fatigue, appetite loss, nausea/vomiting – toxicity-related symptom burden in advanced disease.
Lundström et al., 2003 [56]	Cross-sectional	Advanced cancer, predominantly gastrointestinal cancer (mixed sites; adults incl. older)	Urinary free cortisol	Single timepoint	Symptom scores (fatigue, appetite loss, nausea/vomiting)	Elevated evening cortisol and diurnal mean cortisol associated with shorter progression-free survival
Cash et al., 2024 [25]	Prospective	Head and neck cancer - most patients >50 years (some 65+), late-stage oral/oropharyngeal cancer	Cortisol (salivary) - diurnal slope, mean, waking, evening levels	Twice daily for 6 consecutive days during diagnostic/treatment planning	Progression-free survival (treatment outcomes, not toxicity)	

Note. CAR = cortisol awakening response; CINV = chemotherapy-induced nausea and vomiting; CRCI: cancer related cognitive impairment; DHEA-S = dehydroepiandrosterone sulfate; HPA = hypothalamic–pituitary–adrenal; MDASI = M.D. Anderson Symptom Inventory; NSCLC = non-small-cell lung cancer; QOL = quality of life; UW-QOL = University of Washington QOL.

2.3. Mechanistic Pathways Relevant to Treatment Toxicity

2.3.1. Cortisol's Role

Cortisol dysregulation may contribute to cancer treatment toxicity through multiple, evidence-based biological mechanisms. These mechanisms span direct effects on endocrine signaling, immune suppression, cellular stress responses, and tumor microenvironment remodeling.

Direct disruption of HPA axis function by chemotherapy. Platinum-based agents (e.g., cisplatin, carboplatin) have been shown to suppress serum cortisol levels following infusion, independent of circadian or psychological influences [52]. Whether this transient suppression contributes to symptoms such as nausea or fatigue remains speculative [52]. Further, based on rodent data, cisplatin activates hypothalamic CRH and vasopressin production, possibly exacerbating HPA activation and contributing to the stress burden of treatment [57].

Glucocorticoid receptor (GR)-mediated chemoresistance. Clinical studies show that perioperative dexamethasone increases SGK1 and MKP1/DUSP1 expression in ovarian tumours, suggesting that pharmacologic glucocorticoids can promote chemoresistance [58]. Further, preclinical work demonstrates that physiological cortisol levels can activate GR and induce pro-survival pathways; GR antagonism (e.g., relacorilant) restores chemosensitivity in vitro [59]. Finally, early-phase trials combining relacorilant with nab-paclitaxel improved progression-free and overall survival [60].

Induction of cellular senescence and inflammatory toxicity. Chemotherapy promotes cellular senescence in non-tumor tissues, leading to a persistent pro-inflammatory secretory phenotype that exacerbates tissue damage and impairs recovery [61]. In older adults, this effect is amplified, with biomarkers such as p16INK4a (a cyclin-dependent kinase inhibitor) rising sharply post-treatment, contributing to frailty, fatigue, and reduced treatment resilience [62].

Age-related cortisol accumulation and oxidative stress. With aging, chronic hypercortisolemia enhances chemoresistance via GR-mediated upregulation of metallothioneins, reprogramming cancer cells toward treatment insensitivity [63]. Simultaneously, oxidative stress disrupts HPA axis regulation and hippocampal feedback, particularly in older males, further impairing endocrine-immune homeostasis [64].

Immune suppression and immunotherapy toxicity. Cortisol dysregulation suppresses immune activation by reducing naïve T-cell populations and enhancing T-cell exhaustion, directly undermining responses to immune checkpoint inhibitors [65]. Moreover, anti-CTLA-4 and anti-PD-1/PD-L1 therapies may induce hypophysitis (found in 3.9 % of patients) [66], leading to permanent ACTH and cortisol deficiency, further compromising endocrine balance during immunotherapy [67].

Inflammatory amplification in aging brains. In older patients, elevated cortisol synergizes with pro-inflammatory cytokines (IL-6, TNF- α), leading to neuroinflammation, hippocampal atrophy, and impaired cognitive and treatment recovery [68,69]. Microglial priming in aged brains amplifies this response to chemotherapy, shifting the inflammatory response toward damaging oxidative stress [68].

However, it is essential to acknowledge that current evidence is predominantly associative. The extent to which cortisol dysregulation drives downstream pathology—or merely reflects a biomarker of systemic stress—is an open question. Longitudinal studies with repeated sampling across the treatment continuum are critically needed to clarify directionality and causal roles.

2.3.2. DHEA(S)'s Role

DHEA(S) exerts immunostimulatory, anti-glucocorticoid, and anabolic effects that counterbalance cortisol's impact. Notably DHEA promotes interleukin-2 (IL-2) production by CD4⁺ T cells [70], promoting a Th1-type immune response [71]. In doing so, DHEA acts as a physiological *antiglucocorticoid*, opposing cortisol's immunosuppressive influence [72,73] and helping to preserve immune function during stress or chemotherapy. DHEA and DHEAS also exert anabolic or protective effects on metabolism and tissues: for instance, DHEAS supplementation in animals reduces visceral fat and improves insulin sensitivity [74], and clinically, low DHEA states are associated with greater frailty and sarcopenia (a condition characterized by loss of muscle mass, strength, and function in older adults) [75]. Therefore, an inadequate DHEA(S) response in cancer patients—especially in older individuals—may permit unopposed cortisol activity, impairing immune surveillance and tissue recovery. This imbalance can contribute to heightened treatment toxicity and slower recovery, highlighting the need to consider DHEA(S) alongside cortisol in managing HPA axis dysregulation during cancer therapy.

2.4. Evidence Limitations and Unmet Needs

While the evidence consistently demonstrates high prevalence and clinical correlates of HPA-axis dysregulation in cancer populations, its translation to clinical practice is hampered by several key limitations: (1) Most studies assess survival, fatigue, or global well-being rather than DLTs, hospitalizations, or treatment adherence—outcomes more directly actionable in oncology [17]. (2) Despite age being a primary modifier of HPA function, few studies stratify by age group or include frail or multimorbid older adults. (3) HPA biomarkers are absent from clinical tools predicting treatment toxicity (e.g., Cancer and Aging Research Group CARG [76], Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) [6]), despite their plausible biological role [9,77]. (4) Despite growing interest, cortisol remains primarily a research biomarker, lacking standardized protocols and regulatory qualification in oncology.

Thus, while cortisol abnormalities are consistently linked to adverse symptoms and poor survival, their value as predictive biomarkers for treatment-specific toxicities remains underexplored. This distinction is crucial, as prognostic biomarkers reflect general disease burden or resilience, while predictive biomarkers guide treatment decisions by forecasting modifiable risk. Without prospective validation against standardized toxicity endpoints, the clinical utility of HPA-axis biomarkers in oncology remains speculative.

2.5. Section 2 Summary

- HPA-axis dysregulation is prevalent across tumor types, most commonly manifesting as elevated cortisol levels and blunted circadian rhythms.
- These abnormalities correlate with poorer survival and symptom burden but have not been validated as predictors of treatment toxicity.
- Most evidence is prognostic and lacks specificity for treatment-related toxicities.
- Prospective, age-stratified studies using standardized toxicity endpoints are urgently needed to determine the predictive and monitoring utility of cortisol and DHEA(S) in cancer care.

3. Treatment Outcomes in Older Adults

3.1. Age-Related Changes in Cortisol:DHEA Metabolism

Aging is associated with profound alterations in HPA-axis regulation that shape the endocrine context in which cancer therapy occurs [27,37,45]. These changes include: (1) Elevated basal cortisol secretion, partly driven by increased hypothalamic drive and altered negative feedback at the pituitary and hippocampal levels [78,79]; (2) Impaired glucocorticoid receptor sensitivity, leading to prolonged cortisol exposure and a reduced capacity to terminate stress responses [29,80]; (3) DHEAS declines by approximately 1–2 % per year after the third decade, reaching 20–30 % of peak concentrations by age 70–80 [81]. Thus, in aging, elevated cortisol and this decline in DHEA(S) production reduces the cortisol-buffering effects of DHEA(S) and results in an elevated cortisol:DHEA(S) ratio [32,35].

Together, these changes impair circadian cortisol regulation, yielding blunted diurnal slopes and exaggerated responses to physical or psychological stress. The elevated cortisol:DHEA(S) ratio, in particular, is increasingly recognized as a sensitive marker of endocrine imbalance and systemic vulnerability in older adults. It has been linked to immunosenescence, chronic low-grade inflammation, sarcopenia, and reduced recovery from physiological insults [31,34,35,82,83].

Crucially, these endocrine alterations are not benign background phenomena. Instead, they create a hormonal environment in which physiological resilience is already compromised before treatment begins. This may amplify the impact of cancer-related stressors and therapy-induced toxicity, particularly in the context of multimorbidity, frailty, and functional decline common in geriatric populations [27,63]. Therefore, age-related HPA-axis dysregulation may serve not only as a biomarker of vulnerability, but also as a biological modifier that increases susceptibility to adverse treatment outcomes.

3.2. Lack of Age-Stratified Analyses and Predictive Models

Despite well-documented aging effects on cortisol dynamics, most oncology studies evaluating HPA-axis biomarkers do not stratify analyses by age or adjust for aging-related endocrine shifts. Research cohorts often span wide age ranges without age-specific reference intervals, leading to potential misclassification of normal aging effects as pathological.

Further, few studies contextualize cortisol abnormalities within geriatric assessment domains such as frailty, comorbidity, or functional reserve—despite these being key determinants of treatment tolerance in older adults [84]. The omission of age-adjusted biomarker interpretation critically limits the relevance of existing research for geriatric oncology.

Current predictive models for chemotherapy toxicity in older adults, including the CARG score [76], the CRASH [6], and the G8 screening tool [85], primarily include demographic, functional, and inflammatory variables, showing poor external validation in predicting the risk of chemotherapy severe toxicities in some cohorts [86]. None incorporate endocrine or HPA-axis biomarkers, despite mounting evidence of their clinical relevance [9,41,77,87–90].

Integrating cortisol-based biomarkers into these models offers a promising strategy to enhance precision. For example, a blunted cortisol slope or elevated cortisol:DHEA ratio may uncover physiologic risk in patients who otherwise appear fit on functional screening or who fall into intermediate-risk strata based on age and comorbidities alone. This could be especially useful in tailoring chemotherapy dosing, early supportive care, or prehabilitation strategies.

In future predictive frameworks, cortisol metrics could be incorporated as add-on variables to existing tools (e.g., CARG-plus or CRASH-plus), independent biomarkers within new multimodal indices of endocrine resilience, or as dynamic markers tracked over time to reflect evolving tolerance across treatment cycles.

To support such integration, normative reference ranges and clinically actionable thresholds must be established in older cancer patients, ideally through prospective, age-stratified biomarker validation studies (see Section 5). Until then, the omission of endocrine parameters remains a critical blind spot in toxicity prediction for geriatric oncology.

3.3. Mechanistic Pathways Linking Cortisol Dysregulation to Treatment Outcomes in Older Adults

The intersection of aging physiology and cortisol dysregulation may undermine treatment tolerance through several interrelated mechanisms. While human data support some pathways, others remain theoretical or are extrapolated from preclinical models and require cautious interpretation.

(1) *Exacerbation of immunosenescence.* Aging is characterized by diminished innate and adaptive immune function—marked by thymic involution, T-cell exhaustion, and chronic low-grade inflammation [91,92]. Elevated cortisol levels compound these changes, suppressing immune cell proliferation, altering cytokine profiles, and impairing tumor immune surveillance [80]. Although human data linking cortisol to poor immunotherapy outcomes remain limited, early observational findings suggest that baseline endocrine function may modify immune-related adverse events and treatment efficacy [93].

(2) *Glucocorticoid receptor-mediated treatment resistance.* Cortisol activates glucocorticoid receptors (GRs), modulating transcription of genes involved in cell survival and proliferation [94]. GR activation enhances PI3K/Akt and NF- κ B signaling, promotes anti-apoptotic pathways, and induces drug resistance mechanisms [94–97]. In cancers exhibiting GR overexpression or glucocorticoid resistance, these effects may reduce chemotherapy efficacy [98]. While these mechanisms have been observed across tumor types—including ovarian, breast, and lung cancers—their translation to older patient populations remains speculative, and human studies evaluating cortisol-GR interactions during treatment are lacking.

(3) *Delayed tissue repair.* Cortisol impairs fibroblast activity and collagen synthesis [99,100], which could undermine post-treatment recovery. Human studies have documented age-related declines in extracellular matrix turnover and fibroblast responsiveness [101,102], but direct evidence linking cortisol to impaired post-treatment recovery in cancer patients is limited. The role of DHEA as a counter-regulatory anabolic hormone may be especially relevant here, given its capacity to promote matrix repair and oppose cortisol's effects [103,104]—though this too remains understudied in clinical oncology.

Together, these mechanisms suggest that cortisol dysregulation may not merely reflect systemic stress but actively contribute to treatment intolerance. Importantly, aging appears to magnify the biological impact of HPA-axis dysregulation, particularly in immune, neuroendocrine, and reparative systems already under strain. Further research is needed to determine the relative

contributions of these pathways and whether they can be targeted to enhance resilience and reduce toxicity in geriatric oncology.

3.4. Research Priorities

To translate these insights into clinical practice, future research should pursue the following directions:

- (1) **Conduct age-stratified analyses using reference-adjusted cortisol:DHEA(S) data.** Future studies should explicitly stratify outcomes by age groups (e.g., 65–74, 75–84, ≥85 years) and apply **age-appropriate reference ranges** to distinguish normative aging effects from cancer-related dysregulation. Large-scale normative datasets already exist in endocrinology, but few oncology studies leverage this information to contextualize biomarker abnormalities in older patients.
- (2) **Design longitudinal studies to track cortisol and DHEA(S) trajectories across treatment cycles.** Rather than relying on single-time-point measures, research should evaluate temporal changes in cortisol slope, CAR, evening cortisol, and cortisol:DHEA(S) ratio at baseline, mid-treatment, and treatment completion. These trajectories may offer unique insights into dynamic resilience and physiological recovery. Real-time tracking may also support early toxicity detection and anticipatory supportive care.
- (3) **Integrate endocrine biomarkers into multimodal prediction models.** Validated risk scores such as CARG and CRASH could be enhanced by integrating endocrine markers. Alternatively, a new “Endocrine Resilience Index” incorporating salivary cortisol features, DHEA(S) levels, and clinical frailty indicators could be developed and validated in prospective cohorts.
- (4) **Evaluate feasibility and implementation in vulnerable subgroups.** Special attention should be given to frail, multimorbid, or cognitively impaired patients, who are often underrepresented in biomarker research. Studies should report not only biomarker-outcome associations but also feasibility metrics such as sample collection adherence, cost, acceptability, and usability in real-world geriatric oncology settings.
- (5) **Explore DHEA(S)-specific effects and mechanisms.** Compared to cortisol, DHEA(S) remains understudied in cancer populations. Its immuno-enhancing, anti-glucocorticoid, and anabolic properties may offer protective effects that deserve further exploration, especially in the context of sarcopenia, fatigue, and post-treatment recovery.

3.5. Section 3 Summary

- Older adults exhibit distinct HPA-axis alterations that increase physiological vulnerability to cancer therapy.
- Despite these biological vulnerabilities, most studies do not stratify biomarker data by age or integrate them into predictive models for toxicity.
- Mechanistic pathways—including immune suppression, glucocorticoid receptor signaling, and impaired tissue repair—provide a biologically plausible rationale for the role of cortisol in mediating treatment intolerance.
- Research priorities include age-adjusted reference use, longitudinal biomarker tracking, model integration, feasibility studies, and greater focus on DHEA(S).
- These priorities lay the foundation for the standardization and clinical translation roadmap outlined in Section 5.

4. Methodological Heterogeneity: A Barrier to Clinical Translation

Despite strong biological plausibility and consistent associations with clinical outcomes, the translation of HPA-axis biomarkers into oncology practice remains limited. A significant barrier is the substantial methodological heterogeneity across studies, which undermines reliability, limits comparability, and impedes regulatory qualification. This section outlines key sources of

variability—ranging from matrix selection to endpoint definitions—and offers concrete recommendations to standardize biomarker assessment.

4.1. Sampling Matrices

The biological matrix used to assess cortisol and DHEA(S) strongly influences the physiological interpretation, feasibility, and clinical relevance of results. Current studies use heterogeneous measurement approaches [105,106].

Salivary cortisol reflects the free, biologically active fraction of circulating cortisol, with strong correlation to serum-free cortisol [107–109]. It responds robustly to ACTH and CRH stimulation and is unaffected by cortisol-binding globulin, making it ideal for circadian rhythm profiling and stress reactivity assessment. Given its non-invasiveness, low cost, and ease of repeated sampling, salivary cortisol has become the preferred matrix in psychoneuroendocrinology [107] and is gaining traction in aging and oncology research [38,105,110].

Salivary DHEA, similarly, offers practical advantages: it reflects the bioavailable fraction, correlates well with serum levels ($r \approx 0.86$ in a 358-pair cohort [111]), and remains relatively stable across the day [35,111–113].

The choice between DHEA and its sulfated form DHEAS depends on study objectives, and they should not be used interchangeably [114]. DHEA fluctuates more rapidly and is preferred in studies of acute stress reactivity [113], while DHEAS is more stable and better suited to long-term health profiling [115]. In the context of cortisol:DHEA(S) ratios and cancer and frailty research, a single, pre-specified DHEA sample in the morning—adjusted for time of awakening [116]—offers a feasible and clinically relevant option.

Recommendation: The choice between serum and saliva measurements depends largely on the available analytical approaches and oncology setting (in- or outpatient). DHEA versus DHEAS samplings depend on study objectives and are both defensible scientifically.

4.2. Sample Timing Recommendations

Cortisol secretion follows a diurnal rhythm, with a sharp peak upon awakening and gradual decline across the day. Capturing this rhythm requires carefully timed, repeated measurements. However, timing protocols vary widely across studies—from single morning samples to multi-point curves across 1 to 4 days—hindering comparability and interpretation [17,105,117]. Pairing cortisol with DHEA(S) at the same awakening timepoint further stabilizes the cortisol:DHEA(S) ratio against diurnal phase differences [118], as DHEA(S) shows a flatter but still morning-skewed rhythm (mostly DHEA [113]); two-day morning averages reduce random error relative to single-day sampling [119].

Recommendation: Concerning cortisol sampling, adhere to expert consensus guidelines recommending at least five sampling time points per day (upon awakening, +30 min, noon, afternoon, bedtime) over ≥ 3 consecutive days to improve reliability [105,120,121] and capture key features such as cortisol awakening response (CAR), diurnal slope, evening cortisol, area under the curve (AUC). While full cortisol diurnal profiling adds mechanistic depth, a two-day cortisol:DHEA(S) (with a strict sample timing, adjusted for awakening time [116]) could provide a pragmatic approach for prognostic studies in geriatric oncology. For longitudinal treatment monitoring, sampling should correspond to clinically meaningful milestones (e.g., baseline, mid-cycle, end-of-cycle) and 6-12 months follow-up for long-term pattern evaluation [122,123].

Importantly, feasibility in older adults must be addressed. Cognitive impairment, frailty, or multimorbidity may impair protocol adherence. Pilot studies suggest ~75% compliance in cancer populations [38], though implementation in cognitively impaired or homebound patients requires support (e.g., caregiver assistance, simplified kits) [105].

4.3. Heterogeneity in Clinical Outcomes and Confounders

Clinical outcomes used in HPA-axis studies vary substantially—ranging from survival and fatigue to general quality of life [47,124–126]. However, few studies evaluate treatment-specific toxicities such as CTCAE grade ≥ 3 adverse events, dose reductions or discontinuations, unplanned hospitalizations, or functional decline [17]. This limits the ability to evaluate cortisol as a predictive biomarker of treatment intolerance.

Additionally, key age-specific confounders—such as frailty, cognitive function, polypharmacy, and corticosteroid co-medications—are inconsistently reported or adjusted for [76]. This omission may obscure or exaggerate associations between cortisol and outcomes in older adults.

Recommendation: Standardize outcome definitions using CTCAE criteria and integrate geriatric oncology guidelines (e.g., ASCO, SIOG) for confounder control. Report and adjust for variables such as corticosteroid use, multimorbidity, and frailty indices in all predictive analyses.

4.4. Lack of Reference Ranges for Older Adults

Numerous large population studies—many using gold-standard liquid chromatography tandem mass spectrometry (LC-MS/MS)—have established cortisol and DHEA(S) intervals in older adults [127–130].

In contrast, no authoritative guidelines or peer-reviewed studies have yet been published with universally accepted reference ranges stratified by specific cancer types or discrete treatment phases (e.g., pre-operative vs. adjuvant vs. maintenance). Instead, oncology papers typically report cohort-specific distributions or use general population cut-offs when exploring prognostic associations [25,39,131].

Recommendation: Multi-center validation studies should develop age- and treatment-specific reference intervals for cortisol and DHEA(S), using standardized analytical platforms and harmonized pre-analytical conditions.

4.5. Section 4 Summary

- Biomarker research on cortisol and DHEA(S) is hindered by heterogeneity in matrix selection, sampling protocols, clinical outcome definitions, and covariate control.
- Salivary sampling is currently the most physiologically and logistically appropriate matrix for older cancer patients.
- Timing protocols should balance capturing diurnal variation with real-world feasibility in older adult populations.
- Standardized toxicity definitions, age-specific reference ranges, and rigorous confounder control are needed to enable biomarker qualification.

5. Future Research and Standardization Agenda

Bridging the gap between exploratory cortisol research and clinical application in geriatric oncology requires a comprehensive, staged roadmap. This includes biomarker standardization, predictive validation, interventional testing, and clinical integration.

To support clinical translation and address the current gap in biological risk stratification, the 14-item checklist of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Test Evaluation Working Group (TE-WG) for test evaluation was applied [132]. The resulting analysis, presented in Supplementary File 1, outlines the unmet clinical needs, intended use, and feasibility of cortisol:DHEA ratio testing in older cancer patients, offering a roadmap for biomarker development in geriatric oncology.

In this section, concrete priorities across these domains are outlined to facilitate the development of cortisol and DHEA as predictive and monitoring biomarkers for treatment-related toxicity.

5.1. Standardization Priorities for Biomarker Development

Before cortisol or DHEA(S) can be considered clinically actionable, robust methodological standardization is essential.

Key priorities include:

- Considering cortisol, at a minimum, collect five samples per day (awakening, +30 min, noon, afternoon, bedtime) over ≥ 3 consecutive days. In clinical contexts, simplified protocols (awakening + evening) may be acceptable if validated. Considering cortisol:DHEA(S), a morning two-day morning protocol could reduce random error relative to single-day sampling.
- Time of awakening, medication use (especially corticosteroids), food intake, and sampling adherence must be systematically recorded and adjusted for.
- Use validated immunoassays or LC-MS/MS with established inter-assay reliability.
- Age- and treatment-stratified normative datasets must be established following existing guidance.
- Adopt uniform clinical endpoints such as CTCAE grade ≥ 3 toxicities, dose reductions, treatment discontinuation, and unplanned hospitalizations.

5.2. Prospective Validation Studies

Once standardized, the predictive validity of cortisol and DHEA(S) must be tested in prospective studies focused on older adults with cancer. These studies should (1) recruit treatment-naïve patients ≥ 65 years, including those with frailty or multimorbidity, (2) collect serial salivary samples pre-treatment, mid-treatment, and at treatment completion, (3) assess toxicity-related outcomes including dose-limiting toxicities (DLTs), dose reductions or delays, treatment discontinuations, hospitalizations and functional decline, (4) include comprehensive geriatric assessments to evaluate frailty, comorbidities, functional reserve, and polypharmacy, and (5) report implementation outcomes such as feasibility, adherence, patient burden, and cost.

In addition to testing baseline cortisol features (e.g., blunted slope, elevated evening levels), studies should explore treatment-induced cortisol trajectories as real-time indicators of declining resilience.

5.3. Interventional Research

Establishing causality requires interventional trials targeting cortisol dysregulation to improve treatment tolerance. Two strategies could be pursued:

(1) Behavioral interventions: Mind–body interventions (e.g., mindfulness-based stress reduction, yoga, cognitive-behavioral therapy, or exercise intervention) have been shown to improve diurnal cortisol output and rhythmicity [131,133–138]. Median participant age across biomarker studies hovers at approximately 55–60 years [137]; frail adults ≥ 75 years are seldom enrolled, limiting generalizability to the oldest-old. Randomized controlled trials embedding serial cortisol sampling can determine whether such interventions delay the onset or severity of treatment-related toxicity, normalize HPA-axis profiles, and/or improve physical functioning or quality of life.

(2) Pharmacological modulation: Evidence indicates that while some pharmacological options are under investigation for managing HPA axis dysregulation in older cancer patients (e.g., selective glucocorticoid receptor modulators [60,139] or non-selective glucocorticoid receptor antagonists [140,141]), treatment decisions should be individualized based on the specific type of dysfunction (hyper- vs. hypofunction), underlying cancer type, concurrent treatments, and patient-specific factors. Regular monitoring and multidisciplinary care coordination remain essential for optimal outcomes.

5.4. Clinical Integration Framework

To realize clinical impact, validated HPA-axis biomarkers must be embedded into oncology workflows. I propose a three-part clinical integration strategy (see Table 2: Translational roadmap for HPA-axis biomarkers in older adults with cancer):

(1) Diagnostic workflow inclusion.

- Pilot cortisol and DHEA(S) sampling as part of pre-treatment geriatric assessments.
- Use alongside functional and inflammatory markers.
- Evaluate logistical feasibility (e.g., sampling kits, lab capacity) and stakeholder acceptance.

(2) Risk stratification integration.

- Integrate validated HPA axis features (e.g., blunted slope, high cortisol:DHEA(S) ratio) into existing toxicity prediction tools (e.g., CARG, CRASH) or create new composite endocrine-resilience scores.
- Use automated interpretation platforms (e.g., electronic health record algorithms) to support clinical decision-making.

(3) Demonstration of Clinical Utility.

- Conduct pragmatic trials or hybrid implementation-effectiveness studies [142] assessing if biomarker-informed care reduces severe toxicity rates, improves treatment adherence and dose intensity, and decreases hospitalization or functional decline.

Table 2. Translational roadmap for HPA-axis biomarkers in older adults with cancer.

Phase	Objective	Key Actions	Expected Outputs
1. Methodological standardization	Establish uniform, reproducible biomarker protocols	<ul style="list-style-type: none"> - Select salivary or serum cortisol and DHEA(S) as preferred matrices, depending on analytic tools and study objectives - Define minimum sampling protocol - Standardize pre-analytical variables (e.g., awakening time, corticosteroid use) - Employ validated assays (e.g., LC-MS/MS or calibrated immunoassays) - Stratify data by age, sex, cancer type, and treatment phase - Recruit ≥65-year-old treatment-naïve patients 	<ul style="list-style-type: none"> - Harmonized biomarker assessment protocol - Age- and treatment-specific reference ranges - Enhanced cross-study comparability
		<ul style="list-style-type: none"> - Collect cortisol and DHEA(S) ratio (baseline, mid-, post-treatment) - Assess toxicity endpoints: DLTs, dose reductions, hospitalizations, functional decline - Adjust for frailty, comorbidities, polypharmacy - Track adherence and patient burden 	<ul style="list-style-type: none"> - Predictive models incorporating cortisol:DHEA(S) ratio - Risk thresholds for toxicity stratification - Real-world feasibility and compliance data
2. Prospective Validation	Demonstrate predictive validity for treatment-related toxicity in older adults	<ul style="list-style-type: none"> - Identify patients with abnormal HPA profiles - Randomize to behavioural interventions (e.g., CBT, yoga, exercise) or pharmacologic agents - Embed serial biomarker sampling and toxicity tracking - Evaluate toxicity, functional, and QoL outcomes 	<ul style="list-style-type: none"> - Evidence for causal role of cortisol:DHEA(S) ratio - Demonstration of biomarker-guided toxicity reduction - Interventional proof-of-concept
3. Interventional Trials	Test whether modifying HPA-axis dysregulation improves outcomes		
4. Clinical Integration	Embed biomarkers into oncology care pathways	<ul style="list-style-type: none"> - Pilot salivary sampling in pre-treatment geriatric assessments 	<ul style="list-style-type: none"> - Clinical workflows incorporating HPA-axis assessment

Phase	Objective	Key Actions	Expected Outputs
		- Integrate cortisol/DHEA(S) features into existing tools (e.g., CARG, CRASH) or new endocrine-resilience indices	- Improved patient stratification and individualized supportive care
		- Develop EHR-integrated decision support tools	- Reduced toxicity and treatment discontinuation rates
		- Conduct implementation-effectiveness studies	

5.5. Review Limitations

While this review offers a translational roadmap, several limitations must be acknowledged. First, most studies cited are observational, cross-sectional, or underpowered to assess treatment-specific toxicity outcomes. Second, evidence on DHEA(S) remains sparse relative to cortisol, limiting firm conclusions on the cortisol:DHEA(S) ratio. Third, this is a narrative review, and selection bias may be present despite efforts to prioritize representative and high-quality studies. Fourth, the generalizability of findings to frail, cognitively impaired, or socioeconomically vulnerable older adults is uncertain, as these groups are frequently excluded from primary studies.

5.6. Section 5 Summary

- Translation of HPA-axis biomarkers into geriatric oncology requires standardization, validation, interventional testing, and integration.
- Prospective studies should assess predictive accuracy for treatment toxicity, including in frail and multimorbid patients.
- Interventions targeting cortisol dysregulation—behavioral or pharmacological—should be tested for modifiability of toxicity risk.
- Integration into oncology workflows demands demonstration of clinical utility and interdisciplinary collaboration.

6. Conclusions

Older adults with cancer face a disproportionate risk of treatment-related toxicities, yet current oncology risk stratification models largely omit biomarkers that reflect underlying physiological resilience. The hypothalamic-pituitary-adrenal (HPA) axis—particularly through cortisol and DHEA(S) dynamics—represents a promising but underexplored window into this vulnerability.

This review has synthesized evidence showing that age-related alterations in HPA-axis function (e.g., blunted cortisol slope, reduced DHEA(S)) are biologically linked to key mechanisms of treatment intolerance, including immunosenescence, glucocorticoid-mediated chemoresistance, impaired tissue repair, and neuroinflammation. However, the translational potential of these biomarkers is currently limited by methodological heterogeneity, lack of age-stratified validation, and minimal integration into predictive frameworks.

To advance clinical utility, a structured translational agenda is required. This includes: (1) biomarker standardization using validated salivary assays; (2) prospective studies with age-specific reference thresholds and clinically actionable endpoints; (3) interventional trials assessing whether targeting cortisol dysregulation improves treatment tolerance; and (4) integration into real-world oncology workflows and decision tools.

If implemented, this roadmap could facilitate a paradigm shift in geriatric oncology—from one-size-fits-all toxicity prediction to precision risk assessment based on endocrine resilience. Cortisol and DHEA(S) have the potential not only to predict who is most vulnerable, but also to enable personalized interventions that preserve function, reduce toxicity, and optimize cancer care for older adults.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Acknowledgements: During the preparation of this manuscript, the author used the ChatGPT 4o tool for the purposes of improving academic writing. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Funding: No funding sources to be declared.

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