

Research Article

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Steroid Hormones Modulation of the Tumor Microenvironment in Prostate Cancer

Laura Boldrini¹, Marissa Marczak², Noah Schneider², Savana Watts² and Massimo Bardi^{2*}

¹Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Via Roma, 57, Pisa, Italy

²Department of Psychology and Neuroscience, Randolph-Macon College, Ashland, VA, USA 23005, USA

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***Corresponding author:** Massimo Bardi, Full Professor of Psychobiology and Neuroscience Department of Psychology and Neuroscience 134D Copley Science Center, Randolph-Macon College Ashland, USA, Email: massimobardi@rmc.edu

Abstract

This study aimed to assess the role of steroid hormones, well-known modulators of the crosstalk between the hypothalamic-pituitary-adrenal (HPA) axis and immune activity, in the tumor micro-environment (TME) of prostate cancer (PC). It was hypothesized that DHEA / CORT receptor density within the TME would be positively associated with anti-tumor activity and negatively with immunosuppressive cell activity. Preliminary results showed that IL-6 immunoactivity was related to both DHEA and CORT levels in the TME. It was also found that patients with non- metastatic PC had a significantly higher DHEA / CORT ratio and reported a better quality of life (QoL). The levels of DHEA were also associated with QoL. Taken together, this study showed that the density of the IL-2, IL-6, and DHEA receptors expressed around the tumor can give us a reliable index of the TME's influence on PC. Considering the pressing need to find cost-effective natural treatments for skyrocketing health costs in a progressively aging population, our results could inform future translational research on how improving emotional resilience can increase cancer survivorship.

Keywords: Interleukins; Immune Activity; DHEA; Cortisol; Urogenital Cancer; HPA Axis; Stress

Abbreviations: PC: Prostate cancer; HPA: Hypothalamic Pituitary Adrenal; DHEA: dehydroepiandrosterone; TME: Tumor Micro Environment; ILs: Interleukins; PMOS: Profile of Mood States; PWB: Physical Well Being; SWB: Social Family Well Being; EWB: Emotional Well Being; FWB: Functional Well Being; MDS: Multi-Dimensional Scaling; CNS: central nervous system

Introduction

Prostate cancer (PC) is one of the most diagnosed cancer types in men with the highest incidence occurring in the elderly above the ages of 65 [1, 2]. While more effective therapeutic interventions have increased life expectancy, the combination of an increased incidence and decreased mortality has resulted in a growing number of survivors affected with burdening health conditions during a phase of their lives in which other comorbidities and cognitive impairments are common [3-5]. For these reasons, it is increasingly important to assess holistic models of health conditions in people affected by PC.

It has been established that chronic stress can promote the occurrence and development of tumors [6, 7]. Chronic stress typically refers to the continuous and nonspecific response of the body caused by the activation of the classical hypothalamic-pituitary-adrenal (HPA) axis [7]. Although cortisol is a well-known biomarker of HPA activity, less is known about dehydroepiandrosterone (DHEA), a steroid hormone

precursor also released during the stress response with multiple physiological and neural actions, including emotional regulation [8, 9]. In addition, the release of DHEA can inhibit catecholamine upregulation in the adrenal medulla, inflammatory dysregulation in the tumor-micro-environment (TME), and the tumor initiation process [10]. Considering that DHEA production declines naturally during the aging process [11], assessing the role of the balance between cortisol and DHEA production is of high interest in PC diagnosis [12]. Additionally, the ratio of DHEA secretion in comparison to cortisol secretion can be a reliable indicator of an adaptive response to stress, improving, among other factors, neural protection and anti-inflammatory immune activity [13-15]. Considering that dysregulation of the activity of the HPA axis has been consistently linked to affective disorders and an impaired perception of the quality of life (QoL) [16-18], and in turn QoL can influence cancer disease progression [19], steroid hormones can have a dual effect on the TME.

The HPA axis can influence the TME, and therefore cancer development, by regulating immune functions [20]. The interplay between innate and adaptive immunity plays a crucial role in the trajectory of most cancers, including PC [21-22]. The innate immune system is a non-specific defense mechanism utilized by the host shortly after encountering an antigen and is comprised of phagocytes, dendritic cells, mast cells, and natural killer cells [23]. Whereas, adaptive immunity, which includes T cells and B cells, is antigen-dependent and requires a lag time between antigen exposure and response. The malignant progression in PC is driven by dysregulation in the prostate TME. Specifically, the stroma and tumor cells interact and establish a pro-tumor environment through cytokine production and pro-inflammatory signaling [24-25]. In addition, immunosuppressive cells, including M2 macrophages and regulatory T cells, can infiltrate the TME and downregulate the anti-tumor activity of cytotoxic T cells and natural killer cells resulting in cell growth [26]. These effects are coordinated by cytokines, such as interleukins (ILs), which direct cell-to-cell communication in the TME [27]. Because ILs can also activate the HPA axis response [28], assessing the presence of ILs and HPA axis biomarkers in the TME is essential for PC prevention and treatment.

For the above reasons, the primary aim of this study was to investigate the relationship between immune-endocrine functions and psychological emotional regulation in PC patients. Immunological function was determined by counting the density receptors in the TME of IL-2, generally considered a pro-inflammatory agent, IL-6, and anti-inflammatory messenger, and the steroid biomarkers cortisol and DHEA. Emotional regulation in patients was assessed using the Functional Assessment of Cancer Therapy-General (FACT-G) and the Profile of Mood States (PMOS) questionnaires. Because previous studies showed the immunomodulatory effects of DHEA, including enhancing the activity of cytotoxic cells and reducing regulatory T cell activity [29], it was hypothesized that DHEA / CORT receptor density in the TME would be positively associated with anti-tumor activity and negatively associated with immunosuppressive cell activity. Furthermore, because previous research has indicated that urogenital cancer patients with higher DHEA levels reported greater QoL and lower mood dysfunctions [8, 30], it was predicted that higher DHEA / CORT ratios would correlate positively with psychological resilience and negatively with emotional reactivity. Lastly, it was theorized that patients with higher DHEA / CORT receptor density ratios and higher quality of life would have an increased chance of recovery based on the presence or absence of metastasis.

Methods

Ethical Statement

This study was approved by the University of Pisa Medical

School Ethical Committee (ID # 19005), and it has therefore been performed in accordance with the principles embodied in the World Medical Association Declaration of Helsinki. All participants gave their informed consent prior to their inclusion in the study.

Participants and Procedure

Participants were recruited among patients with PC (n=34) treated at the Azienda Ospedaliera Universitaria Pisana (AOUP). Questionnaires were administered to patients during their routine visits. The Functional Assessment of Cancer Therapy-General (FACT-G) was administered to assess health related quality of life of the patients. The FACT-G is comprised of four subscales: Physical Well-Being (PWB), Social / Family Well-Being (SWB), Emotional Well-Being (EWB), and Functional Well-Being (FWB). Participants responded utilizing a 5-point Likert scale, ranging from 0 (Not at all) to 4 (Very much), to rate their agreement with each statement. The Profile of Mood States (POMS) was administered to measure trait levels of emotional reactivity. It measures the typical ease of activation, intensity, and duration of one's emotional responses. Higher scores indicate higher levels of reactivity in each domain. Both scales have been found to be reliable in assessing emotional regulation in people coping with different diseases, including cancer. Both scales were summarized in an index of overall emotional output by weighing their scores. This index was aimed to assess the self-reported Quality of Life (QoL) of our subjects.

HPA / Immune System Immunohistochemistry

Paraffin-embedded cell blocks were used for hematoxylin-eosin and immunohistochemical staining. The expression of IL-2, IL-6, DHEA and cortisol (mouse polyclonal primary antibody, Roche, Monza, Italy) were assessed using the avidin-biotin peroxidase method for developing the immunoreaction. Immunohistochemical analysis was performed on the Ventana Medical System, with appropriate positive controls run for all cases. Immunoreactive (ir) cell count was averaged using 10 fields at 40X was performed on a Nikon light microscope. Negative controls were checked for every biomarker (Figures 1 & 2).

Statistical Analysis

Bivariate correlations were calculated by Pearson's r test. The differences in the average receptor density by disease progression were quantified using t-tests. To provide an integrative model of the independent association among the variables, a Multi-Dimensional Scaling (MDS) analysis was run. This analysis provides a map of distance created by a proximity matrix, and so the distances between variables in the graph represented the strength of the correlation. S-stress and the percentage of variance explained by the model (R²) were used to assess the reliability of the analysis. Typical acceptable values are 0.15 or less for S-Stress and above 80% for R². All analyses were performed using SPSS 28.1 (IBM, Armonk, NY, USA).

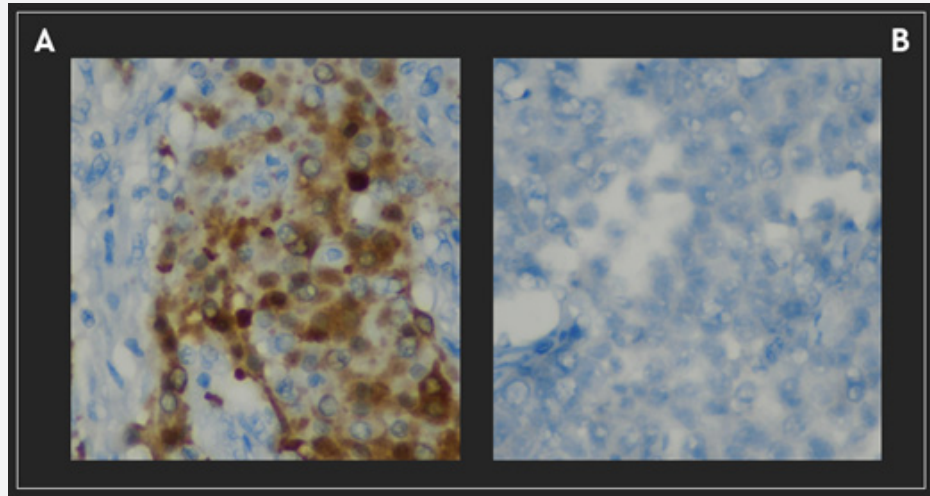


Figure 1: Immunohistochemistry staining of positive (A) and negative (B) expression of DHEA receptors (40x).

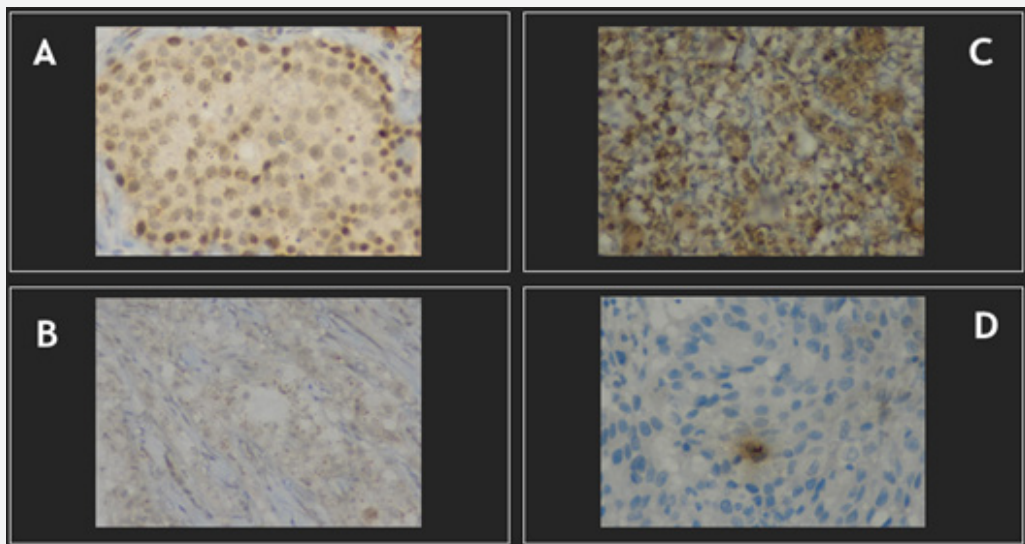


Figure 2: Immunohistochemistry staining of positive (A) and negative (B) expression of IL-2 receptors, and of positive (C) and negative (D) expression of IL-6 receptors.

Results

HPA / Immune System Crosstalk

Immunoreactivity of the IL-2 and IL-6 receptors were inversely related in PC patients ($r=-0.572$, $p<0.01$). IL-2-ir was not associated with DHEA-ir ($r=-0.126$, ns), but it was related to both cortisol-ir ($r=0.445$, $p<0.01$ - Figure 3A) and the DHEA / cortisol ratio ($r=-0.466$, $p<0.01$ - Figure 3B). Similarly, IL-6-ir was not related to DHEA-ir ($r=0.230$, ns), but it was correlated with both cortisol-ir ($r=-0.523$, $p<0.01$ - Figure 3C) and the DHEA / cortisol ratio ($r=0.495$, $p<0.01$ - Figure 3D).

Disease Progression, Emotional Regulation, HPA Activation

Age ranged between 47 and 85 years old, with an average age of 73 ± 9 years old. Of the biomarkers assessed in this study, only DHEA-ir was significantly related to age ($r=-0.347$, $p=0.041$). Ten of the 35 subjects developed metastases. In those cases, IL-2-ir was higher than in the people who did not develop metastases ($t_{33}=26.771$, $p<0.01$ - Figure 4A), and both IL-6-ir and the DHEA / cortisol ratio were significantly lower (IL-6: $t_{33}=24.480$, $p<0.01$ - Figure 4B; DHEA / cortisol: $t_{33}=11.310$, $p<0.01$ - Figure 4C). When

differences in receptors expression were compared by QoL, it was found that only DHEA-ir was significantly different ($t_{33}=4.155$, $p=0.050$ - Figure 4D), whereas all the other markers were not associated with QoL (all p -values >0.319).

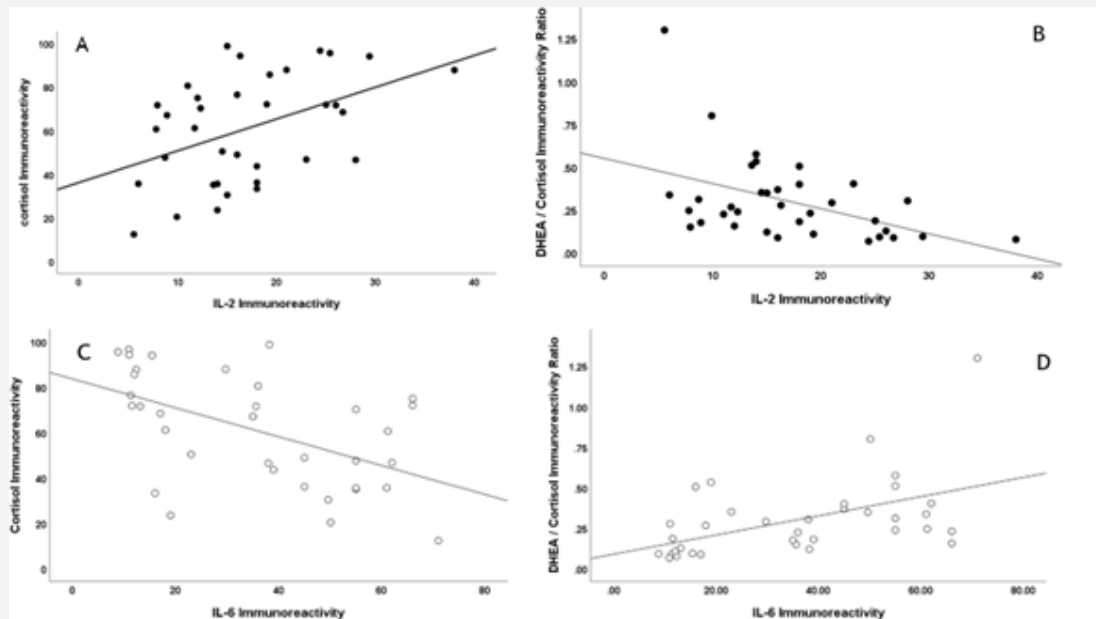


Figure 3: Correlation between inflammatory immune markers and steroid hormone receptors in the TME. (A) Significant positive correlation between the pro-inflammatory IL-2 marker and cortisol receptor expression. (B) Significant inverse correlation between the pro-inflammatory IL-2 marker and the DHEA / cortisol receptor ratio. (C) Significant inverse correlation between the anti-inflammatory IL-6 marker and cortisol receptor expression. (D) Significant positive correlation between the anti-inflammatory IL-6 marker and the DHEA / cortisol receptor ratio.

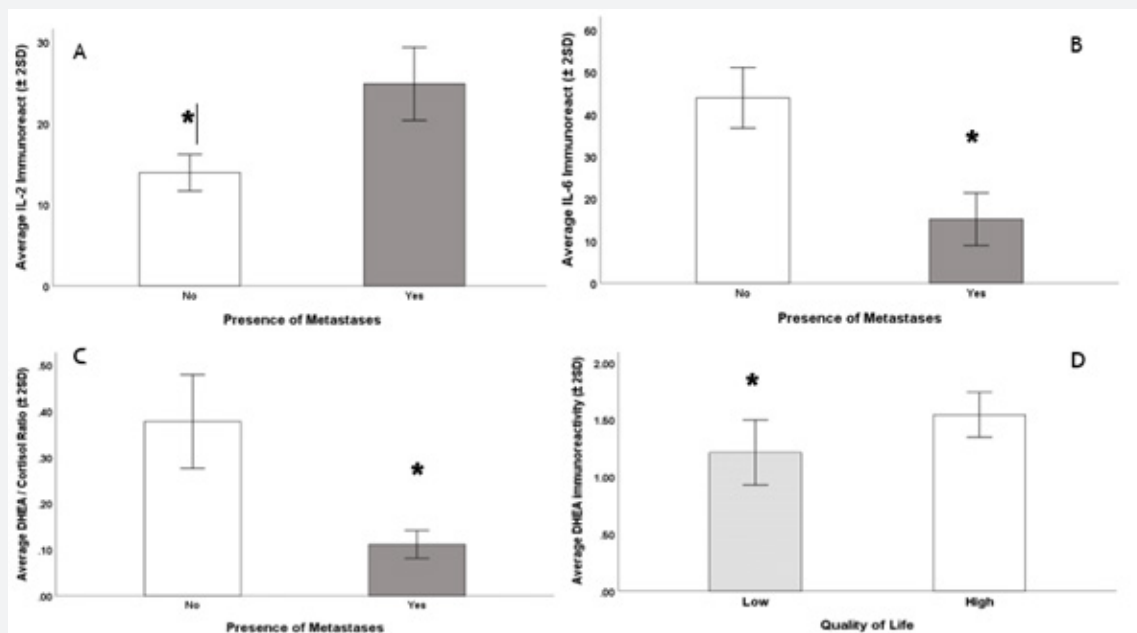


Figure 4: Average expression of biomarkers in the TME by presence of metastases and QoL. Patients with no metastatic tissue expressed significantly lower levels of IL-2 (A), significantly higher levels of IL-6 (B), and significantly higher the DHEA / cortisol expression ratio. Patients who reported a lower QoL expressed significantly lower levels of DHEA receptors (D).

Overall Model

Integrative MDS analysis showed a clear map of association among the biomarkers assessed in this study [30]. The analysis was very reliable (S-Stress=0.02; $R^2=0.91$ – Figure 5). The biomarkers IL-6, DHEA, and DHEA / cortisol ratio formed a cluster in one of the quadrants. Cortisol and IL-2 formed a second cluster

at the opposite side of the map. Age was not related to either cluster. Based on these associations, Dimension 1 was named “Inflammatory Action” and Dimension 2 “Aging Factors”. Individual cases were subsequently mapped based on metastases (Figure 6), and the separation between the two groups of individuals yielded an accuracy of 97% according to the dimensions named above.

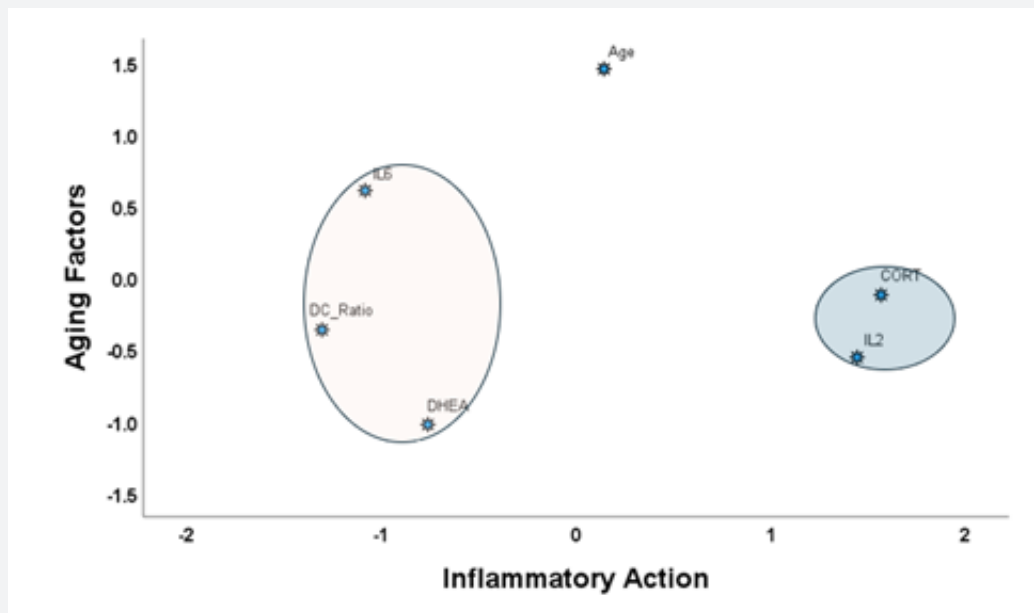


Figure 5: The MDS analysis revealed a clear separation between biomarkers generally considered anti-inflammatory and those considered pro-inflammatory. Age was not related to either cluster.

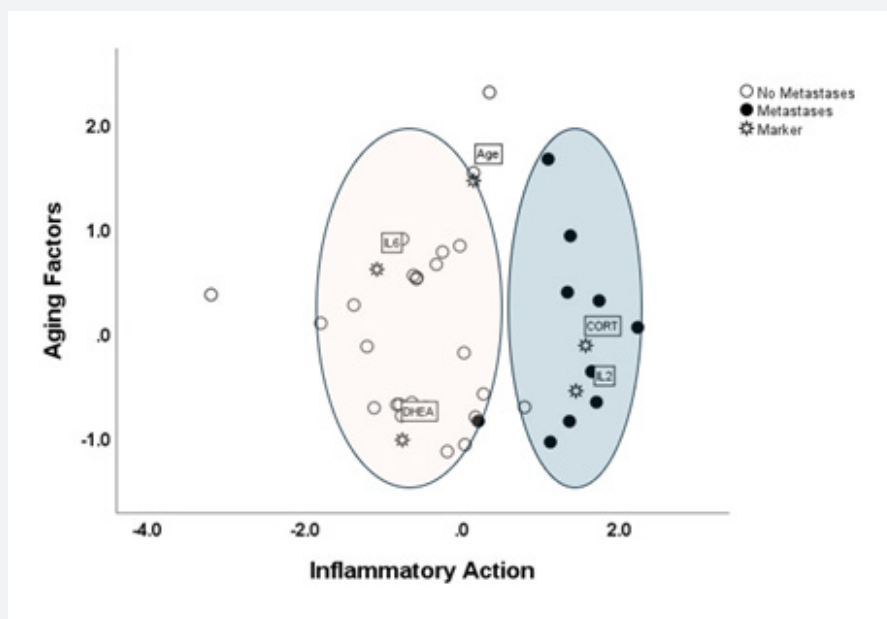


Figure 6: A follow up MDS analysis including the patients grouped by presence / absence of metastases also revealed the two groups were almost completely separated (97%) around the pro- and anti-inflammatory markers.

Discussion

In recent years, the critical role of inflammation in the regulation of homeostasis has gained increasing recognition, from cancer therapy to the study of neurological and psychiatric disorders [31-33]. The interplay between neuroactive steroids and the TME is complex and influenced by many factors such as mental health, sex, age, and individual differences [34-35]. Therefore, it is essential to establish the role of neuroactive steroids in both the regulation of the TME and the subjective experience of people affected by PC. Our results showed that the regulation of neuroactive steroid receptors in the TME is related to the expression of receptors for the immune system messengers regulating inflammation around the cancer. Specifically, high levels of DHEA in comparison to cortisol were positively related to anti-inflammatory markers (IL-6) and negatively correlated with pro-inflammatory markers (IL-2). High levels of this ratio were also significantly related to a better prognosis, considering that these markers were significantly higher in people who had no metastases. Finally, expression of DHEA receptors was associated with a higher QoL in PC patients, clearly pointing toward biological feedback involving the whole organism, from the regulation of the TME to expression of more positive emotions and higher coping skills. Therefore, our data points toward the importance of checking circulating levels of steroid hormones in cancer prevention and therapy.

Although several different scenarios could help interpret our data, we believe that the key resided in a better understanding of the overall homeostatic functions related to stress. Stress has been shown to significantly impact the PC progression. Specifically, individuals with high stress levels and low resilience are at higher risks for poor adjustment during survivorship [36]. Despite clear evidence that links cancer progression with psychosocial resilience, including a significantly lower probability to develop mood disorders and depression symptoms up to five years post-diagnosis [37], holistic models of the role of steroids on PC are still very limited [38]. It is well known that DHEA, among many of its functions, can play a protective role as an antagonist of glucocorticoids during stress responses [17, 39] and modulates dopamine and serotonin neurotransmission [40]. Furthermore, DHEA has been found to inhibit processes associated with PC metastasis, such as proliferation, migration, and secretion of pro-inflammatory molecules [41, 42]. Our results can elucidate one of the possible mechanisms for this dual action: reducing inflammation in tissue. In the central nervous system (CNS), this reduced inflammation can facilitate coping and mental health. In the TME, it can decrease cellular proliferation. Considering that the levels of DHEA naturally decrease in the aging process, it is also understandable why both PC progression and lethality, as well as mood disorders related to neural degeneration, increase exponentially in older people.

In conclusion, our data can help to understand the holistic action of the HPA axis on both emotional regulation and PC progression. Higher inflammation in the TME and in the CNS is a key aspect to investigate when considering innovative cancer strategies for the prevention and therapeutic approach on PC. Clearly, our data was limited in the number of biomarkers and subjects, so our results can only be considered preliminary, even if very promising. Future studies will focus on how DHEA can act as a transcription factor for the regulation of inflammation of the TME.

References

- Gandaglia G, Leni R, Bray F, Fleshner N, Freedland SJ, et al. (2021) Epidemiology and prevention of prostate cancer. *European urology oncology* 4(6): 877-892.
- Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, et al. (2021) Cancer statistics for the year 2020: An overview. *Int J Cancer* 149(4): 778-789.
- Barsouk A, Padala SA, Vakiti A, Mohammed A, Saginala K, Thandra KC, et al. (2020) Epidemiology, staging and management of prostate cancer. *Med Sci (Basel)* 8(3): 28.
- Mundle R, Afenya E, Agarwal N (2021) The effectiveness of psychological intervention for depression, anxiety, and distress in prostate cancer: a systematic review of literature. *Prostate Cancer Prostatic Dis* 24(3): 674-687.
- Yiannopoulou KG, Anastasiou AI, Kontoangelos K, Papageorgiou C, Anastasiou IP (2020) Cognitive and psychological impacts of different treatment options for prostate cancer: a critical analysis. *Curr Urol* 14(4): 169-177.
- Tian W, Liu Y, Cao C, Zeng Y, Pan Y, et al. (2021) Chronic stress: Impacts on tumor microenvironment and implications for anti-cancer treatments. *Front. Cell Dev. Biol* 9: 777018.
- Zhang L, Pan J, Chen W, Jiang J, Huang J (2020) Chronic stress-induced immune dysregulation in cancer: implications for initiation, progression, metastasis, and treatment. *Am J Cancer Res* 10(5): 1294-1307.
- Faviana P, Boldrini L, Gronchi L, Galli L, Erba P, et al. (2023) Steroid Hormones as Modulators of Emotional Regulation in Male Urogenital Cancers. *Int J Behav Med* 30(6): 836-848.
- Ahmed T, Qassem M, Kyriacou PA (2023) Measuring stress: a review of the current cortisol and dehydroepiandrosterone (DHEA) measurement techniques and considerations for the future of mental health monitoring. *Stress* 26(1): 29-42.
- Schwartz AG (2022) Dehydroepiandrosterone, cancer, and aging. *Aging Dis* 13(2): 423-432.
- Ogino Y, Iguchi T, Miyagawa S (2021) Dehydroepiandrosterone. In *Handbook of Hormones*. Academic Press, pp. 915-916.
- Penning TM, Detlefsen AJ (2020) Intracrinology-revisited and prostate cancer. *J Steroid Biochem Mol Biol* 196: 105499.
- Scarola SJ, Perdomo Trejo JR, Granger ME, Gerecke KM, Bardi M (2019) Immunomodulatory effects of stress and environmental enrichment in Long-Evans rats (*Rattus norvegicus*). *Comp Med* 69(1): 35-47.
- Scarola SJ, Bardi M (2021) Environmental enrichment modulates inflammation during development in Long-Evans rats (*Rattus norvegicus*). *Dev Psychobiol* 63(2): 183-191.

15. Nwachukwu K, Rhoads E, Meek S, Bardi M (2021) Back to nature: herbal treatment, environmental enrichment, and social play can protect against unpredictable chronic stress in Long-Evans rats (*Rattus norvegicus*). *Psychopharmacology (Berl)* 238(10): 2999-3012.
16. Young ES, Doom JR, Farrell AK, Carlson EA, Englund MM, et al. (2021) Life stress and cortisol reactivity: An exploratory analysis of the effects of stress exposure across life on HPA-axis functioning. *Dev Psychopathol* 33(1): 301-312.
17. Duteil F, De Saint Vincent S, Pereira B, Schmidt J, Moustafa F, et al. (2021) DHEA as a biomarker of stress: a systematic review and meta-analysis. *Front Psychiatry* 12: 688367.
18. Nenezic N, Kostic S, Strac DS, Grunauer M, Nenezic D, et al. (2023) Dehydroepiandrosterone (DHEA): Pharmacological effects and potential therapeutic application. *Mini Rev Med Chem* 23(8): 941-952.
19. Hui D, Darke AK, Guthrie KA, Subbiah IM, Unger JM, et al. (2022) Association between health-related quality of life and progression-free survival in patients with advanced cancer: a secondary analysis of SWOG clinical trials. *JCO Oncol Pract* 18(4): e442-se451.
20. Ma Y, Kroemer G (2024) The cancer-immune dialogue in the context of stress. *Nat Rev Immunol* 24(4): 264-281.
21. Chang RB, Beatty GL (2020) The interplay between innate and adaptive immunity in cancer shapes the productivity of cancer immunosurveillance. *J Leukoc Biol* 108(1): 363-376.
22. Sun L, Kees T, Almeida AS, Liu B, He XY, et al. (2021) Activating a collaborative innate-adaptive immune response to control metastasis. *Cancer cell* 39(10): 1361-1374.
23. Boraschi D, Toepfer E, Italiani P (2024) Innate and germline immune memory: specificity and heritability of the ancient immune mechanisms for adaptation and survival. *Front Immunol* 15: 1386578.
24. Zhao Y, Shen M, Wu L, Yang H, Yao Y, et al. (2023) Stromal cells in the tumor microenvironment: accomplices of tumor progression? *Cell Death Dis* 14(9): 587.
25. Li D, Xu W, Chang Y, Xiao Y, He Y, et al. (2023) Advances in landscape and related therapeutic targets of the prostate tumor microenvironment: Therapeutic targets of the prostate tumor microenvironment. *Acta Biochim Biophys Sin (Shanghai)* 55(6): 956-973.
26. Erlandsson A, Lundholm M, Watz J, Bergh A, Petrova E, et al. (2023) Infiltrating immune cells in prostate cancer tissue after androgen deprivation and radiotherapy. *Int J Immunopathol Pharmacol* 37: 03946320231158025.
27. Briukhovetska D, Dorr J, Endres S, Libby P, Dinarello CA, et al. (2021) Interleukins in cancer: from biology to therapy. *Nat Rev Cancer* 21(8): 481-499.
28. Dunn AJ (2000) Cytokine activation of the HPA axis. *Ann N Y Acad Sci* 917(1): 608-617.
29. Bongiovanni B, Diaz A, Santucci N, D'Attilio LD, Bottasso O, et al. (2022) The Immunoregulatory Actions of DHEA in Tuberculosis, A Tool for Therapeutic Intervention? *Front Endocrinol (Lausanne)* 13: 892270.
30. Balan I, Boero G, Chéry SL, McFarland MH, Lopez AG, (2024) Neuroactive Steroids, Toll-like Receptors, and Neuroimmune Regulation: Insights into Their Impact on Neuropsychiatric Disorders. *Life (Basel)* 14(5): 582.
31. Sun Y, Koyama Y, Shimada S (2022) Inflammation from peripheral organs to the brain: how does systemic inflammation cause neuroinflammation? *Front Aging Neurosci* 14: 903455.
32. Mantovani A, Allavena P, Marchesi F, Garlanda C (2022) Macrophages as tools and targets in cancer therapy. *Nat Rev Drug Discov* 21(11): 799-820.
33. Zhao H, Wu L, Yan G, Chen Y, Zhou M, et al. (2021) Inflammation and tumor progression: signaling pathways and targeted intervention. *Signal transduction and targeted therapy* 6(1): 263.
34. Paakinaho V, Palvimo JJ (2021) Genome-wide crosstalk between steroid receptors in breast and prostate cancers. *Endocr Relat Cancer* 28(9): R231-R250.
35. Deb S, Chin MY, Pham S, Adomat H, Hurtado-Coll A, et al. (2021) Steroidogenesis in peripheral and transition zones of human prostate cancer tissue. *Int J Mol Sci* 22(2): 487.
36. Varaprasad GL, Gupta VK, Prasad K, Kim E, Tej MB, et al. (2023) Recent advances and future perspectives in the therapeutics of prostate cancer. *Exp Hematol Oncol* 12(1): 80.
37. Sharpley CF, Bitsika V, Wootten AC, Christie DR (2014) Does resilience 'buffer' against depression in prostate cancer patients? A multi-site replication study. *Eur J Cancer Care* 23(4): 545-552.
38. Groarke A, Curtis R, Skelton J, Groarke JM (2020) Quality of life and adjustment in men with prostate cancer: Interplay of stress, threat and resilience. *Plos one* 15(9): e0239469.
39. Lennartsson AK, Arvidson E, Börjesson M, Jonsdottir IH (2022) DHEA-S production capacity in relation to perceived prolonged stress. *Stress* 25(1): 105-112.
40. Pérez-Neri I, Parra D, Aquino-Miranda G, Coffeen U, Ríos C (2020) Dehydroepiandrosterone increases tonic and phasic dopamine release in the striatum. *Neurosci Lett* 734: 135095.
41. Kim W, Ryan CJ, Zhang L, Youngren J, Wilton J, et al. (2016) Dehydroepiandrosterone (DHEA) in metastatic castration-resistant prostate cancer (mCRPC): Preliminary results from the SU2C/PCF/AACR West Coast Dream Team (WCDDT). *Journal of Clinical Oncology* 34(15).
42. Upmanyu N, Buldan A, Failing K, Scheiner-Bobis G (2020) DHEAS prevents pro-metastatic and proliferative effects of 17 β -estradiol on MCF-7 breast cancer cells. *Biochim Biophys Acta Mol Cell Res* 1867(2): 118600.



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