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Review Article

HORMONAL AXIS IN MALIGNANCY - FROM PATHOGENESIS TO THERAPEUTICS: INSIGHTS FROM MODERN ONCOLOGY AND AYURVEDA

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ABSTRACT

Hormonal regulation is central to cancer pathogenesis, influencing cell proliferation, apoptosis, angiogenesis, and immune surveillance. Dysregulation of endocrine axes-including hypothalamus-pituitary-gonadal (HPG), hypothalamus pituitary adrenal (HPA), hypothalamus-pituitary-thyroid (HPT), and pituitary–liver axes-drives hormone-sensitive malignancies such as breast, prostate, ovarian, thyroid, and liver cancers. Genetic, lifestyle, and environmental factors further modulate hormonal balance and cancer susceptibility. Ayurvedic principles provide a complementary framework, linking *Dosha* imbalance, *Dhatu dushti, Srotorodha,* ama accumulation, and *Ojas kshaya* to endocrine dysfunction. Therapeutic strategies include modern hormone-targeted agents (selective receptor modulators, aromatase inhibitors, androgen blockers, PI3K/mTOR/CDK4/6 inhibitors) and context-specific Ayurvedic herbs (*Ashwagandha, Shatavari, Rasayanas*), emphasizing careful monitoring in hormone-sensitive cancers. Integrating modern oncology with Ayurvedic approaches, along with lifestyle modification, may offer holistic strategies for the prevention and management of endocrine-responsive malignancies.

INTRODUCTION

Hormones, derived from the Greek word *hormon* meaning "to set in motion," are chemical messengers that regulate diverse physiological functions via blood circulation.[1] Their dysregulation is implicated in cancer pathogenesis by promoting proliferation, inhibiting apoptosis, and interacting with oncogenic pathways[2]. Ayurveda, with its concepts of *Agni*, *Doṣas*, *Dhatus*, *Ojas*, and *Srotas*, offers a complementary framework for understanding and modulating hormonal imbalances.

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In Ayurveda, the body's functions are governed by subtle energies and principles. *Vata* is responsible for movement and signaling, similar to neuro-hormones, while *Pitta* governs transformation processes like metabolism hormones. *Kapha* supports growth and nourishment, comparable to insulin and sex steroids[3].

Rasa, the fluid tissue, plays a role in transport like plasma, whereas *Meda,* the fat tissue, is closely linked to insulin regulation. *Śukra* governs reproductive functions, analogous to hormones such as testosterone and estrogen[4]. *Ojas,* the essence of all tissues, mirrors the immune-endocrine axis[5], and *Srota*[6], the bodily channels, are akin to the blood and lymphatic pathways facilitating circulation and communication throughout the body. These principles collectively explain how hormonal balance influences health and disease in Ayurvedic thought.

Hormonal Axes and Cancer Pathogenesis

Hormonal axes play a critical role in cancer pathogenesis through their regulatory influence on growth, metabolism, and differentiation. The hypothalamus–pituitary–gonadal (HPG) axis is strongly implicated in hormone-driven malignancies such as breast, prostate, ovarian, and endometrial cancers, where sex steroids promote tumor initiation and progression.[7] The hypothalamus–pituitary–adrenal (HPA) axis contributes to tumorigenesis in adrenocortical carcinoma and Cushing's tumors by altering cortisol and steroid hormone levels.[8] The pituitary–liver axis, through growth hormone and IGF-1 signaling, has been linked to breast, prostate, colorectal, and lung cancers, driving proliferation and resistance mechanisms[9]. Similarly, the hypothalamus–pituitary–thyroid (HPT) axis plays a role in thyroid cancer and shows associations with breast and liver cancers through dysregulated thyroid hormone signaling.[10] Together, these endocrine pathways highlight the complex interplay between systemic hormonal regulation and cancer development. Hormonal mechanisms in tumorigenesis involve multiple pathways that drive cancer initiation and progression. Estrogen and androgen signalling activate MAPK and PI3K/AKT pathways, promoting uncontrolled cell growth, while simultaneously inhibiting apoptosis through the upregulation of anti-apoptotic genes like Bcl-2 and suppression of pro-apoptotic signals. Hormones also modulate the tumor microenvironment by enhancing inflammation and angiogenesis-estrogen stimulates IL-6 and VEGF production-while androgens impair immune surveillance by suppressing T-cell function11[11]. Additionally, oncogenic crosstalk between pathways such as ER/HER2, AR/PI3K, and Wnt/β-catenin further supports cancer cell survival, proliferation, and therapeutic resistance[12,13]

Risk factors related to hormonal imbalance

Risk factors related to hormonal imbalance play a significant role in cancer susceptibility. Genetic predisposition, such as mutations in BRCA1/2, can amplify cancer risk when combined with elevated hormonal exposure. Lifestyle factors also contribute: obesity increases estrogen levels, promotes insulin resistance, and triggers chronic inflammation; dietary habits, including high-fat intake and alcohol consumption, disrupt hormonal homeostasis; physical activity helps regulate hormonal pathways, whereas chronic stress elevates cortisol, leading to immune suppression. Additionally, environmental exposures to endocrine-disrupting chemicals, such as plastics and pesticides, further increase the risk of hormone-related cancers. Together, these factors highlight the complex interplay between genetics, lifestyle, and the environment in influencing hormonal balance and cancer risk.

Ayurvedic insights into Hormone related cancers

The interplay between endocrine axes and cancer risk can be viewed through both modern and Ayurvedic perspectives. The HPO/HPG axis, regulating sex hormones, is influenced by *Shukra* and *Artava Dhatus*, as well as *Garbhashaya/ Upadhatus*; excessive *Kapha–Meda* imbalance can lead to abnormal tissue proliferation, while estrogen dominance may promote stagnation and neoplasm, similar to Ama accumulation. The HPA axis, associated with stress and cortisol, relates to *Manovaha Srotas* and the balance of *Rajas* and *Tamas;* chronic stress aggravates *Vata–Pitta,* depletes *Ojas*, and lowers immune surveillance, increasing cancer susceptibility. The HPT axis governs thyroid hormones and metabolic *Agni*: hypoactive *Agni* promotes *Kapha* dominance and sluggish metabolism favoring tumor growth, whereas hyperactive *Agni* with *Pitta* predominance may cause cellular injury and inflammatory cancers. Finally, the insulin/IGF axis reflects *Kapha–Meda Dushti* and *Prameha*-like pathology, where chronic *Ama–Kapha* accumulation contributes to metabolic cancers, including those of the breast, pancreas, and colon.

In Ayurvedic understanding, hormonal imbalance in cancer can be conceptualized as a result of *Dosha* imbalance, *Dhatu dushti*, *Srotorodha*, *Ama* accumulation, and *Ojas kshaya*. *Kapha* proliferation, *Pitta* transformation, and *Vata* spread create systemic dysregulation, while specific *dhatu dushti* particularly of *Meda, Rakta, Mamsa*, and *Shukra*- alters tissue metabolism and hormonal homeostasis. *Srotorodha*, or blockage of microchannels, parallels receptor and hormonal axis dysfunction, limiting proper cellular signalling. *Ama* accumulation, representing chronic inflammation and mutagenic metabolites, further disrupts tissue integrity, and *Ojas kshaya,* or depletion of vital essence, impairs immune surveillance. Collectively, these imbalances-*Dushti* of *Dhatus*, *Srotas,* and *Agni*-lead to uncontrolled cell proliferation and tumorigenesis, highlighting the integrative connection between traditional Ayurvedic concepts and modern understanding of hormonal dysregulation in cancer.

Therapeutics Targeting Hormonal Axes

Hormone-targeted therapies work by blocking key pathways that drive tumor growth, including estrogen, androgen, and progesterone receptors, as well as GnRH and signaling pathways like PI3K/AKT /mTOR and CDK4/6. Treatments include drugs such as Tamoxifen, Fulvestrant, and aromatase inhibitors for ER-positive cancers[14]; Enzalutamide, Abiraterone, and LHRH agonists for AR-driven tumors; and Mifepristone for PR-positive cancers.[15,16] Targeted inhibitors like Everolimus, Alpelisib, and CDK4/6 blockers further disrupt tumor signaling. These therapies are used before or after primary treatment to slow or stop hormone-dependent cancer growth[17].

Endocrine-responsive cancers are influenced by hormonal signals and include breast, prostate, ovarian, thyroid, testicular, pancreatic neuroendocrine tumors, pituitary tumors, and liver cancer[18]. Breast cancer affects about one-third of women, with most cases being hormone receptor-positive; factors such as early menarche, late menopause, obesity, inactivity, and hormone therapy increase risk[19]. Prostate cancer, driven by androgens, is the fourth most common cancer worldwide, and mutations in androgen receptors can make treatment challenging[20] . Hormones also play a role in lung cancer, especially in non-smoking women[21], and elevated androgens are linked to higher risk of liver cancer in men and postmenopausal women. Some tumors produce hormones that disrupt the body's metabolism, sometimes revealing hidden cancers early through endocrine paraneoplastic syndromes.

Role of ayurvedic herbs in hormone sensitive cancer

Ayurvedic herbs have gained attention for their potential roles in hormone-sensitive cancers, though their effects can be complex and context-dependent. *Ashwagandha* (*Withania somnifera*) is renowned for its anti-stress, anti-inflammatory, and immune-modulatory properties. Its bioactive compounds, particularly withanolides, may enhance testosterone levels, which could theoretically pose risks in androgen receptor-positive (AR+) prostate cancers [22,23,24,25] On the other hand, *Shatavari* (*Asparagus racemosus*) is rich in phytoestrogens that can mimic estrogen activity. While this raises caution in estrogen receptor-positive (ER+) breast cancers, emerging studies suggest that *Shatavari* may exert beneficial effects in triple-negative breast cancer by reducing cell viability and promoting apoptosis[26]. These contrasting actions underscore the importance of context-specific research and careful consideration before integrating these herbs into cancer management strategies.

Clinical Recommendations

1. Perform thorough evaluation (history, labs: TSH, cortisol, estrogen/testosterone).
2. Avoid prolonged use of hormone-active herbs without monitoring.
3. Prefer *Rasayana* herbs with low hormonal effects (*Triphala, Guduchi, Amalaki, Brahmi*).
4. Monitor mood, weight, menstrual cycles, libido.
5. Educate patients about potential hormonal shifts.
6. Encourage yoga, balanced diet, and sleep hygiene.
7. Discourage self-medication with potent herbs in hormone-sensitive cancers.

DISCUSSION

Hormonal axes are critical regulators of cancer initiation and progression. Dysregulation of the HPG, HPA, HPT, and pituitary–liver axes promotes hormone-driven malignancies, including breast, prostate, ovarian, and thyroid cancers, through activation of proliferative pathways (MAPK, PI3K/AKT), inhibition of apoptosis, angiogenesis, and immune evasion. Crosstalk with oncogenic pathways such as HER2, AR/PI3K, and Wnt/β-catenin further supports tumor survival and therapy resistance.

Lifestyle, genetic, and environmental factors compound hormonal imbalance and cancer risk. Obesity, high-fat diets, alcohol, stress, and endocrine-disrupting chemicals alter estrogen, insulin, and cortisol levels, while mutations such as BRCA1/2 amplify susceptibility. Ayurvedic principles provide a complementary framework, with *dosha* imbalance, *Dhatu dushti, Srotorodha, Ama* accumulation, and *Ojas kshaya* reflecting modern endocrine dysfunction. HPG aligns with *Shukra* and *Artava dhatus*, HPA with stress-induced *Ojas* depletion, and the insulin/IGF axis with *Prameha*-like pathology.

Therapeutically, hormone-targeted agents selective receptor modulators, aromatase inhibitors, androgen blockers, and pathway inhibitors (PI3K, mTOR, CDK4/6) remain central to managing endocrine-responsive cancers. Ayurvedic herbs such as *Ashwagandha, Shatavari*, and *Rasayanas* may offer supportive benefits, though their hormonal effects warrant careful monitoring. Integrating modern oncology with Ayurvedic approaches, alongside lifestyle interventions, may enhance

outcomes and provide holistic strategies for hormone-sensitive malignancies.

CONCLUSION

Hormonal imbalance plays a crucial role in cancer pathogenesis and progression, with modern oncology and Ayurvedic principles converging on the importance of regulating endocrine function. Targeted therapies that block hormonal pathways alongside lifestyle interventions and cautious use of herbal medicine provide a holistic approach to managing hormone-sensitive malignancies.

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