Review article

Thyroid disorders and their association with prostate cancer: a literature review

Trastornos de la tiroides y su asociación con el cáncer de próstata: una revisión de la literatura

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Abstract

The prostate gland comprises epithelial cells with androgen receptors that regulate its cell cycle. Endocrine changes associated with aging become one of the main problems for the development of prostatic disorders such as prostate cancer. Thyroid hormones are a set of hormones responsible for regulating basal and energy metabolism, influencing the cell cycle's regulation, and helping cell proliferation and differentiation. Thyroid disorders, each characterized by a particular biochemical profile, are common in the population, and the evidence accumulated to date suggests them as a risk factor for the development of breast, lung, and colorectal cancer. Regarding prostate cancer, in vitro and clinical studies support that hyperthyroidism, characterized by increased serum concentrations of thyroid hormones and decreased TSH, is considered a risk factor for the development of prostate cancer, increasing the probability of cell immortalization by stimulating gene transcription and uncontrolled proliferation. Therefore, thyroid disorders such as hyperthyroidism should be considered a risk factor for prostate cancer. In younger populations it appears that hypothyroidism with increased TSH concentrations affects prostate cells, increasing the risk of cancer in this population. However, there are fewer studies to support this idea.

Keywords:
thyroid hormones, neoplasm prostatic, prostate cancer, hypothyroidism and hyperthyroidism

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Resumen

La glándula prostática está compuesta por células epiteliales con receptores de andrógenos que regulan su ciclo celular. Los cambios endocrinos asociados con el envejecimiento se convierten en uno de los principales problemas para el desarrollo de trastornos prostáticos como el cáncer de próstata. Las hormonas tiroideas son un conjunto de hormonas responsables de regular el metabolismo basal y energético, influyendo en la regulación del ciclo celular y facilitando la proliferación y diferenciación celular. Los trastornos tiroideos, cada uno caracterizado por un perfil bioquímico particular, son comunes en la población, y la evidencia acumulada hasta la fecha los sugiere como un factor de riesgo para el desarrollo de cáncer de mama, pulmón y colorrectal. En cuanto al cáncer de próstata, estudios in vitro y clínicos respaldan que el hipertiroidismo, caracterizado por un aumento de las concentraciones séricas de hormonas tiroideas y una disminución de la TSH, se considera un factor de riesgo para el desarrollo de cáncer de próstata, aumentando la probabilidad de inmortalización celular al estimular la transcripción génica y la proliferación descontrolada. Por lo tanto, los trastornos tiroideos como el hipertiroidismo deben considerarse un factor de riesgo para el cáncer de próstata. En poblaciones más jóvenes, parece que el hipotiroidismo con concentraciones elevadas de TSH afecta a las células prostáticas, aumentando el riesgo de cáncer en esta población. Sin embargo, existen menos estudios que respalden esta idea.

Palabras clave:
hormonas tiroideas, neoplasia prostática, cáncer de próstata, hipotiroidismo e hipertiroidismo

Introduction

Prostatic disorders are common in 50 % of men over 60 years of age and can be classified into benign prostatic hyperplasia (BPH) and prostate cancer (PCa).[1] PCa is currently the leading cause of malignancy in men and the second-leading cause of cancer worldwide;[2,3] with an average age of diagnosis of 68 years, it is considered a geriatric disease, but with the current demographic changes, that age of diagnosis has decreased considerably.[4,5] Epidemiologically, prostate cancer is the leading cause of urological malignancy in the world, with an average of 1.4 million cases per year by 2023 and a mortality rate of 7.3 %.[2] Latin America is considered an emerging region in terms of PCa cases, with an average of 225,985 cases and a mortality rate close to 8.0 %, the principal countries being Brazil, Mexico, and Colombia, representing 60 % of the cases.[6]

The prostate is a gland responsible for sexual processes, helping in the formation of semen and ejaculation.[7] The organ develops from the urogenital sinus and consists of two main parts: the epithelium and the stroma. The epithelium comprises stem cells, stromal cells, and prostatic progenitors and has receptors for androgens and prostate-specific antigens; these receptors allow the coupling of signals that help maintain organ homeostasis and aid in organ differentiation and play essential roles at the cell cycle level.[8,9] The stroma has different cell types, including smooth muscle cells, fibroblasts, myofibroblasts, and immune cells.[10] Endocrine alterations associated mainly with aging, such as decreased testosterone levels, lead to morphological changes in prostate epithelial cells, reducing the rate of apoptosis and leading to cell enlargement (hyperplasia) and organ size.[11] Most prostate cancers are hormone-dependent, and therefore, their main therapeutic component consists of androgen deprivation therapies, which reduce the size of the tumor and lead to temporary solutions where there may be biochemical relapses.[12]

The thyroid gland is responsible for producing thyroid hormones, which have several functions related to energy metabolism, cell differentiation, and proliferation, and their impact on target cells varies depending on the number of receptors it has, the number of deiodinases, nuclear receptors, and co-regulators.[13] The importance of thyroid hormones in regulating the cell cycle has already been demonstrated, and several studies have proposed an association between thyroid disorders and cancer risk. Krashin *et al.* (2021) found that there is an association between serum levels of free T4 and TSH (patients with hyperthyroidism or hyperthyroidism) with the development of breast and colorectal cancer (HR: 1.3).[14] The effect of thyroid hormones on the prostate is controversial, and several studies have established the association between thyroid disorders as a risk factor for PCa.[13] In vitro studies such as Kotolloshi R. *et al.* (2020) found that induction of T3 in prostate cancer cell culture induces senescence and increases the degree of apoptosis.[15] Some more clinical studies, mainly observational, such as the studies by Ovčariček *et al.* (2020) and Hoption *et al.* (2007), found an association between hyperthyroidism (decreased TSH and increased T4) and the risk of prostate cancer,[16,17] even proposing TSH as a marker for the prevention of prostate cancer in the population. Because of this, this article aimed to review the biological effects and clinical linkage of thyroid hormones, especially thyroid disorders, and their association with PCa. It will also review some aspects of epidemiology and the relationship between thyroid hormones and PCa.

Methods

We conducted a narrative review of the published literature on the effects of thyroid disorders on the risk of developing prostate cancer. Only articles published in English and Spanish were reviewed. The bibliographic search was conducted between June and July 2024. Original studies, mainly observational studies, were included, and the STROBE metric was applied to assess their quality and select them. Studies conducted in vitro to see the effect of thyroid hormones on prostate cancer cell lines were also included. The statistical analysis of the studies, the differences achieved, the number of participants, and the ethical guidelines

applied were considered. The PubMed, Science Direct, Google Scholar, and SciELO databases were searched. The following MeSH terms and combinations of keywords were used: thyroid hormones, prostatic neoplasm, prostate cancer, hypothyroidism, and hyperthyroidism.

Epidemiology and risk factors in prostate cancer: A disease on the rise

Epidemiologically, prostate cancer ranks as the leading cause of malignancy in men and the second in the world, with an average of 1.4 million cases per year, representing 53.8 % of all cases of urological cancers and 7.3 % of all cancer cases by 2023.[2,3,18] Currently, it is the most frequent type of cancer in 112 out of 185 countries, second only to breast cancer, and it is the leading cause of death for cancer in a quarter of the countries, being the first in 48 out of 185 countries, by 2022.[2,18] Latin America and the Caribbean is the 4th region in the world with the highest number of cases, surpassed by Europe, Asia, and North America, but with a mortality rate close to 16 %, making it the third deadliest region in the world.[6] Demographic changes, emigration, and lifestyle changes have increased the number of cases in Latin America, estimating an incidence rate of 14.4 cases per 100,000 inhabitants for the next five years, with prostate cancer as the primary malignancy in the region, with an estimated 225,985 cases by 2023 and a mortality rate of 8.1 % [6,19].[6,19] In the area, the countries reporting the highest number of cases are Brazil, with 51.5 % of cases, followed by Mexico, with 13.4 %, and Colombia, with 8.3 % of all prostate cancer cases. As for mortality, it maintains the same behavior as Brazil in first place, with 39.2 % of deaths, followed by Mexico with 14.7 %, and Colombia with 8.6 % in third place.[5,6,19]

The increase in incidence rates in mainly Western countries has led to research into modifiable and non-modifiable risk factors that can prevent the onset of cancer and the problems it causes. The systematic review by Bergengren *et al.* (2022) evaluated the information available to date on risk factors associated with prostate cancer, finding among the non-modifiable risk factors: first,[20] age (finding that the risk increases by 18 % when over 70 years of age), family history (2.5 % risk) and genetic predisposition (with a risk of 58 %).[18,21] Among the modifiable factors are weight, diet (mainly Mediterranean diet), and the development of regular physical activity that decreases inflammation of the prostatic microenvironment.[22] Other studies that have sought to identify modifiable factors include Loh *et al.* (2020), which found that obesity and metabolic disorders offer a risk for the development of PCa and that their improvement through the performance of regular sport.[23] The combination of modifiable and non-modifiable factors, together with screening programs, reduces the risk of developing prostate cancer or allows early detection of prostate cancer, reducing the risk of complications such as metastasis, premature death, and disability.

The prostate and prostate cancer

The prostate is a gland located at the back of the bladder and is responsible for producing secretions that complement semen and ejaculate during sexual intercourse. It is anatomically divided into three regions: central, peripheral, and transitional. Like other glands, the prostate

comprises an epithelium and a stroma, each with epithelial cells, immune cells, and prostatic progenitors, among others, dependent on androgens to ensure its homeostasis and control the cell cycle.[7,24,25] The prostate is a gland dependent on androgens for its differentiation, and being part of the male genital system, testosterone is the primary androgen in charge of its homeostasis process. Relevant endocrine alterations associated with aging, such as a decrease in testosterone concentrations, influence the development of prostate cancer.[26]

Although about 95 % of PCa cases correspond to adenocarcinoma (with 80 % being of acinar origin and the remaining 20 % being of acinar origin,[24] several studies have demonstrated a relevant genomic heterogeneity that has relevant clinical implications such as resistance to treatment and castration, as well as increased risk of metastasis; this has even led to the formation of two cancer cell lines in prostate cancer patients, complicating the treatments associated with it.[27] The high genetic heterogeneity of prostate cancer has led to the reformulation of the different treatment modalities; for example, if it is of epithelial origin, androgen deprivation or hormonal therapy is the best option since this set of cells has receptors for androgens.[28] Prostate cancer that has mainly affected the integrity of the genitourinary organs, providing problems such as urinary incontinence, erectile dysfunction, and pelvic pain.[29,30] In more advanced conditions, prostate cancer produces metastasis affecting mainly bone and, to a lesser extent, liver and lung.[31]

Biological interactions of thyroid hormones in prostatic cells

The thyroid gland, located in the anterior part of the thyroid cartilage, produces thyroid hormones, mainly tetraiodothyronine (T4) and triiodothyronine (T3). Physiologically, the control of thyroid hormones is regulated by the hypothalamic-pituitary axis, where hormones such as thyroid stimulating hormone (TSH) are produced, which is responsible for regulating the production of thyroid hormones by stimulating the gland and controlling the concentrations of these hormones in the peripheral blood.[32] The evaluation of thyroid disorders is done with clinical examination and laboratory measurement of the so-called thyroid profile where the concentrations of TSH, T3, and T4 are measured, as are their free fractions (FT3 and FT4), the evaluation of the set of hormones allows the inference about the thyroid problem and the clinical assessment is done with the confirmation of the same.[33]

The effects of thyroid hormones on target tissues are determined by factors controlling their bioavailability and signaling, such as transporters, integrins, desiodases, nuclear receptors, and co-regulators. Circulating levels of hormones and their transporters determine the serum's free hormone/total hormone ratio. At the same time, the entry of T4 and/or T3 into tissues and the desiodase enzyme system regulate the generation or inactivation of thyroid hormones.[34] As for basic science studies, several studies have shown that thyroid hormones affect cell cultures in vitro. Aksoy *et al.* (2021) found that regulating the μ-crystallin protein (CYMR) responsible for regulating thyroid hormone concentrations intracellularly in prostatic cells and its inactivity is linked to pro-

cesses of increased aggressiveness by cancer cells, becoming a critical regulatory point.[35]

Miro *et al.* (2022) showed that thyroid hormones, significantly an increase in the concentration of T3 and T4, stimulate the proliferation of prostate cancer epithelial cells, increasing the degree of inflammation of the microenvironment, their resistance to apoptosis and the risk of immortalization.[36] Other studies have evaluated the effect of other thyroid profile hormones in prostate cancer, such as Kotolloshi R. (2020), which showed that TSH directly influences senescence and increases the degree of apoptosis in PCa cell lines, becoming a marker of protection (hypothyroidism).[37] Therefore, increased thyroid hormones in vitro regulate the cell cycle of PCa cells and directly influence the risk of prostate cancer development and should be considered as a risk factor.

Thyroid disorders and prostate cancer: Accumulating evidence

Thyroid disorders are classified according to the biochemical behavior of the patients' thyroid profiles (TSH, T4, and T3 concentrations), classifying them into hypothyroidism (decrease of thyroid hormones), hyperthyroidism (increase of thyroid hormones) and euthyroidism (average TSH and thyroid hormone concentration).[38] The relationship between cancer and thyroid disorders has already been demonstrated in other malignancies. For example, Ma *et al.* (2023), in a retrospective cohort study, show that thyroid alterations such as decreased TSH concentrations and increased T4 (hyperthyroidism), with reduced fT3, are related to lung cancer and allow its staging process.[39] Sohn *et al.* (2020) have associated thyroid disorders such as decreased serum FT4, increased risk of liver cancer, and increased mortality compared to other patients who have malignancy but not thyroid disorders.[40] Jha *et al.* (2021) found a statistically significant association between women with hypothyroidism and the risk of developing breast cancer, as well as an increased risk of metastasis.[41]

Regarding prostate cancer, various studies sought the association between thyroid disorders and the risk of developing prostate cancer. Most studies published to date establish that hyperthyroidism is the leading risk factor for the development of prostate cancer, with a biochemical profile of decreased TSH and elevated T4. Krashin *et al.* (2021) conducted an analysis in an Israeli population with thyroid problems, finding a statistically significant association between hyperthyroidism and the development of breast, lung, and prostate cancer.[14] Ovčariček *et al.* (2020) found that even thyroid abnormalities not only influence the risk of developing prostate cancer but also the degree of histological differentiation of the tumor. Patients with hyperthyroidism have a higher Gleason score than euthyroid patients with PCa, with a higher risk of metastasis and complete involvement of the gland and bladder, proposing the evaluation of thyroid function as a risk factor.[16] Similar results have been found by other researchers, such as Khan *et al.* (2016) and Hoption *et al.* (2007), where the decrease in TSH and the increase mainly in serum concentrations of T4 and fT4, becoming serum risk markers for other types of malignancies **(Table 1).**[17,42]

Table 1. Characteristi¡cs of the included studies

Study	Number of Participants	Thyroid disorders	Altered thyroid profile	Conclusion on prostate cancer risk	Age range	P (<0.05)
Krashin *et al.* (2021).[14]	375 635	Hyperthyroidism Subclinical Hyperthyroidism	Elevated T4 Decreased TSH	Increase	< 50	0.0047
Ovčaričeк *et al.* (2020).[16]	140	Hyperthyroidism	Elevated T3	Increases risk of tumor differentiation	>60	<0.001
Khan *et al.* (2016).[39]	10.384	Hyperthyroidism	Elevated T4 Decreased TSH	Increase	>60	0.006
Mondul *et al.* (2012).[42])	29,133	Hypothyroidism	Elevated TSH	Decrease	>60	0.12
Hoption *et al.* (2007).[17]	1452	Hyperthyroidism	Elevated T4 Decreased TSH	Increase	>60	0.047
Chan *et al.* (2017).[41]	3649	Hyperthyroidism	Elevated T4 Decreased TSH	Increase	> 60	0.005
Hellevik *et al.* (2009).[40]	29,691	Hyperthyroidism	Decreased TSH	Increase	< 60	<0.001
Díez *et al.* (2022).[43]	2,414,165	Hypothyroidism	Elevated TSH	Increase	15-64	0.0095
Díez *et al.* (2023).[44]	506,749	Hypothyroidism	Elevated TSH	Depending on age, the risk varies	> 60 < 60	0.011
Liu *et al.* (2023).[45]	11,590	Hypothyroidism	Elevated TSH	Increase	<65	<0.001
Riss *et al.* (2023).[46]	96,825	Hypothyroidism	Elevated TSH	Decrease	> 65	0.84

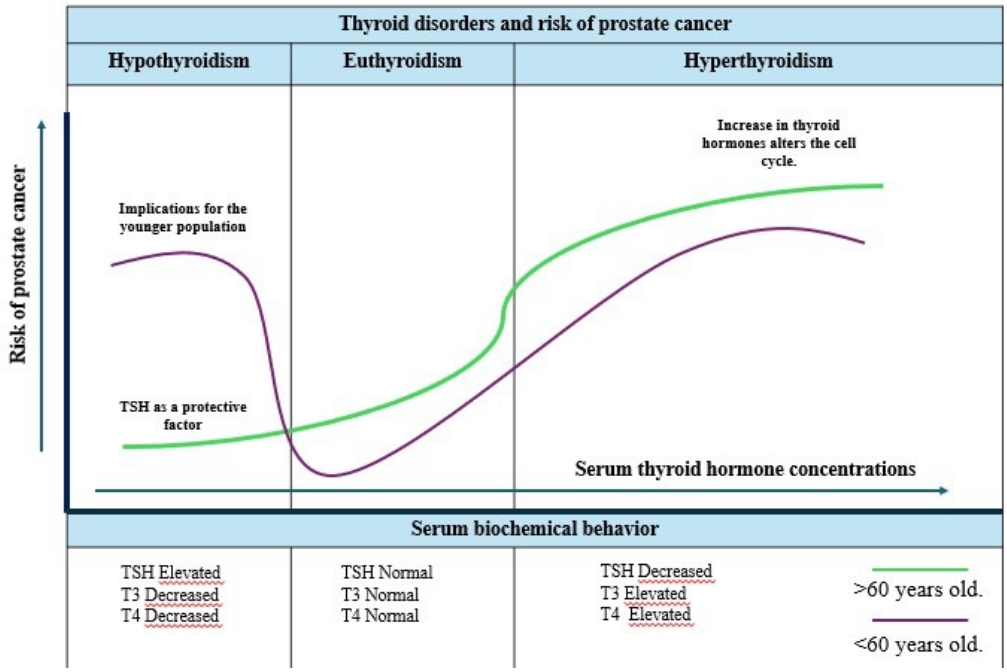
Chan *et al.* (2017) and Hellevik *et al.* (2009) also found similar results regarding the thyroid profile, with hyperthyroidism being the leading risk factor for the development of prostate cancer in patients over 60 years of age, with a decrease in TSH.[43,44] Regarding hypothyroidism, the number of studies published so far differs in the conclusions of the results obtained. Mondul *et al.* (2012) established in their study in which 29,133 people participated in a population with an average age greater than 60 years that the increase in TSH levels and the decrease in thyroid hormone levels reduce the risk of suffering from prostate cancer compared to individuals who have a hypothyroid biochemical profile.[45] Similar results were obtained in the study by Riss *et al.* (2023) in a Danish population of about 96,825 people with hypothyroidism, and no association was found for the risk of developing prostate cancer.[46]

On the other hand, Díez *et al.* (2022), in which hypothyroidism did present a risk for

the development of prostate cancer but with the particularity that this risk is higher in patients under 64 years of age, having statistical differences in the group from 15 to 64 years of age (p> 0.0001), being a smaller population but with a more significant number of cases of hypothyroidism. The same authors analyzed in 2023 a population with hypothyroidism, reaffirming those mentioned above. There is a particular behavior in patients younger than 60 years, increasing the risk of PCa in this group. A randomized study conducted by Lui *et al.* (2023) in more than 10,000 individuals with endocrine disorders found that hypothyroidism is associated with an increased risk of prostate cancer in a population with an average age of less than 65 years.

Most of the studies reported so far propose hyperthyroidism as the central thyroid disorder that poses a risk for the development of prostate cancer. The thyroid profile, where there is a decrease in serum TSH concentrations and an increase in the concentration of thyroid hormones, affects the cell cycle of prostate cells and can be considered an essential element of evaluation and medical surveillance. As for hypothyroidism, it seems that it has a different behavior. The studies evaluated in this literature review show that it increases the risk of developing prostate cancer in patients with a younger age than the average age of common diagnosis of prostate cancer; this presents a particular epidemiological behavior that leads to the formulation of screening systems according to this **(Figure 1).**

Figure 1. The relationship between thyroid disorders and prostate cancer risk



Conclusion

Thyroid disorders directly influence the risk of developing prostate cancer. The evidence accumulated and published so far, both in vitro and observational studies, showed that a hyperthyroid profile, characterized by a decrease in TSH concentrations and an increase in T3 and T4 hormones, influences the regulation of the cell cycle of prostatic epithelial cells and therefore increases the risk of uncontrolled proliferation that can lead to the development of a tumor with a particular degree of differentiation. Thus, hyperthyroidism should be considered as a risk factor for prostate cancer. As for hypothyroidism, it appears to have a greater effect on a younger population with a lower average age of diagnosis than usual for prostate cancer.

Conflict of interest

None of the authors have any conflicts of interest.

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