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Research Article

Thyroid Dysfunction as A Hormonal Aspect of The Pathogenesis of Colorectal Cancer

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Abstract:

Background

Studies show a link between thyroid hormones and cancer development, but their role remains unclear, and colorectal cancer (CRC) is an example.

Material & Methods

Our study's purpose was to examine the manifestations of thyroid dysfunction in patients with CRC. We have selected publications from popular databases for 2019-2024.

Results

The thyroid hormone (TH) levels studies show that, in addition to their biological significance in metabolism and growth, they can influence cancer outcome. Articles point to the cancer-stimulating effect of thyroid hormones. avß3-integrin is of particular importance in the progression of CRC and poor survival.

Conclusions

We concluded that cancer is sensitive to thyroid hormone changes. However, the complex relationships between TG and cancer do not yet allow us to draw unambiguous conclusions about TG as activators or suppressors of tumors. The thyroid dysfunction's influence on cancer requires further research, which may open up new horizons in cancer treatment.

keywords: colorectal cancer; thyroid dysfunction; hyperthyroidism; hypothyroidism; thyroid hormones

Abbreviations

AKT - protein kinase B

CRC – colorectal cancer

D1 - deiodinase type 1

D2 - deiodinase type 2

D3 - deiodinase type 3

ER - estrogen receptor

ERα - estrogen receptor alpha

ERβ - estrogen receptor beta

ERK1/2 - extracellular signal-regulated kinase 1/2

PI3K - phosphatidylinositol 3-kinase

TH – thyroid hormones

TRH - thyrotropin-releasing hormone

TRα - thyroid hormone receptors alpha

TRβ - thyroid hormone receptors beta

TSH - thyroid stimulating hormone

T4 – tetraiodothyronine

T3 - triiodothyronine

Introduction

Modern oncological practice underestimates the role of endocrine glands in the process of carcinogenesis. In many ways, the unpopularity of the endocrine environment in the tactics of managing a cancer patient is associated with the prejudice that in the case of tumor growth and cancer intoxication, in addition to glucose and insulin, tumor growth, for example, adenocarcinoma, is of no importance. At the same time, tumor growth itself reformats metabolism with the shutdown or perversion of the hormonal activity of the endocrine glands. It is believed that antitumor drugs completely turn off the thyroid or gonads indirectly through hepato-depression, or directly on the excretory function of the glandular systems. But this underestimation pushes into the shadows information about the state of the endocrine glands in a patient with adenocarcinoma, for example, colorectal cancer. The emerging situation only "artificially" hides possible solutions in case of unsuccessful management tactics, and makes the solutions more mysterious in case of cancer recurrence. In this regard, we believe that in a patient with tumor activity it is necessary to take into account the role of the endocrine organs.

Materials and methods

The aim of our study was to examine the manifestations of thyroid dysfunction in patients with CRC. Due to the fact that there is no consensus on its dysfunction and the course of pathology at different stages and types of cancer, although any phenomenon in the body develops according to the rules, we set the task of analyzing literature data based on the opinion of specialists and researchers to determine the role of the thyroid gland in carcinogenesis. To search for literature, we used the most reliable databases: PubMed/Medline, semanticscholar.org, scholar.google.com. The first filter applied for selecting studies was the publication period from 1990 to 2024. Subsequently, all articles obtained by searching, were transferred to the Rayyan platform. The Rayyan platform allowed us to significantly simplify the selection of the necessary publications and exclude duplicate studies. To search for literature sources, we used the following words and phrases: "cancer", "colorectal cancer", "hypothyroidism", "hyperthyroidism", "thyroid hormones", "biological mechanism".

Results

Thyroid hormones are key regulators of fundamental cellular processes including proliferation, differentiation, apoptosis, and metabolism. Hypothalamic thyrotropin-releasing hormone (TRH) activates the pituitary gland to synthesize and secrete thyroid stimulating hormone (TSH), which in turn acts on the thyroid gland to stimulate the synthesis and secretion of thyroid hormones (TH). Tetraiodothyronine (T4), the main hormone synthesized in the thyroid gland, is catalyzed to triiodothyronine (T3) by specific iodothyronine deiodinases. T3 acts as a major metabolic agent through the formation of complexes between T3 and the nuclear thyroid hormone receptors alpha (TRα) and beta (TRβ). This T3-receptor complex within the cell nucleus binds to thyroid hormone response elements on specific genes, regulating their transcription. Diseases associated with excess TH (hyperthyroidism) and deficiency of TH (hypothyroidism) are widespread and manifest with distinct clinical symptoms [1]. In addition to the biological significance of TH in metabolism and growth, there is evidence that they may influence the clinical outcome of cancer as well as individual human lifespan [2]. The existence of a link between thyroid hormones and malignancy has been supported by numerous clinical studies showing that hypothyroidism suppresses tumor growth, whereas hyperthyroidism has the opposite effect [3, 4]. In recent decades, many studies have been conducted to determine how thyroid hormones exert their growth-promoting effects [1, 5]. Thyroid hormones mediate their effects on cancer cells through several nongenomic pathways, including activation of the membrane receptor for TH integrin αvβ3 [6, 7]. This receptor has been shown to contain two distinct hormone-binding sites, S1 and S2, each of which mediates unique signaling cascades. Only T3 at physiological concentrations can bind to S1, triggering phosphorylation and activation of the phosphatidylinositol 3-kinase (PI3K) pathway, which promotes cell proliferation and inhibits apoptosis; a second site, S2, binds T4 and has a lower affinity for T3, triggering oncogenic extracellular signal-regulated kinase 1/2 (ERK1/2), promoting a similar side effect while stimulating angiogenesis and the expression of fibroblast growth factor 2, components that are required for rapid tumorigenesis [1, 8, 16]. Binding of integrin αvβ3 promotes the proliferative effects of hormones on cancer cells as well as on blood vessel cells [1, 7, 9]. This ability may be important in various types of cancer, and because malignant cells express higher amounts of integrin αvβ3 compared to normal cells [10]. L ' Heureux A. , Wieland D. R. et al noted that TRβ1 may play a tumor suppressor role in the progression of malignancies. Conversely, overexpression of the thyroid hormone receptor TRα1 appears to be associated with accelerated tumor initiation and progression [11]. Numerous in vitro, in vivo and population studies have demonstrated the cancer-promoting effects of triiodothyronine and thyroxine. They have been shown to mediate tumor growth, proliferation and progression. In addition, hyperthyroidism is also associated with a worse prognosis for cancer development [12]. However, it is very important to take into account the fact that circulating TH levels do not necessarily reflect intracellular levels of these hormones due to the existence of many factors that control intracellular TH levels:

- the number of blood TH transporters may increase/decrease, which affects the actual concentration of free hormones that can enter cells;
- Membrane carriers of TH can be subject to up- or down-regulation, which affects the rate of hormone entry into cells and, as a consequence, also the amount of extracellular hormone that can interact with membrane receptors and trigger intracellular signal transduction pathways.

Thus, general hypo- /hyperthyroidism assessed based on circulating TH levels may provide information that does not correspond to the real intracellular situation [10].

The influence of hormone levels on the incidence of colorectal cancer

Du Q., Zheng Z. et al. found that genetically predicted hyperthyroidism, hypothyroidism, TSH, and T4 were not associated with the risk of CRC (all p>0.05). Stratified analysis showed that their basal metabolic level was significantly associated with colon cancer (OR=1.33, p=0.0074), but not with rectal cancer. Inverse analysis did not reveal an effect of CRC on thyroid function (all p>0.05) [13]. Therefore, the authors concluded that thyroid function changes in relation to CRC occur primarily (i.e., before tumor occurrence), and TH level does not affect the risk of CRC. However, Gagliardi F., Baldini E. et al. suggested that CRC may determine the onset of low T3 syndrome and that decreased peripheral deiodinase type 2 (D2) -mediated conversion of T4 to T3 (regulates local thyroid hormone levels) [14, 15, 16] may be a crucial event. The loss of muscle mass that occurs in cachexia and the subsequent decrease in deiodination (the removal of an iodine atom), as well as the liver injury caused by tumor spread with subsequent impairment of deiodination mediated by deiodinase type 1 (D1)-mediated deiodination (responsible for the salvage of iodine in TH synthesis) [17, 18, 19] may be considered as pathological mechanisms occurring in patients with metastatic CRC. Based on the correlation between altered peripheral deiodination and worse clinical outcome, the authors concluded that the prognostic value of the free T3/free T4 ratio can be taken into account in the assessment of prognostic indicators aimed at assessing life expectancy in patients with metastatic CRC. A correlation between low T3 syndrome and poor clinical outcome was found in patients with hematological, lung, and brain tumors. The authors also found that a state of intracellular hypothyroidism, caused by either decreased expression and/or function of specific nuclear receptors TRβ1 or decreased availability of T3, may contribute to the progression of CRC [21, 22]. Thus, the authors found a significantly higher prevalence of CRC in patients with subclinical hypothyroidism compared to patients with a euthyroid state [22]. As reported above, T4 binding to integrin αvβ3 induces the expression of genes involved in colorectal cancer cell proliferation [7, 9]. T4 activates integrin αvβ3 at physiological concentrations of free hormone, whereas supraphysiological serum levels of the hormone are required to trigger integrin-dependent cell proliferation under the influence of T3 [7]. Estrogens also influence cellular functions by binding to two nuclear estrogen receptors (ER): estrogen receptors alpha (ERα) and beta (ERβ). Like TH, estrogens can influence cellular functions by binding to receptors located either on the cell plasma membrane or on the nuclear membrane. Two ERs have been reported to exert opposing effects on CRC cells: ERα stimulates the ERK/MAPK and PI3K/AKT pathways, resulting in increased colon cancer cell proliferation, and ERβ induces apoptosis of malignant colon cells via the p38/MAPK pathway and caspase 3 activation. Although ERβ is the predominant estrogen receptor in normal colonic epithelium, its expression is often downregulated or abolished during CRC progression, suggesting that estrogen signaling may play a role in disease development. THs have been shown to increase ER expression, and T4, via the integrin receptor αvβ3, can activate MAPK-mediated phosphorylation of nuclear ERα; this phosphorylation influences the ability of ER to interact with chromatin, recruit coregulators, and modulate gene expression even in the absence of estrogen [22]. Asbaghi O., Shimi G. et al. did not find a significant association between hypothyroidism and the risk of developing CRC. Also, in their review, no significant association was found between hyperthyroidism and the risk of developing CRC. In addition, significant associations were found between hypothyroidism and the risk of developing CRC in studies in the Far East, between hyperthyroidism and the risk of CRC in the Middle East, and in studies with a small sample size [23], therefore, it can be assumed that climatic and ethnic factors play a role in the association between hypothyroidism and the risk of developing CRC. Gómez-Izquierdo J., Filion K. B. et al. concluded that subclinical hypothyroidism is associated with an increased risk of cancer incidence, especially colorectal cancer and thyroid cancer, and cancer-related mortality [24]. In colorectal cancer, two additional nuclear receptors with antagonistic effects are involved: TRα1 and TRβ1. Thyroid hormones act on TRα1 to stimulate β-catenin, which induces cell proliferation in the colon. Conversely, TRβ1 blocks cell proliferation when activated by thyroid hormones. Thus, lack of TRβ1 expression is associated with malignant transformation of colon cancer [24]. Furthermore, it has been shown that TH contribute to the depletion of CRC stem cells. The study, presented in L' Heureux A. et al. provide a potential mechanism for the feedback observed in hyperthyroid patients; in their xenografts and in models In vitro, T3-treated CRC stem cells had significantly reduced self-renewal capacity; decreased nuclear β-catenin accumulation; and increased sensitivity to treatment, particularly when deiodinase type 3 (D3) was inhibited [11]. Intracellular T3 may have antitumor properties because it induces differentiation of CRC stem cells [11]. As for T4, its nongenomic action through binding to integrin αVβ3 promotes nuclear β-catenin accumulation and T4 dose-dependently promotes cell viability in CRC cell lines. Therefore, there may be a potential mechanism by which low free T4 levels in primary hypothyroidism may protect against CRC by reducing integrin interaction [11]. Schiera G., Di Liegro C. M. et al. suggest that hypothyroidism correlates with an increased risk of CRC and hepatocellular carcinoma. In particular, THs may control the balance between proliferation and differentiation of CRC stem cells, inducing differentiation and reducing growth, thus acting as an anticancer agent [10].

Discussion

Thyroid function in oncology is today considered an ambiguous phenomenon. There is no consensus on its dysfunction and the course of pathology at different stages and types of cancer, although any phenomenon in the body develops naturally. By avoiding the assessment of endocrine disorders, their observation and analysis, we may be slowing down the development of oncology and supporting existing scientific results. It has long been generally accepted that thyroid hormones are key regulators of basic processes in cells, including cell proliferation, differentiation, apoptosis, and metabolism. However, the question of a similar effect of TH on cancer remains. At the same time, there is already data on the effect of thyroid hormones on the clinical outcome of cancer. However, the mechanisms of influence are different [6]. On the one hand, thyroid hormones mediate their effect on cancer cells through several non-genomic pathways, including activation of the membrane receptor for TH integrin αvβ3. Binding of the latter promotes proliferation of cancer cells [1]. At the same time, malignant cells express a higher amount of integrin αvβ3 compared to normal cells [4]. Most importantly, a chain of interactions is formed that is realized in various types of cancer. The relationship between thyroid function and the risk of developing CRC is also indicated by the binding of T4 to integrin αvβ3, which induces the expression of genes involved in the proliferation of CRC cells. Speaking of T4, there may be a potential mechanism by which low levels of free T4

in primary hypothyroidism can protect against CRC by reducing interaction with integrin [3]. Schiera G., Di Liegro C.M et al. suggested that hypothyroidism correlates with an increased risk of CRC and hepatocellular carcinoma. In particular, TH may control the balance between proliferation and differentiation of CRC stem cells, inducing differentiation and reducing growth, thus acting as an anticancer agent [10]. On the other hand, genetically predicted hyperthyroidism, hypothyroidism, TSH, and FT4 were found to be unrelated to CRC risk, and inverse analysis, no effect of CRC on thyroid function was found [13].

However, the reduction in peripheral T4 to T3 conversion by D2 [12, 15] may be a critical event, and CRC may determine the onset of low T3 syndrome. Subsequent reduction in D1-mediated deiodination [8, 18, 19] is still considered as a pathological mechanism occurring in patients with metastatic CRC. Further supporting the debate about the state of intracellular hypothyroidism, decreased expression and/or function of specific nuclear receptors THRβ1, or decreased availability of T3, which may contribute to the progression of CRC, confirms the significantly higher prevalence of CRC in patients with subclinical hypothyroidism compared to patients with a euthyroid state [22]. Interestingly, in the absence of data on a significant association between hyperthyroidism and the risk of developing CRC, the authors (Gómez-Izquierdo J., Filion KB et al.) conclude that subclinical hypothyroidism is associated with an increased risk of cancer incidence, especially CRC and thyroid cancer, as well as cancer-related mortality [24]. And they prove that in CRC, the absence of TRβ1 expression is associated with malignant transformation of colon cancer [24]. In view of this, it is possible that changes in thyroid function in relation to CRC occur primarily (i.e., before the tumor develops), and the TH level does not affect the risk of CRC. TSH, TH, integrin αvβ3, and deiodinases are involved in cancer proliferation. CRC has high levels of integrin αvβ3-expressing tumor vasculature and is associated with significantly lower disease-free and overall survival compared with patients with low levels of integrin αvβ3 in tumor vasculature [20]. Based on these observations, Liu Y. C., Yeh C. T., et al. suggest that thyroid hormones not only modulate CRC progression through cell surface integrin αvβ3, but also that integrin αvβ3 acts as a prognostic indicator for colon carcinoma. D3 is also involved in CRC progression and has been reported to promote the development of human colon adenoma and adenocarcinoma compared with healthy surrounding mucosa. The β-catenin/T-cell factor complex activated in CRC stimulates D3 expression and T3-induced CRC cell proliferation [20].

Conclusions

Currently available clinical and experimental data provide conflicting results regarding the ability of TH to influence CRC progression. Although some studies have shown that cancer is sensitive to changes in thyroid hormone levels, both when it occurs after the tumor has developed and before. However, the complex and multidirectional links between TH and cancer do not yet allow us to draw firm conclusions about TH as activators or suppressors of cancerous tumors. We assume that the contradictory data are related to complex interactions of thyroid hormones and their receptors in normal and neoplastic colorectal tissues. However, most researchers are inclined to believe that hypothyroidism contributes to the progression of CRC. However, the mechanisms of the influence of hypothyroidism on the progression of CRC are also still unclear and require further research. We aim to decipher and study the underlying cause of the pathogenetic interaction between CRC and thyroid dysfunction. We believe that clarifying this issue and including reasonable correction of thyroid hormone levels in patients with CRC may improve the quality of early cancer diagnosis and treatment outcomes by increasing life expectancy.

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Competing interests

The authors declare that they have no financial or non-financial competing interests.

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References

1. Krashin E, Piekiełko-Witkowska A, Ellis M, et al: (2019). Thyroid Hormones and Cancer: A Comprehensive Review of Preclinical and Clinical Studies. *Front Endocrinol (Lausanne)*.;10: 59.
2. Gauthier BR, Sola- García A, Caliz -Molina MÁ, et al: (2020). Thyroid hormones in diabetes, cancer, and aging. *Aging Cell*. ;19[11]: e13260.
3. Cayrol F, Sterle HA, Montesinos MDM (2023). Editorial: Thyroid hormone actions in cancer. Front Endocrinol (Lausanne). May 25;14: 1219871. https://doi.org/10.3389/fendo.2023.1219871
4. Winder M, Kosztyła Z, Boral A, et al: (2022). The Impact of Iodine Concentration Disorders on Health and Cancer. Nutrients. May 26;14[11]: 2209. https://doi.org/10.3390/nu14112209
5. Deligiorgi MV, Trafalis DT (2022). The Clinical Relevance of Hypothyroidism in Patients with Solid Non-Thyroid Cancer: A Tantalizing Conundrum. *J Clin Med*. ;11[12]: 3417.
6. Davis PJ, Ashur -Fabian O, Incerpi S, et al: (2019). Editorial: Non-Genomic Actions of Thyroid Hormones in Cancer. *Front Endocrinol (Lausanne).*;10: 847.
7. Schmohl KA, Han Y, Tutter M, et al: (2020). Integrin α v β 3-dependent thyroid hormone effects on tumor proliferation and vascularization . *Endocr Relat Cancer*.;27[12]: 685-697.
8. Lasa M, Contreras-Jurado C, et al: (2022). Thyroid hormones act as modulators of inflammation through their nuclear receptors. *Front Endocrinol (Lausanne)*.;13: 937099.
9. Schmohl KA, Mueller AM, Dohmann M, et al: (2019). Integrin α v β 3-Mediated Effects of Thyroid Hormones on Mesenchymal Stem Cells in Tumor Angiogenesis. *Thyroid*.;29[12): 1843-1857.
10. Schiera G, Di Liegro CM, Di Liegro I (2021). Involvement of Thyroid Hormones in Brain Development and Cancer. *Cancers (Basel)*. ;13[11]: 2693.

11. L'Heureux A, Wieland DR, Weng CH, et al: (2019). Association Between Thyroid Disorders and Colorectal Cancer Risk in Adult Patients in Taiwan. *JAMA Netw Open*.;2[5]: e193755.
12. Petranovic Ovčariček P, Verburg FA, Hoffmann M, et al: (2021). Higher thyroid hormone levels and cancer. *Eur J Nucl Med Mol Imaging*.;48[3]: 808-821.
13. Du Q, Zheng Z, Wang Y, et al: (2023). Genetically predicted thyroid function and risk of colorectal cancer: a bidirectional Mendelian randomization study. *J Cancer Res Clin Oncol*.;149[15]: 14015-14024.
14. Deng Y, Han Y, Gao S, et al: (2023). The Physiological Functions and Polymorphisms of Type II Deiodinase. Endocrinol Metab (Seoul).;38[2]: 190-202.
15. Aranda A (2021). MicroRNAs and thyroid hormone action. *Mol Cell Endocrinol*.;525: 111175.
16. Kojima Y, Kondo Y, Fujishita T, et al: (2019). Stromal iodothyronine deiodinase 2 (DIO2) promotes the growth of intestinal tumors in Apc Δ 716 mutant mice. *Cancer Sci*.;110[8]: 2520-2528.
17. Rodriguez-Ruiz A, Braun D, Pflug S, et al: (2022). Insights into the Mechanism of Human Deiodinase 1. *Int J Mol Sci*;23[10]: 5361.
18. Angela De Stefano M, Porcelli T, Schlumberger M, et al: (2023). Deiodinases in thyroid tumorigenesis. *Endocr Relat Cancer*.;30[5]: e230015.
19. Nappi A, De Stefano MA, Dentice M, et al: (2021). Deiodinases and Cancer. *Endocrinology*.;162[4]: bqab016.
20. Liu YC, Yeh CT, Lin KH: (2019). Molecular Functions of Thyroid Hormone Signaling in Regulation of Cancer Progression and Anti-Apoptosis. *Int J Mol Sci*.;20[20]: 4986.
21. Shimi G, Zand H, Pourvali K, et al: (2021). Colorectal cancer causes alteration of thyroid hormone profile in newly diagnosed patients. *Expert Rev Endocrinol Metab*. ;16[5]: 259-262.
22. Gagliardi F, Baldini E, Lori E, et al: (2023). Insights on the Association between Thyroid Diseases and Colorectal Cancer. *J Clin Med*. ;12[6]: 2234.
23. Asbaghi O, Shimi G, Davoodi SH, et al: (2023). Thyroid Hormones Imbalances and Risk of Colorectal Cancer: a Meta-analysis. *J Gastrointest Cancer*.
24. Gómez-Izquierdo J, Filion KB, Boivin JF, et al: (2020). Subclinical hypothyroidism and the risk of cancer incidence and cancer mortality: a systematic review. *BMC Endocr Discord*.;20[1]: 83.

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