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Thyroid Dysfunction as a Key Link in the Concept of Mutual Aggravation of Colorectal Cancer and Metabolic Syndrome: Review

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ABSTRACT

The mutually aggravating role of endocrine glands and metabolic disorders in the process of carcinogenesis is well known, but it is underestimated in modern oncological practice. The study of the manifestations of thyroid dysfunction, its effect on carcinogenesis in patients with metabolic syndrome and the possibility of improvement should become an important direction in refining patient outcomes in colorectal cancer (CRC).

The aim of our review was to study the issue of thyroid dysfunction as a key link in the concept of colorectal carcinogenesis in metabolic syndrome. Current research data demonstrate a link between hypothyroidism and metabolic syndrome, suggesting that they mutually exacerbate each other, thereby worsening the condition of patients. Metabolic syndrome not only contributes to the development and progression of cancer, but also affects patient outcomes.

In clinical practice, an imbalance of thyroid hormones occurs in various types of cancer and is regarded as a confounding factor. Existing data regarding the influence of thyroid hormones on tumors are inconsistent. While hypothyroidism appears to play a role in promoting cancer progression, the underlying mechanisms of this association remain poorly understood and necessitate further research. Despite conflicting evidence regarding the impact of thyroid hormones on CRC development, their significance in influencing a patient's overall condition should not be overlooked. Therefore, it is important to integrate strategies for controlling the endocrine profile and correcting its changes into standard cancer treatment protocols. Moreover, some publications report the effect of levothyroxine replacement therapy on reducing the risk of developing CRC. Investigating the interplay between metabolic syndrome and cancer, particularly through the lens of thyroid dysfunction, may contribute to the development of novel approaches to colorectal cancer management and improve patient outcomes.

Keywords: thyroid dysfunction, cancer, carcinogenesis, thyroid hormones, hyperthyroidism, hypothyroidism, metabolic syndrome

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Дисфункция щитовидной железы как ключевое звено в проблеме лечения колоректального рака в сочетании с метаболическим синдромом: обзорная статья

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РЕЗЮМЕ

Взаимоотягощающая роль желез внутренней секреции и метаболических нарушений в процессе канцерогенеза общеизвестна, но современная онкологическая практика ее недооценивает. Изучение проявлений дисфункции щитовидной железы, ее влияния на канцерогенез у больных с метаболическим синдромом и возможности коррекции должно стать важным направлением в улучшении результатов лечения больных в терапии колоректального рака (КРР).

Целью нашего обзора стало освещение вопроса дисфункции щитовидной железы как ключевого звена в концепции колоректального канцерогенеза при метаболическом синдроме и возможных путей его решения. Актуальные данные исследований демонстрируют связь между гипотиреозом и метаболическим синдромом, указывая на возможность их взаимного усиления, что ухудшает состояние пациентов. Метаболический синдром не только способствует развитию и прогрессированию рака, но и влияет на исход лечения.

В клинической практике дисбаланс тиреоидных гормонов встречается при разных видах рака и расценивается как отягощающий фактор. Существующие положения о влиянии тиреоидных гормонов на опухоль противоречивы, и, хотя гипотиреоз, вероятно, способствует раковому прогрессу, механизмы этого влияния остаются неясными и требуют дальнейших исследований. Несмотря на противоречивость данных о влиянии тиреоидных гормонов на развитие КРР, их роль в состоянии пациента не должна недооцениваться. Поэтому важно интегрировать стратегии контроля гормонального фона и коррекции его изменений в стандартные протоколы лечения колоректального рака. Тем более, что в некоторых публикациях приводится влияние заместительной терапии левотироксином на снижение риска развития КРР. Исследование взаимодействий между метаболическим синдромом и раковым процессом через призму дисфункции щитовидной железы, возможно, поможет в разработке новых стратегий борьбы с КРР и улучшении результатов лечения.

Ключевые слова: дисфункция щитовидной железы, колоректальный рак, канцерогенез, тиреоидные гормоны, гипертиреоз, гипотиреоз, метаболический синдром

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Modern oncological practice tends to underestimate the mutually aggravating role of endocrine dysfunction and metabolic disorders in carcinogenesis. This is due to the widespread perception that the endocrine system does not play a significant pathogenetic role in tumor growth and cancer development. At the same time, tumor growth itself alters the metabolism through the shutdown or distortion of the hormonal activity of endocrine glands, particularly the thyroid gland. In the study

by J.J. Díez et al., which included 506,749 patients, 23,570 (4.7%) were diagnosed with hypothyroidism. The overall incidence of malignancy in the group of patients with hypothyroidism examined was 13.8%, which is significantly higher than the incidence in patients without hypothyroidism [1].

The lack of attention from the scientific and medical communities to the state of endocrine glands in patients with colorectal cancer (CRC) has left one of the most significant links in the pathogenesis unexplored. This, in turn, inevitably leads to an incomplete understanding of the clinical picture, ultimately leading to suboptimal or ineffective treatment strategies. In this regard, we believe that in patients with tumor activity, it is essential to take into consideration the role of the endocrine system and seek ways to address any destabilization in their function.

Thyroid dysfunction, especially hypothyroidism, is closely related to metabolic syndrome (MS), which encompasses a number of disorders, such as insulin resistance, atherogenic dyslipidemia, central obesity, and hypertension [2]. Patients with hypothyroidism frequently exhibit characteristic clinical manifestations, such as overweight or obesity. These conditions are known to be linked to inflammation and the development of metabolic and hormonal imbalances, which may contribute to the formation and growth of malignant tumors [2]. Given these associations, the detection of hypothyroidism is an important element of early diagnosis in oncology, which creates opportunities for active monitoring and, if necessary, screening for CRC.

We hypothesize that implementing this strategy would not merely enable the prompt detection of CRC at its earliest stages, but also substantially enhance treatment efficacy, thereby improving prognosis and survival rates for these patients – an imperative goal amidst contemporary efforts.

The aim of our review was to study thyroid dysfunction as a key link in the concept of carcinogenesis in patients with CRC and MS and possible ways to correct it. Given the absence of a consensus regarding the course of hormonal imbalance in different cancer stages and types, despite every bodily phenomenon adhering to inherent mechanisms, we aim to scrutinize literature guided by expert perspectives and research insights to elucidate the thyroid gland's role in colorectal carcinogenesis.

MATERIALS AND METHODS

A systematic review of the literature was conducted in accordance with the guidelines Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

To identify the literature, we conducted a search using keywords that, when searched in the title and abstract, necessarily varied, combined and included thyroid dysfunction, colon cancer, carcinogenesis, thyroid hormones, hyperthyroidism, hypothyroidism, and metabolic syndrome in the PubMed and Semantic Scientist databases from 1990 to 2024.

The search results turned out to be unexpected and ambiguous, and as this may be of some scientific value, we decided to reflect their characteristics.

Upon further examination, accounting for terminological variations revealed divergent results. Notably, the most prevalent keyword combination emerged as (metabolic syndrome) AND (colorectal cancer) AND (thyroid dysfunction) with seven publications. The next most common combination was (metabolic syndrome) AND (colorectal cancer) AND ((hyperthyroidism) OR (hypothyroidism)) with five publications. Then, in descending order of frequency, the following search results were observed ((metabolic syndrome) AND (carcinogenesis)) AND (thyroid dysfunction) with two publications, (metabolic syndrome) AND (colorectal cancer) AND (thyroid hormones), ((metabolic syndrome) AND (carcinogenesis)) AND (thyroid hormones) and (metabolic syndrome) AND (carcinogenesis) AND ((hyperthyroidism) OR (hypothyroidism)) with one publication each.

Impressive results were obtained from Semantic Scholar, another popular academic search engine. Employing the designated search criteria, the platform retrieved a comprehensive dataset comprising a total of 12,570 relevant publications. For example, a combination (metabolic syndrome) AND (colorectal cancer) AND (thyroid hormones) was found in 5,210 publications. The request (metabolic syndrome) AND (colorectal cancer) AND (thyroid dysfunction) turned out to be the second most common with 3,630 related publications. Search for the combination ((metabolic syndrome) AND (carcinogenesis)) AND (thyroid hormones) resulted in 1,600 publications, and by ((metabolic syndrome) AND (carcinogenesis)) AND (thyroid dysfunction) – 718 publications. Search for combinations such as

(metabolic syndrome) AND (colorectal cancer) AND ((hyperthyroidism) OR (hypothyroidism)) and (metabolic syndrome) AND (carcinogenesis) AND ((hyperthyroidism) OR (hypothyroidism)) resulted in 1,220 and 192 publications, respectively.

At the second stage, all the articles obtained as a result of the search were processed using Rayyan platform, which allowed us to significantly simplify the selection of necessary publications and eliminate repetitive researches.

Three independent authors read all the abstracts and applied the inclusion and exclusion criteria, which were taken from the Oxford Centre for Evidence-Based Medicine (CEBM) criteria. Two reviewers read the selected quotes in full, while the grounds for exclusion were indicated in Covidence. The discussion or participation of a third reviewer was used to resolve disagreements between the reviewers. Duplicate entries were automatically deleted from all uploaded extracted links in Covidence. The titles and abstracts were evaluated by two independent reviewers, who removed the publications that did not meet the inclusion requirements.

The publications selected this way were classified according to the level of evidence from degree I to V and recommendations from A to D within the framework of evidence-based medicine. After this, the authors thoroughly reviewed the selected studies to draw the conclusions presented in this review.

Thus, as of April 7, 2025, we identified 42 publications related to thyroid dysfunction in the context of CRC and MS.

In addition, as a reliable clinical expert of a broad profile, we also used the Jadad scale, which is sometimes known as Jadad scoring, and is a procedure for evaluating the methodological quality of a clinical trial according to objective criteria. It forms a system for assigning ratings from zero to five for different tests and is designed to more accurately reflect the methodological quality of each individual study. It is the most universally adopted method of assessment. Unpublished materials, abstracts of congressional reports, hearing materials, and reviews were excluded. The search results were checked by two current authors separately. Both quantitative and qualitative data were extracted from the studies included in the review by two independent reviewers using AGREED II. If necessary, the data extraction tools were modified to take into account the differences of each included study; our review describes the conclusions in detail. Any disagreements that arose between the reviewers were resolved through discussion or with the help of the third reviewer. If required, we contacted the authors of the articles to request any missing or additional information.

As a result, we selected reviews from the original publications. We received a total of 42 publications appropriate for analysis.

RESULTS

Thyroid hormones (thyroglobulin, TG) are key regulators of major cellular reactions, including proliferation, differentiation, apoptosis, and metabolism. Tetraiodothyronine (T4), the main hormone synthesized in the thyroid gland, is catalyzed to triiodothyronine (T3) by specific iodothyronine deiodinases. T3 acts as the main metabolic agent through the formation of complexes between T3 and the nuclear receptors of thyroid hormones alpha (TRα) and beta (TRβ). This T3 receptor complex within the cell nucleus interacts with thyroid hormone response elements on specific genes, thereby regulating their expression. Disorders associated with elevated TG levels (hyperthyroidism) or TG deficiency (hypothyroidism) are prevalent and have distinct clinical manifestations [3].

Hypothyroidism is one of the most common endocrine disorders, and even subclinical hypothyroidism (SCH) is a widespread and asymptomatic condition, which, unfortunately, often goes unnoticed not only by patients, but also by doctors. SCH is characterized by high levels of serum thyroid-stimulating hormone (TSH) and normal levels of free TG [4]. Cross-sectional studies have additionally revealed a link between hypothyroidism (or SCH) and the components of MS [5, 6]. According to S.S. Alsulami et al., a high normal TSH level is associated with a higher incidence of MS [7]. Previous studies have also demonstrated that elevated TSH levels are linked to an increased risk of MS, particularly in women. Data provided by S.S. Alsulami et al. claimed that age has a significant effect on the severity of SCH [7]. Half of the participants with markedly elevated TSH were older than 50 years.

Dyslipidemia is the most commonly observed metabolic disease associated with hypothyroidism.

Patients with dyslipidemia account for 1.4% to 13.3% of all patients with hypothyroidism [8]. A. Shinkov [6] conducted a cross-sectional study of 2,153 euthyroid subjects and found that, within the normal range, the MS prevalence increased along with TSH levels, mainly manifesting itself as an increase in dyslipidemia.

Thus, MS was more common in the group with the highest TSH levels (34.9%) than in the group with the lowest levels (27%) ($p < 0.001$), as were low HDL-C levels (32% vs. 25%, $p < 0.001$) and hypertriglyceridemia (26.8% vs. 20.4%, $p = 0.015$). Furthermore, treatment for hypothyroidism has been shown to improve lipid metabolism. Some randomized controlled trials have found that T4 replacement therapy has a positive impact on dyslipidemia improving total cholesterol and LDL-cholesterol levels [9, 10].

Most studies suggest that the more MS components a patient has, the higher the risk of developing cancer [11, 12, 54]. At the same time, MS also increases cancer mortality by up to 2.4 times [11]. Individual components of MS appear to have a different impact on carcinogenesis. Mechanisms of interest regarding cancer etiology include the roles of insulin, insulin-like growth factor 1 (IGF-1), hyperglycemia, high triglyceride (TG) levels, and low high-density lipoprotein levels [13].

In addition, increased insulin levels can stimulate the expression of vascular endothelial growth factor and promote the proliferation of vascular endothelial cells in cancer [11]. These changes in the composition and phenotype of immune cells in adipose tissue in obese individuals contribute to hormonal and metabolic alterations that, in combination with inflammation, create an ideal environment for tumor growth. This multistage involvement of metabolic disorders in carcinogenesis may explain the increased risk of severe cancers among individuals with MS [11].

Due to the lack of sufficient information regarding the direct impact of MS on carcinogenesis and patient survival, it is worthwhile considering conditions closely related to MS, specifically non-alcoholic fatty liver disease (NAFLD). The study by Z. Liu et al. included 352,911 people (37.2% with NAFLD), among whom 23,345 developed cancer. Compared with non-NAFLD, NAFLD was significantly associated with 10 of 24 cancers studied, including cancers of the uterus (hazard ratio [HR] = 2.36; 95% CI 1.99–2.80), gallbladder (2.20; 1.14–4.23), liver (1.81; 1.43–2.28), kidneys (1.77; 1.49–2.11), thyroid gland (1.69; 1.20–2.38), esophagus (1.48; 1.25–1.76), pancreas (1.31; 1.10–1.56), bladder (1.26; 1.11–1.43), breast (1.19; 1.11–1.27), and CRC and cancer of the anus (1.14; 1.06–1.23) [14]. Associations between NAFLD and cancers of the liver, esophagus, pancreas, rectum, anus, bladder, and malignant melanoma were increased in men. In contrast, associations with cancers of the kidneys, thyroid gland, and lungs were increased in women [14].

It is important to note that thyroid hormones affect liver lipid metabolism through various mechanisms, including stimulating the transport of free fatty acids into the liver for their re-esterification into triglycerides and enhancing the beta-oxidation of fatty acids, which affects the accumulation of fat in the liver [15].

In their study, A. Bano et al. showed that SCH is associated with the risk of NAFLD [16]. The study by Y. Tao et al. aimed to assess the association of NAFLD with changes in thyroid function within the euthyroid range [17]. Higher TSH levels in euthyroidism have been found in subjects with NAFLD, but they may also be associated with a slight increase in serum alanine aminotransferase (ALT) in the context of MS and insulin resistance. A large population-based study by E.H.Van den Berg et al. demonstrated that NAFLD was associated with higher FT3 levels and lower FT4 levels among severely euthyroid individuals [18]. The findings collectively support the hypothesis that elevated levels of FT3 within the range of euthyroidism may be associated with increased fat accumulation in the liver, likely as part of central obesity [18].

TSH levels are related to body mass index (BMI) and are often higher in obese people than in normal-weight people of the same age, gender, and weight. The study by B. Biondi showed that a genetically predetermined high BMI significantly increased serum TSH levels; as a result, an increase in BMI can cause an increase of FT3 [19]. Moreover, data collected from humans and a mouse model suggest that obesity causes fat accumulation in the thyroid gland. The work by L.Zhong et al. mentioned a study in obese mice that shows that obesity can affect the thyroid gland's ability to produce hormones and cause SCH [20].

As is well known TG and their derivatives play numerous roles in various tissues, including the activation and remodeling of adipose tissue. Recently, it has been demonstrated that some TG metabolites that were previously believed to be inactive products of thyroid hormone metabolism actually possess biological activity. One such example is 3,5-T2 [21]. This metabolite exhibits some TG effects within one hour after administration, and mitochondria are considered as a direct target of 3,5-T2. In addition, *in vivo* studies show that 3,5-T2 has a metabolically beneficial effect on adipose tissue [21].

J. Gómez-Izquierdo et al. concluded that SCH is associated with an increased risk of cancer, as well as mortality associated with it [22]. The study by F. Gagliardi et al. showed that carcinogenesis occurred significantly more often in patients with SCH than in people with euthyroid condition [23]. It has also been reported that CRC involves two additional nuclear receptors with opposing effects, which have been previously mentioned: TRα1 and TRβ1. The effect of TG on TRα1 leads to the activation of β-catenin, which promotes cell proliferation in the colon. Conversely, TRβ1 inhibits cell proliferation when it is activated by TG. In particular, TG can regulate the balance between proliferation and differentiation of CRC stem cells stimulating differentiation and reducing growth, thus acting as an anti-cancer agent [24].

Thus, the lack of TRβ1 expression is associated with malignant transformation in colon cancer [25]. Among other things, TG has been shown to contribute to the depletion of stem cells in the tumor site. The study by A. L'Heureux et al. demonstrates a potential feedback mechanism observed in patients with hyperthyroidism; in their xenografts and *in vitro* models, CRC stem cells treated with T3 had a significantly reduced ability to self-renew, decreased accumulation of nuclear β-catenin, and increased sensitivity to treatment, especially when type 3 deiodinase (D3) was suppressed [26]. Intracellular T3 may have antitumor properties because it induces the differentiation of CRC stem cells [26].

If we discuss T4, its non-genomic activity through binding to the αvβ3 integrin leads to an increase in nuclear β-catenin levels. T4 also promotes cell viability in CRC cell lines in a dose-dependent manner. Thus, there may be a potential mechanism in which low FT4 levels in primary hypothyroidism may protect against cancer by reducing interaction with integrin [26]. The authors also noted that TRβ1 may play a role as a tumor suppressor in the development of malignant tumors. Conversely, overexpression of TRα1 receptor appears to be linked with an accelerated appearance and progression of tumors [26].

G. Schiera et al. suggest that hypothyroidism correlates with an increased risk of CRC and hepatocellular carcinoma [24]. F. Gagliardi et al. suggested that cancer may determine the onset of the low T3 syndrome and that a decrease in the peripheral transformation of T4 to T3, which occurs under the action of type 2 deiodinase (D2), may be a pivotal moment in this process. Using the example of patients with metastatic CRC, the loss of muscle mass that occurs during cachexia and the subsequent decrease in deioding, as well as liver damage caused by tumor spread, followed by impaired deioding mediated by type 1 deiodinase (D1), can be considered as sequential pathological mechanisms. Based on the identified correlation between changes in peripheral deiodination and adverse clinical outcomes, the researchers concluded that the FT3/FT4 ratio may serve as a prognostic indicator for determining the life expectancy of individuals with metastatic CRC. A relationship between low T3 syndrome and adverse clinical outcomes was also observed in patients with hematologic tumors, lung tumors, and brain tumors [24]. -

In addition to the crucial biological importance of TG in metabolism and growth, there is evidence that they can influence the clinical outcome of cancer, as well as individual life expectancy [27]. Numerous *in vitro* and *in vivo* studies, as well as population studies, indicate the cancer-promoting effects of triiodothyronine and thyroxine. These hormones are known to be mediators of tumor growth and proliferation, as well as its progression. This hypothesis is supported by numerous clinical studies that have shown that hypothyroidism can suppress tumor growth, whereas hyperthyroidism can have the opposite effect [27, 28]. In addition, hyperthyroidism is also associated with a poorer prognosis of cancer [29].

Elevated serum TSH levels have been linked to improved treatment outcomes in patients with head and neck cancer, gliomas, and breast cancer (BC). However, these levels have also been associated with poorer outcomes in patients diagnosed with kidney

cancer [30]. This discrepancy indicates differences in oncogenesis between different types of cancer. Hypothyroidism also appears to be associated with a poor prognosis for patients with endometrial cancer (EC). A multicenter study conducted by V. Seebacher et al. [13] in 2013 was the first to study the effect of TSH on the prognosis of patients with EC. Elevated TSH levels have been shown to be independently associated with poor disease-related survival in univariate and multivariate survival analyses ($p = 0.01$ and $p = 0.03$, respectively).

Thus, TSH serum measurements can be utilized as an independent prognostic indicator for the survival of EC patients to determine recurrence during the follow-up period of EC. However, in the aforementioned study [13], no correlations were observed between elevated pre-treatment TSH levels and advanced-stage FIGO tumors, higher histological grades, unfavorable histologic subtypes, elderly patient age, or lifestyle factors, such as obesity, hypertension, or diabetes. Based on this discovery, TSH may be associated with systemic processes that interact with carcinogenesis (for example, hormonal imbalance or inflammation) rather than with local neoplastic transformation. However, the specific mechanism by which serum TSH levels affect EC remains unknown.Over the past few decades, considerable attention has focused on investigating how TG exert tumor-stimulating effect [3, 31]. TG mediate their effect on the cancer cell through several non-genomic pathways, including activation of the membrane receptor for TG integrin αvβ3 [27, 32]. It has been shown that this receptor contains two different hormone-binding sites, S1 and S2, each of which triggers unique signaling cascades. Only T3 in physiological concentrations can bind to S1, triggering phosphorylation and activation of the phosphatidylinositol-3-kinase (PI3K) pathway, which potentiates cell proliferation and inhibits apoptosis. The second site, S2, binds T4 and has lower affinity for T3, triggers oncogenic extracellular signal-regulated kinase 1/2 (ERK1/2), contributing to a similar side effect, while stimulating angiogenesis and expression of fibroblast growth factor 2, as well as components necessary for rapid oncogenesis [3, 26, 33]. Binding of integrin αvβ3 stimulates the proliferative effect of hormones on cancer cells, as well as on blood vessel cells [3, 32, 34].

This ability may be significant not only in CRC, but also in other types of cancer, as malignant cells express a greater amount of integrin avβ3 compared to normal cells [24]. The effect of TG on the expression of the P-gp gene, whether genomic or non-genomic, has also been reported, which increases the likelihood that TG in an oncological patient may contribute to chemoresistance of tumor cells. This possibility has not yet been investigated in CRC cells. However, it has been demonstrated that avß3 integrin, a carrier of the cell surface receptor for T4, plays an important role in doxorubicin resistance in metastatic BC [35]. Potential mechanisms underlying the link between TG and CRC are also reported. Since CRC can be a hormone-dependent cancer, tumor progression is inversely related to the expression of the estrogen beta receptor (ERß) [36].

P.A. Konstantinopoulos et al. reported significantly lower ERß expression in colon cancer cells compared to normal colon epithelium [37]. Decreased ERß expression in CRC may be associated with loss of differentiation and advanced stages of cancer [37]. Moreover, it is reported that the potential for CRC progression is suppressed by ERß expression [28]. Estrogen has been shown to increase ERß expression [37]. The downstream genomic protective effects of estrogen result in gene transcription associated with angiogenesis and cell adhesion. Additionally, ERβ has been reported to induce apoptosis through various mechanisms, including increased p53 signaling in LoVo colon cancer cells and increased DNA fragmentation in COLO205 colon cancer cell lines [28].

An imbalance of thyroid hormones is a possible factor influencing the development of CRC resulting from diseases, such as SCH, Hashimoto's disease, and Graves' (or Bazedow's) disease, and their treatment. In 2010, G. Rennert et al. published a study titled CRC Risk Therapy [38]. Further studies were consistent with these results and showed that high concentrations of TG (but within the acceptable range) reduced the risk of developing CRC. Despite these promising initial results, there are currently only 11 papers available analyzing this issue, both at the molecular and epidemiological levels. The human studies included in this analysis show consistent and promising results [39].

Speaking about the effect of TG on CRC during long-term use as part of hormone replacement therapy

(HRT), G. Rennert et al. in a case-control study involving 2,566 couples showed that levothyroxine use was associated with a statistically significant reduction in the relative risk of CRC (HR = 0.59; 95% CI = 0.43–0.82; $p = 0.001$) [38]. In accordance with the well-known fact that hypothyroidism is much more common in women than in men, the study showed that levothyroxine women were more likely to take dietary supplements than men in the control group (8.2% vs. 2.0%, respectively, $p < 0.0001$). After analyzing the subgroups, the study showed a reduced risk of CRC in postmenopausal women taking levothyroxine (odds ratio (OR) = 0.53; 95% CI: 0.37–0.74; $p < 0.001$). In a fully adjusted model for postmenopausal women, levothyroxine intake was associated with a significant reduction in the risk of CRC (OR = 0.60; 95% CI: 0.4–0.81; $p = 0.001$) [38].

The study by B. Boursi et al. conducted on a large UK population included 20,990 CRC patients and 82,054 matched control patients. Analysis of the relationship between the time of initiation of replacement therapy and the risk of developing CRC showed that the protective effect increased along with the duration of therapy. Moreover, patients with clinical or subclinical hypothyroidism without a history of HRT had a higher risk of developing CRC compared to patients without any thyroid dysfunction (OR = 1.16; 95% CI: 1.08–1.24; $p < 0.001$) [29].

The meta-analysis conducted by Jang et al. among women diagnosed with CRC showed that received HRT users had a reduced risk of mortality compared to women who had not previously taken TG, while the risk remained unchanged in patients who had previously used HRT, suggesting that the relationship between HRT use and survival rate may be complex and depend on the duration of hormone use.

DISCUSSION

The role of thyroid hormones in carcinogenesis is not considered or regarded as an ambiguous phenomenon today. Due to insufficient research, there is currently no unified perspective on the nature of thyroid dysfunction and its course across different stages and types of cancer. There is still a question about the effect of TG on cancer carcinogenesis, while the mechanisms are different. However, there is already evidence of the effect of TG on the clinical outcome of cancer [30]. Hormonal and metabolic alterations associated with obesity, coupled with a persistent state of low-grade chronic inflammation, create a favorable environment for the development of cancer.

Most studies indicate that the greater the number of MS components a patient has, the higher their risk of developing malignancy [11, 12]. At the same time, MS also increases cancer mortality by up to 2.4 times [11]. For example, J.H.Park et al. observed 9,890,917 adults for 7 years and found that the risk of thyroid cancer was higher in the group with MS than in the group without MS (HR = 1.15; 95% CI 1.13–1.17).

This cohort study showed that MS patients tended to have larger tumors, more invasive characteristics, including a greater number of lymph node metastases, and a later stage of AJCC. Blood pressure ≥ 130/85 mm Hg and low levels of HDL cholesterol were risk factors for the development of larger tumors and metastases to lymph nodes. BMI has been used as the main indicator in most studies. However, the distribution of body fat and impaired adipose tissue function rather than the total fat mass may be a better predictor of insulin resistance and associated complications for each patient.

NAFLD is a hepatic manifestation of MS [25]. Associations of NAFLD with cancers of the liver, esophagus, pancreas, rectum, anus, and bladder, as well as malignant melanoma, were increased in men, while associations with cancers of the kidneys, thyroid, and lungs were increased in women. Interestingly, the associations between NAFLD and the risk of liver, kidney, and thyroid cancer remained statistically significant after further adjusting for waist circumference, BMI, and the number of MS components based on the primary models. Thus, NAFLD has been linked to an increased risk of several types of cancer, although the effect varies considerably depending on the specific location. We suppose that NAFLD should be given a higher priority within the current cancer prevention strategy [14].

Associations of metabolic dysfunction with the risk of BC and CRC were observed regardless of BMI, with an increased risk in individuals with metabolically unhealthy normal weight or overweight/obese compared to people with a metabolically healthy normal weight [48]. Thus, metabolic dysfunction is a key risk factor for obesity-related cancer, regardless of obesity status.

Recently, evidence has emerged that some TG metabolites previously considered as inactive products of thyroid hormone metabolism have biological activity, such as 3,5-T2 [21]. This metabolite exhibits some TG effects within one hour after administration, and mitochondria are considered as its direct target. In addition, *in vivo* studies have shown that 3,5-T2 exerts a metabolically favorable effect on adipose tissue [21], which could certainly play an important role in the development of therapeutic approaches not only for isolated MS, but also when combined with CRC and thyroid dysfunction.

G. Schiera et al. suggest that TG can control the balance between proliferation and differentiation of CRC stem cells inducing differentiation and reducing growth, thus acting as an anti-cancer agent [24]. On the other hand, the study found that genetically predicted hyperthyroidism, TSH, and FT4 were not associated with an increased risk of CRC, and the reverse analysis failed to reveal any effect of CRC on thyroid function [42].

On the one hand, TG mediate their effect on the cancer cell through several non-genomic pathways, including activation of the membrane receptor for TG integrin αvβ3. Binding of the latter promotes the proliferation of cancer cells [3]. However, malignant cells express a higher amount of integrin αvβ3 than normal cells [24]. The most important thing is that a chain of interaction is formed, which is realized in various types of cancer, including CRC [26].

The possibility of the P-gp gene expression under the influence of TG has not yet been studied in CRC cells, but it has been shown that integrin αvβ3, which is a carrier of the cell surface receptor for T4, makes an important contribution to doxorubicin resistance in metastatic BC [34], which opens up new directions for in-depth study of the role of TG not only in colorectal cancer, but also in carcinogenesis in general.

There is also evidence of a positive effect of HRT with TG on the outcome of CRC. G. Rennert et al. established that long-term use of levothyroxine was associated with a reduced risk of CRC [38]. B. Boursi et al. in their study demonstrated a lower risk of CRC among HRT users and a higher risk among patients with hyperthyroidism or in hypothyroidism patients who did not receive HRT. The protective association of TG increased along with the duration of treatment and cumulative dose and was higher in colectomy patients and more pronounced in women. The results of the work of Jang et al. also show that current HRT use has been associated with a significant reduction in the risk of CRC and all-cause mortality in women with CRC [41]. These findings confirm our belief that in patients with CRC, special attention should be paid to the hormonal status of TG.

Therefore, strategies to combat CRC in the presence of concomitant MS and thyroid dysfunction should be followed throughout treatment period. Thus, we believe that in addition to targeted, chemotherapy and radiation therapy, it is necessary to include some measures aimed at weight loss and BMI normalization, and most importantly, correction of TG levels, which we believe will significantly reduce the risk of severe forms of CRC and mortality rates.

By avoiding the assessment of endocrine disorders, their observation and analysis, we may be underestimating the patient's condition, missing the opportunity to prescribe proper complex therapy, thereby depriving patients of a cure, inhibiting the development of oncology, and supporting existing scientific results.

The main limiting factor of this review is the scope of studies included. This is due to the limited number of series available in the literature. This circumstance does not allow us to draw clear and definitive conclusions about the mutual influence of TG, MS and CRC, but the trend can still be traced.

CONCLUSION

Currently available clinical and experimental data provide contradictory results on the ability of TG to influence the onset and progression of CRC in the presence of concomitant MS.

However, based on the findings of certain studies, cancer cells appear to be responsive to alterations in thyroid hormone concentrations, both during the process of mutagenesis and following the emergence of a tumor. Yet, the lack of sufficient information combined with the complex and multifaceted interactions between TG, MS, and CRC currently precludes us from drawing definitive conclusions regarding the role of TG in the development or suppression of colorectal tumors. We hypothesize that the discrepancies in the data are due to the intricate interactions between TG and their receptors

in both normal and malignant tissues in the context of MS.

Speaking about the isolated effect of MS components on CRC, most studies indicate their complex effect not only on various types of cancer, but also on carcinogenesis in general. MS can not only contribute to the occurrence, development, and progression of CRC and other cancers, but it also influences patient outcomes after treatment, which highlights its significance and role in understanding colorectal carcinogenesis in thyroid dysfunction.

We set ourselves the task of deciphering and studying the root cause of the pathogenetic interaction of CRC, MS, and thyroid dysfunction. Disrupting this malignant triad will bring us closer to new horizons and strategies for combating cancer. It seems to us that the inclusion of a reasonable correction of thyroid hormone levels using HRT with thyroxine preparations and the control of MS components in patients with CRC can help improve the quality of early cancer diagnosis and treatment outcomes by increasing Life expectancy.

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