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The relationship between thyroid and cancer (focus on breast cancer)

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Introduction/Background

The function of the thyroid gland is very important for metabolic processes including basal metabolic rate, nervous reflexes, temperature regulation, cardiac contractility, intestinal transit and growth and maturation processes of tissues and organs [1]. Therefore, the thyroid affects the function of virtually all organs and systems. Thyroid hormones (THs) called tetraiodothyronine (thyroxine or T4) and triiodothyronine (T3) and a thyroid-stimulating hormone or thyrotropin (THS), play a role in growth, development and metabolism. In adults, diseases commonly associated with the thyroid are caused by excess or lack of THs (hyper or hypothyroidism respectively). However, thyroid hormones and their receptors may play a role in the development and progression of other diseases, namely in the promotion and suppression of tumors [1].

Thyroid hormone production is regulated by feedback from several serum hormone levels. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the release of thyroid-stimulating hormone (TSH) from the pituitary gland. In turn, TSH stimulates the synthesis and release of T4 and T3 by the thyroid. The “feedback” of T3 serum levels in the hypothalamus and pituitary gland regulates the secretion of TRH and TSH, maintaining the production of desirable levels of T3. The hormone T3 is the biologically active hormone and is also formed by the deiodination of T4 into T32. T3 acts by forming complexes with the nuclear receptors of thyroid hormones called alpha (TRα) and beta (TRβ) receptors. These T3 receptor complexes bind to thyroid hormone response elements (TREs), in especific genes, regulating their transcription [3]. Transcriptional activity is also regulated by THs through homo- or hetero-dimers with other nuclear receptors such as RXR (the retinoid X receptor) [4] and VDR (vitamin D receptor) [5].

Besides nuclear receptors, T3 and T4 also interact with target tissues, independent of transcriptional action, via the membrane-bound integrin αvβ3 protein receptor [6]. The thyroid hormone receptor are expressed in both the thyroid and mammary (normal and neoplastic) cells [7]. Studies demonstrated a

relationship between thyroid hormones and proliferation, apoptosis, invasion and angiogenesis of several types of cancer [3]. While αvβ3 receptors are thought to regulate most of the tumor-promoting effects of THs in breast cancer (BC) cells, TRs seem to have tumor-supressing properties in BC [8]. The αvβ3 receptor has two different sites of binding to hormones (S1 and S2), being that each one translates into different signaling cascades [3]. The S1 binds only to T3, leading to activation of the intracellular PI3K (phosphatidylinositol-3-kinase) signaling pathway, and induction of the expression of hypoxia-inducing factor 1 (HIF-1). This factor targets genes with an important role in tumor development, cells growth, invasion and metastasis [9]. In turn, site S2 connects to T4 (with less affinity for T3) and activates the MAPK signaling pathway [10]. This activated pathway induces the fibroblast growth factor-2 (FGF-β), that stimulates angiogenesis and tumor growth. In this way, activation of the αvβ3 integrin receptor facilitates the proliferative action of thyroid hormones on neoplastic cells and stimulates angiogenesis [3]. The MAPK pathway also infuences estrogen receptors activity and localization. Thyroxine may increase the expression of estrogen receptors (ERs) which would in turn promote BC cells migration and invasion and BC growth [11]. Other mechanisms for the anti-apoptotic effects of THs have been described, such as a decreased expression of Tumour necrosis factor α (TNFα) and FAS ligands, which are cell surface factors that activate apoptosis. Another form of THs action is the stimulation of programmed deathligand 1 (PD-L1) gene expression, which has a role in protecting tumor cells from T lymphocytes [12]. THs can also increase the proliferation of neoplastic cells by decreasing the expression of the BTG2 gene (anti-proliferation factor 2) and by by stimulating aerobic glycolysis (Warburg effect) [12].

Specific mechanisms have been described for certain types of tumors. The action of thyroid hormone on estrogen and androgen receptors may contribute to breast and prostate cancers respectively. The interaction between THs and thyroid hormone receptors (TRs) has been linked to stimulation of breast, ovarian and prostate cancer proliferation [13]. However, a cancer protective effect due to mutations in TRs (resulting in lower thyroid hormone level), has been found for lung, breast and liver cancer [14]. Besides αvβ3 integrin receptor, the nuclear receptors (TRs) also have a role in breast cancer depending on the receptor variants or isoforms (TRα1, TRα2, TRβ1, or TRβ2) [15]. The TR isoform expressed in a particular cell determines the genomic effects of thyroid hormones. All of these four variants have been detected in BC cells [16].

Among the THs receptors, TRα and αvβ3 integrin have cancer pro-proliferative action, while TRβ mainly has tumor-suppressing effects [17]. In BC tissue, TRα2 expression is a positive prognostic marker compared to the decrease disease-free survival associated with TRα1 expression [18]. Although, the pathways that TRβ regulates has not yet been totally elucidated, evidence shows it supresses PI3K in both breast and thyroid cancer cells [19]. In breast cancer studies, TRβ protein activation by T3 was associated with the attenuation of the JAK-STAT signaling cascade and of the Runt-related transcription factor 2 (RUNX2), leading to the reduction of metastatic potential [20]. TRβ1 is also represses the vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) axis, that is indispensable for breast cancer angiogenesis [21].

The RXR (retinoid X receptor) and VDR (vitamin D receptor), also showed to exert effects in cancer

cells. The RXR bind to retinoids, resulting in oncosuppressive activity by arresting cancer cells proliferation [22]. However, in breast cancer cells, an increased expression of the isoform RXRα was observed when compared to the benign breast tissue [23]. On the other hand, studies regarding the VDR, have offered different results according to the type of breast cancer (multifocal or unifocal). In multifocal BC, the VDR has been described as an independent marker of worse overall survival prognostic [24]. In an opposite way, VDR was associated with good prognosis in unifocal breast cancer [24]. Observational and epidemiological studies report the existence of a bidirectional risk increase between BC and thyroid dysfunction or thyroid cancer (TC). This could be due to the shared hormonal signaling verified between the thyroid and the breast tissue [25]. Breast cells respond to thyroid hormone signaling, since receptors for ligands of the hypothalamic–pituitary–thyroid axis are expressed in breast tumors. In particular, high-affinity binding sites for T3 have been identified in the mammary gland and are thought to modulate the development and growth of breast tissues [7].

TSH receptors are expressed in the thyroid and in both cancer and non-cancer breast cells [26], although TSH seric levels were found to be significantly higher in tumor tissues, when compared to normal breast tissues [27]. Increased risk of cancer associated with higher TSH seric concentrations is though to be the result of excessive intracellular activation of signaling pathways that estimulate cell proliferation [28]. The sodium iodide symporter (NIS) is a protein membrane that mediates the active transport of iodide not only in the thyroid but also in non-thyroidal tissues, particularly in the lactating mammary gland. Defective cell localization of the NIS protein [29] has been related to iodine deficiency, which leads to over-production of gonadotropin, resulting in high estrogen status and consequently increased risk of BC [30]. However, this association is controversial, since NIS was found not to serve as specific indicator of breast malignancy [31]. Additionaly, NIS protein/mRNA expression with accumulation of iodide was also observed in benign breast pathologies [32], and NIS cDNA expression was even found to be higher in fibroadenoma [33] compared with BC.

Hypothyroidism and Hyperthyroidism vs Breast Cancer

Thyroid dysfunction is generally underdiagnosed, with an estimated prevalence between 4 and 8% of the global population in 2010. In the US NHANES III study, the prevalence of hypothyroidism was higher than hyperthyroidism, with values of 4.6% and 1.3% respectively [34]. Literature reported a higher percentage of thyroid dysfunction in older age and in the the female sex compared to the male sex [35]. Symptoms of thyroid pathology may be vague or absent or confused with side effects of medication and even of oncological therapy [35]. Many experimental studies suggest a link between hyperthyroidism/hypothyroidism and BC. In 2016, Sogaard et al. [36] found an increased risk of breast cancer in Danish women with a medical history of hyperthyroidism. In turn, hypothyroidism was associated with a slightly lower risk of breast cancer during the same period [36]. This indicates an association between thyroid function and the risk of breast cancer. On the contrary, a recent meta-analysis of 12 observational studies showed no association between hypothyroidism and breast cancer risk [27].

Angelousi et al. reported a lower incidence of lymph node metastasis in patients suffering from both

hypothyroidism and BC, thus suggesting that hypothyroidism might be a protective factor min BC outcome [37]. Conversely, hyperthyroidism has been often associated with adverse cancer survival outcomes [38]. Another study reported similar prevalence of hyperthyroidism and hypothyroidism in patients with and without breast carcinoma. However, the same study verified that, patients with breast cancer had more than twice the ocurrence of non-toxic goiter, comparing to non breast cancer patients [39].

When investigating the relationship between thyroid volume and breast cancer, a direct relationship between these two variables was found [40]. In breast cancer patients, the value of mean thyroid volume was significantly greater than in controls of the same age [40]. Furthermore, the number of breast cancer patients with an enlarged thyroid gland was significantly greater than in the control group. In one study [41] that included 103.466 Asian women, both hyperthyroidism and hypothyroidism were associated with an increased risk of developing breast cancer after adjusting for age, use of estrogen-containing medication, and history of radioactive iodine treatment. In all age groups, patients with hyperthyroidism showed an overall 12% increased risk of developing BC while hypothyroid patients, unlike other studies, showed a 18% increased of BC.

Overall, studies suggest that proper thyroid hormone function may protect against advanced breast cancer [42]. In line with this conclusion, drug-induced hypothyroidism [9] with subsequent supplemental T4 therapy, displayed higher probability of greater overall survival than untreated hypothyroidism [42]. The literature suggests a relationship between the intake of thyroid hormone supplements and cancer development [12]. Patients with pancreatic cancer and hypothyroidism taking TH supplementation, compared to patients without thyroid dysfunction, had greater cancer aggressiveness but no difference in terms of survival outcome [43]. Thyroid hormone long-term supplementation (i.e. 6 months to more than ten years of treatment) showed to have a protective effect against colorectal cancer (CRC) [44]. Nonetheless, hyperthyroidism and untreated hypothyroidism were associated with a modestly elevated risk of colorectal cancer (CRC) [44]. A study in adult tawainese sample showed results of decreased risk of colon cancer in hyperthyroid patients and lower risk of rectal cancer in hypothyroid patients [45]. We can conclude that thyroid hormone dysfunction, particularly hyperthyroidism, is associated with increased risk of BC, yet the effects of hypothyroidism are unclear [36]. Regarding cancer severity according to the AJCC Cancer Staging System, patients with normal thyroid function presented mainly AJCC stage I cancer (67.5%), while patients with hypothyroidism had predominantly AJCC stage II-III cancer (12.2%) [46]. Additionaly, a recent analysis showed that, from a sample predominantly of the female sex (12.2%), stage III breast cancer was more frequent among women with hyperthyroidism (52.9%) comparing to those with hypothyroidism (38.6%) or euthyroidism (21.4%) [47].

Hypothyroidism

As mentioned, the reports of the effect of hypothyroidism on cancer are not completely consensual, requiring a more exhaustive and always individualized assessment depending on the type of cancer and hypothyroidism. One of the explanations suggested for the impact of hypothyroidism in breast cancer is that, hypothyroidism can induce the dysregulation of prolactin secretion which possibly affects BC progres-

sion. Evidence suggests that prolactin (PRL), is likely to promote BC progression [26]. In animal studies, contrary to what was found for hyperthyroidism, hypothyroidism was associated with a slower rate of tumor growth and a lower tendency for metastasis. Primary hypothyroidism in women was associated with reduced breast cancer risk, smaller tumor size and lower rates of pathologic lymph node involvement [48]. Increased TSH levels, typical of primary clinical hypothyroidism, have also been found in advanced clinical stages of breast and prostate cancer [9]. Despite being associated with reduced risk for BC, hypothyroidism is associated with obesity, which is a risk factor for the development of estrogen receptor (ER) positive breast cancers [38]. Also, results in hypothyroid rats demonstrated a reduced level of both estradiol and leptin, mantaining abdominal fat mass [49]. This suggests that thyroid function may influence the risk of breast cancer through direct and indirect mechanisms possibly leading to opposite effects.

A longer survival rate has been demonstrated after induction of hypothyroidism in patients with glioblastoma, [9] and neck and breast cancer [1]. There was also a lower recurrence of head and neck cancer in hypothyroidism diagnosed after radiation treatment [9]. In addition, patients with cancers other than thyroid cancer, rendered hypothyroid after treatment with a tyrosine kinase inhibitor had longer overall survival [42] then euthyroid patients. It is necessary to bear in mind that thyroid dysfunction may be difficult to detected in cancer patients due to the complexity of the oncological clinical panorama, older age prevalence, presence of critical illness and/or history of oncological treatment. Untreated or inadequately treated hypothyroidism is associated with high morbidity and mortality and can lead to heart failure, psychosis, birth defects, myxedema, coma and to the reduction of the effectiveness of oncological therapies [49].

An increased risk of BC and also other cancer types has been recurrently described among patients affected with hyperthyroidism. In epidemiological studies of distinct cancers, an increased risk of cancer in hyperthyroid patients was demonstrated not only for BC, but also for colon, lung and prostate cancer [1,9]. Some studies identified high levels of thyroid hormones as a poor prognostic factor for BC) [50]. Several in vitro studies have shown that high levels of thyroid hormones can have estrogen-like effects and similarly promote the proliferation of breast cancer cells and stimulate angiogenesis. Many studies concluded that a high pre-diagnostic fT4 (thyroxine not attached to a blood protein) seric level was positively associated with a high BC risk [51]. In vitro studies have also demonstrated a proliferative effect of T3 in breast tissue [36]. Active T3 promotes the proliferation of breast cancer cells and enhances the effect of 17-beta-estradiolmediated cell proliferation in some breast cancer cell lines [39]. In a swedish study, in postmenopausal women, serum levels of T3 were positively associated with BC risk [49]. At the cellular level, T3 binds to specific nuclear receptors and induces the transcription of target genes that modulate energy homeostasis and cell proliferation. Results from population-based studies, correlated positively T3 levels with breast cancer tumor size and the risk of lymph node metastasis [52]. Furthermore, the metabolites of T4 and T3, namely triiodothyronine (rT3), and 3,5-diiodothyronine (3,5-T2), were found to promote local protumor conditions. The enzime for the conversion of TH into these metabolites was found to be overexpressed in cancer cells [53]. A national population-based study of Asian women [41] reported a significantly increased risk of breast cancer among patients diagnosed with hyperthyroidism under 55 years of age, which may be related to higher thyroid hormone levels, as well as increased physiological estrogen in this age group.

In comparison, a decreased risk of BC was found in patients with hyperthyroidism over 55 years of age although with no statistical significance [41]. This fact is probably related to the menopausal status of these patients, associated with low estrogen levels and therefore lower risk for BC.

In reverse, hyperthyroidism can also be a result of cancer ocurrence as it was verified by by Jonklaas et al. [54]. As suggested mechanism for cancer rendered hypothyroidism, it was described that, the thyroid, being and endocrine gland, may become a target of metastases of several nonendocrine cancers because of its abundant blood supply. This would damage the thyroid tissue resulting incially in hyperthyroidism, with progression to hypothyroidism [54]. Steroid sex hormones role in the link between thyroid function and breast cancer. Besides the thyroid hormones, steroid sex hormones (i.e., PRL, estrogen, progesterone, testosterone) have also shown to influence oncogenesis [55]. Elevated endogenous serum levels of estrogen, progesterone and androgens were associated with an increased risk of BC in both pre and post menopause women [56].

Steroid sex hormones and thyroid hormones are ligands with low binding specificity to receptors within the same structurally related protein superfamily [4,57]. The estrogen receptor (ER) and progesterone receptor (PR) are crucial in BC patient's prognosis. Thyroid hormones can enhance the effects of estrogens on BC proliferation and steroid sex hormones may act on the same receptors as thyroid hormones such as TRs and RXRs [58]. In BC cells, thyroid hormones and estrogen display significant crosstalk through promoter cross reactivity, both with estrogen-induced thyroid hormone response element-binding and thyroid hormone-induced estrogen response element-binding [59]. This is in line with the overexpression of the two nuclear estrogen receptors (ERα and ERβ) observed in thyroid cancer cells [60].

A significant positive association between higher circulating prolactin levels and breast has been found [39]. It is considered that hypothyroidism can trigger the hypersensitization of the mammary glandular epithelium to estrogen and prolactin leading to breast dysplasia and breast neoplasia [39]. Alternatively, since estrogen receptors have been identified in abnormal thyroid tissue cells, a reversal in the relationship between BC and thyroid dysfunction cannot be excluded, with BC acting as a trigger for thyroid dysfunction [61].

Estrogen-activated receptor α(ERα) induces proliferation, angiogenesis, and migration of thyroid cancer cells by activation of signaling pathways (PI3K/AKT/mTOR and the mitogenactivated protein kinase (MAPK) cascade), regulation of the Peroxisome proliferator-activated receptor gamma (PPARγ) and proliferative-associated proteins transcriptional activity [62]. In contrast, estrogen receptor β(ERβ) activation is associated with antiproliferative properties [63].

Also, mutations in the nuclear receptor mutual coregulators (e.g. NCOR-1) of both thyroid and steroid sex hormones, can promote cancer in these organs [64]. Finally, estrogen receptor signaling also has an indirect proliferative effect on thyroid cells by increasing thyroid cell sensitivity to TSH signaling [65]. As for testosterone, this hormone exhibited a direct protumorigenic effect on TC progression and severity resultant from it´s attenuation of tumor suppressor genes [66]. In conclusion, sex hormones, primarily estrogen, appear to have a connection not only to BC, but also to thyroid dysfunction and malignancy [25]. No

conclusive data was obtained for the role of progesterone [67] and androgens [68] in BC occurrence and development.

Thyroid Cancer and Breast Cancer

In 2020, the latest data of the World Health Organization indicates that the number of breast cancer (BC) patients has increased to 2.26 million, becoming the most common cancer around the world. Both thyroid and breast cancer are known to be more prevalent in women [25]. Of all the cancers in women worldwide, breast and thyroid malignancies are the first and eleventh respective leading diagnoses [69]. Both women and men with thyroid cancer are at increased risk for subsequent breast cancer and vice-versa, suggesting a common etiology [70]. This bidirectional relationship [71], is reported worldwide independent of differentiated thyroid cancer treatment. However, the underlying reasons for this co-occurrence are unknown. These cancers often occur metachronously (secondary cancer) with distinct characteristics depending on if it is a breast cancer following a thyroid cancer or vice versa [72].

Radiation and alkylating chemotherapy for the treatment of primary cancers are well-established risk factors for secondary malignancy [73]. Some studies observed an increase of 30% to 42% of primary extra-thyroidal malignancies (EM), after thyroid cancer treatment with radioiodine (iodine-131) therapy (RAI) [26]. However, there is no consensus in literaturas on the influence of this type of treatment in BC risk. Correlation was observed, not only between thyroid cancer and breast cancer, but also between benign thyroid disease (TD) and breast cancer. This correlation supports the theory that other factors besides oncologic treatment may play a role in the initiation and development of secondary malignancies [26].

In fact, genetic drivers are believed to account for the co-occurrence of BC and TC. Breast tumors and thyroid tumors exhibit many similar driver mutations, namely in the PI3K–AKT pathway, in the PARP4 gene (critical for DNA repair) [74], in both the KLLN gene and the SDHx gene (which drive tumorigenesis), and co-mutations to the PTEN gene (phosphatase and tensin homolog gene) [75]. To date, to the best of our knowledge, no other mutations have been described as causal agents linking metachronous breast and thyroid tumors. Besides gene mutations, both diseases show the same upregulation of the mitotically associated long non coding RNA (MANCR), functionaly linked with cell proliferation [76].

Thyroid Dysfunction as a Side Effect of Cancer Treatment

The main drugs that the literature points to as causing potential deviations in thyroid function are the tyrosine kinase inhibitors (TKIs), used in the treatment of renal cell cancer (RCC), pancreatic neuroendocrine tumors, hepatocellular carcinoma and gastrointestinal stromal tumors [35]. Among the TKIs, the drug with the most prominent potential for leading to thyroid dysfunction is sunitinib with a reported association of 32 to 85% [35]. Several mechanisms have been proposed for the induction of hypothyroidism by sunitinib, such as: reduction in thyroid volume due to follicle atrophy, activation of antithyroid antibodies production, degeneration of follicular epithelial cells, thyroid capillary rarefaction or interference with iodine uptake [77]. Other mechanisms such as increased activity of deiodinases type 3 may be present. Other TKIs associated with an increased risk of hypothyroidism include: sorafenib, axitinib, pazopanib, vandeta-

nib, motesanib. Hypothyroidism induced by TKI therapy may persist after completion of therapy [78]. A positive correlation has been reported between the sunitinib-induced hypothyroidism and the remission and survival of patients with renal cell cancer (RCC) [79]. Therefore, regular monitoring of thyroid function is necessary in patients on TKI therapy.

Cytokines including interferons and interleukins also affect hormone secretion by the thyroid. The use of alpha interferon (IFN-α) in the treatment of hepatitis, melanoma, RCC and some hematological malignancies has been associated with the development of autoimmune thyroiditis leading to persistent hypothyroidism [80]. IFN-α induces thyroid dysfunction in 3 to 14% of all treated patients with chronic hepatitis C, leading to hypothyroidism, hyperthyroidism, or thyroiditis [81]. A known side effect of cancer treatment with interleukin-2 (IL2) is autoimmune thyroid pathology (especially thyroiditis with hypothyroidism) and, more rarely, autoimmune hyperthyroidism. A higher incidence of remission in patients developing hypothyroidism after IL2 treatment has been noted in RCC and malignant melanoma cancers [9]. Ipilimumab is a monoclonal antibody approved for the treatment of metastatic melanoma or melanoma without possible resection. Antibodies that target programmed death receptor-1 (PD-1) or one of its ligands, PD-1(e.g., nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab), are active against a broad range of malignancies and are changing the treatment landscape for cancer. These agents are being used as monotherapy or in combination regimens the highest incidences of hypothyroidism (17%), hypophysitis (13%), and hyperthyroidism (10%) were reported for the combinatined therapy with nivolumab and pilimumab82. Therapy with bexarotene, approved for the treatment of cutaneous T-cell lymphoma, was also found as a possible cause for hypothyroidism [83].

In addition to oncological drugs, there are also other drugs, such as lithium, with hypothyroidism described as a possible side effect. This drugs act by inhibition of thyroid hormone secretion, with associated reported rates from 14% to 17% for overt hypothyroidism and from 19% to 35% for subclinical hypothyroidism [84]. Another drug that can affect thyroid function is amiodarone by inducing hypo- or hyperthyroidism due to its effects on thyroid hormone uptake and deiodination [83]. Rifampicin is another active substance that affects thyroid hormone levels as it induces the hepatic metabolism of T4, increasing its elimination rate [83]. Regarding the use of radiation therapy, among the different radiation-induced late effects, thyroid disorders are probably underestimated, even though non-autoimmune hypothyroidism/hyperthyroidism, Hashimoto thyroiditis, Graves' disease, benign adenoma, and thyroid cancers have been reported in the literature [85]. The risk of hypothyroidism is related to the dose given and the percentage of thyroid affected by radiation [86]. Thus, hypothyroidism can be a late effect, with described average onset of 1.5 years, going until 5 years, in 48% of patients after radiation treatment [86]. The induction of hypothyroidism by radiation is multifactorial and may be due to the inhibition of follicular epithelial function with progressive alteration of the endothelium resulting in cellular degeneration and necrosis, follicular disruption, vascular degeneration, thrombosis, chronic and acute inflammation or organization of fibrous structure, and partial epithelial regeneration [87].

One of the most common diagnostic studies for cancer patients is computed tomography (CT), often used with iodinated intravenous contrast medium. The administration of this contrast medium can com-

plicate both imaging studies and the management of thyroid dysfunction in cancer patients. It may also occasionally cause an acute exacerbation of pre-existing Graves' disease [88]. On the other hand, results from several in vitro studies suggest that T3 levels may influence the response to chemotherapy. The T3 hormone increases the sensitivity of breast cancer cells to various chemotherapy through promotion of cell proliferation, mitochondrial activity and cell cycle progression [89]. Likewise, this hormone has been shown to increase the cytotoxic activity of the drugs cisplatin and gemcitabine, when administred to patients with pancreatic cancer [90]. Opposite results were observed for colon cancer patients, through a genomic effect of increased expression of P-glycoprotein (also known as multidrug resistance protein 1-MDR1) that mediates xenobiotic efflux [91]. This process is indicative of T3's potential to interact with colon cancer treatment drugs. However, this hypothesis requires experimental studies to be verified. The literature also refers to the existence of an interaction between the hormones T3 and T4 with the drug bortezomib, used in the treatment of multiple myeloma [92].

Association between cancer and the non-thyroidal illness syndrome (NTIS). The non-thyroidal illness syndrome (NTIS), also called euthyroid sick syndrome (ESS), is characterized by changes in serum hormone levels in euthyroid patients with acute or chronic systemic diseases. These changes include: decreased serum T3 and, in severe illness, decreased serum tetraiodothyronine (T4), increased serum reverse triiodothy-ronine (rT3) and no increase in serum thyroid stimulating hormone (TSH) [93]. A number of reports have documented the association of this syndrome with various cancers. In terms of clinical outcome, NTIS was associated with a worse prognosis in cancer patients (i.e., lung cancer and B cell lymphoma) [94,95]. In breast cancer, NTIS was found to be significantly more prevalent in cancer patients at inicila diagnosis (29.5 %), than in breast benign lesions patients (16.5% vs 7.3%), which suggests that NTIs can be related to malignancy [96]. However, the results obtained regarding cancer patients may not be due to a direct effect of this syndrome on the cancer itself, but as a marker of the severity of pre-existing disease.

Autoimmune Thyroid Disease and Breast Cancer

Case control studies have demonstrated an increased prevalence of autoimmune thyroid disease in breast, gastric, pancreatic cancer, multiple myeloma and myelodysplastic syndrome. A large number of cross-sectional studies [97] and existing meta-analysis [98] have proven higher risk of BC in patients with autommune thyroid disease (AITD). Conversely, in some studies, AIDT was associated with favorable outcomes in the case of cancer, namely a lower risk of breast cancer and lower 5-year mortality and metastasis in patients diagnosed with breast cancer [12]. The two major clinical manifestations of thyroid autoimmunity are: Hashimoto's thyroiditis (most common cause of hypothyroidism) and Grave's disease (GD) (most common cause of hyperthyroidism) [50]. Studies show that Hashimoto's thyroiditis patients are at higher risk for breast cancer [99], nontheless, discrepant data also shows no relationship between Hashimoto's thyroiditis and breast cancer [100]. The insulin-like growth factor receptor 1 (IGF-R1) is one of the components involved in the relationship between breast carcinoma and AITDs. Overexpressing IGF-R1 elicits malignant transformation [101]. Both TSH and IGF-1 receptors collaborate for the regulation of thyroid metabolism [102]. Both T and B lymphocytes have been found to overexpress IGF-1R in GD and IGFR1 has been described as a self-antigen in the development of GD pathogenesis [103].

In a celular approach, in both AITD and BC, there are present the following mechanisms: a disruption of the endoplasmic reticulum (ER) [104], presence of T regulatory cells, expression of the glucocorticoid-induced tumor necrosis receptor [104], and the dowregulation of MHC class I [105]. A significant feature of AITD is the existence of autoantibodies, including thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) [106]. An increased prevalence of this antibodies was described in breast cancer patients [61]. To explain this result, it was proposed that both the tumor and the thyroid gland share the same antigens [50]. T cells directed against thyroid antigens may therefore also attack breast cancer cells expressing similar antigens [12]. Indeed, normal and cancerous breast tissues express structurally similar thyroid peroxidase and TSH receptors that may be cross-reactive to thyroid autoantibodies [25]. Sodium-iodide symporter (NIS) was though to be the principal shared antiged between the breast and thyroid tissues, since they both express this protein61. However, NIS is unlikely to play that role, given that serum NIS antibodies are rare in both autoimmune thyroid and BC [107].

The most suitable antigen for this role is considered to be the TPO enzyme, not only because it is expressed in both thyroid and breast tissues (expressed in the breast by both surrounding adipocytes and mammary cells) but also because, TPOAb were found to be the kind of thyroid autoantibodies more prevalent among BC patients [50]. In contrast, both anti-TPO and anti-thyroglobulin autoantibodies have been described as potential protective agents against breast carcinoma in hypothyroidism. Hypothyroidism can develop due to increased serum levels of TPO-Ab, with concurrent lower seric values for thyroid hormones, and therefore a higher TPO-Ab level has been associated with lower BC risk [108]. In contrast, there has been found a positive correlation between seric TPO-Ab levels and risk of BC. One possible explanation is that BC may stimulate the increase of TPO-Ab seric levels. Additionaly, the presence of thyroid autoantibodies in the serum of breast cancer patients may be relevant, particularly the TPO-Ab, since antibody positivity was associated with a better cancer prognosis [109]. Different BC stages were studied in relation to the autoimune thyroid disease. The results showed no significant differences in the number of patients with autoimmune and non-autoimmune thyroid disease in BC stages 0, I and II. Conversely, BC stage III disease was significantly more common among women with autoimmune thyroid disease [47]. This result may reinforce the hypothesis that a reduced thyroid function, present in most cases of autoimmune thyroiditis (elevated seric TPOAb levels), could predispose to the development of a more advanced stage of BC [109].

Both thyroid and breast require a method of oxidation of I- to I2 (organization) to produce iodine proteins. This involves the presence of H_2O_2 as an oxidizing agent catalyzed by TPO in the thyroid and by the lactoperoxidase enzyme (LPO) in the breast [61]. This way, the increased expression of both TPO and LPO in the breast increased in case of BC, can induce oxidative stress in the breast tissue contributing to BC pathogenesis [110]. TPOAb can also cross-react with the LPO expressed in BC tissue, since it is structurally similar to TPO [111,112]. This cross-reactivity could also be involved in BC pathogenesis, since LPO oxidizes estrogen hormones, resulting in the production of free radicals. In turn, this radicals react with DNA and therefore can initiate or promote the tumoral process [113]. The altered micro-environment within BC tissues may alter the expression and the antigenic properties of LPO and/or TPO and promote autoimmunity [114]. Additionaly, the cytokines, chemokines, and extracellular matrix molecules secreted during the pathogenesis of AITD might aid in the recruitment of molecules that promote cancer [115]. In this way,

increased concentrations of Interleukin 6 (IL-6) during the establishment of graves disease (GD), might promote breast carcinoma [116].

Autoimmune processes affecting the thyroid gland very often also alter it´s function, leading to hypothyroidism or hyperthyroidism [50]. The pre-existence or development of thyroid autoantibodies-related hypothyroidism was associated with a favorable response to immunotherapy [26].

Selenium and Iodine intake and Breast Cancer

Selenium deficiency results in a decrease in selenium-containing antioxidant enzymes, such as glutathione peroxidase, deiodinases and thioredoxin reductases, leading to increased levels of reactive oxygen species. These oxidants are a hallmark of lipid peroxidation, can potencially inactivate enzymes and damage DNA, and have been shown to be associated with breast carcinogenesis. On the other hand, increased serum levels of antioxidants have been associated with reduction of breast cancer risk. Non-consensual results have been found for AITD. Such data offered an association of selenium deficiency with AITD, possibly as a result of increased inflammatory activity, while increasing dietary selenium administration has also been reported to decrease TPO antibody levels [61]. On the other hand, geographic variations in breast cancer incidence have been attributed to differences in dietary iodine intake and an effect of iodide on the breast has been postulated [117]. There is also some evidence that iodide itself may act as an antioxidant. In fact, experimental results have shown that seaweed that is rich in iodine can inhibit breast tumor development [117].

These results are supported by the relatively low rate of breast cancer in Japanese women who consume a diet containing iodine-rich seaweed [61]. An anti-carcinogenic role for iodine in experimental animals was suggested by the work of Turken et al. [61], who found that administering iodine-rich wakame seaweed to rats treated with a carcinogen agent (dimethylbenzanthracene), suppressed the development of mammary tumors. In later studies, the same group demonstrated that seaweed induced apoptosis in human breast cancer cells with greater potency than fluorouracil, a cytotoxic agent used to treat breast cancer [61]. Interestingly, this finding applies to breast cancer rates in both men and women [61]. This evidence favors the theory that low rate of breast cancer can be influenced by environmental factors. The possibility that this protective effect may be lost in patients with AITD remains to be explored. Future studies could determine the role of distinct factors in the relationship between thyroid disease and breast cancer, to determine if it is mostly thyroid-related, iodine-related, or, in the case of thyroid autoimmune disease, whether it is the consequence of an immune response to the carcinoma. Is this response breast specific and related to iodine status? These and many other questions remain to be solved before a definitive role in the natural history of breast carcinoma can be assigned to the thyroid.

In the thyroid, iodide is necessary for hormonogenesis, while in the breast it is necessary for breast milk as a source of neonatal nutrition. There is no other known role for iodine in the normal or diseased breast. It has been postulated that the formation of iodine lipids such as iodine lactones or iodine aldehydes represents a form of thyroid autoregulation. In addition to their role in inhibiting thyroid function, these compounds can act as anti-proliferatives in the thyroid [61,117]. Iodinated compounds can exert inhibitory

effects on the activities of adenylate cyclase, NADPH (nicotinamide adenine dinucleotide phosphate)-oxidase and TPO [118]. This effect seems to require the oxidation of I - to I2 because it can be reversed by compounds that inhibit the TPO enzyme or by I- trapping in the thyroid [119]. It has also been suggested that such inhibitory actions of iodine compounds on cell proliferation may play a role in the breast [120]. The frequent coexistence of iodine and selenium deficiencies and the importance of replacing both to maintain thyroid function is well established. It has also been considered that combined iodine-selenium deficiency may facilitate the breast cancer development [61].

Conclusions: There are inconsistent results from case-control studies and population studies regarding the association between thyroid hormones and cancer [26]. However, most scientific evidence suggests that subclinical and clinical hyperthyroidism increases the risk of several malignant cancers, while the association for hypothyroidism is not yet clear. Epidemiological data suggests the existence of a tumor-promoting effect exerted by thyroid hormones (THs), since the incidence of some tumors (colon, breast, prostate, lung, glioblastoma, RCC) has been shown to be increased with increased TH levels. Nontheless, the same was not true for other tumors such as the hepatocellular carcinoma. Several population studies have demonstrated an increase in cancer mortality in the presence of hyperthyroidism with opposite results for hypothyroidism, reinforcing the theory of cell growth stimulation by thyroid hormones.

Results from clinical studies show that treatment-induced hypothyroidism is associated with a favorable prognosis in several types of cancer, especially RCC. The hypothesis is that the induction of hypothyroidism is one of the mechanisms that leads to reduced tumor growth and higher survival rate. However, caution must be exercised regarding this theory, because hypothyroidism may not influence tumor growth by itself, but merely be a surrogate marker of treatment efficacy due to the presence of higher serum drug levels, altered pharmacokinetics or also the susceptibility of the immune system. A bias may also be present in these studies given that, cancer patients undergoing successful (and therefore possibly long-term) cancer treatment are exposed to higher cumulative doses of drugs and and have more time to present possible side effects such as hypothyroidism, in comparison to patients with faster health deterioration due to less successful cancer treatment. According to scientific evidence, more studies are needed to determine and clarify whether hypothyroidism contributes to an increase in the cancer survival rate and which types of cancer this applies to. Hyper- and hypothyroidism can have an impact not only on cancer patient's quality of life and general health, but also on their tolerance to cancer treatment [35] and possibly on the outcome of the treatment itself. This way, the assessment and management of these thyroid dysfunctions is crucial for maintaining quality of life and optimizing cancer treatment [35]. Cellular thyroid hormone signaling directly impacts estrogen-related therapeutics in BC cells through shared nuclear coregulators, promoter ambiguity, and non-genomic overlap. Furthermore, the question of whether the presence of TPO antibodies in the serum of breast cancer patients is breast specific or part of a generalized immunogenic response needs to be explored. Finally, it remains to be seen whether treatment with iodide or selenium has prophylactic potential.

Conclusion

In conclusion, studies in breast cancer patients, provide clear evidence of a bidirectional relationship between thyroid disease and breast carcer, although the mechanisms underlying this relationship require further study. The controversial results in the literature are mainly due to differences in the experimental design of the studies [26,50], small sized samples and/or unavailable serum measurements of thyroid function. More studies are necessary to explore the relationship between distinct thyroid diseases and breast cancer histology and molecular subtypes [72]. Samples of individuals of different ages and ethnicities should be included in this studies to accound for possible confounding factors [26,72]. Future studies on risk factors for breast cancer should include assessment of thyroid characteristics such as thyroid function, antibody status and volume [39].

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