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Review

Thyroid Diseases and Breast Cancer

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Abstract: Epidemiological studies aimed at defining the association of thyroid diseases with extra-thyroidal malignancies (EM) have aroused considerable interest in the possibility of revealing common genetic and environmental factors underlying disease etiology and progression. Over the years, multiple lines of evidence indicated a significant relationship between thyroid carcinomas and other primary EM, especially breast cancer. For the latter, a prominent association was also found with benign thyroid diseases. In particular, a meta-analysis revealed an increased risk of breast cancer in patients with autoimmune thyroiditis, and our recent work demonstrated that the odds ratio (OR) for breast cancer was raised in both thyroid autoantibody-positive and -negative patients. However, the OR was significantly lower for thyroid autoantibody-positive patients compared to the negative ones. This is in agreement with findings showing that the development of thyroid autoimmunity in cancer patients receiving immunotherapy is associated with better outcome and supports clinical evidence that breast cancer patients with thyroid autoimmunity have longer disease-free interval and overall survival. These results seem to suggest that factors other than oncologic treatments may play a role in the initiation and progression of a second primary malignancy. The molecular links between thyroid autoimmunity and breast cancer remain, however, unidentified, and different hypotheses have been proposed. Here, we will review the epidemiological, clinical, and experimental data relating thyroid diseases and breast cancer, as well as the possible hormonal and molecular mechanisms underlying such associations.

Keywords: thyroid disease; breast cancer; etiology; epidemiology; extra-thyroidal malignancies

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1. Introduction

The association of either benign or malignant thyroid diseases (TD) with extra-thyroidal malignancies (EM) has been highlighted in several epidemiological studies, and whether a causal relationship exists between them has been a matter of debate over the last decades. Primarily, such connections have generated much interest around the possibility of identifying common genetic and environmental factors responsible for the etiology and progression of these diseases. In particular, a number of different reports have described the association between thyroid cancers and other primary EM, including breast cancer (BC) [1–4]. This has led to the hypothesis that the long-term carcinogenic effects of anticancer treatments could be responsible for a second primary cancer. In this area, several researchers evaluated whether the ^{131}I therapy administered to thyroid cancer patients could represent the main cause of a succeeding primary EM. Some of them indicated a

30–42% increased risk of primary EM following ^{131}I exposure, but others did not recognize such correlation. Similarly, studies aimed at clarifying whether anticancer treatments of EM, in particular external beam radiations, may cause subsequent primary thyroid cancers have produced conflicting results. On the other hand, a significant association between benign TD and BC was also shown to occur, which seems to suggest that factors other than oncologic treatment may play a role in the initiation and progression of second malignancies [5–8]. It has to be mentioned, however, that some biases in the epidemiological studies reporting associations between TD and BC could exist: (i) TD and BC are very common diseases increasing with age in the female population, which make difficult to discern a real link from a chance association; (ii) the majority of studies examining the association of TD with BC are retrospective or cross-sectional and thus more susceptible to biases compared to prospective studies; (iii) both BC and TD are heterogeneous diseases, and only in a minority of reports, the different BC characteristics such as histology and/or molecular subtypes (Figure 1) and/or TD types were examined.

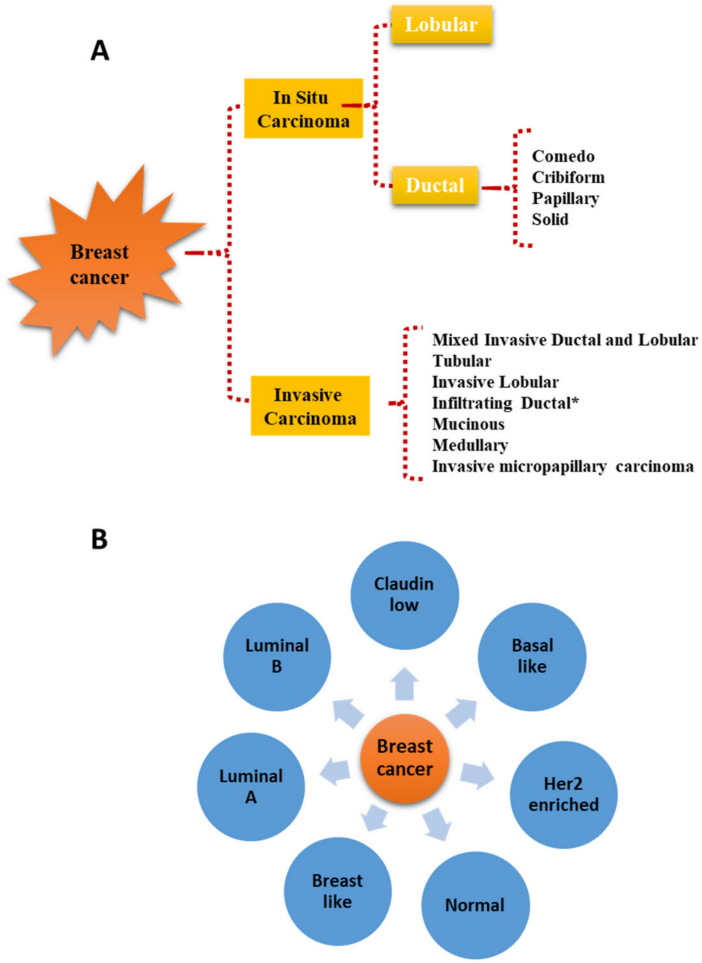

Figure 1. Histological (**A**) and molecular (**B**) classification of breast cancer. * Infiltrating ductal carcinomas evaluated on the basis of nuclear morphology, glandular/tubule formation, and mitotic index are further sub-classified in well-differentiated, moderately differentiated, and poorly differentiated carcinomas.

In the present manuscript, we will review the epidemiological, experimental, and clinical evidence relating benign TD and BC, as well as the potential molecular mechanisms underlying their associations. In particular, approaching the possible role(s) of thyroid gland dysfunctions in promoting breast cancer, we will take into consideration the effects of deregulated thyrotropin (TSH), thyroid hormone (TH), and prolactin (PRL) levels, as well as the effects of thyroid-specific autoantibodies on BC progression.

2. Association of Thyroid Diseases with Breast Cancer: A Historical View

The first clinical evidence of TD and BC association was reported in 1896, when Beatson described the beneficial effects of bilateral oophorectomy and thyroid extract administration in metastatic BC patients [9]. In the 1950s, a number of clinical and experimental results suggested the presence of a causal relationship between hypothyroidism and BC [10–15]. These included the demographic coincidence of the two diseases, the high incidence of goiter or thyroid atrophy in BC patients, the observation that TH treatment reduced the number of recurrences in mastectomized BC patients, and the ability of thyroxine treatment to protect experimental animals against tumor progression, whereas an induced hypothyroid state enhanced tumor growth [10–15]. However, few years later the association between hypothyroidism and BC was put in doubt [16–18]. In particular, epidemiological data showed that despite a dramatic decrease in the state of Michigan of goiter prevalence, from 38.6%, recorded in 1924, to 1.4%, recorded in 1951, the cancer death rate from BC remained unaltered [16,17]. Some studies even reported that breast and other cancers were less frequently encountered in hypothyroid patients [10,19,20]. Backwinkel and Jackson argued that the high incidence of thyroid deficiency in BC patients does not prove a causal relationship but rather reflects the overall incidence of goiter in a given population or area [18]. The same authors, following the analysis of a larger series of patients, documented that the mean age at diagnosis of hypothyroid BC patients was not much different from that of euthyroid ones, and similarly the survival time of BC patients did not differ between euthyroid and hypothyroid individuals [18]. However, when they considered metastatic BC, they found that hypothyroid patients had significantly lower survival [18]. Likewise, Moossa and colleagues showed that, despite the lack of association between the development of BC and hypothyroidism, patients with TD had a shorter survival [21]. At that time, different clinical findings started to indicate a promoter role of thyrotropin (TSH) in TC growth and metastatization [22–24]. This raised the question of whether the increased level of TSH or other trophic hormone(s) released by the pituitary in hypothyroid subjects, rather than the lack of the thyroid hormone itself, unleashed the metastatic spread of BC [18]. Eskin and colleagues, investigating the role of iodine deficiency in the pathogenesis of BC, established a relationship between iodine shortage and breast dysplasia and neoplasia, suggesting that TSH could play an important role in the induction of breast dysplasia in conditions of both iodine deficit and primary hypothyroidism [25,26]. In those years, the ability of thyrotropin-releasing hormone (TRH) to stimulate the release of prolactin (PRL) in addition to TSH was also recognized, thus explaining the presence of high serum levels of PRL and the occurrence of galactorrhea in hypothyroid patients [27,28]. Specific PRL receptors were identified in both normal breast and BC tissues, and the potential involvement of PRL in the pathogenesis of BC emerged from several experiments in animals and clinical observations [29,30]. In addition, Mittra and colleagues hypothesized that circulating TH could regulate the mammotropic effects of PRL and that the increase of PRL activity occurring in the hypothyroidism condition might lead to dysplasia and eventually neoplasia of breast cells [31–33]. Another possible way in which TH could affect BC was proposed in the 1960s, when the effects of TH on estrogen and androgen metabolism as well as on the plasma levels of sex hormone binding globulin (SHBG) began to be recognized [34–37]. Following the diffusion of radioimmunoassays, in the 1970s, some studies described the presence of higher TSH and lower triiodothyronine (T_3) plasma levels in early and advanced BC patients compared to control women [38–40]. A single report showed that the free thyroxine level in BC patients was significantly lower than in healthy individuals and inversely correlated with tumor differentiation [41]. However, other studies did not confirm these findings [42,43]. Interestingly, Shering and colleagues pointed out that while the prevalence of hyper- and hypothyroidism in patients with BC and healthy women was similar, the presence of non-toxic goiter was more than twice as common and thyroid volume was significantly higher in BC patients compared to controls [43]. This led to the hypothesis that also subclinical hypothyroidism could be of some importance in the etiology of BC [32]. Actually, Adami and colleagues reported that the prevalence of TD and the need for thyroxine (T_4) treatment did not differ between control women and BC patients, but the latter had a higher TSH mean value and a lower T_3 mean value, despite no variations being observed in T_4

levels [44]. Such a pattern was found in several non-thyroidal diseases, so it was suggested that it might represent a secondary and probably extrathyroidal metabolic change, most likely due to altered T_4 peripheral conversion [44]. In the 1960s, the first study appeared describing a high incidence of BC among TC patients [45]. In this work, Chalstrey and Benjamin documented the occurrence of BC in 8 out of 92 female patients affected by TC. In three cases, BC preceded TC, in three cases, the opposite occurred, and in two cases, BC and TC were diagnosed at the same time [45]. In 1976, Mittra and colleagues reported the first data on the prevalence of thyroid autoantibodies in Japanese and British BC patients [46]. These authors found that the incidence of thyroid microsomal or thyroglobulin autoantibodies measured by means of immunofluorescence and hemagglutination tests, respectively, was two to three times higher in healthy British women compared to healthy Japanese women. However, no differences in the prevalence of thyroid autoimmunity between BC patients and their relative control groups in either group was recorded [46].

In conclusion, from all the information acquired so far, it appears that alterations of the hypothalamus–pituitary–thyroid axis could affect BC progression in several ways, as schematically depicted in Figure 2. In the next paragraphs, we will attempt to address each of these aspects in the light of the most recent epidemiological, clinical, and experimental findings.

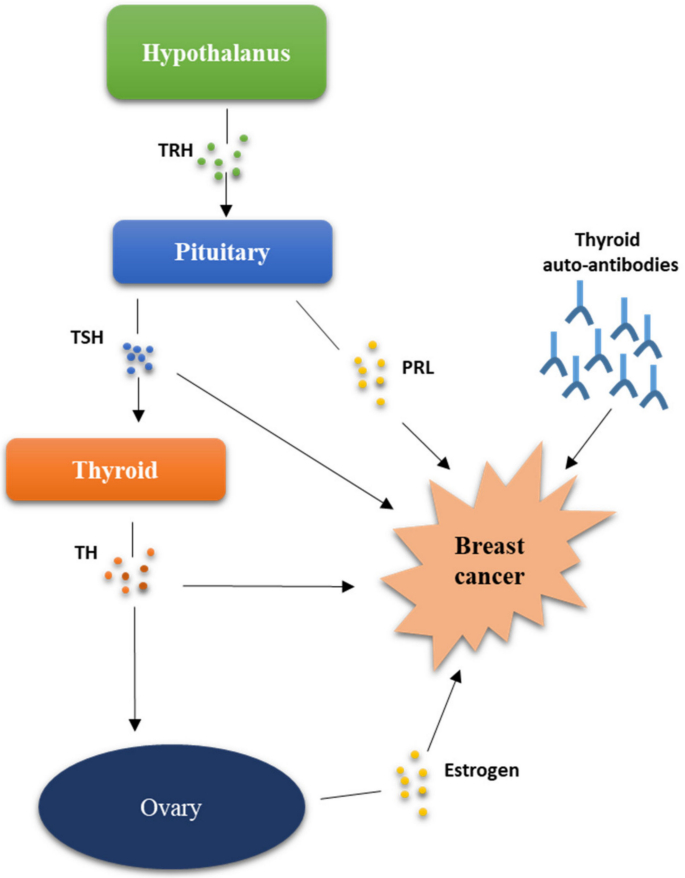

Figure 2. Influence of the hypothalamic–pituitary–thyroid axis on breast cancer progression. Thyrotropin-releasing hormone (TRH); thyrotropin (TSH); prolactin (PRL); thyroid hormone (TH).

3. Thyroid Disease, Prolactin, and Breast Cancer

During pregnancy, increased estrogen levels stimulate lactotroph cell proliferation, leading to increased PRL secretion by the pituitary. The released hormone, along with estradiol, progesterone, placental lactogen, insulin, and cortisol, stimulates mammary gland (MG) growth. In this period, the ability of PRL to induce milk synthesis (lactogenic effect) is inhibited by the high plasma concentration of estrogen. After childbirth, the estrogen level falls, allowing the lactogenic effect of PRL to take place. During lactation, short-term peaks in PRL secretion occur

after nipple stimulation by the suckling infant through a neuro-humoral axis [47,48]. At the cellular level, the action of PRL is mediated by the PRL receptor (PRL-R), a single transmembrane protein belonging to the cytokine/hematopoietin receptor superfamily [47,49]. The PRL-R gene is located on chromosome 5 and is expressed in several tissues including gonads, uterus, breast, liver, kidney, cells of the immune system, and others [47,49]. The PRL-R gene contains 11 exons including 5 alternatives first exons, E11 to E15, each having its own tissue-specific promoter [47,49]. Thus, the pleiotropic effects of PRL may also arise from the tissue-specific expression of PRL-R variants. Upon ligand activation, PRL-R has been shown to activate the intracellular JAK–STAT and mitogen-activated protein kinases (MAPK) signaling pathways [50]. Despite the first evidence being acquired more than 40 years ago, whether PRL and its cognate receptor play a role in BC initiation and progression is still an area of active debate. In addition to the earlier observations previously mentioned, recent works in vitro and in experimental animals appear to confirm a role of PRL in promoting BC [49–54]. In particular, the expression of PRL and its receptor has been detected at both the mRNA and protein levels in more than 90% of invasive human BC, suggesting the presence of autocrine/paracrine effects of PRL within BC tissues [51]. Studies in BC-derived cell lines demonstrated the mitogenic action of PRL [50], and activation of PRL-R has been shown to be sufficient and required for the induction of mammary carcinoma in mice [52–54]. In humans, however, epidemiological studies focused on the promoting role of PRL in BC have produced inconsistent results [49]. In fact, large prospective cohort investigations estimated a significantly increased BC risk in postmenopausal women having serum PRL levels in the top quartile of the normal range compared to age-paired women with PRL serum levels in the bottom quartile [55–58]. Furthermore, this risk was stronger for women with estrogen receptor (ER)-positive tumors [56–58]. On the other hand, two epidemiological studies concerning women with hyperprolactinemia failed to demonstrate in these patients an increased risk of BC [59,60]. To this regard, it could be speculated that locally produced PRL, rather than circulating PRL released by the pituitary, has a role in supporting BC growth. On the whole, the above evidence suggests that PRL, either of pituitary origin or not, likely boosts BC progression.

Deregulated thyroid functions could affect PRL action in promoting BC by at least two different ways. The first one, as mentioned above, implies TRH overstimulation of pituitary PRL secretion in hypothyroidism conditions [27,31–33]; the second one relies on the reported ability of TH to enhance PRL-induced promotion of lobuloalveolar development in breast organ cultures [50,61]. However, the underlying molecular mechanism(s) of such effect remain(s) to be determined.

4. Thyrotropin (TSH), Graves' Disease, and Breast Cancer

Besides its well-known and characterized role in the regulation of thyroid gland development and thyrocytes differentiation and proliferation, TSH is thought to modulate the function of several extrathyroidal tissues. In fact, a growing number of experimental findings evidenced the expression of TSH receptor (TSH-R) in several non-thyroid cells, including murine and human normal and BC tissues [62–67].

In thyrocytes, upon ligand binding, TSH-R interacts with Gs proteins leading to the stimulation of adenylate cyclase (cAMP) formation and protein kinase A (PKA) activation. It also interacts with Gq proteins, resulting in phospholipase C (PLC) stimulation, intracellular Ca++ influx, and increased protein kinase C (PKC) activity. In addition, TSH-R can signal through alternate pathways including p38, p42/44 MAPK, and phosphoinositide 3-kinase (PI3K) [62]. However, the mitogenic action of TSH in thyrocytes seems to depend on the presence of additional growth factors, such as insulin or IGF-1 [68,69]. Moreover, TSH can indirectly stimulate thyrocyte proliferation by increasing the expression of autocrine growth factors or their cognate receptors [68,69]. Clinical observations showing that high serum TSH concentrations are associated with an increased risk of thyroid cancer (TC) and a reduced disease-specific survival have led to consider TSH a tumor promoter in differentiated TC (DTC) patients [70–72]. This effect is presumed to arise from the excessive intracellular activation of pathways associated with the proliferative response [55].

Therefore, a mainstay of the clinical management of these patients is the administration of exogenous L-thyroxine (L-T_4) to reduce or suppress serum TSH levels in patients at low or high risk for DTC recurrences, respectively [73]. All together, these observations suggest that TSH may represent a promoting factor also for EM whose cancer cells express functional TSH-R. For instance, Ellerhorst and colleagues demonstrated the presence of TSH-R in cutaneous melanocytic lesions, including nevi, dysplastic nevi, and melanomas, with the highest expression found in malignant and pre-malignant lesions [74]. In these cells, TSH at physiological concentrations was capable of inducing cAMP formation and MAPK activation, as well as malignant cell proliferation [74].

Govindaraj and colleagues observed the expression of TSH-R mRNA and protein in normal and cancer breast cells, which was significantly higher in tumor tissues compared to normal breast tissues [67]. The observation made by Shi and colleagues in lactating mice is also of interest [66]. They found that breast tissue expresses a TSH-R characterized by a 173 aa deletion in the extracellular domain, causing a less efficient binding to TSH. This could explain the lower expression of natrium iodide symporter (NIS) in lactating breast compared to thyroid tissue [66]. Thus, even if further studies are needed, in vitro results converge to point that TSH may have a role in BC progression, and actually there is clinical evidence supporting this idea [5,75–79]. In particular, a strong association of BC with Graves' disease, caused by autoantibodies to the TSH-R, but not with non-immune hyperthyroidism has been demonstrated [75]. A population-based cohort study in Sweden comprising 18,156 hospitalized Graves' disease patients detected an increased risk of BC in this group [5]. Similarly, a study examining 5025 cases of Graves' disease in Taiwan reported a hazard ratio for developing BC of about 1.6 [76].

To date, a major gap in this knowledge is represented by the lack of in vitro studies on the function(s) of TSH-R in BC cells, which could shed light on the signal transduction pathways actually involved in the proliferative stimulus in this cell type.

5. Thyroid Hormones and Breast Cancer

5.1. Thyroid Hormone Secretion and Mechanisms of Action in Target Tissues

Thyroid hormones are major regulators of growth and development as well as of a number of homeostatic functions in adults, including energy and heat production [80]. Thyroid follicular cells produce two THs, 3,5,3′,5′-L-tetraiodothyronine (thyroxine, T_4) and 3,5,3′-L-triiodothyronine (T_3). Once secreted into the blood, THs are carried by three major transport proteins: thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA or transthyretin), and albumin. The thyroid gland produces about 100 nmol of T_4 and 5 nmol of T_3 every day to maintain a serum total T_4 concentration of about 103 nmol/L and a total T_3 concentration of about 1.8 nmol/L [80]. Only 0.04% of total T_4 (about 19 pmol/L) and 0.4% of total T_3 (about 4.3 pmol/L) circulate in free form and are responsible for the hormonal effects on target tissues [81]. The free THs may act on target cells by two distinct mechanisms: genomic and non-genomic [81,82]. The classical genomic action starts when THs enter the target cells through several plasma membrane transporters, e.g., the monocarboxylate transporters MCT8 and MCT10, the organic anion transporters OATP1 and OATP3, and the L-type amino acid transporter LAT [83]. Once in the cytoplasm, T_4 is deiodinated by deiodinases 1 (D1) or 2 (D2) to form T_3, which binds TH nuclear receptor (THR) with greater affinity compared to T_4 [80]. THRs belong to the nuclear receptor superfamily and act as ligand-dependent transcription factors that bind to specific DNA sequences within promoter regions, known as thyroid responsive elements (TRE), and induce or repress the transcription of downstream target genes [84,85]. Two THR proteins have been identified, THRα and THRβ, encoded by the THRA gene, located on chromosome 17, and the THRB gene, located on chromosome 3 [86–88]. From the THRA gene, three different transcripts are generated, THRα1, THRα2, and THRα3, of which only THRα1 is able to bind T_3 [89,90]. Compared to THRα1, THRα2 and THRα3 proteins differ in sequence and in the length of the C-terminal region. The truncated THRα2 and THRα3 receptors can heterodimerize with the full-length receptor and antagonize T_3-mediated transcriptional regula-

tion [89,90]. The THRB gene provides two receptor isoforms differing in their tissue distribution, THRβ1 and THRβ2, both of which bind T_3 [85].

The second mechanism of THs action, by which THs may elicit rapid cellular responses, is initiated at the plasma membrane, where both T_4 and T_3 may attach to specific regions present in the integrin αvβ3 [81,82,91]. In particular, the latter contains two TH binding sites, termed S1 and S2, of which S1 binds only T_3 at physiological serum concentrations and leads to the intracellular activation of the PI3K, while S2 binds T_4 and, to a lesser extent, T_3, inducing the intracellular activation of extracellular signal-regulated kinases (ERK) 1 and 2 [81,82,92].

5.2. Thyroid Hormones and Breast Development and Cancer

THs have been suggested to play a role, along with other hormones (i.e., PRL, estrogen, progesterone, insulin, growth hormone, and adrenal steroids) in normal breast growth and development [93,94]. In particular, high-affinity binding sites for T_3 have been identified in the mammary gland and are thought to modulate, upon ligand attachment, ductal branching, alveolar budding, and lobules enlargement [95–98]. Moreover, in view of their ability to activate PRL plasma membrane receptors and to enhance casein synthesis induced by PRL, THs are considered lactopoietic [93,94,99,100].

The relevance of ERs overexpression during BC progression is well recognized and is such that the most commonly used drugs, i.e., tamoxifen, fulvestrant, and aromatase inhibitors, are aimed at reducing estrogen levels or blocking ER signaling [101,102]. The extensive use of these drugs in the adjuvant therapy of BC is held accountable for the reduced mortality of patients [103–107]. Experimental evidence suggests that TH could support the estrogen-dependent proliferation of BC cells in several ways: (i) TH may increase the expression of estrogen receptors (ERs) [108,109]; (ii) TRE and the ER response element (ERE) share an identical half-site, and THRs have been shown to bind also to ERE [110]; (iii) thyroxine, through the αvβ3 integrin receptor, may activate MAPK signaling and the phosphorylation of the nuclear ERα [111]. This phosphorylation affects ER ability to interact with chromatin, to recruit coregulators, and to modulate gene expression even in the absence of estrogen [111–113]. In addition, through integrin receptor signaling, THs were found to favor the proliferation of BC cells lacking ER [114,115]. Other than by their effect on the cell cycle, THs have been shown to prompt BC progression by stimulating aerobic glycolysis (Warburg effect), a hallmark of malignant cells [116,117]; BC cell migration and invasion [116,118]; the expression of Programmed Cell Death Ligand 1 (PD-L1), thus preventing the immune destruction of BC cells [116,119]. These observations are in agreement with a number of recent epidemiological investigations indicating that THs may support BC growth in both pre- and postmenopausal women and with clinical data showing that hypothyroidism may have protective effects by reducing the incidence and progression of BC [6,91,120–141]. It is worth considering that T_4 maximally stimulates αvβ3 at physiological free-T_4 concentrations, while supraphysiological free-T_3 concentrations are required to induce cell proliferation via this receptor [113,142,143]. Notably, in a compassionate study comprising patients with far-advanced solid tumors, including BC, Hercbergs and colleagues reported that medically induced euthyroid hypothyroxinemia (pharmacological elimination of T_4 and replacement by T_3) extended patient's survival [113,144]. This represents an attractive new therapeutic approach that deserves larger clinical studies to be confirmed.

Nonetheless, it should be taken into account that, while αvβ3 receptors are thought to mediate most of the tumor-promoting effects of THs in BC cells, nuclear THRs appear to play oncosuppressive functions in BC as well as in other solid tumors [145]. The expression of THRs has been documented in BC tissues [146,147]. In particular, Silva and colleagues demonstrated the presence of THRα1 and THRβ1, but not of THRβ2, at both protein and mRNA levels in 70 sporadic BC tissues [146]. However, the loss of the THRB gene following truncation or deletion of chromosome 3p, where it is located, or loss of heterozygosity (LOH) and gene rearrangement of the THRA gene have been shown to occur in BC samples [92,145,148]. Somatic mutations of THRs leading to reduced ligand affinity and transcription activity, as well as THRB gene promoter hypermethylation with

consequent reduced gene expression, have been also described in BC tissues [145,149–151]. The tumor suppressor role of THRB has been further validated by Park and colleagues, who overexpressed the THRB gene in the human BC-derived cell line MCF-7, endowed with ER and responsive to estrogen stimulation [152]. In a mouse xenograft model, these MCF-7 cells showed a significantly impaired growth due to reduced proliferation and activation of apoptotic pathways [152].

In conclusion, the imbalance of expression and/or activation between membrane and nuclear TH receptors may have detrimental consequences on BC progression.

6. Autoimmune Thyroid Disease (AITD) and Breast Cancer (BC)

Studies aimed at defining the association between BC and benign TD, in particular AITD, have produced conflicting results causing a long-lasting debate [153–164]. In 2002, Sarlis and colleagues performed a meta-analysis of 13 articles published over the previous 50 years including 14,226 women [153]. The authors failed to demonstrate any association between Hashimoto thyroiditis (HT) and BC [153]. Ten years later, Hardefeldt and colleagues accomplished a meta-analysis comprising 28 studies and showed the presence of a higher risk of BC in patients with AITD [7]. In addition, their results testified an increased BC risk associated with the presence of anti-thyroid antibodies and goiter, with Odds Ratios (OR) of 2.92, and 2.26, respectively [7]. The latter data were confirmed in 2020 by Pan and colleagues by means of a meta-analysis on 11 different studies [8]. The authors could establish that patients with BC had higher titers of anti-thyroid peroxidase antibodies (TPOAb) and anti-thyroglobulin antibodies (TgAb) compared to a non-breast disease control group [8]. Similarly, in a very recent meta-analysis involving 21 studies, Chen and colleagues identified TgAb and TPOAb as significantly associated with an increased risk of BC [6]. In our Institute, we analyzed the prevalence of EM in 6386 female patients affected by different TD and we found that a number of EM were associated with TD [79,154]. The EM most frequently recorded was BC (OR 3.94), followed by colorectal (OR 2.18), melanoma (OR 6.71), hematological (OR 8.57), uterus (OR 2.52), kidney (OR 3.40), and ovary (OR 2.62) neoplasms. By age-matched analysis, we observed that the risk of EM was maximal in the age group 0–44 years (OR 11.28), remaining lower but significantly higher than that observed in the general population in the 45–59 and 60–74-years groups [154]. We also showed that when TD patients were dichotomized based on the presence or the absence of TgAb and/or TPOAb, both groups had a higher risk of BC compared to the general population, but the risk was significantly lower in autoantibody-positive patients [79,154]. This finding suggests that amongst TD patients, the presence of thyroid autoantibodies may have a partial protective effect against BC. The latter hypothesis is in agreement with an earlier observation by Smyth and colleagues on TPOAb-positive BC patients, who had a significantly better disease-free and overall survival compared to patients who were TPOAb-negative [155]. In this context, the study by Weijl and colleagues reporting the occurrence of hypothyroidism and anti-thyroid antibodies in patients affected by different types of cancer and undergoing immunotherapy with interleukin-2 is of some interest [156]. They found that the preexistence or development of thyroid autoantibodies-related hypothyroidism was associated with a favorable response to immunotherapy [156]. Similar observations were reported by Franzke and colleagues, who observed that autoimmunity caused by IL-2 and IFN-α2 treatment predicted long-term survival in patients affected by metastatic renal cell cancer [157]. To explain the protective role of thyroid autoantibodies, it has been proposed that cell-mediated cytotoxicity elicited by these antibodies against shared antigens may affect the thyroid gland as well as the tumor [158,159]. This hypothesis is consistent with the expression of NIS and TPO noticed in breast tissues [158,160]. Despite this evidence, however, further prospective large case studies should be undertaken to definitely prove the protective role of thyroid antibodies in BC cancer progression.

7. Conclusions

The impact of thyroid axis dysfunctions on BC progression has been a matter of debate for more than a century, and still today many controversies exist. The available information strongly suggests that TD may affect BC progression in several ways, through (i) altered plasma levels of TSH and THs or production of specific thyroid autoantibodies; (ii) dysregulation of PRL secretion due to hypothyroidism; (iii) alterations in THs responsiveness of BC cells. Thus, different hormonal and molecular players should be taken into consideration in every single patient, when analyzing the association between TD and BC. This knowledge will likely shed light on the potential pathogenic links between TD and BC, possibly allowing a more personalized clinical management of these patients.

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