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TOPIC HIGHLIGHT

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Triiodothyronine and breast cancer

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Abstract

The thyroid hormones (THs), triiodothyronine (T3) and thyroxine (T4), are essential for survival; they are involved in the processes of development, growth, and metabolism. In addition to hyperthyroidism or hypothyroidism, THs are involved in other diseases. The role of THs in the development and differentiation of mammary epithelium is well established; however, their specific role in the pathogenesis of breast cancer (BC) is controversial. Steroid hormones affect many human cancers and the abnormal responsiveness of the mammary epithelial cells to estradiol (E2) in particular is known to be an important cause for the development and progression of BC. The proliferative effect of T3 has been demonstrated in various types of cancer. In BC cell lines, T3 may foster the conditions for tumor proliferation and increase the effect of cell proliferation by E2; thus, T3 may play a role in the development and progression of BC. Studies show that T3 has effects similar to E2 in BC cell lines. Despite controversy regarding the relationship between thyroid disturbances and the incidence of BC, studies show that thyroid status may influence the development of tumor, proliferation and metastasis.

Key words: Thyroid hormone; Triiodothyronine; Breast cancer; Mammary gland and metabolism

Core tip: Breast cancer (BC) is a malignant tumor occurring much more frequently in women than in men; worldwide, the incidence of BC has increased markedly in recent years. It is estimated that 1.7 million women will be diagnosed with BC in 2020, marking an increase of 26%, compared to the current incidence: 1.35 million new cases annually. Countless environmental risk factors, pathological conditions, and physiological agents, as well as thyroid hormones (THs), have been involved in the development of BC. Various lines of evidence suggest tumor-promoting effects of THs. The literature contains controversial reports regarding the relationship between thyroid diseases and BC; furthermore, studies reporting both an excess of and a lack of THs may affect breast development and progression to cancer. Epidemiologically, many studies suggest that hyperthyroidism is a factor in the development of BC. Furthermore, experimental studies have shown that high levels of THs reduce the interval of multiplication of BC cell lines. Therefore, the influence of THs on BC is unclear. However, the majority of BC research suggests a relationship, primarily, when the molecular aspects of these hormones are considered in the progression of this type of tumor.

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INTRODUCTION

Thyroid hormones (THs), 3,5,3',-triiodothyronine (T3) and thyroxine (T4), play critical roles in the differentiation, growth, metabolism, and physiological function of nearly all mammalian tissues[1,2]; in addition, they are required for amphibian metamorphosis[3]. Multiple biological effects of THs depend on intracellular levels of T3, which binds to the thyroid hormone receptor (TR) and is for the most part generated in peripheral tissues by outer-ring deiodination of T4[4]. TH is a key metabolic regulator that coordinates short-term and long-term energy needs[5]. Significant metabolic changes are seen with variations in human thyroid status[6].

Hypothalamus-secreted thyrotropin-releasing hormone (TRH) and thyroid stimulating hormone (TSH), secreted by the anterior pituitary (hypophysis), act in the thyroid gland where THs[7,8] are produced (Figure 1A). TRH and TSH are negatively regulated by T4 and T3 (negative feedback), acting directly on the TSH receptor (TSH-R), expressed on the thyroid follicular cell basolateral membrane[9].

THs regulate a wide range of genes after activation from the prohormone (T4), to the active form (T3)[10]. The signaling pathway is complex and highly regulated because in cells and tissue there is an expression of TH transporters, multiple TR isoforms, as well as interactions with corepressors and coactivators[1,11] (Figure 1B). The functional TR complex consists of a heterodimer with retinoid X receptor (RXR) that binds to a TH response element (TRE) to modulate gene expression. Liganded TR stimulates genes that are positively regulated by triiodothyronine (T3), whereas unliganded TR binds to a TRE to repress those genes. The repressive actions of unliganded TR act in metabolic regulation, particularly in antagonizing the action of other nuclear receptors[12].

TH action has been substantially altered by recent clinical observations of thyroid signaling defects in hormone resistance syndromes and in a broad range of conditions, including profound mental retardation, obesity, metabolic disorders, and a number of cancers[13]. However an uncontrolled study of 3,3'-diiodothyronine (3,3'-T2), iodothyronines as T3 and T4, administration to humans for 4 weeks by an unspecified route was associated with increased metabolic rate and reduced body weight[14], no specific role of 3,3'-T2 in humans has been demonstrated[15]. Animal studies, however, suggest that the 3,5-diiodothyronine and 3,3'-T2 increase metabolic rate[15,16], by acting at the mitochondrial level to increase hepatic cytochrome oxidase activity[17] and supraphysiological dose of T3 causes genotoxicity and potentiates oxidative stress[18].

T3 can influence the mammary gland; this involves the activation of TR present in the mammary gland inducing differentiation and lobular growth in an estrogen-like manner. However, there is controversy regarding the relationship between thyroid disorders and breast cancer (BC) incidence[19].

In this chapter, the influence of T3 on BC will be reviewed. The physiological role of THs in the normal breast will be discussed.

MAMMARY GLAND DEVELOPMENT

Mammary glands are composed of conjunctive tissue and adipose tissue; the latter may vary according to the size of the breast. The development of these glands begins in the embryo phase *via* the extension of ectoderm tissue[20]. This extension is due to allometric growth, which represents the relationship between growth of the ectoderm and the metabolic profile of the epithelial cells[21]. The maintenance and regulation of breast epithelial cells are also controlled by the complex interaction of various hormones including estrogen, progesterone, glucocorticoids, insulin and prolactin[22]. At the onset of puberty, some hormones in the ovary influence the maturation of the mammary glands. They act on the glands by filling a system of branches and lateral ducts surrounding the layer of fat. During pregnancy, mammary glands produce milk due to the high level of estrogen secreted by the placenta. This milk is stored in alveolar secretory units to be supplied later for breastfeeding[21].

During lactation, lipoprotein lipase activity decreases in the adipose tissue and increases in the breast tissue. This indicates an increase in the capture of fatty acids in this tissue[23]. Therefore, the quantity of milk produced is also influenced by the hormone levels; as a result, the physiological process of the epithelial cells is modified[22].

Regarding cell proliferation, studies conducted on human breast tissues report that cell multiplication in mammary epithelium is constant following the complete development of the mammary glands. This mitotic state of proliferation during the luteal phase of the ovarian cycle may coincide with the increase in secretion of estrogen and progesterone[22].

Thus, at this phase, the epithelial cells of the mammary glands may be stimulated by the presence of progesterone or in its synergy with estrogen. After several days of peak cell proliferation, and at the end of the luteal phase, these cells undergo apoptosis. This apoptotic peak coincides with the decrease in estrogen and progesterone secretion from the ovaries; furthermore, a low level of apoptosis occurs in the entire mammary lobule[22].

Based on the foregoing, it is noteworthy that breast tissue constantly undergoes marked physiological cell renovation. This process is due to a response to the levels of estrogen and progesterone secreted by the ovaries. It is also evident that the proliferation and cell replacement of the mammary epithelial cells, after complete development of the breast, plays an important role in the maintenance and tissue function of the normal breast[17].

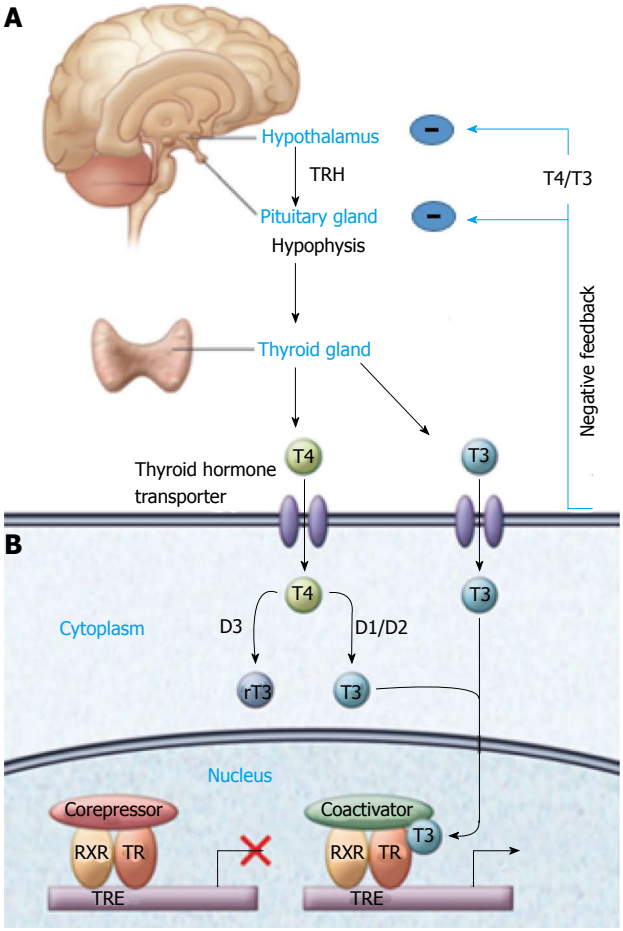

Figure 1 Production and action of thyroid hormone. The key components required for thyroid hormone action are shown, demonstrated by a range of clinical observations. (1) Thyroid hormones (T4 and T3) are produced by the thyroid gland and are regulated by thyroid stimulating hormone (TSH) produced by the hypophysis, which is stimulated by thyrotropin-releasing hormone (TRH). Once released, T4 and T3 exert a negative feedback mechanism on the production of TRH and TSH; and (2) The effects of T4 *in vivo* are mediated *via* T3, T4 is converted to T3 in target tissues by deiodinases 1 and 2 (D1 and D2). Deiodinase 3 (D3) converts T3 to the inactive rT3. Unliganded TR heterodimerizes with RXR and binds to a TRE and then to a corepressor, such as a nuclear receptor corepressor (NcoR); thus, repressing gene expression. T3 binding to the ligand-binding domain results in movement of the carboxyterminal helix 12, disruption of corepressor binding, and promotion of coactivator binding, which then leads to recruitment of polymerase III and the onset of gene transcription. Adapted from Ref.[13].

TRIIODOTHYRONINE EFFECT IN THE MAMMARY GLAND

The hormones that regulate breast development have been known since the 1930s[24] and the involvement of THs in the development and differentiation of normal breast tissue has been established[25-27]. Breast growth and development require the coordinated action of many hormones, such as prolactin, estrogen, progesterone, adrenal steroids, insulin, growth hormone, and THs[28,29]. THs exert a wide variety of biological effects in vertebrate animals; however, their most noteworthy actions may be found in the regulation of cell development and differentiation[30]. From the onset of embryologic development, the mammary glands in women go through a process of ductal development, which supports the creation of alveolar structures during pregnancy, before the onset of lactogenesis. This development includes various stages of proliferation and morphogenesis, which are largely driven by simultaneous changes in the main hormones and growth factors in various reproductive states. Ductal extension is driven by estrogen, growth hormone, growth factor similar to insulin I, and epidermal growth factor; however, ductal branching and alveolar budding are influenced by additional factors, such as progesterone, prolactin, and THs[27].

THs are not essential for the development of the breast ducts; however, they appear to stimulate the development of the lobules of these glands[25]. It is also thought that, in states of excess or lack of this hormone, the process may be negatively affected[31]. In 1986, Vonderhaar *et al*[26] verified that THs influence the development of epithelial cells of the mammary glands in rats. In regard to cell differentiation, the responsiveness of the breast tissue to prolactin in the rat increases *via* the activation of prolactin receptors. In rabbit breast tissue, THs stimulate the synthesis of casein induced by prolactin[32].

BREAST CANCER

This cancer is characterized by a multiphasic process in which a series of genetic and epigenetic changes take place in sequence, leading to the cells' loss of control of the proliferation, differentiation, apoptosis, and repair of DNA[33]. Worldwide, BC is the most common malignant neoplasm in women[34]. It is characterized by epithelial cells and by the tendency to metastasize to distant locations. Most of the tumors are adenocarcinomas, derived from the terminal ductal lobular unit[35].

In Brazil, the estimated incidence in 2012 was 53 thousand new cases, according to the National Cancer Institute[36]. The estimated incidence in the United States for 2011 was 231 thousand cases of BC[37]. The etiology of BC is complex and involves endogenous and exogenous factors that make up the risk factors of the disease[38]. These factors are associated with the onset and development of the tumor; furthermore, they confer a significant histopathologic, genetic, and prognostic variability to this disease[39,40].

Endogenous factors include: family history; an excessive number of ovulatory cycles due to early menarche and/or late menopause; high-density breasts (primarily in post-menopausal women); and genetic mutations (such as BRCA1 and BRCA2). Some examples of exogenous factors are the use of oral contraceptives, hormone replacement therapy, diet, physical exercise, and socioeconomic factors[39,40].

Family history is one of the main risk factors for the development of BC. However, 80%-95% of cases do not have any familial relationships; they are sporadic, resulting from mutations, epigenetic changes, or even the polymorphism of genes involved in metabolism. BC can also

arise from genes that codify components of the paths of hormonal signaling and growth factors or from DNA repair genes. Despite the foregoing causes, BC is primarily related to the exposure of breast tissue to estrogen[41-43].

Epidemiologic studies have shown a possible association between thyroid dysfunction and BC. Postmenopausal BC patients have been reported to have a significant increase in THs, suggesting that an imbalance between estradiol (E2) and T3 fosters the development of BC[44-46]. Conversely, hyperthyroidism has been associated with a reduction in the incidence of BC[47]. The literature describes an increase in survival in hyperthyroid patients with BC, suggesting that hyperthyroidism may protect against the development of BC by increasing steroid hormone binding globulin and by reducing estrogen stimulation of the breast tissue[48].

Despite advances in the knowledge of the pathogenesis and molecular aspects of the disease, little is known about the mechanism whereby T3 modulates its receptor in tumor tissue. Studies are contradictory regarding the type of thyroid pathology and how this influence may take place[48,49].

TRIIODOTHYRONINE AND BREAST CANCER

Experimental studies have shown that THs influence both the differentiation of normal breast cells[44] and the proliferation of BC cells[44,50,51]. The proliferative effect of T3 has been demonstrated in various types of cancer. In BC cell lines, T3 may foster tumor proliferation and increase the effect of cell proliferation by E2; thus, T3 may play a role in the development and progression of BC[52,53]. Apart from this, THs appear to have a stimulating effect on the angiogenesis of certain types of cancer[54,55]. TH levels are related to the risk of BC. As shown by Tosovic *et al*[56], high levels of T3 in postmenopausal women positively correlate with the risk of BC in a dose-response manner. In the case of hyperthyroidism, this correlation was found in postmenopausal women but not in premenopausal woman who had BC[44]. These postmenopausal women with BC had a significant increase in their thyroid/estradiol ratio, suggesting that an imbalance between E2 and T3 fosters the development of BC[44]. Conversely, hyperthyroidism has been associated with a reduction in the incidence of BC[47].

Many *in vitro* and *in vivo* studies have related THs to human cancer since Beatson[57] described the use of thyroid extracts for treating metastatic BC in 1986. Abundant data indicate that the thyroid status affects the formation of a tumor, its growth, and metastasis in both laboratory animals and humans[45]. However, the relationship between thyroid status and the pathogenesis of human BC is currently not elucidated[45].

EXOGENOUS TRIIODOTHYRONINE THERAPY AND BREAST CANCER RISK

The relationship between THs and BC is a controversial topic. The topic was first addressed in 1896 when Beatson used thyroid extract as a treatment for BC[57]; however, some studies reported that THs increased the risk of BC[57,58]. In addition, other studies reported an increase in survival of BC patients who had high TH levels[48]. Some studies that evaluated thyroid pathology reported that BC rarely occurred in hyperthyroid women[58], while others reported that primary hyperthyroidism is associated with a reduced incidence of primary BC[47].

TH replacement therapy primarily entails administering doses of levothyroxine sodium ranging from 1.6 to 1.8 μcg/kg per day[59]. An inhibitory effect of iodine on BC was suggested to be attributable to its antioxidant role[60-62]; however, some *in vitro* experiments have shown a proliferative effect of triiodothyronine on BC cell lines[63,64].

A recently conducted meta-analysis found no statistically significant association between TH replacement and BC risk[19]. One of these studies demonstrated primary hyperthyroidism as a strong protective factor against BC after adjusting for clinical parameters including TH replacement therapy[47].

The literature contains a few studies that show a correlation between TH replacement therapy and BC, despite a tendency towards a non-statistical association between the two. Laboratory studies have demonstrated the ability of triiodothyronines to induce BC proliferation in an estrogen receptor-dependent manner, possibly through crosstalk between the THs and estrogen pathways[50,63,65]. Others THs should be studied in relation to BC, as 3,3'-T2, because Jonklaas *et al*[66] found in their study that the concentrations of 3,3'-T2, T3 and T4 were higher in patients with thyroid cancer, patients who had undergone thyroidectomy, and those who were taking levothyroxine (LT4), than patients without.

A large prospective study should be conducted on women who are undergoing TH replacement therapy to clarify any association with BC.

CONCLUSION

The relationship between THs and the mammary gland can be viewed from various aspects, such as from the influence of these hormones in differentiation and lobular growth in a manner similar to estrogen and even with research that identifies its participation in the development of BC. Thus, it is apparent that controversy is present in the literature in regard to the relationship between thyroid diseases and BC, with research showing that both an excess of and a lack of THs may affect breast development and progression to cancer.

Many epidemiologic studies suggest that hyperthyroidism is a factor that leads to BC. However, experimental studies have shown that high TH levels can reduce the time of multiplication of BC cell lines, pointing, inclusively, to a possible crossing of pathways between the molecular action of THs and estrogen. Research that attempts to determine a relationship between TH replacement therapy and BC found no relationship between the two factors. Thus, a relationship between THs and BC is

not clear. However, a significant amount of research on this topic indicates that there is a relationship, principally when molecular aspects of these hormones are considered in the progression of this type of tumor.

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