

## The Association Between Breast Cancer and Thyroid Function: From Birth to Death

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Breast cancer (BC) is still a common malignancy among women and is the cause of many deaths. Many factors can increase the risk of breast carcinoma and its related mortality. Among these risk factors, some epidemiological studies support the idea that thyroid hormones contribute to many body functions and thyroid regulatory pathways are related to the risk of BC. Although some studies stated that thyroid hormones, whether at high or low levels, increase the risk of BC, controversial evidence is investigated. The current study aimed at investigating different possible associations between thyroid function and BC, after reviewing some general subjects on BC, and thyroid function and hormones.

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## INTRODUCTION

Breast Cancer (BC) is a common cancer among women worldwide, and one of the leading causes of cancer death in many countries [1]. According to epidemiological studies, it is estimated that about 2 million women were diagnosed with BC in 2020 [2]. This multifactorial disorder with different distinct subtypes has various prognostic and therapeutic approaches depending on clinical, pathologic, and molecular features present in this malignancy [3]. Too many environmental risk factors, pathological conditions, physiological agents, and endogenous factors can cause genetic and epigenetic changes leading to uncontrolled proliferation, differentiation, apoptosis, and DNA repair in cells [2]. Family history, age at menarche and menopause, age at first pregnancy, genetic mutations, and breast density are some endogenous factors that play role in BC incidence; on the other hand, exogenous factors,

such as oral contraceptives, lifestyle, radiation, and hormone replacement therapy, like endogenous ones, can cause BC [4]. The etiology of BC is complex and both endogenous, and exogenous factors can increase the risk of BC [3]. There are some epidemiological studies on the higher risk of BC in patients with thyroid disorders and thyroid malignancies; on the other hand, studies denying this correlation are not few [5]. Therefore, given the present disagreements, the current review study aimed at investigating the role of thyroid function and its disorders, and the possible relationship between the function of one of the major body glands and one of the most prevalent malignancies. A comprehensive search was carried out through electronic databases, including Web of Science, PubMed, Scopus, Embase, and Google Scholar, using the keywords "Breast Cancer" and "Thyroid".

All related MeSH terms were included in the search strategy to reduce the risk of missing any related article. Studies on thyroid function and its possible role in the incidence of BC were entered into review.

### Thyroid Gland and Hormones

The thyroid, a butterfly-shaped gland, is located in the lower part of the anterior neck, between C5 and T1 vertebrae, weighing approximately 15-20 g [6, 7]. The thyroid contains lobules consisting of follicles and C cells between them. This rich lymphatic network gland is the only human gland in which the hormonal products are stored extracellularly [8]. Thyroid hormones play role in the development, growth, metabolic regulation, energy expenditure, and functions of the heart and brain [9]. According to the hypothalamic-pituitary-thyroid (HPT) axis, thyroid hormone synthesis and secretion depend on positive and negative feedback from this axis [10]. The first hormone in the HPT axis is thyrotropin-releasing hormone (TRH) released from hypothalamus and affects the pituitary gland. An increase in TRH causes the secretion of thyroid-stimulating hormone (TSH) from the pituitary and, in turn, TSH can mainly affect thyroid function in synthesis and releasing thyroxine (T4) and triiodothyronine (T3), the two major thyroid hormones, into the bloodstream [11]. Note that some other factors, such as adequate levels of iodine, are also required for thyroid hormone synthesis [12]. Thyroid hormones, actually T4, mostly bound to thyroxine-binding globulin (TBG) in plasma, although binding to transthyretin, albumin, unbound T4, and unbound T3 can be detected in circulation [13]. Thyroxine is the prohormone form of thyroid hormones synthesized more than triiodothyronine; although the quantity of T3 is less than T4, it is more active than T4. This peripheral conversion occurs as required in tissue [14]. Most of the effects of thyroid hormones are related to T3; this active form of thyroid hormones can increase cardiac output, heart rate, ventilation rate, basal metabolic rate, catabolism of proteins and carbohydrates involved in brain development, cognitive functions, immune system modulation, female endometrium thickness, play roles in pregnancy and fetal development and potentiate the effects of catecholamines, etc. [15-19]. Many parameters can be measured to investigate the function of the thyroid gland; free T3 and T4 show the hormone activity in the body, total T3 and T4

reflecting the amount of hormone bound to TBG, and TSH level. Nuclear scan and sonography can be helpful to detect some malignancies. Moreover, advanced techniques and fetal hormone testing can be used to detect some disorders prenatally [20-23] (Figure 1).

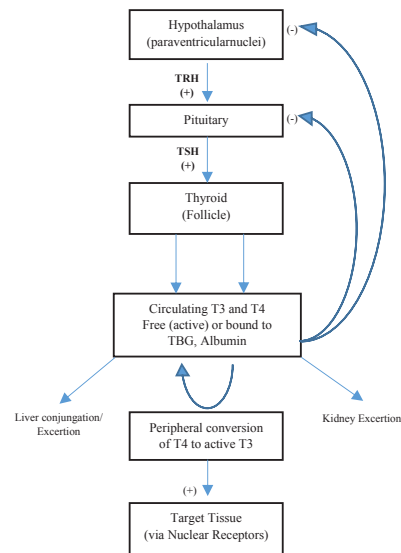


Figure 1: The Flowchart of Thyroid Hormones Regulation [2]

The thyroid releasing hormone (TRH) is synthesized and stored in the hypothalamus. TRH stimulates the secretion of thyroid-stimulating hormone (TSH) from anterior cells of the pituitary. The binding of TSH to its receptors in thyroid cells stimulate thyroid hormones synthesis. T4 is the inactive form of thyroid hormones. Peripheral conversion of T4 to T3 leads to the activation of the hormone and the active form, T3, affects the target tissue. The regulation and elimination pathways of thyroid hormones are also demonstrated in Figure [1]. Similar to many other hormones, hypersecretion or deficiency of thyroid hormones can cause disorders; hyperthyroidism, Graves' disease, hypothyroidism, and Hashimoto thyroiditis are the major ones [24]. In hyperthyroidism and Graves' disease (an autoimmune disease), thyroid hormones, such as free thyroxine, free triiodothyronine, or both, are hypersecreted in circulation. This high serum level of thyroid hormones can cause osteoporosis, atrial fibrillation, hypertension, and congestive heart failure [25-27]. On the other hand, hypothyroidism and Hashimoto thyroiditis are conditions in which thyroid hormone levels in circulation decrease. In hypothyroidism condition, sensitivity to the actions

of narcotics, barbiturates, and tranquilizers are likely; increased susceptibility to infectious diseases, megacolon, psychosis with paranoia, infertility, and myxedema are some complications [26].

### Thyroid Hormones Signaling Pathways

Recent studies indicate that thyroid hormones can trigger two different signaling pathways, genomic and non-genomic.

#### Genomic pathway of thyroid hormones signaling

Free circulating thyroid hormones can activate signaling pathways and transcriptional factors by binding to their specific nuclear receptors [28]. In detail, thyroid hormone receptors include alpha and beta types (TR $\alpha$  and TR $\beta$ ), containing several domains and other functional and regulatory parts [29]. There are four major isoforms for the thyroid hormone receptors, TR $\alpha$ 1, TR $\alpha$ 2, TR $\beta$ 1, and TR $\beta$ 2 encoded by their specific genes. TR $\alpha$ 1 and TR $\alpha$ 2 are expressed by the c-erbA $\alpha$  gene located on chromosome 17, and these receptors can be mostly detected in the kidney, skeletal muscles, lungs, heart, testes, and brain. On the other hand, the c-erbA $\beta$  gene located on chromosome 3 encodes TR $\beta$ 1 and TR $\beta$ 2. TR $\beta$ 1 expression is significant in the brain, thyroid, liver, kidney, and breast, while the TR $\beta$ 2 isoform is specifically expressed in the anterior pituitary, hypothalamus, and non-developed brain [30-33]. Studies indicate that three isoforms of the thyroid hormone receptors, TR $\alpha$ 1, TR $\alpha$ 2, and TR $\beta$ 1, are overexpressed in various tissue but not in the liver [34]. Although several studies demonstrated the lower expression of TR $\beta$ 1 in adenomas and cancers, it is observed that abnormal expression or mutation of TR $\beta$ 1 promotes carcinogenesis. It is interesting that in some studies, the increase in BRCA1-associated BC surveillance was performed when the expression of TR $\beta$ 1 increased [35, 36]. The binding of T3 with the nuclear receptors induces conformational changes in the receptor, and this process finally leads to transcription of the gene

[37]. The effects of thyroid hormones are mediated by the phosphatidylinositol 3-kinase (PI3K), which is a lipid kinase that can phosphorylate phosphatidylinositol (4, 5)-bisphosphate and produce phosphatidylinositol (3, 4, 5)-trisphosphate (PIP3). This process aims to initiate a signaling cascade and mediate the thyroid hormone effect [38]. In the current cascade, PI3K upregulates the effector and AKT to phosphorylate proteins and changes the gene expression. PI3K-AKT promotes cell survival and proliferation and can cause tumorigenesis [39]. In another pathway, T3 can induce the expression of the TGF $\alpha$  and TGF $\beta$  in estrogen-positive BC [40]. Also, in aggressive triple-negative BC, this hormone can increase the Warburg effect, which is a hallmark of cell transformation [41]. In another way, the T3 inhibits the STAT5 signaling pathway. It can associate with TR $\beta$ 1 as a tumor suppressor protein to inhibit mammary hyperplasia development [42]. Also, the overexpression of the T1 gene is seen in breast adenocarcinoma, which is induced by mitogens, serum, specific oncogenes, and cytokines, but this gene is suppressed in high T3 concentrations and, therefore, leads to reduced BC cell proliferation [43]. The other thyroid hormone, T4, induces serine phosphorylation of ER $\alpha$  and leads to transcription activation [44]. Recent studies indicated that T4 could stimulate PD-L1 gene expression and increase in PD-L1 protein can cause defense against immune destruction in BC cells [45] (Table 1).

#### Non-genomic pathway of thyroid hormones signaling

According to some primary studies, thyroid hormones can act through mitochondria and cytoskeleton, besides the nuclear receptors [46]. These rapid actions that are not exerted through genes are called “non-genomic” [47]. The integrin family constitutes structural proteins with 24 isoforms. These proteins mediate cell-cell and cell-extracellular matrix (ECM) interactions. The

**Table 1:** The Summary of Genomic and Non-genomic Signaling Pathways of Thyroid Hormones<sup>a</sup>

TH	Receptor	Pathway	Action	Signaling Pathway
T3	TR $\beta$	T1 gene downregulation	proliferation decrease	genomic
T3	TR $\beta$	STAT5 signaling inhibition	development decrease	
T3, T4	$\alpha$ v $\beta$ 3	activation of MAPK/ERK1/2	proliferation increase	non-genomic

<sup>a</sup> Abbreviations: ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; STAT5, signal transducer and activator of transcription 5; T3, triiodothyronine; T4, thyroxine; TH, thyroid hormone; TR $\beta$ , thyroid hormone receptor-beta

$\alpha v \beta 3$  is one of the integrin isoforms that binding to thyroid hormones near it can cause activation of intracellular signaling through ECM proteins, such as osteopontin, fibronectin, and vitronectin [48, 49]. Based on the interaction of  $\alpha v \beta 3$  with thyroid hormones, mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK 1/2) pathways are activated to regulate multiple cellular physiological processes [47]. This pathway can occur in breast cells; in another word, TH promotes BC cell proliferation by activation of the MAPK/ERK 1/2 pathway via affecting estrogen receptors [44] (Table 1). Studies indicated that in ER-negative BC cells, the  $\alpha v \beta 3$  inhibitor, tetraiodothyroacetic acid (tetrac), prevents the initiation of thyroid hormones cellular action [45].

### **Thyroid Hormones in Different Life Cycles of Women**

#### **Puberty and menstruation**

Since the role of thyroid hormones in normal growth, sexual development, and reproductive functions is of great importance, changes in thyroid hormones function and circulation levels occur during puberty for sexual development and body adaptation. Both hypothyroidism and hyperthyroidism can cause sexual disorders. In detail, hypothyroidism causes delayed puberty or incomplete isosexual precocity; hyperthyroidism, in a long time, may cause menstrual dysfunction and infertility. However, some of these complications are related to both hypo- and hyperthyroidism [50, 51]. Thyroid function is associated with menstruation, and abnormal uterine bleeding, abnormal sexual development, delayed puberty, hirsutism, infertility, and recurrent pregnancy loss might be the outcomes of thyroid dysfunction. In hyperthyroidism, oligomenorrhea, amenorrhea, and anovulatory cycles may occur. On the contrary, polymenorrhea and galactorrhea are common in hypothyroidism. It is crucial to emphasize that thyroid dysfunction is one of the most probable causes of infertility [52-55].

#### **Thyroid hormones and pregnancy**

Definite physiological changes in the maternal thyroid gland are observed during pregnancy. Thyroid hyperplasia and an increase in vascularisation of the gland are among such changes. Due to these conditions, thyroid hormones and related circulatory

factors increase. Consequently, iodine intake is increased [56, 57]. Hypothyroidism is prevalent during pregnancy. Maternal hypothyroidism, which is more common as Hashimoto thyroiditis, is associated with an increased risk of miscarriage and preterm delivery, decreased IQ level, and birth weight of offspring [58]. On the other hand, hyperthyroidism is less common than hypothyroidism, but such conditions- i.e. Graves' disease, can cause stillbirth, preterm delivery, intrauterine growth restriction, preeclampsia, and heart failure [59].

#### **Thyroid hormones and postmenopausal women**

A situation in which there is a year without menses in a woman who had menses before is called menopause. Menopause occurs in the 40s and 50s decade of women's lives, and women often experience complications, such as fatigue, moodiness, irregular periods, sleep problems, loss of sex drive, and weight gain [60, 61]. Due to the physiological and hormonal changes after menopause, degenerated thyroid epithelium and atrophic gland are observed [62]. Therefore, these various changes make hypothyroidism more probable in postmenopause women than hyperthyroidism. These changes also affect other metabolic aspects and functions of the body, which may lead to dangerous conditions, such as the increased risk of atrial fibrillation, coronary heart disease, bone loss, etc. [62-64].

#### **Taking a Glance at the Role of Thyroid Function and Thyroid Hormones Status in Breast Cancer**

Many studies were performed to determine the relationship between BC and thyroid function; however, this correlation is uncertain. The cohort of 142,216 women showed that women with hyperthyroid are at higher risk of BC than those with hypothyroid [65]. Another cohort of 75,076 women aged 20-89 years indicated that the risk of BC and mortality due to this malignancy is related to thyroid function. Also, the incidence of BC in women with hyperthyroidism was more than the ones with hypothyroid. Moreover, the mortality due to breast carcinoma was observed in women over 60 years old with hyperthyroid disorder more than those with hypothyroid disorder [66]. To determine the mechanisms of this phenomenon, many studies were conducted, which had controversial findings. The expression of hypoxia-inducing factor 1 alpha (HIF1A), a protein that regulates the transcription

of cellular and developmental responses to hypoxia, is related to several cancers, including mammary carcinogenesis [67, 68]. Transforming growth factor- $\alpha$  (TGFA) is a member of the epidermal growth factor family that stimulates mitosis and plays a role in cell proliferation, differentiation, and development [67, 69]. Both HIF1A and TGFA can induce angiogenesis. T3 can stimulate the expression of these genes in the MCF7 BC cell line by activating the PI3K pathway [67]. Besides, MCF7 cell proliferation is promoted due to an increase in the activity of ER expression induced by T3 and T47D cells as an estrogen-responsive human ductal carcinoma cell lines, expressing detectable levels of ER. Note that T47D proliferation is regulated by T3 via increasing P53 levels [70, 71]. Although the risk of hypothyroidism is more common in postmenopausal women, controversial results were observed in the relationship between the risk of BC in postmenopausal women and thyroid function. Some studies determined that the lower levels of thyroid hormones decrease the risk of BC, but some others mentioned that both higher and lower serum levels of thyroid hormones could increase the risk of BC [72-76]. The thyroid hormone receptor (TR) is a nuclear receptor activated via thyroid hormone binding. These receptors, with non-genomic effects, act as the second messenger after activation. TRs can affect several metabolic aspects of the cells and their function is necessary for the development of many tissue [77, 78]. One of the other factors related to thyroid function that may influence the risk of BC is TR. TRs can also be associated with BRCA1. The two isoforms of TR may play different roles in BC development and progression; TR $\beta$  is a tumor suppressor, and TR $\alpha$  has the opposite function. The dysfunction of TR $\beta$  can occur during genetic mutations and the regulatory mechanisms mediated by microRNA. Some regions, such as Mkar, Mdb, and AM, in the C-terminal of TR $\beta$ 1 exhibit oncogenic activities, which can cause cell proliferation and suppression of differentiation and apoptosis. Although many studies highlighted the role of TRs in BC, several other studies did not find any relationships, and the exact role of TRs in breast carcinogenesis is unclear [36, 79-81]. Several studies demonstrated the association between autoimmune antibodies,

including thyroid peroxidase antibodies (TPOAbs) and thyroglobulin antibodies (TgAbs), and BC; the higher the level of autoimmune antibodies, a situation similar to Grave disease, the more the risk of BC [82, 83].

## CONCLUSION

BC is a highly prevalent malignancy among women worldwide. Many factors and risk factors can underlie breast carcinoma; moreover, the prognosis and progression of mammary carcinoma, regardless of its type and subtype, can be affected by many endogenous or exogenous factors. The thyroid, an endocrine gland, formation initiates at 3-4 weeks of gestation, and the blood level of two main hormones of this gland is detectable on various timelines; in other words, T4 is detectable at 18-20 weeks and T3 at 10 weeks onward. Thyroid hormone production occurs in thyroid follicles in processes that need iodine, special proteins, and other factors essential for the production and transportation of the hormones. The inactive form of T4 is transformed into the active form, T3, in the target tissue. T3 involves in many functions of the body and has metabolic and developmental roles. The HPT pathway is the main regulator pathway for thyroid functions. According to different periods of life and multi-situations that causing various diseases, the thyroid function and the blood levels of its hormones alter; either increase (hyperthyroidism) or decrease (hypothyroidism). Some studies determined that thyroid function is associated with BC via genomic and non-genomic activities of the thyroid gland, thyroid hormones, thyroid receptors, and related genes. Although many studies support the idea that higher levels of thyroid hormones increase the risk of breast malignancies, studies highlighting the inverse hypothesis are not few. The controversial results of the reviewed studies indicate the necessity for further studies in this field in order to clarify the association.

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## CONFLICT OF INTEREST

The authors declared no conflict of interest.

## ETHICS APPROVAL

Not Applicable.

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