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Differentiated thyroid cancer: Why does it affect predominantly women during the reproductive period and have higher incidence of mutual association with breast cancer?

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ABSTRACT

Differentiated thyroid cancer (DTC) is markedly more common in women than men, and its occurrence and risk for poorer prognosis are associated with pregnancy. Further, it is known that there is a high frequency of co-occurrence of DTC and breast cancer. Although the underlying mechanisms that contribute to these phenomena are not entirely clear, 2 hypotheses are proposed here. First, human chorionic gonadotropin (hCG) produced by the placenta may be involved, since hCG has a similar function to stimulate the thyroid as thyroid-stimulating hormone (TSH), the latter of which is known to play a role in causing DTC and may promote breast cancer through the secretion of thyroid hormones (THs). Second, thyrotropin-releasing hormone (TRH), which is stimulated by suckling in the puerperal period, induces the secretion of not only TSH and thus indirectly THs, but also prolactin (PRL), which can accelerate the development of breast cancer. These hypotheses also explain the pregnancy-associated transient increase in breast cancer risk, while inhibition of estrogen by PRL may have a long-term preventive effect on breast cancer. Pregnancy-associated hyperthyroidism may also account for female preponderance of thyroid disease in general as well as tumors in organs that the thyroid hormone targets such as cardiac myxoma and diffuse-type gastric carcinoma.

Introduction

Thyroid cancer is the most common endocrine malignancy and the most common cancer in Americans aged 16–33 years [1,2]. Thyroid cancer incidence has recently risen mainly due to increased detection of small papillary thyroid cancer through cancer screening [1]. Differentiated thyroid cancer (DTC), which includes papillary, follicular, and Hurthle cell carcinomas, accounts for 95% of all thyroid cancers [1]. DTC is known to have female predominance, with a female-to-male ratio of 3:1–4:1, and further, predominantly affects women of childbirth age [2]. Therefore, hormonal and reproductive factors are assumed to be involved in the pathogenesis. Recent extensive review has demonstrated that the influence of estrogen (E), including age at menarche and menopause as well as oral contraceptive use and/or hormone replacement therapy, is likely to be generally weak [2]. On the other hand, parity is shown to be a risk for DTC incidence, and DTC occurrence during or soon after pregnancy is a risk for poorer prognosis [2]. However, the underlying mechanisms that link DTC and pregnancy are unknown.

Another recent systematic review with meta-analysis has shown that DTC occurrence in women with a history of breast cancer is higher than expected, and the frequency of breast cancer in those with a history of DTC is also greater than expected [3]. It has been proposed that common genetic susceptibility and participation of E may be the causal factors that link DTC and breast cancer, although this remains unclear [3].

Two hypotheses: role of two hormones

Two hypotheses are proposed here to explain both pregnancy-associated DTC and the link between breast and thyroid cancers. First, it is hypothesized that human chorionic gonadotropin (hCG), which is produced by syncytiotrophoblasts of the placenta, is involved (Fig. 1). hCG has a similar function as thyroid-stimulating hormone (TSH) or thyrotropin to stimulate the thyroid to secrete thyroid hormones (THs), which is partly verified by the occurrence of transient nonimmune hyperthyroidism in early pregnancy in about 1–3% of pregnancies [4,5]. Further, morning sickness that manifests as nausea and vomiting is also associated with increased hCG and free thyroid hormones (THs) along with decreased serum TSH [4] since higher THs inhibit TSH secretion in the pituitary gland [6]. In DTC, it was shown that higher serum TSH could be used as a diagnostic tool for and predictor of worsening of DTC, including increased occurrence of extrathyroidal extension and lymph node metastasis, while animal models also suggested that TSH may have a causative role in thyroid cancer [7].

It is well-known that high TH concentrations inhibit not only TSH secretion in the pituitary gland, but also thyrotropin-releasing hormone (TRH) secretion in the hypothalamus [6]. TRH in turn induces both TSH

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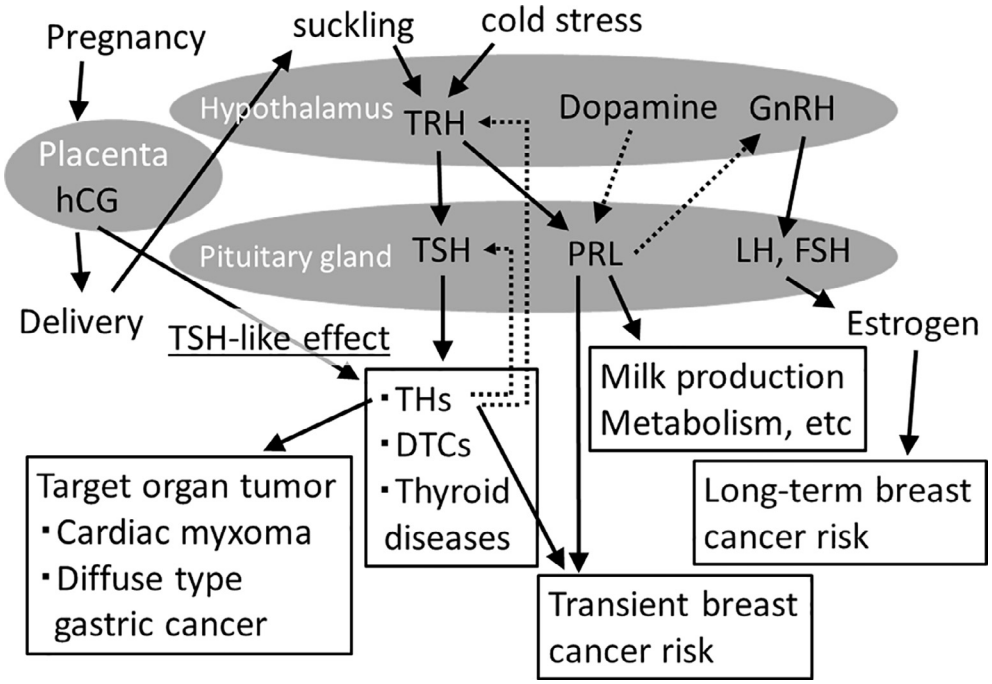

Fig. 1. Relationship of relevant hormones. Arrows show promotion and dotted arrows show inhibition. hCG: human chorionic gonadotropin, TRH: thyrotropin-releasing hormone, TSH: thyroid-stimulating hormone, PRL: prolactin, GnRH: gonadotropin-releasing hormone, LH: luteinizing hormone, FSH: follicle-stimulating hormone, TH: thyroid hormone, DTC: differentiated thyroid cancer.

and prolactin (PRL) secretion in the pituitary gland [8,9], and PRL subsequently decreases serum E levels through inhibition of gonadotropin-releasing hormone (GnRH) secretion in the hypothalamus [10] (Fig. 1). Therefore, one can speculate that pregnancy-associated increase in hCG may also induce breast cancer by increasing TH, decreasing TRH and PRL, and raising E levels, the latter of which is known to be a major player in the initiation, progression, and promotion of breast cancer [11]. Indeed, hypoprolactinemia caused by bromocriptine treatment was demonstrated to bring about significantly higher serum concentrations of E than the placebo group [12]. However, this speculation is inconsistent because there is no evidence of higher serum concentrations of E in hyperthyroidism patients. As baseline secretion of TRH is low, lower TRH secretion may not bring about lower PRL secretion, although TRH-deficient (TRH-/-) mice showed significantly reduced PRL levels during lactation [13].

Nevertheless, evidence shows that increased THs can directly promote breast cancer; breast cancer cell lines that are positive for E receptor (ER) were shown to be stimulated by THs through its E-like effect [14–16]. Indeed, a nationwide cohort study demonstrated an increased risk of breast cancer in women with hyperthyroidism and a slightly decreased risk in those with hypothyroidism [17]. It appears that elevated THs during early pregnancy may have promotive effects on the development of breast cancer since a transient increase in breast cancer risk is observed even several years after pregnancy [18].

However, the above findings contradict those that demonstrate that parity is associated with long-term protective effects against breast cancer [18]. Further, they are also inconsistent with the observation that PRL is elevated during delivery, since TH concentrations inhibit TRH production in the hypothalamus [6], and TRH in turn induces PRL secretion in the pituitary gland [8,9]. Therefore, a second hypothesis is proposed that relates the role of increased TRH during the puerperal period to DTC and breast cancer. It is known that cold stress and suckling promote TRH secretion [9,19]; thus, suckling during the puerperal period induces not only PRL secretion, but also DTC through increased TSH secretion, and further breast cancer through increased THs. The current predominant hypothesis states that pregnancy itself decreases the cumulative number of ovulatory cycles that expose breast tissue to E [11] in order to explain the long-term protective effects of parity against breast cancer [18], however, the role of suckling-associated hypersecretion of PRL (hyper-PRL), which inhibits E, is also plausible.

PRL itself, however, rather promotes breast cancer through enhancing proliferation and motility of cancer cells. This was partly demonstrated by animal studies in which transgenic mice over-expressing PRL developed mammary carcinomas [20], whereas PRL-deficient mice had a reduced incidence of mammary tumors compared with littermates that were hormonally normal [21]. In human breast carcinoma tissues, the PRL receptor was reported to be expressed in more than two-thirds of carcinoma cells by immunohistochemistry [22]. Further, higher plasma PRL levels were shown to be strongly associated with breast cancer risk, particularly among postmenopausal women and patients with ER+ tumors [23]. Therefore, suckling-associated hyper-PRL may also cause a transient increase in breast cancer risk several years after pregnancy [18]. However, the relative risk of breast cancer in 1342 patients, who were treated for hyperprolactinemia in a follow-up period of approximately 5 years, was reported to be only 1.07% (95% confidence interval: 0.50–2.03) [24], which did not show any clear evidence for increased breast cancer risk. Therefore, the promotion of breast cancer by hyper-PRL may be counterbalanced by its protective effect probably through downregulation of E.

With regard to the evolutionary history of PRL, this hormone is fully conserved across the vertebrate phylum [25]. Although PRL is the single most important hormone in the initiation of milk production in mammals [9], its function is divergent including roles in metabolism, reproduction, behavior, immune modulation, growth and development, and water and electrolyte balance [26]. Interestingly, TRH in fish stimulates growth hormone and PRL release, but it does not affect TSH secretion. In amphibians, TRH is a marginal stimulator of TSH release in adult frogs; but in mammals, TRH fully stimulates TSH [25]. It is thought that the original role of TRH was as a PRL-releasing hormone (PRH), and it evolved and acquired its current function to trigger TSH presumably because females who lactate require a high metabolic rate that is supported by THs. Further, cold stress also appears to promote TRH secretion because hypermetabolism can be triggered by THs to defend against cold temperature.

Although effects of hCG (simulating TSH) and TRH (stimulating TSH and PRL) have been highlighted to explain both pregnancy-associated DTC and co-occurrence of DTC and breast cancer in this paper,

involvement of other factors may also be considered. Pregnancy-associated hormones including hCG play a major role in causing immunosuppressive state [27], thus may promote cancer progression. Furthermore, THs are implicated to stimulate tumor-induced angiogenesis [28]. However, these factors cannot completely explain particular occurrence of DTCs after pregnancy and breast cancers after DTCs and vice versa. In order to validate the present hypothesis, at least two measures are conceivable. One is demographical investigations such as comparison of serum hormone levels including hCG and TRH in pregnant and puerperal women with later occurrence rates of DTC and/or breast cancer. The other is clinico-pathological experiments such as comparison of parity with immunohistochemical expression rates of hormone receptors including TSH and PRL in DTC and breast cancer tissues.

The TSH-like effects of hCG and TRH induced by suckling are not limited to promotion of DTC and breast cancer. Since these hormones stimulate the thyroid, they may also account for the fact that thyroid disease in general such as goiter has a 7-fold higher female preponderance [1]. Moreover, this hypothesis may further explain the higher female preponderance of tumors in organs that THs target; THs regulate the physiological homeostasis of the cardiovascular system, gastrointestinal tract, bone tissue, and brain [6,29]. For example, cardiac myxoma is known to have a sex predominance of approximately 70% in females of a relatively younger age (middle age) [30]. Diffuse-type (scirrhous type) gastric carcinoma is also apparently more frequent in females and in relatively younger patients [31]. Unfortunately, no reliable TH-receptor antibody is currently available for detection by immunohistochemistry. In the future, with the development of a better TH-receptor antibody, involvement of THs in these tumors may be verified.

Conclusion

In this paper, two hypotheses are presented to explain both pregnancy-associated DTC and the link between thyroid and breast cancers. Both hCG, which stimulates TSH, and TRH evoked by suckling have roles in thyroid stimulation; they have been shown to accelerate the development of DTC, while increased THs promote breast cancer partly through its E-like effect. Pregnancy-associated breast cancer may be caused by higher THs as well as increased PRL induced by TRH. On the other hand, the long-term protective effects of parity against breast cancer may be attributed to inhibition of E by hyper-PRL. Pregnancy-associated hyperthyroidism may also bring about thyroid disease in general as well as tumors in organs that THs target such as cardiac myxoma and diffuse-type gastric carcinoma.

Conflicts of interest

There are no conflicts of interest to declare.

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Appendix A. Supplementary data

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