RESEARCH ARTICLE

Relationship between Breast Cancer and Levels of Serum Thyroid Hormones and Antibodies: a Meta-analysis

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Abstract

The breast and the thyroid are hormone responsive organs that are closely related with changes of endocrine function and glandular disease. An association between thyroid disorders and breast cancer (BC) risk has been suggested, although the results are inconclusive. The purpose of the present study was to summarize evidence supporting a relationship between BC and the level of thyroid hormones and antibodies. The MEDLINE and EMBASE electronic databases were searched for studies published between 2000 and 2014. The pooled effects were presented as weighted mean differences (WMD) with 95% confidence intervals (CI) using fixed or random effect models. We summarized the results of 8 cross-sectional studies with 4, 189 participants. The overall pooled results showed that the levels of FT_3 and FT_4 were significantly increased in patients with BC (WMD=1.592 pmol/l; 95% CI: 0.15-3.033 and WMD=0.461 ng/dl; 95% CI: 0.015-0.906; *p*=0.043). The TPOAb level in patients with BC was higher than that in the control group (WMD=81.4 IU/ml; 95% CI: 78.7-84.0; *p*=0.000). The overall pooled results of the TgAb with random effects analyses showed that the TgAb level was significantly increased in patients with BC (WMD=101.3 IU/ml; 95% CI: 48.7-153.9; *p*=0.000). The present results indicated that the serum levels of FT_3, TPOAb and TgAb are significantly higher in patients with breast cancer than in healthy controls.

Keywords: Breast cancer - serum thyroid hormones - thyroid antibodies

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Introduction

The breast and thyroid are hormone responsive organs that are closely related with changes of endocrine function and glandular disease. Thyroid diseases (TD) are frequently encountered in clinical practice and are more common among women (Vanderpump 2011). Breast cancer (BC) is a hormone-dependent neoplasm (Turken et al., 2003; Uyeturk et al., 2013). Various thyroid disorders have been detected in breast cancer patients (Smyth et al., 1996; Kuijpens et al., 2005; Ditsch et al., 2010). The results of experimental, clinical and epidemiological studies suggest an association between thyroid disorders and breast cancer risk, although the results are inconclusive (Weiss et al., 1999; Simon et al., 2002).

Thyroid function is evaluated on the basis of the serum levels of thyroid hormones (Turken et al., 2003), such as thyrotropin (TSH), free thyroxine (FT_4) and free triiodothyronine (FT_3). No short-term symptoms have been observed in association with low or suppressed TSH levels and a normal reference range of FT_4, FT_3. This condition is termed subclinical hyperthyroidism, and the long-term consequences of this disease remain uncertain (Vadiveloo et al., 2011). Previous studies have shown that individuals with positive thyroid peroxidase antibodies (TPOAb) have an increased risk of autoimmune hypothyroidism (Hashimoto's thyroiditis), and autoimmune hyperthyroidism (Graves' disease). Here, we summarized evidence supporting a relationship between BC and the level of thyroid hormones and thyroid antibodies by performing a systematic review and meta-analysis of all cross-sectional studies published between 2000 and 2014.

Materials and Methods

Our meta-analysis conforms to the Meta-analysis of Observational Studies in Epidemiology guidelines (Stroup et al., 2000).

Search strategy and selection/exclusion criteria

The MEDLINE and EMBASE electronic databases were searched for studies published between 2000 and 2014. Studies were identified using the following Medical Subject Headings terms: "breast cancer", "thyroid diseases" and "thyroid disorders" without restrictions regarding language and publication form. The reference lists of the retrieved articles were screened to identify

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additional eligible references.

Two reviewers independently screened the titles and abstracts of the search results. Disagreements were resolved by consensus and the remaining full-text articles were evaluated for eligibility on the basis of the following criteria: *(1)*Included subjects were all female adults. *(2)*The design was a quantitative (mean and standard deviation (S.D.), cross-sectional study. *(3)*Data on the levels of TSH, FT_4, FT_3, TPOAb or thyroglobulin antibodies (TgAb) were reported. *(4)*Quantification of TSH, FT_4, FT_3, TPOAb, and TgAb was performed using an immunoassay system. *(5)*Patients with other neoplastic diseases and thyroid disorders such as nodular goiter, thyroid cancer, autoimmune thyroiditis (AIT) and Graves' disease were excluded.

Statistical analysis

Meta-analysis was conducted using STATA version 11.0 (Stata Corp, College Station, TX, USA) with the METAN and METBIAS modules (Altman 1998). The indicators in each study were extracted as mean±S.D. the authors of the study were contacted if information was missing. When units were not uniform, they were transformed into the same unit. The pooled effects were presented as weighted mean differences (WMD) with 95% confidence intervals (CI) using fixed or random effects models (DerSimonian et al., 1986; Harris et al., 2008). Heterogeneity of the studies was assessed using the Cochran Q statistic (Colditz et al., 1995) and quantified by I2, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance (Higgins et al., 2002). Subgroup analyses were performed to investigate between-study heterogeneity focusing on area and years of the study. The difference of 14 years may result in changes in the population characteristics and their environment. Therefore, the period was divided into "years ≥2010" and "years <2010" and areas were classified as "Europe" and "Asia".

Sensitivity analysis was performed to evaluate whether the results were influenced by a single study. Finally, to assess the extent of publication bias, Begg's adjusted rank correlation test (Begg et al., 1994) and Egger's regression asymmetry test (Egger et al., 1997) for publication bias were used.

Results

Selected studies and characteristics

Of the 1062 reports identified, we excluded 1041 studies that were unrelated to the association between BC and thyroid hormones and thyroid antibodies. Twenty-one articles were reviewed to determine their eligibility for the systematic review. Nine studies that did not contain specific data on TSH, FT_4, FT_3, TPOAb or TgAb, 2 that were zoopery studies and 2 that were reviews were excluded. Thus, for our systematic review,

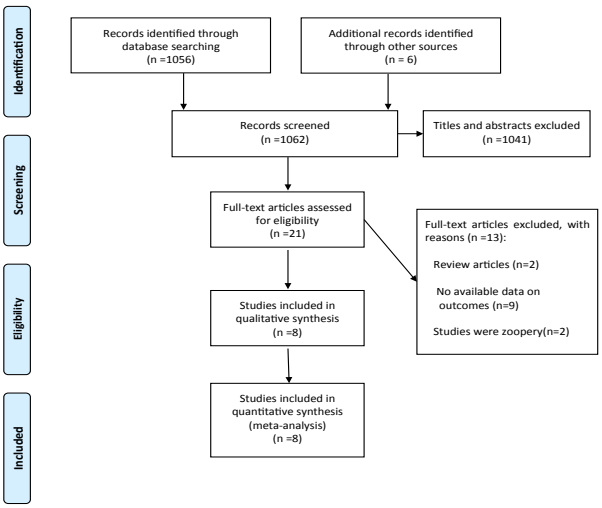

Figure 1. Results of the Literature Search

Table 1. Characteristics of the Studies Included in the Meta-analysis

study	Years of publication	country	Cases number (BC/C)	mean age (or range)	Measurement	TSH cutoff (mU/l)"	FT_3 cutoff (pmol/l)	FT_4 cutoff (ng/dL)	TPOAb positive (IU/mL)	TgAb positive (IU/mL)
Szychta	2013	Poland	499 (9/490)	54.2	---	0.27-4.2	2.27-7.08	0.93-1.7	>35	>115
Giustarini	2006	Italy	136 (36/100)	52.8	RIA	0.4-3.4	4.15-8.77	0.7-1.7	>10	>30
Ali	2011	Kashmir	175 (100/75)	63	RIA	0.3-5.0	2.2-6.8	0.8-2.0	>20	>60
Ditsch	2010	Germany	103 (65/38)	---	Automated immunoassay	0.4-3.8	3.85-6.62	0.9-1.7	>40	>100
Saraiva	2005	Turkey	44 (22/22)	30-85	---	0.3-5.0	1.4-4.4	0.8-2.0	---	---
Kuijpens	2006	Netherlands	2775 (37/2738)	47-54	---	0.4-6.0	---	0.51-1.68	>99	---
Turken	2003	Turkey	249 (149/100)	38-80	RIA	0.3-5.0	2.2-6.8	0.8-2.0	>20	>60
Cengiz	2004	Turkey	204 (136/68)	50.6	RIA	0.2-3.8	2.15-6.31	0.7-2.3	---	>60

*RIA: Radioimmunoassay

Table 2. Data of the Studies Included in the Meta-analysis

study	TSH (mU/l)		FT3 (pmol/l)		FT4 (ng/dL)		TPOAb (IU/mL)		TgAb (IU/mL)	
	BC	C	BC	C	BC	C	BC	C	BC	C
Szychta	1.72±3.62	2.12±5.41	4.43±2.49	5.12±2.94	1.28±0.42	1.34±1.93	157.8±294.8	135.7±206.0	1120.8±1914.9	241.4±565.0
Giustarini	1.9±0.7	1.8±1.4	5.51±1.07	4.92±0.92	0.97±0.27	0.99±0.24	---	---	---	---
Ali	4.12±1.40	1.39±0.79	7.25±0.75	3.42±0.91	2.93±0.57	1.39±0.21	104.57±19.39	24.81±5.16	---	---
Ditsch	1.37±0.87	1.55±1.20	4.69±0.70	4.09±0.55	1.28±0.20	1.15±0.18	128.8±190.3	84.62±255.3		
Saraiva	1.36±0.63	2.41±0.35	5.48±4.83	4.41±4.80	1.40±1.64	1.10±0.83	---	---	---	---
Kuijpens	1.85±2.10	1.99±4.54	---	---	1.01±0.15	0.99±0.17	---	---	---	---
Turken	3.12±1.46	1.46±0.82	8.47±0.75	4.48±0.75	2.64±0.91	1.42±0.31	105.82±21.46	23.08±4.16	140.92±21.5	27.75±7.60
Cengiz	2.07±3.64	1.84±1.58	4.94±2.66	3.75±1.07	1.64±1.94	1.39±0.30	---	---	99.74±248.15	30.17±20.05

Table 3. Subgroup Meta-analysis of Thyroid Hormones

	Category	Subgroup	No. of studies	WMD (95% CI)	*P* value	Heterogeneity %
FT_3	Study region	Europe	3	0.567 (0.320, 0.814)	0.000	13.8
		Asia	4	2.823 (1.717, 3.930)	0.000	97.1
	years	>2010	3	1.324 (-1.310, 3.959)	0.324	99.4
		<2010	4	1.761 (-0.441, 3.963)	0.117	99
FT_4	Study region	Europe	4	0.040 (-0.037, 0.117)	0.311	62.7
		Asia	4	0.896 (0.390, 1.401)	0.001	95.1
	years	>2010	3	0.543 (-0.531, 1.616)	0.322	99.9
		<2010	5	0.389 (-0.120, 0.897)	0.134	98.1
TSH	Study region	Europe	4	-0.034 (-0.289, 0.222)	0.796	99.1
		Asia	4	0.897 (-0.931, 2.725)	0.336	0.0
	years	>2010	3	0.828 (-1.584, 3.240)	0.501	98.2
		<2010	5	0.163 (-1.006, 1.331)	0.785	97.7

Table 4. The Summary Results of the Begg's and Egger's Test for Publication Bias

	TSH	FT_3	FT_4	TPOAb	TgAb
Begg's test	*P*=0.458	*P*=0.881	*P*=0.138	*P*=0.625	*P*=0.602
Egger's test	*P*=0.765	*P*=0.370	*P*=0.355	*P*=0.301	*P*=0.817

*Abbreviations: TSH=thyrotropin; FT3=free triiodothyronine;FT4=free thyroxine; TPOAb=thyroid peroxidase antibodies;TgAb=thyroglobulin antibodies

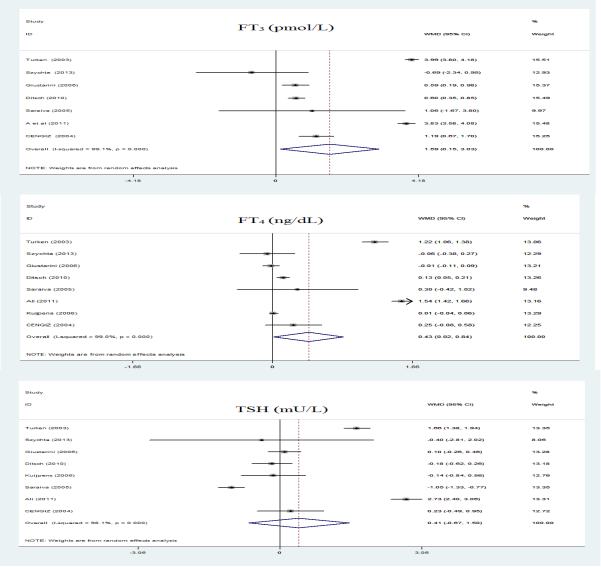

Figure 2. Forrest Plots of Overall Pooled Results of Breast Cancer and Thyroid Hormones

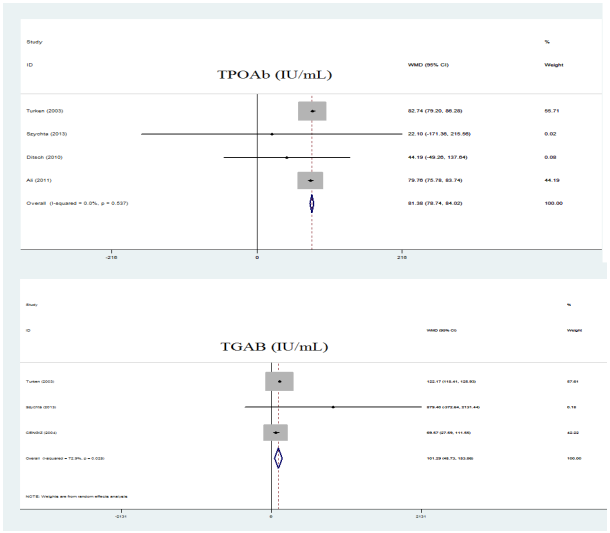

Figure 3. Forrest Plots of Overall Pooled Results of Breast Cancer and Thyroid Antibodies

we summarized the results of 8 cross-sectional studies with 4189 participants (Figure.1) (Turken et al., 2003; Cengiz et al., 2004; Kuijpens et al., 2005; Saraiva et al., 2005; Giustarini et al., 2006; Ditsch et al., 2010; Ali et al., 2011; Szychta et al., 2013) .Tables 1 and 2 show the characteristics and data of all 8 studies included in our analysis.

Meta-analysis

Breast cancer and thyroid hormones: Substantial heterogeneity in the thyroid hormones of the pooled estimates was observed (p<0.001 and I^2>90.0% for every analysis). Thus, random effects models were used. The overall pooled results of the FT_3 and FT_4 parameters showed that the levels of FT_3 and FT_4 were significantly increased in patients with BC (WMD=1.592pmol/l; 95% CI: 0.151-3.033; p=0.030; I^2=99.1%) (WMD=0.431ng/dl; 95% CI: 0.019-0.844; p=0.043; I2=99.0%). The TSH level in patients with BC was higher than that in the control group, although no statistical significance was observed (WMD=0.414mU/l; 95% CI: -0.670-1.498; p=0.454; I^2=98.1%) (Figure.2).

Breast cancer and thyroid antibodies: No heterogeneity in the pooled estimates of TPOAb was observed (I^2 =0.00%, p=0.537). Thus, fixed effects models were used. The TPOAb level in patients with BC was higher than that in the control group (WMD=81.381 IU/ml; 95% CI: 78.738-84.024; p=0.000). The overall pooled results of the TgAb with random effects analyses showed that the TgAb level was significantly increased in patients with BC (WMD=101.293 IU/ml; 95% CI: 48.731-153.855; p=0.025; I^2=72.9%) (Figure.3).

Subgroup of meta-analysis: Because of the high heterogeneity in thyroid hormones, we conducted a series of subgroup analyses to identify the source of heterogeneity. As shown in Table 3, area differences could explain the heterogeneity to some extent. In the "Europe" subgroup, there was a significant increase in FT_3 level in patients with BC (WMD=0.567 pmol/l; 95% CI: 0.320-0.814; p=0.000; I^2=13.8%). In the "Asia" subgroup, heterogeneity was also high. The FT_4 level for "Europe" in patients with BC was higher than that in the control group, but the difference was not significant (p=0.311). The TSH level in "Asia" was not significant (p=0.336). Despite subgroup analysis according to the different ''years'' classes (≥2010 and <2010), heterogeneity was still present within each subgroup regarding serum thyroid hormone levels.

Publication bias

Begg's adjusted rank correlation and Egger's regression asymmetry tests did not provide substantial evidence of publication bias in the parameters assessed. Table 4 is a summary of the results of Begg's and Egger's tests.

Discussion

The present systematic review was based on a meta-analysis of 8 cross-sectional studies to determine the association between BC and thyroid hormones and thyroid

antibodies. We found that BC patients had higher levels of TPOAb and TgAb than controls. However, our findings were in disagreement with those of Prinzi et al. (2014), who showed that the presence of thyroid auto-antibodies is protective against BC. That study differed from the current study in that they used qualitative data to determine thyroid disease, and they showed functional sensitivities for TgAb (positivity>60 U/ml) and TPOAb (positivity>60 U/ml). However, uniform positive criteria for TPOAb and TgAb have not been reported to date (Ditsch et al., 2010; Farahati et al., 2012; Szychta et al., 2013). A meta-analysis conducted in 2012 showed a confirmed relationship between AITD and BC by pooling the results of studies based on positive criteria for TPOAb and TgAb. In the present study, we examined the association between BC and thyroid diseases by analyzing the quantitative level of serum thyroid hormones, which may be more sensitive and accurate than the qualitative data.

Serum thyroid hormone levels are important for the diagnosis of thyroid diseases (Vanderpump 2011; Mittal et al., 2012). In addition, TSH levels are important for diagnosing subclinical diseases. Subclinical hypothyroidism (SCH) is a common endocrine disorder characterized by increased levels of TSH with normal serum levels of FT_4 and FT_3 (Biondi et al., 2008). In the present study, subgroup analysis showed that BC patients in Europe have higher serum FT_3 levels than the control group, although no significant differences in FT_4 and TSH levels were observed. Hellevik et al. reported that low levels of FT_4 and high levels of TSH were associated with an increased risk of BC (Kuijpens et al., 2005). However, another study found no association between TSH levels and breast cancer risk (Hellevik et al., 2009).

Several studies have investigated thyroid function (FT_3 and FT_4 levels) in breast cancer patients. While the exact mechanisms linking thyroid hormones and BC have not been identified to date, a number of hypotheses have been suggested. In preclinical models, FT_3 was able to sustain serum-free proliferation of several cell lines, including breast carcinoma cells (Nogueira et al., 1996; Dinda et al., 2002). Thyroid iodide accumulation is dependent on sodium iodide symporters (Dai et al., 1996). Tazebay et al. (2000) found increased expression of the sodium/iodide symporter (NIS) in BC tissues compared to surrounding breast tissues and tissues from healthy, non-lactating controls. Iodide taken up into thyroid follicular cells by NIS is released to the lumen via pendrin. It is oxidized by thyroid peroxidase (TPO) with hydrogen peroxide (H_2O_2) produced mainly by dual oxidase-2 (DUOX2) and binds to tyrosine residues of Tg accumulated in the lumen. TSH stimulates NIS transcription (Saito et al., 1997; Kogai et al., 2000), prolongs NIS protein half-life, and stimulates the translocation of NIS into the cell membrane (Kogai et al., 2000), maximizing iodide uptake in thyroid cells. Further research is needed to elucidate the mechanism linking BC and thyroid hormones.

Because meta-analyses are observational studies, the present study may be affected by confounding factors and bias (Altman 2001). Although we applied strict inclusion and exclusion criteria to avoid bias, several sources of bias and limitations should be carefully considered in this systematic review. The major limitation of our study was the small sample size and high heterogeneity. The use of a random effects model may be not be enough to adjust for the heterogeneity because of the small sample size of 8 studies. Despite subgroup analysis performed to identify the source of heterogeneity, no plausible factor was found. In addition, age may be an important confounding factor for both of BC and thyroid hormone levels; however, we could not obtain the mean age or age range from each included article. Further studies including a bigger sample are necessary to determine the effect of age. Finally, although recent studies have shown that the incidence of BC is higher in positive TSHRAb females, we did not find enough articles to perform a meta-analysis. Further studies are necessary to confirm the results (Ditsch et al., 2010; Szychta et al., 2013).

In conclusion, The present study indicates that the serum levels of FT_3, TPOAb and TgAb are significantly higher in patients with breast cancer. These results have implications not only for the screening of patients but also for the development of new prognostic markers. Further high-quality prospective studies are needed to explore whether thyroid hormones and thyroid antibodies are potential prognostic markers for patients with BC.

References

Ali AM, Mir R, Bashir S, et al (2011). Relationship between the levels of serum thyroid hormones and the risk of breast cancer. *J Biology Agriculture Healthcare*, **1**, 56-9.

Altman DG (1998). Sbe24: metan-an alternative meta-analysis command. *Stata Tech Bull Reprints*, **8**, 86-100.

Altman DG (2001). Systematic reviews of evaluations of prognostic variables. *BMJ*, **323**, 224-8.

Begg CB, Mazumdar M (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, **50**, 1088-101.

Biondi B, Cooper DS (2008). The clinical significance of subclinical thyroid dysfunction. *Endocr Rev*, **29**, 76-131.

Cengiz O, Bozkurt B, Unal B, et al (2004). The relationship between prognostic factors of breast cancer and thyroid disorders in Turkish women. *J Surg Oncol*, **87**, 19-25.

Colditz GA, Burdick E, Mosteller F (1995). Heterogeneity in meta-analysis of data from epidemiologic studies: a commentary. *Am J Epidemiol*, **142**, 371-82.

Dai G, Levy O, Carrasco N (1996). Cloning and characterization of the thyroid iodide transporter. *Nature*, **379**, 458-60.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials*, **7**, 177-88.

Dinda S, Sanchez A, Moudgil V (2002). Estrogen-like effects of thyroid hormone on the regulation of tumor suppressor proteins, p53 and retinoblastoma, in breast cancer cells. *Oncogene*, **21**, 761-8.

Ditsch N, Liebhardt S, Von Koch F, et al (2010). Thyroid function in breast cancer patients. *Anticancer Res*, **30**, 1713-7.

Egger M, Smith GD, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, *315*, 629-34.

Farahati J, Roggenbuck D, Gilman E, et al (2012). Anti-thyroid peroxidase antibodies are associated with the absence of distant metastases in patients with newly diagnosed breast cancer. *Clin Chem Lab Med*, **50**, 709-14.

Giustarini E, Pinchera A, Fierabracci P, et al (2006). Thyroid autoimmunity in patients with malignant and benign breast diseases before surgery. *Eur J Endocrinol*, **154**, 645-9.

Harris RJ, Bradburn MJ, Deeks JJ, et al (2008). metan: fixed-and random-effects meta-analysis. *Stata J*, **8**, 3-28.
Hellevik AI, Asvold BO, Bjoro T, et al (2009). Thyroid function and cancer risk: a prospective population study. *Cancer Epidemiol Biomarkers Prev*, **18**, 570-4.
Higgins JP, Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med*, **21**, 1539-58.
Kogai T, Curcio F, Hyman S, et al (2000). Induction of follicle formation in long-term cultured normal human thyroid cells treated with thyrotropin stimulates iodide uptake but not sodium/iodide symporter messenger RNA and protein expression. *J Endocrinol*, **167**, 125-35.
Kuijpens JL, Nyklictek I, Louwman MW, et al (2005). Hypothyroidism might be related to breast cancer in post-menopausal women. *Thyroid*, **15**, 1253-9.
Mittal A, Poudel B, Pandeya DR, et al (2012). Metabolic changes enhance the cardiovascular risk with differentiated thyroid carcinoma a case control study from Manipal Teaching Hospital of Nepal. *Asian Pac J Cancer Prev*, **13**, 2335-8.
Nogueira CR, Brentani MM (1996). Triiodothyronine mimics the effects of estrogen in breast cancer cell lines. *J Steroid Biochem Mol Biol*, **59**, 271-9.
Prinzi N, Baldini E, Sorrenti S, et al (2014). Prevalence of breast cancer in thyroid diseases: results of a cross-sectional study of 3, 921 patients. *Breast Cancer Res Treat*, **144**, 683-8.
Saito T, Endo T, Kawaguchi A, et al (1997). Increased expression of the Na+/I- symporter in cultured human thyroid cells exposed to thyrotropin and in Graves' thyroid tissue. *J Clin Endocrinol Metab*, **82**, 3331-6.
Saraiva PP, Figueiredo NB, Padovani CR, et al (2005). Profile of thyroid hormones in breast cancer patients. *Braz J Med Biol Res*, **38**, 761-5.
Simon MS, Tang MT, Bernstein L, et al (2002). Do thyroid disorders increase the risk of breast cancer? *Cancer Epidemiol Biomarkers Prev*, **11**, 1574-8.
Smyth P, Smith D, Dermott EM, et al (1996). A direct relationship between thyroid enlargement and breast cancer. *J Clin Endocrinol Metab*, **81**, 937-41.
Stroup DF, Berlin JA, Morton SC, et al (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*, **283**, 2008-12.
Szychta P, Szychta W, Gesing A, et al (2013). TSH receptor antibodies have predictive value for breast cancer-retrospective analysis. *Thyroid Res*, **6**, 8.
Tazebay UH, Wapnir IL, Levy O, et al (2000). The mammary gland iodide transporter is expressed during lactation and in breast cancer. *Nat Med*, **6**, 871-8.
Turken O, NarIn Y, DemIrbas S, et al (2003). Breast cancer in association with thyroid disorders. *Breast Cancer Res*, **5**, 110-3.
Uyeturk U, Tatli AM, Gucuk S, et al (2013). Risk factors for stage IV breast cancer at the time of presentation in Turkey. *Asian Pac J Cancer Prev*, **14**, 7445-9.
Vadiveloo T, Donnan PT, Cochrane L, Leese GP (2011). The Thyroid Epidemiology, Audit, and Research Study (TEARS): the natural history of endogenous subclinical hyperthyroidism. *J Clin Endocrinol Metab*, **96**, 1-8.
Vanderpump MP (2011). The epidemiology of thyroid disease. *Br Med Bull*, 99, 39-51.
Weiss HA, Brinton LA, Potischman NA, et al (1999). Breast cancer risk in young women and history of selected medical conditions. *Int J Epidemiol*, **28**, 816-23.