Physiol. Res. 53: 693-702, 2004

Autoimmune Thyroid Diseases in Women with Breast Cancer and Colorectal Cancer

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Received June 30, 2003
Accepted January 5, 2004

Summary

The aim of the study was to compare the prevalence of autoimmune thyroid diseases in three groups of women (66 with breast cancer (CaB), 68 with colorectal cancer (CaC) and 49 without oncological diseases as a control group). Serum levels of thyroid-stimulating hormone (TSH), free thyroxin (fT4), antibodies to thyroglobulin (TGB-ab) and thyroperoxidase (TPO-ab) and tumor markers CEA, CA 15-3 and CA 19-9 were investigated in all subjects by using the chemiluminiscence method. In contrast to Graves' disease (no observed case), autoimmune thyroiditis was diagnosed in 24.2 % women with CaB (4.5 % euthyroid and 19.7 % with subclinical or overt hypothyroidism), compared to 16.7 % in women with CaC (2.0 % euthyroid and 14.7 % with subclinical or overt hypothyroidism) and 16.2 % controls (4.0 % euthyroid and 12.2 % with subclinical or overt hypothyroidism). Serum levels of TGB-ab were higher in the group with breast cancer as compared to those with colorectal cancer and the control group (medians: 35.80 vs. 31.75 vs. 27.70, $p<0.001$). Similarly, the percentage of positive TGB-ab and TPO-ab serum levels was higher in women with breast cancer as compared to those with colorectal cancer and the control group. The results of the study support the controversial theory that there is an increased prevalence of autoimmune thyroiditis in women with breast cancer.

Key words

Breast cancer • Thyroid autoantibodies • Thyroid stimulating hormone

Introduction

The association of autoimmune thyroid diseases (AITD) with several autoimmune diseases such as diabetes mellitus type I or celiac disease is generally known (Jiskra *et al.* 2003b). In contrast, although it has been the subject of study for a long period now, the relationship between thyroid diseases and some non-autoimmune diseases, e.g. breast cancer is not fully understood. Previous research and our experience have shown that autoimmune thyroiditis (AIT) with subclinical or manifest hypothyroidism (in contrast to non-AITD) are frequently found in women with breast cancer (in 30 % according to several studies). A sonographic enlargement of the thyroid gland (Smyth *et al.* 1996, Shering *et al.* 1996) and a high percentage of positivity of antibodies to thyroid peroxidase (nearly 34 %) (Shering *et al.* 1996, Smyth *et al.* 1998) have been proved in women with breast cancer in comparison with healthy women. Moreover, in our previous studies increased serum levels

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of the thyroid-stimulating hormone (TSH) with subclinical or manifest hypothyroidism was found in 10.0-19.7 % of women with breast cancer (Límanová *et al.* 1996, 1998, Jiskra *et al.* 2003a). Thyroid enlargement has been described in 80 % and TPO-ab positivity in 28 % of women with benign fibrocystic mastopathies (Smyth *et al.* 1998, Mizia-Stech *et al.* 1998). Decreased trijodthyronine (T3) serum levels without changes in thyroxine (T4) and TSH serum levels have been found in postmenopausal women with benign fibrocystic mastopathies (Zych *et al.* 1996).

An extensive retrospective study of 9520 women with breast cancer in Massachusetts General Hospital has suggested that the survival rate of patients with contemporary autoimmune thyropathies is higher in comparison with women with healthy thyroid glands (Goldman *et al.* 1992). Similar results have been obtained by Smyth *et al.* (1998) and Shering *et al.* (1997). Recently, the positivity of TPO-ab serum levels has been found in 37.7 % of Greek women with breast cancer in comparison with 19 % of women with benign fibrocystic mastopathies and 18.4 % of women without breast diseases. Through the use of fine-needle-aspiration biopsy, autoimmune thyroiditis has been confirmed in 19 of 310 women (13.3 %) (Gogas *et al.* 2001). Serum levels of TSH were not tested in this study.

The aim of our study was to compare the prevalence of AITD in women with breast cancer, colorectal cancer, and in a control group of women without oncological diseases, and to explore the possible relationship of thyroid laboratory parameters to the stage of oncological disease, to the kind of oncological therapy (radiotherapy, chemotherapy and hormonal therapy), and to the serum levels of tumor markers CEA (carcinoembryonal antigen), CA 15-3 and CA 19-9.

Table 1. Characteristics and prevalence of several forms of autoimmune thyroid diseases in relationship to examined groups: women with breast cancer, colorectal cancer and without malignant diseases (controls).

			Breast cancer (n=66)	**Colorectal cancer** (n=68)	**Controls** (n=49)
GRAVES' DISEASE	**With hyperthyroidism**	positive TSH-R-ab TSH < 0.5 mIU.l^{-1} fT4 > 23.1 pmol.l^{-1} ultrasound characteristics of AIT* clinical signs of hyperthyroidism	0	0	0
AUTOIMMUNE THYROIDITIS (AIT)	**Euthyroid**	positive TGB-ab and/or TPO-ab and ultrasound characteristics of AIT* normal TSH (0.5-3.5 mIU.l^{-1}) normal fT4 (9.8-23.1 pmol.l^{-1})	3 (4.5 %)	1 (2.0 %)	2 (4.0 %)
		without clinical signs of hypothyroidism			
	With subclinical hypothyroidism	positive TGB-ab and/or TPO-ab or ultrasound characteristics of AIT* TSH > 3.5 mIU.l^{-1} normal fT4 (9.8-23.1 pmol.l^{-1}) without clinical signs of hypothyroidism	10 (15.2 %)	10 (14.7 %)	5 (10.2 %)
	With overt hypothyroidism	positive TGB-ab and/or TPO-ab or ultrasound characteristics of AIT* TSH > 3.5 mIU.l^{-1} fT4 < 9.8 pmol.l^{-1} with clinical signs of hypothyroidism	3 (4.5 %)	0	1 (2.0 %)

AIT: autoimmune thyroiditis, TSH (mIU.l^{-1}): serum levels of thyroid-stimulating hormone, fT4 (pmol.l^{-1}): serum levels of free thyroxine, TGB-ab (kIU.l^{-1}): serum levels of antibodies to thyroglobulin, TPO-ab (kIU.l^{-1}): serum levels of antibodies to thyroid peroxidase, TSH-R-ab (kIU.l^{-1}): antibodies to TSH receptor, n: number of patients, the differences between the groups were not statistically significant, * ecreased echogenity, non-homogenous structure, increased perfusion in Graves' disease, ■ borderline forms

Methods

We investigated 134 randomly chosen women with oncological diseases, 66 with breast cancer (CaB) with an average age of 63.5±11.8 years and 68 with colorectal cancer (CaC) with an average age of 66.8±10.8 years. All of these patients had undergone a breast or colorectal surgical intervention. Because of the high average age of women with oncological diseases, it was not possible to investigate an age-matched group of healthy women. Therefore, an age-comparable group of 49 women with several non-oncological diseases (ischemic heart disease, arterial hypertension, cerebral stroke, tromboembolic disease, chronic bronchitis, and type 2 diabetes mellitus) admitted to the medical department was used as a control group (C) with an average age of 68.4±12.8 years. All of the patients were from the same geographic area (Prague). Patients with oncological diseases were divided according to the stage to which the oncological disease had progressed and the kind of oncological therapy they were undergoing. Two women with CaB which had been previously treated with thyroid replacement therapy were excluded. Family and personal history with respect to autoimmune, endocrine and oncological diseases were obtained from the subjects, and they all underwent clinical examination and thyroid ultrasonography. The chemiluminescence method was used to investigate the serum levels of thyroid-stimulating hormone (TSH), free thyroxine (fT4), antibodies to thyroid peroxidase (TPO-ab) and antibodies to thyroglobulin (TGB-ab) in all of the women. Likewise, the serum levels of antibodies to TSH-receptor (TSH-R-ab), of tumor markers CEA (carcinoembryonal antigen), CA 15-3 and CA 19-9 were also assessed in part of each group using the chemiluminescence method. Laboratory, clinical and ultrasound characteristics of several forms of AITD are shown in Table 1. According to what is presently known about subclinical hypothyroidism and by using the supersensitive diagnostic methods, the following values were taken as normal ones: TSH 0.5-3.5 mIU.l^{-1} (Vanderpump *et al.* 1995, Bjoro *et al.* 2000, McDermott and Ridgway 2001, Dayan *et al.* 2002), fT4 9.8-23.1 pmol.l^{-1}, TGB-ab <100 kIU.l^{-1}, TPO-ab <20 kIU.l^{-1}, CEA 0-5.0 μg.l^{-1}, CA 15-3 0-31.0 kIU.l^{-1} and CA 19-9 0-37.0 kIU.l^{-1}.

The results were statistically analyzed by the χ^2-test, t-test, the Mann-Whitney test, the Kruskal-Wallis test, the Pearson correlation coefficient and the Spearman rank order correlation coefficient employing the Sigmastat program (Jandel Scientific, USA).

Table 2. TSH, fT4, TGB-ab and TPO-ab serum levels in women with breast cancer, colorectal cancer and women without malignant diseases (controls).

	Breast cancer	**Colorectal cancer**	**Controls**	**p**
	Median (minimum, 25 %, 75 %, maximum)			
n	**66**	**68**	**49**	
Age	**65** (40 54 73 87)	**69** (43 58 75 85)	**70** (39 57 77 90)	NS
TSH	**1.77** (0.15 1.04 2.84 47.9)	**1.68** (0.33 1.15 2.41 9.26)	**1.52** (0.45 0.96 2.66 14.56)	NS
fT4	**15.70** (7.38 14.26 17.37 22.63)	**15.10** (9.9 13.25 16.97 17.29)	**15.19** (10.5 13.0 17.15 21.5)	NS
TGB-ab	**35.80** (26.1 30.8 55.4 6000.0)	**31.75** (24.1 26.5 37.0 445.2)	**27.70** (18.5 23.5 36.8 298.0)	p_1=0.0008 p_2<0.001 p_3=0.057
TPO-ab	**6.10** (6.1 6.1 12.2 871.0)	**6.10** (6.1 6.1 7.2 2211.0)	**6.10** (6.1 6.1 6.1 1621.6)	NS

Data are expressed as median, minimum, lower quartil (25 %), upper quartil (75 %), maximum, TSH (mIU.l^{-1}): serum levels of thyroid-stimulating hormone, fT4 (pmol.l^{-1}): serum levels of free thyroxin, TGB-ab (kIU.l^{-1}): serum levels of antibodies to thyroglobulin, TPO-ab (kIU.l^{-1}): serum levels of antibodies to thyroid peroxidase, n: number of patients, p: level of significance, p_1: breast cancer compared to colorectal cancer, p_2: breast cancer compared to control group, p_3: colorectal cancer compared to controls (Kruskal-Wallis test), NS: not significant

Results

No case of Graves' disease (GD) with hyperthyroidism was found in women with CaB, CaC and the control group. On the basis of the laboratory, clinical and ultrasound criteria, autoimmune thyroiditis (AIT) was diagnosed in 16 (24.2 %) women with CaB, 11 (16.7 %) with CaC and 8 (16.2 %) controls (Table 1). AIT was associated with subclinical hypothyroidism in 10 cases (15.2 %) of CaB group, in 10 cases (14.7 %) of CaC group and in 5 controls (10.2 %). AIT associated with overt hypothyroidism was observed in 3 cases (4.5 %) in CaB group, in no case in the CaC group and in one case (2.0 %) in the controls. Finally, AIT with euthyroidism was found in three (4.5 %) women with CaB, in one (2.0 %) woman with CaC and two (4.0 %) controls. The differences between the groups were not significant.

The TSH serum levels above 3.5 mIU.l^{-1} were observed in 19.7 % of women with CaB, in 14.7 % of women with CaC, compared to 12,3 % of women from the control group (Fig. 1); due to a small number of patients, these differences were not statistically significant. Similarly, individual groups did not significantly differ in median (average) serum levels of fT4 and median serum levels of TSH (Table 2).

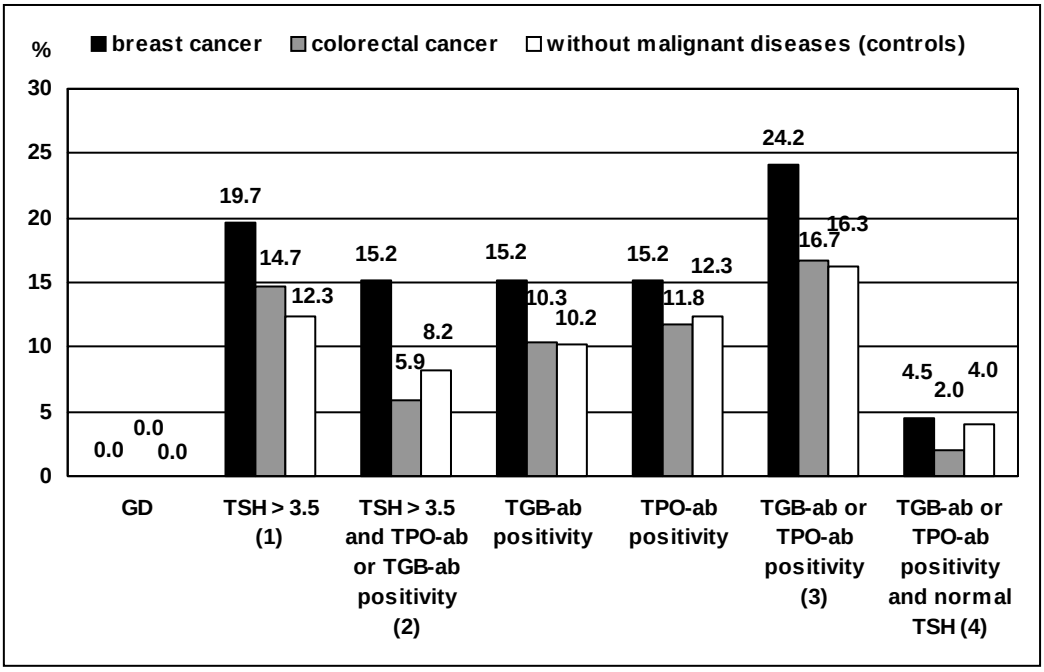

Fig. 1. Prevalence of abnormalities of thyroid laboratory parameters in women with breast cancer, colorectal cancer and women without malignant diseases (controls). TSH: thyroid-stimulating hormone, TGB-ab: antibodies to thyroglobulin, TPO-ab: antibodies to thyroid peroxidase, (1) autoimmune thyroiditis with subclinical/overt hypothyroidism and positivity/negativity of antibodies, (2) autoimmune thyroiditis with subclinical/overt hypothyroidism and positivity of antibodies, (3) autoimmune thyroiditis with/without subclinical/overt hypothyroidism, (4) autoimmune thyroiditis with euthyroidism, the differences between groups were not significant.

Median serum levels of TGB-ab were significantly higher in the CaB group as compared to the CaC group (medians: 35.8 vs. 31.6 kIU.l^{-1}, p=0.0008, averages: 198.3 vs. 49.9), and mainly compared to the control group (medians: 35.8 vs. 27.7 kIU.l^{-1}, p<0.001, averages: 198.3 vs. 45.8) (Fig. 2, Table 2). The serum levels of TPO-ab did not differ significantly between individual groups (Fig. 3, Table 2). The prevalence of positivity of TGB-ab and TPO-ab was higher in the CaB group as compared to the CaC group and the control group (TGB-ab: 15.2 % vs. 10.3 % vs. 10.2 %, TPO-ab: 15.2 % vs. 11.7 % vs. 12.3 %, TGB-ab or TPO-ab: 24.2 % vs. 16.7 % vs. 16.3 %) (Fig. 1); these differences were not significant.

The positivity of TPO-ab and/or TGB-ab together with increased or borderline serum levels of TSH (>3.5 mIU.l^{-1}) were found in 15.2 % women with CaB, compared to 5.9 % with CaC (p=0.0651), and 8.2 % in the control subjects (p=0.123) (Fig. 1). These differences were of borderline statistical significance due to the relatively small number of patients in each group for the statistical test applied (Kruskal-Wallis test).

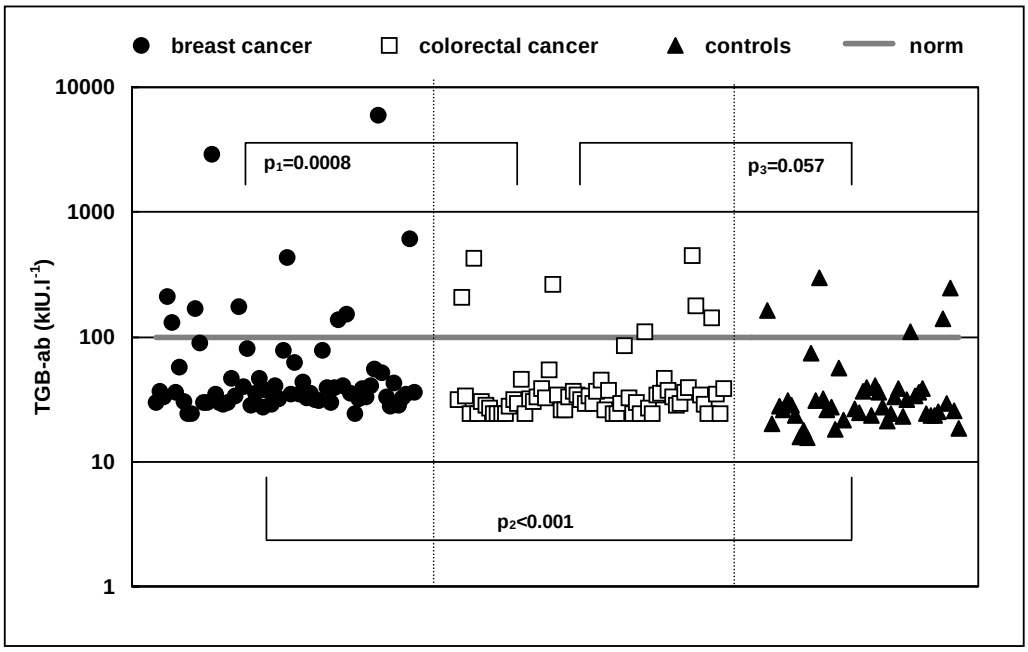

Fig. 2. TGB-ab serum levels in women with breast cancer, colorectal cancer and women without malignant diseases (controls). TGB-ab (kIU.l^{-1}): serum levels of antibodies to thyroglobulin, p: level of significance, p_1: breast cancer compared to colorectal cancer, p_2: breast cancer compared to control group, p_3: colorectal cancer compared to the controls (Kruskal-Wallis test)

In women with TSH above 3.5 mIU.l^{-1} from CaB group, TPO-ab and/or TGB-ab positivity was found in 10 out of 13 (76.9 %) and negativity in three out of 13 women (23.1 %). On the other hand, in women with TSH above 3.5 mIU.l^{-1} from the CaC group, TPO-ab and/or TGB-ab positivity was found in 4 of 10 (40.0 %) and negativity in 6 out of 10 women (60.0 %).

No significant influence of hormonal therapy of tamoxifen and chemotherapy on serum levels of TSH, fT4, TPO-ab and TGB-ab was proved. Due to the small number of patients treated with radiotherapy, its influence on the parameters of thyroid function and thyroid autoimmunity could not be evaluated. No significant relationship was found between positivity of TPO-ab and TGB-ab, TSH and fT4 serum levels and the stage or duration of oncological disease in the CaB group. In spite of the fact that the individual subgroups were age-comparable, in women from the CaC group, in 22 cases with disease diagnosed more than 5 years ago higher TSH serum levels were ascertained, compared to 44 cases with the disease diagnosed less than 5 years ago (medians: 1.99 vs. 1.52 mIU.l^{-1}, p=0.039). Likewise, in the CaC group, higher TGB-ab serum levels were found in 45 women with advanced stage of disease (T3-4) compared to 23 women with stage T1-2 (medians: 34.2 vs. 26.9 kIU.l^{-1}, p=0.01).

In the CaB and CaC groups, a strong positive correlation was ascertained between serum levels of TGB-ab and TPO-ab (Spearman rank order correlation coefficient, CaB: r=0.432, p<0.001, n=66, CaC: r=0.260, p=0.034, n=68), and a negative correlation between serum levels of TSH and fT4 (Spearman rank order correlation coefficient, CaB: r = –0.446, p=0.001, n=66, CaC: r = –0.436, p<0.001, n=68), in contrast to the control group. In all groups, a significant positive correlation between serum levels of TSH and TPO-ab was observed (Spearman rank order correlation coefficient, CaB: r=0.407, p<0.001, n=66, CaC: r=0.609, p<0.001, n=68, Pearson correlation coefficient, C: r=0.438, p=0.002, n=49). In addition, in the control group, serum levels of TSH positively correlated with the levels of TGB-ab (Pearson correlation coefficient, r=0.528, p=0.0002, n=49) and the serum levels of fT4 negatively correlated with the levels of TPO-ab (Spearman rank order correlation coefficient, r = –0.345, p=0.015, n=49), in contrast to women with oncological diseases.

In the CaB group, no significant correlations were found between serum levels of tumor markers (CEA and CA 15-3) and TSH, fT4, TGB-ab and TPO-ab; although lower serum levels of CEA were proved in women with TSH above 3.5 mIU.l^{-1}, compared to women with TSH below 3.5 mIU.l^{-1} (medians: CEA: 0.75 vs. 1.7 ng.l^{-1}, p=0.046).

In the CaC group, the serum levels of TSH negatively correlated with the levels of CEA (Spearman rank order correlation coefficient, r = –0.431, p=0.002, n=51), and the serum levels of CA 19-9 positively correlated with age (Pearson correlation coefficient, r=0.288, p=0.048, n=37). In the CaC group, serum levels of CEA and CA 19-9 were comparable in women with TSH above and below 3.5 mIU.l^{-1}.

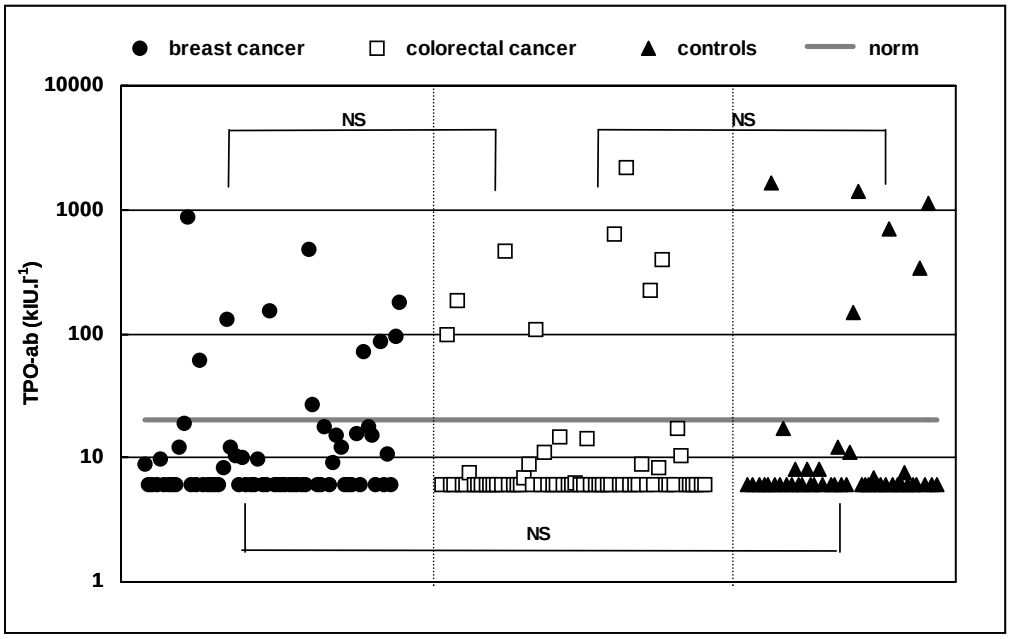

Fig. 3. TPO-ab serum levels in women with breast cancer, colorectal cancer and women without malignant diseases (controls). TPO-ab (kIU.l^{-1}): serum levels of antibodies to thyroid peroxidase, NS: not significant (Kruskal-Wallis test).

In CaC and CaB groups, the serum levels of tumor markers did not differ between patients with positivity or negativity of TGB-ab a TPO-ab. In CaB group, a significant positive correlation between serum levels of CEA and CA 15-3 was found (Spearman rank order correlation coefficient, r=0.423, p=0.005, n=42).

Discussion

With the exception of fT4, (TSH>3.5 mIU.l^{-1}, positivity of TPO-ab and TGB-ab), the prevalence of pathologic results was higher in the CaB group, compared to the CaC and control groups in all of tested thyroid laboratory parameters.

In contrast to Graves' disease (no case observed), autoimmune thyroiditis was diagnosed in 24.2 % women with CaB (4.5 % euthyroid and 19.7 % with subclinical or overt hypothyroidism), compared to 16.7 % in women with CaC (2.0 % euthyroid and 14.7 % with subclinical or overt hypothyroidism) and 16.2 % controls (4.0 % euthyroid and 12.2 % with subclinical or overt hypothyroidism).

The above differences in percentages between the groups were not significant (χ^2 statistical test); this was due to the small number of patients in each group. The percentage of TPO-ab positivity in the CaB group was lower (15.2 %), compared to the results of other authors (nearly 34 %) (Smyth *et al.* 1998). We believe that this discrepancy might be caused by a different geographical iodine intake, because this may play a potential role in the pathogenesis of both thyroid autoimmune and breast diseases. A relatively high percentage of pathologic laboratory results was also observed in the CaC and control groups (2.0-16.7 %). The probable explanation is that thyroid disturbances are common in seniors but are not diagnosed. The highest difference between pathologic results in the CaB compared to the CaC and control groups was found in women with positive serum levels of TPO-ab and/or TGB-ab and simultaneously with increased or borderline serum levels of TSH (>3.5 mIU.l^{-1}) (Fig. 1). These patients are in danger of developing subclinical or manifest hypothyroidism. Chemotherapy, radiotherapy and hormonal (tamoxifen) therapy may affect the function and regulation of the thyroid gland in women with breast or colorectal cancer. According to several studies, treatment with estrogen receptor-antagonists such as tamoxifen is accompanied by an increase of total

serum levels of T4 and T3 (Anker *et al.* 1998). In our study, we did not find any significant influence of tamoxifen therapy and chemotherapy on the serum levels of TSH, fT4, TPO-ab and TGB-ab. Due to the small number of patients treated with radiotherapy, its influence on the parameters of thyroid function and thyroid autoimmunity could not be evaluated.

According to recent research, iodine intake and natrium-iodide symporter (NIS)-mediated iodine uptake have been supposed to play a potential role in the pathogenesis of both AITD and benign or malignant breast diseases. Physiologically, NIS is a membrane protein enabling a transport of iodide ion into the thyroid follicular cells from the circulation (Dohan *et al.* 2003). The energy is delivered through contemporary ATP-splitting (Schmutzler and Kohrle 1998). An adequate concentration of iodide ions in thyroid follicular cells is essential for the synthesis of thyroid hormones. The NIS gene is located on the p-arm of the 19th chromosome (Smanik *et al.* 1997). A mutation of the NIS gene may be one of the causes of congenital hypothyroidism. TSH stimulates the NIS expression and the NIS-mediated transport of iodide ions into the thyrocytes (Schmutzler and Kohrle 1998). In experimental studies, several cytokines (e.g. TNF-α and IL-1) have been shown to inhibit NIS expression in tissue cultures (Ajjan *et al.* 1998). With the exception of the main thyroid autoantigens such as thyroglobulin and thyroid peroxidase, the NIS is considered to be the next autoantigen in patients with AITD (D'Herbomez and Wemeau 2001). Multiple antibody binding sites on human NIS was recently identified (Kemp *et al.* 2001). Although the clinical utility of NIS autoantibody determination is not yet proved, antibodies to NIS were found in 22-24 % of the patients with GD and AIT (Heufelder *et al.* 2001). Moreover, the thyroid autoantibodies from sera of some patients with Hashimoto's thyroiditis inhibited NIS-mediated iodide transport (Schmutzler and Kohrle 1998). Increased NIS expression has been observed in patients with GD and thyroid adenomas, compared to AIT and malignant thyroid tumors (Schmutzler and Kohrle 1998, Smanik *et al.* 1997). According to several authors, the decreased NIS expression may be considered as one of early signs of the malignant transformation of thyroid nodules (Filleti *et al.* 1999). For many years, it has been known that TSH-mediated growth of the thyroid gland occurs under the conditions of iodine deficiency. Although a lower incidence of thyroid carcinomas in areas with high iodine intake has not been proved, the decreased incidence of aggressive follicular and anaplastic carcinomas and increased incidence of less aggressive papillary carcinomas have been observed there. Likewise, prophylactic iodine administration has led to an increase of papillary and the decrease of follicular carcinoma incidence (Feldt-Rasmussen 2001).

Besides thyroid follicular cells, NIS expression has been proved in breast, stomach, salivary glands (Riedel *et al.* 2001), ovaries (Smanik *et al.* 1997), testes, hypophysis, pancreas, adrenal glands, prostate gland, heart, thymus and lungs (Spitzweg *et al.* 1998). This has not been observed in orbital fibroblasts, nasopharynx and the colon (Spitzweg *et al.* 1998). According to experimental studies, the rat cell lines of lactating mammary glands are characterized by NIS overexpression and increased ^{131}I-uptake, which may be inhibited through oxytocin antagonists and dopaminergic agonists such as bromocriptin. Physiologically, NIS translocates the iodide ion into the milk for thyroid hormone biosynthesis when the newborn child is nursed (Dohan *et al.* 2003). The NIS expression has been found in human tissue samples from 88 % ductal carcinomas *in situ* and 76 % invasive breast carcinomas, compared to 30 % samples from peritumoral breasts with normal appearance (Wapnir *et al.* 2003, Dohan *et al.* 2003). In women with invasive ductal breast cancer the NIS expression has been observed even in 90 % of cases (Rudnicka *et al.* 2003). Therefore, the demonstration of NIS expression in CaB cells provides a novel approach to its diagnosis and treatment with the use of radioactive iodine (Spitzweg *et al.* 2002, Upadhyay *et al.* 2003, Wapnir *et al.* 2003). The administration of oxytocin and prolactin has led to a dose-dependent NIS overexpression in cell lines of human CaB (Cho *et al.* 2000). Frequent cell abnormalities have been observed in iodine-deficient mammary glands: dysplasia, neoplasia, a change of RNA/DNA ratio and alterations of cytosolic estrogen receptors (Eskin 1977). Geographical variations in the incidence of breast cancer have been attributed to differences in dietary iodine intake (Smyth 1997). A slower tumor growth, TGF-β overexpression and increased apoptotic index have been documented after the administration of medroxyprogesteron acetate (MPA) and inorganic iodine in experimental 7,12-dimethyl-benzanthracene-induced CaB in rats (Funahashi *et al.* 1996). It has been suggested that increased iodine content may lead to the induction of apoptosis in tumors through the increased expression of TGF-β (Funahashi *et al.*

1999). A higher content of elementary iodine was discovered in tissue samples of human breast fibroadenomas, as compared to the level in breast carcinomas. In the same study, sera from 19 % of women with CaB, 16 % of women with fibroadenomas and 31 % of women with Graves' disease inhibited ^{125}I-uptake, compared to 3 % of age-matched healthy women. Additionally, IgG-mediated ^{125}I-uptake inhibition has been observed in these subjects and the ability of the ^{125}I-uptake inhibition positively correlated with TPO-ab positivity in women with CaB, compared to benign breast diseases (Kilbane *et al.* 2000). One hypothesis is that the inhibition of ^{125}I-uptake may be mediated through thyroid autoantibodies.

In our study, it was mainly the serum levels of TGB-ab which were significantly elevated in women with CaB, compared to the CaC and control groups. It is known that the antigenicity of thyroglobulin is dependent on iodine content in the molecule. Our hypothesis is that in women with CaB, higher iodine intake may lead to increased titers of TGB-ab and contribute to the development of thyroid autoimmunity. At the same time, higher iodine uptake in the mammary gland may be one of the protective factors which prevents malignant transformation, as well as a factor which may improve the effectiveness of oncological therapy and survival rate. This hypothesis is supported by the fact that in our study women from the CaB group with TSH above 3.5 mIU.l^{-1} had significantly lower CEA serum levels, compared to women with TSH below 3.5 mIU.l^{-1}. In the CaC group, a similar difference was not observed, although a significant negative correlation between TSH and CEA was found in this group. However, this correlation may be caused by a non-specific TSH suppression observed in severe chronic illness.

Several cytokines contribute to the pathogenesis of AITD. Likewise, changes in serum levels of some cytokines have been observed in women with CaB. For example, high IL-8 and IL-6 serum levels and a negative correlation between IL-8 and IL-6 and fT3 and fT4 have been observed (Yokoe *et al.* 1997). However, it is not yet known if the changes in serum levels of several cytokines may lead to thyroid disturbances in women with CaB.

In women with advanced CaB increased serum levels of TSH and prolactin and decreased serum levels of fT4 have been found (Yokoe *et al.* 1996). In these cases, the peripheral hypothyroidism and stimulation of adenohypophysis through thyroliberin may be the cause of increased prolactin and TSH serum levels. In terminal states of breast carcinoma a non-specific low T3 syndrome has been observed (Yokoe *et al.* 1996). No relationship was observed between serum levels of TSH, fT3 and fT4 and the individual state of CaB in our study; however, no case in the terminal stage belonged to the CaB group.

The higher incidence of borderline or elevated TSH serum levels (above 3.5 mIU.l^{-1}) and positivity of thyroid autoantibodies in the CaB group, compared to the CaC and control groups, suggest the higher incidence of autoimmune thyroiditis with subclinical or manifest hypothyroidism (about 15.2 % or 4.5 % according to our study) and raises the question of TSH screening in women with CaB. Women with positive titers of thyroid autoantibodies and borderline or barely increased serum levels of TSH may be affected by euthyroid form of autoimmune thyroiditis and are in danger of developing hypothyroidism in the future, or during treatment with several drugs such as cytokines, amiodarone, iodide or lithium. The possible influence of autoimmune thyroiditis with subclinical or manifest hypothyroidism on the improvement of the prognosis and survival rate of women with CaB and the role of cytokines in the pathogenesis of both diseases still remain unknown. Therefore, on the basis of current knowledge, newly diagnosed subclinical or manifest hypothyroidism in women with CaB should be treated with levothyroxine-replacement therapy according to the current guidelines. However, disturbances of NIS, different iodine intake and the changes of cytokine serum levels may be the factors that affect the development of both breast diseases and autoimmune thyroiditis.

Acknowledgements

Supported by the following grants: GA Nr 8130-3/2004 and IGA No 7742-3 of the Czech Ministry of Health and IET101050403 of the Czech Academy of Sciences.

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