# Possible association between breast thyroid carcinoma: analysis of risk factors



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### Possible association between breast thyroid carcinoma: analysis of risk factors

BACKGROUND: Breast cancer (BC) is the most common tumor in women, 523.000 cases were estimated in Europe in 2018 and it remains the third cause of cancer related deaths after lung and colorectal cancer. The incidence of thyroid cancer (TC) in females is higher than in males.

METHODS: We have retrospectively collected all female patients undergone to surgery for breast or thyroid cancer in 2010The aim of the study was to value the incidence of BC in patients with a personal history of differentiated thyroid cancer (DTC) and conversely, the incidence of DTC in patients with previous BC within 5 years from the diagnosis of the first tumor in 2010.

RESULTS: Among 76 BC patients, 11 were death and 22 didn't answer the phone call or refused to re-submit to thyroid ultrasound so they were excluded from the study and only 43 BC were further considered. Thyroid ultrasound was performed in 2010 and in 2016 and it described nodules in 13 (30%) patients in 2010 and in 21 (49%) patients in 2016. In 2010 no FNA was needed while in 2016 6 (14%) patients underwent to FNA with a benign response (Thyr 2). Among 61 DTC patients, 11 didn't answer the phone or the questions so 50 patients were included in the study. Breast cancer family history was reported in 14 (28%) patients and thyroid cancer family history in 8 (16%) patients. No relapse was reported during follow up.All patients underwent to mammography in 2015 or in 2016 within screening programs and no breast cancer were diagnosed.

CONCLUSION: The female predominance of diseases of the thyroid and breast makes difficult the separation of an expected association with a casual linkage The relationship between the co-occurrence of breast and thyroid cancer remains controversial and inconclusive.

KEY WORDS: Breast cancer, Breast surgery, Hormone therapy, Thyroid cancer, Thyroidectomy

## Introduction

Breast cancer (BC) is the most common tumor in women, 523.000 cases were estimated in Europe in 2018 and it remains the third cause of cancer related deaths after lung and colorectal cancer<sup>1-2</sup>. Furthermore, lung

cancer is the first cause of death in Europe among women of 45-74 years old while BC remains the first cause in young and elderly women <sup>3</sup>. However, BC survival rates are progressively increasing, due to improvements in diagnosis and treatment <sup>4</sup>.

It is well known that the incidence of thyroid cancer (TC) in females is higher than in males <sup>5</sup> and the discrepancy in incidence suggests female gender as a possible epidemiologic risk factor <sup>6</sup>. In addition, 10% of Italian people present thyroid functional alterations, and from1 to 23% have goitre (in different regions) <sup>7</sup>. In Italy, every year about 40000 thyroidectomies for benign or malignant lesions are performed in Surgical Units, with specific surgical instruments such as intraoperative

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neuromonitoring (IONM) of the recurrent laryngeal nerves<sup>.8</sup>.

Both thyroid and breast cancers have pick incidence in postmenopausal period <sup>2</sup>. The association between breast and thyroid cancers has been investigated, considering the possible influence of hormonal and genetic factors, though studies did not obtain plain results. Severeal studies have detected a possible association between these two malignancies, suggesting that the overall risk of second primary TC or BC is significantly increased in patients who previously had BC or TC, respectively. <sup>9-11</sup>. However, most of these focused on epidemiological trends without establish a molecular pathogenesis.

It has even been demonstrated that the most common synchronous malignancy of breast cancer is thyroid cancer or vice versa<sup>12,13</sup>.

## Material and Methods

We have retrospectively collected all female patients undergone to surgery at General Surgery Clinic of University hospital of Parma for breast or thyroid cancer in 2010. All operations were performed by expert surgeons dedicated to the breast or to thyroid. The Istitutional Etichs Commettee approved the study protocol (n. 32198) on 20 September 2016.

The aim of the study was to value the incidence of BC in patients with a personal history of differentiated thyroid cancer (DTC) and conversely, the incidence of DTC in patients with previous BC within 5 years from the diagnosis of the first tumor in 2010. Patients with medullary or anaplastic thyroid cancer or those with other tumors at the time of enrolment were excluded from the study.

We considered first primary cancer the cancer the patient experienced for the first time in life and second primary cancer the cancer diagnosed after almost 6 months; tumors diagnosed simultaneously or within a time interval of 6 months are described synchronous primary cancers, according to literature <sup>14</sup>.

Female patients operated for BC in 2010 in our Clinic were 76 while 61 were operated for DTC; overall we considered 137 patients.

Follow up was performed contacting patients by phone 6 years after the operation.

All patients with a previous BC underwent to thyroid ultrasound before the operation and 6 years after it while patients with a previous DTC were evaluated with mammography screening.

Table I	-	Patients	characteristics:	BC	group.
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	BC group		
		2010	2016
Death n		11	
Non responding/refusing n		22	
N. tot		43	
Age at diagnosis (years)		56.5	
BC family history n (%)		21 (49)	
DCT family history n (%)		5 (12)	
Previous pregnancies n (%)		38 (88)	
Hormonal status	Fertile n (%)	16 (37)	1 (2)
	Postmenopausal n (%)	26 (61)	42 (98)
	Hormone-therapy n (%)	1 (2)	0
Thyroid ultrasound	Nodules n (%)	13 (30)	21 (49)
	FNA n (%)	0	6 (14)
	Thyroiditis n (%)	6 (14)	10 (23)
Thyroid drug therapy	Levothyroxine n (%)	7 (16)	11(26)
	Methimazole n (%)	2 (5)	0
Type of operation	Quadrantectomy n (%)	41 (95)	
	Mastectomy n (%)	2 (5)	
Histological type	IDC- ILC n (%)	28 (65)	
0 11	CDIS- CLIS n (%)	13 (30)	
	Others n (%)	2 (5)	
ER – PR positive n (%)		38 (88)	
Lymph node metastasis n (%)		9 (21)	0
Distant metastasis n (%)		0	1 (2)
Chemotherapy n (%)		8 (19)	
Radiotherapy n (%)		35 (81)	
Hormone-therapy n (%)		36 (84)	
BC relapse n (%)		4 (9)	

		DTC group		
		2010		2016
Death n	0			
Non responding/refusing n	11			
N. tot	50			
Age at diagnosis (years)	50.2			
BC family history n (%)	14 (28)			
DCT family history n (%)	8 (16)			
Previous pregnancies n (%)	37 (74)			
Hormonal status	Fertile n (%)	16 (32)		12 (24)
	Postmenopausal n (%)	32 (64)		38 (74)
	Hormone-therapy n (%)	2 (4)		0
Thyroid drug therapy	Levothyroxine n (%)	9 (18)		50 (100)
	Methimazole n (%)	3 (6)		0
Thyroid ultrasound	Single nodule n (%)	27 (54)		
	Multinodular n (%)	22 (44)		
	Thyroiditis n (%)	22 (44)		
Preoperative FNA	Thyr 6 n (%)	23 (46)		
	Thyr 5 n (%)	5 (10)		
	Thyr 4 n (%)	8 (16)		
	Thyr 3 n (%)	4 (8)		
	Thyr 2 n (%)	8 (16)		
	Non eseguito n (%)	2 (4)		
Histological type	Papillary carcinoma n (%)	46 (92)		
	Follicular carcinoma n (%)	4 (8)		
Multifocality n (%)	13 (26)			
Extrathyroid extension n (%)	20 (40)			
Lymph nodes metastasis n (%)	4 (8)			
Distant metastasis n (%)	0			
RAI therapy n (%)	43 (86)			
DTC relapse n (%)	0			

Characteristics of patients were collected, including age at diagnosis, comorbidities, thyroid ultrasound, mammography, pharmacological therapy, preoperative fine needle aspiration, hormonal status at time of diagnosis and follow up, previous pregnancies, family history of breast or thyroid cancer, type of operation, pathological characteristics, histological type, multifocality and extrathyroid extension for DTC, lymph node metastasis, immunohistochemistry in BC (estrogen receptors -ER, progesterone receptors – PR), radio- chemotherapy for BC and RAI for DTC. (Tables I, II) Considering the small number of patient, we decided

not to proceed with the statistical analysis of the data, limiting ourselves to a descriptive evaluation.

#### Results

Among 76 BC patients, 11 were death and 22 didn't answer the phone call or refused to re-submit to thyroid ultrasound so they were excluded from the study and only 43 BC were further considered. The median age at diagnosis in BC group was 56.5. Breast cancer

family history was reported in 21 (49%) patients and thyroid cancer family history in 5 (12%) patients. A total of 38 (88%) patients had previous pregnancies. In 2010, 16 (37%) patients were fertile, 26 (61%) in postmenopausal status and 1 (2%) was taking post-menopausal hormone therapy while in 2016 only 1 (2%) patient was fertile and 42 (98%) in post-menopausal status.

Thyroid ultrasound was performed in 2010 and in 2016 and it described nodules in 13 (30%) patients in 2010 and in 21 (49%) patients in 2016. In 2010 no FNA was needed while in 2016 6 (14%) patients underwent to FNA with a benign response (Thyr 2). Furthermore, in 2010 thyroiditis was reported in 6 (14%) patients and in 2016 in 10 (23%) patients.

In 2010, 41 (95%) patients underwent to mammary quadrantectomy and only 2 (5%) to mastectomy. The histologic type was infiltrative ductal or lobular carcinoma (IDC- ILC) in 28 (65%) patients, ductal or lobular carcinoma in situ (CDIS- CLIS) in 13 (30%) patients and others in 2 (5%) cases. ER and PR were positive in 38 (88%) patients. Lymph nodes metastasis were reported in 9 (21%) cases at definitive histological exam. No distant metastasis were reported in 2010 while 1

		BC	$BC \rightarrow DTC$ group		
		2010		2016	
Death n			0		
Non responding/refusing n			0		
N. tot			3		
Age at diagnosis (years)			52.7		
BC family history n (%)			2 (67)		
DCT family history n (%)			1 (33)		
Previous pregnancies n (%)			3 (100)		
Hormonal status	Fertile n (%)	0		0	
	Postmenopausal n (%)	3 (100)		3 (100)	
	Hormone-therapy n (%)	0		0	
Thyroid drug therapy	Levothyroxine n (%)	1 (33)		3 (100)	
	Methimazole n (%)	0		0	
Type of operation	Quadrantectomy n (%)		3 (100)		
	Mastectomy n (%)		0		
Histological type	IDC- ILC n (%)		2 (67)		
	CDIS- CLIS n (%)		1 (33)		
	Others n (%)		0		
ER – PR positive n (%)			1 (33)		
Lymph node metastasis n (%)			0		
Distant metastasis n (%)			0		
Chemotherapy n (%)			2 (67)		
Radiotherapy n (%)			3 (100)		
Hormone-therapy n (%)			1 (33)		
BC relapse n (%)			1 (33)		
Thyroid ultrasound	Single nodule n (%)		1 (33)		
	Multinodular n (%)		1 (33)		
	Thyroiditis n (%)		1 (33)		
Preoperative FNA	Thyr 6 n (%)		3 (100)		
	Thyr 5 n (%)		0		
	Thyr 4 n (%)		0		
	Thyr 3 n (%)		0		
	Thyr 2 n (%)		0		
	Non eseguito n (%)		0		
Histological type	Papillary carcinoma n (%)		3 (100)		
	Follicular carcinoma n (%)		0		
Multifocality n (%)			1(33)		
Extrathyroid extension n (%)			2 (6/)		
Lymph nodes metastasis n (%)			0		
Distant metastasis n (%) DAL therease $n (0())$			0		
KAI therapy n (%) $DTC$ relapso n (%)			0		
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#### TABLE III - Patients characteristics: $BC \rightarrow DTC$ group.

(2%) patient presented lung metastasis in 2016. Only 8 (19%) patients underwent to chemotherapy after operation while 35 (81%) patients underwent to radiotherapy and 36 (84%) to hormone-therapy; 4 (9%) patients had a reoperation for BC relapse during the follow up. The majority of patients had normal level of thyroid hormones, with a median TSH=1.5325  $\mu$ UI/ml in 2010; 7 (16%) patients took Levothyroxine for hypothyroidism in 2010 and they were all in post-menopausal status, all had ER and PR positive at histological exam and took hormone-therapy too while 2 (5%) patients took Methimazole for hyperthyroidism in 2010 and they were

one in post-menopausal status and one fertile, both had ER and PR positive but only the first took hormone-therapy. In 2016, none took Tapazole and 11 (26%) took Levothyroxine.

We reported 2 (5%) patients already undergone to hemithyroidectomy for a goitre in previous years. Only 1 (2%) patient underwent to total thyroidectomy for a papillary cancer in 2012. She was already hypothyroid in 2010, in post-menopausal status and underwent to a quadrantectomy for infiltrative ductal carcinoma, ER and PR positive, and to postoperative radio- and chemo- and hormone-therapy. No relapse was described during follow up.

Among 61 DTC patients, 11 didn't answer the phone or the questions so 50 patients were included in the study. The median age at diagnosis in DTC group was 50.2. Breast cancer family history was reported in 14 (28%) patients and thyroid cancer family history in 8 (16%) patients. A total of 37 (74%) patients had previous pregnancies. In 2010, 16 (32%) patients were fertile, 32 (64%) in post-menopausal status and 2 (4%) was taking post-menopausal hormone therapy while in 2016 12 (24%) patient was fertile and 38 (76%) in post-menopausal status. At preoperative history, 9 (18%) patients took Levothyroxine and 3 (3%) Methimazole. At preoperative thyroid ultrasound 22 (44%) patients had multinodular goitre and 27 (54%) a single nodule, 22 (44%) had also thyroiditis. At preoperative FNA patients presented 23 (46%) Thyr 6, 5 (10%) Thyr 5, 8 (16%) Thyr 4, 4 (8%) Thyr 3 and 8 (16%) Thyr 2, according to the Bethesda System for Reporting Thyroid Cytopathology<sup>17</sup>.

All patients underwent to total thyroidectomy and the histological response confirmed papillary thyroid carcinoma in 46 (92%) cases and follicular thyroid carcinoma in 4 (8%) cases. Multifocality was described in 13 (26%) cases, extrathyroid extension in 20 (40%) cases and lymph nodes metastasis 4 (8%). Postoperative RAI was reported by 43 (86%) patients. No relapse was reported during follow up.

All patients underwent to mammography in 2015 or in 2016 within screening programs and no breast cancer were diagnosed. Contrariwise, 2 patients reported at personal history previous breast cancer. They both underwent to quadrantectomy. In the first case the patient was fertile at time of diagnosis, was operated for CDIS, ER and PR negative, and had postoperative radiotherapy. In the second case the patient was in postmenopausal status at time of diagnosis, was operated in 2008 for IDC, ER and PR negative, had hormone-therapy and presented a relapse in 2017. She had a second quadrantectomy for ILC, ER and PR negative and had postoperative radiotherapy and chemotherapy.

In conclusion, we reported 3 cases of DTC in patients who had already experience a BC, with a median latency of 3 years and no case of BC in patient with a previous DTC. None was diagnosed with coexisting TC and BC. (Table III)

## Discussion

In general, an increased incidence of second primary cancer has been reported in patients surviving after a diagnosis of any cancer<sup>1</sup>. This increased risk can be associated to a genetic predisposition, behavioral risk factors, long-term effects of chemo-radiotherapies or either to a more intensive screening programs. A European study observed an incidence of 5-7% of second primary cancer within 5 years of diagnosis in patients with a first

malignancy <sup>16</sup>. In our study, we found that 6.8% of BC survivors develop a second primary malignant non-breast tumor in the sequent 6-years follow up, and it was thyroid cancer in all these cases. However, our study has considered only a limited population, who had BC surgery. Other studies reported an increased risk from 4 to 12% of non-breast second primary cancer after BC diagnosis within 5 years <sup>17,18</sup>. In a recent study, Corso et al. confirmed a higher num-

ber of gynecological cancers, thyroid cancer, melanoma and leukemia in BC patients, in comparison to the general population <sup>19</sup>. They did not detect significant correlations between the risk of second primary non-BC cancer and specific BC clinicopathological factors, with the exception for triple negative BC vs. second ovary and lung cancers 20. They have found a strong association between age at diagnosis of BC and risk of second primary cancer; nevertheless, this association was not noticed in case of second primary of ovary and thyroid. Independently from age, they also observed that the risk of being diagnosed with second primary thyroid cancer was particularly increased in patients who received hormonal therapy and decreased in patients who received chemotherapy. It has been already demonstrated that tamoxifen therapy in postmenopausal women increases TBG, with secondary increases in T4<sup>21</sup>.

A higher expression of ER and PR was observed in BC patients with co-existing TC compared with those without, suggesting the possibility that ER or PR signalling might represent common etiological factors in the development of TC and BC 9. Some factors, such as estrogen and reproductive factors that play well-established roles in BC initiation, may be associated with TC. According to this hypothesis, previous studies have described sex steroid receptors in human thyroid tissue and in TC cell lines, and ER levels significantly higher in TC comparing to normal thyroid tissue <sup>22,23</sup>. Other studies have demonstrated that estrogen upregulates the expression of cell cycle-related gene and proto-oncogenes in thyroid cells, which may influence the pathogenesis of TC <sup>24,25</sup>. Estradiol increases proliferation of estrogen receptor (ER)-positive TC, promoting the proliferation of this type of disease, and also alters the expression of estrogen receptor subtypes in TC cell lines <sup>26</sup>. Moreover, it has been reported that thyrotropin 27,28 or common environmental risk factors including exposure to ionizing radiation <sup>29,30</sup>, may contribute to the co-occurrence of BC and TC.

Vice versa, thyroid hormones appear to stimulate lobular development, contributing to the differentiation of normal breast tissue <sup>31</sup> and thyroid hormone receptors (TR) have been described in breast cancer. <sup>32</sup>. There are reports on interference between estradiol and thyroid hormones, suggesting a cross talk between ER and TR in neuroendocrine tissues leading to inhibition of estrogenic effects by thyroid hormone <sup>33</sup>. In our study we have found a higher incidence of thyroid dysfunction in BC group, comparing to general population (21% vs 10%). Nevertheless, this higher incidence may also derive from the fact that all the patients in this study came from an area known to be endemic for low iodine ingestion.

Together with the thyroid, human breast tissue shares the ability to take up circulating iodine <sup>34</sup>, and a sodium/iodide symporter is expressed in lactation and in mammary tumors <sup>35</sup>. Also, alterations of iodide metabolism exist in both the tumor and the normal tissue breast cancer patients <sup>34</sup>. These studies suggest a possible association between breast cancer and alteration in iodine metabolism.

In a recent study, Chiappa et al. found an association between autoimmune thyroid disease, in particular chronic autoimmune thyroiditis, and the onset of breast cancer in young age <sup>7</sup>. In addition, the presence of TPOAb might have a positive effect on the prognosis of women with breast cancer; women treated with surgery and who were positive for TPOAb showed a better prognosis the TPOab-negative women <sup>36</sup>.

However, all these studies were performed in selected groups of patients (women with either breast cancer or thyroid disorders) and did not study prospectively the incidence of breast cancer in relation to thyroid parameters (such as thyroid function testing or TPOAb) in an unselected cohort. <sup>36</sup> One more study was unable to show an increased incidence of breast cancer in patients with various thyroid disorders <sup>11</sup>.

Kuijpens et al. described first low levels of FT4 as being an independent risk factor for the development of breast cancer in an unselected cohort of peri- and postmenopausal women. Also, hypothyroidism appeared to be associated with an increased risk for the development of breast cancer. In addition, they showed that the presence of TPOAb was more prevalent in women with a current or previous diagnosis of breast cancer <sup>(37)</sup>. An association between the presence of TPOAb and breast cancer was also found by various other authors <sup>34,38-40,11</sup>. However, these studies were cross sectional and were performed in selected populations and therefore it was not possible to establish a possible etiological relationship.

Further studies are required to understand the etiological role of all these factors in the link between BC and TC, supporting the epidemiological data with proven pathogenic mechanisms.

## Conclusion

The female predominance of diseases of the thyroid and breast makes difficult the separation of an expected association with a casual linkage. The precise relationship between the co-occurrence of breast and thyroid cancer remains controversial and inconclusive. The understanding of the underlying common pathogenic mechanisms could direct influence the evidence-based clinical practice. Meanwhile, considering that Hormonal therapy should be related with an increased risk of thyroid disease, thyroid and cervical lymph node examination should be suggested in women with BC during hormonal therapy and in postmenopausal status.

#### Riassunto

In considerazione del fatto che il tumore al seno (BC) è il tumore più comune nelle donne, 523.000 casi sono stati stimati in Europa nel 2018 e rimane la terza causa di morte per cancro dopo il cancro del polmone e del colon-retto., e che l'incidenza del carcinoma tiroideo (TC) nelle femmine è più alta che nei maschi, abbiamo raccolto in modo retrospettivo i dati di tutte le pazienti di sesso femminile sottoposte a chirurgia per carcinoma mammario o tiroideo nel 2010.

L'obiettivo dello studio è di valutare l'incidenza di BC in pazienti con anamnesi positiva di carcinoma tiroideo differenziato (DTC) e, viceversa, l'incidenza di DTC nei pazienti con precedente BC entro 5 anni dalla diagnosi del primo tumore nel 2010.

Tra le 76 pazienti con BC, 11 erano deceduti e 22 non rispondevano alla telefonata o rifiutavano di sottoporsi a ecografia tiroidea, quindi furono escluse dallo studio e solo 43 BC furono ulteriormente considerati. L'ecografia tiroidea è stata eseguita nel 2010 e nel 2016 e ha descritto i noduli in 13 (30%) pazienti nel 2010 e in 21 (49%) pazienti nel 2016. Nel 2010 non è stato necessario procedere a FNA mentre nel 2016 6 (14%) pazienti sono stati sottoposti a FNA con una risposta di benignità. (Thyr 2).

Tra le 61 pazienti sottoposte a chirurgia per DTC, 11 non hanno risposto al telefono o alle domande, quindi sono state incluse nello studio 50 pazienti.

Una storia familiare di cancro al seno è stata rintracciata in 14 (28%) pazienti e una storia familiare di cancro della tiroide in 8 (16%) pazienti. Durante il followup non è stata segnalata alcuna recidiva. Tutti le pazienti sono state sottoposte a mammografia nel 2015 o nel 2016 nell'ambito di un programmi di screening e non sono stati diagnosticati tumori al seno.

In conclusione la predominanza femminile delle malattie della tiroide e della mammella rende difficile la separazione di un'associazione attesa con un legame casuale. La relazione tra la conoccorrenza del cancro della mammella e della tiroide rimane controversa e inconcludente anche nella nostra esperienza.

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