

# Thyroid nodules coexisting with either cystic or solid breast nodules: a new clue for this association between nodules coming from ultrasonography

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**Background:** Thyroid and breast nodules (BNs) are common, their prevalence varying based mainly on the population (including age, residence in area of different iodine availability) studied and methods used. The coincidence of thyroid and breast diseases remains controversial and the majority of the studies evaluate the association between breast cancer and thyroid disorders. Here we describe our experience of such association in a non-oncological series.

**Methods:** Between the years 2000 and 2005, 3,372 patients from outpatient clinics were referred for thyroid ultrasonography (US) at our University Hospital; concurrent breast US in the 1,896 women revealed the presence of BNs in 127. The 127 women were divided into two groups, based on the cystic or solid nature of the BN(s).

**Results:** In 84/127 (66.1%) the single or multiple BN was/were cystic (group 1), while in the remaining 43 (33.9%) the single or multiple BN was/were solid [group 2; 19/43 had one thyroid nodule (TN) and the remaining 24/43 had  $\geq 2$  TNs]. When BN were cystic the coexisting TN(s) was/were more likely to be concordant in localization (i.e., right/right or left/left localization) whereas, when the BN were solid, the coexisting thyroid nodule/nodules was/were more likely to be discordant. In women with cystic BNs (CBNs), TNs were more frequently multiple (64% of cases), whereas in cases with solid BNs (SBNs), the frequency of single and multiple TNs was approximately the same. In patients with TNs/CBNs, TNs tend to be subcentimetric and localized in the inferior pole of either thyroid lobe. In patients with TNs/SBNs, TNs tend to be larger and localized in the middle of either thyroid lobe.

**Conclusions:** In women with BNs associated with TNs, there are interesting differences concerning TNs when patients are stratified based on the cystic or solid nature of the BN.

**Keywords:** Thyroid nodules (TNs); breast nodules (BNs); ultrasonography

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## Introduction

Thyroid nodules (TNs) are common, their prevalence varying based mainly on the population (including age, residence in area of different iodine availability) studied and methods used (1). The prevalence is greater in women compared with men, in the elderly compared with adults and children/adolescents, in iodine-deficient areas compared to iodine-sufficient areas, and in persons exposed to radiation compared to non-exposed persons (1). Concerning the methodology for detecting TNs, the reported prevalence ranges from 2% to 6% with palpation, from 19% to 35% with ultrasonography (US), and from 8% to 65% at autopsy (1). With the widespread use of sensitive imaging in clinical practice, incidental TNs are being discovered with increasing frequency (1). US is the most accurate and cost-effective method for the detection and initial evaluation of TNs (1,2).

Breast nodules (BNs) are also common, their prevalence varying based mainly on the population studied (including age and family history of breast cancer) and methods used (3,4). The prevalence is greater in women aged 40–44 years than in those aged 25–29 years, and in women with a family history of breast cancer (3). Concerning the methodology for detecting BNs, the prevalence was reported to range from 54% to 92% using palpation (5), from 50% to 90% using US and from 46% to 86% at autopsy (6,7). Refinement of high-frequency technology, particularly the 7.5–13 MHz probes, has brought out a totally new facet in US breast imaging (8). Harmonic imaging and real-time compounding improve image resolution and lesion characterization (9). More recently, the use of US elastography can improve the specificity and positive predictive value of US in the characterization of breast masses (4). US elastography is useful in discriminating between benign and malignant solid masses (10,11), and it is superior to mammography in diagnosing clinically benign palpable masses (up to 97% accuracy *vs.* 87%) (11). Similar to TNs, the vast majority of BNs are benign (12).

The coincidence of thyroid diseases (TD) and breast diseases remains controversial; the majority of the studies have evaluated the association between breast cancer and thyroid disorders (13–26).

In the clinical setting of an ambulatory US service, we wished to ascertain: (I) the rate of request of both thyroid and breast US; (II) the characteristics of both the TNs and BNs detected by US. The latter aim was because it was our

recent impression that certain characteristics of TN are different based on the cystic or solid nature of the BN (CBN or SBN).

## Methods

### *Study population*

Between the years 2000 and 2005, 3,372 patients from outpatient clinics were referred for thyroid US, 2,235 of whom were found to have one or more TNs (cystic and/or non-cystic ones). Among these 2,235 patients, 1,896 (84.8%) were females and 339 (15.2%) males (age: 66.1±11.8 years for women and 61.3±12.3 years for men); an association with extrathyroidal nodules was searched based on US examinations of other organs. In 391 cases, such association was found (336 or 85.9% F and 55 or 14.1% M). Concurrent breast US in the 1,896 women revealed the presence of BNs in 127. The 127 women were divided into two groups, based on the cystic or solid nature of the BN(s). In 84/127 (66.1%) the single or multiple BN was/were cystic (group 1), whereas in the remaining 43 (33.9%) the single or multiple BN was/were solid (group 2; 19/43 had 1 TN and the remaining 24/43 had ≥2 TNs). Patients with fibrocystic breast disease or changes were excluded.

### *Thyroid US*

Thyroid US was performed at the Oncology Division, with a Logiq by General Electric (Boston, MA, USA) instrumentation equipped with a 7.5–10.0 MHz linear transducer. The thyroid parameters evaluated were volume, echo-texture, vascularization and nodules. Thyroid echo-texture is a fundamental feature to judge if thyroid inflammation is present. If inflammation exists, regardless of thyroid volume, the pattern is one of diffuse and dyshomogeneous hypoechoogenicity with or without pseudonodules. The number, maximum diameter and ultrasonographic characteristics of all nodules were noted. As classically done, TNs were defined micronodules if their maximum diameter was 10 millimeters or smaller. Thyroid pseudonodules, which are encountered frequently in an inflamed thyroid, were not counted as nodules. The results of thyroid US were classified as follows: (I) absence of cysts and nodules; (II) presence of cysts; (III) presence of nodules. In cases of multiple cysts or nodules, we considered the maximum diameter of the largest lesion.

**Table 1** Distribution of thyroid and breast nodules in the two groups of women

Localization	Thyroid, n (%)	Breast, n (%)	Statistics
Group 1 (women with cystic breast nodules, n=84)			
Right	22 (26.2)	16 (19)	Df =2, $\chi^2$ =1.488; P=0.475
Left	14 (16.7)	18 (21.4)	
Bilateral	48 (57.1)	50 (59.5)	
Group 2 (women with solid breast nodules, n=43)			
Right	8 (18.6)	17 (39.5)	Df =2, $\chi^2$ =6.524, P=0.038
Left	10 (23.3)	12 (27.9)	
Bilateral	25 (58.1)	14 (32.6)	

In the intrathyroidal comparison between group 1 and group 2, no difference in the three localizations of nodules was observed (Df =2,  $\chi^2$  =1.351, P=0.51). In contrast, in the equivalent intra-breast comparison a statistical difference existed (Df =2,  $\chi^2$  =9.203, P=0.01).

### Breast US

Breast US was performed at the Oncology division, with a Logiq by General Electric instrumentation equipped with a 7.5–10.0 MHz linear transducer. A cyst is seen on US as a well-defined, round or oval, anechoic structure with a thin wall. In contrast, solid structures were considered nodules. If internal echoes or debris are seen in a cyst, the cyst is called a complex cyst. These internal echoes may be caused by floating cholesterol crystals, pus, blood or milk of calcium crystals (7).

### Statistics

Differences between proportions of categorical variables were handled by the chi-squared test or the Fisher's exact test, as appropriate. For any statistical comparison, which was always two-tailed, a P value of less than 0.05 was considered statistically significant and P values comprised between 0.05 and 0.10 were considered borderline significant.

## Results

### Age

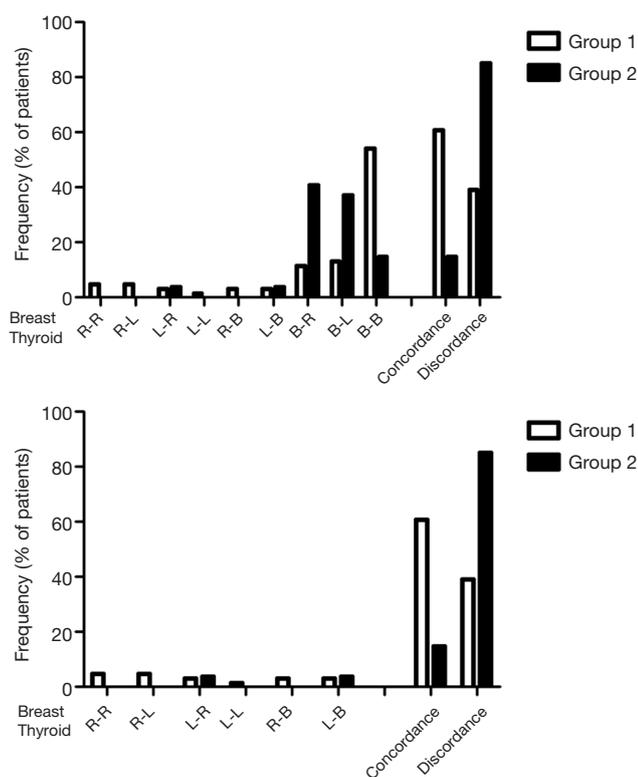
Considering the cystic BNs (CBNs) (group 1), the decades at US most represented were the fifth (41–50 years) and the fourth (31–40 years), in that they accounted for 53.6% and 20.2%, respectively, of all women in group 1. A similar distribution was observed for the solid BNs (group 2), namely 51.1% and 16.2%, with no intergroup statistical

difference (Df =6,  $\chi^2$  =8.12, P=0.229).

### Localization of the thyroid and BNs.

Table 1 shows the 3-tier localization of nodules (right, left, bilateral), with lateralization applying to the lobe for the thyroid (right lobe, left lobe or both) and the breasts for the mammary nodules (right breast, left breast or both). In the 84 women with CBN, the bilateral localization was the predominant one for both the BN and TN (59.5% and 57.1%, respectively). In contrast, in the 43 women with solid BN, the bilateral localization predominated for the TN (58.1%) but not for the BN, in which the leading localization was the right one (39.5%). As a consequence, distribution of the BN and TN among the three sites did not differ significantly in group 1 women ( $\chi^2$  =1.49, P=0.47), but it did so in group 2 women ( $\chi^2$  =6.52, P=0.038) (Table 1). From another perspective, distribution of TN among the three sites did not differ significantly between group 1 and group 2 women ( $\chi^2$  =1.35, P=0.51), but it did so the distribution of the BN ( $\chi^2$  =9.20, P=0.01) (Table 1).

Figure 1 summarizes all the possible combinations in localization of the TN and BN, distinguishing between the 21 women with a single TN (top panel) and the 63 with two or more TNs (bottom panel). Consistently, when BN were cystic the coexisting thyroid nodule/nodules was/were more likely to be concordant in localization (Figure 1, top and bottom panels). In contrast, when the BNs were solid, the coexisting thyroid nodule/nodules was/were more likely to be discordant (Figure 1, top and bottom panels).



**Figure 1** Concordance/discordance of laterality between thyroid nodules (TNs) and breast nodules (BNs), considering patients with single (top panel) and multiple (bottom panel) thyroid nodules. R, right; L, left; B, bilateral.

### Number and localization of TN

In the 84 patients of group 1, 200 (or 2.4 per patient) TNs were found: patients with 1, 2 and  $\geq 3$  nodules were, respectively, 36.9%, 19% and 44%. Considering the localization of the TNs in the two lobes, the classic topography in the upper, middle or lower third (or area or region) was used. Either for the 27 cases with TNs (cystic and/or non-cystic ones) in the left lobe or for the 38 cases in the right lobe, the most represented localization was the lower third which accounted for 20 (74.1%) and 26 (68.4%) cases, respectively. Among the patients with single TN, both for the 9 cases with cystic or non-cystic TN in the left lobe or for the 14 cases in the right thyroid lobe, the most represented was the lower third localization which accounted, respectively, for 6 (66.7%) and 8 (57.1%) cases.

In the 43 patients of group 2, 86 (or 2 per patient) TNs were found: patients with 1, 2 and  $\geq 3$  nodules were, respectively, 48.8%, 20.9% and 30.2% (Df =2,  $\chi^2 = 2.419$ ,  $P=0.298$  vs. group 1). Considering the localization of the

TN in the two lobes, the classic topography in the upper, middle or lower third (or area or region) was used. For the 26 cases with TNs (cystic and/or non-cystic ones) in the left lobe, the most represented localization was the inferior third, whereas for the 17 cases in the right lobe the most represented localization was the middle third. Among the 13 patients with single TN, both middle and inferior third were equally involved in the left lobe (50% of cases, both) ( $P=0.58$  by Fisher's exact test vs. group 1), whereas the middle third localization prevailed for the right thyroid lobe.

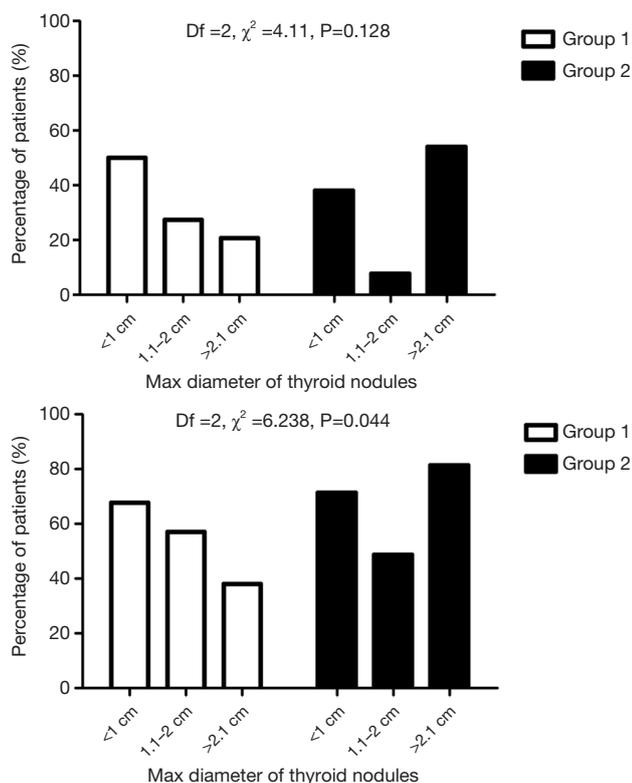
### TN echogenicity

Evaluating echogenicity of TNs in patients of group 1, hypoechoic TNs were the more frequent ones (76 cases or 90.5%). Based on the total number of TNs ( $n=203$ ), hypoechoic TNs remained the most frequent ( $n=151$  or 74.4%). Also among the 23 patients with single cystic or non-cystic TN associated with breast cysts, hypoechoic TNs were the most frequent ones (19 cases or 82.6%).

Considering echogenicity of TNs in patients of group 2, hypoechoic TNs were the most frequent ones (39 cases or 90.7%) (Df =3,  $\chi^2 = 0.568$ ,  $P=0.904$  vs. group 1). Based on the total number of TNs ( $n=66$ ), hypoechoic TNs remained the most frequent ( $n=54$  or 81.8%) (Df =3,  $\chi^2 = 1.439$ ,  $P=0.697$  vs. group 1). Also among the 13 patients with single cystic or non-cystic TN associated with SBN, hypoechoic TNs were the most frequent ones (11 cases or 84.6%). Overall, in group 2, the BN had US features of fibroma ( $n=32$ ), lipoma ( $n=4$ ) or undefined ( $n=7$ ).

### TNs: maximum diameter

Figure 2 shows the 3-tier stratification of single TN (top panel) or multiple TN (bottom panel) based on their maximum diameter. Consistently, when BN were cystic, the coexisting thyroid nodule/nodules was/were more likely to be subcentimetric and less likely to be  $>2.1$  cm in maximum diameter (top and bottom panels). In contrast, when BN were solid, the coexisting thyroid nodule/nodule was/were more likely to be  $>2.1$  cm and less likely to be 1.1–2.0 cm in maximum diameter (top and bottom panels). Because of a smaller number of women with a single TN in group 1 ( $n=31$ ) and group 2 ( $n=19$ ), only the 3-tier partition of multiple TN was significantly different in group 1 compared to group 2 women (Df =2,  $\chi^2 = 6.238$ ,  $P=0.044$ ) (Figure 2).



**Figure 2** Comparison of the diameter of thyroid nodules between the two groups, considering patients with single (top panel) and multiple (bottom panel) thyroid nodules.

## Discussion

We here evaluated the rate with which, at an ambulatory facility for US located in a tertiary care medical center, mammary US is requested as an ancillary exam for a woman whose primary referral reason is thyroid US. We also evaluated the characteristics of the TNs, in light of the cystic or solid nature of the coexisting BNs. Indeed, based on few women observed at the endocrine unit of the same university hospital (see Introduction), some different features depending on the nature (cystic or solid) of the BNs are present in the same woman.

We found that 6.7% (127/1,896) of the women referred for the thyroid US also had undergone a mammary US. BNs were cystic in two-thirds of women (84/127), and solid in the remaining one-third (43/127).

Limitations of the study are the retrospective nature and the lack of cytological diagnosis for those nodules that deserved fine-needle aspiration biopsy (FNAB). Another

limitation could be that we have not looked at the opposite relationship, viz. request of thyroid US in women referred primarily for breast US.

In women with CBNs, TNs were more frequently multiple (64% of cases), whereas in cases with solid BNs, the frequency of single and multiple TNs was approximately the same. The nature (cystic or solid) of the single or all nodules present in the breast/s somehow influenced certain characteristics of the coexisting thyroid nodule/s. When the coexisting breast nodule(s) was/were cystic, the coexisting nodules most frequently detected in the thyroid were the subcentimetric ones (approximately 70% of all TNs). This rate of the subcentimetric TNs and that of the TNs 1.1–2.0 cm in maximum diameter (approximately 55% of all TNs) held when the coexisting breast nodule/s was/were solid. In contrast, the rate of the largest TNs doubled from the approximate 40% in women with cystic breast nodule/s to approximately 80% in women with solid breast nodule(s). This pattern for the largest TNs held when solitary TNs were considered, and in this case, it was evident that such increase occurred at the expense of the other categories (<1.0 and 1.1–2.0 cm).

Excluding the particular association of BN and TN as consequence of breast malignancy that metastasizes to the thyroid (13–26) and a study from Spinos *et al.* (27) which determined cross-sectionally the incidence of solitary TNs and breast fibroadenomas in women with uterine fibroids, the concomitance of TD and breast disease remains controversial. Chung *et al.* (28) conducted a study to clarify the sensitivity of ultrasonographic mass screening for thyroid carcinoma and evaluated 1,401 women who were scheduled to undergo either a breast examination or a follow-up examination for breast cancer. They found that US mass screening for thyroid carcinoma in women who require breast examinations was effective for the detection of subclinical thyroid carcinoma. TNs were detected in 353 (25.2%) of women, 94 (26.6%) of whom were placed in the high-risk group for thyroid cancer, based on suspicious US characteristics and subsequent FNAB on high-risk patients. Among the 94 high-risk patients, 43 underwent thyroidectomy and 37 turned out to have thyroid carcinoma. The detection rate for thyroid cancer was 2.6% (37/1,401). Giani *et al.* (29) provided evidence that the overall prevalence of thyroid disorders is increased in patients with breast cancer. Particularly, Hashimoto's thyroiditis, account to a large extent for the increased prevalence of TD in patients with breast cancer (29). Sun *et al.* (30) analyzed 55,318 Taiwanese women with breast cancer of

whom 28,187 received radiotherapy and 27,131 did not. In that study, only younger (age 20–54 years) women with breast cancer were found to have a significantly higher risk of developing thyroid cancer. Utilizing the surveillance, epidemiology, and End Results-9 database in a retrospective cohort analysis on women older than age 18 years with breast and thyroid cancer, Kuo and colleagues (31) concluded that thyroid cancer survivors are at greater risk for developing breast cancer than the general population. A recent systematic review and meta-analysis including six cohort studies with 17,914 patients found that the relative risk of second primary breast cancer in thyroid cancer survivors treated with radioactive iodine was 0.61 relative to thyroid cancer survivors not treated with radioactive iodine, therefore not increased (32). Interestingly, gene expression profiling analysis of chemokine receptors CXCR7 and CXCR4 in patients with breast cancer and in patients with papillary thyroid cancer showed a role of the chemokine receptors in tumor progression (33,34).

Regulatory subunits of protein kinase A (PKA) are important in cell growth and cell differentiation. PKA hyperactivation has been shown to drive mammary tumorigenesis (35) and increased expression of regulatory subunit R1A of PKA is associated with aggressive and undifferentiated thyroid tumors (36). Another important factor in the pathogenesis of thyroid and BNs and cancer is the environmental exposure to certain chemicals including polychlorinated dibenzo-p-dioxins and dibenzofurans and derivatives (37–39). These chlorinated aromatic compounds are highly soluble in fat and oils and therefore preferentially deposited in such tissues (40).

In 2011, Muller *et al.* (41) evaluated the prevalence of breast cancer in a large group of patients with benign TD and found that the breast cancer prevalence in patients with benign TD was significantly higher compared to BC frequency in the general population, showing the usefulness of screening for breast malignancy of patients with benign TD. Prinzi *et al.* (42) analyzed the prevalence of extra-thyroidal malignancies (EM) in 6,386 female patients affected by different TD. At first, an age-matched analysis of EM in all patients was performed. We then evaluated EM prevalence in four TD diagnostic categories: non-nodular TD (n=2,159); solitary nodule (n=905); multinodular TD (n=2,871); differentiated thyroid cancers (n=451). A total of 673 EM were recorded. EM prevalence in TD patients was higher compared to the general population [odds ratio (OR) 3.21] and the most frequent EM was breast cancer (OR 3.94). Breast cancer showed an increased OR in all

TD, while other cancers associated with specific TD. Women affected by both benign and malignant TD, especially at a younger age, were found to have an increased risk of developing primary EM, thus requiring a careful follow-up and surveillance. Recently, some studies have demonstrated an association between thyroid and breast cancer (43,44). In particular, not only women with a prior history of differentiated thyroid cancer are at an increased risk for breast cancer, but also women with a history of breast cancer are at an increased risk for differentiated thyroid cancer (44).

To the best of our knowledge, studies in the non-oncological literature assessing the coexistence between TNs and BNs have not yet been performed.

In conclusion, in women with BNs associated with TNs, there are interesting differences concerning TNs when patients are stratified based on the cystic or solid nature of the BN. In patients with TNs/CBNs, TNs tend to be subcentimetric and localized in the inferior pole of either thyroid lobe. In patients with TNs/SBNs, TNs tend to be larger and localized in the middle of either thyroid lobe. Our data raise the intriguing possibility that the thyroid follicular epithelium (TFE) positioned along the longitudinal axis of the thyroid gland has differential sensitivity to hypothetical substances, that are produced by CBNs and SBNs and that exert hyperplastic effects on TFE. CBN-secreted substance(s) is/are likely to be distinct from SBN-secreted substance(s), to the hyperplastic stimulus of which the TFE of the inferior pole is refractory.

Frequent performance of thyroid and breast US over many years is required in order to establish which nodule(s) (thyroid or breast) appeared first, and how it/they may influence the US characteristics of the nodule/nodules of the other tissue.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* Notwithstanding the retrospective nature of this original article, the local Ethics Committee (University Hospital of Messina) approved it by giving the

number E-49/99. Informed consent was obtained from all individual participants included in the study.

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