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Original Research

Risk factors for breast cancer development in patients with borderline breast lesions: a retrospective analysis of our outpatient facility

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Summary

Introduction: Women affected by benign or borderline lesions will undergo a follow-up which includes both regular, usually yearly, clinical examinations and imaging repetition. The present study aims to determine how many women with a previous diagnosis of breast lesion of uncertain significance develop breast cancer during follow-up and to assess their risk factors. *Materials and Methods:* This retrospective study included women followed up in the present surgical outpatient facility who underwent a diagnosis of breast lesion of uncertain malignant potential (classified equal or greater than B3 or equal or greater than C3) between January 2003 and June 2014. Main outcomes were the occurrence of breast cancer during follow up and the analysis of possible risk factors for breast cancer development. *Results:* Among 513 included women, 15 developed breast cancer during the follow up for a borderline breast lesion. The cumulative incidence of new breast cancer diagnosis among women with a previous histological or cytological diagnosis of breast lesion of uncertain malignant potential was 4.3% (95% CI, 1.9-6.6%) at seven years of follow up. Furthermore, the presence of atypical ductal hyperplasia (ADH) and lobular intraepithelial neoplasia (LIN) in the surgical excision specimen, as well as the coexistence of hypothyroidism, resulted to be significant risk factors for new breast cancer development among these patients. *Conclusions:* Due to the great heterogeneity of benign breast disease, further studies are required to better define its risk to evolve into breast cancer, and consequently to optimize their follow up and management in order to reduce over-treatment of low-risk patients, while improving breast cancer diagnosis among high-risk women.

Key words: Breast lesions of uncertain malignant potential; Breast cancer; Risk factors; Hypothyroidism; Predictive factors.

Introduction

After the introduction of breast cancer screening program by bi-yearly scheduled mammography and eventual ultrasound breast examination [1, 2] the number of patients found to have a benign breast pathology of uncertain malignant potential has significantly increased. In fact, along with the increased detection rate of early breast cancers, we observed also an increased detection rate of benign lesions with a doubtful radiological aspect or with a borderline histological result. The latter include an heterogeneous group of histological diagnosis, such as atypical epithelial proliferation of ductal type or atypical ductal hyperplasia (ADH), flat epithelial atypia, lobular intraepithelial neoplasia (LIN) that included lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH), radial scar and complex sclerosing lesion, papillary lesion, mucocele-like lesion, phyllodes tumor, and spindle cell lesion [3].

Starting after 50 years of age, the screening program allows the detection of only a minority of this kind of breast lesions, as a wide proportion of benign breast lesions regards women in their fertile age, being usually influenced by hormonal milieu [1, 4]. In these cases women complain of breast palpable masses, pain, or other symptoms that could affect their quality of life [4]. After imaging and clinical assessment, only the most suspicious lesions are submitted to needle core biopsy (NCB), fine-needle aspiration cytology (FNAC), or vacuum-assisted needle core biopsy (VANCB) [4, 5], and again only a minority of them undergoes surgical excision after NCB, FNAC, or VANCB. Within such triple assessment process, the majority of breast lesions result to be benign following the first or second step of the process, whereas after surgical excision they can be classified as benign, malignant or borderline, being of uncertain prognostic significance.

Women affected by benign or borderline lesions will undergo a follow-up which includes both regular, usually yearly, clinical examinations and imaging repetition. In fact, especially in case of borderline lesions, it is very im-

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portant to promptly detect any eventual changes in the clinical or imaging characteristics of the known lesion, in order to eventually submit the patient to surgical excision in case of a doubtful behavior.

The present study aims to determine how many women with a previous history of borderline breast lesion diagnosis (NCB or VANCB histology classified as equal or greater than B3 or FNAC cytology classified as equal or greater than C3) developed breast cancer during the follow-up, and to assess their possible risk factors.

Materials and Methods

This retrospective study included women followed up in the present surgical outpatient facility who underwent a diagnosis of breast lesion of uncertain malignant potential between January 2003 and June 2014. The authors gathered information for patients selection from the outpatient facility files of the Clinic of Surgery. This study follows the dictates of the general authorization to process personal data for scientific research purposes by the Italian Data Protection Authority and it was conducted in accordance with the Declaration of Helsinki.

Only patients that had NCB or VANCB histology classified equal or greater than B3 or FNAC cytology classified equal or greater than C3 were included in this study. All male cases and women with a previous or a synchronous diagnosis of breast cancer were excluded. Main outcomes considered in this study were the occurrence of breast cancer during follow up and the analysis of possible risk factors for breast cancer development.

Patients characteristics were collected as follows: age at diagnosis of the breast lesion of uncertain malignant potential, follow-up time, type of breast surgery, type of diagnosis of the borderline breast lesion, symptoms eventually correlated to the breast lesion, familial history of breast or ovarian cancer, age at first menses, eventual post-menopausal status and age at menopause, eventual parity and age at first pregnancy, duration of lactation of the whole pregnancies, use of systemic estrogen therapy (oral contraceptive pill or hormone replacement therapy), diagnosis of diabetes or hypothyroidism.

Data about the breast lesion of uncertain malignant potential included: imaging characteristics of the lesion (eg. the presence of microcalcifications), histological result of NCB or VANCB, cytological result of FNAC, and eventual definitive histological examination after the surgical resection when performed. Among women with a diagnosis of breast cancer, the authors collected also the following information: cancer histotype, grading, and TNM staging.

According to the European guidelines for quality assurance in breast cancer screening and diagnosis, NCB and VANCB histological results were classified as follows [3]: B1 (normal tissue/uninterpretable), B2 (benign lesion including fibrocystic change, fibroadenoma, duct ectasia, sclerosing adenosis, or other benign lesions), B3 (lesion of uncertain malignant potential including atypical epithelial proliferation of ductal type, flat epithelial atypia, LIN that included lobular carcinoma in situ and ALH, radial scar/complex sclerosing lesion, papillary lesion, and other lesions that included mucocele-like lesion, phyllodes tumor, or spindle cell lesion), B4 (suspicious of malignancy), and B5 (malignant). Moreover, FNAC cytology results were classified as follows: C1 (unsatisfactory), C2 (benign lesion), C3 (atypical, probably benign), C4 (suspicious, probably malignant) or C5 (malignant) [3]. Furthermore, tumor stage was defined according to the VII edition of the TNM classification (AJCC/UICC), tumor histology according to the World Health Organization criteria, as modified by Rosen and Oberman [6]. In addition, the tumor grade was evaluated following the recommendations of Elston and Ellis [6]. Molecular subtypes of breast cancer were evaluated in this study as previously described [7]. In this study, hypothyroidism was defined by the presence of an ongoing thyroxine treatment. Diabetes mellitus was defined by the presence of an ongoing treatment by oral hypoglycemic agents or insulin. The follow up time in this study was defined from the first registered outpatient visit to the last known outpatient visit or the diagnosis of breast cancer.

Surgical open biopsy or lesion removal was carried out by breast conserving surgery or in case of small breast size also by nipple sparing mastectomy or skin sparing mastectomy followed by immediate breast reconstruction (e.g. in case of large phylloid tumors) [8–10]. Non palpable breast lesions were removed by wire hook localization or radio-guided occult lesion localization (ROLL) as previously described [11, 12].

Data analysis was performed using R (version 3.1.0) and considering a p-value <0.05 as significant. Univariate analysis was performed by Fisher exact test or chi-square test in case of categorical variables, Wilcoxon test or t-test in case of continuous variables. The authors also performed a Kaplan-Meier analysis and drown cumulative events curves. Also univariate and multivariate logistic regression analyses were performed considering as dependent variable the development of breast cancer and as independent variables the possible predictive factors found in the univariate analysis. Then, the authors obtained the final multivariate model by a step-wise analyses.

Results

In the present outpatient registries, the authors found 558 patients potentially eligible for this study. Among these, 513 patients were actually eligible for the present study. They excluded from this analysis 17 male patients, 12 women affected by a synchronous breast cancer in association with the borderline breast lesion, and 16 women because of a personal history of a previous breast cancer. The population had a mean age of 49.62 (±12.97) years at the time of borderline breast lesion diagnosis and in Table 1 , the authors show patients' characteristics. The majority of lesions was found by clinical examination [35.5% (182/513)] while lesions found through the screening program by combined mammography and breast ultrasound were 19.7% (101/513). Of the women, 45.8% (215/469) had a post-menopausal status with a mean age at menopause of 49.02 (±6.2) years. Less than half of the included women files reported information about reproductive history. Furthermore, 9.6% (49/513) of the women presented hypothyroidism diagnosis.

The majority of cases were diagnosed by NCB or VANCB histology. In 104 cases, both NCB or VANCB histology and FNAC cytology were performed. Surgical excisional biopsy was omitted only in 52 cases because of patient's personal choice, who decided to wait before surgical excision or biopsy performing only follow up

Table 1. — *Patient population description.*

Women's age (years)	49.62 (±12.97)
Type of breast surgery	
BCS	95.7% (491/513)
NSM/SSM	4.3% (22/513)
Type of diagnosis	
Screening	19.7% (101/513)
Ultrasound	27.3% (140/513)
Mammography	17.5% (90/513)
Clinical examination	35.5% (182/513)
Mammography findings	
Negative	6.2% (32/513)
Well defined mass	11.3% (58/513)
Architectural distortion	4.1% (21/513)
Microcalcification	25.0% (128/513)
Not performed	53.6% (275/513)
Breast ultrasound findings	
Negative	14.2% (73/513)
Architectural distortion	3.7% (19/513)
Hyperechogenic lesion	3.3% (17/513)
Hypo- an-echogenic lesion	61.0% (313/513)
Not performed	17.7% (91/513)
Familial history of cancer	47% (94/200)
Age at menarche (years)	12.68 (±1.59)
Post-menopausal status	45.8% (215/469)
Age at menopause (years)	49.02 (±6.2)
Parity	
Nulliparity	7.8% (40/513)
Multiparity	39.2% (201/513)
Unknown	53% (272/513)
Age at first pregnancy	27.23 (±6.75)
Cumulative lactation (months)	4 (0-12)
Use of systemic estrogens	15% (77/513)
Hypothyroidism	9.6% (49/513)
Diabetes mellitus	2.7% (14/513)

Table 2. — *Histological and cytological characteristics of B3 or C3 lesions and characteristics of patients that developed breast cancer.*

Histological and cytological characteristics of B3 or C3 lesions	
NCB or VANCB histology	
B1	5.7% (22/384)
B2	13% (50/384)
B3	79.2% (304/384)
B4-B5	2.1% (8/384)
FNAC cytology	
C1	1.3% (3/233)
C2	3.9% (9/233)
C3	92.3% (215/233)
C4-C5	2.6% (6/233)
Surgical excision/biopsy	
Negative histology	1% (5/513)
Fibroadenoma	17% (87/513)
Fibrocystic change	17.5% (90/513)
Duct ectasia	1.6% (8/513)
Papillary lesion	18.7% (96/513)
Sclerosing adenosis	6% (31/513)
Lobular intraepithelial neoplasia	2.9% (15/513)
Atypical ductal hyperplasia	9.7% (50/513)
Radial scar/complex sclerosing lesion	8.8% (45/513)
Other benign	6.6% (34/513)
Not performed	10.1% (52/513)
Characteristics of patients that developed breast cancer	
Histological type	
Ductal invasive carcinoma	66.7% (10/15)
Lobular invasive carcinoma	13.3% (2/15)
Ductal and lobular invasive carcinoma	13.3% (2/15)
Ductal in situ carcinoma	6.7% (1/15)
Tumor size and nodal status	
Tis	6.7% (1/15)
T1	80% (12/15)
T2	13.3% (2/15)
N0	80% (12/15)
N1	13.3% (2/15)
N2	0% (0/15)
N3	6.7% (1/15)
Tumor grading	
G1	26.7% (4/15)
G2	73.3% (11/15)
G3	0% (0/15)

imaging and eventual NCB or VANCB.

Table 2 reports further histological and cytological characteristics of B3 and C3 lesions. Median follow up time was 60 (43-82) months and 15 women developed a breast cancer lesion during follow up. Table 2 also shows the characteristics of the new diagnosed breast cancers, the vast majority of which were T1N0G2 cancers. Furthermore, molecular subtype included ten luminal A, three luminal B, and two basal-like tumors. Thereafter, the authors analyzed the cumulative events of new breast cancer diagnosis and we found that after two years of follow up, 0.6% (95% CI, 0-1.3%) of cases developed breast cancer, after five years 2.4% (95% CI, 0.9-3.9%) of cases, and after seven years 4.3% (95% CI, 1.9-6.6%) of cases (Figure 1). In Tables 3 and 4 the authors analyzed the differences between women who developed or not breast cancer during the follow up. Among women with a new breast cancer diagnosis the authors found a significant higher prevalence of hypothyroidism and ADH ($p < 0.05$).

In the logistic univariate and multivariate analyses the authors included all possible predictive factors with a p-value < 0.300. They excluded only reproductive history information because of many missing data. In Table 5 the authors show the univariate and the final multivariate logistic regression models found by step-wise analysis. It resulted that atypical ductal hyperplasia, lobular intra- epithelial neoplasia (both found in the surgical excision specimen), and hypothyroidism were significant risk factors for new breast cancer diagnosis during the follow up. In addition, a diagnosis of papillary lesion resulted to be protective. Finally, the multivariate model achieved a high prediction accuracy with an area under the receiver operator characteristics curve of 80.1% (95% CI, 70.4-89.8%).

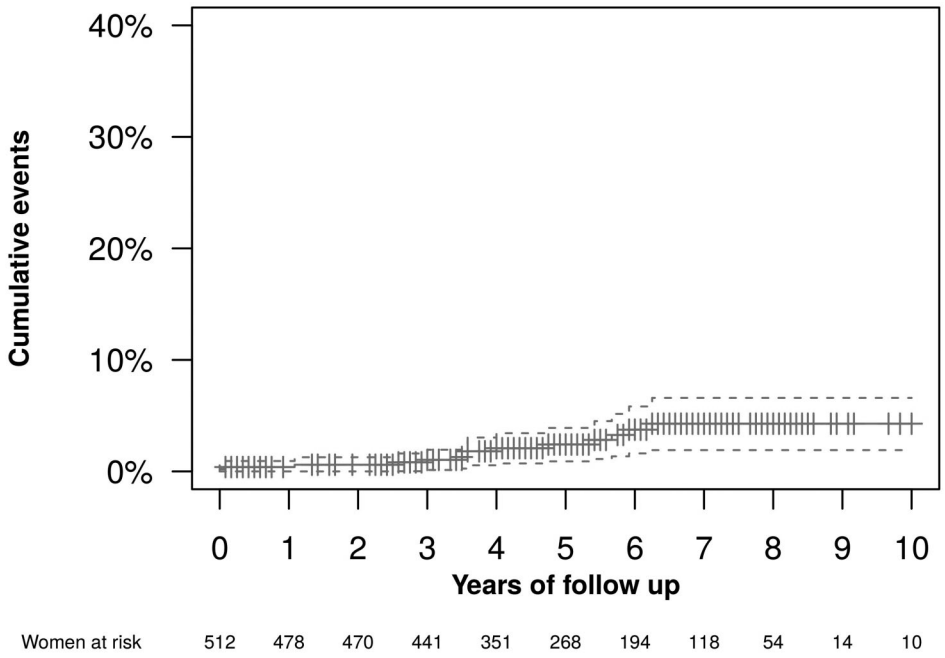

Figure 1. — Occurrence of breast cancer diagnosis during follow up (the plot shows cumulative events and 95% CI lines).

Discussion

In this study, the authors found that the incidence of new breast cancer diagnosis among women with a previous histological or cytological diagnosis of breast lesion of uncertain malignant potential was 4.3% (95% CI, 1.9-6.6%) at seven years of follow up. Furthermore, the presence of ADH and LIN in the surgical excision specimen, as well as the coexistence of hypothyroidism, resulted to be significant risk factors for new breast cancer development among these patients.

The principal limitation of this study are the small number of followed up patients and the retrospective study design. On the other hand, its strengths are the accuracy of data collection and the reproducibility of both imaging and surgical procedures, which were always performed by the same specialists equipe.

Epidemiological studies observed that about one to two women would develop a benign or borderline breast lesion after 20 years of age [13]. In the present population, 15 women with a diagnosis of breast lesion of uncertain malignant potential developed breast cancer during the follow up. Mean age at diagnosis of the breast lesion of uncertain malignant potential was 49.62 (± 12.97) years. Then, the mean age at menopause of this population being 49.02 (± 6.2) years, the authors can deduce that about half of borderline lesions affected premenopausal patients, as well as breast cancers which developed during the follow up for such borderline lesions. On the contrary, mean age at breast cancer diagnosis of the entire female population followed up by this surgical outpatient facility was 60 years, and thus postmenopausal [1].

Hormonal balance of pre- and postmenopausal women are obviously very different, with a progressive reduction with aging of sexual hormones serum concentrations, which have a positive effect on the proliferative trend of the most breast lesions. In fact, in the literature, many studies revealed an increased breast cancer risk among women assuming exogenous hormones, both as contraceptives during their fertile age and as substitutive hormonal therapy after menopause [14–17]. In the present population, the association between breast cancer development and the use of oral contraceptives did not result statistically significant.

Taking into consideration the diagnostic modality, in the 35.5% of cases, diagnosis was performed by self examination, while radiodiagnostic techniques found only 19.7% of borderline lesions. Actually, due to their mean age, women affected by breast lesions of uncertain behavior are usually excluded by the screening programs (in this region screening starts from 50 years of age) [1, 2]. This fact demonstrates also the important role of self-breast examination during the fertile age, which is extremely simple and requires very little time. However, many women without any increased risk of breast malignancy voluntarily undergo periodical breast controls usually associated with mammography and breast ultrasound even before their 50 years of age. In fact, the age at which it should be more opportune to definitely begin the mammographic screening is still argument of great debate, as already from 40 years of age, an augmented risk exists in developing breast cancer [18, 19].

In accordance with the literature, the lesions of uncertain

Table 3. — *Population description subdivided between patients that developed or not breast cancer.*

	Controls	Breast cancer	*p*
Women age's (years)	49.48 (±13.01)	54.2 (±10.89)	0.121
Type of breast surgery			
BCS	95.6% (476/498)	100% (15/15)	0.405
NSM/SSM	4.4% (22/498)	0% (0/15)	0.405
Type of diagnosis			
Screening	19.5% (97/498)	26.7% (4/15)	0.490
Ultrasound	27.3% (136/498)	26.7% (4/15)	0.956
Mammography	17.5% (87/498)	20% (3/15)	0.800
Clinical examination	35.7% (178/498)	26.7% (4/15)	0.469
Mammography findings			
Negative	6.2% (31/498)	6.7% (1/15)	0.944
Architectural distortion	4% (20/498)	0% (0/15)	0.429
Microcalcification	24.5% (122/498)	40% (6/15)	0.172
Well defined mass	11.2% (56/498)	13.3% (2/15)	0.801
Not performed	54% (269/498)	40% (6/15)	0.284
Breast ultrasound findings			
Negative	13.9% (69/498)	26.7% (4/15)	0.248
Architectural distortion	3.8% (19/498)	0% (0/15)	0.441
Hyperechogenic lesion	3.4% (17/498)	0% (0/15)	0.467
Hypo- an-echogenic lesion	61% (304/498)	60% (9/15)	0.935
Not performed	17.9% (89/498)	13.3% (2/15)	0.650
Familial history of cancer	46.4% (89/192)	62.5% (5/8)	0.370
Age at menarche (years)	12.69 (±1.61)	12.57 (±1.13)	0.805
Post-menopausal status	45.7% (208/455)	50% (7/14)	0.751
Age at menopause (years)	49.05 (±6.11)	48.5 (±8.29)	0.879
Parity			
Nulliparity	7.6% (38/498)	13.3% (2/15)	0.417
Multiparity	38.8% (193/498)	53.3% (8/15)	0.254
Unknown	53.6% (267/498)	33.3% (5/15)	0.121
Age at first pregnancy	27.05 (±6.63)	31.25 (±9)	0.421
Cumulative lactation (months)	4 (0-12)	7 (1.5-8.75)	0.994
Use of systemic estrogens	14.7% (73/498)	26.7% (4/15)	0.200
Hypothyroidism	9% (45/498)	26.7% (4/15)	<0.05
Diabetes mellitus	2.6% (13/498)	6.7% (1/15)	0.342

malignant potential which are more frequently associated with cancer development during the follow up are ADH and LIN [20]. In previous literature, also papillary lesions with atypia are significant risk factors for breast cancer developed [21]. However, in the present population of borderline breast lesions, papillary lesions resulted to be a protective factor.

With regards to hypothyroidism, which resulted to be a significant risk factor for cancer development during the follow up of borderline breast lesions, it represents a frequent disease within premenopausal female population, and a recent meta-analysis of European studies described a hypothyroidism prevalence in the female and male population of respectively 5.1% and 0.92% [22]. In fact, thyroxine is known to influence mammary gland development similarly to estrogen, by inducing cellular differentiation and promoting lobular proliferation [23], and many studies discuss the controversial association between dysthyroidism and breast cancer, also supported by the greater incidence of both this pathologies after menopause [24].

In the literature the possible correlation between thyroid diseases and breast cancer was widely investigated. However, the results were inconsistent. In fact some authors observed no significant correlation between thyroid diseases and breast cancer [25], while other authors found hyperthyroidism or hypothyroidism to be associated to breast cancer [24, 26]. In particular, hypothyroidism was found to be a protective factor for breast cancer but also to be a risk factor or to have no influence on breast cancer [27–29]. Despite that a recent meta-analysis found hyperthyroidism and hypothyroidism not to be significant breast cancer risk factors, a link was confirmed between thyroid function and breast cancer. In fact, this meta-analysis found a relationship between autoimmune thyroiditis, diagnosis of goiter, or presence of serum thyroid autoantibodies and breast cancer [24]. Furthermore, in breast cancer cell lines, triiodothyronine may increase tumor proliferation by heightening estrogen effects; thus, triiodothyronine may play a role in breast cancer development or progression [23]. From these studies, it is possible to deduce that even

Table 4. — *Histological and cytological characteristics of B3 or C3 lesions subdivided between patients that developed or not breast cancer.*

	Controls	*Breast cancer*	*p*
NCB or VANCB histology			
B1	5.65% (21/372)	8.33% (1/12)	0.693
B2	13.17% (49/372)	8.33% (1/12)	0.624
B3	79.3% (295/372)	75% (9/12)	0.718
B4-B5	1.88% (7/372)	8.33% (1/12)	0.226
FNAC cytology			
C1	1.32% (3/228)	0% (0/5)	0.796
C2	3.95% (9/228)	0% (0/5)	0.650
C3	92.11% (210/228)	100% (5/5)	0.513
C4-C5	2.63% (6/228)	0% (0/5)	0.713
Surgical excision/biopsy			
Negative histology	1% (5/498)	0% (0/15)	0.697
Fibroadenoma	16.87% (84/498)	20% (3/15)	0.750
Fibrocystic change	17.87% (89/498)	6.67% (1/15)	0.261
Duct ectasia	1.61% (8/498)	0% (0/15)	0.621
Papillary lesion	19.28% (96/498)	0% (0/15)	0.086
Sclerosing adenosis	6.02% (30/498)	6.67% (1/15)	0.918
Lobular intraepithelial neoplasia	2.61% (13/498)	13.33% (2/15)	0.067
Atypical ductal hyperplasia	9.04% (45/498)	33.33% (5/15)	<0.05
Radial scar/complex sclerosing lesion	8.63% (43/498)	13.33% (2/15)	0.526
Other benign	6.63% (33/498)	6.67% (1/15)	0.995
Not performed	10.44% (52/498)	0% (0/15)	0.384

Table 5. — *Univariate and multivariate (*) logistic regression analysis (dependent variable: breast cancer development). (*) Final multivariate model was selected by step-wise analyses.*

	OR (IC95%)	p	OR (IC95%) (*)	*p*
Women's age (years)	1.03 (0.99 - 1.07)	0.159		
Use of systemic estrogens	2.26 (0.74 - 6.95)	0.155		
Microcalcification	2.10 (0.76 - 5.82)	0.155		
B4-B5 NCB or VANCB histology	6.77 (0.98 - 46.68)	0.052		
Papillary lesion	0.13 (0.01 - 2.30)	0.166	0.22 (0.01 - 3.68)	0.289
Atypical ductal hyperplasia	5.21 (1.76 - 15.39)	<0.05	5.15 (1.65 - 16.01)	<0.05
Lobular intraepithelial neoplasia	6.65 (1.49 - 29.64)	<0.05	7.15 (1.47 - 34.76)	<0.05
Hypothyroidism	3.89 (1.24 - 12.17)	<0.05	3.96 (1.23 - 12.70)	<0.05

a substitutive therapy with thyroxine might be associated with an increased risk of breast cancer, representing a possible iatrogenic source of hyperthyroidism. Unfortunately, the authors did not collect the exact dosage of exogenous thyroxine administered, therefore it was impossible to better define this kind of association.

Finally, cancer-related mortality after diagnosis of benign breast disease results lower than 1% [30]. In the present population, no cancer-related mortality was observed among patients who developed breast cancer during the follow up for a breast lesion of uncertain malignant potential. Also, a possible explanation may be the early stage of such tumors at diagnosis thanks to the long, regular follow up. In fact, the most cases were Stage I breast cancers (pT1N0) with intermediate grading (G2).

In conclusion, due to the great heterogeneity of benign breast disease, further studies are required to better define its risk to evolve into breast cancer, and consequently to optimize their follow up and management in order to reduce over-treatment of low-risk patients while improving breast cancer diagnosis among high-risk women.

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