Breast ultrasonography in detecting mammographically occult breast cancer in women at high familiar risk

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Aims and objectives

Early identification of Breast Cancer (BC) through mammography screening programs of general population is amply demonstrated in several studies conducted over the past years, that report a reduction in mortality of about 22% for women aged 50-69 years old [1,5].

Actually Mammography (MMG), although not perfect, can be considered the main screening test in order to detected early BC with a sensitivity of 75%-85% calculated in general population [2], up to 80%-98% in women with fat breast tissue (ACR D1-D2) [3].

Less promising results have achieved for study of dense (estimated as 51%-75% glandular; ACR D3) or extremely dense (as >75% glandular; ACR D4) breast parenchyma, frequent present in more than one half of women younger than 50 years [4,5] with a sensitivity as low as 30% to 50% [2].

High breast density (ACR D3-D4) represents a great limit for mammography performance; its sensitivity is inversely proportional to breast tissue density and leads to a higher probability of occurrence of Interval Breast Cancer (IBC) detected during a screening program [5,6,7,8].

Ultrasound (US), as a MMG support, represents a useful and often indispensable diagnostic tool for detection of invasive BC if compared to MMG alone in young women and with dense breast [5,9].

Still now no medical organization recommends US as an additional screening on the base of breast density, but is true that The American College of Radiology and the Society of Breast Imaging recommend adding US approach to MMG only in a very subgroup of people with a strong hereditary risk (>20% lifetime risk) and/or with contraindications to Magnetic Resonance (MR) [6,10,11].

Lehman et al. study involving symptomatic women between 30 and 39 years with focal, clinical breast signs and risk of malignancy, suggests that US has high sensitivity (95,7%) and high negative predictive value (99,9%) in this setting, considered the first imaging technique of choice; MMG adds low value, but in addition to US approach can be reserved for particular high risk cases, including those with BRCA mutation carriers [12].

The first confirmation about the ability of US in BC screening dates back to 1980. Thanks to technological and physical advances in US, in 1995 Gordon and Goldemberg publish the results of their report about the ability of this imaging modality for identification of mammographically occult, solid tumors, in particular in asymptomatic patients [1].
Since then, other authors analyzed the accuracy of US in women with dense breasts showing its ability to detect hidden cancers to mammography, with a detection rate variable from 0.3% to 0.4%, the majority of which in early stage [9].

It is well known that high breast x-ray density is an important risk factor for general population, but still more representative for hereditary-family risk group of patients [5].

For women with BRCA mutation carriers, the National Comprehensive Cancer Network (NCCN) has issued recommendations for BC surveillance, including monthly breast self-examination, semi-annual clinical breast examination, annual mammogram, and annual breast MR [13].

At the Center of Breast and Ovarian Familiar Tumors, a dedicated Center at the Department of Oncology and Hematology located in Modena, is employed an activity of multimodal breast diagnosis since 1994, for BC prevention and early diagnosis for women at increased, familiar risk.

According to Modena criteria [17], women are incorporated into a surveillance program based on their customized risk profile.

The purpose of this study was to evaluate the contribution of US screening in detecting BC in women at increased, familiar risk, particularly when clinical examination and mammograms were negative.
Methods and materials

At the Center of Breast and Ovarian Familiar Tumors in Modena, 3306 women considered at increased familiar risk for BC were enrolled in a surveillance program from January 1994 to June 2014 and divided into four risk categories depending on familiar history or BRCA status according to Modena Criteria: BRCA mutation carriers (BRCA+), High, Intermediated and Slightly increased risk (Fig.1).

Clinical Breast Examination (CBE), MMG, US and MR are performed annually by experts radiologists of about 10-20 years of breast imaging experience at our dedicated clinic located at the Department of Radiology.

Clinical and instrumental monitoring begins at 25 years in BRCA+, while at 30 years in the other groups.

In BRCA+ patients CBE, MMG and MR are performed annually, while in High risk and senior groups CBE, MMG and US are performed every 2 years up to 36 years, then annually by 40 years at the same place.

In these groups a clinical and instrumental follow-up with CBE and US runs every 6 months for BRCA+, High and Slightly increased risk women by clinicians of the Center of Breast and Ovarian Familiar Tumors in Modena with at least 10 years breast US-experience.

Slightly increased risk women are subjected to CBE, MMG and US every 18-24 months, while the clinical follow-up US is annual (Fig.2).

MMG was conducted with two standard breast projections: one craniocaudal and one angled in a side view (medium-lateral). Other projections, compression views and magnifications may be included when necessary.

Breast US study was performed bilaterally exploring all breast glandular sectors by using a linear array transducer at high frequency (frequency of 7-13 MHz) in radial displacement of sensor and also studied retroareolar region and, when necessary, axillary recess too.

The average time necessary to perform a US examination was about 15-20 minutes.

All lesions US-detected were documented into two spatial planes, localized with scanning in all clock positions and then classified according to Breast Imaging Reporting and Data System Ultrasound Criteria (BI-RADS US categories) in order to standardize terminology and clinical management [14,15].

No breast lesions were categorized as 6 BI-RADS US category.
Each suspicious lesion was verified cytologically with US-guided Fine-Needle Aspiration Cytology (FNAC) or histologically with 14-Gauge needle biopsy.
### High risk

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<th>I) at least 3 relatives diagnosed with BC (or OC) in 2 different generations</th>
<th>II) one BC/OC case is a first-degree relative of the other 2 (if the other 1 if the first criterion is not fulfilled)</th>
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BC diagnosed at age ≤ 35, regardless of family history
BC and OC in the same woman, regardless of family history

### Pedigree classification

- **Hereditary**
- **Suspected Hereditary**
- **Suspected Hereditary**
- **Early Onset**
- **Breast Ovarian Cancer**
- **HBC/HBOC**
- **SHBC/SHBOC**
- **SHBC/SHBOC**
- **EOBC**
- **BOC**

### Intermediate risk

- **Familial**
- **Strongly Suspected Familial**
- **Male Breast Cancer**
- **FBC/FBOC**
- **SFB C+**
- **SFB C+**
- **MBC**

### Slightly increased risk

- **Suspected Familial**
- **Sporadic Breast Cancer**
- **SFB C+**
- **SFB C+**
- **SFB C+**
- **SPO C**
- **SPO C**

* male relatives excluded when calculating the degree of relationship
* if at least two of the malignancies are OC, the pedigree must be classified as HBOC even if the third criterion is not fulfilled.

HBC = hereditary breast cancer; HBOC = hereditary breast/ovarian cancer; SHBC=suspected hereditary breast cancer; SHBOC=suspected hereditary breast/ovarian cancer; EOB C=early onset breast cancer; BO C=breast ovarian cancer; FBC=familial breast cancer; FBOC=familial breast/ovarian cancer; SFB C+=strongly suspected familial breast cancer; SFB C+=strongly suspected familial breast/ovarian cancer; MBO C=familial breast cancer; SPO C=sporadic ovarian cancer

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**Fig. 1:** Modena model.

Fig. 2: Algorithm of Modena Criteria for Breast Cancer Screening Process for each risk category: High (H), Intermediate (I), Slightly increased or Low (L).

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Results

After a median follow up of about 11 years, 150 cancers were diagnosed on 148 patients, of these 134/150 (89%) were Screen Detected Breast Cancers (SDBC), while 16/150 (11%) were Interval Breast Cancer (IBC).

Of 134 SDBC 32 (24%) were detected by US alone, 95 (71%) by MMG alone or plus US, 7 (5%) by MR (Fig.3-4); 60,4% in High risk group and 17,2% in BRCA+ group; patients ages ranged from 32 to 87 years; 43% below age 50 years, while 57% aged #50.

Of 32 cancers US-detected with negative mammograms 15 (47%) were asymptomatic cases, while 17 (53%) with symptoms. 28/32 (87,5%) resulted infiltrating carcinomas and 4/32 (12,5%) in situ forms (DCIS); 20/32 (62,5%) were diagnosed in women with dense breast and 19/32 (60%) in a more favorable stage (pTis,pT1a,pT1b).

Of all Invasive lesions, 21/28 (75%) were Ductal Cancers (IDC) and 7/28 (25%) were Lobular Cancers (ILC); for each of them we have also considered their biological features and breast density (D) according to ACR criteria [4] (Fig.5).

US-only detected a large percentage of cancers in dense breasts than those diagnosed with MMG alone or MMG plus US (62,5% versus 35,5% in ACR D3-D4 group) (Fig.6).

19/32 (60%) were detected in women younger than 50 years.

Asymptomatic BC US-detected were the object of our analysis in order to confirm the great benefit of US-screening alone or in association to negative mammograms for this selected group of patients.

Of these 1/15 was DCIS and 14/15 were infiltrating carcinomas (11 IDC and 3 ILC), 12 of which (86%) in Stage I (S I) and 2 (14%) in Stage II (S II), 13/15 (87%) in a more favorable stage and small size (pTis,pT1a,pT1b) (Fig.7).

US detected 67% of cancers in asymptomatic women aged <-50 years and 33% in those aged #50; about 60% (9/15) of non palpable BC detected in patients with mammographically dense breast.

The Relative Incremental Cancer Detection (RICD) at US in asymptomatic women over MMG detected was 24% in women aged <-50 and 7% in those aged #50 years (Fig.8).
Fig. 3: Distribution of BC.

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**Fig. 4:** Distribution of SDBC according to different imaging techniques (US, MMG/MMG+US, MR).

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**Fig. 5:** Distribution of infiltrating SDBC US-detected with negative mammograms according to histotypes (IDC, ILC), dimensions (pT), Stage (S), ER status (ER positive; ER+), PgR status (PgR positive; PgR+), proliferative index (Mib 1+), breast density (ACR categories: D1-D2/D3-D4) in symptomatic and asymptomatic women.
**Fig. 6:** Distribution of radiological breast density* (ACR D1-D2, ACR D3-D4 categories) of SDBC according to different imaging techniques (MMG/MMG+US and US alone). *Not evaluated radiological density (19 cases).

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**Fig. 7:** Distribution of US-SDBC with negative mammograms according to histotypes (DCIS, ILC, IDC), Stage (S), dimensions (pT), Grading* (G) and breast density (ACR D1-D2, ACR D3-D4 categories) in asymptomatic subjects. *Not evaluate Grading in 2 cases (2 ILC).

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**Fig. 8:** Relative Incremental Cancer Detection (RICD%) at US in asymptomatic women over MMG/MMG+US-detected cancers according to age (<50 and ≥50).

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Conclusion

MMG is a recommended imaging modality for detection of BC in general population, although with a sensitivity that progressively and greatly decreases in a proportional way according to the increment of breast density [10] with low performance for young women where the added value of MMG is very low [12].

In women aged 30-39 years who manifest clinical symptoms, breast US should be the primary imaging approach, while MMG represents the first modality in the older group [12].

In high risk population MMG alone is not so effective. It is necessary to associate MMG to supplemental screening techniques as US and MR in particular in young women [2,10,12,18].

The benefit from adding US to MMG is validated and leads to an increase of sensitivity compared to either modality alone, but its specificity remains low because it comes with a high risk of false positives rate [10,18].

As regards our experience conducted on a selected group of women at high or genetic risk, our outcomes are the consequence of an analysis expressed in terms of Relative Incremental Cancer Detection (RICD) of US-breast screening for identification BC according to different ages of distribution.

Our intensified clinical-US screening led to the identification of a high percentage of BC in a more favorable stage and low proliferative index.

The biggest advantage in term of "Early diagnosis", is obtained in young women (<50 years) where US alone or associated to negative mammograms identified BC for almost half of the total group (60%), of which 62.5% in dense breast cohort (ACR D3-D4).

Encouraging results we have obtained for the asymptomatic cases, the majority of them with negative mammograms, very small radiological size (#1cm:93%) and histological dimensions pT (pTis,pT1a,pT1b:87%), but more frequently infiltrating histotypes (93%) and with low proliferative index (71%) (Fig. 9-10-11-12-13-14).

For this group without clinical signs, US alone, or in addiction to negative mammograms, has increased the detection of BC, showing a higher contribution in subjects aged <50 years (BC:67%; RICD:24%) (Fig. 8).

In conclusion the diagnostic contribution of US screening in the present study is not been negligible. This procedure involves significant additional costs, in economic terms, that may be acceptable in this women at increased risk, because reduces the incidence of IBC (only 11% in our experience) anticipating the diagnosis of BC with a higher contribution in women younger than 50 years and with negative MMG.
Fig. 9: a) Round hypoechoic lesion with indistinct margins (US BI-RADS class 4) in upper, outer quadrant of left breast. Histological diagnosis reveals an IDC (T1a,N0,Mx), diameter of 4 mm. b-c) Negative mammograms (ACR D2).

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Fig. 10: a) Hypoechoic mass with irregular margins and antiparallel orientation (US BI-RADS class 5) in upper, outer quadrant of left breast. Histological diagnosis reveals an IDC (T1b,N0,M0) with a diameter of 7 mm. b-c) Negative mammograms (ACR D4).

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Fig. 11: a) Round, hypoechoic mass with indistinct margins (US-BIRADS class 3), located at three o’clock in left breast. Histological diagnosis reveals an IDC (T1a, N0, M0) with a diameter of 3 mm. b-c) Negative mammograms (ACR D4).

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Fig. 12: a) Oval hypoechoic mass with angled margins (US-BIRADS class 4), located at six o’clock in left breast. b-c) Negative mammograms (ACR D3); histological diagnosis reveals an IDC (T1b, N0, M0) with a diameter of 8 mm.

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Fig. 13: a) Antiparallel hypoechoic mass with angular margins, (US-BIRADS class 5). b-c) located at the inferior, outer quadrant in right breast. b-c) Negative mammograms (ACR D4); histological diagnosis reveals an IDC (T1c,N0,Mx) with a diameter of 10 mm.

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Fig. 14: a) Hypoechoic mass, with irregular margins, (US-BIRADS class 5). b-c-d) located at the inferior, internal quadrant in left breast. Negative mammograms (ACR D2); histological diagnosis reveals an IDC (T1b,N0,Mx) with a diameter of 7 mm.

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References