Magnetic resonance imaging (MRI) in high risk women: benefits and problems

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Purpose

Women with a strong family history of breast cancer (BC) or a predisposing gene mutation such as BRCA1 or BRCA2 have a cumulative lifetime risk of developing BC of 21-65% [1] with a substantial proportion of these cancer diagnosed before the age of 50 years. Prophylactic mastectomy, oophorectomy and chemoprevention with a selective oestrogen receptor modulator such as tamoxifen can reduce this risk but are associated with adverse events, are ethically questionable, and may be unacceptable options for some women. Surveillance of high risk women with breast imaging is recommended as a secondary preventive measure on the assumption that early diagnosis and treatment will confer similar benefits of reduced BC mortality in this population as reported from randomised controlled trials of population screening programs using mammography (MX) in average risk women.

Although MX is a reasonably sensitive test for screening postmenopausal women, it is less sensitive in younger women and those with a genetic predisposition to BC. This has been attributed to increased mammographic density in premenopausal women which can obscure the radiological features of early BC and the faster growth of BC in these populations. Further, it has been suggested that cancer associated with BRCA mutations, in particular BRCA1, are more likely to have a benign appearance on MX [2].

The use of breast ultrasound (US) as a supplemental modality for BC screening has been studied in women with dense breast tissue and in those with an elevated risk for BC. The benefits of US as a screening modality are that it does not use ionizing radiation, is well-tolerated and is optimally amenable for percutaneous biopsy guidance. US is able to identify small non-palpable masses while undeterred by presence of dense breast tissue, which is an inherent limitation of MX; but the vast majorities of cancer that are seen on US are invasive cancers, DCIS is not usually identified by sonography. Furthermore, US is an operator-dependent examination; standardization of the examination and having a skilled, adequately trained sinologist are critical for performance of a whole breastUS.

Emerging evidence that MRI is more sensitive than MX and US for the detection of BC, in particular for DCIS; and recent studies have validated the role of MRI screening in high risk populations. Previous reports in high risk populations have shown overall sensitivity of MRI approximately double that of routine MX [5,6,7]. Unlike MX, MRI is unaffected by breast density and does not use ionizing radiation. The use of breast MRI for screening the general population is not practical because of its high cost, limited availability, and relatively low specificity and the difficulty of sampling lesions visible only on MRI; limiting its use to a very high-risk population is more appropriate.

Several single-center and multicenter studies have evaluated MRI screening in women with hereditary risk for BC.
The study aim is to evaluate pros and cons of breast magnetic resonance imaging (MRI) in a population with high risk of developing breast cancer at "Modena Cancer Centre for Hereditary Breast and Ovarium Cancer".
Methods and Materials

At "Modena Cancer Centre for Hereditary Breast and Ovarium Cancer" subgroups in the population with an elevated risk of BC can be identified by performing genetic testing for BC predisposition mutations or by evaluating family history.

In particular the oncogenetic counseling was performed in accordance with an oncologist-based model of cancer genetic counseling for hereditary breast cancer. Family histories were obtained through detail questionnaires and interviews. Family pedigrees were traced as far backward and laterally as possible, including a minimum of four generations and extended to paternal lines.

A woman is considered to be at high risk for BC because of family or personal history of BC, or because she carries a mutation in one on two breast cancer susceptibility genes BRCA1 or BRCA2, or because the genetic test results positive on a first-degree relative. Previously affected or healthy women with a pathogenetic or unclassified mutation enter into a surveillance program with ultrasound, MR plus mammogram starting at 25 years of age.

Between January 2008 and April 2012, 118 women with high breast cancer risk (mean age 46 years, range 25-75 years) [Table 1] were enclosed in a screening annual program with MX, US and MR.

All women of this study carried BRCA1 or BRCA2 mutation; all age groups are included.

All these techniques were performed on the same day by different doctors, all expert in radiology.

Mammography was performed in two different projections for each breast (cranio-caudal and medio-lateral) with digital indirect technology.

Ultrasound was performed with high frequency probe and breast dedicated preset.

MRI was performed with a 1.5 T magnet and surface coil, during the second or third week of the hormonal cycle. MRI protocol included pre-contrast T2w and DW sequences, coronal dynamic T1w acquisition before and after contrast injection for a total time of 10 minutes and also an axial T1w sequence with late enhancement. The post-processing of dynamic sequence included an automatically images subtraction, the assessment of the intensity-time curves for kinetic enhancement evaluation and the MIP reconstruction. When present MR examinations were compared with the previous round examinations.

When MRI showed some focal areas of enhancement without correspondence with other examinations, second look ultrasound was performed, with a cyto-hysto-evaluation if indicated.
Lesions detected with different techniques were classified according BIRADS-MRI system. In particular we evaluated the tumors screen detected with different imaging techniques.

We evaluated also the US second look number performed after MR in each round and the false positive results with cito-hystology confirmation for each imaging techniques in each round.
<table>
<thead>
<tr>
<th></th>
<th>N</th>
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<tr>
<td>Median age</td>
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<tr>
<td>Postmenopausal</td>
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<tr>
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<tr>
<td>BrCa2</td>
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**Table 1**: Patients' characteristics.

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Results

118 patients were studied with one complete diagnostic round (MX, US, MR), 81 with two complete rounds, 56 with three rounds and 24 with four rounds.

Of the 118 patients undergoing MRI surveillance, 7 had breast cancer [Table 2].

In particular 4 breast cancer were detected with all three imaging techniques [Fig. 5, Fig. 6, Fig. 7]; 1 lesion was visible only at MRI [Fig. 1, Fig. 2, Fig. 3] and 1 only at US examination [Fig. 4]. 1 breast cancer was detected in another medical center, where the patient underwent only breast ultrasound.

Mammography detected 4/6 lesions (67%), US and MRI detected 5/6 lesions (83%).

In one patient with all techniques positive, mammography and US showed one neoplastic lesion, MRI showed multicentric cancer with "non mass like enhancement"; mastectomy confirmed multicentric CDIS.

Breast cancer visible only at US examination had 5 mm diameter and was located at upper-external quadrant in the marginal portion of the breast, partial hidden by artifact movements at MRI [Fig. 4].

At critical revision of previous MRI round, 6/7 breast cancer were visible as non specific enhancement focus with diameter of 3-5 mm [Fig. 7].

The second look ultrasound performed after first MR examination were 6/118, one of which for breast cancer. After second round with MR we performed 1/81 US second look; after the third MR round 3/56 US second look, two of which in patient with breast cancer and 0/24 after the fourth MR round.

The false positive results histologically evaluated were 2 for MX, 2 for US and 4 for MR.

The sensitivity and specificity of different imaging techniques were:

- MX: 67% 99%
- US: 83% 99%
- RM: 83% 98%
**Fig. 1**: PT 1, F, 60 y/o, asymptomatic, with negative mammogram and ultrasound (A), compared with mammography and ultrasound of the previous year (B), even they negative.

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Fig. 2: MRI examination of PT 1 (C) shows focus of enhancement to upper-internal quadrant of the left breast, with irregular margins, with intensity-time curve showing high percentage of enhancement, with rapid wash-in, third peak dynamic and subsequent wash-out. Morphological and dynamic characteristics are suspect for the neoplastic nature.

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**Fig. 3:** The US second look of PT 1 (D) identifies the nodular formation located in depth, that the next histology confirmed as a carcinoma.

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**Fig. 4:** PT 2 is a Female, 55 y/o, asymptomatic, with mammography (A) and MRI (B) negative and evidence only at US (C) of a few millimeters (5 mm) nodular formation, localized at the periphery of the left breast, positive at cytologic sampling.

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**Fig. 5:** PT 3, Female, 62 y/o, asymptomatic. During the annual round, mammogram shows opacity very vanished at the passage of the internal quadrants of the left breast; US shows nodular hypoechoic formation with irregular margins and with a diameter of 7 mm (A).

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**Fig. 6:** PT 3, MRI reveals focus of enhancement with irregular margin and high impregnation; intensity-time curve shows rapid wash-in and following plateau (B). The histological diagnosis was: carcinoma.

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**Fig. 7:** PT 3, Positive MRI (B) compared with MRI of previous year (C) that shows a non-specific enhancement focus with diameter of 3 mm.

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<table>
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<tr>
<th>Age</th>
<th>Risk Group</th>
<th>Type</th>
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<th>Ki67 (%)</th>
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**Table 2:** Characteristics of the seven positive cases of BC diagnosed during this study.

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Conclusion

Several studies have validated the role of breast MRI surveillance in women who are at high risk for breast cancer development [5,6,7].

In particular an Italian study of Sardanelli and colleagues in 17 centres screened 278 women, of whom 63% were tested BRCA mutation carriers or first-degree relatives of a tested carrier. A previous history of BC was present in 44% of the women. Eighteen cancers were detected, giving an MRI sensitivity of 94%, compared with sensitivities of 59% for MX, 65% for US, and 50% for clinical breast examination [8].

Although the sensitivity of surveillance MRI has been shown to be superior to routine MX and/or US imaging, it is limited by lower specificity, high false-positive rates, and increased needs for additional imaging and/or biopsy. Two studies reported data indicating that adding MRI to MX increased a woman’s risk of being recalled for further investigation of a false positive result approximately three to five-fold [7,9], with the number of additional false positive recalls per 1000 screening rounds varying according to the risk of the disease in the screened population. Both studies showed that adding MRI increased the risk of benign percutaneous biopsies by at least three-fold. In contrast, Kuhl and colleagues observed a smaller, non-significant difference in the rate of benign percutaneous biopsies when MRI was added to mammography [6].

The rate of cancer detection in high-risk patients undergoing breast MRI at our institution is similar to that of large, multicenter trials. Adding MRI in breast cancer screening program for high-risk-women, increased the risk of recalled for further investigation of a false positive results, but the sensitivity of surveillance MRI has been shown to be superior to routine MX imaging (83% versus 67%) and similar to US examination.

Considering the disadvantages of breast MRI, we have evaluated number of US second look in 4 consecutive rounds. As expected, 6 women were recalled after the first round of MR, 1 was recalled after the second one, 3 after the third and 0 after the last round. Out of 10 recall, 3 patients (23%) had diagnosis of BC. The present study shows that, excluding patients with cancer diagnosis the percentage of recall is reduced to the increased of the round.

In the 7 BC detected, we also make a critical revision of previous MRI round: 6/7 breast cancer were visible as non specific enhancement focus with diameter of 3-5 mm. In the evaluation of MRI is mandatory an expert breast radiology. The presence of a previous round of MRI should help to recognize the appearance of focus of enhancement also of a few millimeters, that in this population should be considered suspicious and re-evaluated with US second look, and if this is negative these foci should be monitored with a short-term MRI and if necessary they must be submitted to cito-histological findings below MRI guide.
In summary, MRI has replaced MX as the gold standard for screening for breast cancer among high risk women with results similar to US in our population. Issue related to specificity and false positive results of MR is largely solved in this population in particular with the possibility to compare the examination with previous rounds and with second look US. It is likely that in the near future, the use of MRI will be expanded also to women at moderate risk of BC, limited to the high cost of this procedure.
References


