# The Italian Multi-Centre Project on Evaluation of MRI and other Imaging Modalities in Early Detection of Breast Cancer in Subjects at High Genetic Risk[1]

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This report presents the preliminary results of the first phase (21 months) of a multi-centre, non-randomised, prospective study, aimed at evaluating the effectiveness of contrast-enhanced magnetic resonance imaging (MRI), X-ray mammography (XM) and ultrasound (US) in early diagnosis of breast cancer (BC) in subjects at high genetic risk. This Italian national trial (coordinated by the Istituto Superiore di Sanità, Rome) so far recruited 105 women (mean age 46.0 years; median age 51.0; age range 25-77 years), who were either proven BRCA1 or BRCA2 mutation carriers or had a 1 in 2 probability of being carriers (40/105 with a previous personal history of BC). Eight cases of breast carcinomas were detected in the trial (mean age 55.3 years, median age 52.5; age range 35-70 years; five with previous personal history of BC). All trial-detected BC cases (8/8) were identified by MRI, while XM and US correctly classified only one. MRI had one false positive case, XM and US none. Seven "MRI-only" detected cancers (4 invasive, 3 in situ) occurred in both pre- (n = 2) and post-menopausal (n = 5) women. With respect to the current XM screening programmes addressed to women in the age range 50-69 years, the global incidence of BC in the trial (7.6%) was over ten-fold higher. The cost per "MRI-only" detected cancer in this particular category of subjects at high genetic risk was substantially lower than that of an XM-detected cancer in the general women population. These preliminary results confirmed that MRI is a very useful tool to screen subjects at high genetic risk for breast carcinoma, not only in pre-, but also in post-menopausal age, with a low probability of false positive cases.

Key Words: BRCA1 gene mutations, BRCA2 gene mutations, Hereditary breast cancer, Magnetic Resonance Imaging, X-ray mammography, Ultrasound, Surveillance, Screening

Although correctly classified as a sporadic disease, breast cancer (BC) presents a substantial component of genetic, multi-factorial transmission, referred to hereditary forms of autosomal dominant type (1-3). It is estimated that about 5% of all BC cases are likely due to primary genetic causes (3), while as many as 5-15 % show familial clustering (1).

Pathogenetic mutations of two genes, BRCA1 (4-6) and BRCA2 (7,8) are today held responsible for at least 50% of hereditary BC cases, the remaining ones being likely due to still unknown gene mutations (9-11). In BRCA1 and BRCA2 mutation carriers the cumulative life time risk for BC may reach values between 60 and 85% (10,12).

Besides the vertical transmission and aggregation of cases of carcinomas in the family (occurring in breast or in other organs such as ovary, prostate and colon-rectum), hereditary BC has a high probability of early onset, more than 50% of women at high genetic risk being affected by the disease before the age of 50 years (13-17). With respect to BRCA1, BRCA2 mutation carriers present a risk profile shifted to more advanced ages (18). Hereditary BC may develop under the form of multifocal or multicentric lesions, often caused by highly proliferating, poorly differentiated and hormone-receptor negative tumour cells. Moreover, the risk of developing a second cancer in the contralateral breast or an ovary cancer within five years from a previous neoplastic event is estimated to be between 30 and 60% (19,20).

No specific surveillance programmes have been as yet activated at the national level for early diagnosis of breast carcinoma in subjects with hereditary predisposition to this disease.

Current risk reduction strategies propose (besides information, counselling and some changes in lifestyle) the participation in chemoprevention trials (21-24), prophylactic surgery - i.e. preventive bilateral mastectomy (25) and/or oophorectomy (26) - or secondary prevention by adoption of specific recommendations, early diagnosis by screening and follow-up care (27,28). It is reported that a large proportion (40-80%) of asymptomatic carriers of BRCA1/2 mutation are more inclined to surveillance rather than to preventive mastectomy or chemoprevention (29-31).

With respect to a BC screening programme addressed to the general women population (50-69 years), the screening of subjects at high genetic risk requires earlier and closer controls and the use of diagnostic techniques which combine maximum diagnostic sensitivity with high predictive value and independence from breast density. In fact, the sensitivity of X-ray mammography (XM), which is at present the modality of choice for BC

screening, may be severely reduced in case of dense breast, not only in young women, but also at ages over 50 years (32-38). Moreover, some concern has been expressed regarding repetitive exposure to ionising radiation of BRCA1/2 gene mutation carriers, especially at young ages, in view of a suspected higher tissue vulnerability to a DNA-damage producing agent (39-49), as also indicated by studies on model systems (50).

In the light of the benefits expected from the adoption of a more effective surveillance programme for subjects at high genetic risk, even the application of more expensive examinations than those adopted for the general women population might be justified. This view is further supported by the predicted reduction in total health care and social costs deriving from an early diagnosis of hereditary BC, a disease characterised by early onset and fast progression.

Following its first introduction in the 80s (51), dynamic contrast-enhanced magnetic resonance imaging (MRI) progressively developed to become the most sensitive modality today available for BC diagnosis (52-56). As reviewed in other papers of these Proceedings, specific indications to MRI in the area of breast oncology are: multicentric/multifocal disease; assessment of recurrence even in the presence of severe scarring or prostheses; occult tumour (CUP syndrome); monitoring the response to therapy; differential diagnosis of special cases. On the other hand, among drawbacks and limitations of MRI with respect to conventional mammography, are the use of intravenous contrast agents, the longer examination time, a higher dependence on the menstrual cycle, higher costs, and general contraindications to MRI (pace-maker, ferromagnetic vascular clips, claustrophobia, etc.).

Regarding the possible use of MRI in screening subjects at high genetic risk of BC, this technique combines the advantage of being independent from breast density with that of not using ionising radiation. Additional benefits derive from the peculiar feature of MRI of providing *in vivo* measurements of tissue parameters like microvascular permeability and extracellular volume fraction, related to neo-angiogenesis and tumour progression (57-62).

A number of research projects and study groups have been recently activated in Europe and in North America, with the aim of assessing to which extent the combined use of MRI and conventional mammography may enhance the diagnostic accuracy and therefore the effectiveness of a screening programme specifically directed to subjects at high genetic risk of BC (63-68).

In Italy, a network of highly specialised Centres has been activated in 1998 by the Istituto Superiore di

Sanità, Rome, within a research project aimed at evaluating the effectiveness of combining MRI with conventional imaging examinations for the early diagnosis of BC in subjects at high genetic risk. The network presently comprises twelve institutions (five Institutes of Cancer Research and Treatment and seven University General Hospitals). A clinical trial has then been activated in 2000, in the frame of this project. The trial is currently conducted by nine functional units (active in Aviano, Chieti, Genova, Milano, Modena, Napoli, Padova/Udine, Pisa and Torino), each endowed of integrated services of clinical oncology, medical genetics, psycho-oncology counselling, molecular genetics laboratories, breast MRI, XM and high-frequency ultrasound (US).

This report presents a preliminary analysis of the data obtained in the first phase of this trial (June 2000-March 2002).

## Study design

This prospective, non-randomised and comparative study is carried out in different Italian Centres, on the basis of common recruitment criteria and diagnostic protocols.

*Eligibility.* Subjects at very high risk for breast cancer were selected according to one of the following criteria: a) proven carriers of germ line, pathogenetic BRCA1 or BRCA2 mutation; b) first-degree relative with proven BRCA1/2 mutation (but unknown personal mutation status). One woman belonging to a family at very high risk of BC likely associated with a non-BRCA1/2 mutation and one woman belonging to a family at very high incidence of breast cancer, were also entered into the study.

Women could be recruited starting from the age of 25 years, and men (BRCA2+) from 50. Women with personal history of unilateral BC were offered to enter the study, provided that at least one breast had not been removed. Bilateral breast screening was performed as a rule (i.e. also on the breast previously submitted to conserving surgery); for those who had undergone unilateral mastectomy, only the contralateral screening was performed.

Enrolment was offered to eligible subjects and to their eligible relatives, in the context of genetic counselling (and, if necessary, psychological assistance), following informed written consent. Preventive approval by the institutional review board had to be requested locally. In case of hormonal replacement therapy, diagnostic examinations started at least three months after its interruption. Exclusion criteria were: pregnancy, breast-feeding, current chemotherapy, terminal illness or specific contra-indications to MR examinations. The screening protocol consisted of two annual diagnostic packages including XM, US and MRI. For pre-menopausal women, MRI was performed within the second week of the menstrual cycle.

## Techniques

*X-ray mammography.* Examinations were performed on conventional high frequency generator units with rotating anode; focus 0.3-0.1 mm; focus-film distance ≥55 cm; homogeneous breast compression; mobile grid; automatic exposure control, dedicated film-screen system (day-light treatment). Regular (daily and 6-month) quality controls of the system performance were carried out together with controls on exposure dose (<12 mGy/45 mm Plexiglas). Standard medio-lateral oblique and cranio-caudal projections were obtained for each breast. Further views were taken when necessary. Mammographic findings were reported by using the BI-RADS (American College of Radiologists) 5-score system: 1) negative; 2) benign finding; 3) probably benign finding; 4) suspicious abnormality; 5) highly suggestive of malignancy.

*Ultrasound.* Breast US examinations were performed at a frequency ≥7.5 MHz, axial resolution of 0.5 mm and latero/transverse resolution of 1 mm; optimal contrast variable focussing. Regular periodic quality controls were carried out using an appropriate phantom.

*MRI.* Requirements for the MRI equipment were an operative static magnetic field $B_0 \geq 1.0$ T; actively shielded gradients ≥15 mT/m; dedicated, bilateral, synchronous breast coil.

*MR image acquisition.* Dynamic contrast-enhanced MR acquisitions were obtained using a spoiled gradient-echo sequence (e.g. FLASH, SPGR or FFE (52)). Three-dimensional (3D), T1-weighted images were acquired in coronal or axial planes (slice thickness 3 mm; no gap; FOV 350 mm; matrix 128 x 256 for coronal planes; rectangular FOV adapted to the patient for axial planes; number of partitions per breast sufficient to cover the entire mammary tissue (i.e. 40-48); phase encoding axis vertical for coronal planes, horizontal for axial planes; TR and flip angle selected according to the available sequence; TE value selected to avoid fat-water signal opposition).

MRI exam comprised one pre-contrast and five post-

contrast acquisitions. The contrast agent, a two-compartment Gd-chelate (0.1 mmol/kg) was injected as intravenous fast bolus (about 2 ml/s), followed by 20 ml saline solution (NaCl 0.9%) flush. The temporal resolution of post-contrast images was 90 s. The first post-contrast image acquisition started at the same time as the contrast agent injection.

*Post-processing and data storage.* The pre-contrast 3D images were subtracted from the first, second and fifth contrast-enhanced images and the Maximum Intensity Projection (MIP) algorithm was applied to the subtracted images. The curves representing the temporal dependence of signal intensity [SI(t)] and/or that of the percent SI enhancement, [SI(t)-SI(0)]/SI(0) * 100], were then determined in selected small regions of interest (ROI, 3x3 pixel). The acquired, subtracted and MIP-reconstructed images, together with the ROI-based curves, were stored on dedicated magnetic support.

*Lesion classification.* The scoring system adopted for classifying MRI-detected lesions was based upon a combination of morphological features and enhancement kinetics parameters (69), as reported in Table I. Lesions with scores 0-2 were classified as benign; score 3 suggested uncertain lesion; scores 4-8 indicated malignancy. In case of non-benign (scores 3-8) lesion detected only by MRI, the latter was repeated after 1-2 months. If the lesion was confirmed, a US-guided (second look) fine needle aspirate (FNA) cytology or core-biopsy or a MRI-guided biopsy was performed. In these cases, the final diagnosis was established by cytology of FNA, or pathologic exam of core-biopsy or mastectomy specimens.

True negative cases were defined as those for which no suspicion was raised at a given diagnostic examination, nor BCs were detected during follow-up.

Clinical and imaging follow-up was scheduled for at least two years for subjects whose imaging examinations gave negative results in the two-round study.

## Results

In the period June 2000 - March 2002, 105 patients (mean age 46.0 years, median age 51.00, age range 25-77) were enrolled in the first annual round, while 14 of them also underwent a second round. Out of the 105 recruited women, forty (38%) had a previous personal history of BC. Seven patients were found to be affected by BC at the first round and one at the second round, eight in total, for an overall global incidence of 7.6% (8/105). As summarised in Table II, these eight patients had a median age of 52.5 years (mean 55.3, range 35-70). Five of them (63%) had a previous personal history of BC, giving a ratio of with/without previous BC history of 1.7 (5/3) for the patients presently affected versus 0.62 (40/65) for the screened women. Pathology demonstrated: 2 invasive ductal carcinoma (IDC), 2 invasive lobular carcinoma (ILC), 1 IDC+ILC, 2 multifocal DC in situ (DCIS), and 1 DCIS+LCIS. Out of the eight cancers, 7 (88%) were detected only by MRI, 4 invasive and 3 in situ, both in pre- (n=2) and post-menopausal (n=5) women. Only one cancer was detected also by XM and US. MRI had one false positive case, XM and US none. Table II also shows the genetic status of each patient.

## Discussion

The preliminary results of this trial indicated that Gd-enhanced MRI is a very useful tool to screen subjects at high genetic risk of BC, not only in pre-menopausal, but also in post-menopausal age, with a low probability of false positive cases. Previous personal history of BC was associated with higher probability of BC detection during the screening. Although the trial is still at a too early

Table I - Scoring system for the classification of MRI lesions (according to ref. 69)

| Lesion feature | Score | | |
|---|---|---|---|
| | 0 | 1 | 2 |
| shape | round, oval, lobular | linear, dendritic, stellate | — |
| margin | well defined | ill-defined | — |
| enhancement pattern | homogeneous | heterogeneous | rim sign |
| initial SI enhancement | low (<50%) | moderate (50-100%) | high (>100%) |
| SI time dependence | continuous increase | plateau | wash-out |

[1] Total score: 0-2, benign; 3, uncertain; 4-8, malignant.

**Table II - Breast cancers detected in the Italian ISS trial in the period June 2000-March 2002**

| Patient | age(years) | genetic mutation | previous BC | trial-detected BC |
|---|---|---|---|---|
| Mo1 | 69 | BRCA1+ | yes | DCIS, multifocal, high grade. Imaging finding: positive to MRI only. Diameter of the largest focus, 3 mm (PA). MRI-guided FNAC; mastectomy. |
| Mi1 | 35 | BRCA2+ | no | Invasive lobular, T2N0, G2. Imaging finding: positive to MRI only. Lesion dimension, 23x27 mm. FNAC positive before surgery. |
| Mi2 | 61 | unknown [1] | yes | Invasive lobular and ductal, G1. Imaging finding: positive to MRI only. Lesion dimension: 8 mm (MRI), 5 mm (PA). |
| Mi3 | 53 | BRCA1+ | yes | Invasive ductal, G2 (slightly differentiated). Imaging finding: positive to MRI only. Lesion dimension: 7-8 mm (MRI), 6 mm (PA). |
| Mi4 | 61 | FHx | yes | Invasive ductal; bifocal, G1 and G2 (moderately differentiated), recurrent cancer adjacent to surgical scar. Imaging finding: positive to MRI only. Lesions' dimensions: 10 and 6 mm (MRI); 6 and 3 mm (PA). |
| Av1 | 70 | BRCA2+ | yes | DCIS (micropapillary), surrounded by a few LCIS foci. Imaging finding: positive to MRI only. Lesion dimension, 4 mm. |
| Av2[2] | 53 | BRCA2+ | no | Invasive lobular, multifocal, associated with intraductal carcinoma foci, PT1cNo, G1. Imaging findings: positive to XM, US and MRI. Lesion dimension: 1.5 cm. |
| Pi1 before | 41 | BRCA1 [1:2] | no | DCIS, multifocal; scarcely differentiated (G3), with no angio-invasion. Imaging findings:at MRI, suspicious ductal morphology; at retrospective XM evaluation, asymmetric hyperdensity; at second US look, unspecific hypoechogenic area. Echo-guided FNAC mastectomy. |
| 8 cases | mean 55.3 median 52.5 range:(35-70) | | 5/8 previous BC | 5/8 invasive |

[1] For further details, see ref. 70. [2] This case was the only one detected by all diagnostic modalities.

*Abbreviations:* BC, breast cancer; BRCA1⁻, proven BRCA1 mutation carrier; BRCA2⁻, proven BRCA2 mutation carrier; BRCA1 [1:2], 1 in 2 probability of being BRCA1 mutation carrier (i.e. first relative with proven BRCA1 mutation; personal mutation status unknown); FHx, family history indicative of high genetic risk of breast cancer (untested mutation); FNAC, fine needle aspirate cytology; nr, not reported; PA, pathological analysis.

**Table III** - Comparison of MRI, XM and XM+US results reported by non-randomised studies on women at high genetic risk of breast carcinoma

| Trial | Nijmegen 1994-2001 (ref. 63) | Rotterdam 1995-1998 (ref. 64) | Bonn 1996-1998 (ref. 65) | Toronto 1997-2000 (ref. 66) | Italy (ISS) June 2000-March 2002 | Total |
|---|---|---|---|---|---|---|
| enrolled subjects | 179 | 109[(1)] | 192[(2)] | 196 | 105 | 781 |
| age range | 21-71 | 22-68 | 18-65 | 26-59 | 25-77 | 18-77 |
| Previous BC | no | nr | 58 | 55 | 40 | ≥ 153 |
| **Trial-detected BC cases** | | | | | | |
| biopsy-proven | 13 | 3 | 9 | 7 | 8 | 40 |
| invasive | 10/13 | 2/3 | 7/9 | 6/7 | 5/8 | 30/40 |
| age of patients[3] (years) | 30,30,31,35, 40,42,44,44, 46,47,49,50,50 | 29,42,53 | 28,34,36,38, 44,47,48,53,57 | 33,46,49,50, 52,52,53 | 35,41,53,53, 61,61,69,70 | mean 45.6 median 49.0 range 28-70 |
| previous BC | no | nr | nr | 4/7 | 5/8 | ≥ 9/15 |
| genetic status | BRCA1⁺ or BRCA2⁺ or FHx (LTR>15%) | 3FHx (LTR: one 40%, two 25%) | 6 BRCA1⁺ 1 BRCA2⁺ 2 FHx | 4 BRCA1⁺ 2 BRCA2⁻ 1 FHx | 2 BRCA1⁺ 1 BRCA1 [1:2] 3 BRCA2⁺ 1 unknown mutation 1 FHx | |
| **BC diagnosis by different methods** | | | | | | |
| MRI | 13/13 | 3/3 | 9/9 | 6/7 | 8/8 | 39/40 |
| XM | 6/13 | 0/3 | 3/9 | 3/7 | 1/8 | 13/40 |
| XM+US | — | nr[4] | 4/9 | 4/7 | 1/8 | |
| detected by MRI only | 7/13 | 3/3 | 5/9 | 2/7 | 7/8 | 24/40 |
| **False positive cases** | | | | | | |
| MRI | 17 | 6 | 5 | 17 | 1 | 46 |
| XM | 10 | nr | 7 | 1 | 0 | ≥ 18 |

[1] Breast density ≥50%. [2] Six symptomatic subjects (ages 25, 35, 44, 48, 53 and 55) at high genetic risk of breast cancer on the basis of family history, were also analysed: out of these six breast cancer cases, six were detected by MRI, four by XM and four by (XM+US). [3] Age of the patient at the time of breast cancer diagnosis during the trial. [4] MRI-guided US identified suspect lesions in two out of three cases; results of US examinations before MRI, not reported.

Abbreviations: BC, breast cancer; FHx, family history indicative of high genetic risk of breast cancer (untested mutation); BRCA1⁻, proven BRCA1 mutation carrier; BRCA2⁻, proven BRCA2 mutation carrier; BRCA1 [1:2], 1 in 2 probability of being BRCA1 mutation carrier (i.e. first relative with proven BRCA1 mutation, personal mutation status unknown); LTR, lifetime risk; nr, not reported.

stage to allow calculation of the diagnostic indices for each used modality (validation of negative findings is, according to the protocol, still under way), a first comparison can already be made with the results of similar non-randomised studies, conducted in other Countries (Table III).

A retrospective study carried out by Stoutjesdijk et al. (Nijmegen, The Netherlands, November 1944 - February 2001) was aimed at determining whether MRI could play a role in the early detection of BC in women with hereditary risk of the disease (63). To this end, a retrospective group of 179 women (age range 21-71 years) was assembled, in which all subjects had received, besides biannual palpation, annual imaging by MRI, XM or both (258 images and 262 mammograms). Out of the 179 women, 75 had received both MRI and XM examination within a

4-month period. Inclusion criteria were: lifetime risk of BC ≥15%, according to Claus et al. (71), based on family history of breast or ovarian cancer or on the presence of a germ line mutation in the BRCA1 or BRCA2 gene. In this study no patients with personal history of BC were included. In the group of 179 women 13 cancers were detected (7.3%), all revealed by MRI, while only six were identified by XM. MRI was therefore found to be more accurate than XM in the annual BC surveillance of women with hereditary risk of BC, justifying the activation of larger prospective studies to evaluate the role of MRI in dedicated screening programmes.

First experiences in screening women at high risk of BC were reported by Tilanus-Linthorst et al. (64). The study (Rotterdam, The Netherlands, September 1995-April 1998) was aimed at investigating whether MRI, in addition to the normal surveillance, could detect cancers otherwise missed in a group of women (n = 109, mean age 41.5 years, range 22-68) with over 25% risk of BC and more than 50% breast density at mammography. MRI detected three cancers (2.8%) occult at mammography and did not give any false negative; it was false positive in 6 women (resulting in two benign local excisions because FNA cytology confirmed suspicion) and recognized 4 true benign cases.

In the first thirty months of a 5-year study carried out in Bonn, Germany (March 1996 - October 1998), Kuhl et al. (65) identified nine BCs in a group of 192 women who, on the basis of personal or family history or genetic analysis, were suspected or proved to carry a BC susceptibility gene. In the absence of genetic tests, the inclusion criteria followed in this pilot study were: women with personal history or history of a relative corresponding to at least one of the following conditions: BC diagnosed at or before the age of 35 years; ovarian cancer diagnosed at or before the age of 40; bilateral BC; both breast and ovarian cancer; at least two relatives with breast and/or ovarian cancer, one of whom diagnosed at or before 50 years. Men were included in case of personal history of BC or a history of a male relative with BC. The mean age ±SD of the study participants was 39±9 years, the median age 38 and the age range 18-65. Out of nine biopsy-proven cancers (4.7% in the group of 192 subjects) all nine were detected by MRI, three by XM and four by combined XM and US. Five carcinomas were therefore detected only by MRI. Regarding false positive cases, five were due to MRI and seven to XM.

Comparison of breast MRI, XM and US for surveillance of women at high risk of hereditary BC was reported by Warner et al. (66). The study (Toronto, Canada, November 1997 - May 2000) was conducted on 196 women (mean age 43.3 years, age range 26-59). Inclu-

sion criteria were : 1) a germ line BRCA1 or BRCA2 mutation or a first-degree relative with a BRCA1 or BRCA2 mutation (but unknown personal status); or 2) a strong family history of breast or ovarian cancer, i.e. three or more relatives on the same side of the family with cancer diagnosed before the age of 50 years or ovarian cancer. A woman with a past history of BC could be included, provided that her contralateral breast had not been removed. In this case, she could be counted in the number of affected relatives in the reconstruction of the family history. Seven cancers were diagnosed in the screening (3.6%), six detected by MRI, three by XM (four by XM plus US). One case of DCIS was detected only by XM. Out of 23 women who had a result that was suspicious by some of the adopted modalities, MRI was false positive in 17, XM in 1 and US in 13.

The screening studies so far carried out on women at high genetic risk of BC led to the conclusions that MRI was not only an effective modality in the detection of occult cancers (64), but was also more sensitive and significantly more accurate than conventional imaging (65,66).

The preliminary results of our prospective study substantiate these conclusions. The rate of tumour detection (7.6%) was similar to that of the retrospective study carried out in Nijmegen (63), although in the Italian study the monitoring time was as yet much shorter (21 vs. 64 months) and the two populations were not identical. In fact, our study so far enrolled subjects belonging to the highest category of risk of BC and did not exclude women with previous BC.

On the basis of the data so far obtained by the Italian study, higher sensitivity and accuracy can be predicted for MRI with respect to both XM and a combination of XM and US, in agreement with Kuhl et al (65) and Warner et al (66). In addition, the results of our study point to the need of including in a special surveillance programme also women with previous history of BC. In fact, out of eight cancers detected in the trial, five (62%) were identified by MRI (but not by XM or US) in women who had a previous history of the disease.

Concerning the additional costs associated with the introduction of MRI in a screening programme specifically designed for subjects at high genetic risk, an analysis reported by Tilanus et al. (64) on the basis of the results of the Rotterdam trial, showed that the extra cost of breast MRI (in addition to XM and physical examination) was € 13,930 per detected cancer, as compared to the cost of € 9,000 for the diagnosis of one BC patient in the Dutch general screening programme. In consideration of the higher rate of breast cancer detection in the Italian with respect to the Rotterdam trial (7.6% vs

2.7%), and the lower number of MR false positives (1 vs 6, over groups of similar size), the total cost per detected BC case in our study was about € 6,200 (computed from the costs of 119 MRI, 119 XM and 119 US examinations, plus that of one excisional biopsy due to the false positive MRI examination). The extra costs associated with the addition of MRI to XM and US in our special trial devoted to high-risk subjects, were estimated to be about € 41,000 (computed from 119 MRI and one excisional biopsy). This additional expenditure was however very cost-effective, since it allowed the detection of seven BC cases which would have been missed by the other imaging modalities (XM plus US), with an average cost of about € 6,000 per "MRI-only" detected cancer (i.e. about 2/3 the cost afforded by a general XM screening programme for detecting one BC in the general population of women between 50 and 69 years). Obviously, only a very high incidence/prevalence of breast cancer cases in a restricted population of subjects at high genetic risk makes the extra-costs of the MRI-screening affordable and reasonable.

Furthermore, six out of eight cases of BC detected in our trial were diagnosed in women above 50 years. Out of these six cases, five were only detected by MRI, indicating that 83% of these cases would have been missed in the general XM screening programme (50-69 years).

Data of Table III point to the potential of accruing information from different studies which used similar, standardised technical procedures. In spite of some differences in the design of individual trials, some consistent conclusions seem to emerge from the overall body of information so far provided by five studies (Nijmegen, Rotterdam, Bonn, Toronto and Italy) which adopted a combination of MRI and conventional imaging procedures for the screening of women at high genetic risk:

• over a total group of 781 women, 40 biopsy-proven cases of BC were detected (average detection rate 5.1 %, ranging from 2.7% to 7.6%), 30/40 (75%) of these being invasive lesions and 25/40 (62%) diagnosed at ages below 50;

• regarding the sensitivity of individual modalities in BC detection during these trials, 39/40 cases (97.5 %) were identified by MRI and 3/40 (32.5%) by XM; 60% of all trial-detected BC cases were therefore diagnosed by MRI but not by conventional imaging modalities;

• in the total group of 781 women there were 46 false positive cases due to MRI and at least 18 due to XM;

• the average ratio of false positive to true positive cases in MRI was 1.18 (46/39). but there was a large variability among trials (from 0.12 to 2.83).

The preliminary results of this comparative analysis of different studies, point to the need of more extensive,

multi-centre and multi-national trials on the evaluation of benefits and costs associated with the introduction of MRI into appropriate screening programmes specifically addressed to subjects at high genetic risk of BC. These efforts should allow the collection of a sufficient body of data to define to which extent breast MRI could be integrated with XM and US for an effective surveillance of these subjects. This is a non-negligible point in the general problem of the correct use of MR technique in breast imaging, since subjects at high genetic risk of BC represent the only one population for which MRI can be proposed as a screening method.

Additional, important questions should also be asked in the future, in relation to this particular category of subjects. Could an annual single-view (medio-lateral-oblique) XM be enough to exclude microcalcifications (and therefore avoid possible MRI false negative cases, more frequently associated with in situ cancers)? Or do we still need the usually proposed annual two-view XM? Should US be performed after and not before MRI, with the result of immediately increasing the diagnostic sensitivity to the level of that now obtained with the second look examination (that is to say with an MRI-based breast US examination), and therefore changing the diagnostic flow-chart? And last, but not least, what level of familial history of BC will make of MRI a specific screening method for women who refuse genetic tests?

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