UPDATE IN RADIOLOGY

Breast cancer screening in high risk populations

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Abstract We aim to define which patients make up the populations with high and intermediate risk of developing breast cancer, to review the studies of screening with magnetic resonance imaging in addition to mammography in high risk patients (describing the imaging characteristics of the cancers in this group), to review the studies of screening with magnetic resonance imaging in patients with intermediate risk, and to update the guidelines for screening in patients with high or intermediate risk (based on the recent recommendations of the main scientific societies/American and European guidelines).

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Introduction

Breast cancer is a serious health problem. In Western Europe, one in eight women develops breast cancer and approximately 30% die from the disease.¹

The risk of breast cancer is not the same for all population groups. Women at “average risk” have less than 15% risk of developing the disease. Mammography (MX) is the only screening test that has proved to reduce breast cancer mortality (overall reduction of 30%, or even greater).
When examining the recommendations for breast cancer screening in this group of women, we find differences between the American and European guidelines. According to the former, optimal screening would involve annual MX for women aged 40–74 years;1–6 but the screening of women aged 40–49 and older than 70 as well as the time interval between MX are still controversial issues.7–9 Most screening programs in European countries are regulated by the European Guidelines for Quality Assurance in Breast Cancer Screening, which recommend a MX every two years in women aged 50–64 years (but many screening programs are extending the age to 70 years and the decision to start the screening at 45 is a matter of debate).

Patients at "high risk" are those with one or more factors associated with greater chance of developing breast cancer.10 We aim to define which patients constitute high risk (HR) and intermediate risk (IR) populations for breast cancer (where MX screening alone yields more disappointing results); review the studies on screening with magnetic resonance imaging (MRI) used in combination with MX in HR patients (describing the imaging features of breast cancer in this group); and review the studies on breast MRI screening in subsets of patients with IR, offering an update of the recommendations for screening in HR and IR patients (based on the main American and European scientific societies/guidelines).

Risk prediction

The main risk factors for developing breast cancer are summarized in Table 1. Several models have been used to assess breast cancer risk, including Gail MH et al.,11 Claus EB et al.,12 BRCAPRO,13 Cuzyck et al.14 (IBIS), BOADICEA.15

The Gail model uses different risk factors but the family history is not investigated in detail as it does not include the age of onset in the affected relative or paternal relatives, and only includes first-degree relatives. The Gail model does not predict mutation risk.

### Table 1 Main risk factors for breast cancer.

1. Family history/genetic factors (around 5–15% of cancers, approximately 50% of them in BRCA carriers)
2. Reproductive/hormonal factors: estrogen levels play a role in carcinogenesis
3. Proliferative benign breast disease: atypical hyperplasia, lobular carcinoma in situ. Hyperplasia increases risk by 1.5 times and atypia by 4.5 times
4. Mammographic density: a highly dense parenchyma increases the risk by 4–5 times
5. Others: age (very important factor, risk increases with age); race (Caucasian > African women and Hispanic > Asian women); diet (a caloric diet increases risk); physical activity (little exercise/sedentarism increases risk)

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The Claus model uses the number and age of first- and second-degree relatives, but it does not predict mutation risk either.

The last three models are highly dependent on family history and can be used to estimate the probability of a patient carrying a BRCA mutation and developing breast or ovarian cancer in families with known or suspected BRCA carriers.1,16

However, the individual risk varies between models. These models do not strongly correlate as each one takes into consideration risk factors that do not completely coincide. Moreover, these models are flawed because they do not include factors such as third-degree relatives or mammographic density.16

Referral for genetic counseling and testing is recommended in women with at least 10% risk of a BCRA mutation.1

Table 2A summarizes a practical approach to the HR criteria based on family history (according to criteria indicated by the Comunidad de Madrid).

### Table 2 Criteria for increased risk based on family history.

#### A. High risk criteria based on family history (Comunidad de Madrid):

| Three relatives with breast Ca * |
| Two cases of: |
| Breast Ca (<50 years, both relatives) * |
| One breast Ca (<50 years) and one ovarian Ca in two different relatives |
| Ovarian Ca (any age) |
| One breast Ca in a male relative and one Ca (ovarian or breast) in a female relative, at any age |
| One case of: |
| Breast Ca in <30 years |
| Breast Ca in <40 years (triple negative or bilateral) |
| Breast Ca and ovarian Ca (in the same female relative, at any age) |

#### B. Intermediate-risk criteria based on family history (Comunidad de Madrid):

| Two first- or second-degree relatives with breast Ca diagnosed with breast Ca between 50 and 60 years (the sum of their ages <118 years and without fulfilling HR criteria) |
| One first-degree relative with breast Ca between 30 and 50 years and no other relative with breast Ca |
| One first-degree relative with bilateral breast Ca >40 years and no other relative with breast Ca |

Ca: carcinoma. * Taking into account first-, second- and third-degree relatives from the same family branch.

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American and European societies currently recommend the use of breast MRI as an adjunct to the annual MX screening (MX + MRI) in patients with a HR of 20–25% or greater.17–19 Table 3 shows the groups of patients included.
Table 3  Recommendations for breast MRI as an adjunct to mammographic screening in patients with ≥20–25% risk.

1. Women with BRCA 1 (55–85%) and BRCA 2 (25–60%), or with first-degree relatives with BRCA mutations untested
2. Women with 20–25% (or greater) risk as defined by BRCAPRO (or other tests) that are largely dependent on family history
3. Syndromes: Li–Fraumeni (60–90%), Cowden (30–50%), Bannayan–Riley–Ruvalcaba (30–50%), or first-degree relatives
4. History of radiation received <30 years (eight-fold increased risk of breast cancer after radiation of the chest)
5. A combination of the above criteria

1 and 2: evidence-based; 3 and 4: based on experts consensus opinion.

What are the advantages of using breast MRI in addition to mammography in high risk patients?

After examining the results of the main studies evaluating the screening with MX+MRI in HR patients published after 2009, the advantages would be the following:

Increase in number of detected cancers (higher sensitivity)
The number (%) of cancers diagnosed in HR women using MX was 36%, with MX+ultrasound (US) was 52%, and with MX + MRI was 93%.

Breast MRI alone showed a very high sensitivity (S) (71–100%, mean 81%) and a positive predictive value (PPV) of 17–63% (mean 40%).16 Some studies reported a S and PPV >90 and >60%, respectively.13,24

In these studies, 33–44% of tumors were detected using MRI alone.

In addition, MRI proved to be very sensitive in the first screening round and in the subsequent rounds (this is related to the high growth rate of tumors in this population group) and improved the detection of premalignant lesions.

Detection rates using MX + MRI range between 2.4 and 4.8%, which are much higher than rates obtained in MX screening programs in the general population (approximately 0.37% between 40 and 49 years, and 0.58% between 50 and 59 years).

Significantly smaller tumor size and number of tumors with axillary involvement (lower-stage tumors detected)
The median size of cancers detected with MRI was small (7–18 mm), and axillary lymph nodes were involved in approximately 15–16% of cases (versus 30–45% in MX screening).

Lower interval cancer rate
The mean interval cancer rate of the studies was 5.4% (versus 43–60% in MX screening).

Acceptable cost
Recall (8–17%), biopsy (3–15%) and follow-up (7–11%) rates were within acceptable values.

Some studies have already reported that screening with MX + RM in HR patients is cost-effective.29–31

Although the effects of MRI screening on mortality and survival are not proven yet, this technique has higher S than MX, being able to detect smaller tumors with lower rate of axillary node involvement. It is therefore reasonable to extrapolate that the detection of non-invasive tumors (ductal carcinoma in situ, DCIS) and small invasive cancers (IC) will reduce mortality.17

Need to offer magnetic resonance-guided biopsy

Centers that perform MRI screening should have the ability to offer MRI-guided biopsy, since a significant number of enhancing lesions on MR imaging are not seen on the second-look ultrasound (approximately 40%), even in experienced hands. About 14% (9–22%) of these tumors can be malignant.32–36

We present a case of a HR patient with a family history of breast cancer and a diagnosis of DCIS in one breast whose staging MRI demonstrated a non-mass like enhancement (BI-RADS category 4) in the contralateral breast not visible on US examination, that required MRI-guided biopsy (with a diagnosis of DCIS) (Figs. 1–3).

Unusual features of high risk cancers

When performing MRI screening, we should be familiar with the fact that breast cancer in HR patients may exhibit atypical imaging features.

Mammographic findings

These tumors may show features of benignity like oval shape and well-defined margins, which histologically correlates with high-grade tumors and medullary differentiation.17–40

In addition, there is a low prevalence of microcalcifications.41

Ultrasoundographic findings

US findings can be normal or benign (in almost all DCIS and in more than one-third of IC. More than one-third of IC identified at US manifest as BI-RADS category 3 and less than two-thirds as BI-RADS category 4 or 5).41,42

Magnetic resonance findings

MRI characteristics of malignant tumors include:

- Morphologic characteristics commonly seen in benign lesions. The proportion varies between studies (23%,59–68%,41 and 3.7%).43
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Figure 1  (A and B) Sagittal MRI with intravenous (iv) contrast, VIBRANT sequence (digital subtraction). Ill-defined hyperenhancing nodule in the upper medial quadrant of the left breast with previous US-guided CNB (core needle biopsy) and a diagnosis of invasive ductal carcinoma shows an enhancement curve very suspicious/typical of malignancy (type 3). (C) Contrast-enhanced axial 3D MRI with fat saturation shows an ill-defined hyperenhancing nodule in the upper medial quadrant of the left breast with previous US-guided CNB and a diagnosis of invasive ductal carcinoma.

Figure 2  (A and B) Ill-defined non-mass like enhancement involving the upper lateral quadrant/12 o’clock position in the right breast, not visible on the US examination, with progressive kinetic curve, but with rapid enhancement in the first minute (MRI finding of BI-RADS category 4). (C) Axial 3D sequence with iv contrast and fat saturation. Focal ill-defined non-mass like enhancement in the upper lateral quadrant/12 o’clock position in the right breast not visible on the US examination (arrow). The MRI-guided biopsy confirmed the diagnosis of DCIS.
Sensitivity of magnetic resonance for the detection of infiltrating carcinoma and carcinoma in situ and detection of non-invasive cancers

Most of the controversy/disagreement between studies on MRI screening in HR patients is related to the DCIS detection. The results of the Dutch and British studies,\textsuperscript{20,21} which indicate higher DCIS detection with MX, usually through the presence of microcalcifications, are contrary to those reported by the Canadian, Italian, German and Austrian studies,\textsuperscript{23,24,26,27} which indicate higher DCIS detection with MRI. This is basically because the former studies were not based on diagnostic criteria specific for DCIS detection with MRI. A diagnosis of DCIS should be considered not only when typical imaging findings are present (early unilateral non-mass like enhancement with linear or segmental distribution and granular internal enhancement), but also the presence of other findings (minimal enhancement during the late phase not conforming to ductal distribution, or bilateral asymmetric enhancement) should make us consider DCIS and prompt a biopsy.

It seems that low-grade DCISs follow different developmental pathways than high-grade DCISs, more than undergoing progressive differentiation. While high-grade DCIS progresses more rapidly and commonly to high-grade IC, low-grade DCIS usually has a more indolent course or progresses only to specific types of cancer, usually well-differentiated. A diagnosis of high-grade DCIS would be therefore preferred initially.\textsuperscript{44}

MRI appearance of DCIS correlates with its biological aggressiveness.\textsuperscript{44} MRI sensitivity for DCIS is 92% (98% for high-grade DCIS), against 56% diagnosed by MX. MRI can predict which cases diagnosed as high-grade DCISs will progress to IC, but this detection does not represent overdiagnosis.\textsuperscript{44} The recently published results of the German multicenter study (the EVA trial)\textsuperscript{45} confirm the high S of MRI in the detection of DCIS (all MRI-only detected DCISs exhibited intermediate or high grading).

New contributions of recent multicenter studies on the role of the different imaging techniques (mammography, ultrasound, magnetic resonance) in high risk screening

Two similar conclusions can be drawn from both the EVA trial\textsuperscript{45} and the recently published Italian multicenter study (HIBCRT),\textsuperscript{46} which compare the contribution of the different imaging techniques:

- The detection rate for MRI does not significantly increase when combined with MX, US or both.\textsuperscript{45,46}
- Most cancers are detected on annual screening (there were no interval cancers in the German study\textsuperscript{45} and 0.2% in the Italian one).\textsuperscript{46}

The EVA trial demonstrated that an additional US at six-month intervals did not contribute to the detection of additional cancers.\textsuperscript{45}
Sensitivity to radiation

There is evidence that HR patients are more radiosensitive.

The European working group (EUSOMA) recommends that "in HR patients younger than 34 years, MX should be avoided as there is no evidence that the benefits outweigh the radiation risks from MX". The recommendation for screening would be:

- Annual MRI + MX in patients older than 35 years.

In disagreement with these recommendations, the American guidelines (ACS, ACR, SBI, NCCN) recommend annual MX + MRI in patients younger than 35 years arguing that "MX in BRCA carriers is not associated with a large increase in breast cancer risk; with only a modest association in BRCA 1 carriers". These guidelines argue that the benefit of MX screening warrants radiation exposure because BRCA 1 and 2 carriers are 3–6 times at higher risk than the general population and indicate the need for more studies before eliminating MX.

Nonetheless, Sardenelli et al. refute this and argue that when added to MRI, MX does not significantly increase the sensitivity. They point out that some prospective studies show that the rate of MX-only detected cancers account for only 4% and that these cancers are DCIS (those DCIS that are not detected by MRI are usually low-grade cancers, so they would not have a significant impact on mortality).

Follow-up in HR patients after a diagnosis of cancer

When HR patients do not undergo prophylactic mastectomy for the primary cancer, MRI follow-up is recommended because of the high risk of second tumor. BRCA-mutation carriers have 29.5% risk of contralateral cancer at 10 years and a lifetime risk of 40%. The risk is lower in BRCA 2 than in BRCA 1 carriers. Obviously, oophorectomy and therapy with tamoxifen reduce the risk of recurrence.

Intermediate risk

The current debate centers on what to recommend for women at increased risk but who do not meet the criteria for supplemental screening with MRI, for whom MX may be of limited sensitivity. In these women, the use of MRI would be problematic because of the lower prevalence of the disease, the lower cost-effectiveness and the higher false-positive rates. This group would include women with:

1. A personal history of breast cancer.
2. Previous histologic diagnosis of lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH), or atypical ductal hyperplasia (ADH).
3. Intermediate family history.
4. Dense breasts at MX.

Personal history of breast cancer

The risk of local recurrence after conserving surgery and radiation therapy is low (the historically estimated recurrence rate is 1–2% per year). Chemotherapy and hormone therapy reduce recurrence by 37 and 50%, respectively. So that the 10-year recurrence rate is now considered to be lower than 10%.

Therefore, the current recommendations of American and European societies do not include MRI in the screening of this group of patients.

ACS

Although these women have a higher risk of a second cancer, the absolute risk is approximately 10%, which would not warrant MRI screening.

EUSOMA

In women with a previous diagnosis of cancer, supplemental screening with MRI is done only if there are other risk factors (HR).

Gorechlad et al. observed that in their patients the recurrence rate at five years after breast conserving surgery and radiation therapy, and in some cases after hormone therapy, was very low (4%), and that tumor size was small (mean diameter: 1.7 cm). This is in agreement with the recent literature on the subject. Gorechlad concludes that given the small tumor size at detection and the excellent survival of those who recur, screening with MRI in women with a personal history of breast cancer would incur significant cost and would not change the treatment (the treatment for local recurrences is mastectomy) or increase survival.

Since his group of patients did not undergo preoperative MRI, Gorechlad indicates that the use of preoperative MRI would decrease the usefulness of screening with MRI at annual follow-up. One of the conclusions drawn from the study by Fischer et al. was that preoperative staging MRI reduces recurrence rates, but subsequently, the study by Solin et al. drew different conclusions. However, this latter study had serious shortcomings that might have negatively affected the evaluation of the effect of MRI.

Nevertheless, Brennan et al. in the first study that evaluates breast MRI screening in women with a personal history of breast cancer reported a very high recurrence rate, 12% (with a mean tumor diameter of 0.8 cm). This article reminds us that MRI has higher (94–100%) and specificity (89–92%) in the detection of tumor recurrence than MX (better differentiation between scar and recurrent tumor). Only 15% of the patients in this study had a preoperative MRI. Brennan et al. consider that screening with MRI may be beneficial in:

(A) Allowing the use of less-toxic therapies.
(B) As with the original breast cancer, relative survival of patients with recurrent tumor improves with early detection by 27–47%.

This study concludes that although screening MRI in women with a personal history of breast cancer is costly and generates many biopsies and follow-ups, patients without a preoperative MRI and those who have not taken hormonal
therapy may benefit. It was beyond the scope of the study to evaluate the cost-effectiveness and the impact on survival.

Nonetheless, both authors\textsuperscript{50,53} recognize that a randomized prospective study, possibly including thousands of patients during more than 10 years, would be required to determine the effectiveness of MRI screening in women with a personal history of breast cancer.

We present a case of a patient with a history of left mastectomy who presented with a lymph node palpable in the contralateral axilla, positive for malignancy. The MRI revealed a small tumor, only a few millimeters in size, in the right breast that was mammographically occult and that went unnoticed on ultrasound because of its retroareolar location (Figs. 4–6).

Diagnosis by previous biopsy of a high risk lesion

Lobular carcinoma in situ, atypical lobular hyperplasia, and atypical ductal hyperplasia

These are lesions associated with increased risk of developing IC of the breast (risk markers). The lifetime risk in women with a diagnosis of lobular neoplasia (LN)—LCIS and ALH—may exceed 20%, but this risk is continuous and moderate 12 years after local excision (approximately 1/1–2% per year risk for LCIS; 0.5–1/1% per year for ADH).

Additionally, this risk decreases in patients receiving preventive medication. The subset of patients that best benefit from this therapy are those with histologic atypia.

Figure 4  (A and B) Right unilateral mammogram. Craniocaudal (A) and mediolateral oblique (B) views. Patient with a history of left breast cancer who had mastectomy five years ago. No suspicious lesions are visible.

Figure 5  Ultrasound shows lymph node palpable in right axilla with thickened cortex and suspicious appearance. US-guided fine needle biopsy revealed a metastatic lymph node.

Figure 6  (A–C) MRI performed to look for an occult carcinoma in the right breast. Coronal MRI with iv contrast (digital subtraction). Enhancing node in right axilla that corresponds with the palpable metastatic adenopathy (A). Small nodular enhancement, only a few mm in size, in retroareolar region not visible on the mammogram and that was not seen on ultrasound (probably because of its retroareolar location, which may be difficult to evaluate with ultrasound) (B). Axial T1 sequence shows a small node, only a few mm in size, in the retroareolar area (CNB after second-look ultrasound demonstrated infiltrating ductal carcinoma) (C).
Tamoxifen reduces the risk by 86%, but its use is limited because of the adverse effects. The use of this drug has been approved in US but not in Europe.55-58

One study with MRI screening that specifically includes women with LCIS and AH59 has demonstrated a small benefit over MX in the detection of breast cancer in women with LCIS. This benefit was not seen in patients with AH, but the sample size was small. Cancer detection rate was high (4%) and those tumors detected by MRI were stage 0-I (versus the non-MRI group that were I-II). But it should be emphasized that this generated many short-term follow-ups and biopsies (25%) with a PPV of only 13%.

The guidelines from American and European societies do not specifically recommend using MRI as an adjunct to MX in these patients (with the exception of some partial recommendation from the NCCN-09):

- ACS: it does not include recommendations for MRI follow-up in these patients, it should be considered on a case-by-case basis and evaluating other risk factors.
- SBI-ACR: “it can be considered”.
- NCCN guideline (2009): annual MX + MRI is recommended in patients with LCIS.60
- EUSOMA: if the diagnosis of ADH or intraepithelial LN is not accompanied by other risk factors, MRI will not be used for screening.

Intermediate family history

These are patients with a lifetime risk of 15–20% as defined by BRCAPRO, or other previously mentioned tests that are largely dependent on family history.

Table 2B shows a practical approach to the IR criteria based on family history as indicated by the Comunidad de Madrid.

The main American and European societies do not include specifically the recommendation of supplemental MRI in this group of patients:

- ACS, EUSOMA: the evidence is not sufficient to recommend the use of MRI as an adjunct to MX.
- SBI-ACR: “MRI can be considered in women with 10–15% risk taking into account their family history of breast or ovarian cancer’’.

Dense breasts at mammography

Approximately 50% of women under 50 and one-third of women over 50 have dense breasts at MX.66

Percent mammographic density (MXD) has features of IR and genetic factor.61 MXD is the most important predictor of MX sensitivity at any age.62 Those cancers diagnosed during the interval between two screening rounds have poorer prognosis, with higher DMX increasing the risk of interval cancer. It is surprising that the existing models for predicting breast cancer risk do not include DMX despite the fact that women with dense breasts have a four- to five-fold greater risk.66

Single-center trials reviewed by Berg et al.63 and two multicenter trials (the Italian trial/Corsetti and ACRIN 6666, the latter in HR patients)64,65 reported that supplemental screening US in patients with dense breasts has an additional cancer detection yield of 0.27–0.47%. Almost all detected cancers were IC, node-negative and most had small size (mean size 9–11 mm).

Some US-detected cancers were seen retrospectively on MX; therefore, US provides earlier detection of lesions that would otherwise emerge as interval carcinomas.

False positives are more common with screening US than with MRI: PPV 8.8–11.4% (but in the study by Corsetti et al. the PPV was 36.6%).

In addition, in dense breasts the sensitivity is lower in young women. This means higher contribution in women younger than 50 years when using supplemental US, higher

![Figure 7](image)

**Figure 7** Cranio-caudal and mediolateral oblique projection mammograms of both breasts (dense breasts; no lesions visible on the mammograms): (A) right cranio-caudal, (B) left cranio-caudal, (C) right mediolateral oblique, and (D) left mediolateral oblique.
prevalence of US-only detected cancers$^{42,64}$ (almost 50% of patients in the study by Corsetti). US has a low sensitivity for the detection of CDIS, while infiltrating lobular carcinoma (ILC) is an important representative of US-only detected lesions.

The use of US as an adjunct to MX increases the sensitivity for breast cancer detection by 20%.$^{64}$ Although it can be inferred that all women with dense breast could benefit from supplemental US screening, clearly, not all women can be offered screening US given the low prevalence, the cost-effectiveness and false positives. There may be a subpopulation of patients in whom the benefits outweigh the risk, and although more trials are required to better define this subpopulation and the effects on survival, the following patients could be included$^{44}$:

1. HR women who do not tolerate MRI.
2. IR women with dense breasts.

We present a case of dense breasts at MX with no suspicious findings where the US detected two nodules (BI-RADS category 4), one in each breast. The biopsy determined that one lesion was a myxoid fibroadenoma and the other an IDC. Both nodules were seen at the subsequent staging MRI (Figs. 7–9).

To sum up, the recommendations for screening in IR patients are:

- Annual MX (+US in case of dense breasts, especially if any of the previously mentioned IR factors is present).
- To date, the evidence is not sufficient to recommend the use of screening with MRI in IR patients (ACS, EUSOMA, EUSOBI).

But it should be emphasized that MRI has the highest sensitivity while maintaining high specificity. These findings would warrant further research.

A single model that can accurately predict breast cancer risk should be developed, which would integrate all personal and family risk factors, and ideally also the MXD. Additionally, the detection rates of MRI screening alone in IR women (with 15–20% risk of developing breast cancer) need to be determined and these data could be used to better determine the cost-effectiveness of MRI for that risk level.$^5$

**Figure 8 Ultrasound.** (A) Solid nodule with poorly defined margins in upper lateral quadrant of right breast, BI-RADS category 4. The US-guided CNB revealed a myxoid fibroadenoma (consistent). (B) Solid nodule with ill-defined margins in upper inner quadrant of left breast BI-RADS, category 4. The US-guided CNB revealed an infiltrating ductal carcinoma.

<table>
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<tr>
<th>Table 4 Patients undergoing earlier screening.</th>
<th>SBI, ACR, ACS</th>
<th>NCCN</th>
<th>EUSOMA</th>
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<tbody>
<tr>
<td>BRCA 1 and 2 mutation carriers and their first-degree relatives not tested (+MRI):</td>
<td>30 years (not before 25 years)</td>
<td>25 years</td>
<td>-BRCA 1 and 2: before 25–29 years -TP53 (Li-Fraumeni) starting from 20 years. In TP53 mutation carriers of any age annual mammography can be avoided (based on discussion on risks/benefits from radiation exposure: experts’ consensus)</td>
</tr>
<tr>
<td>Mother or sister with premenopausal cancer or ≥20% risk based on family history (maternal or paternal), (+MRI):</td>
<td>30 years (not before 25 years) or 10 years before the age of diagnosis of the younger relative</td>
<td>25 years; 5–10 years before the age of diagnosis of the younger relative</td>
<td>30 years; 5 years before the age of diagnosis of the younger relative</td>
</tr>
<tr>
<td>History of chest radiation therapy (+MRI)</td>
<td>Starting 8 years after the radiation therapy, not before 25 years</td>
<td></td>
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</tr>
<tr>
<td>Previous biopsy (LCIS, CDIS, ALH, ADH, IC, ovarian Ca)</td>
<td>Annually after diagnosis, regardless the age NCCN (+MRI if LCIS)</td>
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Figure 9  (A and B) Sagittal MRI with iv contrast agent of right breast (digital subtraction). (A) Nodule in upper lateral quadrant of right breast with ill-defined margins compatible with a myxoid fibroadenoma after CNB. (B) Progressive enhancement curve, but rapid enhancement within the first minute. (C and D) Sagittal MRI with iv contrast agent of left breast (digital subtraction). (C) Nodule in upper inner quadrant of left breast with ill-defined margins and diagnosis of infiltrating ductal carcinoma after CNB. (D) Suspicious curve, type 3.

Patients undergoing earlier screening

These are patients at high risk and whose screening is recommended to start earlier. Albeit very similar, the recommendations/indications of the different societies/guidelines do not entirely coincide (Table 4).

Conclusion

Recommendations for patients with increased risk.

High risk:

- Annual MRI + US in women aged 25–35 years.
- Annual MRI + MX in women older than 35 years.

Intermediate/moderate risk:

- Annual MX (+US in dense breasts, especially if there is other IR factor).

These are current recommendations, but if we take into consideration the conclusions of the German and Italian multicenter studies, the use of breast MRI alone could be considered sufficient for screening of HR women in the near future.

Issues requiring further study/research

- Development of a single/appropriate model to assess risk that would include all personal and family risk factors as well as the MXD.
- Assessment of the benefit of annual MRI in HR patients in terms of survival. For some authors, randomized studies would be unethical because some patients are excluded from the benefit of MRI screening.
- Study of the risk profile of MRI-only detected lesions (over-diagnosis).
- Usefulness/added value of MRI in HR patients older than 50 (the Italian study has already demonstrated its usefulness).
- Analysis of interval carcinomas. The German and Italian multicenter studies provide valuable information since they reported absence or 0.2% of interval carcinomas, respectively.\textsuperscript{45,}46
- Effect of double reading of MRI on sensitivity and biopsy rate.
- Screening MRI in IR patients.

An important issue is to determine what specialists or what organization, uni- or most probably multidisciplinary, should be in charge of classifying patients into different risk groups. Maybe this is about the benefit or need of generating dedicated medical offices to determine breast cancer risk on a case-by-case basis in each area of population. This would allow specific screening, performed at the appropriate intervals and using the appropriate techniques according to the risk group of the patient, according to the established protocols based on the recommendations of the relevant societies/guidelines. Thus, allowing us to filter the patients who would require referral for genetic counseling.

In the not too distant future, it would be desirable to redefine a screening program that would be consistent, extensive and optimized, and focused on differentiating patients according to their estimated risk of developing breast cancer.

Authorship

1. Responsible for the integrity of the study: SAR.
2. Conception of the study: SAR, SJA, ABDL and VQC.
3. Design of the study: SAR, SJA, ABDL and VQC.
4. Acquisition of data: SAR, SJA, ABDL, VQC and EGC.
5. Analysis and interpretation of data: SAR, SJA, ABDL and VQC.
6. Statistical analysis: N/A.
7. Bibliographic search: SAR and EGC.
8. Writing of the paper: SAR.
9. Critical review with intellectually relevant contributions: SAR, SJA, ABDL and VQC.
10. Approval of the final version: SAR, SJA, ABDL, VQC and EGC.

Conflict of interest

The authors declare not having any conflict of interest.

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