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Review

Accuracy of screening women at familial risk of breast cancer without a known gene mutation: Individual patient data meta-analysis

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Abstract   *Introduction:* Women with a strong family history of breast cancer (BC) and without a known gene mutation have an increased risk of developing BC. We aimed to investigate the accuracy of screening using annual mammography with or without magnetic resonance imaging (MRI) for these women outside the general population screening program.

Methods: An individual patient data (IPD) meta-analysis was conducted using IPD from six prospective screening trials that had included women at increased risk for BC: only women with a strong familial risk for BC and without a known gene mutation were included in this analysis. A generalised linear mixed model was applied to estimate and compare screening accuracy (sensitivity, specificity and predictive values) for annual mammography with or without MRI.

Results: There were 2226 women (median age: 41 years, interquartile range 35−47) with 7478 woman-years of follow-up, with a BC rate of 12 (95% confidence interval 9.3−14) in 1000 woman-years. Mammography screening had a sensitivity of 55% (standard error of mean [SE] 7.0) and a specificity of 94% (SE 1.3). Screening with MRI alone had a sensitivity of 89% (SE 4.6) and a specificity of 83% (SE 2.8). Adding MRI to mammography increased sensitivity to 98% (SE 1.8, P < 0.01 compared to mammography alone) but lowered specificity to 79% (SE 2.7, P < 0.01 compared with mammography alone).

Conclusion: In this population of women with strong familial BC risk but without a known gene mutation, in whom BC incidence was high both before and after age 50, adding MRI to mammography substantially increased screening sensitivity but also decreased its specificity.

1. Introduction

About 15−20% of breast cancer (BC) cases are associated with a family history of BC [1]. Women without a known mutation in a hereditary BC gene, but with a family history of breast with/without ovarian cancer, are at a higher risk of developing BC, the extent of the increased risk depends on the number of affected relatives and the age at cancer diagnosis in the relative(s) [2,3]. These women at familial risk, who have a cumulative lifetime risk of developing BC over 15−20%, are usually offered a BC screening regimen outside of the general population screening program, starting at an earlier age and including more frequent (annual) mammography [4,5].

Results of many prospective trials evaluating the accuracy of adding annual MRI to mammography for screening these women have been published [6−15]. Although these studies emphasised the significantly greater sensitivity of annual magnetic resonance imaging (MRI) and mammography in combination for screening this high-risk population, several issues remain unclear. First, inclusion criteria were heterogeneous and all the studies also included women with known gene mutations. Furthermore, the definition of familial risk for BC varied across countries and centres depending on referral criteria and risk assessment tools. Also, few studies reported results separately for women at familial risk without a known gene mutation [8,11,12] and none of the studies reported results stratified by age for this population.

In this meta-analysis, pooling individual patient data (IPD) from prospective trials, we aimed to assess the accuracy of screening women at familial risk of BC without a known gene mutation, adding MRI to mammography and stratifying outcomes by age.

2. Methods

2.1. Study design

An IPD meta-analysis was conducted, including individual data from 6 of 12 prospective trials, in which women at high risk of BC due to an inherited *BRCA* gene mutation or a strong family history of BC were screened with annual mammography and MRI, and the accuracy of each screening modality was reported separately [16,17]. All studies were performed in developed countries. More details about the study inclusion criteria, data acquisition and assembly and quality assessment were reported in our previous publication which focused on *BRCA1/2* gene mutation carriers [17]. In the present study, we focus only on women with a strong family history of BC (defined as a cumulative lifetime BC risk of at least 15%) and without a known gene mutation. Specific inclusion criteria for the original studies contributing to this IPD meta-analysis, outlining family history criteria and whether women with a personal history of BC were included are summarised in Supplementary appendix 1.

2.2. Study population

Women aged 25 or older, who had a strong family history of BC and no known gene mutation and had

completed at least one screening round, were included in this analysis. A completed screening round was defined as a screening round in which both MRI and mammography were performed within a time interval of less than 3 months, with results of the two tests interpreted separately using blinded methods. Screens were included if there was either a pathology test or at least 1 year follow-up to confirm the presence or absence of BC. Women who were proven to be non-mutation carriers from a *BRCA* family were excluded, as their risk is generally considered to be comparable to that of the general population. Screen-detected or interval cancers were counted in this analysis (BCs found during preventive mastectomy were not considered).

2.3. Primary outcome and definitions

Primary outcomes were screening accuracy including sensitivity, specificity and positive/negative predictive value (PPV/NPV). To adjust for multiple screenings of the same women and differences between studies, the estimates for each modality were model-based with the following: (1) sensitivity defined as the number of BCs detected over the total number of BC diagnosed; (2) specificity defined as the number of true-negative tests over the total number of screens without BC; (3) PPV defined as the number of true-positive over the total number of positive tests; (4) NPV as the number of true-negatives over the total number of negative tests.

Imaging scores of BI-RADS 0, 3, 4 or 5 (Breast imaging-reporting and data system) were considered to be a positive screening result. Using this threshold allowed the harmonisation of the outcomes across studies. The combination of MRI and mammography was classified as a positive result if either one of these tests was positive. BI-RADS 1 or 2 was considered a negative test, and a negative outcome of the combination was based on both tests having negative results. For positive test results, the presence of BC was based on the results of histologic examination. The absence of BC was ascertained by histologic examination or 1 year follow-up with negative screening or stable imaging. Where more than one tumour was diagnosed in a woman in the same screening round, the largest BC was included. Where more than one BC was diagnosed in a woman at different screening years, the first BC was included. For analytic purposes, a BC was considered an interval cancer when it was not detected by a positive screening test (mammography or MRI) and was diagnosed between two annual rounds of screening. The above definitions were applied to all the studies when assembling the individual data to obtain consistency and comparable data from all studies, although there were slight differences between these definitions and the definitions that may have been applied in the original studies.

2.4. Statistical analysis

Characteristics of the women (follow-up time, cancer incidence, median age at entry with interquartile range [IQR]) and cancer characteristics were reported for the total study population and for each age group. Overall cancer incidence in total and stratifying by screening round, were calculated as the number of BCs per 10,000 woman-years and the 95% confidence interval (CI) was computed assuming the incidence follows a Poisson distribution.

A generalised linear mixed model (Procedure Glimmix using the QUAD option for the likelihood method of estimation the binomial distribution with logit link function, SAS version 9.4) was applied to estimate sensitivity, specificity and the predictive values of each screening modality and then compare these measures for the two screening modalities and the combination using Wald tests. One analysis is done for sensitivity and specificity simultaneously and another for predictive values. For sensitivity and specificity, repeated measurements were summarised for each woman to the total number of screens with proven BC, total number of screens without BC, the number of true-positives and the number of true-negatives. Each woman had six records: two ascertained outcomes (with or without proven BC) for each of three screening modalities (mammography, MRI and the combination). In the model, the numbers of true-positive/negative tests followed a binomial distribution with the total number of screens with/without proven BCs and a proportion that was modelled as a function of screening modality. To address heterogeneity between studies, a bivariate random variable with an unstructured correlation matrix was added to model the study effect for each screening modality and each ascertained outcome. Analysis was performed for each age group separately. Sensitivity and specificity were modelled simultaneously to take into account their negative correlation. The same approach was used for positive and NPVs by replacing the ascertained outcomes by modality outcomes (test positive or negative) and number of screens with/without BCs by the number of screens with positive/negative test. Screening accuracy for the three modalities was compared within age groups defined by age at screening, as follows: younger than 40 years, 40–49 years and 50 years and older. In two sensitivity analyses, the year of screening was added to the model to explore its impact on the results, and screening accuracy was estimated for first and subsequent rounds to allow for prevalent cases.

3. Results

3.1. Study population and breast cancers during the study

Data on 2226 women at familial risk with at least one completed screening round were included in this

analysis, representing 7478 woman-years of follow-up (median 3 years, IQR 2−5) with ascertained outcomes (Table 1). There were 106 (4.8%) women with a personal history of BC and 193 (8.7%) women with a negative genetic test result. Amongst these 2226 women with a median age of 41 years (IQR 35−47) at study entry, 87 BCs were diagnosed at a median age of 48 (IQR 43−54) years. BC rate was estimated as 11.6 (95% CI 9.3−14) per 1000 woman-years. BC incidence increased with increasing age: 5.1 (95% CI 2.8−8.6) per 1000 woman-years in women who underwent screening before age 40, 12 (95% CI 8.3−16) per 1000 woman-years in women aged 40−49 and 22 (95% CI 15−30) per 1000 woman-years in women aged 50 and older. Of all BCs, 37 were prevalent cancers (detected at the first screening round); excluding those prevalent cancers, the rate (per 1000 woman-years) was 9.5 (95% CI 7.1−13) in all women, 5.7 (95% CI 2.7−11) in women aged <40, 8.3 (95% CI 4.9−13) in women aged 40−50 and 16.6 (95% CI 10−25) in women aged >50.

Amongst 87 BCs observed in the study population, three were interval cancers: all were invasive, smaller than 2 cm and diagnosed in women aged 37, 46 and 57 years. The youngest group had more invasive BCs and more large invasive BCs than the older age group (Table 1).

3.2. Screening accuracy in all women

In the total study population, mammography sensitivity was 55% (standard error of mean [SE] 7.0) (Table 2). The combination of MRI and mammography had the highest sensitivity but the lowest specificity. The combined sensitivity was 98% (SE 1.8) versus 89% (SE 4.6) for MRI alone (P < 0.001) and 55% (SE 7.0) for mammography alone (P < 0.001). The combination had the lowest specificity of 79% (SE 2.7) versus 83% (SE 2.8) for MRI alone (P < 0.01) and 94% (SE 1.3) for mammography alone (P < 0.01). The PPVs of the three screening modalities were generally comparable around 9%, whereas differences were observed for NPVs, as summarised in Table 2. When adjusting for year at screening (results not shown) or excluding the first screening round (Table 4), the estimates for sensitivity and specificity did not change.

3.3. Cancer detection: contribution of screening modalities in different age groups

Screening with the combination of MRI and mammography had higher sensitivity compared with mammography alone in all age groups (Table 2). In women younger than 40 years, the sensitivity of the combination was 95% (SE 5.6) versus 51% (SE 13) for mammography (P < 0.01) and MRI alone detected seven invasive cancers (of 14 cancers, 50%, four invasive tumours 1−2 cm), which were not detected at mammography (Table 3). In women aged 40−49, the sensitivity of the combination was 98% (SE 2) compared to mammography sensitivity 57% (SE 8.2, P < 0.01) (Table 3) and MRI detected 17 cancers (of 36 cancers, 47%) which were not detected at mammography, among which 12 were invasive cancers (six tumours were ≤1 cm), four were ductal carcinoma in situ (DCIS) and one was unspecified. In women ≥50, sensitivity of the

Table 1
Overview of the women at familial risk and their breast cancers characteristics, stratifying by age at screening (N = 2226; BCs = 87).

	All ages	Age <40	Age 40−49	Age ≥50
Number of women	2226	987[a]	1044[b]	527
Number of BCs	87	14	36	37
Follow-up (in 1000 women years)	7478	2733	2953	1792
BC rate (in 1000 women years)	12 [9.3−14]	5.1 [2.8−8.6]	12 [8.5−17]	21 [15−29]
BC rate first round	17 [12−23]	4.1 [1.1−10]	21 [13−34]	39 [22−64]
BC rate subsequence rounds	9.5 [7.1−13]	5.7 [2.7−11]	8.3 [4.9−13]	17 [10−25]
Age at study entry (median, IQR)	41 [35−47]	35 [31−37]	43 [40−46]	52 [49−57]
Age at BC diagnosis (median, IQR)	48 [43−54]	37 [34−38]	46 [43−48]	55 [53−62]
Screen detected	84	13	35	36
DCIS	17	1	10	6
Invasive	61	12	22	27
Unknown	6	0	3	3
Interval cancer	3 (invasive cancers)	1	1	1
Tumour size of invasive cancers	64	13	23	28
≤10 mm	21 (33%)	1 (7.7%)	9 (39%)	11 (39%)
11−20 mm	27 (42%)	7 (54%)	9 (39%)	11 (39%)
>20 mm	8 (13%)	2 (15%)	3 (13%)	3 (11%)
Unknown	8 (13%)	3 (23%)	2 (8.7%)	3 (11%)

BC, breast cancer; DCIS, ductal carcinoma in situ; IQR, interquartile range.
[a] Of those 987 women included in the model for women age <40, 194 women started their screening before the age of 40 and became 40 in one of the follow-up rounds. These women were also counted in the age group 40−49.
[b] Of those 1044 women included in the model for women age 40−49, 138 women started their screening between age 40−49 and became 50 in one of the follow-up rounds. These women were also counted in the age group ≥50.

Table 2
Screening accuracy in women at familial risk of breast cancer (N = 2226, BCs = 87, median screening rounds: 3 [IQR 2−5]).

Modality (BCs detected [N]; positive tests; [N])	Women at all ages			
	Sensitivity %; SE; (95% CI)	Specificity %; SE; (95% CI)	PPV %; SE; (95% CI)	NPV %; SE; (95% CI)
Mammography (48; 458)	55[a] 7.0 (41−69)	94[c] 1.3 (90−96)	9.7 4.5 (6.3−19)	99[e] 0.0 (99−100)
MRI (75; 997)	89[b] 4.6 (76−96)	83[d] 2.8 (77−88)	8.9 3.3 (4.1−18)	100[f] 0.0 (99.6−100)
Combination (84; 1287)	98 1.8 (86−100)	79 2.7 (73−84)	7.9 2.5 (4.1−15)	100 0.0 (99.8−100)

PPV, positive predictive value; NPV, negative predictive value; SE, standard error of mean.
[a] Compared to the combination sensitivity: P = 0.0008.
[b] Compared to the combination sensitivity: P < 0.0001.
[c] Compared to the combination specificity: P = 0.002.
[d] Compare to the combination specificity: P = 0.002.
[e] Compared to the combination NPV: P = 0.001.
[f] Compared to the combination NPV: P = 0.0002.

combination was 97% (SE 3.0) (compared to 67%, SE 7.8, P > 0.05, for mammography), and MRI alone detected 12 cancers (of 37 cancers, 32%, including two cases of DCIS and one invasive tumour ≤1 cm) that were not detected by mammography (Table 3).

The sensitivity of mammography improved to some extent with increasing age. The sensitivity of mammography was low in women <40 years (51% SE 13) (Table 3). In the women <40 years, mammography visualised 6 of 14 cancers and only for one case, the tumour (DCIS) would have been missed if mammography would not have been performed. In women aged 40−49, mammography sensitivity was 57% (SE 8.2). In this age-group, 18 of 35 cancers could be visualised with mammography, and four cancers (three DCIS and one invasive ≤1 cm) were missed by MRI (Table 3). In women aged ≥50, mammography had a sensitivity of 67% (SE 7.8) (Table 3). Mammography visualised 24 of

Table 3
Screening accuracy in women at familial risk of breast cancer, stratifying by age at screening.

Age groups, N women, BCs, SR	Modality (BCs detected; positive tests)	Sensitivity %; SE; (95% CI)	Specificity %; SE; (95% CI)	PPV %; SE; (95% CI)	NPV %; SE; (95% CI)
Age < 40, N = 987, BCs = 14, SR: 2 [IQR 1−4]	Mammography (6; 131)	51[a] 13 (26−76)	95 1.6 (90−97)	5.1 2.7 (1.7−14)	100 0.1 (99−100)
	MRI (12; 358)	92[b] 8.3 (53−99)	83[c] 3.5 (74−89)	3.9 1.5 (1.8−8.3)	100 0.0 (99.6−100)
	Combination (13; 436)	95 5.6 (60−100)	79 4.8 (67−87)	3.6 1.3 (1.7−7.3)	100 0.0 (99.6−100)
Age 40−50, N = 1044, BCs = 36, SR: 3 [IQR 2−5]	Mammography (18; 215)	57[d] 8.2 (40−73)	91 1.6 (87−95)	8.8 2.2 (5.2−14)	99 0.3 (99−100)
	MRI (31; 470)	92[e] 9.3 (44−100)	80[f] 3.2 (73−86)	7.1 1.5 (4.6−11)	100[g] 0.1 (99−100)
	Combination (35; 613)	98 2.0 (83−100)	75 3.2 (68−81)	6.3 1.1 (4.4−9.1)	100 0.0 (99.6−100)
Age ≥50, N = 527, BCs = 37, SR: 4 [IQR 2−5]	Mammography (24; 113)	67 7.8 (49−81)	94 0.6 (92−95)	24 9.5 (9.4−48)	99 0.3 (98−100)
	MRI (32; 167)	86[h] 5.6 (70−95)	90[i] 2.7 (83−94)	20 6.2 (11−37)	100[j] 0.2 (99−100)
	Combination (36; 236)	97 3.0 (75−100)	85 2.4 (80−90)	19 6.0 (9.5−34)	100 0.0 (99−100)

PPV, positive predictive value; NPV, negative predictive value; SR, screening round, median and IQR; IQR, interquartile range; SE, standard error of mean.
[a] Compared to the combination sensitivity: P = 0.003.
[b] Compared to the combination sensitivity: P = 0.002.
[c] Compared to the combination specificity; P = 0.04.
[d] Compared to the combination sensitivity: P = 0.003.
[e] Compared to the combination sensitivity: P < 0.0001.
[f] Compared to the combination specificity; P = 0.006.
[g] Compared to the combination NPV: P = 0.02.
[h] Compared to the combination sensitivity: P = 0.0003.
[i] Compared to the combination specificity: P = 0.03
[j] Compared to the combination NPV: P = 0.02.

Table 4
Screening accuracy in women at familial risk of breast cancer, stratified by screening rounds.

Screening round	Modality	TP/TP + FN	TN/TN + FP	Sensitivity %; SE; (95% CI)	Specificity %; SE; (95% CI)
First round	Mammography	26/37	1877/2027	70[a], 7.5 (53−83)	92[a],1.7 (88−96)
	MRI	33/37	1624/2027	92[a], 6.2 (67−99)	78[a], 4.4 (68−86)
	Combination	37/37	1538/2027	100, 0.1 (0−100)	74, 4.5 (64−83)
Subsequent rounds	Mammography	22/50	4196/4456	46[a], 7.1 (32−61)	94[a], 0.4 (93−95)
	MRI	42/50	3939/4456	84[a], 7.1 (63−94)	87[a], 2.3 (82−91)
	Combination	47/50	3744/4456	94, 4.4 (76−99)	83, 2.4 (77−87)

CI, confidence interval; MRI, magnetic resonance imaging; TP, true-positive; TN, true-negative; FP, false-positive; FN, false-negative; SE, standard error of mean.

[a] Compare to the combination: P < 0.01.

37 cancers and four of those (one DCIS and three invasive) were not detected by MRI.

3.4. Predictive value of screening modalities in different age groups

The PPV of each modality increased by age, whereas the NPV remained at about 99% or higher: Details are shown in Table 3.

4. Discussion

Our IPD meta-analysis examined the accuracy of screening mammography with or without MRI in women with a strong family history of BC and without a known gene mutation: Based on data for 2226 women, the observed BC incidence rate was high (12 per 1000 woman-years) and this was evident in both younger and older women, highlighting the BC burden in this population. The sensitivity of mammography was only 55% (SE 7.0). However, mammography was the most specific modality compared to MRI alone or the combination of MRI and mammography. Combining MRI and mammography detected the great majority of cancers with a sensitivity of 98%, significantly higher than the 55% sensitivity of mammography or 89% of MRI alone (P < 0.001). The higher sensitivity of the combination of mammography and MRI was evident in all age groups. The combination, however, had the lowest specificity due to a relatively high number of false-positives from MRI.

The accuracy of screening mammography for women at elevated risk due to family history and without a proven mutation was examined in some of the original primary studies contributing data for this IPD meta-analysis, and the results were generally comparable to this IPD meta-analysis, though based on fewer cases. Of those eligible studies that did not participate in this IPD meta-analysis [6,7,9,10,18], one study reported a low mammography sensitivity (25%) in women with an estimated lifetime BC risk of 21−40% [7]. Another study reported that mammography detected two of four BCs in 142 women with >25% lifetime risk of developing BC [18]. Although outside the scope of this IPD, a prospective screening study including women (mean age 55, range 25−91) at familial risk and who had heterogeneously dense or extremely dense parenchyma reported a mammography sensitivity of 50% (95% CI 34−66) [19]. Another retrospective study showed that annual mammography did not contribute to cancer detection over annual MRI in a retrospective cohort of women younger than 40 years with a lifetime risk of more than 20%, in whom four BCs were diagnosed [20]. Similarly, our IPD meta-analysis showed that mammography sensitivity was relatively modest (51% [SE 7.0]), whereas adding MRI increased the sensitivity up to 95% (SE 1.8).

Adding MRI screening has been shown to improve screening accuracy compared to mammography alone in other populations at increased BC risk, specifically in women with BRCA1/2 mutation [16]. However, adding MRI to mammography gave a significantly higher number of false-positive results. In addition, adding MRI is costly. It should be noted that in these studies, MRI and mammography were performed and interpreted independently, and a positive result was referred to whenever either test was positive−joint interpretation may potentially help reduce the number of false-positives. Yet, there still remains a lack of evidence regarding the long-term effects of annual MRI plus mammography compared with annual mammography.

The strength of this IPD meta-analysis is that it collected individual data from six prospective screening studies, creating the first pooled analysis of women with strong family history and without a known gene mutation. Further, it allowed implementation of common definitions and thresholds as well as subgroup analyses, through the collective data sets and through the use of IPD methodology. Nonetheless, there are several limitations to this meta-analysis. First, the number of women and cancers in some subgroup analyses remained too small to obtain either a clear trend or statistical significance. Second, we might have underestimated the accuracy of screening because the data collected in these studies are based on relatively older imaging technology [17]. Although we explored this issue by adding year of screening to our model and

found that it did not substantially change the estimates for sensitivity and specificity. We acknowledge that higher accuracy may be expected for current mammography and MRI technology because of improved MRI technology [21,22], better defined MRI BI-RADS descriptors and diagnostic categories [23] and the increasing use of breast digital tomosynthesis for screening [24,25]. Third, we included IPD from six prospective screening trials, yet each original study had its own recruitment time frame, age at recruitment, inclusion criteria and risk assessment tool for women without a proven mutation (Supplementary 1); thus, there was unavoidable heterogeneity in the format for family history data and probably risk level, reflecting real-life practices. It was therefore not possible to estimate BC risk for all the study population using one common criterion or assessment model without making some assumptions. In addition, despite some small differences between countries, the overall lifetime risk to develop BC in countries where the included studies were performed is 1 in 8 [26,27], which is not expected to have any impact on the here presented results on comparative accuracy. Furthermore, there was no information about *CHEK2* prevalence in these cohorts, and the effect of this gene mutation in screening accuracy was not examined. Future research focussing on the burden of family history and other gene mutations may potentially help refine and personalise screening strategies in these women. Finally, as the included studies investigated screening accuracy and did not report data on long-term outcomes such as survival, we could not include such outcomes in our analysis.

Our IPD meta-analysis highlights that adding MRI to mammography significantly improves BC detection in women with a strong family history of BC and without known gene mutations; however, this should be considered against the higher false-positive rate (lower specificity) caused by adding MRI screening. Our findings might lead to the conclusion that MRI screening alone may be appropriate for these women; however, comparative accuracy studies, such as reported in this work, need to be complemented by health-economic evaluation to determine whether such an approach could be cost-effective. Also, future research in this population of women is critically needed to examine alternate screening approaches, investigating new, faster (and less costly) MRI techniques and tomosynthesis as a replacement for 2-D mammography to develop screening strategies that optimise BC detection without significantly increasing the false-positive recall burden.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.07.055.

References

[1] Lynch HT, Silva E, Snyder C, Lynch JF. Hereditary breast cancer: part I. Diagnosing hereditary breast cancer syndromes. Breast J 2008;14:3—13.

[2] Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 1994;73:643—51.

[3] van Asperen CJ, Jonker MA, Jacobi CE, van Diemen-Homan JE, Bakker E, Breuning MH, et al. Risk estimation for healthy women from breast cancer families: new insights and new strategies. Cancer Epidemiol Biomarkers Prev 2004;13:87—93.

[4] National Institute for Health and Care Excellence. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. 2013. https://www.nice.org.uk/guidance/cg164. [Accessed 19 May 2017].

[5] Integraal Kankercentrum Nederland. Richtlijn mammacarcinoom (Breast Cancer National Guideline). 2012. http://www.oncoline.nl/breastcancer. [Accessed 19 May 2017].

[6] Kuhl C, Weigel S, Schrading S, Arand B, Bieling H, König R, et al. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol 2010;28:1450—7.

[7] Kuhl CK, Schrading S, Leutner CC, Morakkabati-Spitz N, Wardelmann E, Fimmers R, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 2005; 23:8469—76.

[8] Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005;365:1769—78.

[9] Lehman CD, Blume JD, Weatherall P, Thickman D, Hylton N, Warner E, et al. Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. Cancer 2005;103:1898—905.

[10] Lehman CD, Isaacs C, Schnall MD, Pisano ED, Ascher SM, Weatherall PT, et al. Cancer yield of mammography, MR, and

US in high-risk women: prospective multi-institution breast cancer screening study. Radiology 2007;244:381–8.

[11] Riedl CC, Luft N, Bernhart C, Weber M, Bernathova M, Tea MK, et al. Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. J Clin Oncol 2015;33:1128–35.

[12] Rijnsburger AJ, Obdeijn IM, Kaas R, Tilanus-Linthorst MM, Boetes C, Loo CE, et al. BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC screening study. J Clin Oncol 2010;28:5265–73.

[13] Sardanelli F, Podo F, Santoro F, Manoukian S, Bergonzi S, Trecate G, et al. Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk Italian 1 study): final results. Invest Radiol 2011;46:94–105.

[14] Warner E, Plewes DB, Shumak RS, Catzavelos GC, Di Prospero LS, Yaffe MJ, et al. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. J Clin Oncol 2001;19:3524–31.

[15] Trop I, Lalonde L, Mayrand MH, David J, Larouche N, Provencher D. Multimodality breast cancer screening in women with a familial or genetic predisposition. Curr Oncol 2010;17:28–36.

[16] Phi XA, Saadatmand S, De Bock GH, Warner E, Sardanelli F, Leach MO, et al. Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis. Br J Cancer 2016;114:631–7.

[17] Phi XA, Houssami N, Obdeijn I, Warner E, Sardanelli F, Leach MO, et al. Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age >/= 50 Years: evidence from an individual patient data meta-analysis. J Clin Oncol 2014;33:349–56.

[18] Weinstein SP, Localio AR, Conant EF, Rosen M, Thomas KM, Schnall MD. Multimodality screening of high-risk women: a prospective cohort study. J Clin Oncol 2009;27:6124–8.

[19] Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Böhm-Vélez M, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA 2008;299:2151–63.

[20] Narayan AK, Visvanathan K, Harvey SC. Comparative effectiveness of breast MRI and mammography in screening young women with elevated risk of developing breast cancer: a retrospective cohort study. Breast Cancer Res Treat 2016;158:583–9.

[21] Pinker K, Helbich TH, Morris EA. The potential of multi-parametric MRI of the breast. Br J Radiol 2017;90:20160715.

[22] Bickelhaupt S, Laun FB, Tesdorff J, Lederer W, Daniel H, Stieber A, et al. Fast and noninvasive characterization of suspicious lesions detected at breast cancer X-ray screening: capability of diffusion-weighted MR imaging with MIPs. Radiology 2016;278:689–97.

[23] American College of Radiology. ACR BI-RADS® Atlas, breast imaging reporting and data system. Reston, VA; 2013.

[24] Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. Lancet Oncol 2013;14:583–9.

[25] Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fantò C, Ostillio L, et al. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. Lancet Oncol 2016;17:1105–13.

[26] Arnold M, Karim-Kos HE, Coebergh JW, Byrnes G, Antilla A, Ferlay J, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. Eur J Cancer 2015;51:1164–87.

[27] Canadian Breast Cancer Foundation. Breast cancer in Canadian, 2016. 2017. http://www.cbcf.org/ontario/AboutBreastCancerMain/FactsStats/Pages/Breast-Cancer-Canada.aspx. [Accessed 14 July 2017].