Multimodality breast cancer screening in women with a familial or genetic predisposition

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ABSTRACT

Background

Women with a predisposition for breast cancer require a tailored screening program for early cancer detection. We evaluated the performance of mammography (MG), ultrasonography (US), and magnetic resonance imaging (MRI) screening in these women.

Patients and Methods

In asymptomatic women either confirmed as *BRCA1/2* carriers, or having a greater than 30% probability of being so as estimated by BRCAPRO [Berry D, Parmigiani G. Duke SPORE (Specialized Program of Research Excellence) in Breast Cancer. 1999], we conducted a prospective comparative trial consisting of annual MRI and MG, and biannual US and clinical breast examination. All evaluations were done within 30 days of one another. For each screening round, imaging tests were independently interpreted by three radiologists.

Results

The study enrolled 184 women, and 387 screening rounds were performed, detecting 12 cancers (9 infiltrating, 3 *in situ*), for an overall cancer yield of 6.5%. At diagnosis, 7 infiltrating cancers were smaller than 2 cm (T1); only 1 woman presented with axillary nodal metastases. All tumours were negative for the human epidermal growth factor receptor 2. Of the 12 cancers, MRI detected 10, and MG, 7; US did not identify any additional cancers. The overall recall rate after MRI was 21.8%, as compared with 11.4% for US and 16.1% for MG. Recall rates declined with successive screening rounds. In total, 45 biopsies were performed: 21 as a result of an US abnormality; 17, because of an MRI lesion; and 7, because of a MG anomaly.

Interpretation

In high-risk women, MRI offers the best sensitivity for breast cancer screening. The combination of yearly MRI and MG reached a negative predictive value of 100%. The recall rate is greatest with MRI, but declines for all modalities with successive screening rounds.

KEY WORDS

Breast cancer, screening, high-risk, *BRCA1, BRCA2,* magnetic resonance imaging, mammography, ultrasonography

1. INTRODUCTION

It was estimated that, in 2009, 22,700 Canadian women would receive a diagnosis of breast cancer, and 5400 would die from the disease [1]. Although an inherited predisposition for breast cancer is present in fewer than 10%–15% of women diagnosed with breast cancer, the number of breast cancers encountered in families with genetic mutations is very significant [2]. About 50% of breast cancers in high-risk families can be attributed to deleterious *BRCA1* and *BRCA2* mutations, found respectively on chromosomes 17q21 and 13q12–13. Both genes are inherited in an autosomal-dominant fashion with incomplete penetrance [3,4]. The presence of a germ-line mutation in either of these genes confers on a woman a 50%–85% lifetime risk of developing breast cancer, mostly early-onset [2] and often aggressive [3,5–11]. Although estimates indicate that, on average, 1.2/1000 women are carriers of a *BRCA* mutation, the incidence is increased in some subpopulations, including French Canadian women [12]. Among Jewish women of Ashkenazi descent, 2.0%–2.5% are carriers [13,14].

Currently, two prevention strategies can be offered to high-risk women:

- Primary prevention is achieved by risk-reduction surgical interventions (prophylactic mastectomy or salpingo-oophorectomy, or both) [15–17] or

chemoprevention [18]; however, bilateral mastectomy may not be an acceptable option for some women [19].
- Secondary prevention consists of intensified breast surveillance.

For high-risk women, the development of a highly accurate and acceptable surveillance strategy is essential. Mammography (MG) is traditionally offered—a strategy that has been shown to reduce mortality from breast cancer in women aged 50–74 years [20–22]. However, several observational studies have shown that the overall sensitivity of MG in women with inherited *BRCA* mutations is low, and the rate of interval cancers is as high as 48%–55% [11,23,24]. In addition, women diagnosed with breast cancer between the ages of 20 and 39 years—an age group with a proportionately high germline mutation rate—have lower survival ratios compared with older age groups [25]. Clearly, new surveillance strategies are required, and magnetic resonance imaging (MRI) is emerging as the most promising imaging modality for breast cancer detection.

Prospective nonrandomized controlled studies comparing MRI—either as an adjunct to MG, ultrasonography (US), and clinical breast examination (CBE) or to MG alone—showed consistent evidence that MRI significantly improved the sensitivity for breast cancer detection [26–32]. However, reported studies have been heterogeneous in terms of patient population (proportion of women with *BRCA* mutations), screening interval, number of diagnostic modalities, imaging techniques, and centre experience.

Given the evidence that women at high risk for breast cancer may benefit from newer imaging modalities, we introduced in a controlled fashion a multimodal screening program for high-risk women at the Centre Hospitalier de l'Université de Montréal (CHUM). We report here our experience with 184 women who underwent 3 annual screening rounds with MG, US, CBE, and MRI.

2. METHODS

This prospective nonrandomized comparative study is a joint effort of the radiology department and the hereditary cancer clinic at the CHUM and was approved by the institution's ethics review board.

2.1 Patient Selection

Between August 2003 and May 2007, we approached women who were either known carriers of *BRCA1/2* mutations or, if they had declined genetic testing, were known to have a family history of mutation with at least a 30% risk of being a carrier as calculated by BRCAPRO software [Berry D, Parmigiani G. Duke SPORE (Specialized Program of Research Excellence) in Breast Cancer. 1999] [33] for participation in this screening trial. Women were excluded if they had undergone prophylactic mastectomy without reconstruction, if they were or had been pregnant or lactating in the preceding 6 months, or if they were allergic to gadolinium or had other contraindications to MRI. Written informed consent was obtained from all participating women before they entered the study.

2.2 Study Protocol

The 184 study participants underwent 1–3 yearly screening rounds of CBE, US, MG and MRI, with surveillance at 6-month intervals with CBE and US. All evaluations were obtained within 1 month of each other, most within the same week. At each screening round, each imaging study was interpreted by a different radiologist blinded to results from the other imaging modalities. At the time of interpretation, radiologists were aware of the women's risk factors and earlier breast findings; when available, prior examinations of the same type were available to the radiologist for comparison. All images were categorized using the American College of Radiology Breast Imaging—Reporting and Data System (BI-RADS) categories and scored on a 5-point scale [34].

2.3 Imaging Studies

2.3.1 Mammography

Standard two-view per breast MG was performed (DMR analog unit: GE Healthcare, Waukesha, WI, U.S.A.); spot compression, magnification, and additional views were obtained as needed. Mammograms were reviewed by a single radiologist (JD, LL, IT) with at least 10 years of reading experience.

2.3.2 Ultrasonography

High-frequency probes (7.5–14 MHz linear transducer) were used to perform bilateral breast and axillary screening US [Logiq 700, Expert series (later Logiq 9): GE Healthcare]. Patients were directly scanned by one of three breast radiologists (JD, LL, IT).

2.3.3 Magnetic Resonance Imaging

Dynamic bilateral breast MRI was performed on a 1.5-T magnet (EchoSpeed: GE Healthcare) with a four-channel dedicated surface coil. Bilateral axial acquisitions were obtained. Acquisition protocol consisted of a T2-weighted sequence (TR 4850/TE 103.1 ms) and a three-dimensional gradient-echo T1-weighted dynamic sequence (TR 10/TE 4.2 ms) before and after bolus injection of gadoteridol 0.1 mmol/kg (ProHance: Bracco Diagnostics, Milan, Italy), with four repetitions after contrast. The MRI studies were interpreted by one of three breast radiologists (LL, IT, JD) with at least 3 years of experience in breast MRI at the onset of the study. Morphology and enhancement kinetics were both used for assessment.

2.4 Follow-Up and Final Diagnosis

When all imaging modalities revealed only benign findings (BI-RADS categories 1 and 2) and no anomaly was identified in the final surveillance round, cases were categorized as negative. In case of a probably benign finding (BI-RADS category 3), short-term follow-up at 6 months was obtained using the imaging modality that revealed the lesion, and the lesion was re-categorized according to imaging findings at the short-term follow-up. Whenever a modality revealed a suspicious finding (BI-RADS category 4 or 5), a biopsy was performed after integration of findings from all screening examinations.

Biopsies and targeted US were performed following standard clinical practice. Stereotactic biopsies were performed on a digital stereotactic table (Lorad DSM: Hologic, Marlborough, MA, U.S.A.) using an 11-gauge vacuum-assisted biopsy probe (Mammotome: Ethicon Endo-Surgery, Cincinnati, OH, U.S.A.). Ultrasound-guided biopsies were obtained using a 14-gauge core needle and an automated biopsy gun (Manan Medical Products, Wheeling, IL, U.S.A.). Magnetic resonance imaging–guided biopsies were performed using an interventional breast coil (MRI Devices, Orlando, FL, U.S.A.) and a 9-gauge vacuum-assisted biopsy system (ATEC: Suros Surgical Systems, Indianapolis, IN, U.S.A.). A localizing marker was deployed at each biopsy site, and a two-view mammogram was obtained to document marker deployment and final position.

When clinically significant disease was identified, treatment was provided according to prevailing clinical guidelines. Any malignant or atypical result prompted excision, as did any discordant result. Follow-up MRI at 6 months was recommended for all biopsied MRI-identified lesions that yielded a benign result at histopathologic analysis.

2.5 Data Collection and Statistical Analysis

Pertinent sociodemographic and medical variables were obtained from all participants. The results of imaging studies were recorded on a standardized case report form for each modality, reviewed by the study coordinator and entered into a computerized database. Categorization of imaging study results was performed:

- BI-RADS categories 1–3 were coded negative.
- BI-RADS categories 4–5 were coded positive.

At pathology, lesions were grouped into malignant [ductal carcinoma *in situ* (DCIS), invasive ductal or lobular carcinoma], premalignant (atypical ductal or lobular hyperplasia, lobular carcinoma *in situ*, phyllodes tumour), or benign (all other histopathologic findings) categories. Histologically-proven invasive breast cancer and DCIS were the pathologic outcomes of interest.

Sensitivity and specificity estimates were computed for each screening test. The "gold standard" used for these calculations was pathology-proven cancer. The Fisher exact test was used to compare the sensitivity of MRI with that of other modalities.

3. RESULTS

3.1 Study Population and Surveillance Rounds

Between August 2003 and May 2007, 184 women meeting the inclusion criteria were recruited and completed the first round of imaging. Table I summarizes relevant characteristics of the study participants. In the course of the study, 23 women (12.5%) left the study for various reasons [consent withdrawal ($n = 4$), repeated no-show to screening exams ($n = 5$), prophylactic mastectomy ($n = 4$), allergy to gadolinium ($n = 2$), lack of venous access for MRI ($n = 3$), concurrent illness ($n = 2$), death ($n = 3$)]. At study close, 121 women (66%) had completed the second screening round, and 82 (45%), all three rounds, for a total of 387 annual surveillance rounds (Table II).

3.2 Breast Cancers

In the first screening round, 3 cancers were detected among the 184 women who participated (detection rate: 1.6%). In the second round, 7 cancers were

TABLE I Description of the patient population

Variable	*Value*
Patients (*n*)	184
Age (years)	
Median	45
Range	21–75
Gene mutation [*n* (%)]	
BRCA1	75 (41)
BRCA2	68 (37)
BRCAPRO>30%[a]	41 (22)
Cancer history [*n* (%)]	
None	103 (56)
Breast cancer	71 (39)
Other cancer	10 (5)
Menopause [*n* (%)]	
Premenopausal	83 (45)
Natural menopause	27 (15)
Induced menopause	74 (40)

[a] Includes only women who declined genetic testing. BRCAPRO is software developed under the leadership of Berry D and Parmigiani G at the Duke SPORE (Specialized Program of Research Excellence) in Breast Cancer, 1999.

TABLE II Number of participants and tests by screening round

Round	*Participants*	*Participants [*n *(%)] undergoing*		
	*(*n*)*	*Mammography*	*Ultrasonography*	*Magnetic resonance imaging*
1	184	182 (99)	184 (100)	181 (98)
2	121	118 (98)	121 (100)	120 (99)
3	82	78 (94)	82 (100)	79 (96)
Total	387	378 (99)	387 (100)	380 (98)

identified among the 121 participants (detection rate: 5.8%), and in the third round, 2 cancers were found among the 82 participants (detection rate: 2.4%). The overall proportion of women diagnosed with cancer over the course of the study was 6.5% (12/184). Table III provides detailed information about the 12 diagnosed breast cancers [35].

Of the 12 cancers identified in the course of the study, 8 occurred in women previously treated for breast cancer. In 7 women, cancer had previously occurred in the contralateral breast, and of those 7 women, 3 were diagnosed with DCIS, effectively excluding the hypothesis of a metastasis. The other 4 women presented with contralateral breast cancer at 6, 8, 12, and 15 years after the initial cancer episode. In 1 woman, an ipsilateral cancer was detected 11 years after initial diagnosis. In 1 woman who had undergone a right mastectomy that was followed by a left breast cancer 14 years later, an *in situ* carcinoma was diagnosed 3 years later, during the course of the present study. After a mean follow-up of 2 years, 8 women with a cancer detected during the present study were alive and disease-free at the time of writing; 5 of the 8 opted for mastectomy at the time of surgery.

In 4 cases, cancer was diagnosed only on MRI, and in 1 case, only on MG. The 2 cancers that were missed by MRI were mammographically visible. One woman presented an enhancing lesion at MRI that was wrongly interpreted as representing postoperative changes at a prior surgical site (patient 3). Another presented with a small focus of DCIS identified mammographically as a cluster of microcalcifications (patient 10); a corresponding area of enhancement at MRI was interpreted as physiologic and asymmetric because of prior radiotherapy to the contralateral breast. No cancer was diagnosed exclusively by US. At US, identification of abnormal lymph nodes led to detection of 1 breast cancer, although the primary lesion was not detected using this modality (patient 8). No interval cancers were detected.

Neither breast density at MG nor parenchymal background enhancement at MRI contributed to false-negative interpretations. In 2 cases (patients 5 and 7), a diagnosis of breast cancer was made during the second screening round based on enlargement of MRI lesions incorrectly interpreted as probably benign during the first round.

3.3 Performance of Individual Screening Tests

Table IV lists summary sensitivity and specificity measures of the various screening modalities. At 83%, MRI had the highest sensitivity. All tests displayed high specificity (93.6%–95.9%). Because of the limited number of cancers, the sensitivities of MRI and MG (83% vs. 58%, $p = 0.37$) and of MRI and US (83% vs. 42%, $p = 0.09$) were not statistically different.

Table V compares the various imaging tests. Overall, the recall rate (additional tests required for evaluation of a potentially suspicious lesion) declined with successive screening rounds. The highest recall rate was associated with MRI. Among the 83 lesions for which additional work-up was recommended after MRI, second-look targeted US or additional MG views were performed for 51 lesions (61.4%) and a short-term follow-up repeat MRI evaluation was recommended for 28 (33.7%).

4. DISCUSSION

This prospective screening trial evaluated 184 women with a well-defined high risk for breast cancer (78% of the participants were documented *BRCA1/2* mutation carriers), identifying 12 cancers. The screening modality with the highest sensitivity (83%) was MRI, which revealed 4 cancers not diagnosed with MG or US. Combined use of MG and US yielded a sensitivity of 67%. Increased breast density was not associated with false-negative diagnoses at MG (data not shown). Twice-yearly US did not lead to the identification of any unsuspected cancers. Neither did CBE, which otherwise performed poorly, with a sensitivity of 17%. In combination, MRI and MG reached a negative predictive value of 100%.

Of 9 infiltrating tumours, 7 were staged as T1 at the time of diagnosis; an additional 3 tumours were found to be *in situ*. Most cancers were of moderate to high grade, although all DCIS lesions were high grade. Only 1 in 12 tumours revealed axillary node involvement, and none of the lesions overexpressed the human epidermal growth factor receptor 2 (HER2/*neu*). The yearly MG and MRI screening interval allowed for detection of breast cancer at stage 1 for 83% of patients, which should translate into an excellent prognosis [36]. For the 2 patients diagnosed with T2 and T3 tumours (patients 6 and 8), no evidence of disease was seen on MRI or MG 1 year earlier. Tumours presenting in young *BRCA*-positive women are associated with faster growth [37], a finding that must be taken into account when developing a screening strategy. No interval cancers were observed.

A progressive decrease in the recall rate was noted for all imaging modalities during the course of the study. The highest overall recall rate (21.8%) was associated with MRI; a steady decline was noted with

TABLE III Characteristics of women diagnosed with breast cancer, screening rounds, and tumour pathologic and prognostic factors

Patient	*Age (years)*	*Previous breast cancer*	*Genetic status*	*Breast density*[a]	*Screening rounds (n)*	*Clinical breast exam*	*Mammography*	*Ultrasonography*	*Magnetic resonance imaging*	*Tumour size (cm)*	*T stage*	*Histologic*		*Status*		
												Type	*Grade*	*Nodal*	*HER2/neu*	*ER*
Invasive																
1	51	Contralateral	Tested negative	3	1	–	+	+	+	1.5	T1c	IDC	1/3	–	–	+
2	54	None	*BRCA1*	2	1	+	+	+	+	1.2	T1c	IDC	2/3	–	–	–
3	53	Ipsilateral	*BRCA2*	3	1	–	+	+	–	1.6	T1c	IDC	2/3	NP	–	+
4	47	Contralateral	*BRCA1*	3	2	–	–	–	+	2.0	T1c	IDC	3/3	–	–	–
5	46	None	*BRCA2*	4	2	–	–	–	+	1.1	T1c	IDC	2/3	–	–	+
6	35	Contralateral	*BRCA1*	3	2	+	+	+	+	3.4	T2	IDC	3/3	–	–	–
7	41	None	*BRCA2*	2	2	–	+	–	+	0.6	T1a	IDC	1/3	–	–	+
8	42	None	*BRCA1*	3	2	–	–	+	+	6.0	T3	ILC	2/3	2/6	–	+
9	45	Contralateral	*BRCA1*	3	3	–	–	–	+	0.6	T1b	IDC	2/3	–	–	+
In situ																
10	28	Contralateral	*BRCA1*	4	2	–	+	–	–	1.1	Tis	DCIS	3/3	–	NP	–
11	48	Contralateral and ipsilateral	*BRCA2*	3	2	–	–	–	+	0.5	Tis	DCIS	3/3	NP	NP	+
12	44	Contralateral	*BRCA2*	4	3	–	+	+	+	0.4	Tis	DCIS	3/3	NP	NP	+

[a] 1 = predominantly fatty; 2 = scattered fibroglandular densities; 3 = heterogeneously dense; 4 = extremely dense.

HER2/*neu* = human epidermal growth factor receptor 2; ER = estrogen receptor; IDC = infiltrating ductal carcinoma; ILC = infiltrating lobular carcinoma; DCIS = ductal carcinoma in situ; NP = not performed.

TABLE IV Screening test sensitivity and specificity estimates

	Clinical breast exam (CBE)	*Mammography (MG)*	*Ultrasonography (US)*	*CBE + MG + US*	*Magnetic resonance imaging*
Cancers detected	2/12	7/12	5/12	8/12	10/12
Sensitivity (%)	17	58	42	67	83
Specificity (%)	95.9	95.4	93.8	90.3	93.6

TABLE V Additional procedures by screening test

Variable	*Mammography*	*Ultrasonography*	*Magnetic resonance imaging*
Exams (*n*)	378	387	380
Recall rate [*n* (%)]			
Overall	61/378 (16.1)	44/387 (11.4)	83/380 (21.8)
Round 1	32/182 (17.6)	26/184 (14.1)	49/181 (27.1)
Round 2	24/118 (20.3)	12/121 (9.9)	24/120 (20.0)
Round 3	5/78 (6.4)	6/82 (7.3)	10/79 (12.7)
Biopsy rate			
Overall	7/61 (11.5)	21/44 (47.7)	17/83 (20.5)
Positive[a]	5/7 (71.4)	6/21 (28.6)	7/17 (41.2)

[a] A biopsy was considered positive when it revealed malignant (invasive ductal or lobular carcinoma, or ductal carcinoma *in situ*) or premalignant (atypical ductal hyperplasia or lobular carcinoma *in situ*) findings.

successive rounds, from 27.1% at the first round of imaging to 12.7% at the third. This decline underlines the importance of earlier examinations for optimal interpretation. In addition, an experience factor is likely present: retrospective analysis of erroneous interpretations revealed that some MRI lesions were visible but incorrectly labelled as benign on earlier scans (patients 3, 5, 7). Limited access to MRI-guided biopsy in the initial phase of the trial may also have contributed to a tendency to "downgrade" the potential severity of MRI-detected lesions. Notwithstanding these factors, Causer *et al.* [38] reported retrospective visualization for 6 of 7 prospectively missed cancers at MRI.

Our findings compare favourably with those reported in similar trials (Table VI) [26–29,31,32,39]. The sensitivity reported here for MRI is in the lower range, and possible reasons have already been presented. On the other hand, the sensitivities of MG and US both fall among the higher reported estimates. This higher sensitivity comes with a recall rate of 16.1% for MG, above the recommended <10% for screening evaluations; this target was achieved in the third round of screening (6.4%), with the benefit of earlier examinations available for comparison.

The relatively small number of observed cancers makes performance estimates of the imaging tests less precise, and indeed, the differences in the detection rates of the imaging modalities did not reach statistical significance. Our trial was terminated early, after publication of guidelines from the American Cancer Society recommending screening MRI as an adjunct to MG in high-risk women [40].

5. CONCLUSIONS AND FUTURE DIRECTIONS

Yearly screening with MRI is now recommended in the United States for women with >20% to 25% lifetime risk of breast cancer [40]. In Canada, the most recent recommendations on this topic were published in 2007 by the National Hereditary Cancer Task Force [41], whose panel recommended annual MG, complemented by MRI where available, and added that whenever possible, imaging should be delivered by an experienced team of radiologists with expertise in MRI, MG, and US.

The present study provides additional evidence of the increased potential for early breast cancer detection with annual screening MRI. It also underscores the importance of having a dedicated team of professionals to care for these at-risk women. These findings should, we suggest, translate into increased availability of breast MRI across Canada, paralleled by the development of risk-assessment centres to evaluate women at increased risk of breast cancer and to counsel them about optimal surveillance protocols.

TABLE VI Summary of findings from breast cancer screening trials in high-risk women

Reference	*Country*	*Partici-pants* (n)	*Rounds*	*Total cancers*	*Cancers/ round (%)*	*Cancers/ partici-pants (%)*	*Mammography*		*Ultrasonography*		*Magnetic resonance imaging*	
							Snsv. (%)	*Spec. (%)*	*Snsv. (%)*	*Spec. (%)*	*Snsv. (%)*	*Spec. (%)*
Kriege *et al.*, 2004 [27]	Netherlands	1909	1909	44	2.3	2.3	33.3	95	—	—	79.5	89.8
Warner *et al.*, 2004 [29]	Canada	236	457	22	4.8	9.3	36	99.8	33	96	77	95.4
Kuhl *et al.*, 2005 [26]	Germany	529	1542	43	2.8	8.1	33	96.8	40	90.5	91	97.2
Leach *et al.*, 2005 (MARIBS) [28]	United Kingdom	649	1881	35	1.9	5.4	40	93	—	—	77	81
Lehman *et al.*, 2007 [32]	United States	171	171	6	3.5	3.5	33	97.7	17	97.7	100	91.8
Riedl *et al.*, 2007 [39]	Austria	327	672	28	4.2	8.6	50	98	42.9	98	85.7	92
Sardanelli *et al.*, 2007 [31]	Italy	278	377	18	4.8	6.5	59	98.8	65	97.8	94	96.7
Current study	Canada	184	387	12	3.1	6.5	58	95.4	42	93.8	83	93.6

Snsv. = sensitivity; Spec. = specificity.

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