

## Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

## **eAppendix. Characteristics of the Study Cohort**

### ***Clinicopathologic Features and Treatment Data of Initial Breast Cancers***

The median age at the first imaging examination was 44 years (range, 22-52 years) (Table 1). Initial tumor stages of the study participants varied; 55% of the participants had stage 0 or I tumors, and 45% of them had stage II or III tumors. Chemotherapy was administered to 67% (507/754) of the participating women. Of the 557 women with HR-positive tumors, adjuvant endocrine therapy was administered to 545 women (98%). Neoadjuvant or adjuvant trastuzumab was administered to 77% (70/91) of the women with HER2-positive cancers.

### ***Characteristics of Women with Second Breast Cancers***

By univariate analysis, the following variables were significantly associated with women with a second breast cancer: pre- or peri-menopausal status (4% [12/341] vs 1% [5/413] ( $P = .03$ ), ER-negative tumors (4% [9/206] vs 1% [8/545]) ( $P = .03$ ), PR-negative tumors (4% [11/272] vs 1% [6/480]) ( $P = .01$ ), HER2-positive tumors (7% [6/91] vs 2% [11/652]) ( $P = .01$ ), resection margin  $\leq 2$  mm status (3% [12/361] vs 1% [4/391]) ( $P = .03$ ), and no endocrine treatment (4% [9/206] vs 1% [8/545]) ( $P = .03$ ) (eTable 4).

By multivariate analysis including the menopausal status, ER-negativity, resection margin  $\leq 2$  mm status, and HER2-positive tumors, HER2-positive tumors (odds ratio, 4.1; 95% CI, 1.5 - 11.4;  $P = .007$ , c-statistics = .62) remained as an independent variable. All second breast cancers in women with HER2-positive tumors were found in the ipsilateral breast.

**eTable 1.** Summary of Cancer Detection and Tumor Characteristics of 754 Participants

	Detected Cancer					Total
	Mammography Only	MRI Only	Both Mammography and MRI	Both Ultrasound and MRI	Mammography and Ultrasound and MRI	
No. of participants	754	754	754	754	754	NA
No. of screens	2065	2065	2065	2065	2065	NA
No. of cancers	2	3	1	5	6	17
Invasive cancers	1 (50)	2 (67)	0	3 (60)	4 (67)	10 (59)
DCIS	1 (50)	1 (33)	1 (100)	2 (40)	2 (33)	7 (41)
Size of invasive tumor, median (range), mm	8	3 (1-5)	NA	11 (10-75)	20 (8-25)	10.5 (1-75)
Node positive, No. (%)	0	0	0	0	1 (25)	1 (10)
Cancer type, grade, and receptor status, No. (%)						
IDC grade	1 (50)	2 (67)	0	3 (60)	4 (67)	10 (59)
High	0	0	0	3 (60)	3 (50)	6 (35)
Intermediate	1 (50)	1 (33)	0	0	1 (17)	3 (18)
Low	0	1 (33)	0	0	0	1 (6)
ILC	0	0	0	0	0	0
DCIS, nuclear grade	1 (50)	1 (33)	1 (100)	2 (40)	2 (33)	7 (41)
High	0	0	1 (100)	1 (20)	2 (33)	4 (24)
Intermediate	1 (50)	1 (33)	0	0	0	2 (12)
Low	0	0	0	1 (20)	0	1 (6)
Hormone receptor status						
Positive	2 (100)	3 (100)	0	1 (20)	3 (50)	9 (53)
Negative	0	0	1 (100)	4 (80)	3 (50)	8 (47)
HER2 status						
Positive	0	2 (67)	1 (100)	2 (40)	2 (33)	7 (41)
Negative	2 (100)	1 (33)	0	3 (60)	4 (67)	10 (59)

Abbreviations: MRI, magnetic resonance imaging; DCIS, ductal carcinoma in situ; NA, not applicable; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HER2, human epidermal growth factor receptor 2

**eTable 2.** Characteristics of Detected Cancers in Women Treated with Breast Conservation Therapy

Patient No.	Age (years)	BRCA mutation	Stage and Histology of Initial Cancer				Chemotherapy/Endocrine/Anti-HER2 Treatment	Preoperative MRI	Round (No.)	Time from the initial surgery to second breast cancer detection (Months)	MG Density	Laterality of Detected Cancer	Final Assessment Category at Breast Imaging and Reporting Data System			Stage of Detected Cancer			Histology of Detected Cancer				
			Stage	Histologic Grade	Hormone receptor Status*	HER2 Status†							M	U	M	T (Size of Invasive Cancer)	N(Number)	Stage	Type	Nuclear Grade	Histologic Grade	Hormone receptor Status	HER2 Status
1	46	Not done	IIB	Intermediate	+	-	+/+/-	Performed	1	22	3	Contralateral	2	2	3	0	0	0	DCIS	Intermediate	NA	+	+
2	48	Not done	IA	High	-	+	-/-	Performed	1	20	3	Ipsilateral	2	3	4A	0	0	0	DCIS	Low	NA	+	-
3	33	Not done	IA	Intermediate	+	-	+/+/-	Performed	1	13	4	Ipsilateral	2	2	4A	1a (5 mm)	0	IA	IDC	Intermediate	Intermediate	+	-
4	29	Not done	IA	High	+	+	+/+	Performed	1	6	4	Ipsilateral	4B	2	2	1b (8 mm)	0	IA	IDC	Intermediate	Intermediate	+	-
5	44	BRCA 2	IA	High	-	-	-/-	Performed	1	6	4	Contralateral	4A	2	2	0	0	0	DCIS	Intermediate	NA	+	-
6	43	Not done	IIA	High	-	-	+/-	Not	1	6	2	Contralateral	4A	4C	5	1b (8 mm)	0	IA	IDC	High	High	-	-
7	42	Not done	IIIA	High	-	-	+/-	Performed	1	13	4	Ipsilateral	1	4B	5	3 (75 mm)	0	IIB	IDC	High	High	-	-
8	39	BRCA 1	IIA	unknown	-	-	+/-	Performed	1	11	3	Contralateral	5	5	5	2 (25 mm)	0	IIA	IDC	High	High	-	-
9	39	Not done	IA	Intermediate	-	+	-/+	Not	1	27	3	Ipsilateral	4A	1	3	0	0	0	DCIS	High	NA	-	+
10	47	Not done	IIIB	High	+	+	+/+	Not	1	9	3	Ipsilateral	4C	5	5	2 (25 mm)	0	IIA	IDC	High	High	-	+
11	41	Not done	IIA	Low	-	-	+/-	Performed	1	25	3	Ipsilateral	1	4A	5	1c (11 mm)	0	IA	IDC	High	High	-	-
12	49	Not done	0	Unknown	+	+	+/-	Performed	1	30	4	Ipsilateral	3	3	4A	0	0	0	DCIS	High	NA	-	+
13	50	Not done	IIA	Intermediate	+	-	+/-	Performed	2	13	2	Ipsilateral	2	4A	4B	1b (10 mm)	0	IA	IDC	High	High	+	-
14	43	Not done	IA	High	-	+	-/-	Performed	2	6	4	Ipsilateral	1	3	4C	0	0	0	DCIS	High	NA	+	+
15	44	Not done	IA	Intermediate	+	-	+/-	Performed	2	29	3	Contralateral	1	2	4A	1mic (≤ 1 mm)	0	IA	IDC	Low	Low	+	+
16	50	Not done	IA	Low	+	-	+/-	Performed	3	26	3	Contralateral	4A	4B	3	0	0	0	DCIS	High	NA	-	+
17	52	Not done	IIA	Low	-	-	+/-	Performed	3	41	4	Contralateral	4B	4B	4B	1c (15 mm)	1	IIA	IDC	Intermediate	Intermediate	-	+

Abbreviations: HER2, human epidermal growth factor receptor 2; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; M, metastasis; MG, mammography; MRI, magnetic resonance imaging; N, node status; NA, not applicable

\* Hormonal receptor–positive status was ER positive or PR positive. It was defined as the presence of 10% or more positively stained nuclei at  $\times 10$  magnification

† Intensity of ERBB2 staining was scored as 0, 1+, 2+, or 3+. The 3+ score were defined as HER2 positive, and the 0 or 1+ score were defined as negative. For tumors with 2+ score, *HER2* gene copies to the centromeric region of the chromosome 17 ratios of 2.2 or more on fluorescence in situ hybridization was interpreted as amplified

**eTable 3.** Screening Performances for Invasive Cancers in 754 Participants Screened Over 3 Years by Mammography, Ultrasound, and MRI

	Mammography		Ultrasound		MRI		Mammography Plus Ultrasound		Mammography v Mammography Plus Ultrasound	Mammography Plus MRI		Mammography v Mammography Plus MRI
	No./Total of Women	Estimate (95% CI)	No./Total of Women	Estimate (95% CI)	No./Total of Women	Estimate (95% CI)	No./Total of Women	Estimate (95% CI)	p-value*	No./Total of Women	Estimate (95% CI)	p-value*
Yield, per 1000	5/2065	2.4 (0.3, 4.6)	7/2065	3.4 (0.9, 5.9)	9/2065	4.4 (1.5, 7.2)	8/2065	3.9 (1.2, 6.6)	.12	10/2065	4.8 (1.8, 7.9)	.03
AUC		0.73 (0.53, 0.93)		0.92 (0.83, 1.00)		0.97 (0.91, 1.00)		0.92 (0.81, 1.00)	.18		1.0 (0.95, 1.00)	.02
Sensitivity, % <sup>†</sup>	5/10	50 (24, 76)	7/10	70 (40, 89)	9/10	90 (60, 98)	8/10	80 (49, 94)	.16 <sup>#</sup>	10/10	100 (72,100)	.07 <sup>#</sup>
Specificity, %	1969/2055	96 (95, 97)	1853/2055	90 (89, 92)	1843/2055	90 (88, 91)	1795/2055	87 (86, 89)	<.001	1781/2055	87 (85, 88)	<.001
PPV1, % <sup>‡</sup>	5/91	5.5 (0.7, 10.3)	7/209	3.3 (0.9, 5.8)	9/221	4.1 (1.5, 6.7)	8/268	3.0 (0.9, 5.0)	.09	10/284	3.5 (1.4, 5.7)	.41
PPV3, % <sup>‡§</sup>	5/11	45 (21, 72)	7/23	30 (16, 51)	9/51	18 (10, 30)	8/29	28 (15, 46)	.21	10/56	18 (10, 30)	.02

Abbreviations: AUC, area under the curve, PPV, positive predictive value.

\* p-value was adjusted using Sidak method for each screening outcome.

<sup>†</sup> 95% Confidence interval was estimated from Wilson Score method.

<sup>#</sup> p-value by McNemar test

<sup>‡</sup> Defined as the malignancy rate of women with positive test including assessment of BI-RADS 3, 4A, 4B, 4C, or 5.

<sup>§</sup> Defined as the malignancy rate of women who underwent biopsy due to lesions classified as BI-RADS 3, 4A, 4B, 4C, or 5

**eTable 4.** Characteristics of Women With Second Breast Cancers Versus Those Without Cancers

Characteristics	Women with second breast cancer, No. (%) (n = 17)	Women without second breast cancer, No. (%) (n = 737)	<i>P</i>
Age at initial cancer diagnosis (years)			
< 40	5 (2)	237 (98)	>.99
≥ 40	12 (2)	500 (98)	
Menopausal status			
Pre or peri-menopause	12 (4)	329 (96)	.03
Post-menopause	5 (1)	408 (99)	
BRCA 1 or 2 mutation			
Positive	2 (11.8)	15 (88.2)	.61
Negative	3 (6.8)	41 (93.2)	
Unknown	12	681	
Family history of breast cancer			
Absence	11 (2)	596 (98)	>.99
Presence	0 (0)	42 (100)	
Unknown	6	99	
Initial mammographic breast density			
Fatty, scattered, and heterogeneously dense	10 (2)	549 (98)	.12
Extremely dense	7 (4)	188 (96)	
Characteristics of initial cancer			
Pathologic stage			
Stage 0 or I	9 (2)	406 (98)	.86
Stage II or III	8 (2)	331 (98)	
Histologic type			
DCIS	1 (1)	71 (99)	>.99
Invasive cancer	16 (2)	664 (98)	
Unknown	0	2	
Nuclear grade			
Low to intermediate	6 (2)	351 (98)	.29
High	8 (3)	263 (97)	
Unknown	3	123	
Histologic grade			
Low to intermediate	8 (2)	414 (98)	.43

High	7 (3)	240 (97)	
Unknown	2	83	
ER status*			
Negative	9 (4)	197 (96)	.03
Positive	8 (1)	537 (99)	
Unknown	0	3	
PR status*			.01
Negative	11 (4)	261 (96)	
Positive	6 (1)	474 (99)	
Unknown	0	2	
HER2 status†			.01
Negative	11 (2)	641 (98)	
Positive	6 (7)	85 (93)	
Unknown	0	11	
Resection margin status			.03
≤ 2 mm	12 (3)	349 (97)	
> 2 mm	4 (1)	387 (99)	
Unknown	1	1	
Lymphovascular invasion			>.99
Absence	13 (2)	538 (98)	
Presence	4 (2)	183 (98)	
Unknown	0	16	
Chemotherapy			
Not performed	8 (3)	239 (97)	.20
Performed	9 (2)	498 (98)	
Endocrine treatment			.03
Not performed	9 (4)	197 (96)	
Performed	8 (1)	537 (99)	
Unknown	0	3	
Preoperative MRI			.15
Not performed	3 (5)	58 (95)	
Performed	14 (2)	679 (98)	

Abbreviations: DCIS, ductal carcinoma in situ, ER, estrogen receptor, PR, progesterone receptor, HER2, human epidermal growth factor receptor 2

\* ER and PR positivity were defined as the presence of 10% or more positively stained nuclei at 10X magnification

†HER-2 positivity was defined as either HER2 gene amplification (fluorescent in situ hybridization) or were scored as 3+ on immunohistochemistry staging for c-erbB-2 which was scored as 0, 1+, 2+, or 3+.