Letters

RESEARCH LETTER

Association of Mammographic Density With Risk of Ipsilateral Breast Tumor Recurrence and Contralateral Breast Cancer

Mammographic density (MD), which is the reflection of the proportion of fibroglandular tissue in the breast, is a well-known risk factor for breast cancer development.[1] Recent studies have suggested that MD is associated with an increased risk of ipsilateral breast tumor recurrence (IBTR) and contralateral breast cancer development.[2] However, there are conflicting data regarding the association of MD with IBTR and contralateral breast cancer. To address this issue, we investigated the association of MD with IBTR and contralateral breast cancer in a large cohort of patients treated at a single institution to minimize the heterogeneity of MD assessment and breast cancer treatments.

Supplemental content

Methods | In this retrospective cohort study, we reviewed the MD data and clinicopathologic characteristics of 9011 female patients with breast cancer who underwent unilateral breast-conserving surgeries between January 1, 2000, and December 31, 2018, at Seoul National University Hospital, Seoul, South Korea. Information on race and ethnicity was not collected because all patients had Korean nationality, and Korean individuals have high rates of ethnic homogeneity. Excluded patients were those with synchronous or metachronous cancer in other organs, bilateral breast cancer, male breast cancer, and recurrent breast cancer as well as those without an MD assessment within 1 year of cancer diagnosis. This study was approved by the hospital's institutional review board, and informed consent was waived because of the retrospective nature of the study.

The baseline MD for each patient was measured using the digital mammography image obtained within 1 year since the time of diagnosis. Patients were classified as having low MD (ie, grade A or B) or high MD (ie, grade C or D) according to the fifth edition of the Breast Imaging Reporting and Data System recommendation from the American College of Radiology.[3] Detailed information on the definition of events and measurement of MD is described in the eMethods and eFigure in the Supplement. Data were analyzed from July 10 to July 14, 2021, using SPSS, version 25.0 (IBM Corporation). The log-rank test was used to compare survival curves derived from the Kaplan-Meier method. We used the Cox proportional hazards regression model to adjust for the variables affecting the recurrence rate and to estimate the hazard ratio (HR). The threshold for statistical significance was 2-sided $P < .05$.

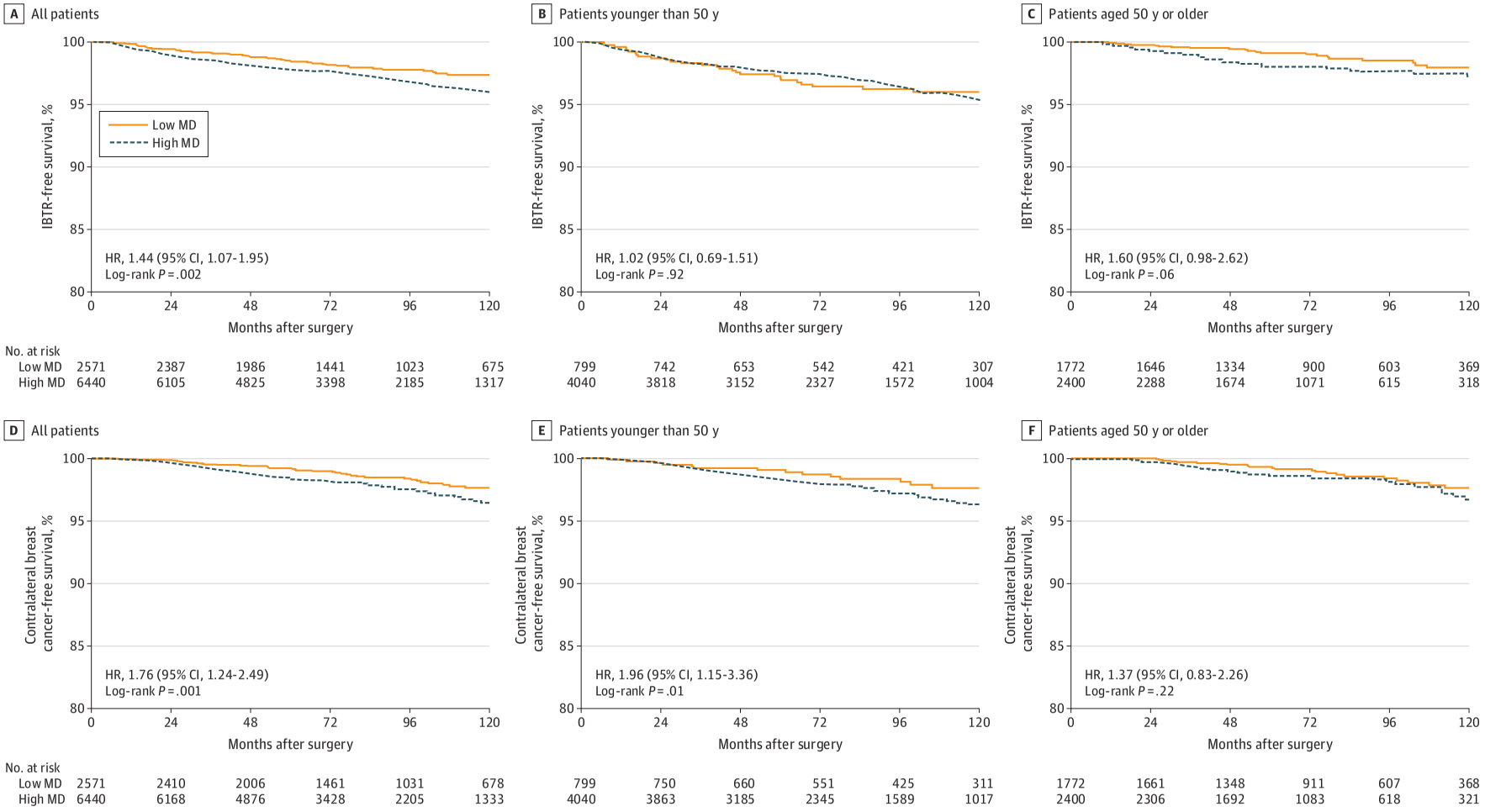
Results | Among the 9011 female patients included in the analysis, more than 95.3% (8584) had T1 or T2 tumors, and 63.5% (5720) had negative lymph nodes. The proportions of hormone receptor–positive and ERBB2 (formerly HER2)-positive tumors were 73.5% and 17.2%, respectively. Whole-breast irradiation was administered in 8333 patients (92.5%). The median (range) age of the patients was 49 (19-88) years, which was similar to that of a Korean nationwide report.[4] Among the 9011 patients, 6440 (71.5%) were classified as having high MD according to their baseline MD measurement. The median (range) follow-up duration was 75.2 (0.4-256.2) months.

The cumulative incidence of IBTR in this patient cohort was 2.1% at 10 years. As shown in **Figure**, A, the high MD group had a higher incidence of IBTR with a HR of 1.44 (95% CI, 1.07-1.95). Age at the time of operation was shown to be a significant risk factor for IBTR (HR, 0.95; 95% CI, 0.94-0.97; $P < .001$), and younger age was also associated with the likelihood of having high MD (HR, 1.05; 95% CI, 1.05-1.06; $P < .001$). To adjust for the association of age with IBTR, we stratified the patients according to their age at operation. When the patients were stratified by their median age, MD was not associated with the development of IBTR (Figure, B and C). Cox proportional hazards regression analysis also revealed that the degree of MD was not an independent risk factor for IBTR development (**Table**).

For contralateral breast cancer, the cumulative rate at 5 years was 1.4%. Similar to the IBTR, high MD and young age were risk factors for developing contralateral breast cancer (Figure, D; Table). However, the risk of contralateral breast cancer among patients with high MD was increased in those who were younger than 50 years of age (Figure, E and F). Furthermore, unlike IBTR, the degree of MD remained an independent risk factor for contralateral breast cancer after adjusting for other risk factors (Table).

Discussion | To our knowledge, this is the largest study investigating the association of MD with IBTR and contralateral breast cancer in patients who underwent breast-conserving surgery. The data show an association between high MD and the risk of contralateral breast cancer, especially in young patients with breast cancer. In contrast, the risk of IBTR was not affected by the degree of MD. These findings suggest that the degree of MD is not a relevant factor to consider when deciding the types of local treatment in patients with early breast cancer. Rather, the degree of MD can be used for the personalized surveillance approach because high MD is associated with an increased risk of contralateral breast cancer. The limitations of this study include its retrospective nature and the lack of patients of different races and ethnicities.

Figure. Kaplan-Meier Survival Curves According to Mammographic Density



The Kaplan-Meier curves for all patients show ipsilateral breast tumor recurrence–free survival (A-C) and contralateral breast cancer–free survival (D-F). After stratification according to median age at operation, the survival curves for different age groups are shown. The *P* value was calculated by using the log-rank test, and hazard ratio (HR) was calculated by using the Cox proportional hazards regression test. IBTR indicates ipsilateral breast tumor recurrence; MD, mammographic density.

Table. Univariate and Multivariate Analyses for IBTR- and Contralateral Breast Cancer–Free Survival

Characteristics	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
IBTR				
Age at cancer diagnosis, y	0.95 (0.94-0.97)	<.001	0.97 (0.95-0.98)	<.001
BMI				
<25.0	1 [Reference]	.06	1 [Reference]	.69
≥25.0	0.74 (0.54-1.02)		0.93 (0.66-1.32)	
T stage[b]				
T1	1 [Reference]	<.001	1 [Reference]	.21
T2	1.27 (0.98-1.66)		1.06 (0.76-1.48)	
T3-4	2.62 (1.66-4.14)		1.73 (0.93-3.22)	
N stage[b]				
N0	1 [Reference]	.65	NA	NA
N1-3	1.06 (0.82-1.38)			
Histologic grade				
I-II	1 [Reference]	<.001	1 [Reference]	.23
III	1.97 (1.51-2.58)		1.24 (0.87-1.76)	
LVI				
Present	1 [Reference]	<.001	1 [Reference]	<.001
Absent	0.48 (0.37-0.63)		0.55 (0.41-0.74)	
Resection margin				
Clear	1 [Reference]	<.001	1 [Reference]	<.001
Involved or closed	2.34 (1.65-3.40)		2.58 (1.74-3.80)	
Hormone receptor status				
Positive	1 [Reference]	<.001	1 [Reference]	.59
Negative	2.22 (1.72-2.86)		1.32 (0.49-3.55)	
ERBB2 receptor status				
Positive	1 [Reference]	<.001	1 [Reference]	.32
Negative	0.53 (0.40-0.70)		0.84 (0.60-1.19)	
Ki-67 index				
<10%	1 [Reference]	<.001	1 [Reference]	.11
≥10%	1.96 (1.51-2.54)		1.31 (0.94-1.81)	
Neoadjuvant chemotherapy				
Administered	1 [Reference]	.03	1 [Reference]	.68
Not administered	0.70 (0.51-0.96)		0.92 (0.60-1.39)	
Adjuvant radiotherapy				
Administered	1 [Reference]	<.001	1 [Reference]	.001
Not administered	2.32 (1.57-3.41)		2.17 (1.39-3.40)	
Adjuvant chemotherapy				
Administered	1 [Reference]	.87	NA	NA
Not administered	0.98 (0.76-1.27)			
Adjuvant endocrine therapy				
Administered	1 [Reference]	<.001	1 [Reference]	.46
Not administered	2.28 (1.77-2.93)		1.44 (0.54-3.86)	
MD				
Low	1 [Reference]	.02	1 [Reference]	.52
High	1.44 (1.07-1.95)		1.13 (0.78-1.62)	
Contralateral Breast Cancer				
Age at cancer diagnosis, y	0.97 (0.96-0.99)	.01	0.98 (0.96-1.00)	.02
BMI				
<25.0	1 [Reference]	.74	NA	NA
≥25.0	0.95 (0.69-1.30)			

(continued)

Table. Univariate and Multivariate Analyses for IBTR- and Contralateral Breast Cancer–Free Survival (continued)

Characteristics	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
T stage[b]				
T1	1 [Reference]	.87	NA	NA
T2	1.08 (0.81-1.43)			
T3-4	1.02 (0.50-2.08)			
N stage[b]				
N0	1 [Reference]	.30	NA	NA
N1-3	0.85 (0.63-1.15)			
Histologic grade				
I-II	1 [Reference]	<.01	1 [Reference]	.59
III	1.51 (1.13-2.03)		0.91 (0.63-1.30)	
LVI				
Present	1 [Reference]	.43	NA	NA
Absent	1.14 (0.82-1.59)			
Resection margin				
Clear	1 [Reference]	.17	NA	NA
Involved or closed	1.40 (0.86-2.27)			
Hormone receptor status				
Positive	1 [Reference]	<.001	1 [Reference]	.54
Negative	2.27 (1.72-3.00)		1.37 (0.50-3.74)	
ERBB2 receptor status				
Positive	1 [Reference]	.22	NA	NA
Negative	0.81 (0.57-1.14)			
Ki-67 index				
<10%	1 [Reference]	<.001	1 [Reference]	.20
≥10%	1.71 (1.28-2.28)		1.26 (0.88-1.79)	
Neoadjuvant chemotherapy				
Administered	1 [Reference]	.04	1 [Reference]	.57
Not administered	0.69 (0.49-0.99)		0.89 (0.60-1.33)	
Adjuvant radiotherapy				
Administered	1 [Reference]	.36	NA	NA
Not administered	0.72 (0.35-1.46)			
Adjuvant chemotherapy				
Administered	1 [Reference]	.56	NA	NA
Not administered	0.92 (0.69-1.22)			
Adjuvant endocrine therapy				
Administered	1 [Reference]	<.001	1 [Reference]	.30
Not administered	2.27 (1.72-3.00)		1.69 (0.63-4.54)	
MD				
Low	1 [Reference]	.001	1 [Reference]	.04
High	1.76 (1.24-2.49)		1.50 (1.03-2.19)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio; IBTR, ipsilateral breast tumor recurrence; LVI, lymphovascular invasion; MD, mammographic density; NA, not applicable.

[a] Variables of $P < .10$ in their univariate analysis were calculated in a Cox regression model.

[b] Stratified according to the American Joint Committee on Cancer seventh TNM stage.

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Accepted for Publication: September 26, 2021.

Published Online: November 24, 2021. doi:10.1001/jamasurg.2021.5859

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Author Contributions: Dr Cheun had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Statistical analysis: Cheun, Lee.
Obtained funding: Moon.
Administrative, technical, or material support: Kim, Lee, Moon.
Supervision: Kim, Han, Moon.

Conflict of Interest Disclosures: Dr Lee reported serving as a current board member for and holding stock and ownership interests in DCGen. Dr Moon reported serving as a current board member for and holding stock in Bertis Inc. No other disclosures were reported.

Funding/Support: This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (grant HA15C0011, Moon). This work was also supported by a National Research Foundation of Korea grant funded by the Korean government (grant NRF-2019R1A2C2005277, Moon).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: The authors thank Su Hyun Lee, MD, PhD, Department of Radiology, Seoul National University College of Medicine, Seoul, South Korea, for critical reading and expert advice during the manuscript preparation. She did not receive compensation beyond her salary for this contribution.

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