Mammographic Predictors of the Presence and Size of Invasive Carcinomas Associated With Malignant Microcalcification Lesions Without a Mass

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OBJECTIVE. Our objective was to determine the degree with which mammographic features predict the presence and size of invasive carcinomas associated with malignant mammographic microcalcification lesions without a mass.

MATERIALS AND METHODS. Mammographic features were correlated with pathologic features in 304 consecutive breast carcinomas manifested by mammographic calcifications only in a prospective evaluation.

RESULTS. Mammographic calcifications associated with breast carcinoma had the final pathologic diagnoses of pure ductal carcinoma in situ (DCIS) in 65% of patients, DCIS with a focus of invasion in 32%, and invasive carcinoma only in 4%. Invasive foci were more likely associated with mammographic calcification size of 11 mm and greater (40%, 77/194) compared with 1–10 mm (26%, 29/110; $p = 0.019$). Invasive foci were also more likely associated with linear calcifications (44%, 55/126) compared with granular calcifications (29%, 51/178; $p = 0.007$). The frequency of invasion did not increase with calcification extents greater than 10 mm. The frequency of invasion ranged from 22% for less than or equal to 5-mm granular calcifications to 45% for linear calcifications of 11 mm and greater. Only 11% of cancers characterized by fine granular calcifications were associated with invasion as compared with 32% of those with coarse and mixed granular calcifications ($p = 0.002$).

CONCLUSION. Mammographic calcification features of malignant lesions cannot predict the absence of invasion with greater than 90% predictive value or predict the presence of invasion with greater than 45% predictive value. Increased extent of calcifications greater than 10 mm was not associated with greater likelihood of invasion.

Mammographic lesions manifested by microcalcifications constitute approximately half of the clinically occult breast carcinomas detected on mammography [1, 2]. Mammographic calcifications associated with malignancy are usually found within ducts and lobules containing ductal carcinoma in situ (DCIS). In general, 26–38% of biopsy-proven malignant microcalcification lesions without a mass also contain an associated focus or foci of invasive carcinoma [2, 3].

Because the presence of an associated invasive carcinoma cannot be excluded without surgical removal and pathologic evaluation of the entire DCIS lesion, knowledge of the risk and the size of invasive carcinomas found in DCIS microcalcifications would be helpful in patient counseling and possibly clinical management, such as selection of patients for axillary lymph node sampling, including sentinel node biopsy techniques.

To our knowledge, little information in the literature describes the associations between mammographic features of malignant microcalcification lesions and the presence and size of an associated invasive carcinoma component. This analysis was undertaken to determine the degree with which the features of patient age, mammographic calcification extent and appearance, and mammographic background parenchymal density predict the presence or absence of associated invasion. The pathologic size of invasive carcinomas associated with malignant mammographic calcification lesions was also determined.

Materials and Methods

This study analyzed all 304 women with breast carcinomas presenting as clinically occult mammographic calcifications without a soft-tissue abnormality who were seen in a mammography center and a multidisciplinary breast clinic in a cancer insti-

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tute between July 1, 1991, and July 1, 2001. The patients represented a mixed primary and tertiary referral population. These data are from a prospective mammography–pathology correlation database in which mammographic features were recorded by cancer institute mammographers before biopsies or pathology reviews. High-resolution film-screen mammography of microcalcifications included orthogonal magnification projections, usually craniocaudad and mediolateral projections. All lesions ultimately underwent surgical excision.

The following data were retrieved from the mammography–pathology correlation database: the age of each patient at the time of diagnosis and the greatest dimension of the suspicious mammographic calcifications based on the prospective analysis of the standard and magnification mammography projections. Mammographic calcification extent was categorized as 1–5 mm, 6–10 mm, 11–20 mm, 21–40 mm, and greater than 40–160 mm. The mammographic appearance or type of microcalcifications was categorized in a manner similar to that of prior mammography–pathology correlation studies of microcalcifications in the literature [3–6]: predominately granular, fine or coarse nonlinear particles of varying size and shape; linear, linear branching or casting calcifications. For the purposes of this analysis, subgroups of granular-type mammographic calcifications used were the following: fine, fine powderlike granular calcifications only; coarse, granular calcifications; mixed, combinations of fine and coarse granular calcifications.

The surrounding mammographic background density was the background mammographic parenchymal density in the region of the mammographic microcalcifications considered to be normal breast parenchymal density by the mammographer. For this analysis, the mammographic surrounding parenchymal density was categorized as dense, greater than 90% dense tissue; fatty, greater than 90% fatty or heterogeneous; any other combination of fatty and dense parenchyma. Pathologic data was obtained from pathology reports of all biopsy and surgical specimens of each malignant lesion by pathology staff of the cancer institute at the time of initial staging.

Whole-specimen radiography was performed during the surgery to confirm and assess the adequacy of excision of the clinically occult mammographic calcifications. The surgical specimens were oriented and stained for histologic margin assessment. For the excised specimens containing mammographic calcifications and for the mastectomy specimens containing extensive mammographic calcifications, sliced-specimen radiography of 4- to 5-mm-thick consecutive slices was performed to precisely identify the location and the distribution of the mammographic calcifications for pathologic evaluation. This tissue was embedded and evaluated in its entirety. The whole- and sliced-specimen radiographs and mammographic–pathologic correlation of calcification have been recommended by several consensus groups and have been described and illustrated previously [3, 7–10]. The adequacy of the excision of the mammographically suspicious calcifications was ultimately confirmed by postexcision mammography including magnification projections of the excision site [3, 11, 12].

TABLE 1 Frequency and Distribution of Malignant Mammographic Calcification Extent and Type

Size (mm)	Totals		Linear		Granular	
	No.	%	No.	%	No.	%
1–10	110	36	18	6[a]	92	30
11–20	58	19	28	9	30	10
21–40	71	23	41	13	30	10
> 40	65	21	39	13	26	9
Total	304	100	126	41	178	59

[a] $p = 0.00$ (comparing linear calcification fractions for 1–10 mm and ≥ 11 mm).

Histologic material derived from a combination of core biopsies and surgical excisions and reexcisions or mastectomy for each patient was stained with H and E for pathologic evaluation and staging. The pathologic diagnoses in this study are based on all the biopsied and excised material. For this analysis, final histologic malignant diagnoses were categorized as pure DCIS without an invasive component, DCIS associated with an invasive ductal carcinoma (IDC) component, IDC only without DCIS, and invasive lobular carcinoma. The pathologic size of the invasive carcinoma was that reported during staging by the attending pathologist at the cancer institute. The greatest histologic dimension of the invasive tumor in any plane was recorded according to the pathology staging standards of the College of American Pathologists [13]. According to the TNM staging classification, for patients with multiple foci of invasive tumors, the greatest dimension of the largest invasive focus was recorded [14]. The size of the pathologic invasive carcinoma as a percentage of the mammographic calcification extent was categorized as less than or equal to 5%, 6–10%, 11–25%, 26–50%, 51–99%, and 100% or greater; it was also categorized as greater than the mammographic calcification extent. The invasive carcinoma extent was recorded as not assessable by the pathologist in some cases when the tumor was received in multiple fragments. The pathologic axillary lymph node status determined by sentinel node biopsy or axillary dissection was also included. Sentinel node biopsy was not performed at the beginning of this study but gradually replaced axillary lymph node dissection as the predominate technique for axillary node sampling for patients with invasive carcinomas.

Statistical comparisons of associations between mammographic features and the presence and sizes of invasive carcinomas were performed using the chi-square test, with a p value of less than 0.05 as the limit of statistical significance [15].

Results

This study group consisted of 304 consecutive patients with clinically occult mammographic calcifications without a mass with findings of breast carcinoma on final pathologic evaluation. The median age of the patients was 54 years (range, 29–86 years). One hundred sixteen (38%) of the patients were 49 years old or younger; 188 (62%) of the patients were 50 years old or older.

The frequency and distribution of malignant mammographic calcification lesion extent and type are shown in Table 1. Thirty-six percent of the mammographic calcification extents were 1–10 mm; the mammographic calcification extents of 11–20 mm, 21–40 mm, and greater than 40 mm were approximately 20% each. Fifty-nine percent ($n = 178$) of the mammographic calcifications were the predominately granular type, and 41% ($n = 126$) were the linear type.

The final pathologic diagnoses of the mammographic calcification lesions in the study are in Table 2. Overall, 65% of the malignant lesions manifested by mammographic calcifications only were pure DCIS. Thirty-two percent were DCIS associated with invasion; only 4% were invasive carcinomas only. The association between patient age and the presence of pure DCIS or invasive carcinoma is shown in Table 3. There were no significant differences between patient age and the presence of invasive carcinoma.

The association between mammographic calcification extent and invasive carcinoma

TABLE 2 Malignant Microcalcification Lesions: Final Histopathology

Histopathology	No.	%
Ductal carcinoma in situ	198	65
Ductal carcinoma in situ and invasive ductal carcinoma	96	32
Invasive ductal carcinoma	5	2
Invasive lobular carcinoma	5	2
Total	304	100

TABLE 3 Patient Age and Invasive Carcinoma

Age (yr)	Totals		Pure Ductal Carcinoma In Situ		Invasive Carcinoma[a]	
	No.	%	No.	%	No.	%
< 40	25	100	12	48	13	52
40–49	91	100	66	73	25	27
50–59	77	100	49	64	28	36
60–69	60	100	37	62	23	38
70–79	40	100	25	63	15	38
≥ 80	11	100	9	82	2	18
≤ 49	116	100	78	67	38	33
≥ 50	188	100	120	64	68	36
Total	304	100	198	65	106	35

[a]p = not significant (comparing fractions with invasive carcinoma in any age subsets).

presence and size is shown in Table 4. Mammographic calcification size of 11 mm and greater was more likely associated with invasive carcinoma: 40% (77/194) of patients, compared with 26% (29/110) for calcification extents of 1–10 mm (p = 0.019). However, there was no difference in the presence of an invasive component between calcification extents of 11–20 mm, 21–40 mm, and greater than 40 mm (range, 41–60 mm).

Overall, 65% (69/106) of the invasive carcinomas were pathologically staged at 10 mm or less. Twenty-one percent (n = 22) of the invasive carcinomas measured 2–5 mm, and 23% (n = 24) measured 1 mm or less. There were no significant differences in these size distributions of associated invasive carcinomas when comparing mammographic calcification extents of 1–10 mm and 11 mm and greater. Among the mammographic calcification extents of greater than 40 mm, 38% had associated invasive carcinoma; 56% of these invasive carcinomas were pathologically staged at 10 mm or less, 16% were 2–5 mm, and 24% were 1 mm or less.

The invasive carcinoma size as a percentage of the mammographic calcification extent is shown in Table 5. The invasive carcinoma size was less than or equal to 50% of the mammographic calcification extent in 62% (65/106) of patients.The invasive carcinoma size was less than or equal to 10% of the calcification extent in 23% of patients. The invasive carcinoma size was 100% or greater relative to the mammographic calcification extent in 21% of patients.

The associations between mammographic calcification types and pure DCIS and invasion are shown in Table 6. Linear mammographic calcifications were more likely to be

TABLE 4 Malignant Mammographic Calcification Lesion Extent and Associated Invasive Carcinoma

Lesion Size (mm)	No.	Pure Ductal Carcinoma In Situ	Invasive Carcinoma	Invasive Carcinoma Size (mm)[a]						
				≤ 1	2–5	6–10	11–15	16–20	> 20	NA
1–5	50	39 (78)	11 (22)	3 (6)	5 (10)	2 (4)	0 (0)	0 (0)	1 (2)	0 (0)
6–10	60	42 (70)	18 (30)	5 (8)	4 (7)	4 (7)	4 (7)	0 (0)	0 (0)	1 (2)
11–20	58	33 (57)	25 (43)[b]	5 (9)	2 (3)	7 (12)	5 (9)	0 (0)	5 (9)	1 (2)
21–40	71	44 (62)	27 (38)[c]	5 (7)	7 (10)	5 (7)	3 (4)	3 (4)	2 (3)	2 (3)
> 40	65	40 (62)	25 (38)[c]	6 (9)	4 (6)	4 (6)	4 (6)	2 (3)	2 (3)	3 (5)
Total	304	198 (65)	106 (35)	24 (8)	22 (7)	23 (8)	15 (5)	5 (2)	10 (3)	7 (2)
1–10	110	81 (74)	29 (26)	8 (7)	9 (8)	6 (5)	4 (4)	0 (0)	1 (1)	1 (1)
≥ 11	194	117 (60)	77 (40)[d]	16 (8)	13 (7)	17 (9)	11 (6)	5 (3)	9 (5)	6 (3)

Note.—Numbers in parentheses are percentages. NA = not assessable.

[a]Pathologic measurement.

[b]p = 0.027 (comparing designated fraction with invasive carcinoma with 1- to 10-mm-size subgroup).

[c]p = not significant.

[d]p = 0.019 (comparing designated fraction with invasive carcinoma with 1- to 10-mm-size subgroup).

TABLE 5 Pathologic Invasive Carcinoma Size as a Percentage of Mammographic Calcification Extent

Calcification Size (mm)	No.	≤ 5%	6–10%	11–25	26–50%	51–99%	≥ 100%	Not Assessable
1–10	29 (100)	0 (0)	0 (0)	7 (24)	5 (17)	4 (14)	12 (41)	1 (3)
11–20	25 (100)	2 (8)	3 (12)	2 (8)	5 (20)	5 (20)	7 (28)	1 (4)
21–40	27 (100)	5 (19)	2 (7)	6 (22)	7 (26)	3 (11)	3 (11)	2 (7)
> 40	25 (100)	9 (36)	3 (12)	6 (24)	3 (12)	1 (4)	0 (0)	3 (12)
Total	106 (100)	16 (15)	8 (8)	21 (20)	20 (19)	13 (12)	22 (21)	7 (7)

Note.—Numbers in parentheses are percentages.

TABLE 6 Mammographic Calcification Types and Invasive Carcinoma

Type	No.	Pure Ductal Carcinoma In Situ		Invasive Carcinoma	
		No.	%	No.	%
Linear	126	71	56	55	44[a]
Granular	178	127	71	51	29[a]
Coarse	108	71	66	37	34
Mixed	42	31	74	11	26
Fine	28	25	89	3	11[b]
Coarse and mixed	150	102	68	48	32[b]
Total	304	198	65	106	35

[a] $p = 0.007$ (comparing designated fractions with invasive carcinoma).

[b] $p = 0.022$ (comparing designated fractions with invasive carcinoma).

TABLE 7 Surrounding Mammographic Density and Invasive Carcinoma

Density	No.	Pure Ductal Carcinoma In Situ		Invasive Carcinoma[a]	
		No.	%	No.	%
Dense	117	79	68	38	32
Heterogeneous	150	93	62	57	38
Fatty	37	26	70	11	30
Total	304	198	65	106	35

[a] p = not significant (comparing fractions with invasive carcinomas).

associated with invasion, 44% (55/126), compared with 29% (51/178) for granular calcifications overall ($p = 0.007$). The fine granular calcification subtype was less likely to be associated with invasion, 11%, as compared with the coarse and mixed granular calcification subtypes, 32% ($p = 0.022$). However, the fine granular calcification subtype constituted only 9% (28/304) of the calcification lesions.

No significant associations were found between dense, fatty, or heterogeneous mammographic parenchymal density surrounding the calcifications and the presence of invasion as shown in Table 7.

Associations between the combined features of mammographic calcification extent and type and the presence of pure DCIS or associated invasive carcinomas are shown in Table 8. The prevalence of associated invasion ranged from 25% for 1- to 10-mm extents of granular calcifications to 45% for 11 mm and greater linear calcifications. Forty-four percent (17/39) of linear calcifications greater than 40 mm extent had associated invasive carcinoma. Among 5-mm or less extent granular-type mammographic calcifications, 22% (10/45) had associated invasive carcinoma.

Seventy-two (68%) of 106 patients with invasive carcinomas in the study had axillary lymph node sampling (Table 9). Sixteen (22%) had positive axillary lymph nodes at pathologic examination, ranging from 9% (1/11) with invasive carcinomas pathologically staged at 1 mm or less to 63% (5/8) of invasive carcinomas staged greater than 20 mm.

Discussion

Mammographic calcifications proven to be malignant lesions are nearly always DCIS or DCIS with a smaller focus of invasion. This analysis shows that mammography, in general, is a poor predictor of either pure DCIS or DCIS associated with an invasive carcinoma. Mammographic calcification extents of greater than 10 mm were more likely associated with invasion than were those with lesser extents; however, there was no increase in the frequency of invasive carcinomas with increasing mammographic calcification extents greater than 10–40 mm. Mammographic linear calcifications had significantly greater association with invasive carcinoma compared with granular calcifications. However, when combining these significant mammographic features, the lowest predictive value features, we found that less than 5-mm granular calcifications were associated with a 22% frequency of invasive carcinoma; the highest predictive value features, linear calcifications 11 mm and greater, were associated with a 45% frequency of invasive carcinoma. The mammographic calcification subtype of fine granular was associated with a frequency of invasive carcinoma of only 11%, but this uncommon subset constituted only 9% of the malignant calcification lesions overall.

TABLE 8 Malignant Mammographic Calcification Lesion Extent and Type and Associated Invasive Carcinoma

Calcification Size (mm)	No.	Pure Ductal Carcinoma In Situ	Invasive Carcinoma	Invasive Carcinoma Size (mm)[a]						
				≤ 1	2–5	6–10	11–15	16–20	> 20	NA
1–10	110	81 (74)	29 (26)[b]	8 (7)	9 (8)	6 (5)	4 (4)	0 (0)	1 (1)	1 (1)
Linear	18	12 (67)	6 (33)	2 (11)	0 (0)	2 (11)	2 (11)	0 (0)	0 (0)	0 (0)
Granular	92	69 (75)	23 (25)	6 (7)	9 (10)	4 (4)	2 (2)	0 (0)	1 (1)	1 (1)
≥ 11	194	117 (60)	77 (40)[b]	16 (8)	13 (7)	17 (9)	11 (6)	5 (3)	9 (5)	6 (3)
Linear	108	59 (55)	49 (45)	11 (10)	7 (6)	11 (45)	7 (6)	3 (3)	7 (6)	3 (3)
Granular	86	58 (67)	28 (33)	5 (6)	6 (7)	6 (7)	4 (5)	2 (2)	2 (2)	3 (3)
Total	304	198 (65)	106 (35)	24 (8)	22 (7)	23 (8)	15 (5)	5 (2)	10 (3)	7 (2)
Linear	126	71 (56)	55 (44)[c]	13 (10)	7 (6)	13 (10)	9 (7)	3 (2)	7 (6)	3 (2)
Granular	178	127 (71)	51 (29)[c]	11 (6)	15 (8)	10 (1)	6 (3)	1 (1)	3 (2)	4 (2)

Note.—Numbers in parentheses are percentages. NA = not assessable.

[a] Pathologic measurement.

[b] $p = 0.019$ (comparing designated fraction with invasive carcinoma component).

[c] $p = 0.07$ (comparing designated fraction with invasive carcinoma component).

TABLE 9 Pathologic Invasive Carcinoma Size and Axillary Lymph Node Status

Node Status	No.	Pathologic Measurement of Invasive Carcinoma Size (mm)					
		1	2–5	6–10	11–20	> 20	Not Assessable
Positive	16 (22)	1 (9)	1 (7)	2 (13)	7 (41)	5 (63)	0 (0)
Negative	56 (78)	10 (91)	14 (93)	14 (88)	11 (61)	3 (38)	4 (100)
Total	72[a] (100)	11 (100)	15 (100)	16 (100)	18 (100)	8 (100)	4 (100)

Note.—Numbers in parentheses are percentages. Thirty-four patients did not have axillary lymph node sampling.
[a]Eighteen patients (25%) had sentinel node biopsy initially; the remainder had axillary dissection initially.

This study describes the modern presentation of these breast carcinomas, the mammographic calcification appearance and extent based on high-resolution film-screen mammography, including orthogonal magnification projections. These projections are important to aid optimally in characterization of linear and granular calcifications in two planes and in assessment of calcification extent, because DCIS often extends in a longitudinal ductal or patchy lobular distribution in the breast [3–6]. The distribution or orientation of the DCIS calcifications was not recorded in this study.

Although it is possible that dense rather than fatty mammographic parenchymal density surrounding a region of mammographic calcifications could more likely obscure a soft-tissue abnormality representing an invasive carcinoma, mammographic surrounding parenchymal density and patient age showed no associations with the presence of invasion, in part, because of the small size (≤ 5 mm) of many of the invasive foci associated with mammographic calcifications.

The observation that the size distribution of the associated invasive carcinomas is similar for different DCIS mammographic calcification extents suggests a DCIS field phenomenon. If one considers the size of the invasive carcinoma as a measure for the age or the degree of malignant transformation of the lesion, these data suggest that both large and small fields of DCIS and mammographic calcifications are at similar points in the malignant transformation process because they contain similar frequency and size distribution of invasive cancers.

It has been well established in the mammography–pathology correlation literature that the extent of mammographic calcifications can underestimate the pathologic extent of DCIS [3, 5]. Also, a discontinuous distribution of mammographic calcifications associated with DCIS is often associated with continuous DCIS pathology in a ductal–lobule system [3, 5]. There may be areas of microscopic DCIS in mammographically normal tissue between clusters of DCIS calcifications.

It has also been shown that in some patients, the extent of mammographically suspicious calcifications may overestimate the pathologic extent of DCIS, especially in those cases of DCIS found in benign adenosis calcifications [3, 16, 17]. However, in prospective clinical management, excision of the entire mammographic region of suspicious calcifications is usually required to exclude the possibility of additional DCIS or invasive carcinoma. Using sliced-specimen mammography–pathology correlation of excised mammographic calcifications, we have shown that in some cases, the calcifications are predominately benign, and we do not recommend further excision of the mammographic calcifications remaining on the postexcision mammogram if the pathologic margins are satisfactorily negative for surgical management [3].

Lagios et al. [16, 17] reported data on 115 mastectomy specimens resected for an initial biopsy diagnosis of DCIS. The pathologic extent of DCIS was determined using the serial subgross and radiographic method modeled after Egan et al. [18]. Lagios et al. correlated the pathologic extent of DCIS, including mammographically occult noncalcified DCIS, with the presence of occult invasion. They defined occult invasion as invasive carcinoma not detected in the original biopsy procedure and not evident as a suspicious focal soft-tissue abnormality on mammograms, including earlier mammographic and xeromammographic techniques. Occult invasion in their series was confined to breasts in which the pathologic size of DCIS exceeded 45 mm, occurring in nearly 50% of breasts with a pathologic extent of DCIS of 55 mm or greater. Their series also included cases in which the DCIS was not evident on mammography at all or in part (noncalcified DCIS).

The case selection, mammographic evaluation, and correlation in our study differs in that only patients with mammographic calcification lesions without a clinical or mammographic mass were included. The mammographic calcification extent appearance and the absence of soft-tissue abnormalities suspicious for invasion were determined with a high-resolution film-screen mammography technique with orthogonal magnification projections, and the prebiopsy mammographic extent of suspicious calcifications, not the final pathologic extent of DCIS, was correlated with the presence of associated invasion after complete surgical removal of the lesion. These data reflect the ability to prospectively predict the presence of associated invasion on the basis of mammographic findings available to clinicians during routine clinical management. Comparison of the mammographic and pathologic size of DCIS is beyond the scope of this study.

The observation that the frequency of associated invasive carcinoma did not increase for mammographic calcification extent greater than 10 mm in our study does not support recent reports in the surgical literature that suggest that sentinel node biopsy be performed selectively for extensive mammographic calcifications associated with DCIS because of an assumed increased risk of associated invasive carcinomas [19–22]. Although 40% of patients with calcification extents 11 mm and greater had associated invasion as compared with 16% with calcification extents of less than or equal to 10 mm, no difference was seen in the frequency of associated invasion for calcification extents of 11–20 mm, 21–40 mm, or greater than 40–160 mm.

The observation that the pathologic size of invasive carcinomas associated with DCIS mammographic calcifications is often much smaller than the extent of calcifications explains the underestimation of invasive carcinoma or stereotactic core biopsies showing DCIS only. Stereotactic core biopsy methods, even large core needle vacuum-assisted techniques, fail to detect the invasive component in 11–20% of core biopsies showing DCIS only [23]. This analysis sheds no light on sampling during core biopsy to increase the detection of the smaller invasive carcinomas, including 1-mm foci, within larger regions of DCIS calcifications.

These data may improve the mammographer's, the surgeon's, and the patient's understanding of mammographic calcifications, DCIS, and associated invasive carcinomas during clinical management as well as provide some mammography-derived empiric observations regarding the biologic associations and characteristics of DCIS and invasive carcinoma.

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