Novel Breast Tissue Feature Strongly Associated With Risk of Breast Cancer

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ABSTRACT

Purpose

Accurate, individualized risk prediction for breast cancer is lacking. Tissue-based features may help to stratify women into different risk levels. Breast lobules are the anatomic sites of origin of breast cancer. As women age, these lobular structures should regress, which results in reduced breast cancer risk. However, this does not occur in all women.

Methods

We have quantified the extent of lobule regression on a benign breast biopsy in 85 patients who developed breast cancer and 142 age-matched controls from the Mayo Benign Breast Disease Cohort, by determining number of acini per lobule and lobular area. We also calculated Gail model 5-year predicted risks for these women.

Results

There is a step-wise increase in breast cancer risk with increasing numbers of acini per lobule ($P = .0004$). Adjusting for Gail model score, parity, histology, and family history did not attenuate this association. Lobular area was similarly associated with risk. The Gail model estimates were associated with risk of breast cancer ($P = .03$). We examined the individual accuracy of these measures using the concordance (c) statistic. The Gail model c statistic was 0.60 (95% CI, 0.50 to 0.70); the acinar count c statistic was 0.65 (95% CI, 0.54 to 0.75). Combining acinar count and lobular area, the c statistic was 0.68 (95% CI, 0.58 to 0.78). Adding the Gail model to these measures did not improve the c statistic.

Conclusion

Novel, tissue-based features that reflect the status of a woman's normal breast lobules are associated with breast cancer risk. These features may offer a novel strategy for risk prediction.

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INTRODUCTION

The medical community's ability to predict risk of breast cancer for individual women is limited.¹⁻³ In other tissues, optimal cancer risk prediction can occur when the tissue at risk is examined for evidence of premalignant change (eg, cervix, esophagus, colon). Presumably, the field of normal tissue, exposed to an individual's endogenous and exogenous risks, responds with a phenotype (eg, proliferation, atypical cells) that reflects the increased risk. Although breast tissue is not readily available for routine clinical assessment, women with benign breast disease have had breast tissue removed in the course of their care and have an increased risk of a later breast cancer.^{4,5}

Current characterization of benign breast tissue focuses primarily on the degree and type of epithelial hyperplasia, but this focus may overlook

other important, easily assessed features.⁴⁻⁶ The breast is organized into 15 to 20 major lobes, each composed of lobules that contain the milk-forming acini. The lobule (or terminal duct lobular unit [TDLU]) is the anatomic substructure thought to give rise to breast cancer.⁷ Normal aging results in the physiologic regression (or involution) of breast lobules (Fig 1).⁸⁻¹¹ With regression, there is progressive loss of acini within the lobular units and replacement of specialized intralobular connective tissue with the collagen more typical of the interlobular region (Fig 1).⁸ We previously showed that breast cancer risk decreases with regression of lobular units, assessed qualitatively as no, partial, or complete involution.¹¹

We hypothesized that a quantitative assessment of involution could be developed as a more precise and physiologic measure of breast cancer risk. Thus, in a nested case-control series within the

Fig 1. (A) Shown is a field of normal lobules (terminal duct lobular units), each composed of multiple acini. (B) Complete regression (involution) of these lobules has occurred, leaving small residual structures largely depleted of acini. Reprinted with permission.¹¹

Mayo Benign Breast Disease Cohort, we have calculated the number of acini within normal lobules and average lobule size. Here, we show the risk prediction capabilities of lobule status and compare these results with the current standard, a Gail model assessment of risk performed in the same women.

METHODS

Study Population

We performed a nested case-control study within the Mayo Benign Breast Disease Cohort. This cohort includes all women ($N = 9,376$) who had an open breast biopsy, with benign findings, at Mayo Clinic between January 1, 1967 and December 31, 1991.^{4,11} Median follow-up time for breast cancer events is 16.9 years.¹¹ For cohort members, we assembled risk factor and outcomes data from a study-specific questionnaire and the Mayo Clinic medical record. Study pathologists characterized the benign biopsies, including the extent of lobule regression.¹¹ All patient contact materials and procedures were reviewed and approved by the Mayo Clinic Institutional Review Board.

For the current study, we selected a random sample of 100 patients who developed breast cancer from the cohort, stratified by 5-year categories of year

Fig 2. (A) We subdivided an intact lobule to facilitate counting of individual acini. (B) Delineation of the circumference of the lobule for calculation of lobule area by the computer software is demonstrated.

of benign biopsy to represent the entire spectrum of the cohort. We matched two controls to each patient case based on age and year of benign biopsy. Of these participants selected, 85 patient cases and 142 controls had adequate tissue available for assessment.

Assessment of Lobular Status

Extent of lobular regression was previously characterized qualitatively by the study pathologist as none (0% TDLUs regressed), partial (1% to 74% regressed), or complete ($\geq 75\%$ regressed).¹¹ For the quantitative assessments, one hematoxylin and eosin-stained slide per participant was scanned into the computer and analyzed using WebSlide Browser software (Bacus Laboratories, Olympus, Center Valley, PA). This software allows the measurement of structural features (lobular area and acini number) as visualized by light microscopy (Fig 2).

The 10 largest normal lobules were assessed for each patient by one observer (K.P.M.) without knowledge of patient status or previous pathologic assessment. If fewer than 10 normal lobules were present, all were assessed. Analysis included counting the number of individual acini per lobular unit and delineating the circumference of the lobule to measure its area in square micrometers (Fig 2). We defined countable acini as nuclei forming a distinct circular pattern with or without the presence of a discernible lumen. Distinct lobules were defined by the presence of intersecting stromal tissue. Abnormal lobules, namely those that contained large portions of terminal ducts, atypical lobular or ductal hyperplasia, sclerosing adenosis, large cysts, or proliferative disease without atypia, were not included.

Reproducibility

A random sample of 82 slides (25 patient cases and 57 controls) was read by a second observer (J.L.C.) using the quantitative manual method described earlier. A different approach, automated analysis, was performed on another random sample of 95 slides (28 patient cases and 67 controls) using the Automated Cellular Imaging System (ACIS) III instrument (DAKO, Carpinteria, CA). The ACIS III automatically scanned the study slides at $\times 4$ magnification to obtain an overall image. The images were then visually analyzed (by D.M.) to determine the 10 largest normal breast lobules (or less if there were not 10 lobules present on the slide). Area measurements were determined by tracing an outline of the lobules using the free-form tracing tool. Breast acini were counted within each lobule using the 100 $\times$ circle scoring tool. Area measurements and the number of acini were calculated by the instrument and exported from the ACIS III program to a spreadsheet for statistical analysis.

Gail Model Calculations

Using age at benign biopsy as the age at risk assessment, the Gail model (National Cancer Institute [NCI] Breast Cancer Risk Assessment Tool, <http://cancer.gov/bcrisktool>) was used to predict the 5-year risk of breast cancer for each of the women using their risk factor profile.^{12,13} To calculate these estimates, we used a FORTRAN program provided to us by the NCI (M. Gail, J. Benichou, D. Pee, personal communication, February 2007), which we have used previously.³ This program contains the code that comprises the underlying calculation machinery used in the NCI's Breast Cancer Risk Assessment Tool. For variables with missing data, we used the standards in the online Gail model. To verify agreement between the code we used and the online tool, we randomly selected 10 participants from our cohort and compared the 5-year and lifetime risk estimates obtained from the code given to us with those from the online risk assessment tool.³ All of the estimates were in complete agreement.

Statistical Analyses

We studied two measures of involution—the number of acini per lobule and lobule size. Primary analyses used the median of the values obtained across the multiple lobules measured for each woman. Secondary analyses that incorporated the values for all lobules were also performed, using repeated measures approaches, but results were similar to those modeling the medians and thus are not shown.

We compared distributions of number of acini and lobule area across demographic and clinical variables using general linear mixed models, accounting for the matched study design by fitting each case-control set as a random intercept term. As a result of data skewness, analyses were run using log-transformed values. The resulting least squares means and 95% CIs were then back-transformed to their original sampling units. We examined correlations between number of acini and lobule area; between these measures and our original three categories of involution (none, partial, and complete); and between the quantitative measures obtained by the two manual observers and the ACIS method, using Pearson correlation coefficients, again based on the log-transformed values.

We assessed associations between number of acini, lobule area, and Gail model risk estimates and breast cancer risk using conditional logistic regression analysis. We first modeled each variable as categorical, pooling values into four to six distinct groups. We then assessed dose-response effects by fitting each as a continuous variable in the logistic model. These latter analyses were carried out using log-transformed values for acini and area because assessments of their functional form revealed suboptimal model fit using the data in their original scale. We examined univariate associations and models with various combinations of the following variables: the 5-year Gail model risk prediction score, number of live births, family history, and histologic findings. Using the risk estimates from the logistic models, we examined the risk prediction capabilities of these variables using concordance (c) statistics. These statistics can be interpreted as the area under the receiver operating characteristics curve or, alternatively, as the average sensitivity of the variable across all possible levels of specificity. We used a modified c statistic to account for the matched study design, calculating the number of case-control pairs in each set, as well as the number of concordant pairs (those for which the patient case's predicted risk exceeded the control's), and then aggregating across all matched

sets. Ninety-five percent CIs were calculated using 5,000 bootstrap samples of case-control sets.

RESULTS

Patient Characteristics

A total of 227 patients were included in the nested case-control study—85 women who went on to develop breast cancer (patient cases) and their 142 age-matched controls. The median follow-up time for all participants was 16.2 years. The median follow-up time was 18.6 years for controls and 9 years for patient cases (follow-up ceases after breast cancer diagnosis). The mean age at benign biopsy was 52.1 years. The patient characteristics are listed in Table 1.

Number of Acini per Lobule (Acinar Count)

As expected, the average number of acini per lobule was associated with the pathologist's qualitative category of involution. Namely, women with no involution had a higher mean acinar count (mean, 32.0 acini per lobule; 95% CI, 26.4 to 38.8 acini per lobule) than women with partial involution (mean, 19.7 acini per lobule; 95% CI, 17.5 to 22.2 acini per lobule) or complete involution (mean, 7.7 acini per lobule; 95% CI, 5.8 to 10.3 acini per lobule; $P < .0001$). When comparing the acinar count with histologic category, the means were not significantly different (nonproliferative: mean, 18.8 acini per lobule; 95% CI, 16.1 to 22.0 acini per lobule; proliferative disease without atypia: mean, 22.1 acini per lobule; 95% CI, 18.6 to 26.3 acini per lobule; and atypical hyperplasia: mean, 18.6 acini per lobule; 95% CI, 13.2 to 26.2 acini per lobule; $P = .309$). The acinar count for women with a family history of breast cancer was 22.9 acini per lobule (95% CI, 19.0 to 27.6 acini per lobule) compared with 18.3 acini per lobule

Table 1. Clinical and Histologic Characteristics

Characteristic	Patient Cases (n = 85)		Controls (n = 142)		Total (N = 227)	
	No.	%	No.	%	No.	%
Age at biopsy, years						
Mean	52.5		51.8		52.1	
SD	10.1		10.1		10.1	
Histologic type						
Nonproliferative	42	49.4	79	55.6	121	53.3
Proliferative without atypia	31	36.5	56	39.4	87	38.3
Proliferative with atypia	12	14.1	7	4.9	19	8.4
No. of live births						
Missing	0	0	1	0.7	1	0.4
Nulliparous	11	12.9	18	12.7	29	12.8
1	7	8.2	15	10.6	22	9.7
2	30	35.3	38	26.8	68	30
3	26	30.6	29	20.4	55	24.2
4+	11	12.9	41	28.9	52	22.9
Family history of breast cancer						
Missing	1	1.2	5	3.5	6	2.6
None	51	60.0	96	67.6	147	64.8
Weak	16	18.8	22	15.5	38	16.7
Strong	17	20.0	19	13.4	36	15.9

Abbreviation: SD, standard deviation.

Table 2. Association of Acini Count and Gail Model With Risk of Breast Cancer (invasive and in situ)

Acini Count and Gail Model	No. of Patient Cases	No. of Controls	Univariate Analysis*			Multivariate Analysis†		
			RR	95% CI	<i>P</i>	RR	95% CI	<i>P</i>
No. of acini per lobule								
0-10	16	37	1.00 (REF)		.0004	1.00 (REF)		.0001
11-20	22	41	2.80	0.88 to 8.93		3.61	1.03 to 12.63	
21-30	13	26	3.23	0.87 to 11.94		4.77	1.14 to 19.99	
31-40	8	18	3.23	0.72 to 14.41		3.95	0.81 to 19.36	
≥ 41	26	20	11.85	2.92 to 48.12		14.03	3.18 to 61.86	
Gail 5-year risk score								
0 to < 1	12	33	1.00 (REF)		.030	1.00 (REF)		.037
1 to < 2	38	72	1.76	0.64 to 4.87		1.58	0.53 to 4.73	
2 to < 3	19	18	4.13	1.28 to 13.32		3.83	1.09 to 13.47	
≥ 3	16	19	3.55	1.05 to 11.98		3.51	0.92 to 13.35	

Abbreviations: RR, relative risk; REF, reference.

*Relative risks and 95% CIs were calculated using conditional logistic regression analysis. Analyses account for the matched nature of the data by modeling set identification as a stratification variable. *P* values assess the dose-response effects of quantitative involution and the Gail model estimate with risk of breast cancer by modeling each as a continuously distributed predictor variable.

†Analyses were additionally adjusted for the 5-year predicted risk of breast cancer based on the Gail model or for the No. of acini per lobule.

(95% CI, 16.4 to 21.6 acini per lobule) for those with no family history (*P* = .068).

When comparing the acinar count between patient cases and controls, women who developed breast cancer had significantly more acini per lobule (24.3 acini) than women who remained unaffected (17.8 acini; *P* = .0008). In Table 2, we show a stepwise increase in risk of breast cancer with increasing numbers of acini per lobule (*P* = .0004). This association was similar, if not slightly stronger, after adjusting for the Gail model 5-year risk score (*P* = .0001, Table 2). We examined acinar count and breast cancer risk by nonproliferative versus proliferative histologies and saw a similar dose-response association in both groups (data not shown). Further adjustment for other potential confounders including parity and family history did not attenuate the observed association.

Because time from benign biopsy to breast cancer varied from 11 months to 27 years in our patient cases, we asked whether involution measures varied by time to breast cancer. To investigate this, we plotted the ratio of involution in patient cases to involution in matched controls (on the log scale) as a function of time. We then fit a least squares regression line to this plot. The line had a slight downward trend but always remained above the back-transformed ratio values of 1.0, indicating that the positive association of acinar count with patient case status was sustained across the entire spectrum of time to cancer and did not vary significantly over time (data not shown).

Lobule Size

Lobule area was strongly correlated with acinar count (*r* = 0.85; 95% CI, 0.81 to 0.88). Women who developed breast cancer had a larger lobular area (64,165 μm^2) than controls (53,759 μm^2 ; *P* = .065). Logistic regression analyses indicated a stepwise increase in risk of breast cancer with increasing lobule size (*P* = .045). Notably, during involution, acini become less cohesive geographically and can drift apart, as seen in Figure 1B, resulting in a larger area than might be expected relative to the number of acini. Although lobule size was associated with breast cancer risk, associations were generally more modest than with number of acini.

Reproducibility

We compared the initial quantitative acinar count with those obtained by a second observer and with the automated ACIS readings. There was strong correlation among the three approaches (first and second observer: *r* = 0.91; 95% CI, 0.87 to 0.94; first observer compared with ACIS: *r* = 0.78; 95% CI, 0.68 to 0.84; second observer compared with ACIS: *r* = 0.79; 95% CI, 0.68 to 0.86).

Gail Model Predictions

The Gail model 5-year estimates were associated with the outcome of breast cancer (*P* = .030, Table 2) for all breast cancer events, including invasive (*n* = 69), in situ (*n* = 13), and invasion status unknown (*n* = 3). When restricting analyses to invasive cancers only, the Gail model results were similar (*P* = .022).

Accuracy of Risk Prediction: Lobule Measures Versus Gail Model

We assessed the accuracy of risk prediction, for individual women, for the Gail model and for acinar count and lobular area using the *c* statistic (Table 3). For the Gail model, it was similar to estimates found in other studies (*c* statistic = 0.60; 95% CI, 0.50 to 0.70).^{14,15} Using acinar count alone, the *c* statistic was 0.65 (95% CI, 0.54 to 0.75). Combining acinar count and lobular area increased the *c* statistic to 0.68 (95% CI, 0.58 to 0.78). Adding the Gail model to this combined set did not add to predictive accuracy (*c* statistic = 0.66).

DISCUSSION

Optimal early detection and prevention strategies for breast cancer require accurate identification of individuals at significantly increased risk for the disease. Despite our knowledge of many determinants of breast cancer risk, both endogenous and exogenous, our ability to predict risk for individual women remains limited.^{1,2} Reasoning that a woman's breast tissue reflects the integration of her exposures to multiple risk-contributing processes, we are working to develop a tissue-based approach to risk prediction for breast cancer. Regression,

Table 3. Assessment of the Predictive Capability of Lobular Measures and the Gail Model Using Concordance Statistics

Predictor	All Patient Cases (n = 85)		Patient Cases With Invasive Cancer Only (n = 69)	
	c Statistic*†	95% CI	c Statistic*‡	95% CI
Gail model	0.60	0.50 to 0.70	0.59	0.47 to 0.71
No. of acini	0.65	0.54 to 0.75	0.69	0.57 to 0.80
Lobular area	0.56	0.47 to 0.67	0.59	0.47 to 0.70
No. of acini + lobular area	0.68	0.58 to 0.78	0.70	0.59 to 0.81
No. of acini + lobular area + Gail model	0.66	0.56 to 0.76	0.69	0.58 to 0.80

*Statistics were calculated using conditional logistic regression analysis, accounting for the matched nature of the data by modeling set identification as a stratification variable.

†c statistic based on both invasive and in situ events.

‡c statistic based on invasive events only.

Fig 3. Whole-breast mounts from (A) preinvolutional and (B) postinvolutional women. Reprinted with permission.²⁴

or involution, of lobules is a physiologic process that occurs as a woman ages.^{8,9} Importantly, it is these same structures that give rise to breast cancer.⁷ Completion of the involution process, assessed in a qualitative manner, is associated with a significant reduction in breast cancer risk.¹¹ We have now quantified extent of lobular regression for individual women via the number of acini per lobule and lobule size and show a strong association with risk of breast cancer. Importantly, these lobular features, assessed on a single hematoxylin and eosin-stained slide, identified those women who would later develop breast cancer more precisely than a Gail model prediction. This held true whether or not comparisons were restricted to invasive events. We have also shown reproducibility of these measures, whether obtained manually or in an automated fashion, with correlation coefficients of 0.78 to 0.91. Of note, these measures seem to be independent of histology, contributing to their risk prediction capabilities.¹¹

Several risk prediction models for breast cancer focus on an individual's likelihood of carrying a hereditary predisposition to the disease.¹⁶⁻²² Outside the hereditary setting, the most widely used tool is the Gail model.¹² This model is available on the NCI's Web site (<http://cancer.gov/bcrisktool>) and is viewed approximately 20,000 to 30,000 times a month,² demonstrating the strong clinical demand for risk assessment for individual women. Although the Gail model has been shown to be well calibrated in predicting the number of invasive cancers likely to develop in groups of women, its discriminatory accuracy in predicting risk for individual women, as measured by c statistics near or less than 0.6, is only slightly better than chance alone. Here, we show that a simple physiologic measure of lobular status is more strongly associated with breast cancer risk than the Gail model.

There are several plausible mechanisms by which progressive degrees of lobular involution may reduce breast cancer risk. The most straightforward is that the dramatic reduction in epithelial cell number that occurs with involution equates to a physiologic prophylactic mastectomy.²³ This can be visualized in Figure 3, where age-related lobular involution has essentially removed the TDLUs from the field of breast tissue.²⁴ Another explanation is that age-related involution invokes some final differentiation-senescence program, rendering the remaining cells resistant to carcinogenic influence. It is somewhat

counterintuitive that an age-related process like involution is associated with reduced breast cancer risk, when breast cancer risk increases with age. Notably, in studying all women older than age 55 years in our cohort, those who had complete involution had a relative risk for breast cancer of 0.92 (95% CI, 0.74 to 1.14) compared with a relative risk of 3.21 (95% CI, 1.90 to 5.08) for women with no involution.¹¹ This suggests that age-related breast cancer risk may be concentrated in women whose lobules fail to regress normally.

Our study has several limitations. First, these findings do not necessarily pertain to all women because our cohort includes women who had a breast biopsy for some concern. Moreover, the present study is based in a nested case-control study from our larger Mayo Benign Breast Disease Cohort. However, we randomly selected this sample from the entire set of patient cases, and our previous results, based on the entire cohort, showed that involution status assessed qualitatively (none, partial, or complete) was strongly associated with breast cancer risk.¹¹ Even if our findings are limited to women with benign breast disease, such women number at least one million per year in the United States alone,²⁵⁻²⁷ and they represent a clinically important group because approximately 25% of women with breast cancer have had a prior benign biopsy.²⁸ A limitation in our comparisons to the Gail model is that our controls were matched to patient cases on age at benign biopsy. Because age is one of the predictor variables in the Gail model, this matching may limit the risk prediction capabilities of the Gail model. Analysis of only one slide per woman could be a limitation. However, we have looked at uniformity of involution across the field of a woman's breast tissue in women who had bilateral prophylactic mastectomy and have demonstrated high concordance in involution status across all eight quadrants of the breast tissue.²⁹ Importantly, our analyses are based on a modest sample size. Although we found statistically significant associations between acinar count and breast cancer risk, CIs are wide. Further studies are needed to confirm our results.

In summary, we have developed a means to assess degree of regression of normal breast lobules quantitatively. We have shown that higher acinar counts within the lobules and larger lobule size are associated with higher risk of breast cancer. These simple physiologic features may offer an alternative strategy for breast cancer risk prediction in women who have had benign breast biopsies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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