Breast Cancer Res Treat (2009) 117:193–196
DOI 10.1007/s10549-008-0082-6

BRIEF REPORT

Lobular involution: localized phenomenon or field effect?

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Received: 21 May 2008 / Accepted: 22 May 2008 / Published online: 1 July 2008

Abstract As women age, the lobules in their breasts undergo involution. We have shown that, in women with benign breast disease, progressive involution assessed near the benign lesion is associated with lower breast cancer risk. However, it is unknown whether the extent of involution is variable or uniform across the entire breast. We compared involution across the four quadrants of both breasts for fifteen women undergoing bilateral prophylactic mastectomy. One pathologist classified involution extent as none (0% involuted lobules), mild (1–24%), moderate (25–74%), or complete (≥75%). We assessed intra-woman concordance using intraclass correlation coefficients (ICCs), kappa coefficients, and pairwise comparisons of agreement. We found strong intra-woman concordance of involution across the eight quadrants of breast tissue (ICC = 0.75, 95% CI 0.59, 0.89). Our study suggests that lobular involution is a homogeneous process, supporting the use of involution measures from a single benign biopsy as a component in breast cancer risk assessment paradigms.

Keywords Breast cancer · Lobular involution

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Introduction

The epithelium of the human breast is organized into approximately 15–20 major lobes, each comprised of terminal duct lobular units (TDLUs, or lobules) which contain the milk-producing acini. These lobules are the anatomic substructure that gives rise to breast cancer [1]. As a woman ages, her lobules involute, with a resulting reduction in the number and size of acini per lobule (Fig. 1) [2–6]. In a recent study, we showed that progressive degrees of lobular involution were associated with lower breast cancer risk in women with pathologically confirmed benign lesions of the breast [7]. That study used a single assessment of involution for each woman based on the normal background lobules at the site of the biopsy. It has been suggested that extent of involution can help predict risk of breast cancer [7, 8]. To do so, the extent of involution in a small tissue sample would need to be representative of the entire field of a woman's breast tissue. To our knowledge no study has examined the uniformity of involution. Thus, we sought to determine if extent of lobular involution was similar across multiple areas of a

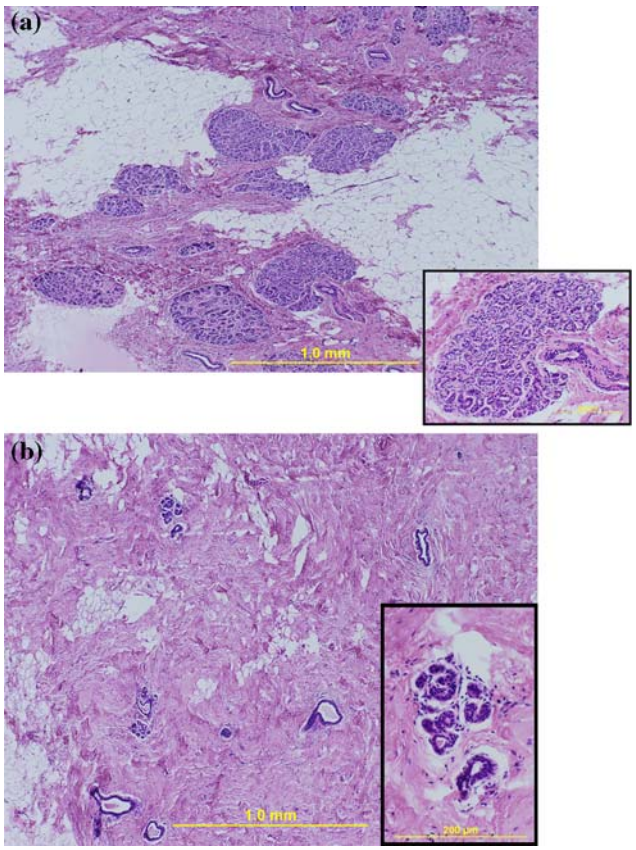

Fig. 1 Histologic features of age-related involution. (**a**) An example of breast tissue with no lobular involution, with multiple intact terminal duct lobular units, each comprised of multiple acini and specialized stroma (Inset). (**b**) An example of complete lobular involution with residual terminal duct lobular units, largely depleted of acini (inset) (Figure 1 was previously published in the following manuscript: Milanese et al. [7])

woman's breasts by studying tissue from women undergoing bilateral prophylactic mastectomy.

Methods

After Institutional Review Board approval, mastectomy specimens from 15 women with no personal history of cancer who had undergone bilateral prophylactic mastectomy at Mayo Clinic between 1998 and 2006 were retrieved from the Tissue Registry. A single section of fibrous breast tissue was sampled from each quadrant of both breasts, for a total of eight samples per individual. For each section, a formalin-fixed, paraffin embedded hematoxylin and eosin slide was prepared for tissue examination. The slides were labeled in a blinded manner, randomly intermixed, and provided to our breast pathologist (CR). Each specimen was categorized by the extent of lobular involution as none (0% involuted lobules), mild (1–24%), moderate (25–74%), or complete (≥75% involuted lobules).

We calculated within-woman concordance of involution extent using intraclass correlation coefficients (ICCs) [9, 10]. We first binned all eight values from a woman into a single class, modeling each woman as an experimental unit. Secondary analyses considered the four readings within a breast to be potentially correlated, but assumed readings across breasts were independent. For these analyses, each woman contributed two classes of four measures, effectively modeling each breast as the experimental unit. Initial ICCs pooled the intermediate involution categories of mild and moderate into one "partial involution" category, identical to the measurement in our previous study [7]. Correlations were then re-examined using the four-level categorization of none, mild, moderate and complete.

We also calculated kappa coefficients as a measure of agreement. We used the generalized multiple-rater kappa coefficient to account for the fact that we have more than two measures within each unit [11], resulting in a conservative, unweighted kappa that does not allow for "partial credit" due to close, but not exact, matches.

To aid in interpretation, we examined and summarized all pairwise comparisons of intra-woman involution values using the three level involution variable defined above (none; partial, pooling mild and moderate; complete). Each woman's eight measures resulted in 28 pairwise comparisons, or 420 total in our group of 15. We classified each paired comparison as a perfect match (the paired observations agree), partial match (the observations differ by one category), or non-match (the observations differ by two categories). Secondary analyses summarized pairwise measurements only for the four values within a breast, resulting in six breast-specific pairwise comparisons, and thus 12 for each woman and 180 overall.

Results

The mean age at mastectomy for our 15 women was 53.9 years (range 37–72). Of the 120 assessments of involution, nine were classified as no involution, 27 as mild, 25 as moderate, and 59 as complete.

Within-woman pairwise comparisons of involution, based on the three level involution variable, are presented in Table 1. Of the 420 total comparisons (28 for each of the 15 women), 341 (81%) were classified as perfect matches, 76 (18%) as partial matches, and 3 (1%) as non-matches. The proportion of perfect and partial matches was similar when confining the pairwise comparisons to readings within the same breast.

Table 1 Measures of concordance of involution in 15 women undergoing bilateral prophylactic mastectomy

Measure	Result
Treating each woman as the experimental unit	
Intraclass correlation (95% CI)	0.75 (0.59, 0.89)
Kappa coefficient (95% CI)	0.67 (0.59, 0.75)
Pairwise comparisons, *N* (%)[a]	
Perfect matches	341 (81)
Partial matches	76 (18)
Non-matches	3 (1)
Treating each breast as the experimental unit	
Intraclass correlation (95% CI)	0.74 (0.60, 0.85)
Kappa coefficient (95% CI)	0.66 (0.53, 0.78)
Pairwise comparisons, *N* (%)[a]	
Perfect matches	145 (81)
Partial matches	34 (19)
Non-matches	1 (1)

Eight quadrants assessed per woman (four per breast)

Results are based on the three-level assessment of involution: none (0% involuted lobules), partial (1–74%), and complete (≥75%). Analyses using a four-level assessment, stratifying the partial involution category into mild (1–24% involuted lobules) and moderate (25–74%), yielded similar results

[a] Pairwise comparisons of involution measures within a woman. When treating woman as the experimental unit, the eight involution reads result in 28 pairwise comparisons per woman, or 420 overall in our group of 15 women. When treating each breast as an experimental unit, the four involution reads result in six pairwise comparisons per breast, or 12 per woman and thus 180 overall

We observed strong correlation among involution measures (Table 1). ICCs for both the four-level and three-level involution variables were identical (ICC = 0.75; 95% CI = 0.59, 0.89). Correlations were similar when modeling each breast as the experimental unit, indicating that patterns of involution were similar within each breast and across both breasts within a woman.

Kappa statistics also demonstrated strong agreement. Using generally accepted categorizations [12], the kappa for the three level involution variable fell into the "substantial" agreement category (kappa = 0.67, 95% CI 0.59, 0.75, Table 1), while the four-level involution kappa fell into the "moderate" category (kappa = 0.56, 95% CI 0.49, 0.62).

Discussion

We found high concordance of lobular involution values across multiple areas of breast tissue in women undergoing bilateral prophylactic mastectomy. Measures of agreement incorporating the eight quadrants across both breasts were similar to those obtained when treating each breast independently, indicating uniformity of effect in the entire field of breast tissue.

We previously reported a strong dose-response association of lobular involution with lower breast cancer risk among women with benign breast disease based on the background tissue surrounding the benign lesion [7], suggesting that assessing involution extent could improve risk prediction capabilities [7, 8]. Our current findings provide evidence that the assessment of involution extent from a single area of the breast is representative of the entire field of breast tissue.

Our study is limited by the large group of specimens falling under the intermediate categories of mild and moderate involution. It is possible that concordance would increase with more objective determinations of involution. We are currently exploring quantitative measures of lobule regression that may better define the involution status of women [13].

In summary, we observed moderate to high uniformity among measures of age-related lobular involution from multiple areas of breast tissue within a woman. This finding suggests that involution is a consistent physiological process across the field of breast tissue, supporting the use of measures from a single benign biopsy for breast cancer risk prediction.

Acknowledgements We are indebted to Teresa Allers, Romayne Thompson, Joanne Johnson, Melanie Kasner, and Mary Campion for data collection; to Shaun Maloney for database design and data management; to Tia Milanese for initial study set-up; to Ann Hart for tissue requests and tracking; and to Vicki Shea for help in preparing the manuscript. Supported by a Department of Defense Center of Excellence Grant (FEDDAMD17-02-1-0473-1), a grant (R01 CA46332) from the National Institutes of Health, and grants from Martha and H. Bruce Atwater Jr. and the Regis Foundation for Breast Cancer Research.

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