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PRECLINICAL STUDY

Histologic findings in normal breast tissues: comparison to reduction mammaplasty and benign breast disease tissues

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Abstract Investigations of breast carcinogenesis often rely upon comparisons between cancer tissue and nonmalignant breast tissue. It is unclear how well common reference sources of nonmalignant breast tissues reflect normal breast tissue. Breast tissue samples were evaluated from three sources: (1) normal donor tissues in the Susan G. Komen for the Cure® Tissue Bank at Indiana University Simon Cancer Center (KTB), (2) women who underwent reduction mammaplasty (RM) at Mayo Clinic Rochester, and (3) the Mayo Clinic Benign Breast Disease Cohort Study (BBD). Samples were examined histologically and assessed for proliferative disease and degree of lobular involution. Univariate comparisons were performed among the study groups, and multivariate analyses were performed with logistic regression to assess the association between study group and the presence of epithelial proliferative disease and complete lobular involution. Histologic data were collected for 455 KTB samples, 259 RM samples, and 319 BBD samples. Histologic findings and the frequency of epithelial proliferation were significantly different among the groups. Histologic abnormalities were seen in a minority of the KTB samples (35%), whereas an abnormality was present in 88% of RM tissues and 97.5% of BBD samples. The presence of proliferative disease (with or without atypical hyperplasia) was present in 3.3% of normal donors (3.3%), 17% of RM samples, and 34.9% of BBD samples ($P < 0.0001$ for each comparison). Multivariate analyses confirmed that these differences remained significant and also showed higher likelihood of complete lobular involution in the normal donor samples compared to RM and BBD tissues. Compared to benign breast disease tissues and reduction mammaplasty tissues, breast tissue samples from normal donors have significantly fewer histologic abnormalities and a higher frequency of more complete lobular involution. Breast tissue samples from normal donors represent a unique tissue resource with histologic features consistent with lower breast cancer risk.

Keywords Normal breast tissue · Benign breast disease · Reduction mammoplasty

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Introduction

In tissue-based studies of breast carcinogenesis, non-cancerous breast tissue is often utilized as a control tissue for comparison. Non-cancerous breast tissues are generally

selected on the basis of convenience—usually these are excess tissues with a benign histologic appearance that were banked from surgical procedures. However, it could be argued that almost all surgically resected breast tissues have been removed for some abnormality or state of high risk for breast cancer. Sources of non-cancerous control breast tissue used for research (and sometimes called "normal") may include unaffected ipsilateral or contralateral breast tissue from a patient with cancer, prophylactic mastectomy tissues, neighboring breast tissue from women with benign breast lesions, or, most commonly, reduction mammaplasty tissue [1–5]. While these tissue sources lack cancer, they may not represent truly normal breast tissue, since there is usually a clinical abnormality or high-risk condition that is motivating the removal of the tissue for clinical purposes. Reduction mammaplasty tissues may be regarded as the best representation of the normal state since the patient does not have cancer and the tissue removal is not targeted to a specific abnormality or high-risk state.

Our group has interest in developing tissue biomarkers of future breast cancer risk, with the ultimate goal of improving individualized risk stratification via biomarker assessment of the at-risk breast tissue. We have pursued this goal via the platform of benign breast disease, assembling a large cohort of women with benign breast biopsy tissues and long-term follow-up information on breast cancer events [6]. Histologic features and biomarkers have been identified that stratify cancer risk in the setting of benign breast disease (BBD) [7–10]. If such a tissue-based model can be developed in women who have had a clinical biopsy, that same concept could be considered in "normal" women. Defining the ability of such features to predict breast cancer risk for normal women could greatly enhance public health benefit, since the majority of women in the general population who develop breast cancer are not previously identified as being at increased risk [11]. As a first step in considering biomarkers of breast cancer risk in the general population, it is necessary to understand the characteristics of breast tissues in women without clinical breast disease.

Recently a team of breast cancer researchers and advocates at the Indiana University Melvin and Bren Simon Cancer Center recognized a critical need in breast cancer research to develop a repository of normal breast tissues to provide high quality samples to be used for breast cancer research. They successfully pursued efforts to establish a unique resource of normal breast tissues, resulting in the Susan G. Komen for the Cure® Tissue Bank at the IU Simon Cancer Center [12]. These tissue samples were obtained from healthy women who have no known palpable or imaging abnormality.

In this study, our aim was to perform histologic review of normal breast tissue samples in the Komen Tissue Bank (KTB) to provide the first histologic characterization of a large sample of normal breast tissues, and to compare these tissues to two other sources of non-cancerous breast tissue: (1) breast tissues from women who underwent reduction mammaplasty (RM), and (2) breast tissues from women with BBD. We planned to compare two specific histologic features of breast tissue that have been shown to correlate with subsequent breast cancer risk—the degree of epithelial proliferation and the extent of lobular involution.

Epithelial proliferation is well-established as a histologic feature that discriminates breast cancer risk among women with benign breast disease [6, 13–15], with increasing relative risk for breast cancer in non-proliferative disease (RR 1.3), proliferative disease without atypia (RR 1.9), and atypical hyperplasia (RR 4.2) [6]. Our group has also reported that lobular involution, which is the normal regression of breast lobules that occurs with aging, is a novel histologic finding associated with breast cancer risk [8, 16]. Specifically, we found that more complete involution in the normal-appearing background tissue of benign breast biopsies is associated with reduced breast cancer risk, and this association is independent of epithelial proliferation.

Our goal was to determine how samples of breast tissue from normal donors compare to reduction mammaplasty samples (the source of "normal" tissue used in most research) and benign breast biopsy tissues. We hypothesized that breast tissues from normal donors would have fewer histologic abnormalities with epithelial proliferation and more complete lobular involution than both reduction mammaplasty and benign breast disease tissues.

Methods

Study samples

Formal approvals were obtained from the Mayo Clinic Institutional Review Board and the Komen Tissue Bank for histologic review of breast tissues. KTB samples are obtained from women without breast cancer who volunteer to donate their breast tissue for breast cancer research. Normal donor breast tissue collections occur five times a year in an ongoing basis. Under local anesthetic, tissue donors provide three large cores of breast tissue from the upper outer quadrant of either breast via 10 gauge vacuum-assisted biopsy. Two cores are cryopreserved; the third is formalin-fixed and paraffin-embedded. At the time this project was initiated, the KTB had approximately 500 breast tissue samples with an H&E slide available for review.

Two groups of breast tissues were obtained from the Mayo Clinic Tissue Registry, which maintains an extensive

archive of tissues. The Mayo Clinic Benign Breast Disease Cohort is a large, well-described cohort of ~9,000 women who underwent breast biopsy with benign findings from 1967 to 1991 [6]. Recently this cohort has been expanded to include benign breast biopsies through 2001, including those performed with core needle technique (most in the years 1994–2001). Since KTB samples were obtained using core biopsies, we selected only those BBD samples that were obtained with core biopsy for evaluation in this comparison study. A list was compiled of all reduction mammaplasty procedures performed at Mayo Clinic Rochester during a similar timeframe (1995–2001), and a random sample of 350 were selected for histologic review of the archived H&E slides. Among all three groups, any women with a personal history of breast cancer were excluded from eligibility for histologic review of tissues.

Histologic review of breast tissues

All H&E slides were reviewed together by a single breast pathologist (DWV) along with the first author (ACD). No clinical information was known about the donor/patient at the time of histologic review. Samples without any breast tissue or samples consisting of only fat without any lobules or ductal structures were considered ineligible for review. All histologic findings for each eligible sample were recorded, with an overall histologic impression category assigned based upon the greatest degree of abnormality according to the following groups: (1) no histologic abnormality, (2) non-proliferative disease, (3) proliferative disease, or (4) atypical hyperplasia. Non-proliferative disease included cysts, fibrosis, non-complex fibroadenoma, apocrine metaplasia, mild ductal hyperplasia, and columnar cell change without hyperplasia. Proliferative disease included papilloma, sclerosing adenosis, moderate to florid ductal hyperplasia, and columnar cell change with hyperplasia. Atypical hyperplasia included either atypical ductal hyperplasia or atypical lobular hyperplasia (cases of LCIS were previously excluded from the BBD group and none were identified in the KTB or RM samples).

For each sample, a single tissue slide was examined. The total number and the number of each type of lobule present (normal or fibrocystic) were recorded, and the size of the tissue specimen was measured in millimeters. In the case of core biopsy samples, the number, length, and width of individual cores were measured and recorded. Lobule number and specimen size were used to calculate lobule density, defined as the number of lobules per square millimeter of tissue on the slide. Samples containing one or more normal lobules were judged on the degree of involution seen among normal lobules and were classified as none, mildly involuted (1–24%), partially involuted (25–74%), or completely involuted (≥75%). Involution could not be assessed in samples without any normal lobules.

Statistical analysis

Univariate comparisons between the three study groups were performed using one-way ANOVA in the case of continuous variables, chi-square tests in the case of nominal variables, and Kruskal–Wallis tests in the case of ordinal variables. When the omnibus test was statistically significant, pairwise comparisons were performed using two-sample t tests, chi-square tests, and Wilcoxon rank-sum tests as appropriate. Multivariate analysis was performed using logistic regression to adjust for confounding variables in assessing the association between study group and two separate response variables: presence of any proliferative disease and complete involution. Covariates considered in multivariate analysis included tissue specimen group, age, lobule density, involution status, and any proliferative disease. P values < 0.05 were considered statistically significant. Analysis was performed using SAS (Version 9.2, SAS Institute Inc., Cary, NC).

Results

In the KTB group, samples from 496 women were initially eligible, of which 41 (8%) were excluded due to absence of breast tissue, leaving 455 samples. Among the 350 randomly selected RM samples, slides were not available for 83 (24%) and 8 additional samples were excluded (no breast tissue seen), resulting in 259 samples. There were 375 Mayo BBD core biopsy samples eligible for review, of which 45 (12%) had no available slides and 11 were excluded, leaving 319 samples for analysis.

Sample characteristics by group

Normal donors and reduction mammaplasty patients were similar in age (mean age 39 and 38, respectively) and were generally younger than BBD subjects (mean age 49, see Table 1). BBD core biopsy samples had a higher number of cores (mean 4.5) compared to KTB samples (mean 1.0). Each group differed significantly from every other group with respect to the specimen area, the mean number of lobules, and lobule density. The area of tissue on H&E slide that was available for evaluation was largest in the RM group (mean 240 mm^2), intermediate in the BBD group (mean 67 mm^2), and lowest in the KTB group (mean 34 mm^2). The mean total number of lobules present in the samples was also highest in the RM group (28), intermediate in the BBD group (12), and lowest in the KTB group

(7). However, after accounting for the size of the tissue specimen by calculating the density of lobules per square mm of tissue, the KTB and RM groups were reversed, with the highest mean density of lobules seen in the Komen normal tissues (0.22 lobules/mm^2) and the lowest in the RM tissues (0.13 lobules/mm^2).

Histologic findings by group

The majority of the normal donor tissue samples (65%) had no histologic abnormality (see Table 2). Conversely, almost all BBD tissues (97.5%) and most RM samples (87.6%) had some histologic abnormality, with the majority of abnormalities consisting of non-proliferative lesions (Fig. 1). The presence of proliferative disease (without or with atypical hyperplasia) was present in only 3.3% of KTB samples compared to 17.0% of RM tissues ($P < 0.0001$) and 34.9% of BBD samples ($P < 0.0001$). By univariate analysis across the three groups, lobular involution did not appear to vary significantly (Table 3), but multivariate analyses were performed due to the known strong association of age and lobular involution.

Multivariate analyses

For the response variable of proliferative disease, multivariate analyses were performed adjusting for age and lobule density (Table 4, Model 1) and also for involution status when available (Table 4, Model 2). In these analyses, each study group remained significantly different from every other group with respect to the finding of any proliferative disease. The largest effect was expected and confirmed between BBD and KTB tissues (OR = 10.5, 95% CI 5.5 and 20.0), but RM tissues were also significantly more likely than KTB tissues to have proliferative disease (OR = 5.5, 95% CI 2.7 and 11.1); (Table 4, Model 2). Increasing age showed a small but significant association with the likelihood of finding proliferative

Table 1 Demographic and sample characteristics compared across groups

	KTB $N = 455$	RM $N = 259$	BBD $N = 319$	P value
Age at biopsy/surgery[a] (years)				
Mean (SD)	38.9 (14.6)	38.0 (13.5)	48.6 (12.2)	<0.0001
Median (range)	38 (18, 77)	36 (18, 75)	48 (18, 82)	
Age group[a], *n* (%)				<0.0001
18–35	205 (45.3)	125 (48.3)	34 (10.7)	
36–45	91 (20.1)	61 (23.6)	99 (31.0)	
46–55	81 (17.9)	44 (17.0)	99 (31.0)	
>55	76 (16.8)	29 (11.2)	87 (27.3)	
Unknown	2	0	0	
Number of cores				
Mean (SD)	1.0 (0.1)	NA	4.5 (2.4)	<0.0001
Median (range)	1 (1, 2)		4 (1, 20)	
Specimen size[b] (mm^2)				
Mean (SD)	33.7 (12.3)	240.4 (117.3)	66.9 (67.1)	<0.0001
Median (range)	33 (5, 75)	216 (60, 714)	42 (4, 695)	
Number of lobules[c]				
Mean (SD)	6.9 (6.9)	28.4 (22.9)	11.7 (14.4)	<0.0001
Median (range)	5 (0, 44)	20 (2, 124)	6 (0, 103)	
Patients with zero lobules[c], *n* (%)	64 (14.1)	0	19 (6.0)	<0.0001
Lobule density[b] (lobules/mm^2)				
Mean (SD)	0.22 (0.21)	0.13 (0.10)	0.18 (0.16)	<0.0001
Median (range)	0.17 (0, 1.03)	0.10 (0.01, 0.69)	0.13 (0, 1.0)	

KTB Komen Tissue Bank normal donor group, *RM* reduction mammaplasty group, *BBD* Benign Breast Disease group

[a] Age is missing for two patients from the KTB group

[b] Four patients from BBD group, one patient from KTB group, and two patients from Reduction Mammaplasty group are missing measurements necessary to calculate specimen size and thus lobule density

[c] Number of lobules is calculated as the sum of fibrocystic, normal, and hyperexpanded lobular units (HELUs) on one slide

Table 2 Histologic impression by group

	KTB $N = 455$	RM $N = 259$	BBD $N = 319$	P value
Histologic impression[a], n (%)				<0.0001
No histologic abnormality	296 (65.1)	32 (12.4)	8 (2.5)	
Non-proliferative disease	144 (31.6)	183 (70.7)	199 (62.6)	
Proliferative disease without atypia	12 (2.6)	42 (16.2)	85 (26.7)	
Atypical hyperplasia	3 (0.7)	2 (0.8)	26 (8.2)	
Missing	0	0	1	
Any proliferative disease, n (%)	15 (3.3)	44 (17.0)	111 (34.9)	<0.0001
Atypical hyperplasia, n (%)	3 (0.7)	2 (0.8)	26 (8.2)	<0.0001

KTB Komen Tissue Bank normal donor group, *RM* reduction mammaplasty group, *BBD* Benign Breast Disease group

[a] Category for worst lesion

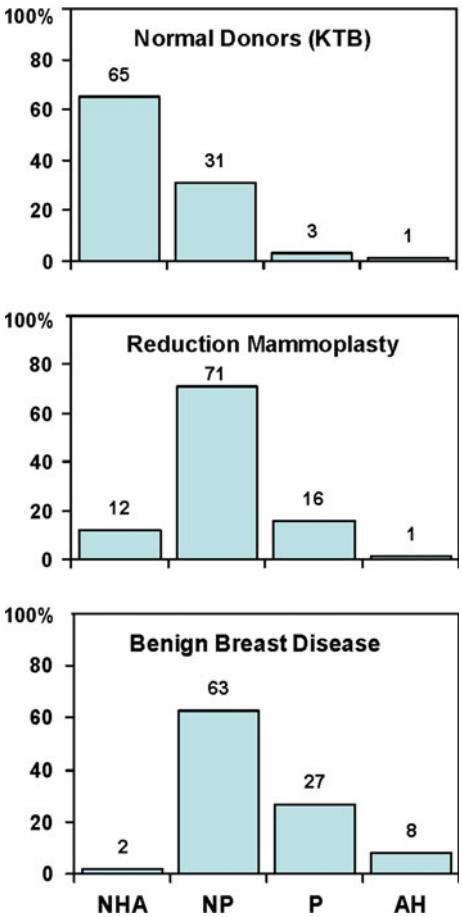

Fig. 1 Proportions of samples with no histologic abnormality (NHA), non-proliferative disease (NP), proliferative disease (P), or atypical hyperplasia (AH)

disease (OR 1.06 per 1 year increase). Tissues categorized as having partial lobular involution were more likely to have proliferative disease than completely involuted tissues, while the density of lobules within the breast tissue specimens was not related to the presence of proliferative disease.

Since lobular involution is known to be strongly associated with age, multivariate analysis was also performed to evaluate differences in complete involution among the three groups (Table 5). Although complete involution was slightly more frequent in the BBD group (46%) compared to the KTB group (43%), in multivariate analysis adjusting for age, lobule density, and any proliferative disease, the BBD group was less likely to demonstrate complete involution compared to the KTB group (OR = 0.55, $P = 0.005$). The RM group was also less likely to demonstrate complete involution compared to the KTB group, while the BBD and RM groups did not differ significantly in their likelihood of having complete involution. Furthermore, both increasing lobule density and the presence of any proliferative disease also remained significant independent predictors of a decreased likelihood of complete involution ($P < 0.0001$ for each).

Discussion

In this histologic review of non-cancerous breast tissues from three distinct sources, we found that KTB normal donor tissues were characterized by less epithelial proliferation and more complete involution than both reduction mammaplasty and benign breast disease tissues. These histologic features are consistent with the expectation of lower breast cancer risk in the KTB donors. While histologic abnormalities are expected in BBD tissues, we were surprised to find that 88% of RM tissues also harbored some abnormality. The proportion of samples with proliferative disease among BBD tissues is approximately one-third in this study sample, concordant with multiple large BBD cohort studies [13–15]. We found that proliferative disease was rare among the KTB normal donor tissue samples (as expected) but was significantly more common in RM tissues, a tissue source that is often used to represent the normal state. The RM tissues had a frequency

Table 3 Univariate analysis of involution status by group (excluding patients with 0 normal lobules)

	KTB $N = 381$	RM $N = 249$	BBD $N = 293$	P value
Involution category, n (%)				0.11
None	7 (1.8)	6 (2.4)	9 (3.1)	
1–24%	40 (10.5)	26 (10.4)	23 (7.8)	
25–74%	170 (44.6)	126 (50.6)	126 (43.0)	
≥75%	164 (43.0)	91 (36.5)	135 (46.1)	
Missing	0	1	0	
Complete involution[a], n (%)	164 (43.0)	91 (36.5)	135 (46.1)	0.08

KTB Komen Tissue Bank normal donor group, *RM* reduction mammaplasty group, *BBD* Benign Breast Disease group

[a] Defined as involution ≥75%

Table 4 Multivariate model for the presence of proliferative disease

	Model 1 ($n = 1023$)		Model 2 ($n = 913$)	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Group		<0.0001 (overall)		<0.0001 (overall)
BBD vs KTB	11.8 (6.6, 20.9)	<0.0001	10.5 (5.5, 20.0)	<0.0001
RM vs KTB	6.6 (3.5, 12.4)	<0.0001	5.5 (2.7, 11.1)	<0.0001
BBD vs RM	1.8 (1.2, 2.7)	0.009	1.9 (1.2, 3.0)	0.006
Age, per 1 year increase	1.04 (1.03, 1.06)	<0.0001	1.06 (1.04, 1.08)	<0.0001
Lobule density, per 0.10 increase	0.99 (0.87, 1.12)	0.85	0.87 (0.75, 1.02)	0.08
Involution status				<0.0001 (overall)
None			2.1 (0.4, 10.8)	0.39
1–24%			2.9 (1.2, 7.2)	0.02
25–74%			3.7 (2.2, 6.0)	<0.0001
≥75%			1.0 (reference)	

Model 1 includes only study group, age, and lobule density, while model 2 also includes involution status. Subjects with missing response or covariate values are excluded

KTB Komen Tissue Bank normal donor group, *RM* reduction mammaplasty group, *BBD* Benign Breast Disease group

Table 5 Multivariate model for complete involution

	$n = 913$	
	Odds ratio (95% CI)	P value
Group		0.0001 (overall)
BBD vs KTB	0.55 (0.37, 0.84)	0.005
RM vs KTB	0.42 (0.28, 0.64)	<0.0001
BBD vs RM	1.33 (0.86, 2.04)	0.20
Age, per 1 year increase	1.08 (1.07, 1.10)	<0.0001
Lobule density, per 0.10 increase	0.49 (0.43, 0.56)	<0.0001
Any proliferative disease	0.32 (0.20, 0.51)	<0.0001

Patients with 0 normal lobules and missing response or covariate values are excluded

KTB Komen Tissue Bank normal donor group, *RM* reduction mammaplasty group, *BBD* Benign Breast Disease group

distribution of proliferative disease that more closely resembled the BBD tissues rather than the KTB tissues, raising questions about the suitability of RM tissues as normal breast tissue controls.

A similarly high frequency of histologic abnormalities in RM tissues has been reported by Pitanguy et al. [17]. In that retrospective review of RM tissues from 2488 women, 81% had fibrocystic or fibroadipose change and 4% were

reported as normal [17]. Proliferative and non-proliferative fibrocystic findings were not distinguished (e.g., sclerosing adenosis was included in the larger category of fibrocystic change). They reported a separate category of "atrophy" in 9%. If this group of women described as atrophy had normal involuted breast tissue, then that would increase the proportion of normals to 13%, very close to our proportion of 12% of RM samples that were histologically normal. The authors concluded that "…the concept of [the use of RM tissue as] normal breast tissue was questioned" [17].

Regarding lobular involution, we found that KTB normal donor samples showed a higher likelihood of complete involution compared to RM and BBD tissues, after adjusting for age and other factors. Lobular involution is an age-related process of atrophy of the breast lobules, and complete involution is associated with reduced breast cancer risk [16]. The more frequent state of complete involution in normal donor tissues provides histologic evidence of lower breast cancer risk than in BBD or RM tissues. This finding may seem confusing in light of reports that RM patients do not have increased breast cancer risk. Two studies have shown that among women who underwent RM, breast cancer risk after the procedure is reduced compared to the general population [18, 19]. This reduction in risk would appear to be related to the removal of a large amount of breast tissue, removing the cancer risk associated with that portion of tissue. To our knowledge, no study has addressed long-term breast cancer risk in women with macromastia severe enough to warrant surgery but who have not undergone RM.

There are several notable strengths of our study. This is the first review of histologic findings in a large sample of breast tissues from normal donors stored in the KTB. Pathology review was performed by a single breast pathologist who has extensive experience in breast research. Another strength is the comparison of KTB samples with RM samples, the current standard of normal tissue used in most research. For KTB and BBD samples, care was taken to evaluate samples obtained with the same biopsy method by selecting BBD samples obtained with core needle biopsy from more recent years to approximate the era of tissue harvest from KTB donors. Furthermore, multivariate analyses permitted adjustment for multiple variables in assessing the differences in involution and proliferative disease among the groups.

We acknowledge several limitations to our study. First, indications and methods of breast tissue sampling varied among the three groups and might affect our findings. The KTB donors represent a convenience sample of women who had no specific indication for tissue removal. Considering that BBD tissue samples result from the intentional targeting of a palpable or mammographic abnormality, a higher level of histologic abnormalities is to be expected in the BBD group. In RM, the indication for tissue removal is excess breast tissue rather than a specific breast lesion.

In addition to differing indications for tissue biopsy among the three groups, there were technical differences in how the tissues were obtained. With a large volume of surgically resected tissue in RM cases, areas of apparent gross abnormality are most likely to be selected for pathologic sectioning and histologic review. This selective tissue sampling approach in RM specimens is the standard of care in our clinical practice for RM specimens and was also the approach of Pitanguy et al. [17]. Therefore, based on tissue processing with intentional sampling of grossly firm or abnormal areas, the RM tissues may be more likely to demonstrate abnormalities than other areas within the RM tissue designated as surgical waste. As a result, the RM tissue samples may be more likely to demonstrate abnormalities than a single non-directed random core sample of breast tissue from the normal donors. However, when considering RM tissues as a source of normal comparison tissues to be used in breast cancer research, the RM samples that are available in archived slides and preserved in tissue blocks would be those same areas containing histologic abnormalities and would be unlikely to provide areas of normal breast tissue for study.

Selection bias could also be present within the population of KTB donors, since women who are willing to undergo an invasive procedure (albeit a minor procedure) might be motivated to contribute to research by a higher than average personal risk of breast cancer or a family history of breast cancer. However, among 221 KTB donors in whom a Gail risk score was available, the mean lifetime risk score was 12.0% (median 10.8%), which matches the 12% expected Gail risk score for the general population [20]. Despite these reassuring risk estimates, we must accept the possibility that this volunteer group may be at higher risk than the general population. However, if that were the case then our findings would represent an underestimation of the true differences between low-risk normal breast tissues and the RM and BBD tissues.

The KTB tissue samples are small in size and randomly obtained from one breast, yet there is good evidence that a single breast tissue sample may provide valuable information that reflects a woman's overall field of breast tissue and cancer risk. Women with BBD have an increased risk of breast cancer longterm that is similar for both breasts [6], and this is also true for women with atypical hyperplasia [7]. Lobular carcinoma in situ is another entity commonly found in multiple areas of both breasts [21] and indicates similarly increased cancer risk for both breasts [22], suggesting that genetic or environmental/hormonal

exposures that predispose to breast abnormalities may have pervasive effects across the field of breast tissue in a woman. Whereas a random sample of breast tissue cannot determine if any proliferative lesions exist throughout the entire field of breast tissue, it can provide information on the degree of lobular involution in the background breast lobules. Random periareolar fine needle aspiration can provide cytologic samples to help differentiate risk, primarily in high-risk women with atypia [23], but this technique cannot provide intact lobular units to assess architectural tissue features that may stratify risk in the much larger proportion of women without atypia or known increase in risk. Our group has shown that lobular involution in a single biopsy sample is representative of the involution status in tissue from both breasts [24]. Since lobular involution is judged by background lobules (apart from any fibrocystic lesions), it is a histologic feature of risk that is less dependent on sampling techniques than specific benign breast lesions requiring targeted clinical biopsy. Therefore, it is reasonable that a single sample of breast tissue from a woman may provide a representative sample of certain histologic findings to help inform breast cancer risk.

In summary, we found that the majority of breast tissue samples from normal donors have histologic features consistent with lower breast cancer risk—less epithelial proliferation and more complete involution. In contrast, most reduction mammaplasty tissue samples show some degree of abnormality, calling into question the suitability of RM tissues as normal controls in breast cancer research. Breast tissue samples from normal donors represent a unique tissue resource with histologic features of lower breast cancer risk.

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