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BRIEF COMMUNICATIONS

Association of Genetic Ancestry With Terminal Duct Lobular Unit Involution Among Healthy Women

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Abstract

Reduced age-related terminal duct lobular unit (TDLU) involution has been linked to increased breast cancer risk and triple-negative breast cancer. Associations of TDLU involution levels with race and ethnicity remain incompletely explored. Herein, we examined the association between genetic ancestry and TDLU involution in normal breast tissue donated by 2014 healthy women in the United States. Women of African ancestry were more likely than European women to have increased TDLU counts (odds ratio $[OR]_{trend} = 1.36$, 95% confidence interval [CI] = 1.07 to 1.74), acini counts per TDLU (OR = 1.47, 95% CI = 1.06 to 2.03), and median TDLU span ($OR_{trend} = 1.44$, 95% CI = 1.08 to 1.91), indicating lower involution, whereas East Asian descendants were associated with decreased TDLU counts ($OR_{trend} = 0.52$, 95% CI = 0.35 to 0.78) after controlling for potential confounders. These associations are consistent with the racial variations in incidence rates of triple-negative breast cancer in the United States and suggest opportunities for future work examining whether TDLU involution may mediate the racial differences in subtype-specific breast cancer risk.

Terminal duct lobular units (TDLUs) represent the main source of breast cancers and their precursors. With aging, TDLUs undergo a reduction in number and size, and the number of acini (substructures) per TDLU (1). Studies have demonstrated that reduced or delayed TDLU involution is associated with increased breast cancer risk among women with benign breast diseases (2-5). The extent of TDLU involution has also been linked to multiple breast cancer risk factors, including age at full-term pregnancy, breastfeeding (6), mammographic density (7-11), circulating hormone levels (12-15), and 313 single nucleotide polymorphism-based polygenic risk score (16), suggesting that TDLU involution may serve as a histologic marker of breast cancer risk.

Previously, we found that reduced TDLU involution was more frequently observed in normal breast tissues surrounding triple-negative breast cancer (TNBC) than in normal breast adjacent to other cancer subtypes (17,18). Additionally, higher proportions of African ancestry have been associated with TNBC or basal-like subtype (enriched with TNBC patients) (19-22). To address whether TDLU involution, as a risk factor and intermediate phenotype for breast cancer, may vary by genetic ancestry, we examined TDLU involution levels with 3 standardized quantitative measures—number of TDLUs per tissue area (TDLUs/mm^2), median TDLU span, and median category of acini per TDLU (acini per TDLU)—as previously described (5,6,11,13), in relation to inferred continental-level ancestry based on 41 single nucleotide polymorphisms or ancestry-informative markers (23) in 2014 healthy women who donated breast tissue to the Susan G. Komen Tissue Bank (Supplementary Methods, available online) (24,25). All statistical tests were 2-sided and considered statistically significant at $P < .05$.

Based on genetic ancestry, 1387 women were identified as European, 318 as African, 120 as Middle Eastern, 106 as East Asian, and 83 as Central and South Asian descendants (Table 1). Age, body mass index (BMI), and reproductive factors varied by genetic ancestry. Specifically, African descendants tended to have a higher prevalence of obesity (BMI > 30 kg/m^2), earlier age at menarche, and younger age at full-term first birth and were

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Table 1. Participant characteristics by genetic ancestry among 2,014 healthy women who donated breast tissue to the Susan G. Komen Tissue Bank

Characteristics	Total, No.	European (n = 1,387) No. (%)	African (n = 318) No. (%)	Middle Eastern (n = 120) No. (%)	East Asian (n = 106) No. (%)	Central South Asian (n = 83) No. (%)	P[a]
Age, y							
18-29	467	362 (26.1)	43 (13.5)	24 (20.0)	16 (15.1)	22 (26.5)	<.001
30-39	417	267 (19.3)	85 (26.7)	21 (17.5)	24 (22.7)	20 (24.1)	
40-49	476	318 (22.9)	89 (28.0)	25 (20.8)	25 (23.6)	19 (22.9)	
50-59	391	279 (20.1)	56 (17.6)	26 (21.7)	18 (17.0)	12 (14.5)	
60-84	263	161 (11.6)	45 (14.2)	24 (20.0)	23 (21.7)	10 (12.0)	
Body mass index, kg/m^2							
<25	678	496 (35.8)	53 (16.7)	40 (33.3)	53 (50.0)	36 (43.4)	<.001
25-29	568	397 (28.6)	86 (27.0)	39 (32.5)	27 (25.5)	19 (22.9)	
30-34	366	253 (18.2)	69 (21.7)	19 (15.8)	10 (9.4)	15 (18.0)	
≥35	399	238 (17.2)	110 (34.6)	22 (18.4)	16 (15.1)	13 (15.7)	
Unknown	3	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Self-reported race and ethnicity[b]							
American Indian or Alaskan Natives	4	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.2)	<.001
Asian[c]	101	0 (0.0)	0 (0.0)	0 (0.0)	94 (88.7)	7 (8.4)	
Black	306	3 (0.2)	300 (94.3)	1 (0.8)	0 (0.0)	2 (2.4)	
Hispanic (includes all races)	109	57 (4.1)	6 (1.9)	13 (10.8)	1 (0.9)	32 (38.6)	
White	1445	1304 (94.0)	0 (0.0)	104 (86.7)	1 (0.9)	36 (43.4)	
Other	44	18 (1.3)	11 (3.5)	1 (0.8)	9 (8.5)	5 (6.0)	
Unknown	5	3 (0.2)	1 (0.3)	1 (0.8)	0 (0.0)	0 (0.0)	
Menopausal status							
Premenopausal	1281	884 (63.7)	206 (64.8)	70 (58.4)	63 (59.4)	58 (69.9)	.01
Postmenopausal	679	459 (33.1)	110 (34.6)	46 (38.3)	41 (38.7)	23 (27.7)	
Unknown	54	44 (3.2)	2 (0.6)	4 (3.3)	2 (1.9)	2 (2.4)	
Age at menarche, y							
<13	1011	658 (47.5)	195 (61.3)	63 (52.5)	52 (49.0)	43 (51.8)	<.001
13	550	408 (29.4)	62 (19.5)	29 (24.2)	27 (25.5)	24 (28.9)	
≥14	450	319 (23.0)	61 (19.2)	28 (23.3)	27 (25.5)	15 (18.1)	
Unknown	3	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	
No. of children							
0	101	64 (4.6)	21 (6.6)	6 (5.0)	6 (5.7)	4 (4.8)	<.001
1	277	177 (12.8)	69 (21.7)	14 (11.6)	13 (12.3)	4 (4.8)	
2	545	377 (27.2)	86 (27.0)	30 (25.0)	28 (26.4)	24 (28.9)	
3+	348	228 (16.4)	58 (18.2)	26 (21.7)	18 (17.0)	18 (21.7)	
Unknown	743	541 (39.0)	84 (26.5)	44 (36.7)	41 (38.6)	33 (39.8)	
Age at first full-term birth, y[d]							
<25	492	325 (41.6)	119 (55.9)	26 (37.1)	5 (8.5)	17 (37.0)	<.001
25-29	345	254 (32.5)	45 (21.1)	27 (38.6)	9 (15.3)	10 (21.7)	
≥30	274	198 (25.3)	48 (22.5)	16 (22.9)	3 (5.1)	9 (19.6)	
Unknown	59	5 (0.6)	1 (0.5)	1 (1.4)	42 (71.1)	10 (21.7)	
Breastfeeding[d]							
Yes	865	583 (74.6)	135 (63.4)	57 (81.5)	48 (81.4)	42 (91.3)	.001
No	298	193 (24.7)	78 (36.6)	12 (17.1)	11 (18.6)	4 (8.7)	
Unknown	7	6 (0.7)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	
Fat tissue in tissue area of interest, %							
≤25	188	134 (9.7)	15 (4.7)	11 (9.2)	10 (9.4)	18 (21.7)	<.001
26-50	187	127 (9.2)	22 (6.9)	9 (7.5)	17 (16.0)	12 (14.4)	
51-75	386	270 (19.5)	50 (15.7)	27 (22.5)	22 (20.7)	17 (20.4)	
>75	1,253	856 (61.7)	231 (72.7)	73 (60.8)	57 (53.8)	36 (43.5)	
Absence of TDLU in tissue area of interest (complete involution of TDLU)[e]							
Overall	684	478 (34.5)	96 (30.2)	41 (34.2)	44 (41.5)	25 (30.1)	.25
Premenopausal	382	263 (29.8)	64 (31.1)	16 (22.9)	21 (33.3)	18 (30.5)	.70
Postmenopausal	287	207 (45.1)	31 (28.2)	22 (47.8)	22 (53.7)	5 (21.7)	.002

[a]Result was obtained from χ^2 or Fisher exact test whichever was appropriate. TDLU = terminal duct lobular unit.
[b]Mutually exclusive self-reported race and ethnicity was identified based on 2 closed-ended questions: 1) Are you Hispanic or Latino? Yea or No; 2) What is your race? White or Caucasian, Black or African American, Asian, American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, Unknown, Other.
[c]Includes Asian and Native Hawaiian or Asian Pacific Islander.
[d]Among parous women.
[e]Presented for overall and stratified by menopausal status.

Table 2. Association of genetic ancestry with terminal duct lobular unit (TDLU) involution of the normal breast in 2,014 women who donated breast tissue to the Susan G. Komen Tissue Bank

	European (n = 1,387) No. (%)	African (n = 318) No. (%)	Middle Eastern (n = 120) No. (%)	East Asian (n = 106) No. (%)	Central South Asian (n = 83) No. (%)	African vs. European[a] OR (95% CI)	Middle Eastern vs. European[a] OR (95% CI)	East Asian vs. European[a] OR (95% CI)	Central South Asian vs. European[a] OR (95% CI)	P[a]
Overall										
TDLU count per 100 mm^2										
0	478 (34.5)	96 (30.2)	41 (34.2)	44 (41.5)	25 (30.1)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
1-7	477 (34.3)	125 (39.3)	41 (34.2)	43 (40.6)	24 (28.9)	1.46 (1.07 to 1.99)	1.02 (0.64 to 1.63)	0.75 (0.46 to 1.21)	0.70 (0.38 to 1.31)	
8+	432 (31.2)	97 (30.5)	38 (31.6)	19 (17.9)	34 (41.0)	1.57 (1.09 to 2.27)	1.09 (0.62 to 1.92)	0.32 (0.17 to 0.63)	0.91 (0.47 to 1.75)	.004
P_{trend}						1.36 (1.07 to 1.74)	1.10 (0.76 to 1.59)	0.52 (0.35 to 0.78)	0.97 (0.63 to 1.51)	.001
Median category of acini counts per TDLU[b]										
1	491 (54.0)	113 (50.9)	45 (57.0)	37 (58.7)	30 (51.7)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
1.5 to 5	418 (46.0)	109 (49.1)	34 (43.0)	26 (41.3)	28 (48.3)	1.47 (1.06 to 2.03)	0.94 (0.57 to 1.55)	0.92 (0.53 to 1.61)	1.14 (0.64 to 2.04)	.20
Median of TDLU spans, μm										
53.0-263.0	306 (33.7)	72 (32.4)	33 (41.8)	26 (41.2)	13 (22.4)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
263.5-377.0	312 (34.3)	68 (30.6)	28 (35.4)	20 (31.8)	22 (37.9)	1.09 (0.74 to 1.60)	0.85 (0.49 to 1.46)	0.86 (0.46 to 1.62)	1.84 (0.88 to 3.87)	
377.5-1,375.0	291 (32.0)	82 (37.0)	18 (22.8)	17 (27.0)	23 (39.7)	1.60 (1.08 to 2.36)	0.58 (0.31 to 1.10)	0.79 (0.40 to 1.57)	2.17 (1.01 to 4.67)	.06
P_{trend}						1.44 (1.08 to 1.91)	0.73 (0.47 to 1.12)	0.85 (0.52 to 1.38)	1.59 (0.95 to 2.66)	.01
Premenopausal women[c]										
TDLU count per 100 mm^2										
0	263 (29.8)	64 (31.1)	16 (22.9)	21 (33.3)	18 (31.0)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
1-8	325 (36.8)	79 (38.4)	23 (32.9)	27 (42.9)	15 (25.9)	1.10 (0.74 to 1.64)	1.00 (0.50 to 2.02)	0.75 (0.39 to 1.45)	0.43 (0.20 to 0.93)	
9+	296 (33.4)	63 (30.5)	31 (44.2)	15 (23.8)	25 (43.1)	1.17 (0.73 to 1.85)	1.36 (0.65 to 2.84)	0.42 (0.19 to 0.95)	0.68 (0.31 to 1.47)	.18
P_{trend}						1.09 (0.80 to 1.48)	1.23 (0.76 to 1.99)	0.59 (0.36 to 0.98)	0.87 (0.51 to 1.47)	.21
Median category of acini counts per TDLU[b]										
1 to 1.5	348 (56.0)	66 (46.5)	32 (59.3)	19 (45.2)	19 (47.5)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
2 to 5	273 (44.0)	76 (53.5)	22 (40.7)	23 (54.8)	21 (52.5)	1.67 (1.13 to 2.46)	0.86 (0.48 to 1.53)	1.58 (0.83 to 3.01)	1.41 (0.72 to 2.75)	.05
Median of TDLU spans, μm										
84.0-342.0	324 (52.2)	68 (47.9)	34 (63.0)	22 (52.4)	13 (32.5)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
342.5-1,143.0	297 (47.8)	74 (52.1)	20 (37.0)	20 (47.6)	27 (67.5)	1.36 (0.92 to 2.00)	0.61 (0.34 to 1.10)	0.93 (0.49 to 1.77)	2.06 (1.02 to 4.16)	.05
Postmenopausal women[c]										
TDLU count per 100 mm^2										
0	207 (45.1)	31 (28.2)	22 (47.8)	22 (53.7)	5 (21.7)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
1-4	124 (27.0)	37 (33.6)	11 (23.9)	13 (31.7)	8 (34.8)	2.18 (1.26 to 3.76)	0.91 (0.41-2.02)	0.62 (0.28 to 1.41)	1.99 (0.60 to 6.62)	
≥5	128 (27.9)	42 (38.2)	13 (28.3)	6 (14.6)	10 (43.5)	3.16 (1.77 to 5.62)	1.68 (0.74-3.80)	0.26 (0.09 to 0.78)	2.47 (0.69 to 8.87)	<.001
P_{trend}						2.33 (1.54 to 3.52)	1.34 (0.73-2.45)	0.42 (0.21 to 0.84)	1.76 (0.75 to 4.13)	<.001
Median category of acini counts per TDLU[b]										
1	193 (76.6)	59 (74.7)	18 (75.0)	18 (90.0)	16 (88.9)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
1.5 to 5	59 (23.4)	20 (25.3)	6 (25.0)	2 (10.0)	2 (11.1)	1.30 (0.69 to 2.44)	1.41 (0.51-3.96)	0.46 (0.10 to 2.20)	0.50 (0.11 to 2.39)	.57
Median of TDLU spans, μm										
53.0-261.5	130 (51.6)	36 (45.6)	10 (41.7)	14 (70.0)	9 (50.0)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
262.0-1,375.0	122 (48.4)	43 (54.4)	14 (58.3)	6 (30.0)	9 (50.0)	1.40 (0.81 to 2.43)	1.69 (0.69-4.15)	0.67 (0.23 to 1.93)	1.43 (0.51 to 4.06)	.47

[a]Polytomous logistic regression, overall or stratified by menopausal status, was constructed for each of the 3 TDLU measures, separately. The genetic ancestry variable was included as an independent variable (Europeans as the referent group) and the TDLU measure was included as the dependent variable, adjusted for age (5-year bands, ordinal), BMI (≤24.9, 25-29.9, 30-34.9, ≥35), fat% (≤25%, 26%-50%, 51%-75%, >75%), age at menarche (<13 years, 13 years, ≥14 years), and parity (nulliparous, parous). The statistical significance of the association between genetic ancestry and TDLU involution was determined by $P<0.050$, where P was obtained from multinomial logistic regression and P_{trend} from cumulative logit models. The coefficient for the genetic ancestry variable was based on the Wald χ^2 statistics. CI = confidence interval; OR = odds ratio; TDLU = terminal duct lobular unit.

[b]Categories of acini count per TDLU were defined as 1 (2-10), 2 (11-20), 3 (21-30), 4 (31-50), and 5 (51-100). The median category, evaluated among up to 10 sequential TDLUs, was chosen to represent the acini count of an individual. When the individual had the same number of category 1 (2-10) and category 2 (11-20), 1.5 was assigned as the median value.

[c]Different categorizations of TDLU involution measures were used in the stratified analysis by menopausal status due to substantial reduction of TDLU measures among postmenopausal women.

less likely to have breastfed than other groups (Table 1). All TDLU measures tended to decline with age in all groups (Supplementary Figure 1, available online), but the proportion of women with complete TDLU involution varied by ancestry, especially among postmenopausal women, ranging from 22% among Central and South Asian descendants to 54% among East Asian descendants (Table 1).

Genetic ancestry was statistically significantly associated with TDLU involution measures when tested using polytomous logistic regression models adjusted for age (5-year bands), BMI (≤24.9, 25-29.9, 30-34.9, ≥35), age at menarche (<13 years, 13 years, ≥14 years), parity (parous, nulliparous), and percentage of fat area on slides (≤25%, 26%-50%, 51%-75%, >75%) (Table 2). Specifically, compared with European descendants, African descendants were more likely to have greater TDLU counts (odds ratio $[OR]_{trend} = 1.36$, 95% confidence interval [CI] = 1.07 to 1.74), acini counts per TDLU (OR = 1.47, 95% CI = 1.06 to 2.03), and TDLU span ($OR_{trend} = 1.44$, 95% CI = 1.08 to 1.91). Contrarily, East Asian descendants overall had fewer TDLUs ($OR_{trend} = 0.52$, 95%CI = 0.35 to 0.78), indicating increased involution, compared with European descendants. Interestingly, the associations for Central and South Asian descendants varied depending on TDLU measures. Like East Asian descendants, Central and South Asian descendants also had fewer TDLUs but were more likely than European descendants to have a longer TDLU span when the analyses were restricted to premenopausal women (Table 2). No statistically significant differences were found between European and Middle Eastern descendants. Associations were generally consistent across strata by menopausal status, BMI, or breastfeeding, yet the associations for African descendants with higher TDLU measures appeared to be stronger among postmenopausal than premenopausal women (Table 2), among women with lower (<25 kg/m^2) than with higher BMI (Supplementary Table 1, available online), and among women with 3 and more children than women with 1 or 2 children (Supplementary Table 2, available online).

The associations of reduced TDLU involution with African ancestry are consistent with those from a previous TDLU analysis based on self-reported race and ethnicity in a subset of these participants (6). The consistent results may reflect the good agreement between genetically defined ancestry and self-reported race among European and African descendants (Cohen $\kappa = 0.83$ and 0.96, respectively; Supplementary Table 3, available online). In the previous Susan G. Komen Tissue Bank report of TDLU metrics by self-reported race and ethnicity (6), there were too few self-reported Asian women (n = 25) to draw conclusions. In this study, using genetic markers to capture Asian ancestry and to distinguish between East Asian and Central and South Asian ancestry, we found increased TDLU involution among East Asian descendants compared with European descendants as well as heterogeneity in TDLU measures between East Asian and Central and South Asian descendants. Notably, the agreement between genetic ancestry and the self-reported race was relatively poor among Asian descendants ($\kappa = 0.68$) due to substantial discrepancy, particularly among Central and South Asian women, only 8.4% of whom described themselves as Asian descendants (Table 1).

The observed reduced TDLU involution among African descendants and the increased TDLU involution among East Asian descendants are consistent with the disproportionately higher risk of TNBC among Black women and lower risk of TNBC among Asian women in the United States (22.8 and 8.6 per 100 000 person-years in 2014-2018, respectively) compared with White women (12.1 per 100 000) (26). Together, these findings suggest opportunities for future work examining whether differential levels of TDLU involution may be linked to population differences in subtype-specific breast cancer incidence.

Strengths of our study include the use of standardized tissue sampling procedures and genetic marker information to infer ancestry, which has provided a unique opportunity to examine TDLU involution in normal breast tissues among women of diverse ancestry backgrounds. Study limitations include residual confounding, especially by factors not measured in the study; the small sample size in non-European or non-African groups, especially for stratified analyses; and lack of representativeness of some ancestry groups, such as women of North or South American descent (n = 32), which were excluded because of small sample size. Our test for associations did not account for sociocultural and systematic factors that may interact with factors associated with either TDLU involution or genetic ancestry or both.

The observed heterogeneity in breast cancer risk factors by genetic ancestry may be driven by racism as well as biology. Large studies in diverse populations with detailed information on tissue composition, genomic markers, reproductive and behavioral factors, and variables related to socioeconomic and systematic determinants of health are needed to further understand the complex relationships between ancestry, race, and ethnicity; TDLU involution; and breast cancer etiology.

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Data Availability

The data are available through the Susan G. Komen Tissue Bank's virtual repository or VTB (https://virtualtissuebank.iu.edu/). The data, which comply with regulatory data sharing restrictions, will be shared at reasonable request to the corresponding author.

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