**Supplementary Table S1.** The eight terminal duct lobular unit (TDLLU) involution measures in this study were calculated by combining data from multiple images for each participant and the following values extracted from the computational method: tissue areas (total, adipose, non-adipose; mm2), TDLU area (mm2), TDLU span (µm), and number of acini per TDLU.

|  |  |  |
| --- | --- | --- |
| **Quantitative Measure** | **Origin** | **Formula** |
| Median TDLU span (µm) | Standardized measure established by Figuoera et al, 2014. | {(number of TDLUs + 1)/2}th value of TDLU span |
| TDLU counts/mm2 | number of TDLUs/non-adipose tissue area |
| Median acini counts/TDLU | {(number of acini per TDLU + 1)/2}th value |
| Median TDLU area (mm2) | Novel measures established in this current study | {(number of TDLUs + 1)/2}th value of TDLU area |
| % TDLU area (total) | (TDLU area/tissue area)\*100 |
| % TDLU area (non-adipose) | (TDLU area/non-adipose tissue area)\*100 |
| Acini counts/mm2 | number of acini per TDLU/non-adipose tissue area |
| Median acini density | {(number of acini per TDLU/TDLU area) + 1)/2}th value |

**Supplementary Table S2.** The association between quantitative terminal duct lobular units (TDLUs) and parity, with parous women further subdivided by number of births, and time between last birth and benign breast disease (BBD) biopsy. Data are presented as age-adjusted means (95% confidence interval); age was adjusted as a continuous variable.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***n*** | **Median TDLU span (µm)** | **TDLU counts/mm2** | **Median acini counts/TDLU** | **Median TDLU area (mm2)** | **% TDLU area (total)** | **% TDLU area (non-adipose)** | **Acini counts/mm2** | | **Median acini density** |
| **Number of births** |  |  |  |  |  |  |  |  | |  |
| Nulliparous | 101 | 0.48 (0.46,0.51) | 0.33 (0.30,0.38) | 5.18 (4.70,5.71) | 0.08 (0.07,0.08) | 4.40 (3.69,5.24) | 5.42 (4.56,6.45) | 3.51 (2.91,4.23) | | 73.74 (67.98,79.99) |
| Primiparous (1 birth) | 94 | 0.51 (0.49,0.53) | 0.42 (0.37,0.48) | 5.66 (5.12,6.26) | 0.09 (0.08,0.09) | 5.93 (4.95,7.10) | 7.27 (6.08,8.69) | 4.75 (3.92,5.76) | | 73.67 (67.77,80.10) |
| Multiparous (≥2 births) | 884 | 0.51 (0.50,0.52) | 0.47 (0.46,0.49) | 6.69 (6.48,6.92) | 0.09 (0.08,0.09) | 7.24 (6.82,7.68) | 8.93 (8.43,9.47) | 6.70 (6.29,7.13) | | 86.70 (84.37,89.09) |
| *p-*value |  | 0.087 | **<0.001** | **<0.001** | 0.08 | **<0.001** | **<0.001** | **<0.001** | | **<0.001** |
| **Time between last birth and BBD biopsy** | | | | | | | | | | |
| 0 years (i.e., nulliparous) | 101 | 0.49 (0.47,0.51) | 0.33 (0.30,0.37) | 5.24 (4.76,5.78) | 0.08 (0.07,0.09) | 4.40 (3.68,5.26) | 5.43 (4.55,6.48) | | 3.48 (2.88,4.20) | 73.57 (67.82,79.80) |
| <20 years (among parous women) | 567 | 0.52 (0.51,0.53) | 0.48 (0.46,0.51) | 7.11 (6.79,7.43) | 0.09 (0.09,0.09) | 7.55 (6.95,8.20) | 9.32 (8.59,10.11) | | 7.04 (6.45,7.68) | 88.25 (84.99,91.63) |
| ≥20 years (among parous women) | 381 | 0.49 (0.47,0.50) | 0.46 (0.42,0.49) | 5.85 (5.50,6.21) | 0.08 (0.07,0.08) | 6.24 (5.58,6.99) | 7.74 (6.92,8.65) | | 5.69 (5.05,6.42) | 83.12 (78.96,87.49) |
| *p-*value |  | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | | **<0.001** | **<0.001** |

**Supplementary Table S3.** Quantitative terminal duct lobular unit (TDLU) measures, age at menopause, and elapsed time between menarch and menopause among 332 post-menopausal controls. Data presented for age are means (95% confidence interval). Data for other variables are presented as age-adjusted means (95% confidence interval); age was adjusted as a continuous variable.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***n*** | **Median TDLU span (µm)** | **TDLU counts/mm2** | **Median acini counts/TDLU** | **Median TDLU area (mm2)** | **% TDLU area (total)** | **% TDLU area (non-adipose)** | **Acini counts/mm2** | | **Median acini density** |
| **Age at menopause** |  |  |  |  |  |  |  |  | |  |
| <40 years | 45 | 0.43 (0.40,0.46) | 0.35 (0.29,0.42) | 4.16 (3.73,4.63) | 0.06 (0.05,0.07) | 2.89 (2.15,3.89) | 3.75 (2.79,5.04) | 2.60 (1.95,3.48) | | 78.85 (70.50,88.19) |
| 40-49 years | 158 | 0.47 (0.46,0.49) | 0.37 (0.34,0.41) | 4.76 (4.50,5.03) | 0.07 (0.07,0.08) | 4.00 (3.43,4.67) | 5.20 (4.46,6.07) | 3.23 (2.78,3.75) | | 72.73 (68.61,77.10) |
| 50-59 years | 121 | 0.45 (0.43,0.46) | 0.43 (0.39,0.49) | 4.76 (4.46,5.08) | 0.06 (0.06,0.07) | 4.31 (3.61,5.16) | 5.45 (4.56,6.51) | 3.78 (3.17,4.50) | | 82.37 (76.98,88.14) |
| p-value |  | **0.01** | 0.09 | 0.07 | **0.01** | 0.08 | 0.10 | 0.09 | | **0.02** |
| **Elapsed time between menarche and menopause** | | | | | | | | | | |
| <30 years | 63 | 0.44 (0.42,0.47) | 0.36 (0.30,0.42) | 4.56 (4.16,5.00) | 0.06 (0.06,0.07) | 3.46 (2.69,4.46) | 4.49 (3.49,5.77) | | 3.09 (2.42,3.95) | 80.27 (72.97,88.30) |
| 30-39 years | 209 | 0.47 (0.45,0.48) | 0.38 (0.34,0.41) | 4.70 (4.48,4.94) | 0.07 (0.07,0.07) | 3.92 (3.42,4.49) | 5.03 (4.40,5.76) | | 3.19 (2.80,3.63) | 74.18 (70.50,78.05) |
| 40-49 years | 50 | 0.44 (0.41,0.47) | 0.50 (0.41,0.60) | 4.74 (4.28,5.25) | 0.06 (0.06,0.07) | 4.68 (3.53,6.20) | 6.00 (4.53,7.95) | | 4.28 (3.25,5.63) | 85.19 (76.60,94.74) |
| *p-*value |  | 0.14 | **0.02** | 0.82 | 0.12 | 0.31 | 0.33 | | 0.14 | **0.04** |

**Supplementary Table S4.** The association between automated terminal duct lobular unit (TDLU) measures and breast cancer risk was evaluated using unconditional logistic regression models to estimate odd ratios (ORs) and 95% confidence intervals (CI).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | ***p-trend*** |
| **Median TDLU span** |  |  |  |  |  |
| Cases/Controls, *n* | 65/271 | 72/270 | 73/271 | 77/271 |  |
| Model 1 | Ref | 1.07 (0.73,1.57) | 0.98 (0.67,1.45) | 0.96 (0.65,1.43) | 0.75 |
| Model 2 | Ref | 0.94 (0.64,1.39) | 0.92 (0.62,1.37) | 0.89 (0.59,1.33) | 0.56 |
| Model 3 | Ref | 0.99 (0.65,1.51) | 0.95 (0.62,1.46) | 0.91 (0.59,1.41) | 0.65 |
| **TDLU counts/mm2** |  |  |  |  |  |
| Cases/Controls, *n* | 67/271 | 73/270 | 71/271 | 76/271 |  |
| Model 1 | Ref | 1.10 (0.75,1.60) | 1.06 (0.73,1.55) | 1.17 (0.80,1.71) | 0.45 |
| Model 2 | Ref | 1.04 (0.71,1.53) | 0.96 (0.65,1.41) | 1.15 (0.79,1.69) | 0.49 |
| Model 3 | Ref | 1.07 (0.71,1.61) | 1.05 (0.7,1.58) | 1.25 (0.83,1.87) | 0.28 |
| **Median acini counts/TDLU** |  |  |  |  |  |
| Cases/Controls, *n* | 26/121 | 79/348 | 89/311 | 93/303 |  |
| Model 1 | Ref | 1.02 (0.63,1.71) | 1.21 (0.75,2.02) | 1.19 (0.73,1.99) | 0.40 |
| Model 2 | Ref | 0.94 (0.57,1.57) | 1.00 (0.61,1.69) | 1.05 (0.64,1.77) | 0.59 |
| Model 3 | Ref | 0.97 (0.58,1.68) | 1.07 (0.63,1.85) | 1.13 (0.66,1.97) | 0.47 |
| **Median TDLU area** |  |  |  |  |  |
| Cases/Controls, *n* | 58/271 | 78/270 | 66/271 | 85/271 |  |
| Model 1 | Ref | 1.29 (0.88,1.91) | 0.99 (0.66,1.49) | 1.19 (0.79,1.78) | 0.72 |
| Model 2 | Ref | 1.15 (0.78,1.71) | 0.87 (0.57,1.31) | 1.10 (0.73,1.66) | 0.90 |
| Model 3 | Ref | 1.26 (0.82,1.93) | 0.89 (0.57,1.4) | 1.13 (0.73,1.77) | 0.95 |
| **% TDLU area (total)** |  |  |  |  |  |
| Cases/Controls, *n* | 58/271 | 82/270 | 63/271 | 84/271 |  |
| Model 1 | Ref | 1.34 (0.92,1.98) | 0.99 (0.66,1.48) | 1.18 (0.79,1.78) | 0.82 |
| Model 2 | Ref | 1.15 (0.78,1.71) | 0.86 (0.57,1.30) | 1.04 (0.69,1.58) | 0.90 |
| Model 3 | Ref | 1.20 (0.79,1.82) | 0.89 (0.57,1.38) | 1.09 (0.70,1.70) | 0.97 |
| **% TDLU area (non-adipose)** | |  |  |  |  |
| Cases/Controls, *n* | 58/271 | 87/270 | 57/271 | 85/271 |  |
| Model 1 | Ref | 1.42 (0.97,2.08) | 0.89 (0.59,1.34) | 1.22 (0.82,1.82) | 0.81 |
| Model 2 | Ref | 1.23 (0.84,1.82) | 0.80 (0.52,1.21) | 1.10 (0.73,1.66) | 0.98 |
| Model 3 | Ref | 1.27 (0.84,1.93) | 0.81 (0.52,1.27) | 1.16 (0.75,1.8) | 0.82 |
| **Acini counts/mm2** |  |  |  |  |  |
| Cases/Controls, *n* | 64/271 | 71/270 | 69/271 | 83/271 |  |
| Model 1 | Ref | 1.09 (0.74,1.61) | 0.99 (0.67,1.47) | 1.10 (0.75,1.63) | 0.72 |
| Model 2 | Ref | 0.98 (0.67,1.45) | 0.86 (0.58,1.29) | 1.03 (0.69,1.53) | 0.83 |
| Model 3 | Ref | 1.06 (0.70,1.61) | 0.87 (0.57,1.33) | 1.09 (0.72,1.67) | 0.70 |
| **Median acini density** |  |  |  |  |  |
| Cases/Controls, *n* | 57/271 | 89/270 | 61/271 | 80/271 |  |
| Model 1 | Ref | 1.59 (1.09,2.33) | 1.08 (0.72,1.62) | 1.33 (0.91,1.96) | 0.49 |
| Model 2 | Ref | 1.54 (1.05,2.27) | 1.05 (0.70,1.58) | 1.36 (0.92,2.01) | 0.41 |
| Model 3 | Ref | 1.72 (1.15,2.60) | 1.08 (0.69,1.68) | 1.46 (0.96,2.22) | 0.37 |

Each quantitative TDLU measure was categorized into quartiles as defined by the distribution among the controls. Model 1 adjusted for matching factors. Model 2 adjusted for matching factors and BBD histological subtypes. Model 3 adjusted for matching factors, BBD histological subtypes, parity, and menopausal status. The median value for each quartile was included as a continuous variable in the unconditional logistic regression for Model 1, 2, and 3, to obtain the *p-trend* value (Wald test).

**Supplementary Table S5.** Automated terminal duct lobular unit (TDLU) measures and breast cancer risk stratified by parity. Data were analyzed using unconditional logistic regression models adjusting for the matching factors and BBD histological subtypes to estimate odd ratios (ORs) and 95% confidence intervals (CI).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | ***p-*trend** |
| **Median TDLU span** |  |  |  |  |  |  |
| Nulliparous women | Cases/Controls, *n* | 8/25 | 3/25 | 10/25 | 7/26 |  |
|  | Model | Ref | 0.36 (0.07,1.53) | 0.96 (0.28,3.27) | 0.78 (0.22,2.71) | 0.96 |
| Parous women | Cases/Controls, *n* | 59/245 | 67/244 | 62/244 | 71/245 |  |
|  | Model | Ref | 0.95 (0.63,1.44) | 0.86 (0.56,1.31) | 0.85 (0.56,1.31) | 0.43 |
| **TDLU counts/mm2** |  |  |  |  |  |  |
| Nulliparous women | Cases/Controls, *n* | 3/25 | 11/25 | 3/25 | 11/26 |  |
|  | Model | Ref | 3.41 (0.87,17.28) | 0.77 (0.12,4.91) | 3.42 (0.88,17.22) | 0.30 |
| Parous women | Cases/Controls, *n* | 62/244 | 64/245 | 68/244 | 65/245 |  |
|  | Model | Ref | 1.01 (0.68,1.52) | 0.99 (0.66,1.48) | 1.05 (0.70,1.58) | 0.82 |
| **Median acini counts/TDLU** |  |  |  |  |  |  |
| Nulliparous women | Cases/Controls, *n* | 1/19 | 8/18 | 11/33 | 8/31 |  |
|  | Model | Ref | 7.56 (1.13,152.06) | 7.04 (1.14,138.17) | 5.58 (0.87,110.06) | 0.55 |
| Parous women | Cases/Controls, *n* | 25/102 | 67/314 | 80/282 | 87/280 |  |
|  | Model | Ref | 0.75 (0.45,1.28) | 0.81 (0.48,1.40) | 0.85 (0.51,1.48) | 0.81 |
| **Median TDLU area** |  |  |  |  |  |  |
| Nulliparous women | Cases/Controls, *n* | 6/25 | 8/25 | 6/25 | 8/26 |  |
|  | Model | Ref | 1.40 (0.39,5.20) | 0.87 (0.21,3.54) | 1.51 (0.42,5.67) | 0.64 |
| Parous women | Cases/Controls, *n* | 52/245 | 72/244 | 58/244 | 77/245 |  |
|  | Model | Ref | 1.16 (0.77,1.76) | 0.83 (0.54,1.29) | 1.04 (0.68,1.62) | 0.86 |
| **% TDLU area (total)** |  |  |  |  |  |  |
| Nulliparous women | Cases/Controls, *n* | 2/25 | 8/25 | 7/25 | 11/26 |  |
|  | Model | Ref | 3.67 (0.76,27.32) | 3.29 (0.65,25.20) | 5.81 (1.17,45.07) | 0.09 |
| Parous women | Cases/Controls, *n* | 55/245 | 75/244 | 53/244 | 76/245 |  |
|  | Model | Ref | 1.10 (0.73,1.66) | 0.76 (0.49,1.17) | 0.93 (0.60,1.45) | 0.53 |
| **% TDLU area (non-adipose)** |  |  |  |  |  |  |
| Nulliparous women | Cases/Controls, *n* | 1/25 | 10/25 | 5/25 | 12/26 |  |
|  | Model | Ref | 8.88 (1.42,174.29) | 4.13 (0.54,86.21) | 12.3 (1.93,245.06) | 0.05 |
| Parous women | Cases/Controls, *n* | 55/245 | 78/244 | 48/244 | 78/245 |  |
|  | Model | Ref | 1.15 (0.77,1.73) | 0.69 (0.44,1.07) | 1.02 (0.67,1.58) | 0.79 |

**Supplementary Table S5.** Continued.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | ***p-*trend** |
| **Acini counts/mm2** |  |  |  |  |  |  |
| Nulliparous women | Cases/Controls, *n* | 5/25 | 4/25 | 8/25 | 11/26 |  |
|  | Model | Ref | 0.85 (0.17,4.03) | 1.56 (0.38,7.01) | 2.64 (0.70,11.28) | 0.08 |
| Parous women | Cases/Controls, *n* | 58/245 | 65/244 | 66/244 | 70/245 |  |
|  | Model | Ref | 0.97 (0.65,1.47) | 0.88 (0.58,1.33) | 0.91 (0.59,1.39) | 0.65 |
| **Median acini density** |  |  |  |  |  |  |
| Nulliparous women | Cases/Controls, *n* | 8/25 | 6/25 | 5/25 | 9/26 |  |
|  | Model | Ref | 0.83 (0.22,3.01) | 0.64 (0.16,2.38) | 1.55 (0.47,5.40) | 0.52 |
| Parous women | Cases/Controls, *n* | 50/245 | 81/244 | 60/244 | 68/245 |  |
|  | Model | Ref | 1.51 (1.01,2.28) | 1.11 (0.73,1.71) | 1.24 (0.82,1.89) | 0.68 |

Each quantitative TDLU measure was categorized into quartiles as defined by the distribution among the controls. The median value for each quartile was included as a continuous variable in the unconditional logistic regression together with matching factors and BBD histological subtypes to obtain the *p-*trend value (Wald test).

**Supplementary Table S6.** Automated terminal duct lobular unit (TDLU) measures and breast cancer risk stratified by menopausal status. Data were analyzed using unconditional logistic regression models adjusting for the matching factors and BBD histological subtypes to estimate odd ratios (ORs) and 95% confidence intervals (CI).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | ***p-*trend** |
| **Median TDLU span** |  |  |  |  |  |  |
| Pre-menopausal women | Cases/Controls, *n* | 52/167 | 38/166 | 56/167 | 52/167 |  |
|  | Model | Ref | 0.72 (0.44,1.16) | 1.03 (0.66,1.61) | 0.91 (0.57,1.45) | 1.00 |
| Post-menopausal women | Cases/Controls, *n* | 14/83 | 13/83 | 18/83 | 18/83 |  |
|  | Model | Ref | 0.78 (0.33,1.82) | 1.09 (0.50,2.44) | 1.05 (0.47,2.35) | 0.68 |
| **TDLU counts/mm2** |  |  |  |  |  |  |
| Pre-menopausal women | Cases/Controls, *n* | 49/167 | 50/166 | 47/167 | 52/167 |  |
|  | Model | Ref | 1.08 (0.68,1.72) | 0.93 (0.58,1.49) | 1.25 (0.79,1.98) | 0.40 |
| Post-menopausal women | Cases/Controls, *n* | 15/83 | 11/83 | 18/83 | 19/83 |  |
|  | Model | Ref | 0.63 (0.26,1.47) | 1.11 (0.51,2.43) | 1.1 (0.51,2.40) | 0.50 |
| **Median acini counts/TDLU** |  |  |  |  |  |  |
| Pre-menopausal women | Cases/Controls, *n* | 36/123 | 43/158 | 69/212 | 50/174 |  |
|  | Model | Ref | 1.01 (0.61,1.71) | 1.06 (0.66,1.72) | 0.99 (0.60,1.64) | 0.93 |
| Post-menopausal women | Cases/Controls, *n* | 11/72 | 14/89 | 11/73 | 27/98 |  |
|  | Model | Ref | 0.86 (0.36,2.10) | 0.83 (0.33,2.12) | 1.22 (0.54,2.87) | 0.42 |
| **Median TDLU area** |  |  |  |  |  |  |
| Pre-menopausal women | Cases/Controls, *n* | 51/167 | 38/166 | 54/167 | 55/167 |  |
|  | Model | Ref | 0.77 (0.47,1.25) | 0.99 (0.63,1.56) | 1.01 (0.64,1.06) | 0.70 |
| Post-menopausal women | Cases/Controls, *n* | 11/83 | 15/83 | 21/83 | 16/83 |  |
|  | Model | Ref | 1.20 (0.51,2.90) | 1.59 (0.71,3.72) | 1.09 (0.46,2.65) | 0.94 |
| **% TDLU area (total)** |  |  |  |  |  |  |
| Pre-menopausal women | Cases/Controls, *n* | 49/167 | 48/166 | 47/167 | 54/167 |  |
|  | Model | Ref | 0.85 (0.53,1.36) | 0.92 (0.58,1.47) | 1.00 (0.63,1.61) | 0.80 |
| Post-menopausal women | Cases/Controls, *n* | 9/82 | 17/84 | 19/83 | 18/83 |  |
|  | Model | Ref | 1.43 (0.60,3.60) | 1.64 (0.69,4.13) | 1.37 (0.56,3.52) | 0.72 |
| **% TDLU area (non-adipose)** |  |  |  |  |  |  |
| Pre-menopausal women | Cases/Controls, *n* | 51/167 | 47/166 | 47/167 | 53/167 |  |
|  | Model | Ref | 0.84 (0.53,1.33) | 0.88 (0.55,1.40) | 1.00 (0.63,1.6) | 0.81 |
| Post-menopausal women | Cases/Controls, *n* | 8/82 | 20/84 | 18/83 | 17/83 |  |
|  | Model | Ref | 1.91 (0.80,4.92) | 1.72 (0.70,4.51) | 1.49 (0.60,3.98) | 0.87 |

**Supplementary Table S6.** Continued.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | ***p-*trend** |
| **Acini counts/mm2** |  |  |  |  |  |  |
| Pre-menopausal women | Cases/Controls, *n* | 43/167 | 47/166 | 57/167 | 51/167 |  |
|  | Model | Ref | 1.03 (0.64,1.67) | 1.24 (0.78,1.97) | 1.22 (0.76,1.96) | 0.36 |
| Post-menopausal women | Cases/Controls, *n* | 11/83 | 13/83 | 22/83 | 17/83 |  |
|  | Model | Ref | 1.00 (0.41,2.44) | 1.61 (0.73,3.73) | 1.12 (0.48,2.71) | 0.79 |
| **Median acini density** |  |  |  |  |  |  |
| Pre-menopausal women | Cases/Controls, *n* | 44/167 | 59/166 | 45/167 | 50/167 |  |
|  | Model | Ref | 1.41 (0.89,2.25) | 1.05 (0.65,1.72) | 1.20 (0.75,1.94) | 0.78 |
| Post-menopausal women | Cases/Controls, *n* | 13/83 | 15/83 | 21/83 | 14/83 |  |
|  | Model | Ref | 1.11 (0.49,2.55) | 1.26 (0.58,2.83) | 1.00 (0.43,2.34) | 0.96 |

Each quantitative TDLU measure was categorized into quartiles as defined by the distribution among the controls. The median value for each quartile was included as a continuous variable in the unconditional logistic regression together with matching factors and BBD histological subtypes to obtain the *p-*trend value (Wald test).

**Supplementary Table S7.** Automated terminal duct lobular unit (TDLU) measures and breast cancer risk stratified by benign breast disease (BBD) histological subtypes. Data were analyzed using unconditional logistic regression models adjusting for the matching factors to estimate odd ratios (ORs) and 95% confidence intervals (CI).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | ***p-*trend** |
| **Median TDLU span** |  |  |  |  |  |  |
| Non-proliferative | Cases/Controls, *n* | 12/76 | 12/75 | 13/76 | 22/76 |  |
|  | Model | Ref | 1.01 (0.41,2.50) | 1.04 (0.42,2.59) | 1.66 (0.70,4.03) | 0.18 |
| Proliferative without atypia | Cases/Controls, *n* | 42/156 | 29/156 | 38/156 | 40/157 |  |
|  | Model | Ref | 0.66 (0.39,1.13) | 0.67 (0.40,1.12) | 0.65 (0.38,1.10) | 0.14 |
| Atypical hyperplasia | Cases/Controls, *n* | 15/39 | 22/38 | 25/39 | 17/39 |  |
|  | Model | Ref | 1.26 (0.56,2.89) | 1.22 (0.54,2.81) | 0.83 (0.34,2.01) | 0.57 |
| **TDLU counts/mm2** |  |  |  |  |  |  |
| Non-proliferative | Cases/Controls, *n* | 20/75 | 15/76 | 10/76 | 14/76 |  |
|  | Model | Ref | 0.71 (0.33,1.52) | 0.46 (0.19,1.04) | 0.70 (0.32,1.51) | 0.37 |
| Proliferative without atypia | Cases/Controls, *n* | 28/156 | 39/156 | 36/156 | 46/157 |  |
|  | Model | Ref | 1.32 (0.77,2.30) | 1.28 (0.74,2.25) | 1.63 (0.96,2.80) | 0.09 |
| Atypical hyperplasia | Cases/Controls, *n* | 24/39 | 16/38 | 18/39 | 21/39 |  |
|  | Model | Ref | 0.75 (0.33,1.67) | 0.78 (0.36,1.69) | 0.82 (0.38,1.75) | 0.66 |
| **Median acini counts/TDLU** |  |  |  |  |  |  |
| Non-proliferative | Cases/Controls, *n* | 9/34 | 13/105 | 19/85 | 18/79 |  |
|  | Model | Ref | 0.39 (0.15,1.05) | 0.60 (0.22,1.66) | 0.61 (0.22,1.77) | 0.83 |
| Proliferative without atypia | Cases/Controls, *n* | 13/76 | 48/189 | 36/186 | 52/174 |  |
|  | Model | Ref | 1.59 (0.82,3.27) | 1.04 (0.53,2.17) | 1.47 (0.76,3.00) | 0.71 |
| Atypical hyperplasia | Cases/Controls, *n* | 4/11 | 18/54 | 38/50 | 19/40 |  |
|  | Model | Ref | 0.89 (0.26,3.64) | 1.81 (0.54,7.21) | 0.93 (0.24,4.03) | 0.76 |
| **Median TDLU area** |  |  |  |  |  |  |
| Non-proliferative | Cases/Controls, *n* | 11/76 | 14/75 | 15/76 | 19/76 |  |
|  | Model | Ref | 1.25 (0.51,3.12) | 1.28 (0.52,3.22) | 1.48 (0.58,3.86) | 0.46 |
| Proliferative without atypia | Cases/Controls, *n* | 36/155 | 34/157 | 35/156 | 44/157 |  |
|  | Model | Ref | 0.83 (0.49,1.42) | 0.71 (0.41,1.23) | 0.82 (0.48,1.41) | 0.49 |
| Atypical hyperplasia | Cases/Controls, *n* | 14/39 | 24/38 | 17/39 | 24/39 |  |
|  | Model | Ref | 1.57 (0.69,3.61) | 1.03 (0.43,2.47) | 1.23 (0.51,3.02) | 1.00 |

**Supplementary Table S7.** Continued.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | ***p-*trend** |
| **% TDLU area (total)** |  |  |  |  |  |  |
| Non-proliferative | Cases/Controls, *n* | 14/76 | 11/75 | 14/76 | 20/76 |  |
|  | Model | Ref | 0.74 (0.30,1.77) | 0.78 (0.32,1.85) | 1.15 (0.49,2.76) | 0.42 |
| Proliferative without atypia | Cases/Controls, *n* | 31/156 | 35/156 | 35/155 | 48/158 |  |
|  | Model | Ref | 0.98 (0.56,1.70) | 0.94 (0.54,1.63) | 1.04 (0.60,1.81) | 0.84 |
| Atypical hyperplasia | Cases/Controls, *n* | 19/39 | 30/38 | 14/39 | 16/39 |  |
|  | Model | Ref | 1.50 (0.71,3.22) | 0.64 (0.27,1.50) | 0.58 (0.24,1.39) | 0.06 |
| **% TDLU area (non-adipose)** |  |  |  |  |  |  |
| Non-proliferative | Cases/Controls, *n* | 15/76 | 8/75 | 16/76 | 20/76 |  |
|  | Model | Ref | 0.50 (0.19,1.23) | 0.86 (0.38,1.96) | 1.17 (0.51,2.69) | 0.27 |
| Proliferative without atypia | Cases/Controls, *n* | 32/156 | 36/156 | 35/156 | 46/157 |  |
|  | Model | Ref | 0.98 (0.57,1.68) | 0.90 (0.52,1.55) | 1.00 (0.58,1.74) | 0.96 |
| Atypical hyperplasia | Cases/Controls, *n* | 16/39 | 34/38 | 12/39 | 17/39 |  |
|  | Model | Ref | 1.93 (0.90,4.21) | 0.73 (0.29,1.77) | 0.74 (0.31,1.78) | 0.12 |
| **Acini counts/mm2** |  |  |  |  |  |  |
| Non-proliferative | Cases/Controls, *n* | 16/76 | 8/75 | 17/76 | 18/76 |  |
|  | Model | Ref | 0.44 (0.17,1.09) | 0.88 (0.40,1.97) | 0.91 (0.40,2.12) | 0.59 |
| Proliferative without atypia | Cases/Controls, *n* | 35/156 | 29/155 | 38/157 | 47/157 |  |
|  | Model | Ref | 0.77 (0.44,1.34) | 0.92 (0.54,1.57) | 1.03 (0.61,1.73) | 0.59 |
| Atypical hyperplasia | Cases/Controls, *n* | 13/39 | 30/38 | 21/39 | 15/39 |  |
|  | Model | Ref | 2.61 (1.16,6.09) | 1.37 (0.58,3.29) | 0.83 (0.32,2.15) | 0.15 |
| **Median acini density** |  |  |  |  |  |  |
| Non-proliferative | Cases/Controls, *n* | 16/76 | 17/75 | 14/76 | 12/76 |  |
|  | Model | Ref | 1.14 (0.53,2.49) | 0.95 (0.42,2.15) | 0.74 (0.31,1.68) | 0.41 |
| Proliferative without atypia | Cases/Controls, *n* | 31/156 | 38/156 | 31/156 | 49/157 |  |
|  | Model | Ref | 1.37 (0.80,2.36) | 1.08 (0.61,1.89) | 1.54 (0.93,2.60) | 0.17 |
| Atypical hyperplasia | Cases/Controls, *n* | 17/39 | 23/38 | 15/39 | 24/39 |  |
|  | Model | Ref | 1.29 (0.58,2.88) | 0.79 (0.34,1.86) | 1.29 (0.58,2.89) | 0.70 |

Each quantitative TDLU measure was categorized into quartiles as defined by the distribution among the controls. The median value for each quartile was included as a continuous variable in the unconditional logistic regression together with matching factors to obtain the *p-*trend value (Wald test).

**Supplementary Table S8.** Automated terminal duct lobular unit (TDLU) measures and breast cancer risk defined by tumor estrogen receptor (ER) expression. Data were analyzed using polytomous logistic regression models to estimate odd ratios (ORs) and 95% confidence intervals (CI).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | **ER-positive breast cancer (*n*=179)** | | | | | | | | **ER-negative breast cancer (*n*=51)** | | | | | | |
|  | | | **T1** | **T2** | | **T3** | | | ***p-trend*** | | **T1** | **T2** | | **T3** | | | ***p-trend*** |
|  |  |  | | |  | |  |  | |  | | |  | |  |
| **Median TDLU span** | | |  |  | |  | | |  | |  |  | |  | | |  |
| Cases/Controls, *n* | | | 60/358 | 55/366 | | 64/359 | | |  | | 15/358 | 14/366 | | 22/359 | | |  |
| Model 1 | | | Ref | 0.84 (0.56,1.26) | | 0.95 (0.63,1.42) | | | 0.83 | | Ref | 0.82 (0.39,1.76) | | 1.16 (0.56,2.37) | | | 0.61 |
| Model 2 | | | Ref | 0.78 (0.52,1.18) | | 0.89 (0.59,1.35) | | | 0.64 | | Ref | 0.81 (0.38,1.74) | | 1.14 (0.56,2.35) | | | 0.63 |
| Model 3 | | | Ref | 0.81 (0.53,1.26) | | 0.96 (0.62,1.49) | | | 0.92 | | Ref | 0.83 (0.38,1.81) | | 1.11 (0.53,2.35) | | | 0.70 |
| **TDLU counts/mm2** | | |  |  | |  | | |  | |  |  | |  | | |  |
| Cases/Controls, *n* | | | 51/358 | 68/367 | | 60/358 | | |  | | 17/358 | 18/367 | | 16/358 | | |  |
| Model 1 | | | Ref | 1.33 (0.90,1.98) | | 1.22 (0.82,1.83) | | | 0.40 | | Ref | 1.04 (0.53,2.06) | | 0.96 (0.48,1.95) | | | 0.90 |
| Model 2 | | | Ref | 1.23 (0.82,1.83) | | 1.17 (0.77,1.76) | | | 0.52 | | Ref | 1.03 (0.52,2.04) | | 0.95 (0.47,1.93) | | | 0.88 |
| Model 3 | | | Ref | 1.32 (0.86,2.01) | | 1.21 (0.78,1.87) | | | 0.48 | | Ref | 1.03 (0.51,2.09) | | 0.96 (0.47,1.98) | | | 0.90 |
| **Median acini counts/TDLU** | | |  |  | |  | | |  | |  |  | |  | | |  |
| Cases/Controls, *n* | | | 49/307 | 61/394 | | 69/382 | | |  | | 11/307 | 17/394 | | 23/382 | | |  |
| Model 1 | | | Ref | 0.96 (0.64,1.44) | | 1.04 (0.69,1.58) | | | 0.75 | | Ref | 1.13 (0.52,2.47) | | 1.37 (0.64,2.92) | | | 0.40 |
| Model 2 | | | Ref | 0.91 (0.60,1.38) | | 0.97 (0.64,1.48) | | | 0.98 | | Ref | 1.11 (0.51,2.42) | | 1.33 (0.62,2.85) | | | 0.44 |
| Model 3 | | | Ref | 0.96 (0.62,1.50) | | 1.03 (0.65,1.64) | | | 0.81 | | Ref | 1.19 (0.53,2.68) | | 1.30 (0.57,2.97) | | | 0.57 |
| **Median TDLU area** | | |  |  | |  | | |  | |  |  | |  | | |  |
| Cases/Controls, *n* | | | 55/357 | 67/368 | | 57/358 | | |  | | 13/357 | 14/368 | | 24/358 | | |  |
| Model 1 | | | Ref | 1.13 (0.76,1.67) | | 0.91 (0.59,1.41) | | | 0.57 | | Ref | 0.97 (0.44,2.13) | | 1.51 (0.71,3.20) | | | 0.21 |
| Model 2 | | | Ref | 0.98 (0.65,1.47) | | 0.82 (0.53,1.28) | | | 0.35 | | Ref | 0.94 (0.43,2.08) | | 1.49 (0.70,3.16) | | | 0.22 |
| Model 3 | | | Ref | 1.03 (0.67,1.58) | | 0.90 (0.56,1.43) | | | 0.60 | | Ref | 0.98 (0.43,2.21) | | 1.47 (0.67,3.26) | | | 0.26 |
| **% TDLU area (total)** | | |  |  | |  | | |  | |  |  | |  | | |  |
| Cases/Controls, *n* | | | 52/358 | 69/366 | | 58/359 | | |  | | 14/358 | 17/366 | | 20/359 | | |  |
| Model 1 | | | Ref | 1.26 (0.85,1.88) | | 1.00 (0.64,1.54) | | | 0.73 | | Ref | 1.06 (0.51,2.22) | | 1.11 (0.52,2.36) | | | 0.78 |
| Model 2 | | | Ref | 1.09 (0.73,1.64) | | 0.89 (0.57,1.39) | | | 0.48 | | Ref | 1.03 (0.49,2.17) | | 1.10 (0.52,2.37) | | | 0.78 |
| Model 3 | | | Ref | 1.18 (0.76,1.82) | | 0.96 (0.60,1.54) | | | 0.66 | | Ref | 1.00 (0.46,2.16) | | 1.10 (0.50,2.41) | | | 0.77 |
| **% TDLU area (non-adipose)** | | |  |  | |  | | |  | |  |  | |  | | |  |
| Cases/Controls, *n* | | | 56/358 | 65/367 | | 58/358 | | |  | | 15/358 | 17/367 | | 19/358 | | |  |
| Model 1 | | | Ref | 1.09 (0.74,1.61) | | 0.93 (0.61,1.42) | | | 0.64 | | Ref | 0.99 (0.48,2.03) | | 1.01 (0.48,2.10) | | | 0.97 |
| Model 2 | | | Ref | 0.93 (0.62,1.39) | | 0.81 (0.53,1.25) | | | 0.33 | | Ref | 0.96 (0.46,1.98) | | 0.99 (0.47,2.10) | | | 0.99 |
| Model 3 | | | Ref | 0.97 (0.63,1.49) | | 0.86 (0.55,1.36) | | | 0.50 | | Ref | 0.91 (0.43,1.94) | | 0.97 (0.45,2.10) | | | 1.00 |

**Supplementary Table S8.** Continued.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **ER-positive breast cancer (*n*=179)** | | | | **ER-negative breast cancer (*n*=51)** | | | |
|  | **T1** | **T2** | **T3** | ***p-trend*** | **T1** | **T2** | **T3** | ***p-trend*** |
| **Acini counts/mm2** |  |  |  |  |  |  |  |  |
| Cases/Controls, *n* | 46/358 | 72/367 | 61/358 |  | 13/358 | 14/367 | 24/358 |  |
| Model 1 | Ref | 1.50 (1.01,2.25) | 1.25 (0.81,1.93) | 0.58 | Ref | 0.98 (0.45,2.14) | 1.57 (0.76,3.24) | 0.14 |
| Model 2 | Ref | 1.32 (0.88,1.99) | 1.13 (0.73,1.75) | 0.86 | Ref | 0.95 (0.44,2.09) | 1.55 (0.74,3.22) | 0.15 |
| Model 3 | Ref | 1.39 (0.90,2.15) | 1.20 (0.75,1.91) | 0.72 | Ref | 0.98 (0.43,2.22) | 1.58 (0.73,3.40) | 0.16 |
| **Median acini density** |  |  |  |  |  |  |  |  |
| Cases/Controls, *n* | 54/358 | 71/367 | 54/358 |  | 17/358 | 13/367 | 21/358 |  |
| Model 1 | Ref | 1.29 (0.88,1.89) | 1.00 (0.66,1.50) | 0.93 | Ref | 0.73 (0.35,1.53) | 1.16 (0.60,2.24) | 0.58 |
| Model 2 | Ref | 1.23 (0.83,1.83) | 1.03 (0.68,1.56) | 0.93 | Ref | 0.71 (0.34,1.49) | 1.16 (0.60,2.25) | 0.58 |
| Model 3 | Ref | 1.39 (0.92,2.09) | 1.00 (0.64,1.57) | 0.93 | Ref | 0.67 (0.31,1.45) | 1.07 (0.54,2.12) | 0.75 |

Each quantitative TDLU measure was categorized into tertiles (T1, T2, and T3) as defined by the distribution among the controls. Model 1 adjusted for matching factors. Model 2 adjusted for matching factors and BBD histological subtypes. Model 3 adjusted for matching factors, BBD histological subtypes, parity, and menopausal status. The median value for each quartile was included as a continuous variable in the polytomous logistic regression for Model 1, 2, and 3, to obtain the p-trend value (Wald test).