

# Supplemental Table 1

| <b>Table 1. Comparing Demographic Characteristics of Multiple Biopsy Set vs. BBD Cohort</b> |                                 |                         |                    |                     |                                  |
|---|---------------------------------|-------------------------|--------------------|---------------------|----------------------------------|
|   | Rest of BBD Cohort<br>(N=12340) | Mult Bx Set<br>(N=1115) | Total<br>(N=13455) | p-value             | Adjusted<br>p-value <sup>a</sup> |
| <b>Age at initial biopsy</b>  |                                 |                         |                    | <0.001 <sup>c</sup> |                                  |
| <45   | 3879 (31.4%)                    | 513 (46.0%)             | 4392 (32.6%)       |                     |                                  |
| 45-55   | 3571 (28.9%)                    | 378 (33.9%)             | 3949 (29.3%)       |                     |                                  |
| 55+   | 4890 (39.6%)                    | 224 (20.1%)             | 5114 (38.0%)       |                     |                                  |
| <b>Duration of follow-up (years)</b>  |                                 |                         |                    | <0.001 <sup>d</sup> | <.001                            |
| N   | 12340                           | 1115                    | 13455              |                     |                                  |
| Mean (SD)   | 16.75 (9.57)                    | 21.92 (9.50)            | 17.18 (9.67)       |                     |                                  |
| Median  | 15.43                           | 20.73                   | 15.79              |                     |                                  |
| <b>Breast Cancer Status</b>   |                                 |                         |                    | 0.957 <sup>c</sup>  | 0.876                            |
| Control   | 11173 (90.5%)                   | 1009 (90.5%)            | 12182 (90.5%)      |                     |                                  |
| Case  | 1167 (9.5%)                     | 106 (9.5%)              | 1273 (9.5%)        |                     |                                  |
| <b>Overall impression</b>   |                                 |                         |                    | 0.014 <sup>c</sup>  | <.001                            |
| NP  | 7789 (63.1%)                    | 667 (59.8%)             | 8456 (62.8%)       |                     |                                  |
| PDWA  | 3897 (31.6%)                    | 398 (35.7%)             | 4295 (31.9%)       |                     |                                  |
| AH  | 654 (5.3%)                      | 50 (4.5%)               | 704 (5.2%)         |                     |                                  |
| <b>Involution</b>   |                                 |                         |                    | <0.001 <sup>c</sup> | <.001                            |
| Missing <sup>b</sup>  | 1255                            | 0                       | 1255               |                     |                                  |
| None (0-25%)  | 1955 (17.6%)                    | 300 (26.9%)             | 2255 (18.5%)       |                     |                                  |
| Partial (26-75%)  | 6025 (54.4%)                    | 534 (47.9%)             | 6559 (53.8%)       |                     |                                  |
| Complete (76-100%)  | 3105 (28.0%)                    | 281 (25.2%)             | 3386 (27.8%)       |                     |                                  |
| <b>Family history of breast cancer</b>  |                                 |                         |                    | <0.001 <sup>c</sup> | <.001                            |
| Missing <sup>b</sup>  | 815                             | 38                      | 853                |                     |                                  |
| None  | 7210 (62.6%)                    | 530 (49.2%)             | 7740 (61.4%)       |                     |                                  |
| Weak  | 2821 (24.5%)                    | 372 (34.5%)             | 3193 (25.3%)       |                     |                                  |
| Strong  | 1494 (13.0%)                    | 175 (16.2%)             | 1669 (13.2%)       |                     |                                  |
| <b>Number of children</b>   |                                 |                         |                    | 0.258 <sup>c</sup>  | 0.541                            |
| Missing <sup>b</sup>  | 3295                            | 148                     | 3443               |                     |                                  |
| Nulliparous   | 1246 (13.8%)                    | 152 (15.7%)             | 1398 (14.0%)       |                     |                                  |
| 1   | 959 (10.6%)                     | 107 (11.1%)             | 1066 (10.6%)       |                     |                                  |
| 2   | 2690 (29.7%)                    | 291 (30.1%)             | 2981 (29.8%)       |                     |                                  |
| 3+  | 4150 (45.9%)                    | 417 (43.1%)             | 4567 (45.6%)       |                     |                                  |

**Supplemental Table 1. Comparison of demographic characteristics between multiple biopsy cohort and rest of BBD cohort.** Abbreviations: AH, atypical hyperplasia; BBD, benign breast disease; NP, nonproliferative disease; PDWA, proliferative disease without atypia; TDLU, terminal duct lobular units.

<sup>a</sup>Adjusted for age at initial biopsy using a multivariate logistic regression.

<sup>b</sup>Information not available.

<sup>c</sup>Pearson  $\chi^2$  test comparing distribution of characteristics across presence in the multiple biopsy set.

<sup>d</sup>Kruskal-Wallis test comparing the median duration of follow-up across presence in the multiple biopsy set.

## Supplemental Table 2

| Characteristic               | Entire BBD Cohort |                 |                 |                           |                      | Multiple biopsy cohort |                 |                 |                           |                      |
|------------------------------|-------------------|-----------------|-----------------|---------------------------|----------------------|------------------------|-----------------|-----------------|---------------------------|----------------------|
|                              | No. Women         | Observed Events | Expected Events | SIR <sup>a</sup> (95% CI) | p-value <sup>b</sup> | No. Women              | Observed Events | Expected Events | SIR <sup>a</sup> (95% CI) | p-value <sup>b</sup> |
| <b>Overall</b>               | 13455             | 1273            | 773.40          | 1.65 (1.56, 1.74)         |                      | 1115                   | 106             | 78.37           | 1.35 (1.11, 1.64)         |                      |
| <b>LI at initial biopsy</b>  |                   |                 |                 |                           | <.001                |                        |                 |                 |                           | 0.811                |
| None (0-25%)                 | 2255              | 246             | 118.29          | 2.08 (1.83, 2.36)         |                      | 300                    | 27              | 19.08           | 1.41 (0.93, 2.06)         |                      |
| Partial (26-75%)             | 6559              | 676             | 400.96          | 1.69 (1.56, 1.82)         |                      | 534                    | 55              | 39.43           | 1.39 (1.05, 1.82)         |                      |
| Complete (76-100%)           | 3386              | 218             | 197.34          | 1.10 (0.96, 1.26)         |                      | 281                    | 24              | 19.85           | 1.21 (0.77, 1.80)         |                      |
| <b>Overall impression</b>    |                   |                 |                 |                           | <.001                |                        |                 |                 |                           | 0.002                |
| NP                           | 8456              | 627             | 483.21          | 1.30 (1.20, 1.40)         |                      | 667                    | 48              | 46.21           | 1.04 (0.77, 1.38)         |                      |
| PDWA                         | 4295              | 496             | 255.14          | 1.94 (1.78, 2.12)         |                      | 398                    | 48              | 29.30           | 1.64 (1.21, 2.17)         |                      |
| AH                           | 704               | 150             | 35.06           | 4.28 (3.62, 5.02)         |                      | 50                     | 10              | 2.86            | 3.49 (1.67, 6.43)         |                      |
| <b>Age at initial biopsy</b> |                   |                 |                 |                           | 0.015                |                        |                 |                 |                           | 0.576                |
| <45                          | 4392              | 342             | 189.00          | 1.81 (1.62, 2.01)         |                      | 513                    | 43              | 28.49           | 1.51 (1.09, 2.03)         |                      |
| 45-55                        | 3949              | 459             | 268.06          | 1.71 (1.56, 1.88)         |                      | 378                    | 39              | 32.54           | 1.20 (0.85, 1.64)         |                      |
| 55+                          | 5114              | 472             | 316.35          | 1.49 (1.36, 1.63)         |                      | 224                    | 24              | 17.34           | 1.38 (0.89, 2.06)         |                      |

**Supplemental Table 2. Standard Incidence Ratios of breast cancer development for overall BBD cohort and multiple biopsy cohort.** Comparison of number of observed breast cancers versus number expected using age-year specific incidence rates of breast cancer from the Iowa SEER registry. Abbreviations: AH, atypical hyperplasia; BBD, benign breast disease; NP, nonproliferative disease; PDWA, proliferative disease without atypia; SIR, standardized incidence ratio; TDLU, terminal duct lobular units.

<sup>a</sup>The SIR compares the observed number of breast cancer events with the number expected on the basis of Iowa Surveillance, Epidemiology, and End-results data. All analyses account for the effects of age and calendar period.

<sup>b</sup>p-values test heterogeneity across levels of the covariate.

## Supplemental Table 3

| Characteristic               | Entire BBD Cohort  |                    |                          |                              | Multiple Bx Cohort |                   |                          |                              |
|------------------------------|--------------------|--------------------|--------------------------|------------------------------|--------------------|-------------------|--------------------------|------------------------------|
|                              | Total<br>(N=13455) | Events<br>(N=1273) | Hazard Ratio<br>(95% CI) | Wald<br>p-value <sup>a</sup> | Total<br>(N=1115)  | Events<br>(N=106) | Hazard Ratio<br>(95% CI) | Wald<br>p-value <sup>a</sup> |
| <b>Involution</b>            |                    |                    |                          | <.001                        |                    |                   |                          | 0.911                        |
| None                         | 2255               | 246 (10.9%)        | 1.00 (ref)               |                              | 300                | 27 (9.0%)         | 1.00 (ref)               |                              |
| Partial                      | 6559               | 676 (10.3%)        | 0.82 (0.70, 0.96)        |                              | 534                | 55 (10.3%)        | 0.99 (0.61, 1.60)        |                              |
| Complete                     | 3386               | 218 (6.4%)         | 0.63 (0.51, 0.78)        |                              | 281                | 24 (8.5%)         | 1.12 (0.59, 2.11)        |                              |
| <b>Overall impression</b>    |                    |                    |                          | <.001                        |                    |                   |                          | <.001                        |
| NP                           | 8456               | 627 (7.4%)         | 1.00 (ref)               |                              | 667                | 48 (7.2%)         | 1.00 (ref)               |                              |
| PDWA                         | 4295               | 496 (11.5%)        | 1.62 (1.42, 1.84)        |                              | 398                | 48 (12.1%)        | 1.82 (1.21, 2.75)        |                              |
| AH                           | 704                | 150 (21.3%)        | 3.91 (3.22, 4.75)        |                              | 50                 | 10 (20.0%)        | 4.49 (2.14, 9.43)        |                              |
| <b>Age at initial biopsy</b> |                    |                    |                          | <.001                        |                    |                   |                          | 0.076                        |
| <45                          | 4392               | 342 (7.8%)         | 1.00 (ref)               |                              | 513                | 43 (8.4%)         | 1.00 (ref)               |                              |
| 45-55                        | 3949               | 459 (11.6%)        | 1.55 (1.33, 1.81)        |                              | 378                | 39 (10.3%)        | 1.15 (0.73, 1.80)        |                              |
| 55+                          | 5114               | 472 (9.2%)         | 2.03 (1.70, 2.41)        |                              | 224                | 24 (10.7%)        | 1.99 (1.09, 3.65)        |                              |

**Supplemental Table 3. Breast cancer hazard ratios for overall BBD cohort and for multiple biopsy cohort.** Hazard ratios are presented for involution status at initial biopsy, histologic impression, and age of BBD. Abbreviations: AH, atypical hyperplasia; BBD, benign breast disease; NP, nonproliferative disease; PDWA, proliferative disease without atypia; TDLU, terminal duct lobular units. All shown covariates were modeled simultaneously in a single multivariate model.

<sup>a</sup>p-value is from an overall type 3 Wald test.

# Supplemental Table 4

|                        |            | Age at initial biopsy <45 |       |       |        | Age at initial biopsy 45-55 |       |       |        | Age at initial biopsy 55+ |       |       |        |                     |
|------------------------|------------|---------------------------|-------|-------|--------|-----------------------------|-------|-------|--------|---------------------------|-------|-------|--------|---------------------|
|                        |            | 0-25                      | 26-50 | 51-74 | 75-100 | 0-25                        | 26-50 | 51-74 | 75-100 | 0-25                      | 26-50 | 51-74 | 75-100 | LI at Second Biopsy |
| time between biopsies: | <2 years   | 0-25                      | 20.7% | 6.9%  | 5.7%   | 2.3%                        | 6.5%  | 3.2%  | 6.5%   | 0.0%                      | 0.0%  | 0.0%  | 2.2%   | 0.0%                |
|                        |            | 26-50                     | 3.4%  | 17.2% | 8.0%   | 2.3%                        | 3.2%  | 11.3% | 11.3%  | 1.6%                      | 0.0%  | 4.3%  | 0.0%   | 0.0%                |
|                        |            | 51-74                     | 1.1%  | 10.3% | 5.7%   | 2.3%                        | 0.0%  | 6.5%  | 14.5%  | 4.8%                      | 0.0%  | 0.0%  | 6.5%   | 4.3%                |
|                        |            | 75-100                    | 0.0%  | 4.6%  | 2.3%   | 6.9%                        | 0.0%  | 3.2%  | 8.1%   | 19.4%                     | 0.0%  | 0.0%  | 8.7%   | 73.9%               |
| LI at Initial Biopsy   |            |                           |       |       |        |                             |       |       |        |                           |       |       |        | p-value: 0.361      |
| time between biopsies: | 2-5 years  | 0-25                      | 13.3% | 19.0% | 6.7%   | 3.8%                        | 7.5%  | 11.8% | 3.2%   | 5.4%                      | 1.5%  | 3.0%  | 0.0%   | 1.5%                |
|                        |            | 26-50                     | 1.9%  | 21.9% | 12.4%  | 1.9%                        | 1.1%  | 4.3%  | 7.5%   | 3.2%                      | 0.0%  | 0.0%  | 4.5%   | 3.0%                |
|                        |            | 51-74                     | 0.0%  | 4.8%  | 3.8%   | 1.9%                        | 0.0%  | 7.5%  | 20.4%  | 6.5%                      | 0.0%  | 3.0%  | 11.9%  | 10.4%               |
|                        |            | 75-100                    | 0.0%  | 1.9%  | 2.9%   | 3.8%                        | 0.0%  | 2.2%  | 4.3%   | 15.1%                     | 0.0%  | 1.5%  | 13.4%  | 46.3%               |
| LI at Initial Biopsy   |            |                           |       |       |        |                             |       |       |        |                           |       |       |        | p-value: <0.001     |
| time between biopsies: | 5-10 years | 0-25                      | 12.7% | 12.7% | 11.2%  | 4.5%                        | 3.1%  | 1.0%  | 9.4%   | 2.1%                      | 0.0%  | 0.0%  | 0.0%   | 0.0%                |
|                        |            | 26-50                     | 0.7%  | 11.9% | 11.2%  | 8.2%                        | 0.0%  | 9.4%  | 8.3%   | 8.3%                      | 0.0%  | 3.1%  | 3.1%   | 4.6%                |
|                        |            | 51-74                     | 0.7%  | 5.2%  | 7.5%   | 4.5%                        | 0.0%  | 0.0%  | 12.5%  | 21.9%                     | 0.0%  | 3.1%  | 9.2%   | 9.2%                |
|                        |            | 75-100                    | 0.7%  | 2.2%  | 2.2%   | 3.7%                        | 0.0%  | 2.1%  | 1.0%   | 20.8%                     | 1.5%  | 0.0%  | 4.6%   | 61.5%               |
| LI at Initial Biopsy   |            |                           |       |       |        |                             |       |       |        |                           |       |       |        | p-value: 0.001      |
| time between biopsies: | 10+ years  | 0-25                      | 7.0%  | 11.8% | 12.3%  | 12.8%                       | 0.0%  | 2.4%  | 6.3%   | 13.4%                     | 0.0%  | 0.0%  | 0.0%   | 6.5%                |
|                        |            | 26-50                     | 0.0%  | 7.5%  | 12.3%  | 12.8%                       | 0.0%  | 2.4%  | 11.0%  | 18.9%                     | 0.0%  | 0.0%  | 2.2%   | 4.3%                |
|                        |            | 51-74                     | 0.5%  | 0.5%  | 4.8%   | 8.0%                        | 0.0%  | 2.4%  | 8.7%   | 19.7%                     | 0.0%  | 2.2%  | 13.0%  | 15.2%               |
|                        |            | 75-100                    | 0.5%  | 0.5%  | 1.6%   | 7.0%                        | 0.0%  | 0.0%  | 0.8%   | 14.2%                     | 0.0%  | 2.2%  | 4.3%   | 50.0%               |
| LI at Initial Biopsy   |            |                           |       |       |        |                             |       |       |        |                           |       |       |        | p-value: <0.001     |
|                        |            |                           |       |       |        | p-value: 0.463              |       |       |        | p-value: - <sup>a</sup>   |       |       |        |                     |
|                        |            |                           |       |       |        | p-value: 0.01               |       |       |        | p-value: 0.706            |       |       |        |                     |
|                        |            |                           |       |       |        | p-value: <0.001             |       |       |        | p-value: - <sup>a</sup>   |       |       |        |                     |
|                        |            |                           |       |       |        | p-value: - <sup>a</sup>     |       |       |        | p-value: - <sup>a</sup>   |       |       |        |                     |

**Supplemental Table 4. LI status progression by age at initial biopsy and time between biopsies in the multiple biopsy cohort.** Bowker’s test of symmetry was used to test significance of change in LI between biopsies. Tests were stratified by age of first biopsy and time between biopsies. In age categories <45 with 2+ years between biopsies, significantly more women progressed in LI than those who regressed (P < 0.001 for all categories). Intensity of shading indicates larger percent of patients within each age- and biopsy interval-subsetted category.

<sup>a</sup> Test could not be performed due to requirement of Bowker’s test to have data present in the same rows/columns for each variable.

## Supplemental Table 5

| Characteristic              | Total<br>(N=834) | Events<br>(N=82) | Multivariate             |                 |
|-----------------------------|------------------|------------------|--------------------------|-----------------|
|                             |                  |                  | Hazard Ratio<br>(95% CI) | Wald<br>p-value |
| <b>Involution at Index</b>  |                  |                  |                          | 0.474           |
| 0-25% TDLU                  | 300              | 27 (9.0%)        | 1.00 (ref)               |                 |
| 26-50% TDLU                 | 286              | 29 (10.1%)       | 0.87 (0.51, 1.49)        |                 |
| 51-75% TDLU                 | 248              | 26 (10.5%)       | 0.70 (0.39, 1.25)        |                 |
| <b>Change in Involution</b> |                  |                  |                          | 0.041           |
| Progression                 | 507              | 39 (7.7%)        | 1.00 (ref)               |                 |
| Stasis                      | 327              | 43 (13.1%)       | 1.64 (1.02, 2.64)        |                 |
| <b>Overall impression</b>   |                  |                  |                          | <.001           |
| NP                          | 475              | 31 (6.5%)        | 1.00 (ref)               |                 |
| PDWA                        | 317              | 42 (13.2%)       | 2.08 (1.30, 3.33)        |                 |
| AH                          | 42               | 9 (21.4%)        | 5.74 (2.64, 12.48)       |                 |

**Supplemental Table 5. Breast cancer hazard ratios for multiple biopsy cohort including effect of LI progression.** Four-level involution assessments were used to determine LI progression vs LI stasis. Follow-up time was stratified on time since first biopsy (<10 years, 10+ years). Abbreviations: AH, atypical hyperplasia; BBD, benign breast disease; NP, nonproliferative disease; PDWA, proliferative disease without atypia; TDLU, terminal duct lobular units. All shown covariates were modeled simultaneously in a single multivariate model.

<sup>a</sup>p-value is from an overall type 3 Wald test.