

## Supplemental Online Content

Han Y, Moore JX, Colditz GA, Toriola AT. Family history of breast cancer and mammographic breast density in premenopausal women. *JAMA Netw Open*. 2022;5(2):e2148983. doi:10.1001/jamanetworkopen.2021.48983

**eTable 1.** Associations of Family History of Breast Cancer With Dense Volume and Non-Dense Volume (N=375)

**eTable 2.** Associations of Family History of Breast Cancer With BI-RADS Breast Density Categories 1 in Validation Set, Stratified by Race

**eTable 3.** Associations of Family History of Breast Cancer With BI-RADS Breast Density Categories, Pre- and Post-5th Edition of BI-RADS

This supplementary material has been provided by the authors to give readers additional information about their work.

| <b>eTable 1.</b> Associations of family history of breast cancer with dense volume and non-dense volume (N=375). |          |  |                            |  |                            |
|--|----------|--|----------------------------|--|----------------------------|
| <b>Characteristics</b>   | <b>N</b> | <b>Dense Volume (cm<sup>3</sup>)<sup>a</sup></b> | <b>p value<sup>b</sup></b> | <b>Non-dense Volume (cm<sup>3</sup>)<sup>a</sup></b> |                            |
|  |          | <b>exp<sup>β</sup> (95% CI)</b>                  |                            | <b>exp<sup>β</sup> (95% CI)</b>                      | <b>p value<sup>b</sup></b> |
| <b>FHBC</b>  |          |  |                            |  |                            |
| <i>Model 1<sup>c</sup></i>   |          |  |                            |  |                            |
| No   | 275      | Reference  |                            | Reference  |                            |
| Yes  | 87       | 1.16 (1.05 – 1.29)                               | <b>0.006</b>               | 0.91 (0.81 – 1.03)                                   | 0.12                       |
| Unknown  | 13       | 0.79 (0.62 – 1.01)                               | 0.06                       | 0.79 (0.60 – 1.03)                                   | 0.09                       |
| <i>Model 2<sup>d</sup></i>   |          |  |                            |  |                            |
| No   | 275      | Reference  |                            | Reference  |                            |
| Yes  | 87       | 1.16 (1.04 – 1.29)                               | <b>0.007</b>               | 0.91 (0.81 – 1.03)                                   | 0.13                       |
| Unknown  | 13       | 0.74 (0.58 – 0.95)                               | <b>0.02</b>                | 0.74 (0.56 – 0.98)                                   | <b>0.04</b>                |
| <b>FHBC in mothers alone</b>   |          |  |                            |  |                            |
| <i>Model 1<sup>c</sup></i>   |          |  |                            |  |                            |
| No   | 301      | Reference  |                            | Reference  |                            |
| Yes  | 67       | 1.21 (1.08 – 1.36)                               | <b>0.001</b>               | 0.91 (0.80 – 1.04)                                   | 0.15                       |
| Unknown  | 7        | 0.91 (0.66 – 1.27)                               | 0.59                       | 0.88 (0.61 – 1.28)                                   | 0.49                       |
| <i>Model 2<sup>d</sup></i>   |          |  |                            |  |                            |
| No   | 301      | Reference  |                            | Reference  |                            |
| Yes  | 67       | 1.21 (1.07 – 1.36)                               | <b>0.002</b>               | 0.91 (0.79 – 1.04)                                   | 0.15                       |
| Unknown  | 7        | 0.88 (0.63 – 1.22)                               | 0.44                       | 0.84 (0.58 – 1.22)                                   | 0.36                       |
| <b>FHBC in sisters alone</b>   |          |  |                            |  |                            |
| <i>Model 1<sup>c</sup></i>   |          |  |                            |  |                            |
| No   | 339      | Reference  |                            | Reference  |                            |
| Yes  | 26       | 1.07 (0.90 – 1.28)                               | 0.45                       | 0.98 (0.80 – 1.19)                                   | 0.82                       |
| Unknown  | 10       | 0.75 (0.57 – 0.99)                               | <b>0.04</b>                | 0.72 (0.53 – 0.98)                                   | <b>0.04</b>                |
| <i>Model 2<sup>d</sup></i>   |          |  |                            |  |                            |
| No   | 339      | Reference  |                            | Reference  |                            |
| Yes  | 26       | 1.08 (0.91 – 1.29)                               | 0.38                       | 0.99 (0.81 – 1.21)                                   | 0.95                       |
| Unknown  | 10       | 0.71 (0.53 – 0.93)                               | <b>0.01</b>                | 0.68 (0.50 – 0.93)                                   | <b>0.02</b>                |
| <b>Number of affected relatives with FHBC</b>  |          |  |                            |  |                            |
| <i>Model 1<sup>c</sup></i>   |          |  |                            |  |                            |
| 0  | 275      | Reference  |                            | Reference  |                            |
| 1  | 81       | 1.16 (1.04 – 1.29)                               | <b>0.01</b>                | 0.99 (0.81 – 1.21)                                   | 0.95                       |
| ≥2   | 6        | 1.25 (0.87 – 1.78)                               | 0.23                       | 0.68 (0.50 – 0.93)                                   | <b>0.02</b>                |
| Unknown  | 13       | 0.79 (0.62 – 1.01)                               | 0.06                       | 0.99 (0.81 – 1.21)                                   | 0.95                       |
| <i>Model 2<sup>d</sup></i>   |          |  |                            |  |                            |
| 0  | 275      | Reference  |                            | Reference  |                            |
| 1  | 81       | 1.15 (1.03 – 1.28)                               | <b>0.01</b>                | 0.91 (0.80 – 1.03)                                   | 0.14                       |
| ≥2   | 6        | 1.32 (0.92 – 1.89)                               | 0.13                       | 0.91 (0.61 – 1.37)                                   | 0.66                       |
| Unknown  | 13       | 0.74 (0.58 – 0.95)                               | <b>0.02</b>                | 0.74 (0.56 – 0.98)                                   | <b>0.037</b>               |

Abbreviations: CI, confidence interval, exp, Exponentiated; FHBC, Family history of breast cancer; N, Number.

<sup>a</sup> Continuous mammographic measurements were log transformed in the analysis. The beta coefficients were back transformed and exponentiated for easier interpretation. Effect measures represent proportion for percentage difference.

<sup>b</sup> p value derived from linear regression.

<sup>c</sup> Model 1 was adjusted for current age and body mass index (BMI)

<sup>d</sup> Model 2 was adjusted for current age, BMI, parity, race, age at menarche, and alcohol use.

**eTable 2.** Associations of family history of breast cancer with BI-RADS breast density categories<sup>a</sup> in validation set, stratified by race.

| Characteristics                               | Non-Hispanic White<br>(N = 8,010) |              |                                   |                      | Black/African American<br>(N = 5,292) |              |                                   |                      |
|---|-----------------------------------|--------------|-----------------------------------|----------------------|---------------------------------------|--------------|-----------------------------------|----------------------|
|   | Dense breast<br>(N)               | Total<br>(N) | Dense breast vs. non-dense breast |                      | Dense breast<br>(N)                   | Total<br>(N) | Dense breast vs. non-dense breast |                      |
|   |                                   |              | OR (95% CI)                       | p value <sup>b</sup> |                                       |              | OR (95% CI)                       | p value <sup>b</sup> |
| <b>FHBC</b>                                   |                                   |              |                                   |                      |                                       |              |                                   |                      |
| <i>Model 1<sup>c</sup></i>                    |                                   |              |                                   |                      |                                       |              |                                   |                      |
| No  | 3464                              | 6632         | Reference                         | <0.001               | 1578                                  | 4572         | Reference                         | <b>0.03</b>          |
| Yes   | 787                               | 1378         | 1.30 (1.13 – 1.49)                |                      | 279                                   | 720          | 1.23 (1.02 – 1.49)                |                      |
| <i>Model 2<sup>d</sup></i>                    |                                   |              |                                   |                      |                                       |              |                                   |                      |
| No  | 3464                              | 6632         | Reference                         | <0.001               | 1578                                  | 4572         | Reference                         | <b>0.03</b>          |
| Yes   | 787                               | 1378         | 1.29 (1.13 – 1.49)                |                      | 279                                   | 720          | 1.23 (1.02 – 1.49)                |                      |
| <b>FHBC in mothers alone</b>                  |                                   |              |                                   |                      |                                       |              |                                   |                      |
| <i>Model 1<sup>c</sup></i>                    |                                   |              |                                   |                      |                                       |              |                                   |                      |
| No  | 3129                              | 6059         | Reference                         | <0.001               | 1371                                  | 4065         | Reference                         | <b>0.003</b>         |
| Yes   | 572                               | 998          | 1.27 (1.09 – 1.49)                |                      | 173                                   | 448          | 1.25 (0.99 – 1.58)                |                      |
| Unknown                                       | 550                               | 953          | 1.36 (1.16 – 1.59)                |                      | 313                                   | 779          | 1.32 (1.10 – 1.57)                |                      |
| <i>Model 2<sup>d</sup></i>                    |                                   |              |                                   |                      |                                       |              |                                   |                      |
| No  | 3129                              | 6059         | Reference                         | <0.001               | 1371                                  | 4065         | Reference                         | <b>0.003</b>         |
| Yes   | 572                               | 998          | 1.27 (1.08 – 1.49)                |                      | 173                                   | 448          | 1.25 (0.99 – 1.58)                |                      |
| Unknown                                       | 550                               | 953          | 1.32 (1.12 – 1.55)                |                      | 313                                   | 779          | 1.34 (1.11 – 1.60)                |                      |
| <b>FHBC in sisters alone</b>                  |                                   |              |                                   |                      |                                       |              |                                   |                      |
| <i>Model 1<sup>c</sup></i>                    |                                   |              |                                   |                      |                                       |              |                                   |                      |
| No  | 3126                              | 6054         | Reference                         | <0.001               | 1371                                  | 4064         | Reference                         | <b>0.003</b>         |
| Yes   | 150                               | 284          | 1.36 (1.03 – 1.79)                |                      | 85                                    | 234          | 1.18 (0.87 – 1.62)                |                      |
| Unknown                                       | 975                               | 1672         | 1.31(1.15 – 1.49)                 |                      | 401                                   | 994          | 1.32 (1.12 – 1.56)                |                      |
| <i>Model 2<sup>d</sup></i>                    |                                   |              |                                   |                      |                                       |              |                                   |                      |
| No  | 3126                              | 6054         | Reference                         | <b>0.002</b>         | 1371                                  | 4064         | Reference                         | <b>0.003</b>         |
| Yes   | 150                               | 284          | 1.37 (1.04 – 1.80)                |                      | 85                                    | 234          | 1.21 (0.88 – 1.66)                |                      |
| Unknown                                       | 975                               | 1672         | 1.28 (1.13 – 1.46)                |                      | 401                                   | 994          | 1.33 (1.13 – 1.57)                |                      |
| <b>Number of affected relatives with FHBC</b> |                                   |              |                                   |                      |                                       |              |                                   |                      |
| <i>Model 1<sup>c</sup></i>                    |                                   |              |                                   |                      |                                       |              |                                   |                      |
| 0   | 3125                              | 6053         | Reference                         | <b>0.001</b>         | 1369                                  | 4061         | Reference                         | <b>0.006</b>         |
| 1   | 660                               | 1168         | 1.30 (1.12 – 1.50)                |                      | 236                                   | 620          | 1.20 (0.98 – 1.47)                |                      |
| ≥2  | 31                                | 57           | 1.27 (0.70 – 2.31)                |                      | 11                                    | 31           | 1.54 (0.68 – 3.49)                |                      |
| Unknown                                       | 435                               | 732          | 1.35 (1.13 – 1.62)                |                      | 241                                   | 580          | 1.38 (1.13 – 1.69)                |                      |
| <i>Model 2<sup>d</sup></i>                    |                                   |              |                                   |                      |                                       |              |                                   |                      |
| 0   | 3125                              | 6053         | Reference                         | <b>0.006</b>         | 1369                                  | 4061         | Reference                         | <b>0.005</b>         |
| 1   | 660                               | 1168         | 1.30 (1.12 – 1.50)                |                      | 236                                   | 620          | 1.21 (0.98 – 1.48)                |                      |
| ≥2  | 31                                | 57           | 1.24 (0.68 – 2.26)                |                      | 11                                    | 31           | 1.56 (0.69 – 3.52)                |                      |
| Unknown                                       | 435                               | 732          | 1.30 (1.08 – 1.56)                |                      | 241                                   | 580          | 1.40 (1.14 – 1.73)                |                      |

Abbreviations: BI-RADS, The Breast Imaging, Reporting and Data System; CI, confidence interval, FHBC, Family history of breast cancer; N, Number; OR, Odds ratio.  
<sup>1</sup> Dense breast defined as BI-RADS 3 and 4. Non-dense breast (referent) defined as BI-RADS 1 and 2. Logistic regression examines odds of having dense breast.  
<sup>2</sup> Type III chi-square p values derived from logistic regression.  
<sup>3</sup> Model 1 was adjusted for current age and BMI  
<sup>4</sup> Model 2 was adjusted for current age, BMI, parity, age at menarche, and alcohol use.

| <b>eTable 3. Associations of family history of breast cancer with BI-RADS breast density categories, pre- and post-5<sup>th</sup> edition of BIRADS.</b> |   |                     |                      |  |                     |                      |
|--|---|---------------------|----------------------|--|---------------------|----------------------|
| Characteristics  | Visited Before December 31, 2012<br>(N = 6,900) |                     |                      | Visited After January 1, 2013<br>(N = 7,140) |                     |                      |
|  | Dense Breast (BI-RADS) <sup>a</sup>             |                     |                      |  |                     |                      |
|  | N <sup>b</sup>                                  | Odds Ratio (95% CI) | p value <sup>c</sup> | N <sup>b</sup>                               | Odds Ratio (95% CI) | p value <sup>c</sup> |
| <b>FHBC</b>  |   |                     |                      |  |                     |                      |
| <i>Model 1<sup>d</sup></i>   |   |                     |                      |  |                     |                      |
| No   | 2717  | Reference           | <b>0.02</b>          | 2806   | Reference           | <b>&lt;0.001</b>     |
| Yes  | 469   | 1.22 (1.03 – 1.43)  |                      | 643  | 1.52 (1.16 – 1.55)  |                      |
| <i>Model 2<sup>e</sup></i>   |   |                     |                      |  |                     |                      |
| No   | 2717  | Reference           | <b>0.01</b>          | 2806   | Reference           | <b>&lt;0.001</b>     |
| Yes  | 469   | 1.23 (1.04 – 1.45)  |                      | 643  | 1.36 (1.17 – 1.58)  |                      |
| <b>FHBC in mothers alone</b>   |   | 6                   |                      |  |                     |                      |
| <i>Model 1<sup>d</sup></i>   |   |                     |                      |  |                     |                      |
| No   | 2446  | Reference           | <b>0.01</b>          | 2476   | Reference           | <b>&lt;0.001</b>     |
| Yes  | 327   | 1.23 (1.02 – 1.50)  |                      | 441  | 1.30 (1.10 – 1.55)  |                      |
| Unknown  | 413   | 1.25 (1.05 – 1.48)  |                      | 532  | 1.40 (1.19 – 1.63)  |                      |
| <i>Model 2<sup>e</sup></i>   |   |                     |                      |  |                     |                      |
| No   | 2446  | Reference           | <b>0.01</b>          | 2476   | Reference           | <b>&lt;0.001</b>     |
| Yes  | 327   | 1.24 (1.02 – 1.51)  |                      | 441  | 1.31 (1.10 – 1.56)  |                      |
| Unknown  | 413   | 1.24 (1.04 – 1.47)  |                      | 532  | 1.39 (1.18 – 1.63)  |                      |
| <b>FHBC in sisters alone</b>   |   |                     |                      |  |                     |                      |
| <i>Model 1<sup>d</sup></i>   |   |                     |                      |  |                     |                      |
| No   | 2442  | Reference           | <b>&lt;0.01</b>      | 2477   | Reference           | <b>&lt;0.001</b>     |
| Yes  | 102   | 1.10 (0.82 – 1.48)  |                      | 154  | 1.55 (1.18 – 2.03)  |                      |
| Unknown  | 642   | 1.28 (1.11 – 1.48)  |                      | 818  | 1.31 (1.15 – 1.50)  |                      |
| <i>Model 2<sup>e</sup></i>   |   |                     |                      |  |                     |                      |
| No   | 2442  | Reference           | <b>&lt;0.01</b>      | 2477   | Reference           | <b>&lt;0.001</b>     |
| Yes  | 102   | 1.12 (0.83 – 1.52)  |                      | 154  | 1.58 (1.20 – 2.09)  |                      |
| Unknown  | 642   | 1.27 (1.10 – 1.48)  |                      | 818  | 1.31 (1.14 – 1.50)  |                      |
| <b>Number of affected relatives with FHBC</b>  |   |                     |                      |  |                     |                      |
| <i>Model 1<sup>d</sup></i>   |   |                     |                      |  |                     |                      |
| 0  | 2442  | Reference           | <b>0.01</b>          | 2474   | Reference           | <b>&lt;0.001</b>     |
| 1  | 403   | 1.22 (1.03 – 1.46)  |                      | 533  | 1.32 (1.13 – 1.55)  |                      |
| ≥2   | 13  | 0.91 (0.42 – 1.97)  |                      | 31   | 1.89 (0.99 – 3.60)  |                      |
| Unknown  | 328   | 1.29 (1.07 – 1.57)  |                      | 411  | 1.36 (1.14 – 1.63)  |                      |
| <i>Model 2<sup>e</sup></i>   |   |                     |                      |  |                     |                      |
| 0  | 2442  | Reference           | <b>0.02</b>          | 2474   | Reference           | <b>&lt;0.001</b>     |
| 1  | 403   | 1.23 (1.03 – 1.47)  |                      | 533  | 1.34 (1.14 – 1.57)  |                      |
| ≥2   | 13  | 0.95 (0.44 – 2.06)  |                      | 31   | 1.83 (0.96 – 3.51)  |                      |
| Unknown  | 328   | 1.27 (1.04 – 1.55)  |                      | 411  | 1.34 (1.12 – 1.61)  |                      |

Abbreviations: BI-RADS, The Breast Imaging, Reporting and Data System; CI, confidence interval; exp, Exponentiated; FHBC, Family history of breast cancer; N, Number.

<sup>a</sup> Dense breast defined as BI-RADS 3 and 4. Non-dense breast (reference) defined as BI-RADS 1 and 2. Logistic regression examines odds of having dense breast.

<sup>b</sup> Represents the proportion of patients with dense breast within the exposure strata (i.e., among those with or without a family history of breast cancer).

<sup>c</sup> Type III chi-square p values derived from logistic regression.

<sup>d</sup> Model 1 was adjusted for current age (continuous, years) and BMI (continuous, kg/m<sup>2</sup>).

<sup>e</sup> Model 2 was adjusted for current age (continuous, years), BMI (continuous, kg/m<sup>2</sup>), parity (0, 1, 2, ≥3), race (non-Hispanic white/African American/others), age at menarche (continuous, years), and alcohol consumption (yes/no).