MRI background parenchymal enhancement, breast density and breast cancer risk factors: A cross-sectional study in pre- and post-menopausal women

Jennifer D. Brooks1,2, Rebecca A. G. Christensen2, Janice S. Sung2, Malcolm C. Pike3, Irene Orlow3, Jonine L. Bernstein3 and Elizabeth A. Morris2,4

Breast tissue enhances on contrast MRI and is called background parenchymal enhancement (BPE). Having high BPE has been associated with an increased risk of breast cancer. We examined the relationship between BPE and the amount of fibroglandular tissue on MRI (MRI-FGT) and breast cancer risk factors. This was a cross-sectional study of 415 women without breast cancer undergoing contrast-enhanced breast MRI at Memorial Sloan Kettering Cancer Center. All women completed a questionnaire assessing exposures at the time of MRI. Prevalence ratios (PR) and 95% confidence intervals (CI) describing the relationship between breast cancer risk factors and BPE and MRI-FGT were generated using modified Poisson regression. In multivariable-adjusted models a positive association between body mass index (BMI) and BPE was observed, with a 5-unit increase in BMI associated with a 14% and 44% increase in prevalence of high BPE in pre- and post-menopausal women, respectively. Conversely, a strong inverse relationship between BMI and MRI-FGT was observed in both pre- (PR = 0.66, 95% CI 0.57, 0.76) and post-menopausal (PR = 0.66, 95% CI 0.56, 0.78) women. Use of preventive medication (e.g., tamoxifen) was associated with having low BPE, while no association was observed for MRI-FGT. BPE is an imaging marker available from standard contrast-enhanced MRI, that is influenced by endogenous and exogenous hormonal exposures in both pre- and post-menopausal women.

RESULTS
Distribution of Breast Cancer Risk Factors
The median age at MRI was 49 years, 48% of women were postmenopausal, and 90% self-identified as White (Table 1). Most women (82% of premenopausal and 88% of postmenopausal), were having an MRI for high-risk breast cancer screening purposes. As expected, BPE and MRI-FGT were both higher in premenopausal than in postmenopausal women (P < 0.0001 for both) (Table 2). Weighted Cohen’s kappa coefficients for repeat reads of BPE and MRI-FGT were 0.87 (95% CI 0.76, 0.98) and 0.92 (95% CI 0.83, 1.00) (i.e., ‘almost perfect agreement’), respectively. Notably BPE and MRI-FGT were not correlated (Pearson correlation coefficient and p-value: postmenopausal women r = −0.00658, p = 0.93; premenopausal women: r = −0.09307 p = 0.17). The distribution of different breast cancer risk factors in the study population are shown in Tables 1 and 3.

INTRODUCTION
Mammographic percent density (MPD) is a measure of the proportion of the normal breast occupied by fibroglandular tissue (FGT), seen as dense (white) areas on a mammogram. While MPD is considered to be one of the strongest, established risk factors for breast cancer1, there are other features (e.g., texture features) on mammogram that have also been implicated in risk2.

In the United States women at a high risk of breast cancer (i.e., ≥20% lifetime risk) are recommended to undergo annual screening with contrast-enhanced magnetic resonance imaging (MRI) in addition to mammography3. The amount of fibroglandular tissue in the breast can be assessed volumetrically on MRI (MRI-FGT) and is known to be correlated with MPD4,5. Much like MPD, MRI-FGT has been shown to be associated with breast cancer risk6, and sensitive to endogenous (e.g., menopause) and exogenous (e.g., tamoxifen, aromatase inhibitors) hormonal exposures7–9. Like mammogram, there are other image features from MRI that may be associated with breast cancer risk.

Contrast-enhanced MRI uses an intravenously injected contrast agent, to help visualize tumors through the identification of distinct patterns of contrast dispersion10,11. The MRI signal from normal FGT also enhances to varying degrees and is called background parenchymal enhancement (BPE). BPE is recorded as the proportion of FGT in the breast that enhances. Having high BPE has been associated with an increased risk of breast cancer in some6,12–17, but not all18,19 studies. Notably, this association is thought to be independent of MRI-FGT16. BPE has been shown to be highly influenced by both endogenous (e.g., menopausal status20, serum estrogen concentrations20, body mass index [BMI]21,22) and exogenous (e.g., menopausal hormone therapy [MHT]23,24, tamoxifen9,25, aromatase inhibitors8,26) hormonal exposures. However, many of these studies have been small or did not consider relevant confounders.

The objective of this study was to contribute to our understanding of BPE and MRI-FGT as imaging markers of breast cancer risk by examining their relationship with established breast cancer risk factors.

1Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada. 2Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA. 3Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA. 4Department of Radiology, University of California Davis, Sacramento, CA, USA. 5email: jennifer.brooks@utoronto.ca
Association between BPE and MRI-FGT with breast cancer risk factors

Table 4 shows results from multivariable-adjusted models for BPE and MRI-FGT in premenopausal women. A positive association between BPE and BMI was observed, but this result did not reach statistical significance (PR = 1.14, 95% CI 0.96, 1.35). There was also a positive association between BPE and use of oral contraceptives at the time of MRI, such that women who reported using oral contraceptives tended to have a higher prevalence of high BPE, however, this finding did not reach statistical significance (PR = 1.45, 95% CI 0.98, 2.15). Conversely, premenopausal women with documented BRCA mutations were less likely to have higher BPE than non-carriers (PR = 0.40, 95% CI 0.19, 0.83). It was thought that this relationship could be explained by use of preventive medications (e.g., tamoxifen) in this high-risk group. However, none of the women identified as premenopausal BRCA mutation carriers reported use of preventive medications at the time of MRI. In multivariable-adjusted models of MRI-FGT in premenopausal women, BMI was significantly associated with MRI-FGT, with increasing BMI associated with a lower prevalence of high MRI-FGT (PR = 0.66, 95% CI 0.57, 0.77 per five-unit increase in BMI). We also found a significant positive association between having a personal history of LCIS and the prevalence of high MRI-FGT (PR = 1.22, 95% CI 1.02, 1.45).

In postmenopausal women (Table 5), BPE tended to be lower with increasing age, although this did not reach statistical significance (p = 0.09). A significant positive association between BMI and BPE was observed such that each five-unit increase in BMI was associated with a 44% higher prevalence of high BPE (PR = 1.44, 95% CI 1.08, 1.93). Compared to women who were nulliparous, those who were 30 years or older at the time of first full-term pregnancy had a lower prevalence of high BPE (PR = 0.33, 95% CI 0.13, 0.86). Only BMI was significant associated with MRI-FGT in postmenopausal women, with a 34% decrease in the prevalence of high MRI-FGT seen with every five-unit increase in BMI (PR = 0.66, 95% CI 0.56, 0.78) (Table 5).

Sensitivity analyses

Sensitivity analyses were conducted restricting to women who self-reported White/Caucasian or reported having an MRI for high-risk screening purposes and the results did not differ (results not shown).

BPE and MRI-FGT and use of preventive medications

Finally, the use of preventive medications was associated with low BPE in both pre- and post-menopausal women (Table 6). The impact of these medications on BPE is so strong that all women using these medications had low BPE (p = 0.07 in premenopausal women and p = 0.05 in postmenopausal women). We therefore could not include these variables in the multivariable models for BPE due to small (zero) cell counts. No association between current use of preventive medications and MRI-FGT was observed (p > 0.05) (Table 6).

Table 1. Characteristics of the study population by menopausal status at the time of MRI.

| Patient characteristics, N (%) | Premenopausal (N = 217) | Postmenopausal (N = 198) |
|-------------------------------|-------------------------|--------------------------|
| Age at MRI, median (range)    | 43 (25–58)              | 57 (39–77)               |
| Reason for MRI*               |                         |                          |
| Abnormal screening mammogram  | 33 (15.0)               | 36 (18.1)                |
| Lump in breast                | 23 (10.5)               | 13 (6.5)                 |
| High-risk breast cancer       | 180 (81.8)              | 175 (87.9)               |
| Other                         | 9 (4.1)                 | 11 (5.5)                 |
| Race                          |                         |                          |
| White/Caucasian               | 194 (88.2)              | 179 (90.0)               |
| Black/African American        | 11 (5.0)                | 11 (5.5)                 |
| Asian or Pacific Islander     | 8 (3.6)                 | 4 (2.0)                  |
| Other                         | 7 (3.2)                 | 5 (2.5)                  |
| Body mass index (BMI, kg/m²), median (range) | 22.1 (17.7, 43.6) | 23.8 (17.9, 50.1) |
| <18.5                         | 9 (4.1)                 | 5 (2.5)                  |
| 18.5–<25                      | 154 (70.0)              | 116 (58.3)               |
| 25–<30                        | 38 (17.3)               | 43 (21.6)                |
| ≥30                           | 19 (8.6)                | 35 (17.6)                |
| Age at menarche, Median (range) | 12 (9–18)              | 13 (7–17)                |
| <13 years                     | 102 (46.4)              | 103 (51.8)               |
| ≥13 years                     | 118 (53.6)              | 96 (48.2)                |
| Parity                        |                         |                          |
| Nulliparous                   | 81 (36.8)               | 52 (26.1)                |
| Parous                        | 139 (63.2)              | 147 (73.9)               |
| Number of full-term pregnancies |                       |                          |
| Nulliparous                   | 81 (36.8)               | 52 (26.1)                |
| 1                             | 26 (11.8)               | 27 (13.6)                |
| 2                             | 79 (35.9)               | 80 (40.2)                |
| ≥3                            | 34 (15.5)               | 40 (20.1)                |
| Age first full-term pregnancy, (years) |               |                          |
| <25                           | 10 (7.2)                | 25 (17.0)                |
| 25–<29                        | 38 (17.3)               | 37 (18.1)                |
| ≥30                           | 91 (65.5)               | 65 (44.2)                |

MRI diagnostic imaging, BMI body mass index, BPE background parenchymal enhancement, MRI-FGT amount of fibroglandular tissue on MRI, ADH atypical ductal hyperplasia, ALH atypical lobular hyperplasia, LCIS lobular carcinoma in situ, NA not applicable, VUS variants of unknown significance.

*Women were asked to indicate all that apply.

**Median age at menarche in the full study population was 13 years.

Table 2. Distribution of background parenchymal enhancement (BPE) and fibroglandular tissue (MRI-FGT) in pre- and postmenopausal women.

| MRI Measurement, N (%) | Premenopausal (N = 217) | Postmenopausal (N = 198) |
|------------------------|-------------------------|--------------------------|
| Background Parenchymal Enhancement (BPE) |                        |                          |
| Minimal                | 42 (19.1)               | 109 (54.8)               |
| Mild                   | 102 (46.4)              | 66 (33.2)                |
| Moderate               | 55 (25.0)               | 16 (8.0)                 |
| Marked                 | 21 (9.5)                | 8 (4.0)                  |
| Fibroglandular Tissue (MRI-FGT) |                    |                          |
| Predominantly fatty     | 7 (3.2)                 | 24 (12.1)                |
| Scattered densities     | 38 (17.3)               | 55 (27.6)                |
| Heterogeneously dense   | 98 (44.5)               | 107 (53.8)               |
| Extremely dense         | 77 (35.0)               | 13 (6.5)                 |
DISCUSSION

BPE and MRI-FGT are characteristics of normal breast tissue that are routinely assessed by radiologists from standard contrast-enhanced MRI. Prior studies have shown these markers to be independently associated with breast cancer risk, contributing distinct information about a woman's risk. To better understand these relationships and how they could be used to inform recommendations for screening and prevention, it is necessary to understand the factors that impact these imaging markers. The results of the current study show that BPE is highly dependent on

| Table 3. Distribution of breast cancer risk factors by menopausal status at the time of MRI. |
|-----------------------------------------------|
| Patient Characteristics, N (%)               |
|                  | Premenopausal (N = 217) | Postmenopausal (N = 198) |
| First degree family history of breast cancer |
| No               | 56 (25.5)               | 60 (30.3)               |
| Yes             | 164 (74.5)              | 138 (69.7)              |
| BRCA mutation status |
| Negative        | 40 (18.2)               | 47 (23.6)               |
| BRCA1-positive  | 22 (10.0)               | 22 (11.1)               |
| BRCA2-positive  | 26 (11.8)               | 21 (10.6)               |
| Positive        | 2 (0.9)                 | 0 (0.0)                 |
| (unknown type)  |                       |                       |
| BRCA1- and BRCA2-positive | 1 (0.5) | 0 (0.0) |
| VUS             | 2 (0.9)                 | 1 (0.5)                 |
| Not tested      | 127 (57.7)              | 108 (54.3)              |
| Oophorectomy    |
| No              | 217 (98.6)              | 119 (59.8)              |
| Yes             | 3 (1.4)                 | 11 (5.5)                |
| Yes (both ovaries removed) | 0  | 69 (34.7) |
| History of high-risk lesion |
| No              | 178 (81.3)              | 125 (63.1)              |
| Atypical hyperplasia (ADH and ALH) | 11 (5.0) | 27 (13.6) |
| LCIS            | 30 (13.7)               | 46 (23.2)               |
| Hormonal Medications at the time of MRI |
| Oral contraceptives |
| No              | 160 (73.1)              | NA                     |
| Yes             | 59 (26.9)               | 166 (83.4)              |
| Menopausal hormone therapy |
| No              | NA                      | 33 (16.6)               |
| Yes             | 166 (83.4)              | 33 (16.6)               |
| Tamoxifen       |
| No              | 214 (97.3)              | 196 (98.5)              |
| Yes             | 6 (2.7)                 | 3 (1.5)                 |
| Raloxifene      |
| No              | 220 (100)               | 179 (90.0)              |
| Yes             | 0                      | 20 (10.0)               |
| Aromatase inhibitor |
| No              | NA                      | 198 (99.5)              |
| Yes             | 1 (0.5)                 | 1 (0.5)                 |
| Other Exposures at the time of MRI |
| Usual alcohol consumption |
| None            | 29 (13.2)               | 47 (23.6)               |
| <7 drinks per week | 170 (77.3)             | 131 (65.8)              |
| ≥7 drinks per week | 21 (9.5)               | 21 (10.6)               |
| Smoking status  |
| No              | 207 (94.5)              | 196 (98.5)              |
| Yes             | 12 (5.5)                | 3 (1.5)                 |

Table 4. Multivariable adjusted prevalence ratios (PR) and 95% confidence intervals (CI) for the relationship between breast cancer risk factors and BPE and MRI-FGT in premenopausal women.

| Variable                        | BPE* | p value | MRI-FGT* | p value |
|---------------------------------|------|---------|----------|---------|
| Age at MRI (years)              | 0.96 | 0.59    | 0.97     | 0.32    |
| BMI (kg/m²)                     | 1.14 | 0.14    | 0.66     | 0.76    |<0.0001 |
| Family history of breast cancer |
| No                              | 1.00 | --      | 1.00     | --      |
| Yes                             | 0.94 | 0.81    | 1.01     | 0.71    |
| BRCA mutation status            |
| Negative                        | 1.00 | --      | 1.00     | --      |
| Positive                        | 0.40 | 0.01    | 0.94     | 0.53    |
| Not tested                      | 0.94 | 0.78    | 0.96     | 0.64    |
| History of breast biopsy        |
| No                              | 1.00 | --      | 1.00     | --      |
| Yes                             | 0.98 | 0.91    | 1.07     | 0.30    |
| History of high-risk benign lesion |
| No                              | 1.00 | --      | 1.00     | --      |
| Atyypical hyperplasia           | 1.25 | 0.56    | 0.64     | 0.14    |
| LCIS                            | 0.77 | 0.50    | 1.22     | 0.03    |
| Age at menarche                 |
| <13 years                       | 1.00 | --      | 1.00     | --      |
| ≥13 years                       | 0.88 | 0.50    | 0.97     | 0.68    |
| Number of full-term pregnancies |
| Nulliparous                     | 1.00 | --      | 1.00     | --      |
| 1                               | 0.91 | 0.79    | 1.04     | 0.70    |
| 2                               | 1.25 | 0.36    | 1.04     | 0.64    |
| ≥3                              | 1.32 | 0.33    | 1.03     | 0.76    |
| Age first full-term pregnancy (years) |
| Nulliparous                     | 1.00 | --      | 1.00     | --      |
| <25                             | 1.36 | 0.42    | 1.15     | 0.54    |
| ≥25                                      | 1.12 | 0.47    | 1.11     | 0.17    |
| Use of oral contraceptive at the time of MRI |
| No                              | 1.00 | --      | 1.00     | --      |
| Yes                             | 1.45 | 0.07    | 1.01     | 0.92    |
| Use of preventative medications at the time of MRI |
| No                              | --   | --      | 1.00     | --      |
| Yes                             | 0.93 | 0.60    | 0.93     | 0.80    |
| Usual alcohol consumption at the time of MRI |
| None                            | 1.00 | --      | 1.00     | --      |
| <7 drinks per week              | 0.98 | 0.95    | 1.00     | 0.98    |
| ≥7 drinks per week              | 1.48 | 0.26    | 1.01     | 0.90    |
| Smoking status at the time of MRI |
| No                              | 1.00 | --      | 1.00     | --      |
| Yes                             | 1.01 | 0.98    | 1.14     | 0.35    |

*PR (95% CI) adjusted age, BMI, family history of breast cancer, BRCA mutation status, history of biopsy, history of high-risk benign lesion, age at menarche, number of full-term pregnancies, use of oral contraceptives at time of MRI, number of drinks per week, and smoking status. BPE is categorized as minimal and mild versus moderate and marked. MRI-FGT is coded as fatty and scattered versus heterogeneously dense and dense. bPer 5 unit increase in age (years) and BMI (kg/m²), respectively.
and post-menopausal women. This relationship was most clear

between BMI (postmenopausal women only) and a strong inverse

association with use of preventive medications (e.g., tamoxifen,

(hormonal exposures, with a positive association observed

between BMI (postmenopausal women only) and a strong inverse

association with use of preventive medications (e.g., tamoxifen,

BPE was found to be positively associated with BMI in both pre-

and post-menopausal women. This relationship was most clear

and statistically significant) for postmenopausal women where for

every 5-unit increase in BMI the prevalence of high BPE increases

by about 40%. While a positive association was also observed in

premenopausal women, this association did not reach statistical

significance. These results are consistent with those of two prior

studies observing a positive association between BMI and BPE. In a

small study of 214 women, Hellgren et al.21 found that women with

obesity (BMI > 30 kg/m²) had an almost 5-fold higher odds

(95% CI 1.2, 19.4) of having high versus low BPE compared to

women with a BMI < 25 kg/m². A second study found an

association between BMI and BPE in unadjusted analyses22. Ours

is the largest multivariable-adjusted study to-date, able to also

consider the use of preventive medications at the time of MRI and BPE.

BMI is positively associated with breast cancer risk in

postmenopausal women and inversely associated with risk in premenopausal women27. This relationship is likely explained in part by the relationship between BMI and hormones (e.g., estradiol)28, where in postmenopausal women, adipose tissue becomes the primary source of circulating estrogens29. There is a growing body of evidence showing BPE to be associated with both endogenous and exogenous hormonal exposures. BPE has been shown to increase with the use of MHT32,24 and to decrease with menopause2 and oophorectomy20, and in response to treatment with tamoxifen30,33, or aromatase inhibitors34,35. Recently we also showed that BPE is significantly positively associated with serum estradiol levels in postmenopausal women20. Together this suggests a plausible mechanism through which BMI could be impacting BPE in postmenopausal women. Further, there is some indication that the relationship between BPE and breast cancer risk may be modulated by BMI, however, this requires further investigation16.

In the current study, we found a strong relationship between

the use of hormonal medications at the time of MRI and BPE.

Specifically, the use of preventive medications (e.g., tamoxifen)

was so strongly associated with low BPE in both pre- and

postmenopausal women, that all women using these medications

Table 5. Multivariable adjusted prevalence ratios and 95% confidence intervals (CI) the relationship between breast cancer risk factors and BPE and MRI-FGT in postmenopausal women.

| Variable | BPE a | p value | MRI-FGT a | p value |
|----------|-------|---------|-----------|---------|
| Age at MRIb (years) | 0.78 (0.59, 1.04) | 0.09 | 0.99 (0.91, 1.07) | 0.71 |
| BMI (kg/m²)b | 1.44 (1.08, 1.93) | 0.01 | 0.66 (0.56, 0.78) | -0.0001 |
| Family history of breast cancer | | | |
| No | 1.00 | - | 1.00 | - |
| Yes | 1.51 (0.47, 4.78) | 0.49 | 1.13 (0.85, 1.49) | 0.41 |
| BRCA mutation status | | | |
| Negative | 1.00 | - | 1.00 | - |
| Positive | 0.44 (0.13, 1.48) | 0.18 | 0.86 (0.58, 1.28) | 0.45 |
| Unknown | 0.58 (0.26, 1.31) | 0.19 | 1.04 (0.79, 1.39) | 0.76 |
| History of breast biopsy | | | |
| No | 1.00 | - | 1.00 | - |
| Yes | 1.49 (0.47, 4.71) | 0.50 | 1.09 (0.82, 1.47) | 0.54 |
| History of high-risk benign lesion | | | |
| No | 1.00 | - | 1.00 | - |
| Atypical hyperplasia | 1.12 (0.34, 3.69) | 0.85 | 0.97 (0.71, 1.33) | 0.87 |
| LCIS | 1.42 (0.45, 4.46) | 0.54 | 1.12 (0.79, 1.58) | 0.52 |
| Age at menarche | | | |
| <13 years | 1.00 | - | 1.00 | - |
| ≥13 years | 0.89 (0.39, 2.02) | 0.77 | 0.97 (0.79, 1.19) | 0.79 |
| Number of full-term pregnancies | | | |
| Nulliparous | 1.00 | - | 1.00 | - |
| 1-2 | 0.14 (0.02, 1.19) | 0.07 | 1.15 (0.82, 1.60) | 0.41 |
| 2 | 0.63 (0.28, 1.44) | 0.27 | 0.81 (0.63, 1.04) | 0.10 |
| ≥3 | 0.43 (0.15, 1.22) | 0.11 | 0.93 (0.67, 1.28) | 0.64 |
| Age first full-term pregnancy (years) | | | |
| Nulliparous | 1.00 | - | 1.00 | - |
| <25 | 0.96 (0.35, 2.64) | 0.94 | 0.69 (0.44, 1.08) | 0.10 |
| 25-29 | 0.38 (0.13, 1.11) | 0.08 | 0.74 (0.55, 1.01) | 0.06 |
| ≥30 | 0.33 (0.13, 0.86) | 0.02 | 1.11 (0.88, 1.41) | 0.37 |
| Use of menopausal hormone therapy at the time of MRI | | | |
| No | 1.00 | - | 1.00 | - |
| Yes | 2.54 (0.80, 8.01) | 0.11 | 0.92 (0.61, 1.40) | 0.69 |
| Use of preventative medications at the time of MRI | | | |
| No | 1.00 | - | 1.00 | - |
| Yes | 1.00 | - | 0.81 (0.57, 1.16) | 0.25 |
| Usual alcohol consumption at the time of MRI | | | |
| None | 1.00 | - | 1.00 | - |
| ≥1 drink(s) per week | 0.58 (0.25, 1.33) | 0.20 | 0.95 (0.73, 1.23) | 0.68 |
| Smoking status at the time of MRI | | | |
| No | 1.00 | - | 1.00 | - |
| Yes | 5.63 (0.53, 60.26) | 0.15 | 1.25 (0.29, 5.31) | 0.76 |

*PR (95% CI) adjusted age, BMI, family history of breast cancer, BRCA mutation status, history of biopsy, history of high-risk benign lesion, age at menarche, number of full-term pregnancies, use of hormone replacement therapy at time of MRI, ever preventative medication use, number of drinks per week, and smoking status. BPE is categorized as minimal and mild versus moderate and marked. MRI-FGT is coded as fatty and scattered versus heterogeneously dense and dense.

Table 6. Distribution of BPE and MRI-FGT by preventive medication use at the time of MRI in pre- and postmenopausal women.

| BPE | Minimal/Mild, N (%) | Moderate/Marked, N (%) | p valuea |
|-----|---------------------|------------------------|---------|
| Premenopausalb | | | |
| No | 138 (64.5) | 76 (35.5) | 0.07 |
| Yes | 6 (100.0) | 0 (0.0) | |
| Postmenopausal | | | |
| No | 151 (86.3) | 24 (13.7) | 0.05 |
| Yes | 24 (100.0) | 0 (0.0) | |
| MRI-FGT | Fatty/Scattered, N (%) | Heterogeneously Dense/Dense, N (%) | |
| Premenopausal | | | |
| No | 43 (20.1) | 171 (79.9) | 0.60 |
| Yes | 2 (33.3) | 4 (66.7) | |
| Postmenopausal | | | |
| No | 86 (38.9) | 107 (61.1) | 0.51 |
| Yes | 11 (45.8) | 13 (54.2) | |

aCochran Mantel Henzel p-value.
bPreventive medications used by premenopausal women included tamoxifen only (see Table 3).
had low BPE. We also found that use of oral contraceptives at the time of MRI was associated with a higher prevalence of high BPE, however, this association did not reach statistical significance. Prior work has shown that current or recent use of oral contraceptives is associated with increased breast cancer risk. These results support the hypothesis that BPE is a reflection of current/recent hormonal exposures (endogenous and exogenous) experienced in the breast, however further investigation of the influence of oral contraceptive use on BPE is warranted.

Prior work has shown a positive association between BPE and breast density (MD)12,13,24. We found that use of MHT at the time of MRI was associated with a non-significant increase in the prevalence of high BPE. This is likely due to the small number of women reporting use of MHT, and the high proportion of those reporting use of local therapy. Specifically, of the 33 women who reported MHT use at the time of MRI, 21 reported use of estrogen-only therapy and 16 of these women reported use of local therapy (e.g., Vagifem, Estrin). We did not have the sample size to conduct analyses further stratified by subtype, but since it is thought that BPE may be an indicator of local and systemic hormonal exposures this could have important implications for the use of local estrogen therapy in women undergoing treatment for breast cancer with aromatase inhibitors. Notably we did not see similar associations with MRI-FGT.

MDP has been studied extensively, and it is known to be highly variable across the population. Overall it has been shown to decrease with increasing age, increasing the number of births34,36, and increasing BMI34. MPD has also been shown to be influenced by hormonal exposures, decreasing with meno-pause, and with tamoxifen use in postmenopausal women37, and increasing with administration of combined estrogen and progesterin MHT (but not estrogen alone therapy)38. Similarly, we observed an inverse relationship between MRI-FGT and BMI. This was expected given that MRI-FGT is a volumetric measure of the amount of fibroglandular tissue in the breast that has been shown to correlate with MDP12,39. Other factors (e.g., parity, MHT) previously associated with MDP were not associated with MRI-FGT in this study. We hypothesize that this is because the current analysis is focused on exposure status at the time of MRI. Prior work by our group has shown that BPE is highly dynamic and responsive to the hormonal environment of the breast, whereas changes in MRI-FGT take longer to be observed on MRI6,12. This supports the idea that BPE may be an imaging biomarker of current hormonal exposures in the breast and could be used as an indicator of response to hormonal medications. Further, by dichotomizing BPE as low (min/mild) and high (moderate/marked), external validity is increased by reducing the potential for discordance.

Further limitations include the lack of racial diversity in the study population, with 89% of women self-identifying as White, limiting our ability to examine the impact of race on BPE or MRI-FGT. We also lacked information on the timing of MRI with respect to week of the menstrual cycle for pre-menopausal women. The American College of Radiology recommends that MRIs be performed in week 2 of the menstrual cycle when BPE is thought to be at its lowest, thereby maximizing the sensitivity of the MRI for cancer detection. Information on menstrual cycle week was not consistently available for study participants and so is not part of the current analysis. The impact of this is likely negligible as recent papers have found no association between menstrual cycle week and BPE34,35. Finally, we did not have information on all breast cancer risk factors. Of particular interest could be the relationship between physical activity and BPE. Physical activity is a potentially modifiable risk factor that has been shown to be associated with both circulating hormone levels and body composition36,47.

Prior work has found BPE to be a promising new marker of breast cancer risk providing information beyond that provided by assessment of breast density. The development of abbreviated MRI screening protocols likely means that MRI will increasingly be used to screen women that do not meet the high-risk criteria. This could include women with dense breasts or those at higher than average (elevated) risk. This highlights the need to understand the factors that influence BPE. Here we show that BPE is significantly positively associated with BMI in premenopausal women. Further, use of preventive medications led to an almost complete reduction in BPE. The hormonally responsive nature of BPE, supported by this and prior studies, suggests that BPE could be an imaging biomarker of hormonal exposures in the breast, potentially used as an indicator of response to hormonal medications, or to further stratify women at high risk of breast cancer undergoing MRI screening.

METHODS

This study was reviewed and approved by the Memorial Sloan Kettering Cancer Center (MSK) Institutional Review Board, and written informed consent was obtained at the time of recruitment from all study participants.

Study population

Patient recruitment and data collection have been published previously. Briefly, women (N = 504) who had no prior history of any cancer (including ductal carcinoma in situ (DCIS), but excluding nonmelanoma skin cancer) as...
noted in their medical record were approached in the MRI screening clinic at MSK between August 2012 and March 2014. Of the 449 women (88.9%) who volunteered to participate in the study, 30 were ultimately determined to be ineligible. Reasons for exclusion included insufficient proficiency in English (n = 2), prior personal history of cancer not previously identified during medical record review (n = 14), incomplete study questionnaire (n = 2) and diagnosis of cancer within the six months following MRI (n = 12). Individuals missing information on any covariates were also excluded (3 premenopausal women and 1 postmenopausal woman). This left a study population of 415 women for the current analysis.

Data collection
All women completed a self-administered questionnaire at the time of their MRI capturing information related to reproductive history, use of hormonal medications, family history of breast cancer and other risk factors. These included: age at menarche and menopause, parity (number of full-term pregnancies, age at first full-term pregnancy, time since last full-term pregnancy), use of hormonal medications at the time of MRI (e.g., MHT, tamoxifen, raloxifene, aromatase inhibitors), weight and height at the time of MRI, family history of breast cancer, and history of oophorectomy. Data from questionnaires was confirmed, when possible, through review of medical records.

Contrast-enhanced MRI and assessment of BPE and MRI-FGT
Breast MRIs were conducted using standard imaging protocols as described previously20. BPE and MRI-FGT were assessed by a single reader using the proposed American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS)21. BPE was classified as: minimal, mild, moderate or marked, and MRI-FGT as: a. almost entirely fatty, b. scattered fibroglandular tissue, c. heterogeneous fibroglandular tissue, or d. extreme fibroglandular tissue. The radiologist was blinded to all clinical characteristics of the patients. BPE and MRI-FGT are usually similar between breasts21. To confirm this, readings were conducted in both breasts and were only found to be discordant in one individual. In this instance, the higher value of the two breasts was assigned. Finally, to assess agreement between repeat reads, a set of MRIs (n = 19) were randomly selected to be re-read for both BPE and MRI-FGT.

Statistical Analysis
This was a cross-sectional study examining the relationship between BPE, MRI-FGT and breast cancer risk factors. BI-RADS categories of BPE and MRI-FGT were collapsed to create dichotomous variables categorizing BPE as minimal/mild and moderate/markd, and MRI-FGT as predominantly fatty/scattered and heterogeneous/extreme.

Breast cancer risk factors considered included: age at MRI (continuous), menopausal status (see below), current BMI (continuous), first-degree family history of breast cancer (yes, no), personal history of breast biopsy (yes, no), history of high-risk benign lesions (none, atypical hyperplasia [atypcal ductal hyperplasia [ADH] or atypical lobular hyperplasia [ALH]), lobular carcinoma in situ [LCIS], age at menarche (<13 years of age, ≥13 years of age, based on the median age at menarche in the study population), parous (yes/no), number of full-term pregnancies (nulliparous, 1, 2, ≥3), and age at first full-term pregnancy (nulliparous, <25, 25–<29, ≥30 years). BRCA1/2 mutation status categories were collapsed (negative, positive [BRCA1-positive, BRCA2-positive, BRCA1- and BRCA2-positive, positive-unknown type, variant of unknown significance [VUS], untested [Table 3]) because of insufficient numbers in some subgroups. Use of hormonal medications at the time of MRI was also captured and included use of oral contraceptives (premenopausal women only; yes/no), MHT (postmenopausal women only; yes (any type)/no), and preventive medications (current use of tamoxifen, raloxifene, aromatase inhibitors; yes/no). Other exposures including smoking status (yes/no), alcohol consumption (yes/no), and the number of drinks per week (none, <7, ≥7) were also examined.

If a woman reported that she had not had a menstrual period in the previous 12 months or had a personal history of a bilateral oophorectomy she was considered postmenopausal at the time of MRI. Five women were either missing information on age at the last menstrual period (n = 2) or had a period between 6 and 12 months of enrollment (n = 3). Eleven women, ranging in age from 44 to 64 years reported having had a simple hysterectomy, making it challenging to determine their menopausal status. For these groups of women, a prior analysis in this study population that included serum measurements of estradiol and estrone found that all had hormone levels were within the postmenopausal range. This indicated that they were indeed postmenopausal at the time of MRI20.

Mutually adjusted prevalence ratios (PR) and 95% confidence intervals (CI) were estimated using modified Poisson regression (i.e., Poisson regression using a log link and with robust error variance)23. Models did not include an adjustment for MRI-FGT because there was no association between BPE and MRI-FGT in our data (thus it did not meet the requirement of a confounder). Further, for analyses related to BMI, there was concern about over-adjustment given the strong relationship between BMI and MRI-FGT. All analyses were conducted stratified by menopausal status. Analyses were also conducted restricting to women who were having an MRI for high-risk screening purposes (i.e., excluding women with an abnormal mammogram or lump, N = 348) and then again in those that self-reported White/Caucasian race/ethnicity (N = 369).

Concordance between repeat BPE and MRI-FGT reads was assessed using Cohen’s kappa coefficients. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary NC) and all p values are 2-sided.

DATA AVAILABILITY
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Received: 11 February 2022; Accepted: 13 July 2022; Published online: 25 August 2022

REFERENCES
1. McCormack, V. A. & dos Santos Silva, I. Breast Density and Parenchymal Patterns as Markers of Breast Cancer Risk: A Meta-analysis. Cancer Epidemiol. Biomark. Prev. 15, 1159–1169 (2006).
2. Hopper, J. L. et al. Going Beyond Conventional Mammographic Density to Discover Novel Mammogram-Based Predictors of Breast Cancer Risk. J. Clin. Med 9, 627 (2020).
3. Saslow, D. et al. American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography. CA: a cancer J. clinicians 57, 75–89 (2007).
4. Thompson, D. J. et al. Assessing the usefulness of a novel MRI-based breast density estimation algorithm in a cohort of women at high genetic risk of breast cancer: the UK MARIBS study. Breast Cancer Res 11, R80–R80 (2009).
5. Klifa, C. et al. Magnetic resonance imaging for secondary assessment of breast density in a high-risk cohort. Magn. Reson Imaging 28, 8–15 (2010).
6. King, V. et al. Background parenchymal enhancement at breast MRI and breast cancer risk. Radiology 260, 50–60 (2011).
7. King, V. et al. Impact of menopausal status on background parenchymal enhancement and fibroglandular tissue on breast MRI. Eur. Radiol. 22, 2641–2647 (2012).
8. King, V. et al. Effect of aromatase inhibitors on background parenchymal enhancement and amount of fibroglandular tissue at breast MRI imaging. Radiology 264, 670–678 (2012).
9. King, V. et al. Impact of tamoxifen on amount of fibroglandular tissue, background parenchymal enhancement, and cysts on breast magnetic resonance imaging. breast J. 18, 527–534 (2012).
10. Turnbull, L. W. Dynamic contrast-enhanced MRI in the diagnosis and management of breast cancer. NMR biomedicine 22, 28–39 (2009).
11. Morris, E. A. Diagnostic breast MR imaging: current status and future directions. Magn. Reson. imaging Clin. North Am. 18, 57–74 (2010).
12. Dontchos, B. N. et al. Are Qualitative Assessments of Background Parenchymal Enhancement, Amount of Fibroglandular Tissue on MR Images, and Mammographic Density Associated with Breast Cancer Risk. Radiology 276, 371–380 (2015).
13. Arasu, V. A. et al. Population-Based Assessment of the Association Between Magnetic Resonance Imaging Background Parenchymal Enhancement and Future Primary Breast Cancer Risk. J. Clin. Oncol. 37, 954–963 (2019).
14. Grimm, L. J. et al. Relationship between Background Parenchymal Enhancement on High-risk Screening MRI and Future Breast Cancer Risk. Academic Radiol. 26, 69–75 (2019).
15. Telegrafo, M., Rella, L., Stabile Ianora, A. A., Angelelli, G. & Moschetta, M. Breast MRI background parenchymal enhancement (BPE) correlates with the risk of breast cancer. Magn. Reson Imaging 34, 173–176 (2016).
16. Watt, G. P. et al. Association of breast cancer with MRI background parenchymal enhancement: the IMAGINE case-control study. Breast Cancer Res 22, 138–138 (2020).
17. Niell, B. L. et al. Quantitative Measures of Background Parenchymal Enhancement Predict Breast Cancer Risk. Afr. Am. J. Roentgenol. 217, 64–75 (2021).
