# Role of Clinical and Imaging Risk Factors in Predicting Breast Cancer Diagnosis Among BI-RADS 4 Cases

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## Abstract

**Overdiagnosis of breast cancer is an ongoing concern, particularly in women who receive a Breast Imaging Reporting and Data System (BI-RADS) 4 assessment. Using a population-based quality improvement registry of 1978 women (2138 examinations), we examined clinical and imaging risk factors using cross-validated logistic regression models, identifying significant predictors such as age, the presence of a lump, history of breast cancer, the number of high-risk triggers, BI-RADS score, and qualitative breast density. This analysis supports the potential added value of utilizing relevant information from the patient's medical history when deciding between active surveillance and biopsy.**

**Purpose:** To analyze women with suspicious findings (assessed as Breast Imaging Reporting and Data System [BI-RADS] 4), examining the value of clinical and imaging predictors in predicting cancer diagnosis. **Patients and Methods:** A set of 2138 examinations (1978 women) given a BI-RADS 4 with matching pathology results were analyzed. Predictors such as patient demographics, clinical risk factors, and imaging-derived features such as BI-RADS assessment and qualitative breast density were considered. Independent predictors of breast cancer were determined by univariate analysis and multivariate logistic regression. **Results:** In univariate analysis, age, race, body mass index, age at first live birth, BI-RADS assessment, qualitative breast density, and risk triggers were found to be independent predictors. In multivariate analysis, age, BI-RADS score, breast density, race, presence of a lump, and number of risk triggers were the most predictive. An integrative logistic regression model achieved a performance of 0.84 cross-validated area under the curve. No variable was a constant independent predictor when stratifying the population on the basis of the BI-RADS score. **Conclusion:** While BI-RADS assessment remains the strongest predictor of breast cancer, the inclusion of clinical risk factors such as age, breast density, presence of a lump, and number of risk triggers derived from guidelines improves the specificity of identifying individuals with imaging descriptors associated with BI-RADS 4A and 4B that are more likely to be diagnosed with breast cancer.

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## Introduction

Mammography screening is associated with a reduction in mortality from breast cancer[1] and continues to be the recommended procedure for diagnosing early-stage breast cancer.[2] However, its benefits have been debated in relation to potential harms such as overdiagnosis of indolent cancers,[3] additional testing and anxiety associated with falsely positive screening mammography,[4] an erroneous sense of security from falsely negative mammograms, and radiation exposure.[5] An estimated 1.7 million breast biopsies are performed annually in the United States alone.[6] A large proportion


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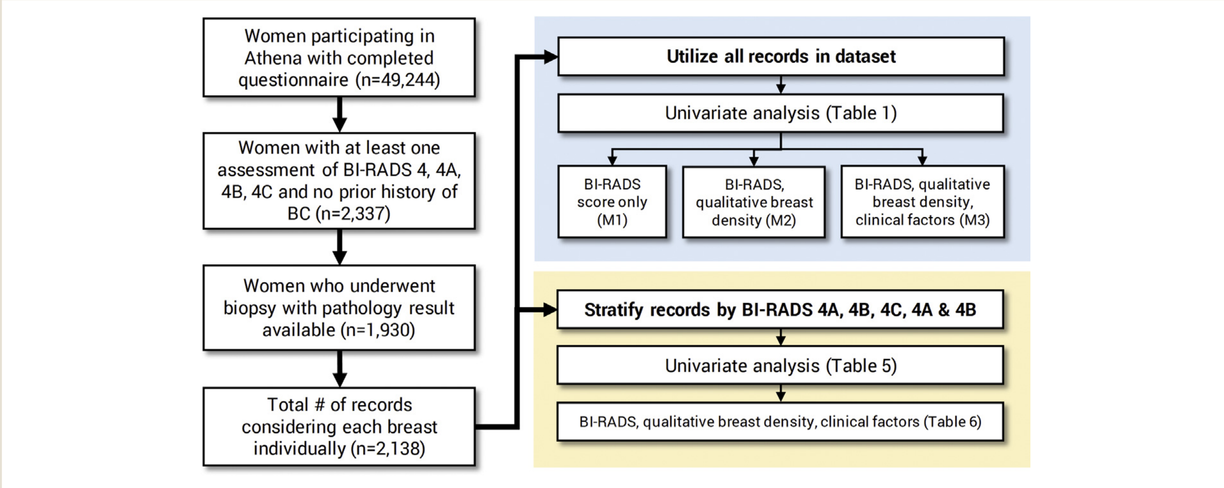
Figure 1 Flowchart Summarizing Patient Selection and Modeling Procedure




of these biopsies, however, result in benign pathology, indicating a false-positive imaging examination result. An analysis of Breast Cancer Surveillance Consortium data representing 1.6 million women showed that 66.8% of biopsy results were benign.[7] The cumulative risk of a false-positive examination result in women undergoing annual mammograms in a 10-year period ranges from 49.1% to 61.3%.[8] False-positive mammograms are associated with short-term anxiety and discomfort for the patient[4,9] and add to health care spending.[10]

In general, mammograms are assigned 1 of 7 final assessment categories (0 through 6) defined by the Breast Imaging Reporting and Data System (BI-RADS).[11] Suspicious findings of malignancy are assigned a BI-RADS category of 4 or 5 on the basis of diagnostic imaging. Category 4 is further divided into 4A (mild suspicion, positive predictive value [$PPV_3$, where $PPV_3$ is defined as the percentage of examinations with an abnormal final interpretation where it is known that a biopsy was performed as a result of the abnormal diagnostic examination within 1 year and that the diagnosis from the biopsy is cancer] of breast cancer between $> 2$ to $\leq 10\%$), 4B (moderate suspicion with a $PPV_3$ between $> 10$ to $\leq 50\%$), and 4C (high suspicion, $PPV_3$ between $> 50$ to $< 95\%$). Individuals with category 4 or 5 lesions are typically referred for biopsy.[12] Given the low cancer risk among category 4A and the wide range of cancer risk in category 4B lesions, better approaches to stratify and manage patients who fall into these categories are needed. For example, Flowers et al[13] propose reclassifying BI-RADS 4A as low-risk lesions that can be clinically evaluated and followed rather than immediately sampled via biopsy.

This study investigated the value of various clinical and imaging risk factors in predicting whether the individual will have in-situ or invasive breast cancer, particularly in low and moderately suspicious cases (ie, category 4A or 4B). Our objective was to evaluate the value of family risk and imaging factors that are readily available in the patient record in aiding radiologists with determining whether an individual would be a better candidate for active surveillance rather than biopsy.

## Patients and Methods

### *Patient Population*

Figure 1 summarizes the process, approved by our institutional review board, that was used to define the study population and subsequent modeling tasks. Between 2010 and 2015, a total of 49,244 women underwent mammography screening at our institution as part of a prospective population-based quality improvement and registry project, called the Athena Breast Health Network. Athena is an initiative coordinated among the 5 University of California medical and cancer centers to collect and analyze information from heterogeneous patient populations in real time with the goal of assessing an individual's risk of getting breast cancer and providing recommendations for prevention and risk-based screening.[14] All women screened under this program were given a standardized patient intake questionnaire as part of the standard of care that was completed at each screen. These questionnaires covered all relevant clinical factors needed to calculate risk using the Gail, Claus, and BRCAPro models. In addition, imaging-derived variables such as BI-RADS assessment and qualitative breast density were semiautomatically abstracted from the radiology report using a combination of keyword matching and manual review for each study.

Within the entire UCLA Athena cohort, we restricted our sample to 1978 women who had at least one diagnostic mammogram with an assessment of BI-RADS 4, no prior history of breast cancer, and not lost to follow up. A biopsy was performed on women who had a final BI-RADS assessment of 4 between 2010 and 2015 with a recommendation for core-needle biopsy, fine-needle aspiration, or surgery. A single patient may have received more than one recommendation for biopsy of separate suspicious findings (n = 221). As a result, a total of 2138 biopsy results were considered in our analysis. Table 1 provides a summary of the patient characteristics.

**Table 1 Summary Statistics for Patient Characteristics and Risk Factors**

| Covariate | No Cancer | Cancer | P |
|---|---|---|---|
| Sample size (total 2138) | 1675 | 463 | |
| Age (years), mean (SD) | 4.9 (1.4) | 5.8 (1.3) | < .001* |
| **Age** | | | < .001* |
| < 40 years | 436 (26) | 38 (8) | |
| 40-49 years | 517 (31) | 121 (26) | |
| 50-59 years | 376 (22) | 104 (22) | |
| 60-69 years | 228 (14) | 122 (26) | |
| 70-74 years | 50 (3) | 29 (6) | |
| > 74 years | 68 (4) | 49 (11) | |
| **Race** | | | .018* |
| Asian | 177 (11) | 50 (11) | |
| Black | 129 (8) | 40 (9) | |
| Hispanic | 114 (7) | 24 (5) | |
| Other | 470 (28) | 100 (22) | |
| White | 785 (47) | 249 (54) | |
| BMI (kg/m$^2$), mean (SD) | 24.6 (5.7) | 25.9 (6.0) | < .001* |
| **BMI** | | | < .001* |
| < 25 kg/m$^2$ | 1073 (64) | 247 (53) | |
| 25-30 kg/m$^2$ | 352 (21) | 121 (26) | |
| > 30 kg/m$^2$ | 250 (15) | 95 (21) | |
| **Age at Menarche** | | | .481 |
| ≤ 11 years | 335 (20) | 93 (20) | |
| 12 to 13 years | 841 (50) | 249 (54) | |
| ≥ 14 years | 429 (26) | 104 (22) | |
| NA | 70 (4) | 17 (4) | |
| **Age at First Live Birth** | | | < .001* |
| < 20 years | 69 (4) | 24 (5) | |
| 20-30 years | 390 (23) | 146 (32) | |
| > 30 years | 382 (23) | 123 (27) | |
| Never given birth | 580 (35) | 128 (28) | |
| NA | 254 (15) | 42 (9) | |
| **BI-RADS Assessment** | | | < .001* |
| 4 | 65 (4) | 17 (4) | |
| 4A | 1013 (60) | 62 (13) | |
| 4B | 528 (32) | 187 (40) | |
| 4C | 69 (4) | 197 (43) | |
| **Breast Density** | | | < .001* |
| A | 61 (4) | 34 (7) | |
| B | 554 (33) | 228 (49) | |
| C | 611 (36) | 155 (33) | |
| D | 269 (16) | 38 (8) | |
| NA | 180 (11) | 8 (2) | |
| Presence of lump | 498 (30) | 130 (28) | .526 |
| Noticeable changes in breast | 264 (16) | 67 (14) | .515 |
| **No. of Risk Triggers** | | | .005* |
| 0 | 1536 (92) | 414 (89) | |
| 1 | 127 (8) | 36 (8) | |
| 2 | 10 (1) | 12 (3) | |
| ≥ 3 | 2 (0) | 1 (0) | |
| 5-year Gail risk > 1.66% | 74 (4) | 25 (5) | .382 |

Data are presented as mean (SD) for continuous variables, n (%) for categorical variables. *P* values were obtained by *t* test for continuous variables and Fisher exact test for categorical variables where $P < .05$ were considered significant. BI-RADS categories are as follows: A, almost entirely fat; B, scattered fibroglandular tissue; C, heterogeneously dense; D, extremely dense; BC, breast cancer; NA, not available (missing). Noticeable changes in breast include presence of a new or unusual lump, bloody nipple discharge, or pain.
*Statistically significant.

### *Data Extraction*

Patient questionnaires were completed during each screening visit either using an electronic survey administered on a tablet or a machine-readable form. Information related to patient characteristics, Gail risk factors, family history of breast cancer, risk triggers, and use of hormone therapy were collected. We defined a set of risk triggers on the basis of risk criteria that are derived from the United States Preventive Services Task Force (USPSTF) guidelines for breast screening (Table 2). Associated with each mammography examination was a BI-RADS score assigned to each identified finding and the side of the breast where the finding was located. Breast density was qualitatively assessed using 4 categories defined

**Table 2 Summary of Risk Triggers Derived From USPSTF Recommendations**

- Do you have 2 or more first-degree relatives with BC, at least one of whom was initially diagnosed under age 50?
- Do you have 3 or more first- and second-degree relatives with BC?
- Do you have women in your family who have ever been diagnosed with both BC and OC?
- Do you have relatives who have ever been diagnosed with bilateral BC?
- Do you have a male relative diagnosed with BC?
- Do you have at least one Ashkenazi first-degree relative with BC or OC?
- Do you have at least 2 Ashkenazi second-degree relatives on same side with BC or OC?
- Do you have 2 or more first- and second-degree relatives with BC or OC at least one with OC?
- Do you have 2 or more first- and second-degree relatives with OC?
- Do you have a personal history of atypical hyperplasia?
- Have you have ever had genetic testing for BC risk?

Abbreviations: BC = breast cancer; OC = ovarian cancer; USPSTF = United States Preventive Services Task Force.

by BI-RADS. After a biopsy procedure, the pathology results were manually matched to the final BI-RADS assessment and as part of the workflow of routine clinical care at our institution, reviewed by board-certified radiologists and pathologists during regular radiologic—pathologic correlation meetings. A true-positive biopsy recommendation was defined as a diagnosis of ductal carcinoma-in-situ (DCIS) or of invasive cancer. A false-positive biopsy recommendation was defined by radiologic—pathologic concordance and the lack of an invasive or in-situ carcinoma diagnosis within 1 year of the screening examination. Table 3 provides a breakdown of suspicious imaging descriptors and their positive predictive value by BI-RADS score.

### *Statistical Analysis*

Descriptive statistics were used to summarize variables: continuous variables were summarized using their means and standard deviations; categorical variables were summarized using counts of observations that fall into each group and their percentages. Univariate analysis was performed by *t* test for continuous variables and Fisher exact test for categorical variables, and $P < .05$ was considered significant.

Three logistic regression models were fit to the data. The first model (M1) only included the BI-RADS score as the covariate; the second model (M2) included both the BI-RADS scores and breast density; the third integrative model (M3) included the BI-RADS score, breast density, and other clinical risk factors such as family history. In training these models, we considered BI-RADS assessments from the same subject as independent. As a sensitivity analysis, the aforementioned logistic regression models were refitted using the generalized estimating equation method[15] to account for the fact that some women underwent multiple biopsies and that these biopsy outcomes were inherently correlated. However, because only a small number of women had multiple biopsies, we found that the generalized estimating equation method gave almost identical results to the one presented here, so the choice of the model fitting method does not affect the results. Both the method of DeLong[16] and the likelihood ratio test were used to compare the performance of the 3 models (M1 vs. M2, M1 vs. M3, and M2 vs. M3). In addition, we report the 5-fold cross-validated area under the curve (cv-AUC) for each model. We also performed subgroup analysis by fitting the same logistic regression model for each subcategory of BI-RADS 4 to determine whether any variables were consistently predictive of a cancer diagnosis. For the integrative model, 3 different types of features selection methods were evaluated: stepwise Akaike information criterion, LASSO, and the Knockoff filter[17] at a false discovery rate of 0.2. Two-sided *P* values were used, and $P < .05$ was considered statistically significant. R 3.2.3 software was used to perform all analyses.

**Table 3 Breakdown of Suspicious Finding Descriptors by BI-RADS Score**

| Descriptor | N | % | No Cancer | Cancer | PPV (%) |
|---|---|---|---|---|---|
| Mass | 1198 | 60.9 | 919 | 279 | 23.3 |
| Calcifications | 594 | 30.2 | 453 | 141 | 23.7 |
| Architecture distortion | 90 | 4.6 | 64 | 26 | 28.9 |
| Asymmetry | 85 | 4.3 | 65 | 20 | 23.5 |
| **BI-RADS 4** | | | | | |
| Mass | 55 | 67.9 | 47 | 8 | 14.5 |
| Calcifications | 16 | 19.8 | 12 | 4 | 25.0 |
| Architecture distortion | 4 | 4.9 | 2 | 2 | 50.0 |
| Asymmetry | 6 | 7.4 | 4 | 2 | 33.3 |
| **BI-RADS 4A** | | | | | |
| Mass | 647 | 69.1 | 616 | 31 | 4.8 |
| Calcifications | 215 | 23.0 | 193 | 22 | 10.2 |
| Architecture distortion | 31 | 3.3 | 29 | 2 | 6.5 |
| Asymmetry | 43 | 4.6 | 38 | 5 | 11.6 |
| **BI-RADS 4B** | | | | | |
| Mass | 289 | 43.1 | 203 | 86 | 29.8 |
| Calcifications | 309 | 46.1 | 234 | 75 | 24.3 |
| Architecture distortion | 42 | 6.3 | 26 | 16 | 38.1 |
| Asymmetry | 31 | 4.6 | 22 | 9 | 29.0 |
| **BI-RADS 4C** | | | | | |
| Mass | 207 | 74.2 | 53 | 154 | 74.4 |
| Calcifications | 54 | 19.4 | 14 | 40 | 74.1 |
| Architecture distortion | 13 | 4.7 | 7 | 6 | 46.2 |
| Asymmetry | 5 | 1.8 | 1 | 4 | 80.0 |

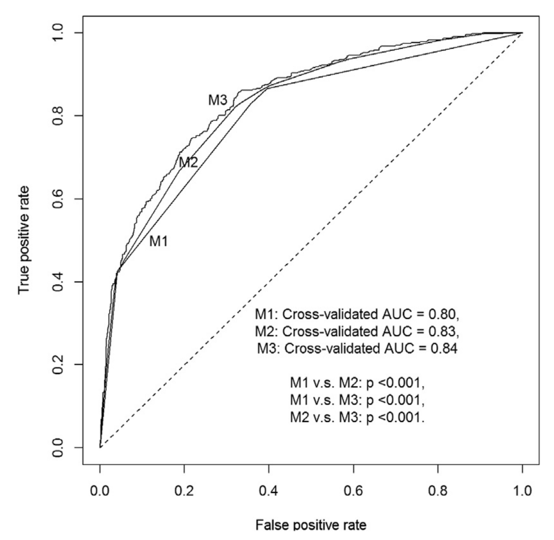
Not all records had explicit mentions of these finding descriptors in impression section of radiology report, which may have resulted in underestimation of certain finding descriptors.
Abbreviations: BI-RADS = Breast Imaging Reporting and Data System; PPV = positive predictive value.

**Table 4 Logistic Regression Results for Full Data Set**

| Covariate | BI-RADS (M1) | | | BI-RADS and Breast Density (M2) | | | Integrative Model (M3) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* | OR | 95% CI | *P* | OR | 95% CI | *P* | Stepwise AIC | LASSO | Knockoff at FDR 0.2 |
| **BI-RADS (Ref = 4A)** | | | | | | | | | | | | |
| 4 | 4.3 | 2.3, 7.6 | < .001* | 4.1 | 2.2, 7.4 | < .001* | 3.9 | 2.1, 7.1 | < .001* | Y | Y | Y |
| 4B | 5.8 | 4.3, 7.9 | < .001* | 5.0 | 3.7, 6.8 | < .001* | 4.8 | 3.5, 6.7 | < .001* | Y | Y | Y |
| 4C | 46.6 | 32.3, 68.5 | < .001* | 41.2 | 28.4, 60.8 | < .001* | 36.9 | 25.3, 54.8 | < .001* | Y | Y | Y |
| **Density (Ref = B)** | | | | | | | | | | | | |
| A | — | — | — | 1.2 | 0.7, 2.1 | .446 | 1.2 | 0.7, 2.0 | .586 | Y | Y | N |
| C | — | — | — | 0.7 | 0.5, 0.9 | .016* | 0.8 | 0.6, 1.1 | .161 | Y | Y | N |
| D | — | — | — | 0.4 | 0.3, 0.6 | < .001* | 0.5 | 0.3, 0.8 | .009* | Y | Y | N |
| NA | — | — | — | 0.2 | 0.1, 0.4 | < .001* | 0.3 | 0.1, 0.6 | .003* | Y | Y | Y |
| Age (unit = 10 years) | — | — | — | — | — | — | 1.2 | 1.1, 1.4 | < .001* | Y | Y | Y |
| **Race (Ref = White)** | | | | | | | | | | | | |
| Asian | — | — | — | — | — | — | 1.0 | 0.7, 1.6 | .837 | N | N | N |
| Black | — | — | — | — | — | — | 0.9 | 0.6, 1.5 | .750 | N | N | N |
| Hispanic | — | — | — | — | — | — | 0.7 | 0.4, 1.2 | .215 | N | Y | N |
| Other | — | — | — | — | — | — | 0.7 | 0.5, 0.9 | .016* | N | Y | N |
| **BMI (Ref = < 25 kg/m$^2$)** | | | | | | | | | | | | |
| 25-30 kg/m$^2$ | — | — | — | — | — | — | 1.0 | 0.7, 1.4 | .908 | N | N | N |
| > 30 kg/m$^2$ | — | — | — | — | — | — | 1.0 | 0.7, 1.4 | .993 | N | N | N |
| **Age at First Live Birth (Ref = < 20)** | | | | | | | | | | | | |
| 20-30 years | — | — | — | — | — | — | 1.1 | 0.6, 2.1 | .757 | N | Y | N |
| > 30 years | — | — | — | — | — | — | 1.1 | 0.6, 2.1 | .809 | N | N | N |
| Never given birth | — | — | — | — | — | — | 0.9 | 0.5, 1.7 | .777 | N | Y | N |
| NA | — | — | — | — | — | — | 0.9 | 0.4, 1.7 | .669 | N | Y | N |
| Presence of lump (Ref = Yes) | — | — | — | — | — | — | 1.6 | 1.1, 2.2 | .006* | Y | Y | N |
| Noticeable changes in breast (Ref = Yes) | — | — | — | — | — | — | 1.1 | 0.7, 1.5 | .749 | N | N | N |
| No. of risk triggers | — | — | — | — | — | — | 1.5 | 1.1, 2.1 | .017* | Y | Y | N |
| 5-year Gail risk ≥ 1.67% | — | — | — | — | — | — | 1.0 | 0.5, 1.7 | .893 | N | N | N |

Sample size included 2138 records (1930 women). In-sample and cross-validated area under the curve were, respectively, 0.80 and 0.80 for M1; 0.83 and 0.83 for M2; and 0.84 and 0.83 for M3.
BI-RADS categories are as follows: A, almost entirely fat; B, scattered fibroglandular tissue; C, heterogeneously dense; D, extremely dense; BC, breast cancer; NA, not available (missing). Noticeable changes in breast include presence of a new or unusual lump, bloody nipple discharge, or pain.
Abbreviations: AIC = Akaike information criterion; BI-RADS = Breast Imaging Reporting and Data System; CI = confidence interval; FDR = false discovery rate; OR = odds ratio.
*Statistically significant, defined as $P < .05$.

**Figure 2** ROC Curves Comparing Models. Models are as Follows: M1, Only BI-RADS Score; M2, BI-RADS and Breast Density; M3, BI-RADS, Breast Density, and Select Clinical Covariates. *P* Values Were Obtained From DeLong Test for Comparing Area Under ROC Curves




Abbreviations: BI-RADS = Breast Imaging Reporting and Data System; ROC = receiver operating characteristic.

## Results

### *Univariate Analysis*

Table 1 summarizes the results of conducting univariate analysis using data on the entire population. Age ($P < .001$), race ($P = .018$), body mass index ($P < .001$), age at first live birth ($P < .001$), BI-RADS assessment ($P < .001$), qualitative breast density ($P < .001$), and the number of risk triggers ($P = .005$) had statistically significant differences in observed proportions between subjects with or without cancer (invasive or in-situ).

### *Relationship Among Body Mass Index, Breast Density, and Cancer Diagnosis*

When body mass index (BMI) is considered separately from other risk factors, patients were found to be 50% more likely to have a cancer diagnosis if overweight (25-29.9 kg/m$^2$; odds ratio [OR] = 1.5; 95% confidence interval [CI], 1.2-1.9; $P = .002$) and 65% more likely if obese (> 30 kg/m$^2$; OR = 1.7; 95% CI, 1.3-2.2; $P < .001$) compared to patients with BMI < 25 kg/m$^2$. A prior study reported that overweight and obese patients were 68% (OR = 1.7; 95% CI, 0.8-3.5) and 94% (OR = 1.9; 95% CI, 1.0-3.8) more likely to have breast cancer, respectively, using a univariate analysis.[18] Our analysis confirms these previously reported trends with higher confidence, given the larger population. In a multivariate analysis that includes breast density, whether the individual was overweight (OR = 1.0; 95% CI, 0.7-1.4, $P = .91$) or obese (OR = 1.0; 95% CI, 0.7-1.4, $P = .99$) was not significantly associated with a cancer diagnosis. In examining the relationship between BMI and breast density, a Spearman correlation analysis showed an inverse relationship (increasing BMI was associated with decreasing breast density) with a coefficient of −0.42 ($P < .001$). When a radiologist noted a suspicious abnormality in fatty breasts, the odds of such finding being cancerous was 40% more likely compared to a finding identified in scattered fibroglandular breasts. Conversely, a woman with dense breast tissue and a suspicious finding was 2.5 times less likely to have a cancer diagnosis compared to a suspicious finding identified in a breast with a higher ratio of fat.

### *Multivariate Analysis*

The logistic regression model to predict the diagnosis of cancer using just BI-RADS (M1) performed the worst (cv-AUC = 0.80). The model that utilized BI-RADS and breast density (M2) was significantly better (cv-AUC = 0.83, M2 vs. M1: $P < .001$). The integrative model (M3) achieved the best prediction ability (cv-AUC = 0.84, M3 vs. M1: $P < .001$; M3 vs. M2: $P < .001$). Table 4 highlights the clinical and imaging variables and values that were or were not significantly associated with a cancer diagnosis for each of the 3 models. The variables that were consistently selected by all 3 selection methods during training of the integrative model were BI-RADS assessment, category "D" breast density, unreported breast density, and age. Figure 2 graphically compares receiver operating characteristic curves for M1, M2, and M3. Comparing M1 and M3 showed a significant difference in performance (ΔAUC = 0.04, DeLong test $P < .001$; likelihood ratio test $P < .001$), underscoring the value of additional information beyond BI-RADS assessment in predicting cancer diagnosis.

### *Number of USPSTF-Derived Risk Triggers Is a Significant Predictor*

Risk triggers encompass factors such as family history of breast cancer, potential genetic risk factors (eg, Ashkenazi background), and personal history of atypical ductal hyperplasia (ADH). The number of risk triggers was found to be significant in univariate analysis ($P = .005$) and significantly associated with a cancer diagnosis in women with BI-RADS 4 undergoing biopsy in multivariate analysis (Table 4; OR = 1.5; 95% CI, 1.1-2.1; $P = .017$). Each unit increase in the number of risk triggers was associated with a 2-fold increase in the likelihood of cancer diagnosis for BI-RADS 4A cases (Table 6; OR = 2.1, 95% CI, 1.1-3.9; $P = .016$). Conversely, reinforcing previously reported data,[18] individuals considered high risk on the basis of a 5-year Gail score of ≥ 1.67% were not found to be significantly associated with a cancer diagnosis (Table 4; OR = 1.0; 95% CI, 0.5-1.7; $P = .893$).

### *No Single Variable Was Consistently Predictive in Subgroup Analysis*

As a secondary analysis, the sample was split into subgroups on the basis of the BI-RADS score to determine whether any variable was universally informative in predicting cancer diagnosis. While no single variable was significant across all BI-RADS scores, age and breast density were found to be significant in 2 of the 4 groupings (Table 5). In fitting logistic regression models for each subgroup, models achieved a cv-AUC between 0.57 and 0.67 (Table 6). In low-suspicion (BI-RADS 4A) cases, variables such as age ($P < .001$)

**Table 5 Univariate Summary and Comparison Within Each BI-RADS Subgroup**

| | BI-RADS = 4 | | | BI-RADS = 4A | | | BI-RADS = 4B | | | BI-RADS = 4C | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Covariate** | **Cancer = No** | **Cancer = Yes** | ***P*** | **Cancer = No** | **Cancer = Yes** | ***P*** | **Cancer = No** | **Cancer = Yes** | ***P*** | **Cancer = No** | **Cancer = Yes** | ***P*** |
| No. of subjects | 65 | 17 | | 1013 | 62 | | 528 | 187 | | 69 | 197 | |
| **Age** | | | .443 | | | < .001* | | | .009* | | | .260 |
| < 40 years | 19 (29) | 3 (18) | | 326 (32) | 4 (6) | | 80 (15) | 15 (8) | | 11 (16) | 16 (8) | |
| 40-49 years | 21 (32) | 5 (29) | | 319 (31) | 23 (37) | | 159 (30) | 51 (27) | | 18 (26) | 42 (21) | |
| 50-59 years | 11 (17) | 3 (18) | | 205 (20) | 9 (15) | | 146 (28) | 48 (26) | | 14 (20) | 44 (22) | |
| 60-69 years | 10 (15) | 3 (18) | | 113 (11) | 17 (27) | | 91 (17) | 41 (22) | | 14 (20) | 61 (31) | |
| 70-74 years | 3 (5) | 1 (6) | | 23 (2) | 3 (5) | | 19 (4) | 15 (8) | | 5 (7) | 10 (5) | |
| > 74 years | 1 (2) | 2 (12) | | 27 (3) | 6 (10) | | 33 (6) | 17 (9) | | 7 (10) | 24 (12) | |
| **Race** | | | .182 | | | .573 | | | .278 | | | .340 |
| Asian | 5 (8) | 1 (6) | | 112 (11) | 7 (11) | | 54 (10) | 21 (11) | | 6 (9) | 21 (11) | |
| Black | 8 (12) | 2 (12) | | 72 (7) | 4 (6) | | 42 (8) | 23 (12) | | 7 (10) | 11 (6) | |
| Hispanic | 7 (11) | 0 (0) | | 72 (7) | 5 (8) | | 31 (6) | 9 (5) | | 4 (6) | 10 (5) | |
| Other | 15 (23) | 1 (6) | | 290 (29) | 12 (19) | | 143 (27) | 40 (21) | | 22 (32) | 47 (24) | |
| White | 30 (46) | 13 (76) | | 467 (46) | 34 (55) | | 258 (49) | 94 (50) | | 30 (43) | 108 (55) | |
| **BMI** | | | 1.000 | | | .578 | | | .218 | | | .635 |
| < 25 kg/m$^2$ | 9 (14) | 2 (12) | | 210 (21) | 13 (21) | | 116 (22) | 49 (26) | | 17 (25) | 57 (29) | |
| 25-30 kg/m$^2$ | 42 (65) | 12 (71) | | 667 (66) | 38 (61) | | 326 (62) | 102 (55) | | 38 (55) | 95 (48) | |
| > 30 kg/m$^2$ | 14 (22) | 3 (18) | | 136 (13) | 11 (18) | | 86 (16) | 36 (19) | | 14 (20) | 45 (23) | |
| **Age at Menarche** | | | .142 | | | .368 | | | .468 | | | .344 |
| ≤ 11 years | 14 (22) | 1 (6) | | 210 (21) | 12 (19) | | 95 (18) | 40 (21) | | 16 (23) | 40 (20) | |
| 12-13 years | 14 (22) | 8 (47) | | 268 (26) | 14 (23) | | 130 (25) | 37 (20) | | 17 (25) | 45 (23) | |
| ≥ 14 years | 34 (52) | 8 (47) | | 499 (49) | 36 (58) | | 279 (53) | 103 (55) | | 29 (42) | 102 (52) | |
| NA | 3 (5) | 0 (0) | | 36 (4) | 0 (0) | | 24 (5) | 7 (4) | | 7 (10) | 10 (5) | |
| **Age at First Live Birth** | | | .964 | | | .093 | | | .004* | | | .186 |
| < 20 years | 3 (5) | 1 (6) | | 39 (4) | 3 (5) | | 25 (5) | 10 (5) | | 2 (3) | 10 (5) | |
| 20-30 years | 10 (15) | 3 (18) | | 226 (22) | 13 (21) | | 131 (25) | 44 (24) | | 15 (22) | 63 (32) | |
| > 30 years | 14 (22) | 3 (18) | | 237 (23) | 20 (32) | | 114 (22) | 66 (35) | | 25 (36) | 57 (29) | |
| Never given birth | 23 (35) | 7 (41) | | 355 (35) | 23 (37) | | 184 (35) | 43 (23) | | 18 (26) | 55 (28) | |
| NA | 15 (23) | 3 (18) | | 156 (15) | 3 (5) | | 74 (14) | 24 (13) | | 9 (13) | 12 (6) | |
| **Breast Density** | | | .725 | | | < .001* | | | .003* | | | .440 |
| A | 3 (5) | 2 (12) | | 33 (3) | 5 (8) | | 21 (4) | 9 (5) | | 4 (6) | 18 (9) | |
| B | 22 (34) | 7 (41) | | 282 (28) | 27 (44) | | 221 (42) | 101 (54) | | 29 (42) | 93 (47) | |
| C | 18 (28) | 3 (18) | | 172 (17) | 7 (11) | | 69 (13) | 12 (6) | | 10 (14) | 16 (8) | |
| D | 17 (26) | 4 (24) | | 372 (37) | 22 (35) | | 199 (38) | 64 (34) | | 23 (33) | 65 (33) | |
| NA | 5 (8) | 1 (6) | | 154 (15) | 1 (2) | | 18 (3) | 1 (1) | | 3 (4) | 5 (3) | |

**Table 5 Continued**

| Covariate | BI-RADS = 4 | | | BI-RADS = 4A | | | BI-RADS = 4B | | | BI-RADS = 4C | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cancer = No | Cancer = Yes | P | Cancer = No | Cancer = Yes | P | Cancer = No | Cancer = Yes | P | Cancer = No | Cancer = Yes | P |
| Presence of lump | 26 (40) | 4 (24) | .266 | 355 (35) | 15 (24) | .098 | 95 (18) | 41 (22) | .235 | 22 (32) | 70 (36) | .660 |
| Noticeable changes in breast | 14 (22) | 5 (29) | .526 | 179 (18) | 8 (13) | .392 | 58 (11) | 24 (13) | .505 | 13 (19) | 30 (15) | .569 |
| **No. of risk triggers** | | | .471 | | | .014* | | | .112 | | | .798 |
| 0 | 57 (88) | 14 (82) | | 944 (93) | 54 (87) | | 469 (89) | 164 (88) | | 66 (96) | 182 (92) | |
| 1 | 7 (11) | 2 (12) | | 59 (6) | 4 (6) | | 58 (11) | 20 (11) | | 3 (4) | 10 (5) | |
| 2 | 1 (2) | 1 (6) | | 8 (1) | 4 (6) | | 1 (0) | 3 (2) | | 0 (0) | 4 (2) | |
| 3 | 0 (0) | 0 (0) | | 2 (0) | 0 (0) | | 0 (0) | 0 (0) | | 0 (0) | 1 (1) | |
| 5-year Gail risk ≥ 1.67% (%) | 4 (6) | 2 (12) | .599 | 41 (4) | 2 (3) | 1.000 | 25 (5) | 9 (5) | 1.000 | 4 (6) | 12 (6) | 1.000 |

Data are presented as n (%) unless otherwise indicated.
Breast Imaging Reporting and Data System (BI-RADS) categories are as follows: A, almost entirely fat; B, scattered fibroglandular tissue; C, heterogeneously dense; D, extremely dense; BC, breast cancer; NA, not available (missing). Noticeable changes in breast include presence of a new or unusual lump, bloody nipple discharge, or pain.
P values were obtained by Fisher exact test.
*Statistically significant.

and the number of risk triggers ($P = .016$) were significant. In moderately suspicious cases (BI-RADS 4B), variables such as age ($P = .047$), extremely dense breast ($P = .043$), and the presence of a lump ($P = .004$) were significant. In highly suspicious cases (BI-RADS 4C), race was implicated; in particular, Asian women were significantly less likely to have a cancer diagnosis compared to white women ($P = .043$). Among BI-RADS 4A and 4B cases, which have the highest diagnostic uncertainty, age ($P < .001$), category "C" and "D" breast densities ($P = .029$ and .001, respectively), the presence of a lump ($P = .025$), and the number of risk triggers ($P = .025$) were identified as significant predictors.

## Discussion

The determination of whether a patient should undergo a targeted biopsy for a suspicious finding is multifactorial. Although the BI-RADS score remains the single most informative variable in predicting cancer diagnosis, the additional consideration of breast density and other clinical information such as age and history of breast cancer can potentially improve the specificity with which the cancer diagnosis is determined. Using logistic regression models, we demonstrated how additional variables slightly increased the performance of predicting cancer (cv-AUC = 0.84). While no single variable is consistently informative in predicting cancer diagnosis within subgroups defined by BI-RADS 4, this study demonstrates the value of taking these variables such as age, breast density, presence of a lump, and number of USPSTF-derived risk triggers into account when interpreting whether a suspicious finding warrants immediate biopsy or may be considered for active surveillance. We also note that the decision for biopsy is not solely made on the basis of a set of objective variables considered in this study; patient preference and the anxiety associated with nonintervention may drive a patient to undergo a biopsy even if the probability of cancer is low.

As population-based screening programs are increasingly taking a risk-stratified approach to patient management, studies such as this provide guidance on potential variables that could be used to stratify the population for different management strategies. In our study, BI-RADS 4A had a $PPV_3$ of 6.9%, which is within the performance benchmark (2-10%) for biopsies performed. The results summarized in Table 6 showed that age, denser breasts, the presence of a lump, and the number of risk triggers were significant predictors within the BI-RADS 4A and 4B population, with a cv-AUC of 0.67. These results underscore the value of considering such variables at the time of interpretation that helps identify women who may be good candidates for active surveillance as an alternative to biopsy. Pragmatic trials such as the WISDOM study may yield additional evidence on the efficacy of risk-stratified screening.[19] Furthermore, new serum biomarkers such as the Provista biomarker assay are being explored as ways to improve specificity regarding whether a patient should continue imaging surveillance or undergo a biopsy.[20] The combination of radiologic assessment, breast density, and clinical risk factors could be used to identify which individuals would benefit from the addition of a serum biomarker test before proceeding with a biopsy.

Two prior studies have examined the utility of clinical or imaging risk factors in predicting cancer among BI-RADS 4 cases. Flowers et al[13] conducted a pilot analysis of 124 women to examine the

**Table 6 Logistic Regression Results for Data Set Stratified by BI-RADS Assessment**

| | Subgroup Analysis by BI-RADS 4 Assessment | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 4A | | | 4B | | | 4C | | | 4A and 4B Combined | | |
| Covariate | OR | 95% CI | *P* | OR | 95% CI | *P* | OR | 95% CI | *P* | OR | 95% CI | *P* |
| **Density (Ref = B)** | | | | | | | | | | | | |
| A | 1.5 | 0.5, 4.3 | .474 | 1.0 | 0.4, 2.2 | .910 | 1.2 | 0.3, 4.6 | .820 | 0.9 | 0.5, 1.7 | .807 |
| C | 0.7 | 0.4, 1.4 | .312 | 0.8 | 0.6, 1.3 | .433 | 0.8 | 0.4, 1.7 | .550 | 0.7 | 0.5, 1.0 | .029* |
| D | 0.6 | 0.2, 1.5 | .308 | 0.5 | 0.2, 1.0 | .043* | 0.4 | 0.1, 1.4 | .162 | 0.4 | 0.2, 0.7 | .001* |
| NA | 0.1 | 0.0, 0.8 | .077 | 0.1 | 0.0, 0.8 | .063 | 0.3 | 0.1, 2.1 | .210 | 0.1 | 0.0, 0.3 | < .001* |
| Age (unit = 10 years) | 1.5 | 1.2, 1.8 | < .001* | 1.2 | 1.0, 1.4 | .047* | 1.2 | 0.9, 1.5 | .237 | 1.3 | 1.2, 1.5 | < .001* |
| **Race (Ref = White)** | | | | | | | | | | | | |
| Black | 0.8 | 0.3, 1.9 | .573 | 1.1 | 0.6, 2.0 | .689 | 0.8 | 0.3, 2.2 | .623 | 1.1 | 0.7, 1.8 | .678 |
| Asian | 0.8 | 0.2, 2.3 | .634 | 1.4 | 0.8, 2.7 | .255 | 0.3 | 0.1, 1.0 | .043* | 1.2 | 0.8, 2.0 | .388 |
| Hispanic | 1.1 | 0.4, 3.0 | .894 | 0.7 | 0.3, 1.5 | .340 | 0.4 | 0.1, 1.4 | .141 | 0.8 | 0.4, 1.5 | .486 |
| Other | 0.7 | 0.4, 1.5 | .421 | 0.8 | 0.5, 1.2 | .293 | 0.5 | 0.2, 1.0 | .067 | 0.8 | 0.6, 1.1 | .210 |
| **BMI (Ref = < 25 kg/m$^2$)** | | | | | | | | | | | | |
| 25-30 kg/m$^2$ | 0.7 | 0.3, 1.4 | .357 | 1.2 | 0.8, 1.9 | .410 | 1.3 | 0.6, 2.9 | .519 | 1.0 | 0.7, 1.4 | .829 |
| > 30 kg/m$^2$ | 0.7 | 0.3, 1.5 | .376 | 1.2 | 0.7, 1.9 | .555 | 1.5 | 0.6, 3.8 | .351 | 0.9 | 0.6, 1.4 | .743 |
| **Age at First Birth (Ref = 20-30)** | | | | | | | | | | | | |
| < 20 years | 0.9 | 0.3, 4.1 | .863 | 1.9 | 0.8, 4.5 | .156 | 0.4 | 0.1, 2.0 | .322 | 1.4 | 0.7, 2.8 | .385 |
| > 30 years | 0.7 | 0.2, 3.5 | .650 | 1.4 | 0.6, 3.5 | .484 | 1.0 | 0.1, 5.2 | .979 | 1.2 | 0.6, 2.4 | .684 |
| Never given birth | 1.1 | 0.3, 5.0 | .896 | 0.9 | 0.4, 2.3 | .883 | 0.7 | 0.1, 3.6 | .707 | 1.0 | 0.5, 2.1 | .968 |
| NA | 0.4 | 0.1, 2.7 | .363 | 1.5 | 0.6, 3.9 | .449 | 0.3 | 0.0, 1.6 | .171 | 1.3 | 0.6, 2.8 | .541 |
| Presence of lump | 1.3 | 0.7, 2.6 | .388 | 2.0 | 1.2, 3.3 | .004* | 1.8 | 0.9, 3.7 | .080 | 1.5 | 1.0, 2.2 | .025* |
| Noticeable changes in breast | 0.8 | 0.3, 1.7 | .615 | 1.1 | 0.6, 1.9 | .752 | 0.9 | 0.4, 2.0 | .724 | 1.0 | 0.6, 1.5 | .867 |
| No. of risk triggers | 2.1 | 1.1, 3.9 | .016* | 1.2 | 0.7, 2.1 | .412 | 2.2 | 0.9, 8.9 | .147 | 1.6 | 1.0, 2.3 | .025* |
| 5-year Gail risk ≥ 1.67% | 0.4 | 0.1, 1.7 | .280 | 1.0 | 0.4, 2.3 | .973 | 1.5 | 0.4, 7.2 | .551 | 0.8 | 0.4, 1.6 | .505 |
| Cross-validated AUC | 0.63 | | | 0.61 | | | 0.57 | | | 0.67 | | |

BI-RADS categories are as follows: A, almost entirely fat; B, scattered fibroglandular tissue; C, heterogeneously dense; D, extremely dense; BC, breast cancer; NA, not available (missing). Noticeable changes in breast include presence of a new or unusual lump, bloody nipple discharge, or pain.
Abbreviations: AUC = area under the curve; BI-RADS = Breast Imaging Reporting and Data System; CI = confidence interval; OR = odds ratio.
*Statistically significant.

effect of increasing thresholds (ie, $\geq$ 50% for DCIS and $\geq$ 10% for invasive cancer) on cancer-to-biopsy yields as estimated by an experienced radiologist. They reported that if the biopsy threshold was increased to invasive cancer risk estimates $\geq$ 10%, the $PPV_3$ would be 47%, avoiding 48% of biopsies. However, 4% of DCIS and invasive cancer lesions would have been recommended for a 6-month follow-up. McCarthy et al[18] performed a multivariate analysis of 464 women and demonstrated an association among age, single nucleotide polymorphism panel, body mass index, and breast cancer diagnosis. Compared to existing studies, we studied a larger population (1978 women) and included qualitative breast density as a variable.

Several limitations of this study must be noted. The analyzed data were collected from a subset of 2 imaging centers that perform mammogram examinations within a single large academic medical center. Because the data were collected as part of a longitudinal observational study, data sources such as patient questionnaires and radiology reports contained missing information such as breast density because the study commenced before the use of a fully structured reporting system for breast imaging. While a standardized BI-RADS lexicon was used to report suspicious findings and qualitative breast density, we used a rule-based automated extraction tool that searches for specific BI-RADS lexical phrases (eg, "heterogeneously dense") to parse through the full-text radiology report and identify categorize breast density. This process yielded missing values for 7.9% of cases (10% in the noncancer cohort and 3% in the cancer cohort). We explicitly modeled the presence of these missing values and found that they were significantly associated with lower odds of cancer. Furthermore, while we analyzed the breakdown of imaging descriptors (eg, mass, calcification) associated with each BI-RADS score, we did not assess the predictive value of these imaging descriptors on cancer diagnosis by incorporating them into our models. We also did not incorporate age of menarche as part of our multivariate analysis.

In summary, our study utilizes a large population-based registry to identify potential clinical and imaging risk variables that are predictive of breast cancer diagnosis. Our analysis reinforces prior, smaller studies about predictive variables and provides preliminary evidence of how such factors could better inform management decisions within different BI-RADS categories. Future analyses will include validating the identified risk factors in a larger cohort of patients, such as the broader Athena population.

### *Clinical Practice Points*

- Considering routinely collected clinical information as part of biopsy decisions for BI-RADS 4 cases may help reduce the number of false-positive biopsy results.
- A BI-RADS 4 assessment is assigned to suspicious abnormalities that have a broad range of cancer risk (2-95%). Age and body mass index have been shown to be predictive of cancer diagnosis among women with a mammographic finding of BI-RADS 4.
- Our study, which examined a large sample of 2138 biopsy results, demonstrated that age, the presence of a lump, breast density, and USPSTF-derived risk triggers are significant predictors of breast cancer diagnosis.
- Our results complement prior studies in identifying several clinical variables as being informative in making individualized decisions about whether to undergo active surveillance or biopsy.

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## Disclosure

The authors have stated that they have no conflict of interest.

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