

Model for Predicting Breast Cancer Risk in Women With Atypical Hyperplasia

Amy C. Degnim, Stacey J. Winham, Ryan D. Frank, V. Shane Pankratz, William D. Dupont, Robert A. Vierkant, Marlene H. Frost, Tanya L. Hoskin, Celine M. Vachon, Karthik Ghosh, Tina J. Hieken, Jodi M. Carter, Lori A. Denison, Brendan Broderick, Lynn C. Hartmann, Daniel W. Visscher, and Derek C. Radisky

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Amy C. Degnim, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: degnim.amy@mayo.edu.

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A B S T R A C T

Purpose

Women with atypical hyperplasia (AH) on breast biopsy have an aggregate increased risk of breast cancer (BC), but existing risk prediction models do not provide accurate individualized estimates of risk in this subset of high-risk women. Here, we used the Mayo benign breast disease cohort to develop and validate a model of BC risk prediction that is specifically for women with AH, which we have designated as AH-BC.

Patients and Methods

Retrospective cohorts of women age 18 to 85 years with pathologically confirmed benign AH from Rochester, MN, and Nashville, TN, were used for model development and external validation, respectively. Clinical risk factors and histologic features of the tissue biopsy were selected using L1-penalized Cox proportional hazards regression. Identified features were included in a Fine and Gray regression model to estimate BC risk, with death as a competing risk. Model discrimination and calibration were assessed in the model-building set and an external validation set.

Results

The model-building set consisted of 699 women with AH, 142 of whom developed BC (median follow-up, 8.1 years), and the external validation set consisted of 461 women with 114 later BC events (median follow-up, 11.4 years). The final AH-BC model included three covariates: age at biopsy, age at biopsy squared, and number of foci of AH. At 10 years, the AH-BC model demonstrated good discrimination (0.63 [95% CI, 0.57 to 0.70]) and calibration (0.87 [95% CI, 0.66 to 1.24]). In the external validation set, the model showed acceptable discrimination (0.59 [95% CI, 0.51 to 0.67]) and calibration (0.91 [95% CI, 0.65 to 1.42]).

Conclusion

We have created a new model with which to refine BC risk prediction for women with AH. The AH-BC model demonstrates good discrimination and calibration, and it validates in an external data set.

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INTRODUCTION

Approximately 10% of all benign breast biopsies demonstrate atypical hyperplasia (AH).¹ With approximately 1 million benign biopsies per year in the United States, there are approximately 100,000 women who are newly diagnosed with AH annually. AH has been recognized for years as a phenotype of increased risk of breast cancer (BC) among women with benign breast disease (BBD).²⁻⁵ As a group, women with AH have an approximate four-fold increase in risk compared with the general population, which translates to an absolute risk of 1% to 2% per year.^{3,6} Because clinical management decisions, such as screening and prevention

therapies, are made for individual women, a tool that provides accurate individualized risk prediction in the AH setting is needed.

Two BC risk prediction models that are commonly used for women after a benign breast biopsy—the Gail (Breast Cancer Risk Assessment Tool) and Tyrer-Cuzick International Breast Cancer Intervention Study models^{7,8}—incorporate AH into their predictions; however, they do not provide accurate individualized estimates of risk within this subset of high-risk women.^{9,10} We recently developed the BBD-BC model for BC risk prediction in women with a benign breast biopsy.¹¹ Here, we present a model for individualized risk prediction that is specifically for women with AH.

ASSOCIATED CONTENT



Appendix
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PATIENTS AND METHODS

Study Populations

Model-building sample. The Mayo BBD cohort has been described previously^{12,13} and includes women age 18 to 85 years who had a benign breast biopsy between 1967 and 2001 at the Mayo Clinic (Rochester, MN). Clinical and demographic information was ascertained from medical records and questionnaires. The study breast pathologist (D.W.V.) reviewed archived hematoxylin and eosin (H&E) slides from benign biopsies and recorded histologic features. The 699 women who were found to have AH formed the model-building sample. We identified BC events, including both ductal carcinoma in situ (DCIS) and invasive, from study questionnaires, the Mayo Clinic tumor registry, and our review of medical records. This study was approved by the Mayo Clinic Institutional Review Board in keeping with the Mayo Clinic Federal-wide Assurance.¹² To reduce the possibility of including undetected BC, the first 12 months of postbiopsy follow-up for each woman was removed from the analysis.

Model validation sample. Model validation was performed in an independent external sample of women with AH from the Nashville Breast Cohort.¹³ This cohort similarly represents a retrospective collection of women with benign breast biopsies that were reviewed for histologic features and in whom follow-up BC events were ascertained. Within the Nashville Breast Cohort of patients who underwent breast biopsy between 1952 and 1989, 461 women had AH and no BC within 12 months of benign biopsy. H&E slides from these women were reviewed by the study pathologist (D.W.V.) to confirm AH and record the number of foci of AH using the same criteria as that of the model-building sample.

Statistical Approach

Full analysis details can be found in the Appendix (online only). In brief, follow-up was calculated as the number of days from 12 months after the initial diagnosis of AH to BC, death, prophylactic mastectomy, reduction mammoplasty, lobular carcinoma in situ, or last follow-up. Restricted B-splines¹⁴ suggested a quadratic age effect on BC risk (Fig 1); therefore, age was modeled in all analyses using both linear and quadratic terms.

Least absolute shrinkage and selection operator-based Cox proportional hazards regression was used to select risk-associated variables in the model-building sample. Age, age-squared, and 17 other clinical, demographic, and histologic variables were considered—year of biopsy, age at menarche, age at first live birth combined with number of children,

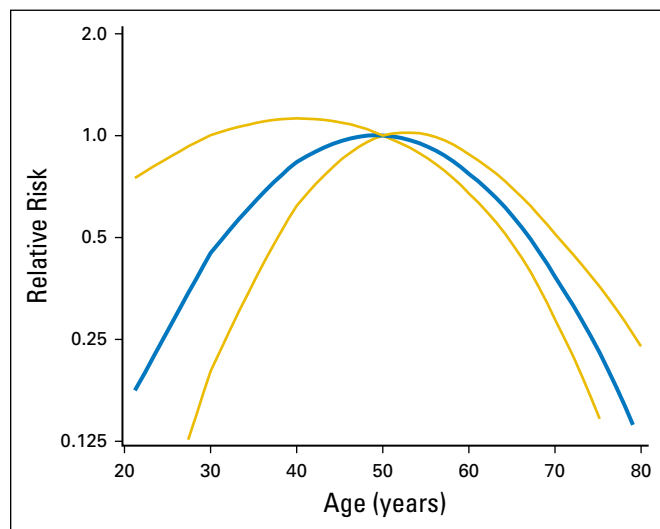


Fig 1. Predicted relative risk and 95% CI of breast cancer suggesting a quadratic association of age and breast cancer using Fine and Gray regression with age and age squared with referent at age 50 years.

breastfeeding history, body mass index, family history of BC, indication for biopsy, number of atypical foci, type of atypia, lobular involution, and the presence of a radial scar, fibroadenoma, calcifications, sclerosing adenosis, columnar alterations, cysts, or fibrosis. All analyses after this variable selection procedure were carried out using Fine and Gray regression models to account for death as a competing risk.¹⁵ Individual predicted probabilities were generated by applying the model coefficients to the observed follow-up times and were grouped into three categories to represent lower, intermediate, and higher predicted BC risk. Model discrimination was assessed using C-statistics, and internal calibration was assessed by comparing observed BC counts with predicted BC counts. Performance of the AH model was compared with our BBD-BC model, calculating absolute BC risks using both models in 5-year follow-up intervals and comparing model discrimination and calibration.

The final model was validated using the Nashville Breast Cohort. Estimated absolute risk from the model development set was applied to the external validation set for each covariate combination using parameter estimates that were derived from the Mayo cohort, and women were classified into three risk tertiles as described above.

Analyses were carried out using SAS (SAS/STAT User's Guide, Version 9.4; SAS Institute, Cary, NC) and R (version 3.1.1; The R Foundation, Vienna, Austria). A nomogram was created in the software package R using the nomogram function from the rms library.

RESULTS

Patient Characteristics

The Mayo model-building sample consisted of 699 women with 142 BC events (median follow-up, 8.1 years), and the external set from the Nashville Breast Cohort consisted of 461 women with 114 BC events (median follow-up, 11.4 years; Table 1). The two

Table 1. Clinical and Histologic Characteristics of Women With Atypical Hyperplasia From the Mayo and Nashville Benign Breast Disease Cohorts

Characteristic	Mayo (n = 699)	Nashville (n = 461)
Vital status		
Alive	534 (76.4)	363 (78.7)
Deceased	165 (23.6)	98 (21.3)
Breast cancer status		
Unaffected	557 (79.7)	347 (75.3)
Breast cancer	142 (20.3)	114 (24.7)
Age at benign biopsy, mean (SD)	57.6 (11.8)	49.8 (10.7)
Age at benign biopsy		
< 45 years	96 (13.7)	141 (30.6)
45-55 years	235 (33.6)	206 (44.7)
> 55 years	368 (52.6)	114 (24.7)
Year of biopsy		
< 1967	0 (0.0)	185 (40.1)
1967-1981	105 (15.0)	176 (38.2)
1982-1991	236 (33.8)	100 (21.7)
1992-2001	358 (51.2)	0 (0.0)
Type of atypia		
ADH	315 (45.1)	174 (37.7)
ALH	339 (48.5)	253 (54.9)
Both ADH and ALH	45 (6.4)	34 (7.4)
Number of atypical foci		
1	403 (57.7)	235 (51.0)
2	178 (25.5)	103 (22.3)
≥ 3	118 (16.9)	123 (26.7)

NOTE. Data are presented as No. (%) unless otherwise noted. Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; SD, standard deviation.

cohorts had similar characteristics, although women in the Mayo model-building set were slightly older (mean age, 57.6 years) compared with the Nashville validation set (mean age, 49.8 years). In addition, the model-building set had fewer women with 3+ atypical foci (16.9% v 26.7%).

Model Building

Variable selection. Frequency distributions of the features in the model-building set are shown in Appendix Table A1 (online only). Parameter tuning via cross-validation in the penalized Cox proportional hazards regression analysis indicated that the prediction model would include age (and age squared), number of atypical foci, and extent of lobular involution. However, the model C-statistic and Akaike Information Criterion were not substantially improved with involution added; therefore, for simplicity, this variable was not included in the final model.

Final AH model. Relative risk estimates from the final model of age, age squared, and number of atypical foci for the model-building set are presented in Table 2. Younger women (age < 40 years), older women (age ≥ 75 years), and women with one focus of AH had lower risk than those who were diagnosed with AH at age 45 to 70 years and those with two or more atypical foci. Absolute risks and 95% CIs in 5-year follow-up intervals for each combination of age and number of atypical foci can be obtained either with a table (Fig 2), a nomogram (Appendix Fig A1, online only), or with an online calculator.¹⁶ The online calculator generates risk predictions after entering age and the number of atypical foci in a user-friendly format.

Model Performance Assessment

Distribution of case-control counts among risk groups within the model-building and validation sets. All possible combinations of covariates in the model were enumerated, and 5-year risks were calculated for each of the 36 possible combinations of age categories and number of atypical foci. The 12 combinations with the lowest 5-year risks (1% to 3%) defined the lower-risk group, the middle 14 risks (4% to 7%) defined the intermediate-risk group, and the top 10 risks (8% to 14%) defined the higher-risk group. Comparison of risk group distributions in the Mayo and Nashville sets (15.5% and 12.8% lower risk, 53.1% and 48.6% intermediate risk, and 31.5% and 38.6% higher risk, respectively) indicated that

the Nashville cohort had slightly more high-risk women. Individuals in these groups demonstrated differences in the cumulative incidence of BC for both data sets (Figs 3A and 3B).

Model performance in the Mayo data set. Discrimination of the AH model was good and comparable to that of the BBD-BC model that was applied to this AH subcohort, with C-statistics of 0.650 and 0.641 at 10 years, and 0.636 and 0.624 at 20 years, respectively (Table 3 and Fig 3A). The AH model displayed superior calibration compared with the BBD-BC model, as the BBD-BC model overpredicted the number of cases irrespective of the follow-up interval, whereas the new AH model was well calibrated across all time points that were assessed (ratios of predicted-to-observed cancers were 0.96, 0.87, and 0.92 at 5, 10, and 20 years, respectively; Table 4 and Appendix Fig A2, online only).

Model performance in the external validation set. Discrimination was also good in the Nashville data set, with C-statistics of 0.591 (95% CI, 0.510 to 0.671) at 10 years, and 0.606 (95% CI, 0.541 to 0.670) at 20 years. The model overpredicted the number of cancers in the Nashville cohort in the first 5 years (1.46 predicted-to-observed ratio), but was well-calibrated at 10 years (0.91 predicted-to-observed ratio) and 20 years (1.02 predicted-to-observed ratio; Tables 3 and 4). In the Nashville cohort, the model overestimated the risk in higher-risk women, but performed better in women with intermediate or lower predicted risk.

DISCUSSION

We developed a parsimonious model for risk prediction in women with AH and validated this in an external cohort. In the past, we assessed the Gail and Tyrer-Cuzick models for predicting BC risk in women with AH and found that neither model performs better than chance alone in this group of high-risk women.^{9,10} We reported previously that the number of foci of AH stratifies future BC risk,^{3,13,17} and we now have demonstrated that the addition of age at biopsy further improves individualized risk estimation for women with AH. For women with AH, this model provides similar discrimination, but better calibration, than our prior BBD-BC model. Of importance, we confirmed the performance of our model—derived from the Mayo BBD cohort—in an independent external validation data set. Risk estimates that were derived from these efforts are provided in table format and have been merged

Table 2. Associations Between Age, Number of Atypical Foci, and Breast Cancer Risk in the Mayo Clinic and Nashville Cohorts Using Fine and Gray Regression

Characteristic	Mayo Clinic Cohort			Nashville Cohort		
	No.	Hazard Ratio (95% CI)	P	No.	Hazard Ratio (95% CI)	P
Modeled hazard ratios*						
Age†						
Ordinal effect	699	1.98 (1.33 to 2.93)	< .001	461	1.36 (0.93 to 1.99)	.114
Age squared‡						
Ordinal effect	699	0.94 (0.91 to 0.97)	< .001	461	0.97 (0.93 to 1.00)	.062
Number of atypical foci‡						
Ordinal effect	699	1.47 (1.21 to 1.80)	< .001	461	1.47 (1.18 to 1.82)	< .001

*Presents hazard ratio estimates for the atypia model.

†Age was modeled with the following categories: 0 = < 30, 1 = 30-34, ..., 10 = 75-80, 11 = ≥ 80 years. Age squared was consequently modeled as follows: 0 = < 30, 1 = 30-34, ..., 100 = 75-80, 121 = ≥ 80 years.

‡Number of foci was modeled as follows: 0 = one focus, 1 = two foci, and 2 = three or more foci.

Model for Breast Cancer Risk in Atypical Hyperplasia

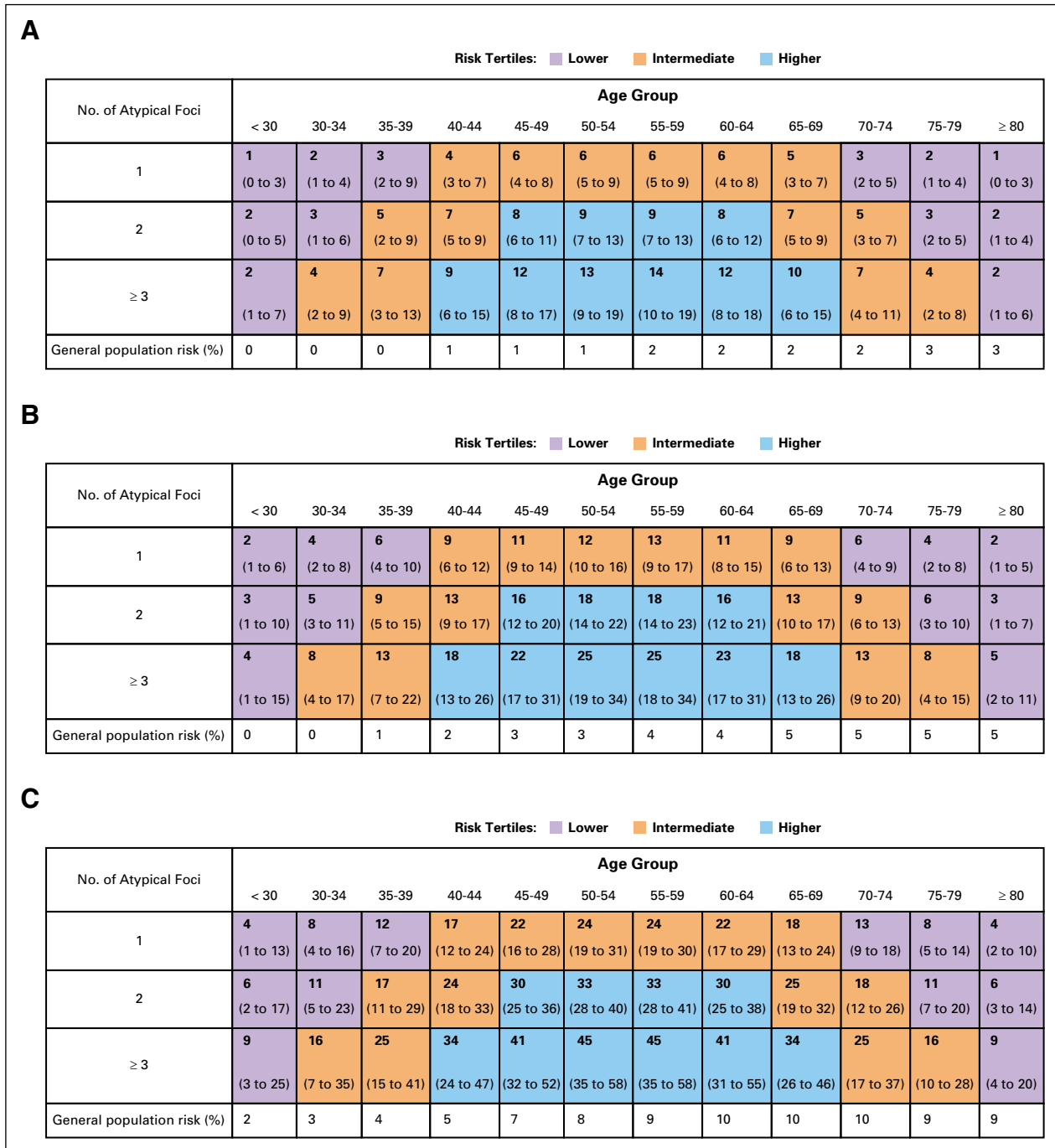


Fig 2. Predicted absolute risk, 95% confidence interval, and population-based expected absolute risk by duration of follow-up. (A) Five-year risk; (B) 10-year risk; (C) 20-year risk. Absolute risk is expressed as percentages and displayed as predicted (95% CI) and expected. Expected risk calculated using breast cancer incidence rates from Iowa SEER. Shading represents assignments to the three risk tertiles of lower (purple), intermediate (orange) and higher (blue) risk, respectively.

into our BBD-BC Web-based platform to create one unified Web-based risk prediction tool, dubbed the BDDAH-BC model.

Accurate risk prediction for women with AH is important because clinical management can be refined on the basis of risk level. Data from independent cohorts show the incidence of BC in this group of women is approximately 1% to 2% per year in the absence of prevention therapy.^{6,18} Although the majority of women with AH do not develop BC, risk is substantially increased for many. Furthermore, we have reported that the number of foci of

AH is a strong factor stratifying risk,¹⁸ and this finding has also been validated externally.¹³ In the majority with a single focus of AH, 20-year risk is approximately 17%, but among the 23% with two foci of AH, the 20-year incidence is 28%, and in the 17% of women who were found to have three foci of AH, the 20-year incidence of cancer is 40%.¹⁸ Here, we have further refined risk stratification, modeling risk with both age and the number of foci of AH. The ability to determine which individuals are at higher and lower risk makes it possible to better tailor clinical management

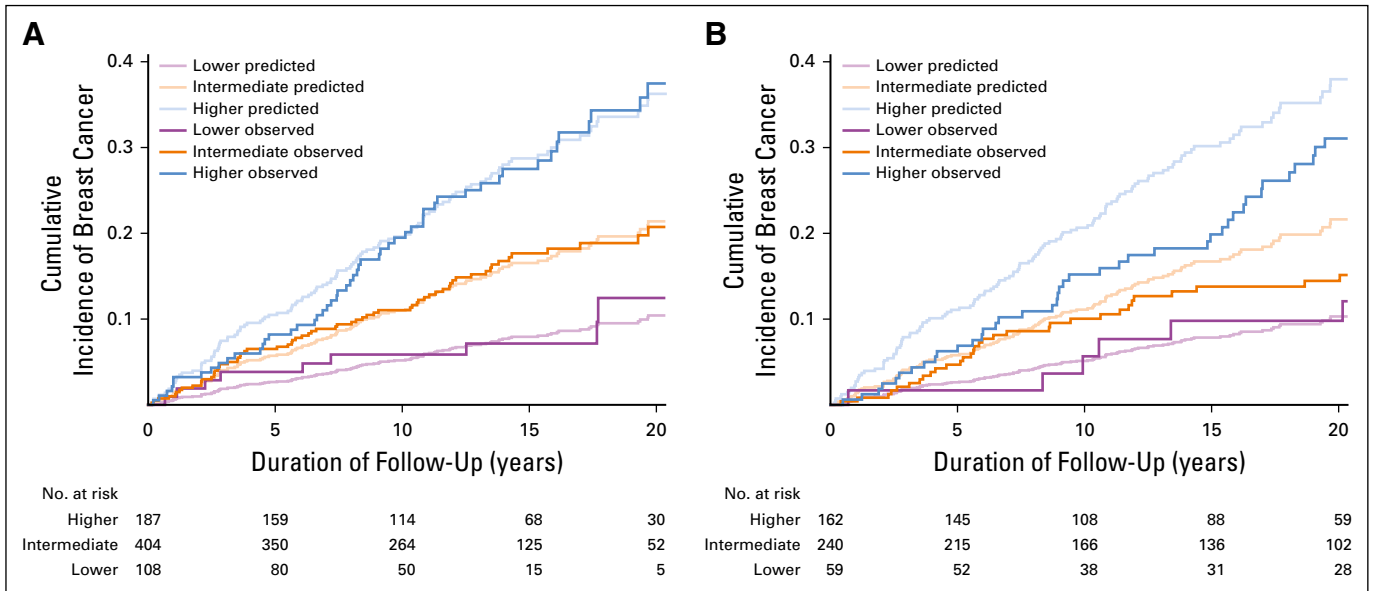


Fig 3. (A) Predicted and observed cumulative incidences of breast cancer in women with atypical hyperplasia (grouped by tertiles of risk) in the Mayo model-building set. (B) Predicted and observed cumulative incidences of breast cancer in women with atypical hyperplasia (grouped by tertiles of risk) in the Nashville external validation set.

decisions to the individual patient, whether it is to recommend aggressive surveillance or prevention strategies for women with AH who are at increased risk or to reassure women with AH who have a relatively lower risk.

The prediction algorithm that we have developed and validated can be used to better inform individual women and decisions about managing their risk. For instance, 6.7% of women in the combined Mayo and Nashville cohorts had a calculated 20-year risk of less than 12%, of which only 6.4% developed BC, which put them at or below the average population risk and ruled out the need for increased surveillance. Conversely, 30.0% of women had a predicted 20-year risk that exceeded 25%—among whom 32.7% developed BC—for whom intensive surveillance and risk reduction programs should be considered. In the American Cancer Society magnetic resonance imaging (MRI) screening guidelines from 2007,¹⁹ AH is enumerated as a condition with insufficient data to justify MRI screening. In light of growing recent literature from various sources that corroborates an absolute risk of 1% to 2% per year in women with AH,^{6,18} in combination with results of this study, we believe that a 20-year risk prediction of 25% from our AH model justifies MRI screening and that a lifetime risk prediction of > 25% by this model should be a qualifying addition to current MRI screening guidelines. Of

more importance, women with AH who are at intermediate or higher risk should be counseled to use prevention therapy, which has high efficacy—70% risk reduction—in women with AH.^{6,20-23}

Early findings from our cohort suggested a cumulative risk of 1% per year in women with AH.¹⁷ Since then, we have demonstrated a similar degree and long duration of increased risk within the Nashville Breast Cohort.¹³ Recently, these findings were challenged by a report of lower absolute risk in women with AH who were diagnosed by core needle biopsy in the Breast Cancer Surveillance Consortium.²⁴ In that study, 10-year BC risk was 6% (an average of 0.6% per year); however, BC risk was possibly underestimated because DCIS events were excluded, which lowers incidence by approximately 20%. Furthermore, that study depended on existing registry databases, which resulted in a higher likelihood of under ascertaining BC events. In contrast, another recent study of a cohort of women with high-risk biopsy findings (1987 to 2010) demonstrated an average 10-year cumulative absolute risk of 17% for atypical ductal hyperplasia and 24% for atypical lobular hyperplasia—even greater absolute risks than those observed in the Mayo and Nashville cohorts.⁶ Thus, the preponderance of data indicates that women with AH as a group have an absolute risk of at least 1% per year, including

Table 3. Concordance Statistics

Cohort	Model	5 Years			10 Years			20 Years		
		No.	No. BC (%)	Concordance (95% CI)	No.	No. BC (%)	Concordance (95% CI)	No.	No. BC (%)	Concordance (95% CI)
Mayo	BBD-BC	699	45 (6.4)	0.631 (0.546 to 0.715)	699	83 (11.9)	0.650 (0.587 to 0.713)	699	128 (18.3)	0.636 (0.583 to 0.689)
	Atypia	—	—	0.610 (0.526 to 0.694)	—	—	0.641 (0.579 to 0.704)	—	—	0.624 (0.573 to 0.675)
Nashville	Atypia	461	22 (4.8)	0.563 (0.441 to 0.684)	461	49 (10.6)	0.591 (0.510 to 0.671)	461	77 (16.7)	0.606 (0.541 to 0.670)

NOTE. Concordance was calculated by censoring follow-up at 5, 10, and 20 years. Abbreviations: BBD, benign breast disease; BC, breast cancer; Obs, observed; Pred, predicted.

Table 4. Calibration Statistics

Cohort	Model	0-5 Years			5-10 Years			15-20 Years		
		Observed	Predicted	Pred/Obs (95% CI)	Observed	Predicted	Pred/Obs (95% CI)	Observed	Predicted	Pred/Obs (95% CI)
Mayo	BBD-BC	45	67.5	1.50 (1.17 to 2.11)	38	62.7	1.65 (1.27 to 2.37)	14	30.4	2.17 (1.34 to 4.24)
	Atypia	—	43.2	0.96 (0.75 to 1.33)	—	33.1	0.87 (0.66 to 1.24)	—	12.9	0.92 (0.56 to 1.83)
Nashville	Atypia	22	32.1	1.46 (1.02 to 2.30)	27	24.6	0.91 (0.65 to 1.42)	13	13.3	1.02 (0.63 to 2.06)

NOTE. Calibration was calculated in 5-year intervals of follow-up. Only events that occurred within the time interval were included as observed. Predicted risk was derived as the difference in predicted risk at the beginning and end—or last follow-up if it occurred after the beginning but before the end—of the interval. Patients with an event or who were lost to follow-up before the interval were not included in the calculation. Deceased patients were carried forward after death to be consistent with the Fine and Gray methods.
Abbreviations: BBD, benign breast disease; BC, breast cancer; Obs, observed; Pred, predicted.

DCIS events. Furthermore, in the Mayo cohort, 82% of BCs were invasive, of which 22% were node positive at diagnosis, which indicates the potential lethality of BC subsequent to a diagnosis of AH. Our new model further stratifies BC risk for women with AH into low-, medium-, and high-risk categories, which will facilitate individualized treatment strategies.

An interesting finding was the relationship of age and risk (Figs 1 and 2). We observed a quadratic effect of age with BC risk in the Mayo cohort—and to a slightly lesser degree in the Nashville Cohort. In a prior publication, we reported that the relative risk (RR) of BC in women with AH is significantly higher for young women (RR, 6.8 for age < 45 years) compared with their peers versus an RR of 2.9 for women age > 55 years compared with their peers.¹⁷ For that analysis, RR was calculated in comparison with women of similar age in the Iowa SEER population, most of whom would not have AH. In contrast to these RR findings, the current analysis demonstrates that absolute risk in women with AH is highest in middle age years and lower at the extremes of age. Mazzola et al²⁵ have recently reported a similar finding—that is, that absolute risk in women with AH does not follow the expected pattern of increasing risk at older age. The reason for the lower risk at younger ages is presumably a result of the lower age-specific BC incidence for younger women, whereas the lower risk for older women is a result of competing mortality from other causes—these women, on average, are not living long enough to develop BC. Regarding risk in younger women with AH, the perimenopausal years comprise the timeframe when the breast gland undergoes tissue remodeling with age-related involution, which likely presents a permissive microenvironment for premalignant epithelium to progress to cancer. A parallel may be found around the time of pregnancy—also a time of increased BC risk—during which an extensive inflammatory response has been linked to BC progression.²⁶ Regardless of the biologic basis for our finding on age and BC risk in women with AH, from a risk-modeling perspective, this finding underscores the importance of examining the non-linear relationships between risk factors and absolute cancer risk. We look forward to the validation of the seemingly parabolic relationship of age and BC risk for women with AH in other cohorts.

Our study has several strengths. The large group of women with AH with long-term follow-up and data on multiple clinical and pathologic features allowed for the consideration of many variables in model building. We have validated this model in an external data set and found that it works well in women with AH

who are at intermediate risk and very well for women with AH who are at lower risk (Fig 3B). Furthermore, our final AH model is easy to use—either online or in table format—and its simplicity will aid the feasibility of use. Although we were not able to evaluate mammographic density as a risk factor in our model because of a lack of data in the majority of women, in the subset of women with AH in whom mammographic density is available, we recently reported no association of mammographic density with BC risk for women with AH, so this is unlikely to have affected the model.²⁷ Our model may not apply well in the minority of women who have AH in multiple biopsies over time. Among the 699 women in our cohort with AH, only 65 underwent repeat biopsies, 23 with AH at later biopsy (only 3% of women with AH). We recently evaluated this issue and found that women with two AH biopsies over time were 75% more likely to develop BC compared with those without AH at second biopsy (RR, 1.75; 95% CI, 0.30 to 10.0), but the difference was not statistically significant ($P = .53$).²⁸ Finally, although this model offers improved performance in women with AH compared with the Gail, Tyrer-Cuzick, and BBD-BC models, there is room for additional improvement in discrimination. All of our reported C-statistics cluster around 0.6 or slightly higher, which indicates that for any random case-control pair of individuals with a history of AH, our model would correctly classify the one to develop BC only 60% of the time. Development of prediction models for breast and other cancers remains challenging and lags behind that of other phenotypes, such as cardiovascular disease and diabetes, which have reported C-statistics that exceed 0.8.^{29,30}

Improvement of prediction models through the addition of genetic variants seemed to be challenging initially, as reported by Wacholder et al³¹; however, continued advances in germline variant assessment³² and breast tissue-based gene expression³³ hold promise for achieving clinical risk prediction with C-statistics of 0.70 and higher. Adding genomic risk information to clinical risk models can improve risk prediction³⁴ and is a strategy that we and other research teams are actively pursuing.

In conclusion, we created the AH-BC model to predict BC risk in women with AH on the basis of age at biopsy and the number of foci of atypia. This model provides good discrimination and improved calibration in women with AH compared with the original BBD-BC model, and we have evaluated its performance in an external cohort. This model is an important step in improving risk prediction for women with AH.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Amy C. Degnim, V. Shane Pankratz, William D. Dupont, Robert A. Vierkant, Marlene H. Frost, Celine M. Vachon,

Karthik Ghosh, Lynn C. Hartmann, Daniel W. Visscher, Derek C. Radisky

Collection and assembly of data: Amy C. Degnim, V. Shane Pankratz, William D. Dupont, Robert A. Vierkant, Marlene H. Frost, Jodi M. Carter, Lori A. Denison, Daniel W. Visscher, Derek C. Radisky

Data analysis and interpretation: Amy C. Degnim, Stacey J. Winham, Ryan D. Frank, V. Shane Pankratz, Tanya L. Hoskin, Celine M. Vachon, Tina J. Hieken, Brendan Broderick

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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Affiliations

Amy C. Degnim, Stacey J. Winham, Ryan D. Frank, Robert A. Vierkant, Marlene H. Frost, Tanya L. Hoskin, Celine M. Vachon, Karthik Ghosh, Tina J. Hieken, Jodi M. Carter, Lori A. Denison, Brendan Broderick, Lynn C. Hartmann, and Daniel W. Visscher, Mayo Clinic, Rochester, MN; V. Shane Pankratz, University of New Mexico Health Sciences Center, Albuquerque, NM; William D. Dupont, Vanderbilt University, Nashville, TN; and Derek C. Radisky, Mayo Clinic, Jacksonville, FL.

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Model for Predicting Breast Cancer Risk in Women With Atypical Hyperplasia

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Amy C. Degnim

No relationship to disclose

Stacey J. Winham

No relationship to disclose

Ryan D. Frank

No relationship to disclose

V. Shane Pankratz

No relationship to disclose

William D. Dupont

No relationship to disclose

Robert A. Vierkant

No relationship to disclose

Marlene H. Frost

No relationship to disclose

Tanya L. Hoskin

No relationship to disclose

Celine M. Vachon

Employment: Hil-Rom (I)

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Karthik Ghosh

No relationship to disclose

Tina J. Hieken

No relationship to disclose

Jodi M. Carter

No relationship to disclose

Lori A. Denison

No relationship to disclose

Brendan Broderick

No relationship to disclose

Lynn C. Hartmann

No relationship to disclose

Daniel W. Visscher

No relationship to disclose

Derek C. Radisky

No relationship to disclose

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Appendix

Statistical Approach

Modeling age and risk. To reduce the possibility of including undetected breast cancer (BC), the first 12 months of postbiopsy follow-up for each woman was removed from the analysis; thus, the duration of follow-up was calculated as the number of days since 12 months after the initial diagnosis of atypical hyperplasia (AH) to BC, death, prophylactic mastectomy, reduction mammoplasty, lobular carcinoma in situ, or last follow-up. Similar to the approach used in the Breast Cancer Risk Assessment Tool, we mapped ages into an ordinal variable that reflected 5-year age intervals ($0 \leq 30$, $1 = 30$ to 34 , ..., $10 = 75$ to 79 , $11 = \geq 80$) and used this ordinal variable to model stepwise changes in BC risk as a function of 5-year age categories. A restricted B-spline that was estimated in a Cox proportional hazards regression model suggested that the log hazard ratio for the association between age and BC risk in the Mayo benign breast disease (BBD) cohort was consistent with a parabolic shape, and we therefore added a squared version of the ordinal age term to capture this curvature.¹⁴ This quadratic effect persisted when modeled with the Fine and Gray approach, which accounted for death as a competing risk¹⁵ (Fig 1). Therefore, in all subsequent analyses, we modeled this relationship as a linear plus quadratic function of the ordinal age variable.

Model building. In addition to age (and age squared) at biopsy, the model-building effort considered 17 additional variables, including clinical/demographic—year of biopsy, age at menarche, a combined categorization of age at first live birth and number of children, breastfeeding history, categorized body mass index, family history of BC, and indication for biopsy; and histologic—number of atypical foci, type of atypia (atypical ductal hyperplasia, atypical lobular hyperplasia, or both), lobular involution (none, partial, or complete; defined previously; Milanese TR, et al: *J Natl Cancer Inst* 98:1600-1607, 2006), and the presence of a radial scar, fibroadenoma, calcifications, sclerosing adenosis, columnar alterations, cysts, or fibrosis.

Associations of these previously identified risk factors with BC risk in the model development set were examined using penalized Cox proportional hazards regression with a least absolute shrinkage and selection operator–based (L1) penalty using the glmnet R package (Friedman J, et al: *Biostatistics* 9:432-441, 2008; Simon N, et al: *Stat Sin* 22:983-1001, 2012). Because it is a well-established risk factor for BC, age (and age squared) was forced into the least absolute shrinkage and selection operator model without penalty. Tuning parameters were selected with cross validation. All analyses after this variable selection procedure were carried out using Fine and Gray regression models to account for death as a competing risk.¹⁵ The absolute risk of BC at 5-year follow-up intervals was derived for each covariate combination by applying the model coefficients to the observed follow-up times using a product limit estimator approach (Gooley TA, et al: *Stat Med* 18:695-706, 1999; So Y, et al: *Proc SAS Global Forum*, 2015). Risk estimates were subsequently grouped into three categories—approximate tertiles—in an effort to represent lower, intermediate, and higher predicted BC risk. Predicted curves for each of the tertiles were derived by calculating weighted means of the covariate combination–specific risk estimates defined above with weights defined on the basis of their prevalence in the tertile.

Assessing model performance. Model discrimination was assessed overall and at 5-year follow-up intervals with C-statistics that were calculated by truncating follow-up and BC status at each 5-year interval and using the method described by Ruan and Gray (Ruan PK, et al: *Stat Med* 27:5709-5724, 2008). Of note, although the same final model coefficients were used to calculate discrimination at each 5-year interval, differences in follow-up times as a result of competing mortal risks across women will cause predicted absolute risks to shift from interval to interval, which will result in differing C-statistics over time.

Calibration was defined as the ratio of expected-to-observed number of BC events. As with absolute risks described above, calibration was assessed at each 5-year time interval. The number of observed events was calculated as the number of BCs that occurred between the beginning and end of the interval of interest. For instance, for 5-year risk estimates, the observed number of BCs was simply the number that occurred less than 5 years after the diagnosis of AH. The expected number of events for a given time interval was estimated using methods described by Crowson et al (Crowson CS, et al: *Stat Methods Med Res* 25:1692-1706, 2016). The predicted BC risk of each woman was first transformed into an individual-specific expected number of events using the formula:

$$Exp = -1 * \ln(1 - risk) * \frac{\text{minimum}(\text{duration of followup, end of time interval})}{\text{end of time interval}}$$

The total number of expected events was then calculated by simply summing the individual expected numbers. For women who were still alive at last follow-up and who were observed past the end of the interval of interest, predicted risk was calculated as the difference in risk at the beginning and end of the time period. For nondeceased women whose last follow-up occurred within the interval of interest, the difference between risk at last contact and the beginning of the interval was used. Women who died without experiencing progression to BC were used in all calculations—that is, carried forward past their death date—to be consistent with the Fine and Gray approach of accounting for competing risks. Their predicted risk was calculated as the difference in risk at the beginning of the interval and that at the end of the interval, regardless of death date.

Comparison with the BBD-BC Model. We compared the performance of this AH model with that of our BBD-BC model in women with AH. Absolute risks of BC were calculated using both models in 5-year follow-up intervals, and model discrimination and calibration were compared.

External validation. The final model was validated using the Nashville Breast Cohort. For comparison with the final model estimates from the model development set, hazard ratios were estimated using the Fine and Gray regression approach. Estimated absolute risk from the model development set was directly applied to the validation set for each covariate combination using parameter estimates that were derived from the Mayo cohort. Women were classified as lower-, intermediate-, and higher-risk categories using the combinations that had been identified previously in the model development set. Analyses were carried out using SAS (version 9.4) and R (version 3.1.1).

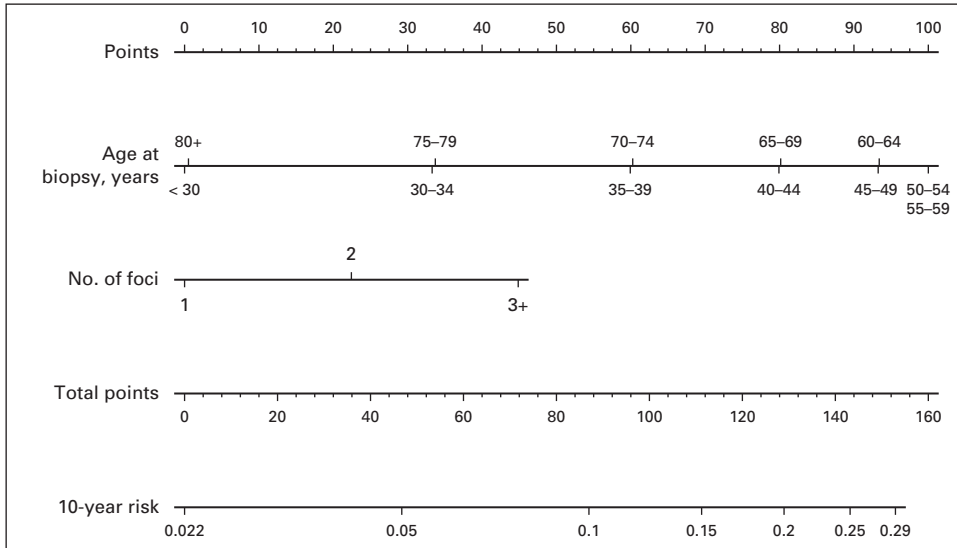


Fig A1. Nomogram representing proposed atypia model.

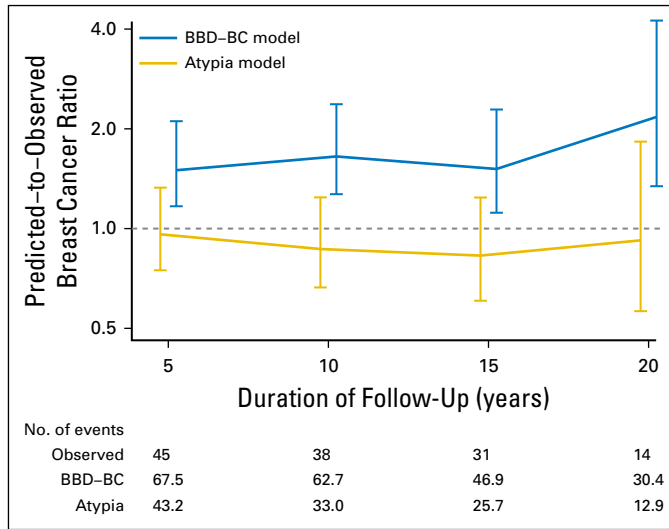


Fig A2. Calibration of the benign breast disease–breast cancer (BBD-BC) model and atypia model for Mayo participants, represented as the ratio of predicted-to-observed breast cancers at 5-year intervals.

Model for Breast Cancer Risk in Atypical Hyperplasia

Table A1. Clinical and Histologic Characteristics of Women With Atypical Hyperplasia From the Mayo Benign Breast Disease Cohort

Characteristic	Value
Breast cancer status	
Unaffected	557 (79.7)
Affected	142 (20.3)
Age of BBD, mean (SD)	57.6 (11.8)
Year of biopsy	
1967-1981	105 (15.0)
1982-1991	236 (33.8)
1992-2001	358 (51.2)
Indication for biopsy	
Missing, No.	104
Lump	235 (39.5)
Mammogram	360 (60.5)
Number of atypical foci	
1	403 (57.7)
2	178 (25.5)
≥ 3	118 (16.9)
Type of atypia	
ADH	315 (45.1)
ALH	339 (48.5)
Both ADH and ALH	45 (6.4)
Involution	
Missing, No.	30
None	70 (10.5)
Partial	429 (64.1)
Complete	170 (25.4)
Radial scar	
Absent	589 (84.3)
Present	110 (15.7)
Fibroadenoma	
Absent	598 (85.6)
Present	101 (14.4)
Calcifications	
Missing, No.	1
Absent	177 (25.4)
Present	521 (74.6)
Sclerosing adenosis	
Missing, No.	3
Absent	310 (44.5)
Present	386 (55.5)
Columnar alteration	
Missing, No.	3
Absent	155 (22.3)
Present	541 (77.7)
Cyst	
Absent	217 (31.0)
Present	482 (69.0)
Fibrosis	
Missing, No.	7
Absent	227 (32.8)
Present	465 (67.2)
Age of menarche, years	
Missing, No.	158
< 12	91 (16.8)
12-13	307 (56.7)
≥ 14	143 (26.4)
Age at first live birth, years/No. of children	
Missing, No.	70
< 21, ≥ 1	132 (21.0)
≥ 21, ≥ 3	186 (29.6)
≥ 21, 1-2	218 (34.7)
Nulliparous	93 (14.8)
Breastfeeding history	
Missing, No.	165
No	341 (63.9)
Yes	193 (36.1)

(continued in next column)

Table A1. Clinical and Histologic Characteristics of Women With Atypical Hyperplasia From the Mayo Benign Breast Disease Cohort (continued)

Characteristic	Value
BMI at biopsy	
Missing, No.	57
≤ 21	92 (14.3)
22-25	210 (32.7)
26-29	174 (27.1)
≥ 30	166 (25.9)
Family history of breast cancer	
Missing, No.	26
None	361 (53.6)
Weak	175 (26.0)
Strong	137 (20.4)

NOTE. Data are presented as No. (%) unless otherwise noted.
Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; BBD, benign breast disease; BMI, body mass index; SD, standard deviation.