Assessment of the Accuracy of the Gail Model in Women With Atypical Hyperplasia

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ABSTRACT

Purpose

An accurate estimate of a woman's breast cancer risk is essential for optimal patient counseling and management. Women with biopsy-confirmed atypical hyperplasia of the breast (atypia) are at high risk for breast cancer. The Gail model is widely used in these women, but has not been validated in them.

Patients and Methods

Women with atypia were identified from the Mayo Benign Breast Disease (BBD) cohort (1967 to 1991). Their risk factors for breast cancer were obtained, and the Gail model was used to predict 5-year- and follow-up-specific risks for each woman. The predicted and observed numbers of breast cancers were compared, and the concordance between individual risk levels and outcomes was computed.

Results

Of the 9,376 women in the BBD cohort, 331 women had atypia (3.5%). At a mean follow-up of 13.7 years, 58 of 331 (17.5%) patients had developed invasive breast cancer, 1.66 times more than the 34.9 predicted by the Gail model (95% CI, 1.29 to 2.15; $P < .001$). For individual women, the concordance between predicted and observed outcomes was low, with a concordance statistic of 0.50 (95% CI, 0.44 to 0.55).

Conclusion

The Gail model significantly underestimates the risk of breast cancer in women with atypia. Its ability to discriminate women with atypia into those who did and did not develop breast cancer is limited. Health care professionals should be cautious when using the Gail model to counsel individual patients with atypia.

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INTRODUCTION

An accurate estimate of a woman's risk of developing breast cancer is an integral component of patient counseling. It enables physicians to tailor clinical management to the patient's needs and guide patients in the selection of appropriate medical and surgical management. Women with biopsy-confirmed atypical hyperplasia of the breast (atypia) are known to be at high risk for the development of breast cancer.¹⁻⁵ Widespread public awareness of breast disease along with routine use of screening mammograms has led to the increased detection of atypia on breast biopsy.¹ Women with atypia are often counseled to pursue heightened screening and risk reduction strategies such as chemoprevention with tamoxifen or raloxifene. To assist a woman with atypia in making an informed decision, an accurate assessment of her risk is needed.

The original Gail model was developed using data from women who were actively participating in the Breast Cancer Detection and Demonstration Project, a breast cancer screening program.⁶ It was updated and validated across a population of women in the National Surgical Adjuvant Breast and Bowel Project P-1 study.⁷ This updated version of the model (called model 2 in Costantino et al⁷) has been implemented in a variety of formats. It is incorporated in the Breast Cancer Risk Assessment Tool (BCRAT, also referred to in this article as the Gail model), which is available on the National Cancer Institute (NCI) Web site (<http://cancer.gov/bcrisktool>) and is viewed 20,000 to 30,000 times per month, suggesting strong demand for this information.⁸ The Gail model provides individualized risk estimates of the probability that a woman with specific characteristics will develop invasive breast cancer during the next 5 years, and by age 90 years.

The Gail model incorporates information on risk factors such as age, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, number of prior breast biopsies, and presence of atypia on biopsy. It is currently the main tool used for breast cancer risk assessment in patients with atypia. Despite its widespread use, the Gail model has not been validated in patients with atypia. Therefore, we evaluated the Gail model in a well-annotated, well-characterized cohort of women with atypia on open breast biopsy.^{1,2}

PATIENTS AND METHODS

Details of the study cohort have been previously described.^{1,2,9} Briefly, the Mayo Benign Breast Disease (BBD) cohort comprises 9,376 women age 18 to 85 years who underwent open breast biopsy at the Mayo Clinic (Rochester, MN) between 1967 and 1991, with benign pathologic findings. Women with a history of ductal carcinoma in situ, lobular carcinoma in situ, or invasive breast cancer were excluded. Benign breast tissue from all women in the cohort was rereviewed by our study pathologists (C.R. and Daniel W. Visscher, MD) without knowledge of the original histologic diagnosis or patient outcome. A diagnosis of atypia (atypical ductal hyperplasia, atypical lobular hyperplasia, or both) was made in 331 women (3.5%) using the standard criteria and histologic classification of Dupont and Page.^{1,3,10} The study was approved by the institutional review board of the Mayo Clinic and all patient contact materials were reviewed and approved.

Each individual's risk factors for the development of invasive breast cancer were obtained via a study-specific questionnaire and from medical record review. The most current data available for each risk factor were used. Follow-up was calculated as the number of days from benign biopsy to the date of invasive breast cancer diagnosis, prophylactic mastectomy, death, or last contact. Last contact was either last return visit to the Mayo Clinic or the date of return of the study questionnaire, whichever occurred later. Patients were classified as having either developed invasive breast cancer or not. No women developed lobular carcinoma in situ, and those who developed ductal carcinoma in situ were included in the second of these two groups, given that the Gail model only predicts invasive breast cancer.

Using age at biopsy as the age at risk assessment, the Gail model was used to predict 5-year risk for each individual with atypia using her risk factor profile.⁷ Risk estimates corresponding with length of follow-up for each woman (termed follow-up-specific risk estimates) were also calculated. To obtain these breast cancer risk estimates, we employed a Fortran program that was provided to us by NCI (M. Gail, J. Benichou, D. Pee, personal communication, February 2007), which contains the code comprising the underlying calculation machinery used in NCI's BCRAT. The standards used in the online Gail model were used for variables with missing data. Women with unknown age at menarche were assigned menarche at 14 years of age or older. Women with unknown age at first live birth were classified as giving birth before age 20 years. Women with missing family history were classified as having no family history. To verify agreement between the code we used and the online tool, we randomly selected 10 patients and compared the 5-year and lifetime risk estimates obtained from the code given us to those from the online risk assessment tool. All of the estimates were in complete agreement.

The Gail model risk factors of the women with atypia were summarized using counts and percentages, or means and standard deviations, both overall and also according to invasive breast cancer status. The cumulative incidence of breast cancer was estimated using methods that corrected for the competing risk of death.¹¹ Cox proportional hazards regression models were used to assess associations between the risk of breast cancer and each of the Gail model risk factors. Hazard ratios, their 95% CIs, and *P* values assessing the associations were obtained.

Gail model predictions were summarized across the study group. Ranges of the predictions were extracted, together with means and standard deviations, for 5-year and follow-up-specific risk estimates. The distributions of the follow-up-specific risk estimates, by invasive breast cancer status, were obtained by computing the proportion of individuals whose risk predictions fell

into specified categories. A graph was obtained by plotting these percentages against the center of the risk prediction categories, and linearly interpolating the points. The 5-year risk predictions and the follow-up-specific probabilities were aggregated to obtain estimates of the number of breast cancers predicted by the Gail model, both overall and by the categories of the Gail model risk factors. The expected numbers of breast cancers were compared with the observed diagnoses by computing the ratio of observed to expected invasive breast cancers. Tests of significance and 95% CIs were obtained using the Poisson distribution.

The precision with which the Gail model predictions agreed with ultimate breast cancer events was assessed with the concordance statistic (termed *c*-statistic). This statistic is equivalent to the area under the receiver operating characteristic curve for diagnostic tests, and reflects the ability of the risk predictions to correctly order individuals relative to the timing of the observed breast cancer outcomes. For time-to-event outcomes, it is computed by forming all possible pairs of patients where the patient with the shorter follow-up time experienced breast cancer, and by tallying the number of pairs where the patient with the early event had a higher breast cancer risk score.¹² CIs for the *c*-statistics were obtained via a bootstrap approach. Given that several risk factors had missing data, a second set of analyses was performed to assess the accuracy and precision of the Gail model in the women with complete covariate information.

RESULTS

Of the 9,376 patients in the Mayo BBD cohort, 331 women (3.5%) had atypia. At a mean follow-up of 13.7 years, 58 of the 331 women with atypia (17.5%) developed invasive breast cancer (the cases), eight in the first 5 years after biopsy. Among the 331 patients with atypia, 75 women (22.7%) died while in active follow-up. Nine of the deaths were among the patients who developed cancer and 66 were among the remainder of the atypia cohort.

In Table 1 we list the Gail model features for the 331 women with atypia. In Figure 1 we show the age-specific cumulative incidence of breast cancer, along with population expectations and Gail model predictions for this cohort. Table 1 also lists associations between Gail model risk factors and invasive breast cancer onset. When comparisons were made in this cohort of women with atypia, in whom 58 invasive breast cancers were observed, no statistically significant associations were apparent.

Aggregate Performance

The Gail model predicted an average 5-year breast cancer risk of 4.2% (standard deviation, 2.7%; range, 0.3% to 18.8%). This equated to a predicted total of 13.9 breast cancers within 5 years. In this time interval, eight invasive breast cancers were observed. The ratio of observed to predicted events was 0.58 (95% CI, 0.29 to 1.15, *P* = .120).

When used to predict the risk of breast cancer by the end of the current follow-up, the mean Gail model risk was 10.5% (standard deviation, 8.2%; range 0.4% to 54.1%). These risk estimates predicted that 34.9 women would experience an invasive breast cancer during the time for which follow-up was available. The observed count of 58 events during the observation period was significantly higher than predicted (ratio, 1.66; 95% CI, 1.29 to 2.15; *P* < .001).

Table 2 summarizes the number of events observed in our cohort and the number of events predicted by the Gail model for each Gail model risk factor. The Gail model underestimated the number of breast cancers, both overall and in the majority of the risk-factor defined subgroups.

Table 1. Characteristics of the Women With Atypia According to Whether They Developed Breast Cancer

Characteristic	All Patients (n = 331)		No Invasive Cancer (n = 273)		Invasive Cancer (n = 58)		Hazard Ratio*	95% CI*	P†
	No.	%	No.	%	No.	%			
Age at biopsy, years									.903
< 46	46	13.9	37	13.6	9	15.5	1.04	0.71 to 1.51	
46-55	100	30.2	78	28.6	22	37.9	1.07	0.80 to 1.42	
> 55	185	55.9	158	57.9	27	46.6	Ref		
Mean	58.0		58.7		54.5		0.99	0.96 to 1.01	.252
Standard deviation	12.0		12.5		9.0				
Age at menarche, years									.398
< 12	39	11.8	29	10.6	10	17.2	1.85	0.86 to 3.99	
12-13	119	36.0	100	36.6	19	32.8	Ref		
> 13	57	17.2	46	16.8	11	19.0	1.31	0.63 to 2.76	
Unknown	116	35.0	98	35.9	18	31.0	1.53	0.80 to 2.92	
Age at first live birth, years									.269
Nulliparous	43	13.0	35	12.8	8	13.8	1.45	0.62 to 3.38	
< 20	39	11.8	35	12.8	4	6.9	0.60	0.20 to 1.80	
20-24	104	23.3	88	32.2	16	27.6	Ref		
25-29	73	22.1	55	20.1	18	31.0	1.68	0.86 to 3.30	
≥ 30	31	9.4	27	9.9	4	6.9	0.92	0.31 to 2.75	
Unknown	41	12.4	33	12.1	8	13.8	1.76	0.75 to 4.12	
First-degree relatives with breast cancer									.263
0	200	60.4	159	58.2	41	70.7	Ref		
1	73	22.1	63	23.1	10	17.2	0.69	0.25 to 1.92	
≥ 2	14	4.2	13	4.8	1	1.7	1.16	0.75 to 1.79	
Unknown	44	13.3	38	13.9	6	10.3	1.19	0.97 to 1.45	
No. of biopsies‡									.491
1	229	69.2	189	69.2	40	69.0	Ref		
≥ 2	102	30.8	84	30.8	18	31.0	1.10	0.83 to 1.46	

Abbreviation: Ref, reference.

*Hazard ratios and corresponding 95% CIs from a Cox proportional hazards regression model.

†P value testing the null hypothesis that all categories for the feature of interest have equal breast cancer risk.

‡As an enrollment criterion, each of the women in the cohort had at least one biopsy.

Individual-Specific Performance

Figure 2 shows the distributions of the Gail model risk estimates for women who did and did not develop invasive breast cancer. These distributions are shown adjusted to the mean follow-up time of 13.7 years and to the mean age at atypia of 58.0 years. This was done to eliminate bias induced by the controls' having longer follow-up than the patients, given that follow-up for patients stops at the time of diagnosis of breast cancer, and to account for differential risk estimates by age at diagnosis of atypia. With a model that perfectly discriminates between groups, the two distributions would not overlap. Here, there is extensive overlap between risk estimates for the patients and non-cases. The age and follow-up adjusted average risk predictions are slightly lower in the patients ($10.0\% \pm 5.4\%$ v $10.7\% \pm 7.3\%$), although not significantly ($P = .465$).

The concordance between observed and predicted invasive breast cancer events after 5 years, as measured by the c-statistic, was 0.47 (95% CI, 0.21 to 0.73), not significantly different from the value of 0.5 that would be expected by chance ($P = .792$). When using the risk estimates specific to the length of follow-up, the c-statistic was 0.50 (95% CI, 0.44 to 0.55), not significantly different from the value of 0.5 expected by chance ($P = .915$).

To determine the degree to which missing data affected estimates of the accuracy of the Gail model predictions, we recomputed the

prediction accuracy within the 192 individuals (58%) with complete data. As an additional sensitivity analysis, we also recomputed the prediction accuracy in all participants after imputing the value that would lead to the highest risk prediction. The observed-to-expected ratio of invasive breast cancers in those with complete data, at 1.44 (95% CI, 1.04 to 2.00), was somewhat lower than the value of 1.66 observed in all 331 women. However, this still reflected a significant discrepancy between the Gail model predictions and the observed invasive cancers among this subgroup of women with complete data ($P = .028$). The c-statistic in the complete-data subset was somewhat higher (0.53) than what we observed in the entire cohort (0.50). Even when imputing in a way that leads to the highest possible number of expected cancers, the observed-to-expected ratio was still significantly inflated (1.32; 95% CI, 1.02 to 1.70; $P = .036$), whereas the c-statistic (0.52) was similar to what was observed in the complete-data subset.

DISCUSSION

We studied the Gail model in a well-defined cohort of women with atypia with an average follow-up of nearly 14 years. Measuring the performance of the model, the model slightly overpredicted the number of invasive breast cancers during the first 5 years, but

Fig 1. Cumulative incidence of invasive breast cancer among women with atypical hyperplasia (atypia) as a function of age. The red line represents the cumulative incidence, corrected for the competing risk of death, in the atypia cohort. For comparison, two lines representing the Gail-predicted and the baseline population risks are included. The blue line reflects the cumulative incidence predicted by the Gail model in this cohort, and the gray line represents the cumulative incidence that serves as the baseline risk for white women in the Gail model calculations.

substantially underpredicted the number of invasive breast cancers during the 13.7 years of follow-up. The individual-specific agreement between the Gail model predictions and actual breast cancer outcomes was low. For the first 5 years after biopsy the c-statistic was 0.47 (95% CI, 0.21 to 0.73), no better than chance alone.

During the entire 13.7 years of follow-up, the Gail model predictions were concordant with invasive breast cancer outcomes 50% of the time (95% CI, 44% to 55%), also not significantly better than chance. This finding is lower than assessments of the Gail model in other cohorts, where c-statistics of 0.58 to 0.59^{13, 14} have been reported, although the upper limit of the CI approaches these previously reported values.

This cohort consists of a large collection of women with atypia. However, as we assessed the quality of the risk predictions of the Gail model, there were women for whom complete covariate information was not available (Table 1). When we recomputed the risk estimates in the subset of women with complete data, the estimates were similar. The c-statistic in the complete-data subset indicated performance similar to what was observed in the entire cohort. Even in the situation where the missing data were imputed in such a way as to produce the maximum number of predicted breast cancers, the Gail model still predicted a significantly lower number of breast cancer events than were observed. Thus, it seems unlikely that the level of missing data can explain the underestimate of breast cancer risk that is reported here.

Clinical management of women diagnosed with atypia includes quantitative breast cancer risk assessment, comprehensive discussion of risk reduction strategies, and recommendations for future breast cancer screening. The currently available risk reduction options include chemoprevention with agents such as tamoxifen or raloxifene,^{15,16} surgical therapy with prophylactic mastectomy, and/or lifestyle modification. Unfortunately, lifestyle modifications,

Table 2. Comparison of Observed and Predicted Breast Cancer Events by Gail Model Risk Factors for Invasive Breast Cancer After Diagnosis of Atypia

Characteristic	Subjects		Person-Years	Observed Events	Predicted Events*	Ratio Observed:Predicted Events	95% CI
	No.	%					
Overall	331		4,543.2	58	34.9	1.66	1.29 to 2.15
Age, years							
< 46	46	13.9	678.2	9	3.9	2.28	1.19 to 4.38
46-55	100	30.2	1,540.0	22	10.7	1.90	1.36 to 3.14
> 55	185	55.9	2,325.0	27	20.3	1.15	0.91 to 1.94
Age at menarche, years							
< 12	39	11.8	562.9	10	5.0	1.99	1.07 to 3.69
12 to 13	119	36.0	1,878.7	19	15.3	1.24	0.79 to 1.95
> 13	57	17.2	841.8	11	6.8	1.62	0.90 to 2.93
Unknown	116	35.0	1,259.9	18	7.8	2.32	1.46 to 3.68
Age at first live birth, years							
Nulliparous	43	13.0	531.3	8	4.3	1.88	0.94 to 3.76
< 20	39	11.8	610.4	4	4.2	0.96	0.36 to 2.56
20-24	104	23.3	1,475.2	16	11.5	1.39	0.85 to 2.27
25-29	73	22.1	1,030.2	18	8.5	2.12	1.34 to 3.36
≥ 30	31	9.4	433.0	4	3.9	1.04	0.39 to 2.77
Unknown	41	12.4	463.2	8	2.6	3.07	1.54 to 6.15
First-degree relatives with breast cancer							
0	200	60.4	2,735.2	41	16.2	2.52	1.86 to 3.43
1	73	22.1	1,042.7	10	11.5	0.87	0.47 to 1.62
≥ 2	14	4.2	208.9	1	4.3	0.23	0.03 to 1.64
Unknown	44	13.3	556.4	6	2.8	2.15	0.97 to 4.79
Number of biopsies							
1	229	69.2	2,991.3	40	21.0	1.90	1.40 to 2.60
≥ 2	102	30.8	1,552.0	18	13.9	1.30	0.82 to 2.06

*Calculated by applying observed person-years of follow-up to Gail model risk prediction estimates.

Fig 2. Distributions of Gail model risk probabilities in women with atypia who developed breast cancer (cases) and those who did not (noncases). The plot contains estimates for individualized risk at the end of the available follow-up. Given that risk predictions depend on age at benign breast disease (BBD) and length of follow-up, the risk predictions were corrected for these factors before comparison. The graph represents the percent of women whose Gail model risk predictions fell within categories ranging from 0.0 to 0.5 in 0.05 increments. Points connected with lines to facilitate comparison between case and noncase percentages. Though the cases received more predictions in the 10% to 15% interval than the noncases, their average risk prediction was slightly, although not significantly, lower.

such as adoption of a healthy diet, maintenance of a healthy weight, and avoidance of smoking and smoking environments do not seem to provide a substantive reduction in risk of breast cancer. Chemoprevention requires consideration of the risks and benefits of the medications and surgical intervention can be associated with significant morbidity. Gail et al¹⁷ provide a useful overview regarding the risks and benefits of using tamoxifen, and demonstrate that the use of tamoxifen in women with atypia provides a net benefit. With more reliable assessments of breast cancer risk, it will be possible to provide even better counsel to patients as they consider risk reduction strategies.

Atypia was not included in the initial development of the Gail model due to a lack of pathologic assessment for all women in the Breast Cancer Detection and Demonstration Project. Thus, atypia was added to the original model using estimates of the population prevalence of atypia, and the relative risk for breast cancer associated with atypia. This modification was based on a prevalence of atypia of 7.8%, and relative risk for breast cancer of 1.96.⁶ However, recent studies evaluating the risk of atypia, based on the more stringent criteria of Dupont and Page,³ have all reported higher relative risks with atypia (3 to 5.3),¹⁻⁵ and lower prevalence (approximately 4%). This may explain the underestimates that we report here.

Another potential explanation of the observed underestimate is that the Gail model is intended as a prospective risk prediction tool, and accounts for death as a competing risk. This results in lower predicted probabilities. In our study, we used the Gail model to predict risk in women for whom outcomes, including death, had already been observed. To assess the degree to which the competing risk of death might have influenced the results of our comparison to the Gail model, we recomputed the Gail model risk probabilities while accounting for death as a competing risk in the most extreme way possible. That is, we considered women who died to still have been at

risk until they would have reached age 90 years. Even in this extreme case, the Gail model significantly underpredicted the number of breast cancer events (observed-to-expected ratio, 1.44; 95% CI, 1.11 to 1.86; $P = .006$). However, this approach did result in a higher c-statistic (0.55; 95% CI, 0.49 to 0.60).

The Gail model has been studied in several settings; however, to our knowledge, data regarding atypia were not available in those validation studies.^{13,18-21} In general, the model has fulfilled its original goal—to identify groups of at-risk women suitable for chemoprevention trials.^{8,13,22,23} However, the model is increasingly used clinically to predict risk of individual women, and here the Gail model (and others) falls short of the precision required to make treatment recommendations for individual patients.^{8,13,22,23} Better performance for a population than an individual by these models is explained because the models were derived by averaging information across groups of individuals. When such models are based on large representative groups of patients, this leads to predictions that are well calibrated within an entire group, but do not guarantee accurate predictions for specific individuals within these groups.

To our knowledge, this article is the first report on the Gail model exclusively in women with atypia. It uses data from a large cohort, defined by contemporary pathology review, with detailed risk factor information and long-term follow-up. It is limited predominantly by the small number of patients that developed breast cancer and use of data from open, rather than core, biopsy.

The Gail model uses demographic and clinical factors. It is possible that risk assessment could be improved through use of tissue-based risk factors, which should be feasible for all women who undergo a breast biopsy with benign findings (an estimated one million such women in the United States alone each year).²⁴⁻²⁶ One of the hypotheses of breast cancer development is the existence of a continuum, wherein breast cells undergo successive alterations at a molecular level that lead from normal epithelium, to excess proliferation, and then to atypia, carcinoma in situ, and ultimately invasive carcinoma.²⁷ If this hypothesis is accurate, then tissue-based and molecular assessments that reflect the current state of the at-risk tissue will likely provide information leading to more accurate risk predictions. For example, in this atypia cohort the risk factors included in the Gail model do not stratify risk (Table 1). Presumably, the risk inherent in these factors (eg, family history) is already reflected in the tissue phenotype of atypia. We have recently shown that pathologic assessment of number of foci with atypia on biopsy stratifies risk of these patients.¹ We have also shown that the presence of lobular involution in background breast tissue and cyclo-oxygenase 2 overexpression further stratifies risk in women with atypia.^{9,28} Additional work in groups of women with measurements of tissue-based biomarkers as well as breast cancer outcomes is likely to provide important information.

In summary, our findings suggest that Gail model risk estimates for our cohort of women with atypia are significantly lower than what was observed with long-term follow-up. At the level of the individual, there was low concordance between the Gail model predictions and actual breast cancer events. This study underscores the need for caution when using the Gail model to counsel individual women with atypia regarding their risk of developing invasive breast cancer. Additional research is required to identify highly predictive markers of breast cancer risk, and to incorporate these markers into a more accurate model for use in this high-risk population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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