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ORIGINAL REPORT

Evaluation of the Tyrer-Cuzick (International Breast Cancer Intervention Study) Model for Breast Cancer Risk Prediction in Women With Atypical Hyperplasia

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ABSTRACT

Purpose
Accurate breast cancer risk assessment is vital to personalize screening and risk reduction strategies. Women with atypical hyperplasia have a four-fold higher risk of breast cancer. We evaluated the performance of the Tyrer-Cuzick model, which was designed to predict 10-year risk of breast cancer development, in a well-defined cohort of women with atypia.

Patients and Methods
The Mayo Benign Breast Disease cohort includes 9,376 women who had a benign breast biopsy between 1967 and 1991. Among those, 331 women with atypia were identified by our study pathologists. Risk factor data for the Tyrer-Cuzick model were collated for each woman and used to predict individual risk of developing invasive breast cancer within 10 years.

Results
Over a median follow-up of 14.6 years, 64 (19%) of the 331 women developed invasive breast cancer. In the first 10 years after biopsy, 31 women developed invasive breast cancer whereas the Tyrer-Cuzick model predicted 58.9. The observed-to-predicted ratio was 0.53 (95% CI, 0.37 to 0.75). The concordance statistic was 0.540, revealing that the Tyrer-Cuzick model did not accurately distinguish, on an individual level, between women who developed invasive breast cancer and those who did not.

Conclusion
The Tyrer-Cuzick model significantly overestimated risk of breast cancer for women with atypia, and individual risk estimates showed poor concordance between predicted risk and invasive breast cancer development. Thus, we cannot recommend the use of the Tyrer-Cuzick model to predict 10-year breast cancer risk in women with atypical hyperplasia.

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INTRODUCTION

The growing public awareness of breast cancer and its risk factors, coupled with the availability of medical and surgical risk reduction options, has led to many women consulting their doctors regarding their breast cancer risk. Women with atypical hyperplasia have an approximately four-fold increased risk of breast cancer,[1,2] and they frequently seek counseling regarding their actual risk of breast cancer development. Multiple prediction models have been developed to assist with breast cancer risk prediction efforts. Among these tools are the Gail model,[3] the Tyrer-Cuzick model,[4] the Claus model,[5] and several others.[3,6-10] The National Cancer Institute (NCI) Gail model Web site is accessed 20,000 to 30,000 times per month,[11] demonstrating a strong demand for this information. The Gail model adjusts for differential breast cancer risk associated with the presence or absence of atypical hyperplasia but has been shown to underestimate the risk of breast cancer in women with atypical hyperplasia.[12] Some have suggested that the Tyrer-Cuzick model (also called the IBIS [International Breast Cancer Intervention Study] Breast Cancer Risk Evaluation Tool) performs better in atypical hyperplasia than the Gail model.[13] This is a reasonable supposition because the Tyrer-Cuzick model was developed to include extensive family history information, endogenous estrogen exposure, and benign breast disease.[14] The Tyrer-Cuzick model is also the only other risk assessment model that explicitly accounts for differences in breast cancer risk, given the presence of atypical hyperplasia.[4] Nevertheless, to our knowledge the Tyrer-Cuzick model has not been validated in patients with atypia. Thus, we sought to

evaluate the performance of the Tyrer-Cuzick model in a well-defined cohort of women with atypical hyperplasia.

PATIENTS AND METHODS

Patients

The Mayo Clinic Benign Breast Disease cohort is made up of 9,376 women, age 18 to 85 years, who had an open breast biopsy between 1967 and 1991. The subset of patients who had atypical hyperplasia at the time of open biopsy has been previously defined.[1,12,15] All tissue was re-reviewed for this study by a breast pathologist, and the women with atypical hyperplasia serve as the cohort of interest for this study. Briefly, a diagnosis of atypical ductal hyperplasia or atypical lobular hyperplasia was made using the criteria and histologic classification of Dupont et al[16] and Page et al.[17] The study was approved by the institutional review board of the Mayo Clinic. Individuals' risk factors were obtained from a study-specific questionnaire and review of the medical records. Follow-up was performed via a search of the Mayo Tumor Registry, Mayo medical records, and by direct patient questionnaire. No patients were lost to follow-up, and 287 (86.7%) had a minimum of 5 years of follow-up. Follow-up data through May 2009 were used in all model assessments.

Methods

The Tyrer-Cuzick model estimates the risk of breast cancer using information about *BRCA1/2* mutation carrier status and other risk factors including age at menarche, parity, age at first childbirth, age at menopause, atypical hyperplasia, lobular carcinoma in situ, height, and body mass index. The risk factors required by the Tyrer-Cuzick model were collated for each woman and entered into the model using the computer program developed for the IBIS-II breast cancer prevention study (J. Cuzick, personal communication, May 2007). Several assumptions were required to incorporate this large cohort of patients into the Tyrer-Cuzick model. For women reporting a family history, we used the reported data to reconstruct the most detailed pedigree possible to capture the pattern of breast and ovarian cancer reported by the participant. The patient's age at the time of the benign breast biopsy was used as the age of risk assessment, and the Tyrer-Cuzick model was used to predict each woman's risk of developing invasive breast cancer within the following 10 years. For women with $<$ 10 years of follow-up, the risk prediction was modified by dividing the 10-year risk by 10 and multiplying the result by the actual number of years of follow-up.[14] Because more than half the cancers in this cohort occurred after 10 years of follow-up, we sought to evaluate the performance of the model beyond 10 years. Thus, we extrapolated the 10-year risk generated by the Tyrer-Cuzick model to the full length of follow-up available for each woman. To do this, we made the assumption that the cumulative risk estimates are approximately linear as a function of follow-up length. This appears appropriate since nearly 75% of the women in our atypia cohort were 49 years of age or older at biopsy, and the Tyrer-Cuzick risk predictions appear to increase in an approximately linear fashion in women age 50 years or older.[4,14]

To compare the Tyrer-Cuzick model 10-year risk prediction in our cohort to the Gail model over a similar time frame, the Gail model 10-year risk predictions were calculated. To obtain these breast cancer risk estimates, we employed a Fortran program that contains the code that comprises the underlying calculation machinery used in the NCI's Breast Cancer Risk Assessment Tool and was provided to us by the NCI (M. Gail, J. Benichou, and D. Pee, personal communication, February 2007).[12]

Statistical Analyses

The Tyrer-Cuzick risk factors of the women with atypical hyperplasia were summarized using counts and percentages, or means and standard deviations, both overall and also according to invasive breast cancer status. χ^2 tests or t tests were used to compare the risk factors between those who developed invasive breast cancer within 10 years of the biopsy and those who did not. The distributions of breast cancer–predicted risk probabilities were graphically summarized by 10-year breast cancer status.

The expected number of breast cancer cases that occurred within 10 years of the biopsy and showed atypical hyperplasia was computed by summing the predicted breast cancer risks of all women with atypia. To assess overall model calibration across the group of women with atypia, this expected number of breast cancers was compared with the observed number of invasive breast cancer diagnoses by computing the observed-to-expected ratio of invasive breast cancers. Tests of significance and 95% CIs were obtained using the Poisson distribution.

The individual precision with which the Tyrer-Cuzick model predictions agreed with 10-year breast cancer events was assessed with the concordance statistic (termed "c-statistic"). This statistic is equal to the area under the receiver operating characteristic curve for diagnostic tests and represents a composite measure of the ability of the risk predictions to correctly classify individuals as being cases or noncases. CIs for the c-statistics were obtained via a bootstrap approach. The same summaries were obtained for the 10-year breast cancer risk predictions from the Gail model.

Additional analyses were performed to further examine the Tyrer-Cuzick model within specific groups of patients. In particular, individuals were

Table 1. Characteristics of 331 Women With Atypical Hyperplasia According to Their 10-Year Breast Cancer Status

Characteristic	Unaffected (n = 300) No.	%	Breast Cancer Within 10 Years (n = 31) No.	%	Total (N = 331) No.	%	P*
Age, years							.640
Mean		58.1		57.2		58.1	
SD		12.2		10.6		12.0	
Age at menarche, years							.758
Mean		12.8		12.7		12.8	
SD		1.5		1.4		1.5	
Parity							.525
Nulliparous	37	12.3	6	19.4	43	13	
Parous	226	75.3	21	67.7	247	74.6	
Unknown	37	12.3	4	12.9	41	12.4	
Age at first live birth, years							.570
Mean		24.1		24.3		24.1	
SD		4.7		3.7		4.6	
Menopause status							.159
Premenopausal	161	53.7	13	41.9	174	52.6	
Perimenopausal	3	1	1	3.2	4	1.2	
Postmenopausal	96	32	15	48.4	111	33.5	
Unknown	40	13.3	2	6.5	42	12.7	
Year of biopsy							.303
1967-1981	84	28	6	19.4	90	27.2	
1982-1991	216	72	25	80.6	241	72.8	
Menopause age, years							.929
Mean		52.5		53.1		52.6	
SD		4.4		3.0		4.1	
Body mass index							.389
Mean		27.3		26.6		27.3	
SD		13.6		9.2		13.2	
Menopausal hormone therapy use							.175
Never	78	26	14	45.2	92	27.8	
$>$ 5 years ago	6	2	1	3.2	7	2.1	
$<$ 5 years ago	95	31.7	8	25.8	103	31.1	
Current user	66	22	3	9.7	69	20.8	
Unknown	55	18.3	5	16.1	60	18.1	
Menopausal hormone therapy type (use within 5 years or current users)							.550
Estrogen only	36	22.4	4	36.4	40	23.3	
Combined	23	14.3	1	9.1	24	14	
Unknown	102	63.4	6	54.5	108	62.8	
Menopausal hormone therapy length of use (former users), years							.054
Mean		9.2		4.4		8.8	
SD		15.7		11.8		15.4	
No. of first-degree relatives with breast cancer							.280
0-1	177	59	23	74.2	200	60.4	
2	67	22.3	6	19.4	73	22.1	
3+	14	4.7	0	0	14	4.2	
Unknown	42	14	2	6.5	44	13.3	

Abbreviation: SD, standard deviation.
*χ^2 tests for categorical variables and t tests for continuous variables.

Table 2. Performance of the Tyrer-Cuzick and Gail Models in a Cohort of 331 Women With Atypical Hyperplasia, 31 of Whom Developed Invasive Breast Cancer Within 10 Years of Biopsy

Model	Predicted No. of Breast Cancers in 10 Years	Observed No. of Breast Cancers in 10 Years	Observed:Predicted Ratio	95% CI	Concordance Statistic	95% CI
Tyrer-Cuzick	58.9	31	0.53	0.37 to 0.75	0.54	0.42 to 0.65
Gail	30.7	31	1.01	0.71 to 1.43	0.45	0.35 to 0.56

grouped by family history status, and model calibration and precision were assessed within these subsets.

RESULTS

Of the 9,376 patients in the Mayo Benign Breast Disease cohort, 331 women diagnosed with atypical hyperplasia were identified. Median follow-up available on the 331 patients was 14.6 years. Seventy-five women died during their time of active follow-up. Table 1 summarizes the features used in the Tyrer-Cuzick model for the women with atypical hyperplasia who did and did not develop breast cancer within 10 years of their biopsy.

Tyrer-Cuzick Model: 10-Year Risk

Sixty-four patients (19%) have developed invasive breast cancer since their diagnosis of atypical hyperplasia. An additional four women developed ductal carcinoma in situ and are not included in the breast cancers for this analysis, because the Tyrer-Cuzick model predicts risk of invasive disease within 10 years of evaluation. Thirty-one of these patients were diagnosed with invasive breast cancer within the first 10 years after diagnosis with atypical hyperplasia.

The Tyrer-Cuzick model predicted that, over 10 years, 58.9 patients in our cohort would have developed breast cancer. In this time interval, 31 breast cancers were observed. As detailed in Table 2, the ratio of observed-to-predicted events was 0.53 (95% CI, 0.37 to 0.75; $P < .001$). The concordance between observed and predicted breast cancer events within 10 years, as measured by the c-statistic, was 0.54 (95% CI, 0.42 to 0.65), not significantly different from the value of 0.5 that would be expected by chance ($P = .503$). Figure 1 summarizes the individual predicted breast cancer risks generated by the Tyrer-Cuzick model for the women with atypical hyperplasia by 10-year breast cancer status, and Figure 2 shows the receiver operating characteristic curve for the ability of the Tyrer-Cuzick risk prediction to classify women by their 10-year breast cancer status.

We also evaluated the performance of the Tyrer-Cuzick model in women with varying degrees of family history of breast cancer. Two family history groups were formed: those with zero or one, or those with two or more first-degree relatives with breast cancer. In the 200 individuals with zero or one first-degree relative(s) with breast cancer, the Tyrer-Cuzick model predicted 34.7 invasive cancers over 10 years, while 23 were observed, for an observed-to-expected ratio of 0.66 (95% CI, 0.44 to 0.99; $P = .048$). The c-statistic in this subset was 0.57 (95% CI, 0.43 to 0.70). In the 87 women with two or more first-degree relatives with breast cancer, the Tyrer-Cuzick model predicted 15.3 invasive cancers and six developed, for an observed-to-predicted ratio of 0.39 (95% CI, 0.18 to 0.87; $P = .022$). The c-statistic in this subset was 0.57 (95% CI, 0.33 to 0.81), not higher than what was observed for the family history–negative subset.

Comparison to the Gail Model 10-Year Risk Prediction

The Gail model predicted that over 10 years, 30.7 cases of invasive breast cancer would develop in our cohort. The ratio of

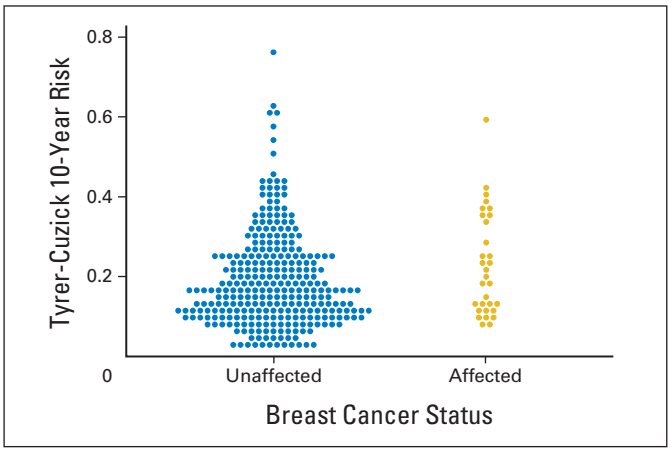

Fig 1. Risk predictions from the Tyrer-Cuzick model for the women with atypical hyperplasia by 10-year breast cancer status.

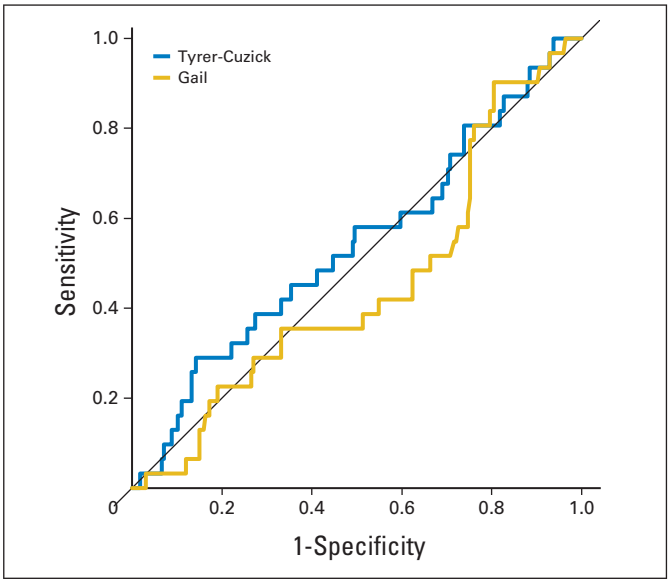

Fig 2. Receiver operating characteristic curves for the 10-year risk predictions generated by the Tyrer-Cuzick and Gail models in women with atypical hyperplasia. A diagonal reference line is provided that corresponds to a concordance statistic of 0.5.

observed-to-predicted events was 1.01 (95% CI, 0.71 to 1.43; $P = .963$). This was significantly better than the observed-to-predicted ratio seen with the Tyrer-Cuzick model in these women ($P < .001$). However, the concordance of the Gail model between observed and predicted breast cancer events within 10 years was 0.45 (95% CI, 0.35 to 0.56; $P = .348$). This concordance was lower than that seen with the Tyrer-Cuzick model, although the difference was not statistically significant ($P = .209$). Table 2 summarizes the calibration and precision of the Tyrer-Cuzick and Gail models with reference to the observed breast cancers within 10 years of biopsy showing atypical hyperplasia.

Extrapolation of the Tyrer-Cuzick Model Beyond 10 Years

This extrapolation allows for the use of outcome data for the full length of follow-up—median 14.6 years—during which we observed 64 invasive breast cancers. This extrapolation of the Tyrer-Cuzick model risk estimates predicted 89.5 events over the entire observed follow-up period, for an observed-to-predicted ratio of 0.72 (95% CI, 0.56 to 0.91; $P = .007$). While this observed-to-predicted ratio is somewhat improved over the 10-year estimate, it still represents a significant overprediction of risk. This extrapolation results in a c-statistic of 0.54, no better than what was observed at 10 years after follow-up.

DISCUSSION

We have studied the Tyrer-Cuzick model in women with atypical hyperplasia. Overall the Tyrer-Cuzick model overpredicted the number of breast cancers within the first 10 years in this group of women by a factor of almost two. The individual specific agreement between the 10-year Tyrer-Cuzick predictions and the individual patient breast cancer outcomes was low, with a c-statistic of 0.54.

The Tyrer-Cuzick model includes a comprehensive family history as part of its risk assessment. We therefore hypothesized that this model would perform better in women with a strong family history of breast cancer. However, this subgroup analysis within our atypia cohort did not show any improvement in risk prediction. Among our 331 women with atypical hyperplasia, only 68 women had a strong family history of breast cancer. The small number of patients with strong family history may have an impact on the ability to detect an improvement in model performance in this patient subgroup.

Looking at aggregate predictions for the group of women with atypia, the Gail 10-year risk estimates proved to be well calibrated with the number of cases of invasive breast cancer that developed in our cohort. However, the individual concordance between observed cancer status and the Gail model 10-year predictions was still poor. Thus, while the Gail model did well at predicting average group risk at 10 years, it did not predict an individual woman's breast cancer outcome better than chance alone and thus does not have clinical superiority over the Tyrer-Cuzick model.

What are the alternatives for predicting risk of individual women with atypical hyperplasia? The 10-year risk of 9.2% observed in this study is a reasonable estimate of the absolute risk of invasive breast cancer among women with atypia. Figure 3 shows the cumulative risk of breast cancer, corrected for the competing risk of death, among women with atypia. The figure is augmented with absolute risk estimates shown at 5-year intervals. This figure, and the corresponding cumulative risk estimates, can be used by clinicians who counsel women with atypia regarding their risk of subsequent breast cancer.

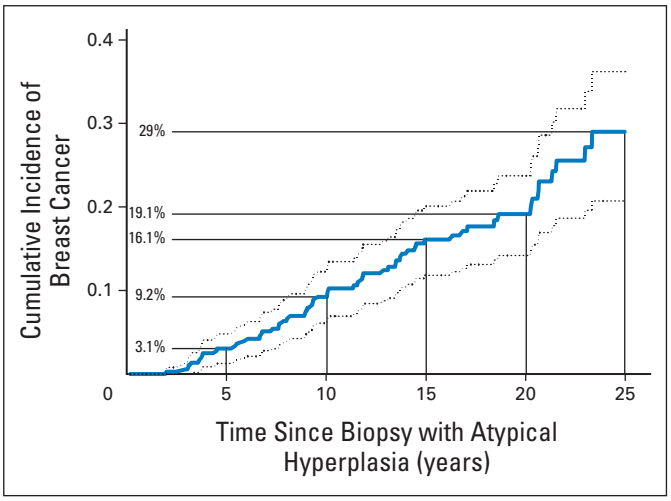

Fig 3. Cumulative risk of breast cancer after breast biopsy for women with atypical hyperplasia. The dotted lines indicate the upper and lower 95% pointwise confidence bands.

One limitation of this study relative to the Tyrer-Cuzick model pertains to the assessment of family history. In patients with a family history of breast cancer, the exact pedigree was not always available; in earlier years, family history was not documented as clearly in the clinical record because of less frequent use of genetic counselors and in-depth questioning of explicit family history (eg, which aunt—maternal or paternal—had breast cancer). However, we did not observe a major difference in model performance among groups on the basis of degree of family history, suggesting that the overestimation of risk by the Tyrer-Cuzick model was not due to any limitations of our family history data. We also acknowledge that the Tyrer-Cuzick model was not designed to predict risk after 10 years of follow-up. In our effort to extrapolate beyond 10 years, we noted that the model produced risk estimates for some women that exceeded 100%, suggesting that such a linear extrapolation may not be appropriate for the long follow-up times available for many of the women in our cohort. Thus, the extrapolated risk predictions beyond 10 years should be viewed with some caution.

It is theoretically possible that the overestimated risk predictions seen in this group of women with atypia were due to an overall lower breast cancer risk in our cohort. This is unlikely because the relative risk of breast cancer in these women with atypical hyperplasia is 4.2,[1] which is concordant with other established estimates of breast cancer risk for women with atypical hyperplasia.[2,15,16,18,19]

The representativeness of this cohort of women with atypia, with surgical biopsies performed from 1967 to 1991, could be questioned in the modern era of mammographic screening. However, the impact of mammographic screening is already apparent in this cohort, with 72% of patients accrued in 1982 to 1991 (Table 1), when mammography was used more frequently. A mammographic abnormality was the most frequent indication for biopsy. Regarding the use of surgical versus core biopsies, most atypias on core biopsy today are still removed via surgical excision.

Despite these limitations, this study was carried out on one of the largest cohorts of women with atypical hyperplasia confirmed by contemporary pathology review.[12,15] The cohort has been followed for a considerable length of time, with data available from medical records and from study-specific questionnaires providing an average length of follow-up of more than 14 years.

Accurate risk prediction is vital to help guide clinical risk assessment and to assist patients with their risk reduction options, which can vary from close observation to medical therapy or surgical procedures such as bilateral mastectomy. With ongoing debate surrounding the recommendations for mammographic screening,[20] accurate prediction of an individual woman's risk of breast cancer development would enable physicians to personalize recommendations for breast cancer screening with mammograms as well as individualize risk reduction strategies. Overprediction of breast cancer risk could lead to unwarranted use of risk-reduction strategies. Alternatively, significant underprediction can leave patients without intervention who might have benefited from appropriate management of their increased risk.

Although the Tyrer-Cuzick model uses more variables than the Gail model, it does not improve breast cancer risk prediction for women with atypia. It is likely that the risk inherent in a new variable may already be accounted for in features present in an existing model. This phenomenon may be more likely when tissue features are available, such as atypia. As an example, we and others have shown that a positive family history does not convey additional risk in women with atypia.[15,21] In this instance, endogenous hereditary risk is presumably one driver of the development of atypia; hence, the presence of atypia already incorporates the risk of a positive family history. It is sobering that neither major risk factors like breast density nor recently identified common genetic variants associated with breast cancer risk have added significantly to current risk prediction models.[22-24] In the future, other novel biomarkers of breast cancer risk will likely be identified that may improve breast cancer risk prediction. Previous studies from our group have shown that the number of foci of atypical hyperplasia, the extent of lobular involution, cyclooxygenase 2 overexpression, and proliferation extent can further stratify risk in women with atypical hyperplasia.[15,25-27]

Our study shows that the Tyrer-Cuzick model significantly overpredicts the risk of breast cancer development at 10 years in women with atypical hyperplasia, and that it is not able to accurately classify women into higher and lower risk groups. Neither the Tyrer-Cuzick model nor the Gail model predict individual risk in women with atypia better than chance alone. Therefore, when counseling women with atypical hyperplasia, we suggest that physicians use cumulative incidence data that reflect actual breast cancer events.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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