BRIEF REPORT

Management of Women at High Risk for Breast Cancer

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Background: **Primary care clinicians screen for breast cancer risk factors and assess the risk level of their patients. Women at high risk for breast cancer (eg, 5-year risk of at least 3% or lifetime risk of ≥20%) are eligible for enhanced screening and/or chemoprophylaxis. However, many clinicians do not identify women at high risk and offer appropriate referrals, screening, or chemoprophylaxis.**

Methods: **We reviewed a sample of 200 charts of women ages 35 to 50 years old with a family history of breast cancer. We identified factors that contribute to their risk for breast cancer and used the Tyrer-Cuzick Risk Assessment Calculator to determine their personal lifetime risk. We then assessed whether these patients received counseling for chemoprophylaxis, referrals, or screening. We also looked for correlations between combinations of risk factors and increased lifetime risk.**

Results: **Out of 200 charts reviewed, 71 women were identified as high risk for breast cancer (lifetime risk of ≥20%). Of those 71 women, just 17 were referred to a high-risk clinic for enhanced screening and/or chemoprophylaxis. Three risk factors, mammographic breast density of category C or D, first degree relatives with breast cancer, and age first given birth if after 30 years old had a significant impact on lifetime risk for breast cancer.**

Discussion: **Primary care clinicians can use these independent risk factors as cues to pursue a more formal calculation of a woman's lifetime risk for breast cancer and make appropriate referrals for enhanced screening and chemoprophylaxis counseling if indicated. (J Am Board Fam Med 2023;00:000–000.)**

Keywords: **Breast Cancer, Diagnostic Imaging, Chemoprophylaxis, Cancer Screening, Family Health History, Mammography, Referral and Consultation**

Introduction and Background

Breast cancer is the most common cancer found in women in the US. Primary care clinicians screen and counsel women who are both average and high risk for breast cancer during routine visits. Women who are at high risk (eg, 5-year risk of at least 3% or lifetime risk of ≥20%) are eligible for chemoprophylaxis (5 years of tamoxifen or an aromatase inhibitor to reduce risk of hormone-dependent cancer) and enhanced screening (addition of annual MRI to mammograms).[1–3] Enhanced screening is indicated specifically for lifetime risk of ≥20%, and chemoprophylaxis can be indicated for both a 5-year risk of at least 3% or lifetime risk of ≥20%. Evaluation of risk includes obtaining family history as well as using 1 of several available risk models. Up to 15% of women may meet criteria for high risk status.[4] Although the Gail model is most widely known and efficient, most genetic counselors in the US use the Tyrer-Cuzick model due to its inclusion of breast density as well as both first- and second-degree relatives.[5] Data suggests that primary care clinicians ask about family history but are not equipped or interested in counseling about chemoprophylaxis.[5] Any assessment of risk, however, takes time which is limited in a busy primary care clinic. Many clinicians do not identify women at high risk.[6] We hypothesized that a low percentage of women who classified as high risk would be identified as such and offered supplemental

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screening or referral to specialty services for consideration of chemoprophylaxis.

We performed a chart review of 200 women in the UW Health system who had a family history of breast cancer. The aims of this project were to

1. Measure how many of the identified women had a lifetime risk of brest cancer ≥20% (high risk).
2. Determine whether those at high risk were referred to a specialty clinic, had enhanced screening, or offer of chemoprophylaxis.
3. Elucidate whether there are specific combinations of risk factors that predict high risk status, thus making identification of high-risk women easier for primary care clinicians.

Methods

This study was approved for an exemption by the University of Wisconsin IRB.

A chart review was conducted on a sample of 200 patient charts from within the UW Health System. Inclusion criteria limited the review to women ages 35 to 50 years old who were born with a uterus and ovaries and had a family history of breast cancer in a first- or second-degree relative documented in their electronic health record. The charts were identified using 1 of the following qualifiers:

1. A visit diagnosis with an ICD-10 code of Z80.3 (family history of malignant neoplasm of breast)
2. Diagnosis on the problem list not of the above ICD-10 code.
3. In the "family history" section of the EHR, documented "Cancer Breast" and/or "Hereditary Breast and Ovarian Cancer Syndrome"

An age of 35 was chosen as it is often a time that clinicians begin discussions about breast cancer risk. In addition, these women were required to have a primary care physician in family medicine and have had a preventative visit with their provider within the last 3 years. Women were excluded from the review if they had a current cancer diagnosis of any type, except for skin cancer. (Women with a skin cancer diagnosis were included in the review if the cancer had not metastasized and the lesion was fully excised.) Out of an initial list of 6730 charts, 340 were chosen using a random numbers table. One hundred and forty were excluded leaving 200 charts eligible for the study.

The risk factors for breast cancer that were identified as the focus of the chart review included breast density (in the women who had a mammogram), number of first- or second-degree relatives with breast or ovarian cancer, history of genetic testing, age at menarche, age at menopause, age at first live birth, and whether they had ever had an atypical breast biopsy.

On chart review completion, the collected data along with the women's age, height, and weight were entered into the Tyrer-Cuzick Risk Assessment Calculator to determine if their personal lifetime risk of breast cancer was ≥ 20%, representative risk that would justify enhanced screening and referral to assess for chemoprophylaxis. For those at high-risk, we determined whether they had been referred to a high-risk clinic or had received additional counseling or enhanced screening.

A *t* test (continuous variables) and Chi-square or Fisher's exact test (categorical variables) and univariate logistic regression models were used to examine the association between each risk factor for breast cancer and high lifetime risk status. Risk factors that had a significant association with high lifetime risk were then further examined with a multivariate logistic regression model.

Results

Seventy-one of the 200 women reviewed (35.5%) were calculated to be at a high lifetime risk for breast cancer using the Tyrer-Cuzick calculator. Of these 71, 17 women (23.9%) were identified as high risk by their provider and referred to a specialty clinic for enhanced screening and/or counseling about chemoprophylaxis. 180 of the 200 charts (90%) were identified as white patients, with 13 charts (6.5%) identified as nonwhite patients, and 7 charts (3.5%) with missing race information. (Table 1).

For each additional first-degree family member with a history of breast cancer, the odds of a high lifetime risk were significantly higher. Presence of second-degree relatives with breast cancer did not significantly impact lifetime risk with the univariate model, but did have significant impact in the multivariate model. Women with mammographic breast density of C or D had significantly higher breast cancer risk than A or B. Women who had given birth after the age of 30 also had significantly higher breast cancer risk compared with nulliparous women or women who had given birth at age 29 or younger. (Table 2).

In the multivariate regression model including all 200 women with variables of family history and

Table 1. Population Characteristics

	Overall (n = 200)
Age	
Mean (SD)	42.8 (4.38)
Median [Min, Max]	43.0 [35.0, 50.0]
Race	
Non-white	13 (6.5%)
White	180 (90.0%)
Missing	7 (3.5%)
BMI	
Mean (SD)	31.4 (9.48)
Median [Min, Max]	28.8 [18.2, 82.5]
Age of 1st menses	
Mean (SD)	12.6 (1.41)
Median [Min, Max]	12.0 [9.0, 18.0]
Have child(ren)	
No	50 (25.0%)
Yes	150 (75.0%)
Age of 1st birth	
29 or younger	94 (47.0%)
30 or older	56 (28.0%)
Has not given birth	50 (25.0%)
Had mammogram	
No	60 (30.0%)
Yes	140 (70.0%)
Breast Density	
A or B	56 (28.0%)
C or D	83 (41.5%)
Missing	61 (30.5%)
Gone through menopause	
No	189 (94.5%)
Yes	11 (5.5%)
Age at menopause	
Mean (SD)	40.0 (10.0)
Median [Min, Max]	46.0 [26.0, 50.0]
Missing	189 (94.5%)
Number of 1st degree relatives with breast cancer	
0	150 (80%)
1	50 (20%)
Number of 2nd degree relatives with breast cancer	
0	30 (15%)
1	135 (67.5%)
2	23 (11.5%)
3	11 (5.5%)
4	1 (0.5%)

Abbreviation: SD, standard deviation.

age first given birth, for each additional first-degree relative with a history of breast cancer (as compared with zero first-degree relatives with breast cancer) the odds of a woman having a high lifetime risk score is significantly higher (OR 8.82 with a p-value <0.001). For each additional second-degree relative with a history of breast cancer (as compared with zero second-degree relatives with breast cancer), the odds of a woman having a high lifetime risk score was also significantly elevated but not as high as a first-degree relative (OR 2.54, p-value 0.013).

When evaluating the narrower population of women who have had mammograms (n = 138) via a multivariate regression model including breast density and age first given birth, for every additional first-degree relative with a history of breast cancer women continued to have a significant higher odds ratio of 9.43 (p-value = 0.003). For every additional second-degree relative with breast cancer women had a non-significant odds ratio of 2.13 (p-value = 0.358). Women who had a breast density of C or D had a significant elevated odds ratio of 11.16 (p-value <0.001) compared with the reference value odds ratio of 1 for a breast density of A or B.

Women who gave birth after the age of 30 had a significant elevated odds ratio of 1.94 ($P = .003$) compared with women who gave birth age 29 or younger (odds ratio 0.32, $P = .003$).

Discussion

This study raises some key findings. Of the 200 women included, 71 women (35.5%) were calculated to be at a high lifetime risk of breast cancer using the Tyrer-Cuzick model and warranted discussion of enhanced screening and referral to a specialty clinic for potential chemoprophylaxis. Yet less than one-quarter of the high-risk women were identified by their primary care provider and subsequently referred or had a discussion regarding chemoprophylaxis. This supports previous data that suggests that many clinicians have difficulty identifying women as high risk.[6,7]

Three variables contributed to an increased odds ratio for high lifetime risk. These included the number of first-degree relatives with breast cancer history, mammographic breast density category C or D, and age first given birth (after 30 years of age).

Given these findings, we propose that to assist clinicians in more quickly and easily identifying women as high risk they can consider the independent risk factors of a first-degree relative with history of breast cancer, breast density of C or D on mammography, and age first given birth if after 30 years old as cues to prompt a more formal calculation of a woman's risk for breast cancer. Calculating

Table 2. Estimates of Multivariate and Univariate Logistic Regression Models (n = 200)

Variable	Sub-Category	OR – Multivariate Model (95% CI)	Adjusted *p*-Value	OR – Univariate Model (95% CI)	Adjusted *p*-Value
Number of 1st Degree Relatives with Breast Cancer		8.82 (3.7, 22.91)	<0.001	3.86 (1.99, 7.63)	0.002
Number of 2nd Degree Relatives with Breast Cancer		2.54 (1.5, 4.52)	0.013	1.3 (0.87, 1.95)	1
Age at 1st Live Birth	Has not given birth	1 (referent)	0.003	1 (referent)	0.003
	29 or younger	0.32 (0.13, 0.76)		0.41 (0.19, 0.87)	
	30 or older	1.94 (0.83, 4.65)		1.82 (0.84, 4.01)	

Abbreviations: OR, odds ratio; CI, confidence interval.

individual lifetime risk for breast cancer is complex and time consuming.[8,9] We hope that these results will stimulate a more frequent and efficient evaluation for high risk of breast cancer in the primary care setting as well as appropriate and timely referral to specialty clinics for enhanced screening and chemoprophylaxis discussion if indicated.

There are several limitations to this study. The small sample size of 200 women likely relates to the larger confidence intervals seen in the regression analyses. The demographics of the charts are also relatively homogenous with regards to race. This relatively uniform population from a race standpoint does not fully represent all women. In addition, the charts reviewed were from 1 single health system, which also has implications on how it can be applied to other populations. Our health system uses EPIC as an electronic health record which provides ample opportunity to document family history of breast cancer. We also have availability of a high-risk breast health clinic. Busy clinicians may not be able to review family history at an already crowded preventive visit. We would support further research to identify other members of the health care team that could contribute to making breast cancer risk assessment easier and more efficient. Due to lack of information from the charts, the odds ratios for the risk factors of age at menarche and age at menopause were not able to be calculated. Further investigation of these risk factors, expansion of the sample size, and including a more heterogeneous population could be future avenues of exploration to consolidate these findings.

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