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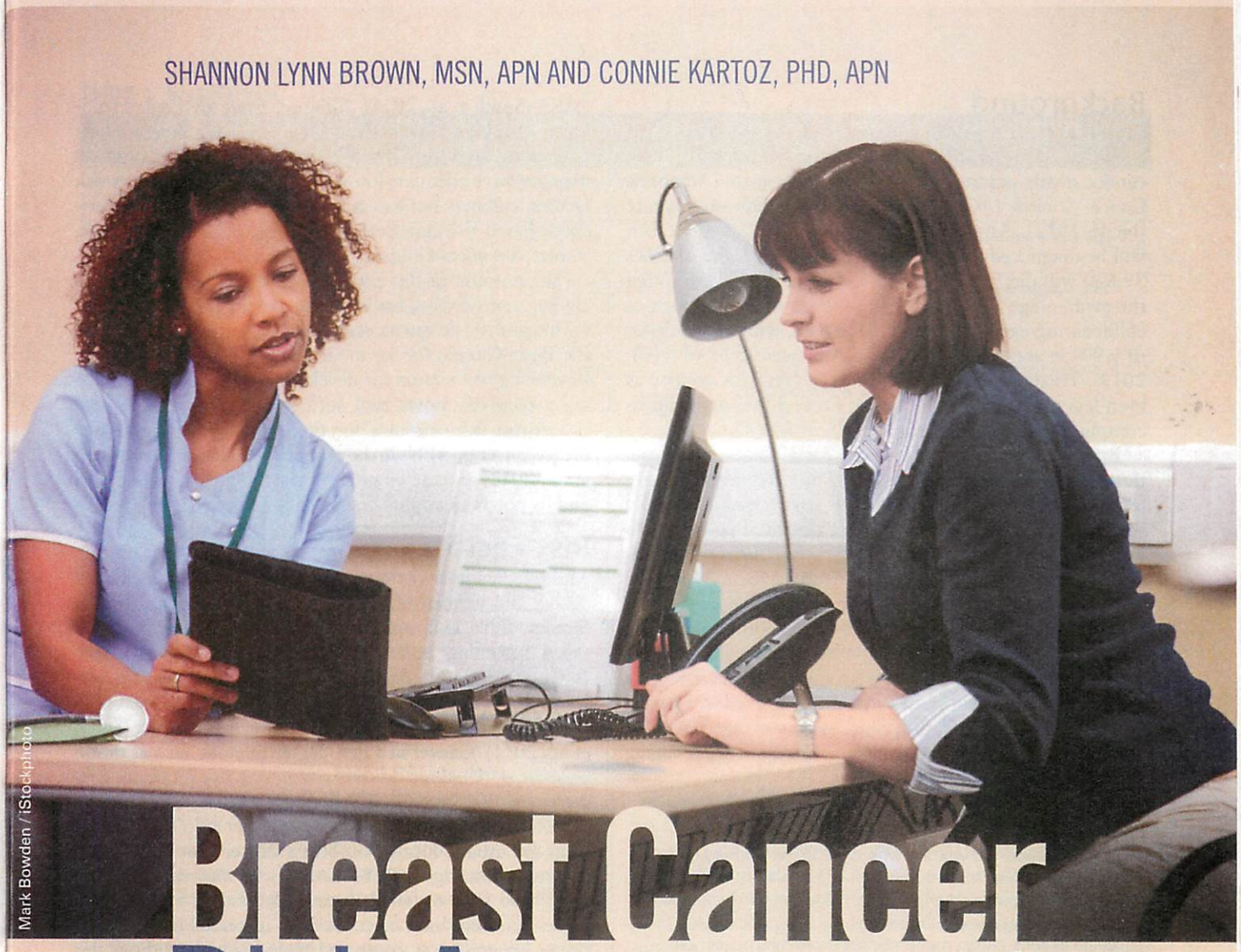

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Breast Cancer Risk Assessment IN PRIMARY CARE

Abstract

Breast cancer is the most common cancer (when excluding skin cancers) in women and the second most common cause of cancer death in women, with a lifetime prevalence of 12.5% (American Cancer Society [ACS], 2013a, 2013b; National Cancer Institute [NCI], 2012). Breast cancer screening reduces risk of cancer death, thereby increasing rate of survival to up to 89% for women with stage 1 and 2 breast cancer (Bleyer & Welch, 2012; Howlader et al., 2012). Despite these data, undue harm may occur with unnecessary screening because overidentification of risk, and excessive, costly biopsies may result. Costs and benefits of screening must be weighed. Nurses at all levels can play a pivotal role in promotion of appropriate breast cancer screening and subsequently breast cancer prevention by using accurate screening tools, such as the Tyrer–Cuzick model. Although there are some limitations with this tool, screening at the primary care level has demonstrated improved clinical outcomes (Roetzheim et al., 2012). Its use can help nurses accurately assess a woman's breast cancer risk, by promoting appropriate screening at the primary care level (Roetzheim et al., 2012).

Key words: Breast cancer; Cancer screening; Primary care; Risk assessment.

Background

Breast cancer is the most common cancer diagnosis (when excluding skin cancers) and the second leading cause of cancer death among all cancers for women (American Cancer Society [ACS], 2013a; National Cancer Institute [NCI], 2012). As predicted by the ACS, 232,340 women will be diagnosed with breast cancer in 2013 and another 39,620 will die from this disease (ACS, 2013a). Although the median age of diagnosis is 61 years of age, women of childbearing age can be affected as well, with an incidence of 1.8% in ages 20 to 34 and 9.6% in ages 35 to 44 (NCI, 2013). Fortunately, breast cancer in pregnant women is even less common, with 1 out of every 3,000 pregnancies complicated by this diagnosis (NCI, 2010).

Breast cancer is curable in its early stages; therefore, timely screening and early diagnosis are required to lower associated mortality. Benefits of early mammography screening must be weighed against potential costs, which include overscreening, emotional distress caused by screening (e.g., anxiety, depression), and costly, excessive biopsies (Elmore & Fletcher, 2012). Proper identification of risk allows advance practice nurses (APNs) who order radiologic breast screening to be selective when referring women for screening. Detailed familiarity with cancer risk factors helps more accurately identify those at increased risk for breast cancer, and guides appropriate selection of radiologic screening methods such as magnetic resonance imaging (MRI) (Smith et al., 2011). Although there are limited studies reporting on nurses' knowledge of genetic breast cancer risk and use of screening tools, existing data suggest nurses may not have adequate knowledge about breast cancer risk factors, and may not assess for breast cancer risk using evidence-based risk assessment tools (Edwards, Maradiegue, Seibert, Saunders-Goldson, & Humphreys, 2009).

The purpose of this article is to review risk factors, including genetic risks, for breast cancer, as well as to present an integrative literature review regarding one risk model, the Tyrer–Cuzick, for use in identifying women at high risk. Reviewing risk factors for developing breast cancer and using a relatively novel tool such as the Tyrer–Cuzick risk model can help increase the detection rate of early-stage breast cancer by APNs in the primary care setting (Roetzheim et al., 2012). A case example is provided using this model and its potential impact on clinical practice (Figure 1).

FIGURE 1. Case Example.

L.P. is a 48-year-old woman who went to her primary care office to be screened because of a family history of breast cancer. L.P.'s personal and family history was collected by the APN and entered into the Tyrer–Cuzick model. She is of Italian decent, began menarche at age 10, has never been pregnant, is premenopausal, and has never used HRT. She is 5 feet 6 inches tall. Her medical history is unremarkable and she has no personal history of cancers or breast biopsies. Her paternal aunt was diagnosed with breast cancer at 42 years old, her paternal first cousin was diagnosed at age 36, and L.P.'s sister was diagnosed with breast cancer at age 44. L.P.'s BRCA 1/2 status is unknown. There is no cancer noted on the maternal side of the family.

Using the Tyrer–Cuzick model L.P.'s lifetime risk of developing breast cancer is 33.55% compared to the lifetime population risk of 8.6% (Tyrer et al., 2004). This risk places L.P. above the 20% to 25% lifetime risk recognized by ACS as high risk (Smith et al., 2011). Based on the results of the Tyrer–Cuzick model, the APN can recommend that L.P.'s three relatives with positive breast cancer history should be genetically tested for the BRCA mutations according to the U.S. Preventive Services Task Force (USPSTF) and ACS guidelines (Smith et al., 2011; USPSTF, 2005). If her relatives are unwilling to be genetically tested, there is a significant enough family history for genetic testing to be ordered for L.P. She should receive yearly breast MRIs and yearly mammograms according to the ACS guidelines (Smith et al., 2011). This case study shows the importance of collecting both the maternal and paternal family history. The Tyrer–Cuzick model, unlike many models, takes into consideration both the paternal and maternal history.

Risk Factors

Multiple factors contribute to the risk of developing breast cancer and women of all ages should be screened for risk factors (Table 1) in order to identify the need for more detailed screening and/or preventive counseling strategies (NCI, 2012; Smith, Brooks, Cokkinides, Saslow, & Brawley, 2013). The ACS has defined certain high-risk factors as "red flags" that indicate the need for genetic testing (Smith et al., 2011). Cancer in a first-degree relative, such as mother, sister, or daughter, doubles a woman's risk for breast cancer (ACS, 2013b; NCI, 2012). Family history is significant as genetics also play a role in breast cancer risk. These mutations are usually located on breast cancer gene 1 (BRCA1) or breast cancer gene 2 (BRCA2). Gene mutations account for 5% to 10% of female breast cancers and families with these mutations have up to an 80% increased risk of developing breast cancer compared to individuals without this mutation (ACS, 2013b; NCI, 2012). Guidelines for genetic testing can be found on the National Comprehensive Cancer Network (NCCN) website (www.nccn.org/professionals/physician_gls/f_guidelines.asp#detection).

Risk Assessments

Risk assessments can be used to determine which women are more likely to develop breast cancer. Although current recommendations (ACS, 2013a) suggest 40 years of age as the first year for radiologic screening, risk assessments can be used in women of childbearing age under 40 years of age who have red flags for risk on history during routine annual exams (Smith et al., 2013).

Numerous risk assessment models are available that focus on the chance of developing breast cancer and/or the chance of carrying a high-risk gene; however, many of the most commonly used models have limitations (Evans & Howell, 2007). Table 2 provides comparison of models. The Gail model focuses on nongenetic risk factors with limited focus on family history, whereas the Claus model uses family history to estimate risk (Amir, Freedman, Seruga, & Evans, 2010; Evans & Howell, 2007). The BRCAPRO model provides estimates for the likelihood of BRCA gene mutations in a family but does not include nonhereditary risk factors (Evans & Howell,

TABLE 1. Risk Factors

Red Flags	Non Modifiable Risk	Modifiable Risk	OB/GYN Risks
BRCA gene, known mutation	Age greater than 60	Increased alcohol intake	Menarche before age 12
Breast and ovarian cancer in same person	Female sex	Overweight/obesity in menopause	Menopause after age 55
Two or more primary breast cancers in the same first- or second-degree family member, with one cancer diagnosed before age 50	Family history	HRT	First pregnancy after age 30
Male breast cancer at any age	BRCA gene	Current oral contraceptive use	Never being pregnant
Personal history of early onset of breast cancer diagnosed before age 45	Dense breasts	Heavy smoking history	
Multiple first- or second-degree relatives with breast or ovarian cancer on the same side of the family (particularly if diagnosed at 50 years of age or younger)	Tall—above average height		
	Ashkenazi origin		
	Exposure to DES		
	Radiation exposure to chest before age 30		

Note. All red flags and risk factors are from NCI (2012) and ACS (2013a, 2013b).

2007). An advantage of the BRCAPRO is that it includes information of affected and nonaffected relatives (Amir et al., 2010). The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model uses an algorithm to predict mutation probabilities and cancer risk in individuals with a family history of breast or ovarian cancers (Amir et al., 2010).

The Tyrer–Cuzick model was developed using the dataset from the International Breast Intervention Study (IBIS) and the Mayo Clinic Benign Breast Disease cohort (Tyrer, Duffy & Cuzick, 2004). This model includes questions about extensive family history, genetic carrier status, estrogen exposure, age at first menarche, parity, age at first childbirth and menopause, atypical hyperplasia, lobular carcinoma in situ, height, BMI, lifetime risk (LTR), and the probability of genetic predisposition and the need for genetic testing (Tyrer et al., 2004). Because of the comprehensive inclusion of risk factors, the Tyrer–Cuzick model is one of the recommended screening measures of the ACS, NCCN, and The American Roentgen Ray Society (ACS, 2013b; Berg, 2009; NCCN, 2013). Currently, the American College of Obstetricians and Gynecologists (ACOG) does not have any guidelines recommending this tool.

Literature Review

A literature review regarding breast cancer screening tools was conducted with a focus on the Tyrer–Cuzick model. A literature search using Google Scholar, Pubmed, Cochrane library, and EBSCOhost is the basis for this article. Additional literature from the ACS, U.S. Preventive Services Task Force, NCI, Centers for Disease Control and Prevention, and ACOG is included. Journal article reference lists were also reviewed. The following key words were used: Tyrer–Cuzick, IBIS, breast cancer risk, empiric models, risk assessment, and cancer syndrome. Articles are included in this review if they are empirical, peer reviewed, in English, include the Tyrer–Cuzick model, and compare risk with identified diagnosis. Six articles met inclusion criteria. They are discussed in this analysis in reverse chronological order of publication.

Ozanne et al. (2013) explored LTR of developing breast cancer using the BRCARPO, Claus, and Tyrer–Cuzick models to determine MRI eligibility based on ACS guidelines that women with an LTR over 20% should receive yearly MRIs in addition to yearly mammograms (Saslow et al., 2007). A retrospective analysis examining sensitivity of tools in identifying those in need of MRI took place on a sample of women (N = 5,894) who received mammography screening at a community hospital. Women previously exposed to hormone replacement therapy (HRT) were excluded from this analysis, whereas the women who had sufficient risk information to run all three models were included. Of the 342 women eligible for MRI, the Tyrer–Cuzick model identified more women eligible for MRI than the Claus and BRCARPO models, respectively (5.6%, 0.9%, 0.4%, respectively). A limitation of this study is that patients exposed to HRT were excluded, yet the Tyrer–Cuzick includes HRT as a potential risk factor.

Quante, Whittemore, Shriver, Strauch, and Terry (2012) conducted a prospective cohort study on a sample of women (N = 1,857) from the New York site of the Breast Cancer Family Registry. These authors compared the Gail and Tyrer–Cuzick models in quantifying the risk of breast cancer (Quante et al., 2012). Women between the age of 20 and 70 with an increased risk for breast cancer by family or personal history were included. Exclusion criteria included a history of prophylactic mastectomy or lobular and ductile

carcinoma in situ. Mean follow-up was 8.1 years. The women were placed into four quartiles based on their predicted 10-year risk. For each of the quartiles survival data were used to estimate the "observed" 10-year risk of developing breast cancer after assessment or death due to other causes. The Gail and Tyrer–Cuzick models (BCRAT and IBIS, respectively) underperformed in identifying risk when compared to the cohort's 10-year cumulative observed probability of developing breast cancer (3.18%, 5.49%, 6.25%, respectively, 95% CI = 5.0–7.8%). The researchers calculated an assigned risk cutoff of 80% specificity and identified the Tyrer–Cuzick model to have 44.6% sensitivity compared to 30.1% for the Gail model. A limitation to this study is that not all participants were followed up for 8.1 years; 4% of the cohort was followed for 1 year or less. An additional limitation is that women with a history of lobular and ductile carcinoma in situ were excluded and history of lobular carcinoma in situ is included in the Tyrer–Cuzick risk assessment.

Metcalfe et al. (2010) used a cohort to study of a sample of Canadian women (N = 2,080) between the age of 25 and 80 who self-identified as Jewish. A family history questionnaire and a blood or saliva sample to detect BRCA 1 and 2 genetic mutations were collected (Metcalfe et al., 2010). These authors used the Tyrer–Cuzick model to calculate the LTR of developing breast cancer and the risk of carrying a BRCA mutation for each woman. The overall actual mutation prevalence for this cohort was 1.1% (Metcalfe et al., 2010). The Tyrer–Cuzick model estimated the mean risk of carrying the BRCA 1 or 2 mutations for the entire study group as 1.2% (range, 0–48%). The mean lifetime breast cancer risk for women who were found to carry a BRCA mutation was 12.8% (range, 3.1–44.9%) and was similar to that for women without a mutation (mean, 10.6%; range, 1.0–49.7%; p = .25 for difference). The mean risk of carrying a mutation was greater for those with a BRCA mutation than for those without a mutation (3.9% vs. 1.2%; p = .23). It should be noted that the prevalence of mutations in this study was similar to what was predicted by the Tyrer–Cuzick model.

Boughey et al. (2010) compared the Tyrer–Cuzick and Gail models in women with atypical hyperplasia (N = 331) to determine their 10-year risk of developing invasive breast cancer. Women from the Mayo Clinic Benign Breast Disease cohort aged 18 to 65, who had an open breast biopsy between 1967 and 1991 and who had atypical hyperplasia were included in the study. The Tyrer–Cuzick model overestimated the number of women who would develop invasive breast cancer in comparison to those who actually developed breast cancer (58.9 women vs. 31 women, respectively). The observed-to-predicted events were 0.53

TABLE 2. Validation and Risk Factor Variables Included in Risk Estimation Models

Model	Gail	Claus	BRCAPRO	Tyrer–Cuzick	BOADICEA
Predication					
Validation	0.48	0.56	0.49	0.81	Not assessed
95% CI	0.54–0.90	0.59–0.80	0.52–0.80	0.85–1.41	Not assessed
Personal Information					
Age 20–70	√	√	√	√	√
BMI				√	
Hormonal/Reproductive					
Age at:					
-Menarche	√			√	
-First live birth	√			√	
-Menopause				√	
HRT				√	
Personal History of					
Breast biopsies	√			√	
Atypical ductal hyperplasia				√	
Lobular carcinoma in situ				√	
Breast density					
Family History					
First-degree relatives	√	√	√	√	√
Second-degree relatives		√	√	√	√
Third-degree relatives					√
Age of onset of breast cancer		√	√	√	√
			√	√	√
Bilateral breast cancer			√	√	√
Ovarian cancer			√		√
Male breast cancer					

Note. The validation and 95% confidence interval (CI) is from Amir et al. (2003) and all other variables are from Evan and Howell (2007). BMI, body mass index; HRT, hormone replacement therapy; ca, cancer. The check mark (√) signifies that the information is included in the model.

(95% CI, 0.37–0.75; $p < 0.001$). In this study the Gail model was more accurate predicting 30.7 cases of invasive breast cancer with an observed-to-predicted event of 1.01 (95% CI, 0.71–1.43, $p = 0.963$). Therefore, the Tyrer–Cuzick model is not recommended for use in counseling women with atypical hyperplasia (Boughey et al., 2010).

A comparative study by Jacobi, Bock, Siegerink, and van Asperen (2009) evaluated the differences and similarities between seven risk assessment models (Gail-2, Claus Model, Claus Tables, BOADICEA, Jonker Model, Claus-Extended Formula, and Tyrer–Cuzik Model) and the LTR of developing breast cancer by assessing two hypothetical "counselees" at age 40. The two counselees (A and B) are examples of women who seek information about their LTR of developing breast cancer. Based on these hypothetical counselees, the study demonstrates that including age of menarche and age at first-born child in risk assessment increases the LTR for developing breast cancer. The researchers conclude that the Gail and Claus tend to underestimate the LTR of developing breast cancer, whereas the Tyrer–Cuzick and BOADICEA, which incorporate personal risk factors, increase the accuracy of risk estimates (Jacobi et al., 2009).

Amir et al. (2003) assessed the discriminatory accuracy of the Tyrer–Cuzick model against the Gail, Claus, Ford, and Manual on a sample of women (age range 21–73) without cancer ($N = 3,150$) from the Family Clinic at the University Hospital of South Manchester. Mean follow-up was 5.27 years. Results show that the Tyrer–Cuzick model performs best in accurate prediction (E/0 = 1.09; 95% CI, 0.85–1.41), whereas the Gail (E/0 = 0.69; 95% CI, 0.54–0.90), Claus (E/0 = 0.76; 95% CI, 0.59–0.99), and Ford (E/0 = 0.66; 95% CI, 0.52–0.86) underpredict breast cancer occurrence. The Manual overpredicts cancer risk (E/0 = 1.22; 95% CI, 0.95–1.58). Amir et al. (2003) conclude that the Tyrer–Cuzick model provides the most consistent accurate risk estimation for women at high risk based on family history and hormonal factors.

Many studies, including Ozanne et al. (2013), Quante et al. (2012), Metcalfe et al. (2010), Jacobi et al. (2009), and Amir et al. (2003), report the Tyrer–Cuzick model to be the most sensitive tool for the assessment of breast cancer risk in both women of childbearing age and those who are postmenopausal. Although it increases likelihood of overdiagnosis due to low specificity, this problem is especially evident in women with atypical hyperplasia (Boughey et al., 2010). All of the models predict general risk well, but have low discriminatory power for individual women, with the Gail model having the lowest (Assi, Warwick, Cuzick, & Duffy, 2011; Howell et al., 2012).

Inclusion of modifiable and nonmodifiable risk factors such as age, parity, HRT use, and BMI in the Tyrer–Cuzick model differentiates it from older models and contributes to increased identification of women at risk. This model's assessment of multiple factors may reduce specificity contributing to overprediction of disease, and thereby lead to increased screening. The comprehensive nature of the Tyrer–Cuzick model contributes to superior sensitivity, and therefore provides the most useful, precise, and accurate assessment of breast cancer risk.

There are gaps in the current literature, which include no randomized controlled trial samples, no lifelong follow-up periods, and lack of inclusion of protective factors such as lifetime exercise and breastfeeding. Future studies should clarify Tyrer–Cuzick's validity with multiple levels of risk. Although this article suggests the use of the Tyrer–Cuzick model in primary care, additional research regarding the tool's reliability and validity in the primary care setting is needed to support its use.

Clinical Implications

As most of the reviewed literature includes women of childbearing age, nurses and APNs who conduct screening with the Tyrer–Cuzick should be aware of implications for childbearing issues related to both prevention and possible detection of breast cancer (Smith et al., 2013). Pregnant women may receive radiographic evaluation of a palpable mass, but not radiologic *screening* (NCI, 2012). Thus, for women at elevated risk, screenings can be scheduled around planned conception. Although treatment of breast cancer during pregnancy is beyond the scope of this article, it can be noted that pregnancy termination has not been shown to improve outcomes (NCI, 2010).

Women with an elevated risk based on the Tyrer–Cuzick or other models who have yet to complete childbearing should be informed that breastfeeding may offer some protection from breast cancer (Smith et al., 2013). Women with an elevated risk under 30 can be informed that having a first child after 30 years of age may increase risk (ACS, 2013a, 2013b). Women of all ages should undergo comprehensive risk reduction counseling (Smith et al., 2013).

Women scoring 20% or greater on the Tyrer–Cuzick model are at high risk for breast cancer (Amir et al., 2003; Smith et al., 2011), and therefore meet criteria for both breast MRI and mammogram performed yearly starting as early as age 30 (ACS, 2013a, 2013b; Smith et al., 2011). The Tyrer–Cuzick model can be used by APNs to guide annual screening recommendations, taking care to not use it in women with a history of atypical hyperplasia. Nurses should be aware of low specificity so as not to alarm women because overprediction of cancer risk may take place when using this model (Bleyer & Welch, 2012).

This model and its newest Version 7 are available for download at www.ems-trials.org/riskevaluator/. Although the program states that it is for research purposes only, the ACS, NCCN, and the ACCR suggest and support its use in assessing women's breast cancer risk in the clinical setting (ACS, 2013a, 2013b; Berg, 2009; NCCN, 2013).

Both private and government insurance companies, such as Aetna and Mass Health, find breast MRI a medically necessary adjunct to mammography for screening women who are considered to be at high genetic risk of breast cancer when a woman has a lifetime breast cancer risk of 20% or greater as estimated with a validated risk assessment model (BRCAPRO, Gail, Tyrer–Cuzick, or similar models); (Aetna, 2013; Mass Health, 2011). Nurses must be well educated regarding breast cancer risk factors to ensure not only appropriate use of the Tyrer–Cuzick model, but also that after use of this model, appropriate screening and testing take place.

Suggested Clinical Implications

Selection of proper radiologic screening for breast cancer reduces mortality from breast cancer

Women with a greater than 20% LTR of breast cancer are eligible for MRI screening

Several screening tools exist to identify those at risk (Tyrer–Cuzick, Gail, BRCAPRO, Claus, and BOADICEA)

Nurses must be well educated regarding breast cancer risk factors to ensure not only appropriate use of the Tyrer–Cuzick model, but also that after use of this model, appropriate screening and testing take place

The Tyrer–Cuzick represents the most comprehensive, sensitive, and accurate of available screening tools

Summary

Breast cancer is a significant cause of morbidity and mortality in women. The Tyrer–Cuzick model provides the most comprehensive and sensitive assessment of breast cancer risk in comparison with other tools (Table 2). There are conflicting data regarding validity of this tool in women of average risk. This tool is reliable for assessing women identified as high risk as a method to provide further screening and determine the most appropriate imaging technique. Appropriate imaging recommendations contribute to early identification, and thus reduce morbidity and mortality. ✣

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The authors declare no conflict of interest.

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