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WHITE PAPER

Breast Density Improves Breast Cancer Risk Stratification in the New Tyrer-Cuzick v8 Model

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Christina Robert, PhD
Clinical Marketing Specialist

Julian Marshall
Chief Knowledge Officer

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Introduction

Breast cancer risk prediction relies on mathematical models that estimate a woman's risk of developing breast cancer in the future. Each model requires a range of information about her personal, clinical, and family history, although different models are based on slightly different factors.

The risk models produce different types of output, such as BRCA1/2 mutation carrier probability, short-term risk, and residual lifetime risk of developing breast cancer. They are used to counsel women about their individual risk and to triage women for preventive therapy such as tamoxifen[1,2] or an aromatase inhibitor,[3] genetic testing,[1,4] and/or additional screening with MRI or other modalities.[1,5,6,7]

This paper demonstrates how breast density is now being used to improve breast cancer risk stratification using the new Tyrer-Cuzick v8 (IBIS Breast Cancer Risk Evaluation Tool, http://www.ems-trials.org/riskevaluator/).

Risk Factors and Performance

The available risk models rely on a set of risk factors with the intention of identifying women who may be at increased risk. Current risk factors can identify a fraction of women at increased risk, but many are not identified. Researchers continue to try to identify new risk factors to increase the fraction of women who are at high risk and in need of more surveillance or preventive measures, and to identify those at low risk in whom less screening may be acceptable. This is important partly because the very strongest known risk factors, such as family history, genetic predisposition, or proliferative benign disease, are present only in a small minority of the population.[1,8,9,10] No model can identify with certainty which women will develop the disease and which women will not, but many models have been shown to provide risk assessments that accurately identify a fraction of women at increased risk.[11,12]

The number of risk factors and models can be expected to continue to evolve over time. As will be shown in the balance of this paper, the addition of breast density as a new risk factor to the well-performing[13] Tyrer-Cuzick model (TC) provides an example where improved risk stratification can be achieved beyond that obtainable from only classical questionnaire factors.

Breast Density as a Risk Factor

Wolfe first identified breast parenchymal tissue patterns (the subjective visual arrangement of ducts and parenchymal tissue on the mammogram) as a novel use of the mammogram for prediction of the risk of future breast cancer—in addition to its standard use for early detection of breast cancer.[14] Since that time, research has moved from parenchymal *patterns* towards breast density (the proportion of the breast consisting of fibroglandular tissue), which is now widely accepted as a factor that in many cases confers two to six times the relative risk (for women in the highest categories of density compared to the lowest).[15] Researchers are now evaluating parenchymal texture (various descriptors of the complexity and distribution of parenchymal tissue, often based on objective features) as a potential risk factor for breast cancer; however, despite showing promising early results, these measures are still experimental and require validation in independent datasets.[16]

The quantitative assessment of mammographic density, an estimate of true breast density derived from x-ray imaging of the breast, has been clearly shown to be an important risk factor for breast cancer with both a high relative risk[17] and high prevalence in the population.[18] Engmann recently reported that 39% of premenopausal and 26% of postmenopausal breast cancers, respectively, were attributable to having dense breasts (BI-RADS®[a] c or d).[10] Furthermore, when using a different method of dense breast classification, based on the visually assessed percentage of the mammographic image covered by dense tissue, between 16% and 28% of all breast cancers were attributed to breast density of 50% or greater.[19, 29]

[a] American College of Radiology Breast Imaging Reporting and Data System.

In view of this strong relationship, it is important to include breast density—ideally measured in an objective reproducible way—in future risk models.[21,22,23,24] To date, most of the widely used breast cancer risk models have not taken breast density into account.[25]

Mammographic density is associated with a masking risk for breast cancer detection with mammography, as breast lesions and dense tissue have similar x-ray attenuation characteristics.[26] Thus, women with dense breasts risk lesions not being found during mammography, or only being detected at a later stage than they would be in non-dense breasts. They are at increased risk of interval breast cancers, which are often detected symptomatically between regular screening appointments.[27]

Breast density is also an independent risk factor for *de novo* development of breast cancer, as shown by the fact that women with dense breasts have an increased risk of having cancer detected at screening.[18,20] The risk associated with density remains elevated for up to at least 10 years after the initial determination of density.[19] The underlying reason for the increased risk may be because dense tissue corresponds to a greater amount of epithelium[28] (where most breast cancers arise)[29] as well as factors that can promote proliferation and migration of cancer cells.[30]

Risk as a Means of Triage

For decades, mammography has been the primary screening modality because it is the only method to have demonstrated a mortality reduction.[31] Most screening programs are age-based and targeted for average-risk women.[32] More recently, there is great interest in personalized screening programs that selectively incorporate other modalities to find cancers at an early stage in women for whom mammography is less effective.[33] The question becomes how to best identify those women.

Practitioners are now discussing changes to how breast surveillance is offered to women. First, each woman's personal breast cancer risk[34] is assessed. Then, clinicians evaluate how effective different screening modalities and schedules will be for her, based on existing guidelines and offer her the modalities and screening intervals that best balance early detection and cost.[1,7]

MRI Screening for Women at High Risk

Breast MRI has much higher sensitivity than mammography, which has led the American Cancer Society (ACS) and the UK National Institute for Health and Care Excellence (NICE) to recommend MRI screening for women at high risk.

Compared to mammography, MRI is a costly and time-consuming procedure and in some studies, identifies more false-positive cases than mammography. Thus, it is currently not used for population-based screening.[35] Instead, many screening programs limit the use of MRI to those at high risk of developing breast cancer. In this manner, MRI can provide a cost-effective, clinically beneficial approach.

Some US insurers require ≥20% lifetime risk of breast cancer using a model that is "largely dependent on family history" (which is specified by ACS guidelines to mean "capable of pedigree analysis of first-degree and second-degree relatives on both the maternal and paternal sides"); they also reimburse for MRI procedures when that risk is attributed to other factors.[7,36] Carriers of a BRCA1/2 mutation (or first-degree relatives of carriers, if the person has not been tested themselves), women who have received radiation therapy to the chest at ages 10 y to 30 y, or patients (or first-degree relatives of patients) with Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndromes are also considered to be at high risk under the ACS guidelines.

It should be noted that ultrasound is an additional modality often used for supplementary screening, particularly in women with dense breasts.[37] However, ACS does not mention ultrasound in relation to screening of women at high risk,[7] while NICE recommends it only when screening MRI is not suitable.[1] Thus, ultrasound screening is not discussed in this paper.

Tyrer-Cuzick v8 Risk Model

The TC model estimates the absolute risk of developing invasive breast cancer, as well as the probability of carrying a high-risk BRCA1/2 mutation in women aged 40–84 y. It was originally developed to assess the appropriateness of tamoxifen administration as a preventive therapy in high-risk women, based on personal and family history risk factors.[38] It has been widely accepted by insurers because it fulfills their stated criteria for family history.[36] The model is only valid for women with no personal history of breast cancer.

The eighth version of the TC model (TC8) now includes mammographic density[39] as a personal risk factor, as shown in figure 1. Volpara believes that the presence of mammographic density as an input to the model will heighten awareness of breast density as a significant risk factor.

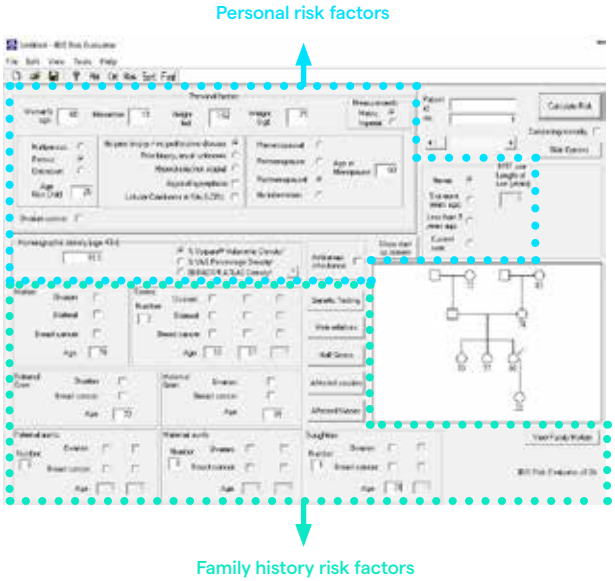

Figure 1. Personal and family history risk factor inputs to the Tyrer-Cuzick v8 risk model.

Primary Inputs

The most important breast cancer risk factors are age and being female. TC8 is for female breast cancer and requires age as an input; all other inputs are optional. If a risk factor is unknown, the user enters "?" for that value and the model uses a population average value for that factor[40]—for family history, this corresponds to assuming an unaffected relative with unknown age, but a "u" may be entered when it is unknown whether the relative has ever been diagnosed with breast cancer.

As more information is provided the model becomes more personalized, and better reflects a woman's personal risk.

The relative risk used for each factor comes from large epidemiological cohort and case-control studies.[38] TC8 calculates genetic risk in terms of the likelihood of carrying any high-penetrance BRCA1/2 gene mutations or a single lower-penetrance dominant "unknown gene" that is inferred from the family history but is not specifically identified. The personal risk and genetic risk based on family history are then combined with population rates of incidence of first breast cancer to produce an estimate of lifetime and 10-year absolute risk (note that the latter period is user-adjustable). Results of BRCA1/2 genetic testing, if available, are also included.

The user must select one of three calibration populations used in TC8 (the United Kingdom, Sweden, or Slovenia). This is accomplished by most closely matching the local rates of first incidence of breast cancer by age to those in the available calibration populations. For the United States, the UK population is the best match.[41] Competing mortality from causes other than breast cancer can also be taken into account for risk calculations.

Mammographic Density

TC8 incorporates three alternative inputs of mammographic density (table 1):[40]

- **BI-RADS ATLAS Density (BI-RADS)** – the human-assessed density according to the ACR BI-RADS Atlas 5th Edition. BI-RADS is commonly used in the clinic and requires breast composition to be classified into one of four categories.[42]
- **% VAS Percentage Density (% VAS)** – a visual density score from a human assessment of percentage dense area. The user estimates % VAS on a continuous scale of 0 to 100%.[23]
- **% Volpara® Volumetric Density (% Volpara)** – the volumetric breast density value from the Volpara® TruDensity™ clinical function, a computer-based measure of breast density that is both automated and objective.[43]

Table 1. Comparison of density inputs to TC8.

Method	Type	Type	Requires
BI-RADS	Area	Discrete (4 values)	Trained reader
% VAS	Area	Continuous percentage	Two trained readers
% Volpara	Volume	Continuous percentage	Computer software

All three measures of breast density have a positive relationship with increased risk,[10,44] but vary in their clinical implementation.

The BI-RADS and % VAS methods rely on subjective human assessment and have considerable inter- and intra-observer variability.[45,46] The VAS method is area based. Clinicians using the BI-RADS density measure also tend to estimate density based on area, even though the BI-RADS Atlas suggests that estimations should be volumetric in nature.[42]

The % VAS and % Volpara methods assess breast density on a continuous scale, which has the advantage of producing a continuous output that can be expected to better differentiate women's risk.

Volpara provides the additional unique advantages of being fully automated and objective.

Primary Outputs

There are two primary outputs of TC8 (figure 2). The first is an estimate of an individual woman's absolute risk of developing breast cancer over her remaining lifetime, and over the next 10 years. The average population-level risk of the disease for a woman of the same age is shown for comparison.

The second output uses family history and any provided information on genetic testing in the woman or her family members to estimate the risk of the woman carrying a high-risk BRCA1 or BRCA2 mutation. The population-level risk of being a mutation carrier is also shown for comparison.

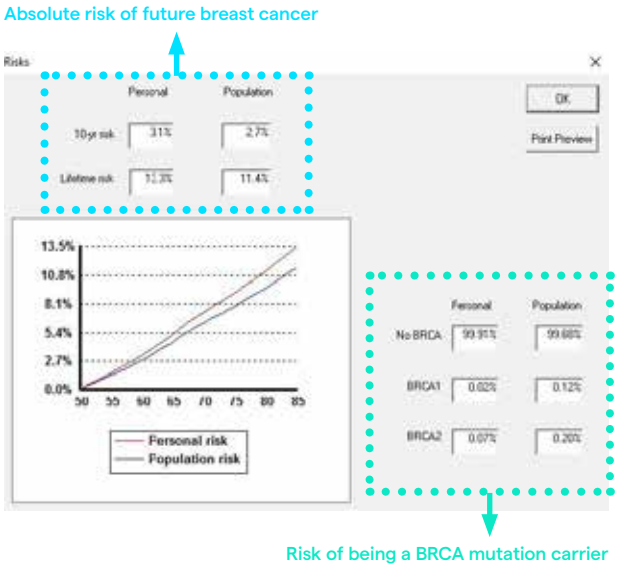

Figure 2. Outputs of the TC8 risk model.

Risk Assessment in Practice

The absolute risk of future breast cancer is used to classify women as "average," "moderately increased," or "high" risk. However, the choice of the thresholds for these categories is not uniform, and different thresholds have been used in the United States and United Kingdom in making recommendations for supplementary screening and risk prevention measures (table 2 and table 3).

Table 2. Breast cancer risk thresholds used by the US ACS and NCCN, and US-specific recommendations for at-risk women.

US GUIDELINES

Risk level (US)	Risk percentage	Consider for
High	Lifetime risk ≥20%	• Annual MRI from age 30 y[7] • Annual mammography from age 30 y[5]
	5-year risk ≥3%, for tamoxifen administration	• Tamoxifen preventive therapy (if 5-year risk ≥3%)[2]
Moderately increased	Lifetime risk 15–20%	• Annual mammography ages 40–79 y[5]
Average	Lifetime risk <15%	• Annual mammography ages 45–54 y; opportunity for annual screening ages 40–45 y; biennial screening age ≥55 y[7]

Table 3. Breast cancer risk thresholds used by the UK NICE and UK-specific recommendations for at-risk women.[1]

UK GUIDELINES

Risk level (UK)	Risk percentage	Consider for
High	Lifetime risk from age 20 y:≥30% 10-year risk ages 40–50 y: >8%	• Annual mammography, age 40–59 y for women with no personal history of breast cancer and with 30% or lower probability of being a BRCA or TP53 mutation carrier (women with a higher carrier probability qualify for annual MRI surveillance). Consider annual mammography from age 30 y • Annual MRI for women aged 30–49 y with a personal history of breast cancer who remain at high risk • Continued screening past age 70 y • Preventive therapy recommended—tamoxifen, raloxifene, or anastrozole (if postmenopausal)
Moderately increased	Lifetime risk from age 20 y: 17% up to 30% 10-year risk ages 40–50 y: 3-8%	• Annual mammography, age 40–49 y (consider annual mammography to age 59 y) • Continued screening past age 60 y • Preventive therapy discussed—tamoxifen, raloxifene, or anastrozole
Average	Lifetime risk from age 20 y: <17% 10-year risk ages 40–50 y: <3%	• Triennial mammography, age 50–70 y

Although the TC model is often used for assessing risk, NICE guidelines mention BOADICEA and the Manchester scoring system as examples of risk assessment tools for assessing the probability of BRCA1/2 mutations. The BOADICEA model allows a more detailed family history including information on cancer histology and relatives diagnosed with prostate or pancreatic cancer. TC is a recognized method, at least as a precursor to using the BOADICEA model.[1,47] Women who have a 10% chance of being a BRCA1/2 mutation carrier are offered genetic testing, and those with a 30% chance of being a carrier are eligible for annual mammography and MRI.

The Impact of Breast Density on Risk Assessment with TC8

The risk prediction output from TC8 differs depending on the breast density measure used.

Figure 3 shows an example of how different alternative inputs of mammographic density affect lifetime risk prediction in TC8 for a hypothetical average 50-year-old woman (Subject A) with no family history of breast cancer and population average values for all the other risk factors.

This example assumes UK-specific rates of breast cancer and accounts for competing mortality. If Subject A has extremely dense breasts, the maximum lifetime risk predicted would be as follows:

- 13.4% if she were determined to be a BI-RADS d—considered "average risk" by ACS guidelines.
- 20.7% if she had % VAS of 100%—considered "high risk" by ACS guidelines.
- 20.0% if she had % Volpara of 18.5% or higher—also considered "high risk" by ACS guidelines.

Note that the lifetime risk would increase or decrease according to age or inputs of other risk factors.

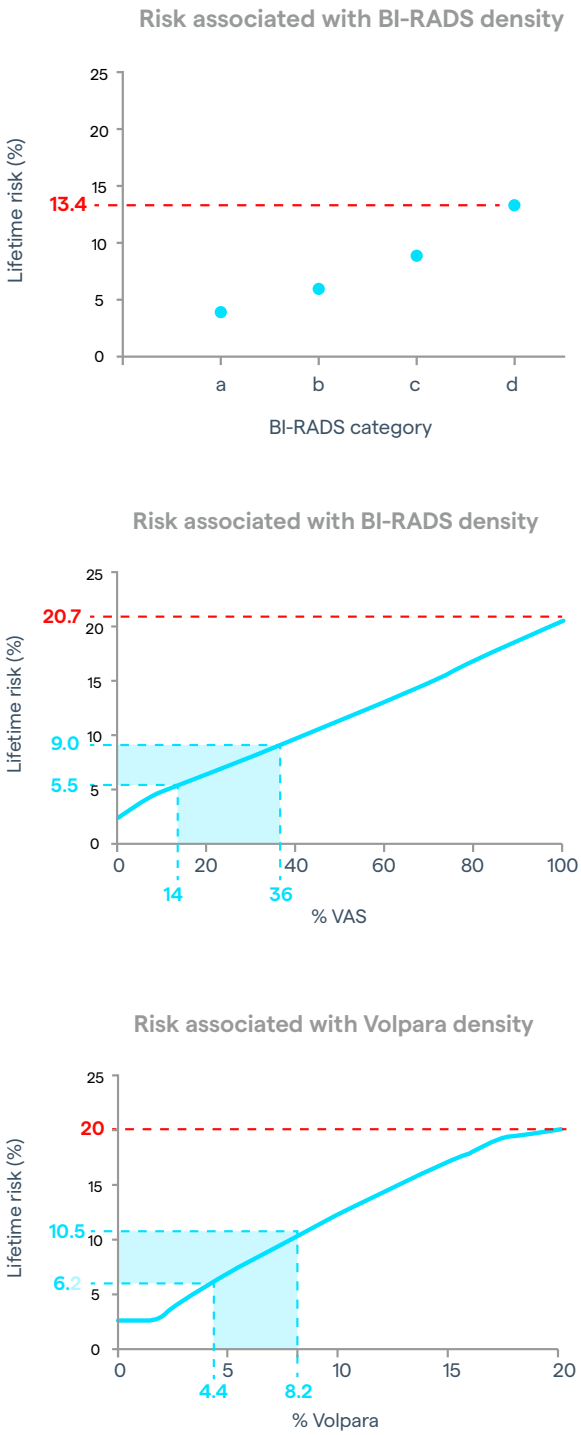

Figure 3. Comparison of lifetime risk for different density methods. Maximum risk is indicated by red lines. The blue boxes denote the range of density for the intermediate 50% of women (25th to 75th percentiles) in PROCAS.[48] Thus, the expected range of predicted risk for these women is expected to fall in the range indicated by the boxes.

Coarseness and Range of Density Values

A limitation of using BI-RADS for risk assessment is that it fails to distinguish between low and high "d" density, which most clinicians agree are likely to carry different risks. Although not yet proven, continuous measures of density may be preferred for providing more accurate risk prediction.

The range of mammographic density values differs significantly between volumetric and area-based density estimates; the volumetric estimates are always lower. The % Volpara values are rarely above 20%, whereas much higher levels are seen with % VAS, which can be up to 100%. The TC8 model accommodates the breadth of density values found in the population for each alternative input.

Breast Density, Risk, and Clinical Decisions

It is common practice to provide additional screening with MRI to women found to be at high risk. As we have learned, the addition of mammographic density as an input to the TC8 model can increase not only an individual woman's risk, but also the fraction of women offered supplemental screening. Also, the form of mammographic density input used in TC8 affects the fraction of women found to be at high risk.

Suppose Subject A had the very highest breast density; if she were evaluated as a BI-RADS d, TC8 would not consider her to be at high risk. Because BI-RADS d encompasses a wide range of % Volpara, all values 15.5% and above, women with very extreme breast density (especially those with a "high" BI-RADS d) will not be considered at high risk with TC8 if BI-RADS is used instead of a continuous density measure such as % VAS[†] or % Volpara (figure 4).

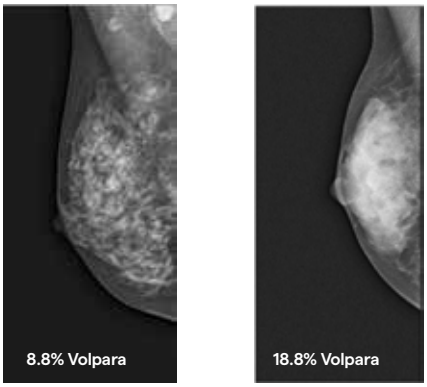

Figure 4. Two BI-RADS d mammograms with very different % Volpara measures.

One possible effect of trying to improve the stratification of women according to their risk is that more women may be directed to screening MRI. The choice of % Volpara as the mammographic density input in TC8 is a practical choice that may ensure that women at truly high risk are offered that service.

Case Study: Breast Screening Facility, NC, USA[‡]

Data from a breast screening facility in North Carolina, USA (figure 5) showed that the inclusion of breast density in TC8 increased the fraction of women who would be considered at high risk (assuming a population-average BMI).

In this study, 1856 women presented for screening. Their age and % Volpara were entered into TC8 with the following assumptions:

- no family history of breast or ovarian cancer
- first breast cancer incidence rates similar to those in the UK

All other risk factors were left as unknown, assuming population average values. Competing mortality was selected in the TC8 model to produce a more conservative estimate of risk.

Without % Volpara, all the women in this study would be considered "average risk". The addition of % Volpara as a TC8 input classified 4.3% of the population as "high risk," qualifying them for annual MRI screening due to a lifetime risk of 20% or greater.

[†] As VAS is not automated, it is impractical for widespread clinical use and therefore not discussed in further detail.

[‡] From internal Volpara data, on file.

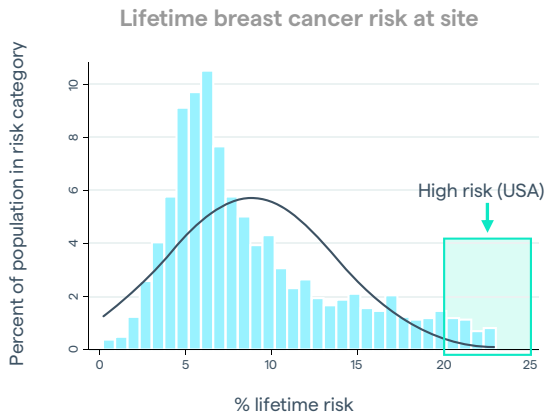

Figure 5. Distribution of TC8 lifetime risk within a US screening population.

Summary

Tyrer-Cuzick v8 (IBIS Breast Cancer Risk Evaluation Tool) is based on Tyrer-Cuzick v7, a risk model that has worldwide acceptance and is widely recognized by regulatory and advisory bodies. It has been shown to improve prediction accuracy[13] and better guide the care of women at increased risk of breast cancer relative to other models. Including breast density in the model strengthens its ability to provide decision support for supplementary screening and risk minimization strategies. A *continuous* breast density method in the model is likely to strengthen its ability to differentiate women who are at varying levels of risk.

Using % Volpara as the automated mammographic density input to TC8 is expected to have a major influence on refining a woman's predicted risk of developing breast cancer.

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Contact

info@volparahealth.com
support@volparahealth.com
volparahealth.com

US +1 855 607 0478
AUS 1800 370 623
NZ 0800 444 148

Europe +44 203 051 1029
Global +64 4 499 6029

Connect

@VolparaHealth @volpara Volpara Health

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