

A large, light blue abstract shape, resembling a stylized 'V' or a large arrow pointing right, is positioned on the left side of the page.

WHITE PAPER

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

2019

Christina Robert, PhD
Clinical Marketing Specialist

Julian Marshall
Chief Knowledge Officer

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

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-performing¹³ 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 risk¹⁷ 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 epithelium²⁸ (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 risk³⁴ 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

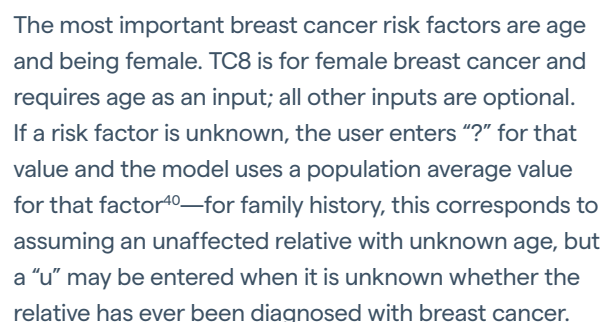
Breast MRI has much higher sensitivity than mammography, which has led the American Cancer Society (ACS) and the UK National Institute for Health and Care Excellence (NICE) to recommend MRI screening for women at high risk.

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 $\geq 20\%$ 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.

The eighth version of the TC model (TC8) now includes mammographic density³⁹ 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.



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.

- **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.

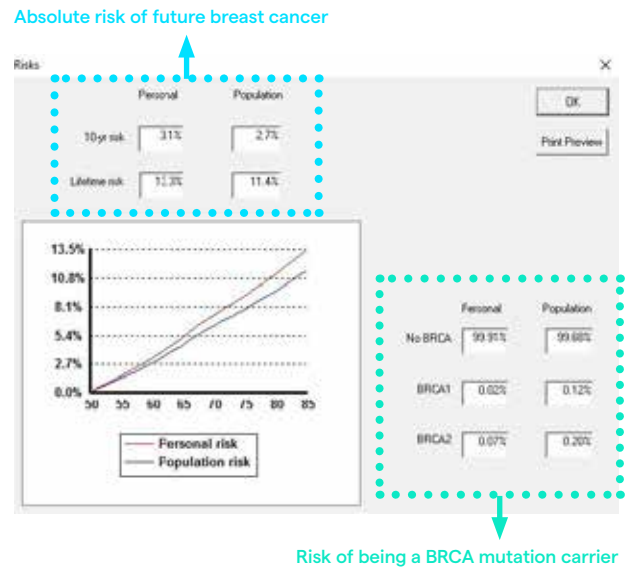


Figure 2. Outputs of the TC8 risk model.

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 $\geq 20\%$	<ul style="list-style-type: none"> Annual MRI from age 30 y⁷ Annual mammography from age 30 y⁵
	5-year risk $\geq 3\%$, for tamoxifen administration	<ul style="list-style-type: none"> Tamoxifen preventive therapy (if 5-year risk $\geq 3\%$)²
Moderately increased	Lifetime risk 15–20%	<ul style="list-style-type: none"> Annual mammography ages 40–79 y⁵
Average	Lifetime risk $< 15\%$	<ul style="list-style-type: none"> Annual mammography ages 45–54 y; opportunity for annual screening ages 40–45 y; biennial screening age ≥ 55 y⁷

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: $\geq 30\%$	<ul style="list-style-type: none"> 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
	10-year risk ages 40–50 y: $> 8\%$	<ul style="list-style-type: none"> 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%	<ul style="list-style-type: none"> Annual mammography, age 40–49 y (consider annual mammography to age 59 y)
	10-year risk ages 40–50 y: 3–8%	<ul style="list-style-type: none"> 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: $< 3\%$	<ul style="list-style-type: none"> 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.

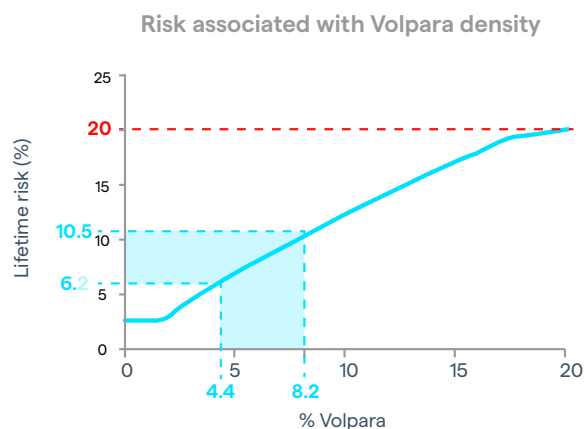
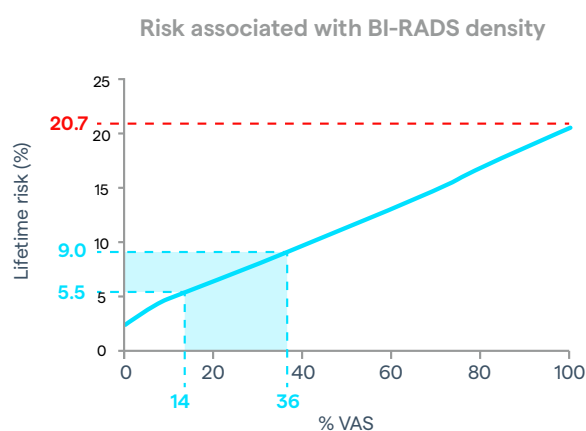
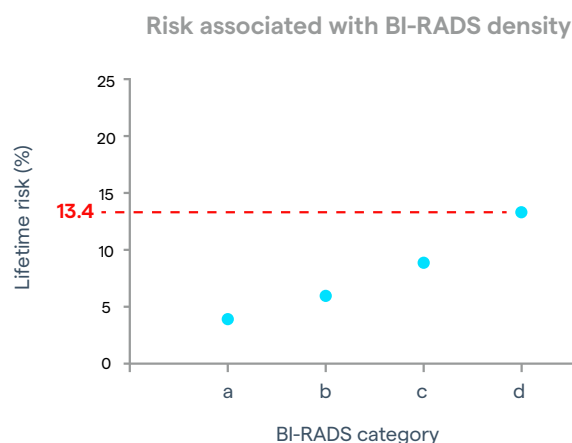


Figure 3. Comparison of lifetime risk for different density methods. Maximum risk is indicated by red lines. The blue boxes denote the range of density for the intermediate 50% of women (25th to 75th percentiles) in PROCAS.⁴⁸ Thus, the expected range of predicted risk for these women is expected to fall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

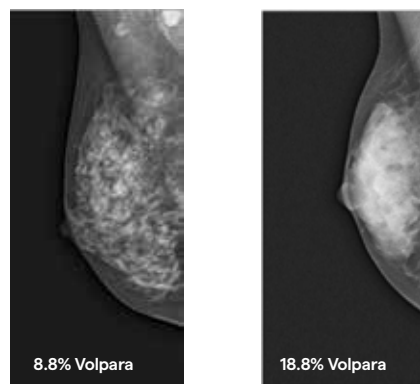


Figure 4. Two BI-RADS d mammograms with very different % Volpara measures.

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.

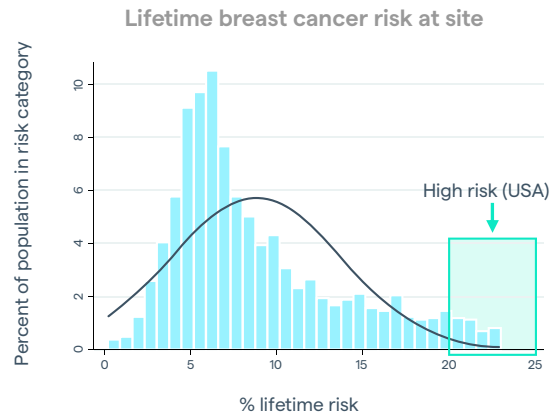


Figure 5. Distribution of TC8 lifetime risk within a US screening population.

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 accuracy¹³ 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.

- ¹ NICE, The National Institute for Health and Care Excellence CG164 *Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer*. 2013 [cited 2016 23 May]; Available from: <https://www.nice.org.uk/guidance/cg164>.
- ² USPSTF, US Preventive Services Task Force Recommendation Statement Medications for Risk Reduction of Primary Breast Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement. 2016 [cited 2016 25 Nov]; Available from: <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-medications-for-riskreduction>.
- ³ Cuzick, J., et al., *Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial*. *Lancet*, 2014. 383(9922): p. 1041-8.
- ⁴ Moyer, V.A., *Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement*. *Ann Intern Med*, 2014. 160@: p. 271-81.
- ⁵ Kim-Sing, C., L. Weir, and U. Kuusk, *Breast cancer risk management for moderate-risk and high-risk women*. *BCM J*, 2004. 46@: p. 397-401.
- ⁶ NCCN, National Comprehensive Cancer Network Breast Cancer Risk Reduction. 2016 [cited 2016 18 Nov]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf.
- ⁷ Smith, R.A., et al., *Cancer screening in the United States, 2016: A review of current American Cancer Society guidelines and current issues in cancer screening*. *CA Cancer J Clin*, 2016. 66@: p. 96-114.
- ⁸ Tice, J.A., et al., *Breast Density and Benign Breast Disease: Risk Assessment to Identify Women at High Risk of Breast Cancer*. *Journal of Clinical Oncology*, 2015. 33(28): p. 3137-43.
- ⁹ Foulkes, W.D., *Inherited Susceptibility to Common Cancers*. *New England Journal of Medicine*, 2008. 359(20): p. 2143-2153.
- ¹⁰ Engmann, N.J., et al., *Population-attributable risk proportion of clinical risk factors for breast cancer*. *JAMA Oncol*, 2017. 3@: p. 1228-36.
- ¹¹ Amir, E., et al., *Assessing women at high risk of breast cancer: a review of risk assessment models*. *J Natl Cancer Inst*, 2010. 102(10): p. 680-91.
- ¹² Meads, C., et al., *A systematic review of breast cancer incidence risk prediction models with meta-analysis of their performance*. *Breast Cancer Res Treat*, 2012. 132@: p. 365-77.
- ¹³ Amir, E., et al., *Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme*. *J Med Genet*, 2003. 40(11): p. 807-14.
- ¹⁴ Wolfe, J.N., *Risk for breast cancer development determined by mammographic parenchymal pattern*. *Cancer*, 1976. 37@: p. 2486-92.
- ¹⁵ Destounis, S., et al., *Qualitative versus quantitative mammographic breast density assessment: applications for the US and abroad*. *Diagnostics (Basel)*, 2017. 7@: p. E30.
- ¹⁶ Gastounioti, A., E.F. Conant, and D. Kontos, *Beyond breast density: a review on the advancing role of parenchymal texture analysis in breast cancer risk assessment*. *BCR*, 2016. 18: p. 91.
- ¹⁷ McCormack, V.A. and I. dos Santos Silva, *Breast density and parenchymal patterns as markers of breast cancer risk: a metaanalysis*. *Cancer Epidemiol Biomarkers Prev*, 2006. 15@: p. 1159-69.
- ¹⁸ Kerlikowske, K., *The mammogram that cried Wolfe*. *N Engl J Med*, 2007. 356@: p. 297-300.
- ¹⁹ Byrne, C., et al., *Mammographic features and breast cancer risk: effects with time, age, and menopause status*. *J Natl Cancer Inst*, 1995. 87(21): p. 1622-9.
- ²⁰ Boyd, N.F., et al., *Mammographic density and the risk and detection of breast cancer*. *N Engl J Med*, 2007. 356@: p. 227-36.
- ²¹ Tice, J.A., et al., *Mammographic breast density and the Gail model for breast cancer risk prediction in a screening population*. *Breast Cancer Res Treat*, 2005. 94@: p. 115-22.
- ²² Chen, J., et al., *Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density*. *J Natl Cancer Inst*, 2006. 98(17): p. 1215-26.
- ²³ Warwick, J., et al., *Mammographic breast density refines Tyrer-Cuzick estimates of breast cancer risk in high-risk women: findings from the placebo arm of the International Breast Cancer Intervention Study I*. *Breast Cancer Res*, 2014. 16@: p. 451.
- ²⁴ Brentnall, A.R., et al., *Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening cohort*. *Breast Cancer Res*, 2015. 17@: p. 147.
- ²⁵ Nayak, L., et al. (2016). "Impact of breast density legislation on breast cancer risk assessment and supplemental screening: a survey of 110 radiology facilities." *Breast J* 22@: 493-500.
- ²⁶ Johns, P.C. and Yaffe, M.J., *X-ray characterisation of normal and neoplastic breast tissues*. *Phys Med Biol*, 1987. 32@: p. 675-95.
- ²⁷ Destounis, S., et al., *Using volumetric breast density to quantify the potential masking risk of mammographic density*. *Am J Roentgenol*, 2017. 208@: p. 222-7.
- ²⁸ Li, T., et al., *The association of measured breast tissue characteristics with mammographic density and other risk factors for breast cancer*. *Cancer Epidemiol Biomarkers Prev*, 2005. 14@: p. 343-9.
- ²⁹ Blanpain, C., *Tracing the cellular origin of cancer*. *Nat Cell Biol*, 2013. 15@: p. 126-34.
- ³⁰ Huo, C.W., et al., *Mammographic density-a review on the current understanding of its association with breast cancer*. *Breast Cancer Res Treat*, 2014. 144@: p. 479-502.
- ³¹ Lauby-Secretan, B., et al., *Breast-cancer screening — viewpoint of the IARC working group*. *NEJM*, 2015. 372(24): p. 2353-58.
- ³² American Cancer Society. *American Cancer Society Breast Cancer Screening Guideline*. [cited 2017 13 Nov]; Available from <https://www.cancer.org/latest-news/special-coverage/american-cancer-society-breast-cancer-screening-guidelines.html>.
- ³³ Drukteinis, J.S., et al., *Beyond mammography: new frontiers in breast cancer screening*. *Am J Med*, 2013. 126@: p. 472-9.

³⁴ Evans, D.G. and A. Howell, *Can the breast screening appointment be used to provide risk assessment and prevention advice?* Breast Cancer Res, 2015. 17: p. 84.

³⁵ Saslow, D., et al., *American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography*. CA Cancer J Clin, 2007. 57(2): p. 75–89.

³⁶ Blue Cross Blue Shield. *Medical policy: MRI of the breast*. 2016 [cited 2017 10 April]; Available from: https://www.empireblue.com/medicalpolicies/policies/mp_pw_a053263.htm.

³⁷ Tagliafico, A.S., et al., *Adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts: interim report of a prospective comparative trial*. J Clin Oncol, 2016.

³⁸ Tyrer, J., et al., *A breast cancer prediction model incorporating familial and personal risk factors*. Stat Med, 2004. 23(2): p. 1111–30.

³⁹ Cuzick, J. *IBIS Breast Cancer Risk Evaluation Tool*. [cited 2017 7 March]; Available from: <http://www.ems-trials.org/riskevaluator/>.

⁴⁰ Cuzick, J. and A. Brentnall, *Models for assessment of breast cancer risk, in DI Europe*. 2016. p. 54–5.

⁴¹ IARC, International Agency for Research on Cancer, *GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012*. [cited 2017 8 May]; Available from: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx.

⁴² American College of Radiology. *BI-RADS® Atlas*, 5th ed.; American College of Radiology: Reston, VA, USA, 2013.

⁴³ Highnam, R., et al., *Robust breast composition measurement—Volpara™*, in *Lecture Notes in Computer Science*, J. Marti and A. Oliver, Editors. 2010, Springer Berlin Heidelberg: Berlin, Heidelberg. p.342–9.

⁴⁴ Astley, S., et al. *A comparison of four methods of mammographic density measurement in the UK Predicting Risk of Cancer at Screening (PROCAS) study*. in *24th Biennial congress of the European association for cancer research*. 2016. Manchester, UK.

⁴⁵ Sergeant, J.C., et al., *PB.17: Inter-observer agreement in visual analogue scale assessment of percentage breast density*. Breast Cancer Research: BCR, 2013. 15 (Suppl 1): p. P17.

⁴⁶ Sprague, B.L., et al., *Variation in Mammographic Breast Density Assessments Among Radiologists in Clinical Practice: A Multicenter Observational Study Variation in Mammographic Breast Density Assessments Among Radiologists*. Annals of Internal Medicine, 2016. 165(2): p. 457–64.

⁴⁷ UK Genetic Testing Network. *Developing testing criteria for familial breast and ovarian cancer: incorporating NICE guidelines*. 2014 [cited 2017 26 April]; Available from: https://ukgtn.nhs.uk/fileadmin/uploads/ukgtn/Documents/Resources/Library/Reports_Guidelines/UKGTN%20breast%20cancer%20Final%20161014.pdf.

⁴⁸ Evans, D.G., et al., *Programme grants for applied research, in Improvement in risk prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme and family history clinics: a dual cohort study*. 2016, NIHR Journals Library.

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