Mammographic Breast Density: A New Era for Breast Cancer Screening and Prevention

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This article discusses how high mammographic breast density lowers the sensitivity of breast cancer screening and increases breast cancer risk.

Declaration of interest

Dr Birrell is the Executive Director and Chief Medical Officer of Wellend Health, a company with a patient treatment program incorporating hormonal therapeutics demonstrated to reduce high mammographic breast density. He is also the Chief Medical Officer and Co-Founder of HAVAH Therapeutics, Wellend Health's sister company. HAVAH Therapeutics' lead drug candidate is currently undergoing clinical trials into the reduction of mammographic breast density and breast cancer prevention.

Introduction

High mammographic breast density is one of the strongest independent risk factors for the development of breast cancer.[1] It is estimated that over 40% of Australian women aged forty to sixty-five years have high mammographic breast density,[2] and these women are two to six times more likely to get breast cancer than those with low mammographic breast density.[3] Reductions in breast density significantly reduce breast cancer risk. For example, using tamoxifen to lower mammographic breast density by greater than 10% translates to a greater than 60% decrease in breast cancer risk.[4]

Take Home Messages

- High mammographic breast density lowers the sensitivity of mammography.
- High mammographic breast density is a major independent risk factor for breast cancer.
- High mammographic breast density increases breast tissue instability.
- Lowering mammographic breast density can result in a significant decrease in breast cancer risk.
- Lowering mammographic breast density can result in improved imaging sensitivity.
- Menopause hormone therapy should be used with caution in women with high mammographic breast density.
- Increasing mammographic breast density in response to menopause hormone therapy should be monitored with an annual mammogram.

In Australia identifying women with high mammographic breast density is not yet routine; only some private radiology services and BreastScreen WA currently report breast density as part of their service. However, BreastScreen Australia is currently investigating how to incorporate this information into their reporting procedures.[5,6]

Technological advances have often driven our understanding of disease and lead to significant improvements in healthcare. From the first X-ray in 1895 to today's positron emission tomography (PET) scans, medical technology has been evolving. Digital mammography, 3D tomosynthesis and breast density volumetric measurement software (i.e., Quantra™ and Volpara™) have brought together all of the variables necessary to measure, assess and analyse mammographic breast density.[7] While there have been major advances in the treatment of breast cancer in the last thirty years, there has been little change in breast screening.

Is It Now Time to Overhaul Breast Cancer Screening to Improve Detection Rates?

What is Mammographic Breast Density?

Mammographic breast density (MD) is the percentage of total breast volume that is active glandular and stromal tissue (distinct from fat), as measured by a mammogram; the higher the fat concentration in the breast, the lower the mammographic breast density. It is important to note that breast density cannot be determined by the size, shape or palpation of a breast. It can only be assessed by a mammogram, or similar radiological imaging.

High mammographic breast density:

- Is a strong risk factor for developing breast cancer, even stronger than a family history;[8] and the higher the density, the greater the risk.[3]
- Makes mammograms less sensitive as a cancer detection method; at the highest MD levels, mammograms have less than a 50% sensitivity to detect breast cancer.[9]
- Is the most common reason for false negative results of mammograms.[9]
- Is the number one reason for interval breast cancers in screening services.[9]

What Causes High Mammographic Breast Density?

The incidence of high mammographic breast density appears consistent across many geographic regions, with a few ethnic variations.[10] In one study, the percentage of mammographic breast density was found to be high among native Hawaiians and Japanese women in Hawaii, and lowest among Norwegian women.[10] Breast density is generally higher in younger women and declines with age. If mammographic breast density does not decline at the time of menopause, it is likely to remain high for the remainder of a woman's life.[1]

Risk factors associated with high mammographic breast density include:

1. Genetic factors: High mammographic breast density is a strongly inherited trait, although environmental and reproductive factors can modify this inheritance.[11]
2. Exogenous hormone usage, especially prolonged oral contraception (particularly when commenced at an early age)[12] and hormone replacement therapy.[13]
3. Being nulliparous or having pregnancies later in life.[14]
4. Fertility treatment, especially exposure to *in vitro* fertilisation medications.[15]

Most of these factors point to an excess of oestrogen over androgens and in affected women, this biased ratio towards oestrogen occurs throughout a woman's reproductive life.

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Although the manifestation and promotion of breast cancer is predominantly post-menopausal, there is evidence that the initiation of malignancy commences at a much younger age, and high mammographic breast density increases breast tissue instability.[16,17]

Measuring Mammographic Breast Density

Radiologist Scoring of Mammograms: The American College of Radiology BI-RADS® ATLAS

The Breast Imaging Reporting and Data System (BI-RADS®), produced by the American College of Radiology, provides a systematic way of reporting mammographic breast density. Figure 1 illustrates the BI-RADS® system with BI-RADS® 'A' is the lowest score and 'D' is the highest score; however, there is more descriptive analysis within each category describing the distribution of the mammographic breast density within the breast.

There are inherent problems with the BI-RADS® system, including the significant inter-observer variability; the lack of reproducibility between mammography equipment and the fact that no further calculation of density is undertaken once the BI-RADS® 'D' score is given. It is now known that within this extreme category there is a wide range that ideally warrants further categorisation.

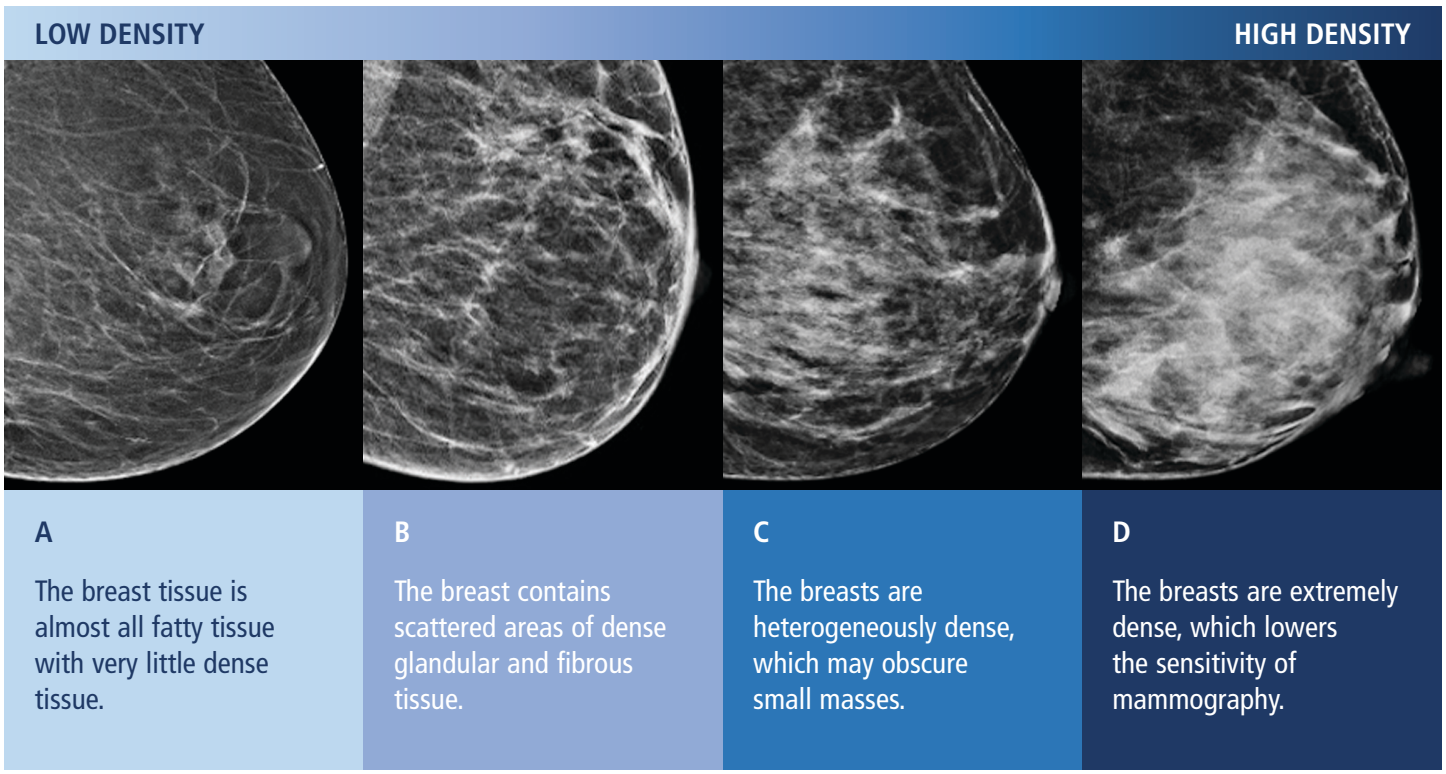

Figure 1. Breast mammograms illustrating the BI-RADS® reporting system for mammographic breast density ratings A, B, C and D.
*(Permission for use has been granted from the individual patients concerned).

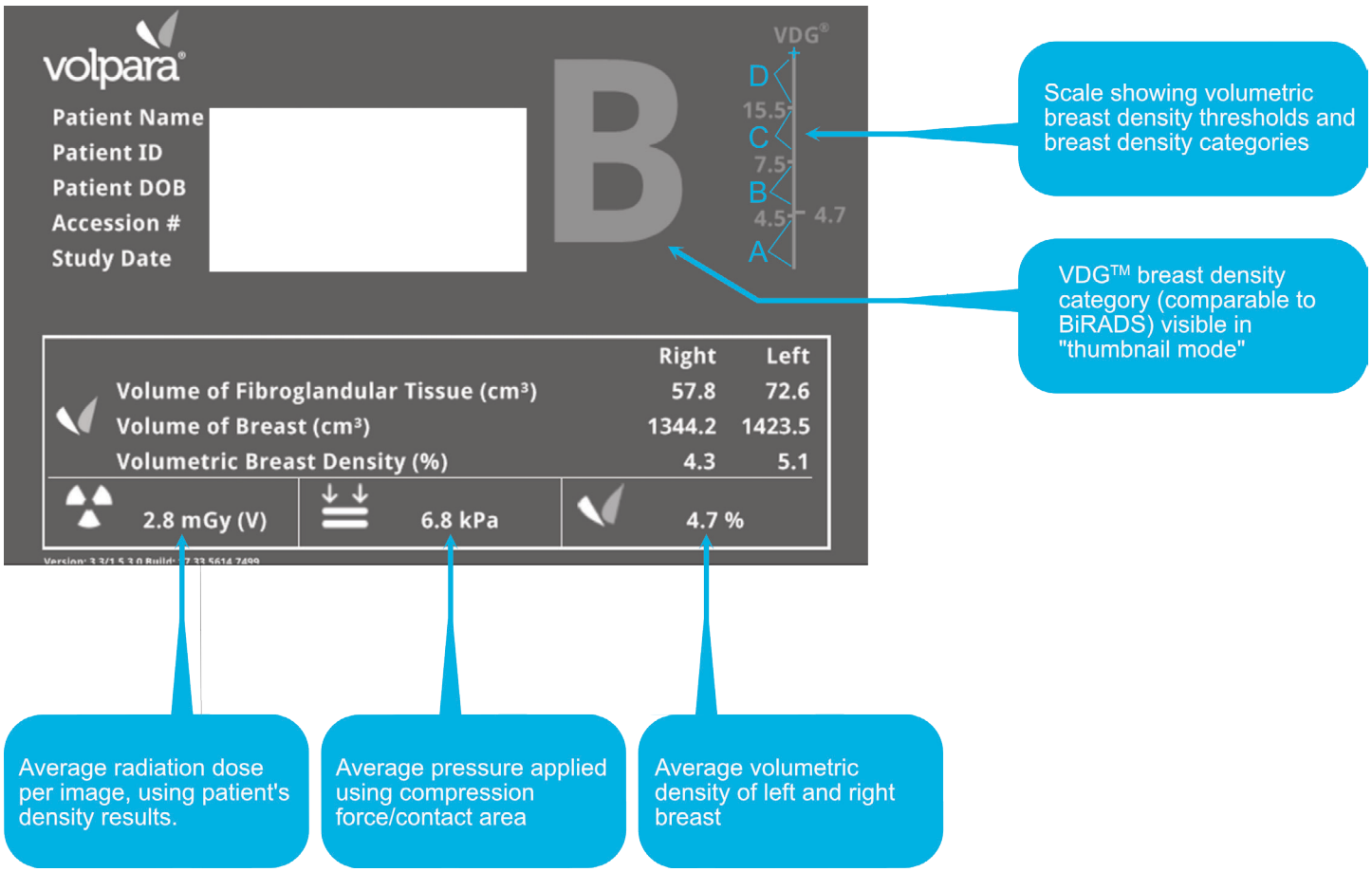

Figure 2. Output from the VolparaDensity™ 3D imaging analysis tool. (Image reprinted with permission of Volpara Solutions Ltd).

Three Dimensional Imaging Analysis

Automated three-dimensional (3D) imaging analysis represents a major advance in screening for women with high mammographic breast density. Although radiologists can use two dimensional (2D) mammograms to estimate the percentage of breast tissue that is dense, there is inevitable imprecision in using 2D information to assess a 3D structure. This would result in a general inaccuracy, so women at high risk cannot be reliably identified in a systematic way.

Digital mammogram data is processed in 3D imaging analysis algorithms using specialised software that assesses the percentage of tissue volume that is fibroglandular. However, only a small number of Australian centres currently use 3D imaging analysis at this time. The outcome is automated, thus removing the issue of inter-observer variability. Figure 2 shows typical output including volumetric breast density thresholds and categories. As there is increasing awareness of the importance of mammographic breast density, it is probable that this new technology will soon be used in both diagnostic centres and screening services.

The Problem with High Mammographic Breast Density

Masking Effect

High mammographic breast density leads to a significant reduction in the ability to detect breast cancer. Indeed, when a woman's breast density is at the 'extreme' level, the mammogram has lost 50% of its power to detect malignancy. A large study of approximately 250,000 women undergoing screening demonstrated a remarkable reduction in the sensitivity of mammography to detect breast cancer. The results of this study, which used both BI-RADS® density categories and 3D imaging analysis, showed that sensitivity of detection was significantly reduced in the high mammographic breast density categories (Figure 3).[7]

High mammographic breast density was also the most important variable in predicting a cancer occurring in the interval to the next mammogram. This points to the extreme masking effect that occurs in the presence of high mammographic breast density. A recent report from the Dutch screening programme found an eight-fold increased interval cancer risk in those with high volumetric density as determined by 3D imaging analysis.[18]

Increased Breast Cancer Risk

Mammographic breast density does not just mask breast cancer; high mammographic breast density is also associated with the risk of breast tissue instability and the genesis of malignancy.[16]

It has been well established that the parameters of breast density correlate with breast cancer risk, with a two- to six-fold increase in risk between women with high versus low density.[3] This magnitude of risk is only topped by age and BRCA 1 or 2 mutations.[7] A meta-analysis that included forty-two studies (14,000 cases and 226,000 controls) found that greater mammographic breast density was consistently associated with an increased risk of breast cancer.[20]

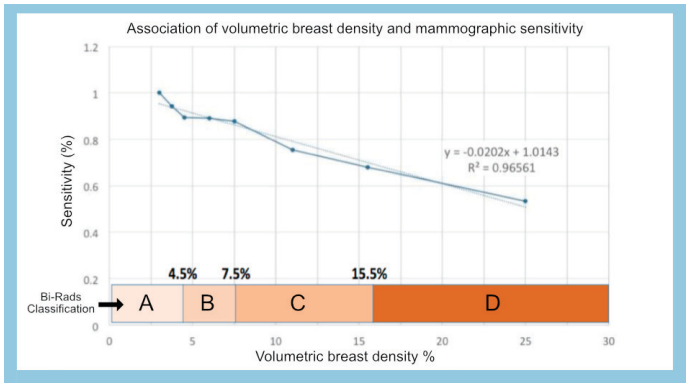

Figure 3. Sensitivity of mammography versus volumetric breast density (number of screen-detected cancers/total number of cancers).[7] Orange shaded regions represent cut-offs for BI-RADS® density grades A,B,C and D. (adapted from Destounis *et al.*, 2016)[9]

Another meta-analysis of breast cancer risk factors included 18,000 breast cancer patients and concluded that 'Breast density was the most prevalent risk factor for both premenopausal and postmenopausal women and had the largest effect on the population-attributable risk proportion.'[21]

Mammographic breast density does not just mask breast cancer; high mammographic breast density is also associated with the risk of breast tissue instability and the genesis of malignancy.

Mammographic breast density has recently been integrated into one of the most frequently used breast cancer risk assessment tools, the Tyrer-Cuzick model (also known as the 'IBIS Breast Cancer Risk Evaluation Tool'). This is an important tool for counselling women on their breast cancer risk and is free to download (www.ems-trials.org/riskevaluator).

Breast Cancer Risk Examples

The Tyrer-Cuzick model highlights the importance of mammographic breast density in risk assessment. We can illustrate this using the following case studies:

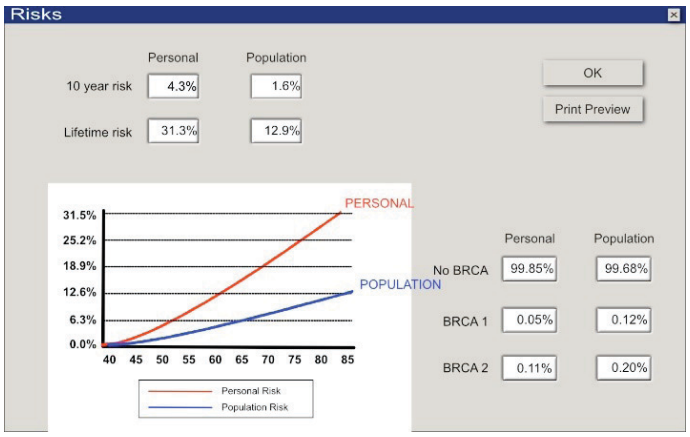

Figure 4. IBIS risk assessment for case study 1. (adapted from screenshot)

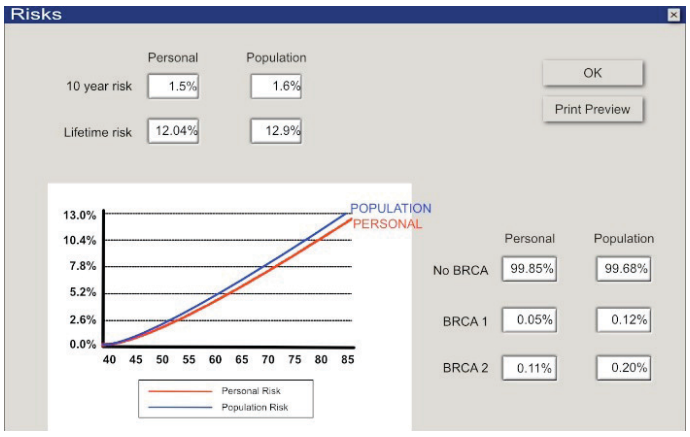

Figure 5. IBIS risk assessment for case study 2.

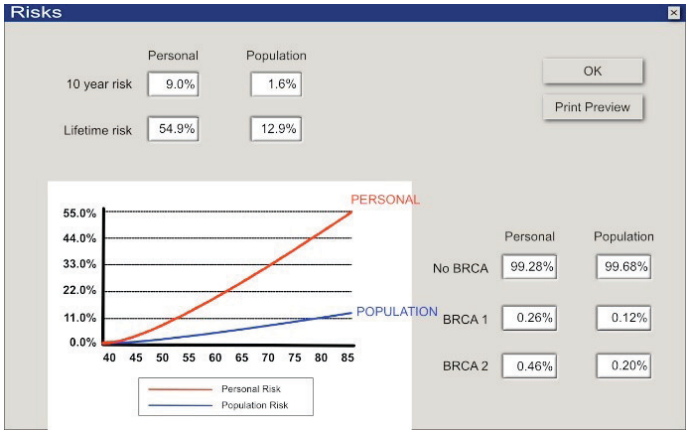

Figure 6. IBIS risk assessment for case study 3

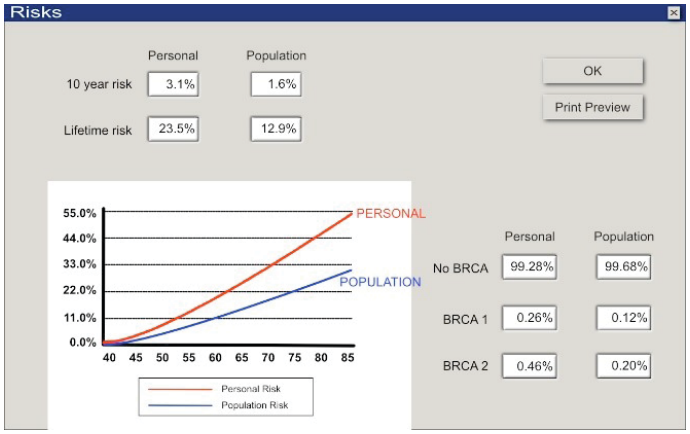

Figure 7. IBIS risk assessment for case study 4.

*(Permission for use granted by Prof Jack Cuzick Wolfson Institute of Preventive Medicine and Head, Centre for Cancer Prevention, University of London).
**The input into IBIS includes multiple parameters and the above examples have been deliberately simplified. For more detailed risk assessment (such as being BRCA1 or 2 positive, or having Ashkenazi Jewish ancestry), see http://www.ems-trials.org/riskevaluator/documents/Program_details.ppt .

Case Study 1

A forty-year-old woman has no risk factors for developing breast cancer except for a high mammographic breast density.

The risk-evaluator indicates an almost three-fold increased risk of this woman developing breast cancer in her lifetime. This is compared to the population average of one woman in eight developing breast cancer during a lifetime (https://breast-cancer.canceraustralia.gov.au/statistics). Without the information about mammographic breast density, this woman would be unaware that she was at increased risk of developing breast cancer (see Figure 4).

Case Study 2

A forty-year-old woman has no risk factors for developing breast cancer and has an average mammographic breast density.

The risk-evaluator indicates a less than one in eight chance of developing breast cancer in her lifetime. Figure 5 shows that she has almost exactly the average risk of this condition.

Case Study 3

A forty-year-old woman has a family history of breast cancer; her mother developed breast cancer at fifty-five years of age and her sister at forty-five years of age. She also has high mammographic breast density.

The risk-evaluator indicates a greater than one in two risk of developing breast cancer in her lifetime (see Figure 6).

Case Study 4

A forty-year-old woman has a family history of breast cancer; her mother developed breast cancer at fifty-five years of age and her sister at forty-five years of age. She has average mammographic breast density.

The risk-evaluator indicates a greater than one in four risk of developing breast cancer in her lifetime, less than half the risk compared to the above example with the same history and high mammographic breast density (Figure 7).

Reducing and Reversing High Mammographic Breast Density: New Opportunities for Lowering Breast Cancer Risk

Mammographic breast density as a surrogate marker for breast cancer risk

There is good evidence that mammographic breast density is a surrogate marker for breast cancer risk and that reducing mammographic breast density may be effective in reducing the risk of developing breast cancer.[22] There is evidence that mammographic breast density is also an excellent marker of response to adjuvant hormonal breast cancer treatment. Improved survival rates have been observed for women whose breast density decreases on cessation of menopausal hormonal treatment, or following adjuvant hormone treatment such as tamoxifen.[23] This is not unexpected, as mammographic breast density is a measure of whole body hormone response; the extent of the correlation, however, is remarkable.

Reducing high mammographic breast density

In order to lower the risk of breast cancer, it is essential that factors associated with increases in mammographic breast density are minimised. A recent re-analysis of The Women's Health Initiative Study, a double-blind randomised controlled trial of oral oestrogen and synthetic progestin in postmenopausal women, demonstrated that the increase in the risk of developing breast cancer occurred exclusively in those women whose mammographic breast density went up on therapy. Furthermore, women with the most extreme mammographic breast density increases (i.e. the top 20th percentile) had a three-fold increased risk of developing breast cancer.[13]

Caution should therefore be used before commencing menopausal hormonal therapy in the subgroup of women who either have a high baseline mammographic breast density, or whose breast tissue responds adversely to menopausal hormonal therapy. Ideally, women with high mammographic breast density should not use hormone replacement therapy. If they do, it is necessary for their mammographic breast density to be closely monitored by annual mammography. If their breast density rises, their therapy should be changed or ceased.

Although there is no strong epidemiological data supporting the increased risk of developing breast cancer whilst on the oral contraceptive pill (OCP), there are some concerning trends. Young women starting the OCP early in their reproductive history are at highest risk of subsequently developing high mammographic breast density.[12] Consideration should be given to counselling such young women that they should try to change as soon as practicable to an alternative form of contraception, such as a progestin-containing intrauterine device.

Reversing high mammographic breast density

Tamoxifen was the first medication to be used as a preventative agent for breast cancer. Ongoing analysis of results from the original tamoxifen clinical trial ('IBIS': www.ibis-trials.org) has found that the 42% of women who had significant reduction in mammographic breast density benefited from long-term treatment. This group of women (who had a greater than 10% reduction in mammographic breast density) had a 63% risk reduction in breast cancer.[4] This risk reduction persisted after cessation of treatment and is still ongoing twenty-five years after the study commenced.[24] However, there is a problem with tamoxifen: Only 2% of potential candidates complete five years of dosing due to the side-effects.

Women need cancer prevention but they also value their quality of life

Due to tamoxifen's ability to significantly reduce a woman's breast cancer risk, other treatments are being explored that are as efficacious, but without the debilitating side-effects.

Unfortunately, trials involving substances such as vitamin D, retinoic acid, metformin and salicylic acid have not had the same potent effect on mammographic breast density as tamoxifen in reducing the incidence of breast cancer in premenopausal women.[24]

A number of clinical trials investigating the various aspects of mammographic breast density are currently underway. A preliminary study has shown that a combined therapy of an androgen and an aromatase inhibitor ('A plus Ai'), in the form of a subcutaneous implant, has been shown to be more effective and better tolerated than tamoxifen. This treatment is currently being developed by an Australian biopharmaceutical company.[26,27]

Another promising therapy is endoxifen (the active by-product of tamoxifen). This is currently being researched as a transdermal application applied to the breast to reduce mammographic breast density, whilst hopefully not inducing the side-effects of tamoxifen. The results of this trial are expected in 2019. Metformin still may be a treatment option for obese women, specifically. The trial is still ongoing.[28]

Screening in the Presence of High Mammographic Breast Density

Population-based screening

In the United States of America, United Kingdom and Japan, it is becoming routine to inform women about their mammographic breast density. Yet in Australia, out of all the BreastScreen locations, only BreastScreen WA reports mammographic breast density to women. There are ongoing discussions regarding failure to inform women of their mammographic breast density among many, but not all, breast screening providers in Australia. A recent medicolegal conference on mammographic breast density at the Queensland University of Technology raised many issues about the nature of informed consent and duty of care with regard to information obtained on a mammogram.[29]

It is essential that we move to a system where women are given information regarding their mammographic breast density…

Prof. Jack Cuzick, OBE, FRS, The John Snow Professor of Epidemiology Queen Mary College, The University of London, was recently quoted as saying:

> "…[he] believes doctors have been 'reluctant' to tell women about the dangers of high-density breasts because they thought there hasn't been anything you can do about it".

But there are things you can do about it: you can give these women additional screening and some of them could take preventative drugs like tamoxifen to reduce breast density."[30]

Women with high mammographic breast density have the right to know that:

1. Their risk of breast cancer is higher than normal.

2. 2D mammograms have a reduced sensitivity for breast cancer detection.

3. There are strategies to reduce their mammographic breast density and consequently, lessen their risk of breast cancer.

Women should also be informed that there are chemoprevention treatments available, like tamoxifen. This was recently listed on the Pharmaceutical Benefits Scheme for breast cancer prevention in women at moderate to high risk of breast cancer (http://www.abc.net.au/news/2016-10-01/breast-cancer-prevention-drug-tamoxifen-listed-on-pbs/7895378).

Individualised risk factor assessment and screening

At the recent 8th International Breast Density and Cancer Risk Assessment Workshop in San Francisco June 2017, many of the leading cancer institutions and experts were advocating stratifying screening processes based on risk factors that incorporated mammographic breast density. A synopsis of these recommendations is shown in Figure 8.

If a woman has a BRCA mutation or a very strong family history of early-onset breast or ovarian cancer, they should automatically be referred to a high-risk breast clinic or a breast specialist.

The general consensus is that women should have a baseline mammogram at forty years of age, and even younger if they have several risk factors for high mammographic breast density. BreastScreen offers mammograms from forty years of age to all women, but only actively recruits women from fifty years, because it is after this age that most breast cancers occur. But for an individual, knowing one's mammographic breast density at age forty years opens a critical window of opportunity to implement breast cancer risk reduction strategies *before* cancer initiation. Once a baseline mammographic breast density is established, the algorithm shown in Figure 8 is suggested.

Two vital pieces of information are required as input to determine an appropriate individualised screening regimen. Firstly, the woman's mammographic breast density. Ideally this should be determined with an automated 3D measurement system, but failing this, BI-RADS® interpretation of routine mammograms can be conducted by a radiologist. The second piece of information that is required is a risk analysis using the Tyrer-Cuzick model (IBIS risk-evaluator). Once armed with these two pieces of information, the algorithm in the table below is recommended.

Approximately 60% of women fall into the A to B categories, with the majority having a breast cancer risk evaluation (IBIS) of < 20%.[31] If a woman has an A or B Bi-RADS® and yet her breast cancer risk evaluation is calculated as greater than a 20% lifetime risk, she should be referred to a specialist, undergo regular screening and consider genetic testing.

Approximately 30% of women fall into category C and 10% into category D. Mammographic breast density scores of C and D are considered 'high' breast density, and although there is still some on-going debate on the best threshold, there is little argument that category D is 'extreme' breast density.

Once they have been given a specialist opinion, the individualised screening of high risk patients could be shared with their GP, so that rural women and others with limited access to specialists receive ongoing high quality care.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is the premier investigation for detecting lesions in women with high mammographic breast density. The problem with this investigation to date is three-fold.

1. There is no Medicare rebate available for breast MRI in Australia unless there is a strong family history **and** the woman is under fifty years old, irrespective of breast density;

2. Up until now, the length of time in the MRI scanner has been prohibitively long (at around forty-five minutes) and also involved an uncomfortable body position. This is about to change with the wider adoption and acceptance of an abbreviated MRI protocol that takes only five to ten minutes and has (hopefully) corresponding cost reduction;

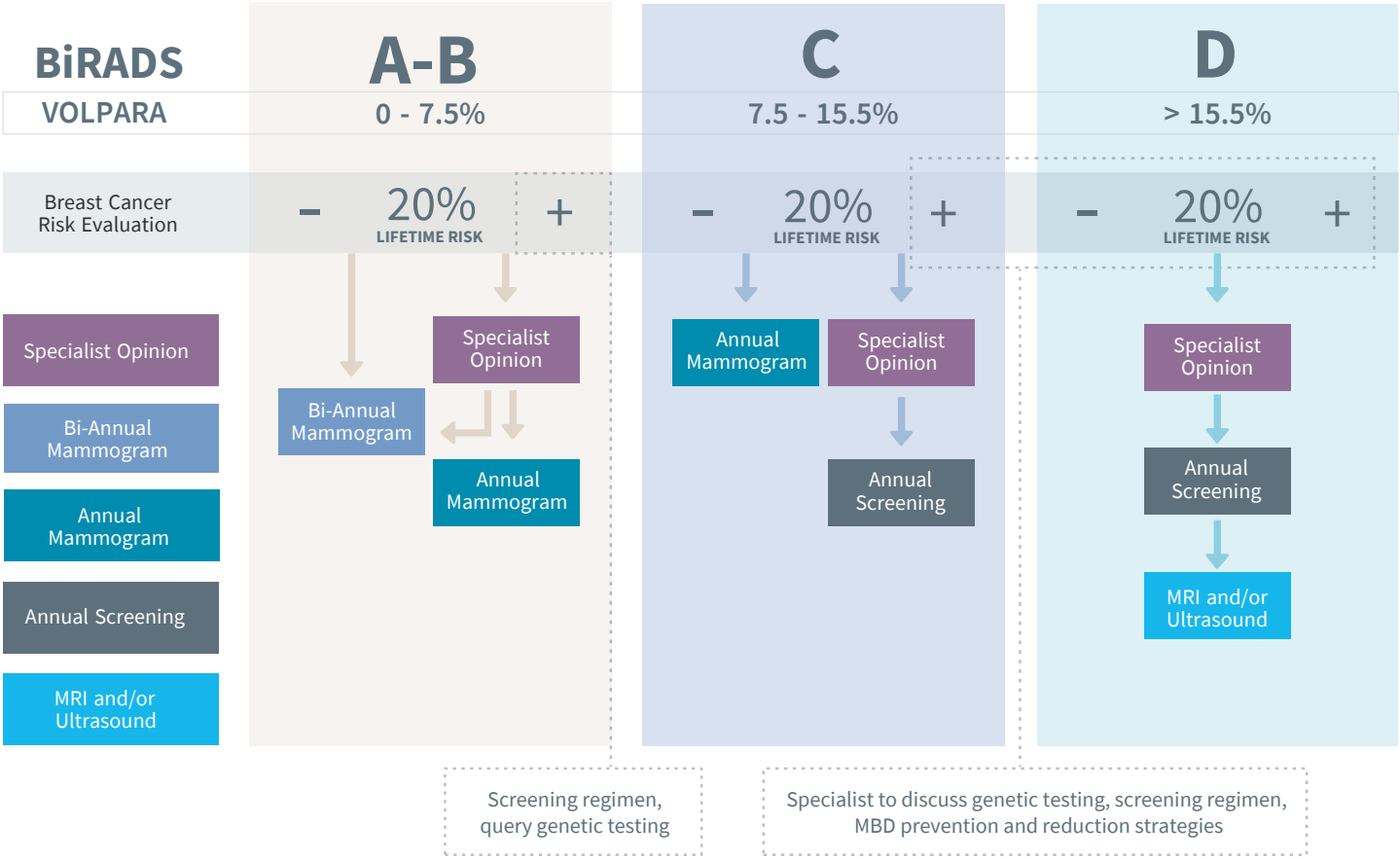

Figure 8. Individualised Breast Screening Protocol with input of 3D automated imaging (VolparaDensity™) or BI-RADS® and IBIS risk-evaluator's lifetime risk parameters. (Image reprinted with permission of Wellend Health).

3. Gadolinium contrast medium can accumulate in the central nervous system. There are no currently known adverse consequences to this accumulation, but this fact must be weighed against the risk undetected malignancy.

Conclusion

Internationally, breast screening is undergoing a paradigm shift and it is only a matter of time before BreastScreen Australia modifies its protocols and starts routinely reporting mammographic breast density.

A woman's mammographic breast density is a critical piece of health data and a strong breast cancer risk determinant. Given that breast cancer is one of the most common cancers experienced by women in mid-life, mammographic breast density measurement gives a unique insight into a woman's risk and how to manage a preventative strategy.

In this new era of breast screening and prevention, it is vital that General Practitioners have an in-depth understanding of the implications of high mammographic breast density, a knowledge of prevention and treatment options, and an awareness of emerging treatments and how to implement individualised screening regimens.

Further Reading

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A list of references is included in the online version of this article. Go to www.healthed.com.au/monographs

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