Improving our Breast Screening Protocols
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New Zealand's population-based breast screening programme[1], where we screen women aged 45-69 years for breast cancer utilising digital mammography has, along with improved treatments, seen a reduction in breast cancer mortality. Despite these improvements we continue to experience too many deaths - close to 600 annually and there is evidence that there is inequity in our breast cancer outcomes. BCAC's Secretary, Fay Sowerby stresses, "We need to investigate whether some in New Zealand, based on risk, may need to begin screening at an earlier time, with tailored frequency and consideration given to the form of screening used beyond digital mammography. These issues need to be addressed now that more sensitive and affordable screening options are becoming available. By tailoring our screening to risk, while maintaining participation rates, we are more likely to reduce breast cancer mortality, by finding invasive cancers early."

Breast cancer risk assessment

Our current screening programme assumes everyone has an average risk of getting breast cancer, but this is not so. Some women are at higher risk than others. For example, those with genetic mutations, such as a BRCA mutations, a family history of breast cancer, clinical or lifestyle factors, a previous breast cancer diagnosis, previous radiation therapy to the chest, or with dense breast tissue[2] are at higher than average risk of breast cancer. There are methods available to assess personal breast cancer risk, such as a gene panel available through the Genetic Health Service in New Zealand. Although some variants confer a small risk it is estimated that approximately 13% of women are considered at high to moderate risk based on multiple risk factors[3] and this information could be used to inform decisions about when to start screening, how often to screen and which imaging technologies to use.

Imaging technologies

Breast imaging has gone through technical improvements in the last 20 years to improve sensitivity (can the cancer be detected), specificity (can we tell if it is invasive cancer rather than something more benign), accuracy (fewer false positives, fewer false negatives and interval cancers (those found between screening appointments)) and a desire to reduce cost and improve efficiency. Helpfully biopsies today collect larger tissue samples which means, as more sensitive screening is introduced, a false positive can be identified prior to surgery and treatment[4].

- Screen-film mammography has been replaced by digital mammography (4-5 cancers detected per 1000 women screened[5,6,7]) reducing radiation exposure combined with improved efficiencies and detection. Sensitivity varies depending on the nature of the population screened, but overall sensitivity is between 50 and 90% (79.9%[8], 84%[6], 86.9%[10], 89.0%[9], 50%[15]) and specificity up to 88.9%[10]. It is acknowledged that digital mammography detects more DCIS than other forms of screening[17] and is preferable for those with the BRCA2 mutation[11]. It is less sensitive for other above average risk individuals compared to other methods. This has been demonstrated by a number of international trials for above average risk populations. There is also concern that it is not detecting our most invasive cancers. Individuals with above average risk would benefit from

other options. It is used by our breast screening programme. It costs approximately NZ$150-200.

- Breast ultrasound (4-7 cancers detected per 1000 screened) has been shown in multiple studies to improve cancer detection in women at elevated risk as a supplemental tool[12]. However, this is accompanied by less accuracy for biopsy compared with mammography or MRI. Breast ultrasound costs approximately NZ$150-200. Automated breast ultrasound has been developed to address the poor reproducibility of conventional hand-held breast ultrasound which relies on operator expertise.

- Digital breast tomosynthesis (DBT) (4-8 cancers detected per 1000 screened) has demonstrated an improvement over mammography. It is superior to mammography for the first screen but on subsequent screens its benefits vary with age and breast density. Recent research has shown that those with extremely dense breasts gain no benefit at all from DBT[13]. On subsequent screenings women with heterogeneously dense breasts and women aged 50-59 years with scattered fibro glandular density benefited from DBT, with fewer requiring recall for more imaging and more cancers being detected than with digital mammography. In some instances, reduction in recall may not significantly reduce interval cancer rates (cancers found between screening appointments). Nor is it as efficient given the number of images to be reviewed although AI (artificial intelligence) is beginning to be used to assist with this. DBT in NZ costs about $300-400.

- Contrast-enhanced breast magnetic resonance imaging (CE-MRI)[14] (17-18 cancers detected per 1000 screened) is generally available only to clinical practice in the private sector because of its cost (close to NZ$2,000) or for specific high-risk groups, for screening and diagnostic purposes. By using contrast (gadolinium), which allows for visualisation of early blood vessel formation around small tumours, there is a steep increase in sensitivity of CE-MRI compared to ultrasound, mammography and DBT. CE-MRI sensitivity can range from 75–100% but is often 95- 100%, as demonstrated by large-scale multi-centre trials for high risk individuals.

- Contrast enhanced mammography (CEM)[15] (14-15 cancers detected per 1000 screened) also exploits the uptake of contrast, this time iodine. CEM which utilises low- and high-energy images is not new outside of New Zealand, having been in use 16 years. It has been experimentally introduced in diagnostic work and screening, for women at increased risk or with dense breasts. Due to its morpho functionality (both the form and functioning of the breast tissue can be visualised with the use of contrast) CEM consistently improved diagnostic performance when compared to digital mammography, ultrasound, and DBT, frequently matching CE-MRI's overall performance. Patient experience and preferences also show that CEM is often preferred against CE-MRI in high-risk women in both the screening and problem-solving setting. Patients find its shorter examination time and less demanding procedure easier to tolerate when they need to be screened frequently.

- In New Zealand, CEM is being trialed by Dr Monica Saini, Senior Breast Radiologist Hutt Hospital and other team members. This machine has been converted with software valued at approximately NZ$50K along with a contrast injector at a cost of NZ$8K. With just four images to view it is very efficient from a resource perspective. The estimated cost of CEM is NZ$600-700. We are also aware a retrospective research project studying the association of breast density, ethnicity, family history, and age on interval cancers in the Wellington region is underway and we are hopeful this may be followed by a prospective trial.

- Another efficient (time and cost) screening option for New Zealand is abbreviated breast MRI (AB-MRI) (9-15 cancers detected per 1,000 screened). Once again this has been in use globally for several years but is just beginning to be seen in New Zealand. It can substantially reduce the MRI screening time to 10 to 15 min compared to 30 to 40 min for conventional CE-MRI. In addition, its reading time is 30 s to 3 min compared to 3 to 9 min for CE-MRI. Preliminary data recently reported[16,17] demonstrated that the sensitivity and specificity of AB-MRI were comparable to those of conventional CE-MRI. Comstock et al.[18] also evaluated the outcomes of AB-MRI for the surveillance of women with previously treated breast cancer, focusing on the diagnostic performance and limitation of AB-MRI. In this study, 1444 women of average risk with heterogeneously or extremely dense breasts completed both AB-MRI and DBT. AB-MRI detected 11.8 cancers per thousand women and DBT 4.8. Sensitivity was 95.7% for AB-MRI and 39.1% for DBT. Specificity was 86.7% for AB-MRI versus 97.4% for DBT. The team concluded that women with dense breasts undergoing screening with AB-MRI compared to DBT had a significantly higher rate of detection of invasive breast cancer. This is important because we are concerned that New Zealand's breast screening programme is missing some of these more worrying cancers.

- Following the introduction of AB-MRI, a range of studies have reported that AB-MRI could be used in clinical practice, mainly for screening purposes. Compared with CE-MRI, AB-MRI showed no statistically significant differences, with sensitivity of 82% to 100% and specificity of 45% to 97%. Cancer detection rate was 13.3 per 1000 women in a high-risk screening group.

- We have learned from Dr Sundgren Reddy, Specialist Radiologist, Mercy Radiology, Auckland, who is trialling AB-MRI that by reducing protocol sequences the screen scanning time is halved and so are the costs. With CE-MRI in New Zealand costing close to $2000, AB-MRI costs approximately $800-1000 while improving specificity. Dr Sundgren does add that should something be found a full protocol may be recommended.

Why is this important?

BCAC is raising these issues because results from a New Zealand, University of Waikato, study (Lawrenson et al. 2018)[19] showed serious inequities in breast cancer incidence and outcomes for Māori and Pasifika women. Pacific women diagnosed with breast cancer are twice as likely to die from the disease after 5 years than New Zealand European women. They are diagnosed with breast cancer younger than other groups, and the cancer is almost twice as likely to be an aggressive form. Māori women diagnosed with breast cancer also have a higher mortality (times 1.76) after 5 years than New Zealand European women. They are less likely to be diagnosed through mammographic screening and there is a suspicion they may have greater volumetric breast density[20].

This research also showed that the greatest inequity occurs when women detect their cancer symptomatically i.e., they find it themselves rather than having it detected by screening[19]. Information available does not help us to understand whether this is as a result of a screening failure or through lack of participation. We are focussing in this article on screening to build everyone's understanding of the range of options available so that if a person is at higher than average risk, they know there may be cost effective options available to them.

Age of screening and risk assessment

The Society of Breast Imaging in the US and American College of Radiology Guidelines were recently updated (February 2020)[21,22] and they now call for all women to have a risk assessment at age 30 to determine whether screening earlier than 40 is needed. Debra Monticciolo, MD, FACR, Chair, stressed that "…. the new guidelines will help save more lives." [21] In New Zealand, the breast screening programme is highly reliant on digital mammography and is not augmented with supplemental screening based on risk. In addition, BSA does not advise women of their density, nor collect or hold data regarding breast density, or other risk factors. We understand this is partly driven by system and/or resource limitations. We want this to change. Libby Burgess Chair of BCAC says "Clearly, one size does not fit all when it comes to getting the best out of our breast screening programme. Optimising the programme so that those at higher risk receive closer attention by being screened earlier, more often or with different imaging techniques, will lead to earlier detection of breast cancer and therefore better outcomes for all New Zealand women. Detecting cancers earlier when they are more easily treatable also makes economic sense, with savings for both the health system and the women themselves."

Modality of screening based on risk

In assessing above-average breast cancer risk, trials in Australia, US and Europe are seeking to improve outcomes by complementing or optimising population-based screening programmes. Risk-based tools are used to identify who may have higher than average risk: at an earlier age, have heterogeneous or extremely dense breasts, family history or genetic, clinical and lifestyle differences.

The screening tools mentioned are options we need to learn about as we are not all the same and for some of us a digital mammogram may not be the best option. For others it will be highly suitable.

CEM, especially if it is dual energy, AB-MRI, and CE- MRI all seem to be good options for screening high risk women and/or those with dense breasts; these imaging technologies could also be used for other diagnostic purposes.

Given a growing body of evidence regarding screening sensitivity and specificity of different screening modalities for differing levels of risk, consideration of the personal and economic impact of treatment when a cancer is not detected early needs to be taken into account alongside the current focus on participation levels alone and concerns about false positives and potential over-diagnosis. False positives diminish significantly in the second year and subsequent years for most modalities as demonstrated by Bakker et al. [23].

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