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Outcomes of women at high familial risk for breast cancer: an 8-year single-centre experience

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Management of Familial Breast Cancer Risk

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ABSTRACT

Objectives:

The value of a high-risk surveillance program for mutation carriers and women at high familial breast cancer risk has not been extensively studied. A Breast and Ovarian Cancer Risk Management Clinic (BOCRMC) was established at the Royal Melbourne Hospital in 2010 to provide multimodality screening and risk management strategies for this group of women. The aims of this study were to evaluate the program and describe breast cancer diagnoses for *BRCA1*, *BRCA2* and other germline mutation carriers as well as high risk non-carriers attending the BOCRMC.

Methods:

Clinical data from mutation carriers and non-carriers with a $\geq 25\%$ lifetime risk of developing breast cancer who attended between 2010 and 2018 were extracted from clinic records and compared. The pattern and mode of detection of cancer were determined.

Results:

A total of 206 mutation carriers and 305 non-carriers attended the BOCRMC and underwent screening on at least one occasion. Median age was 37 years. After a median follow-up of 34 months, 15 (7 invasive) breast cancers were identified in mutation carriers, with 7 (6 invasive) breast cancers identified in non-carriers. Of these, 20 (90.9%) were detected by annual screening, while 2 (9.1%) were detected as interval cancers (both in *BRCA1* mutation carriers). Median size of the invasive breast cancers was 11 mm (range: 1.5-30 mm). The majority (76.9%) were axillary node negative. In women aged 25-49 years, the annualised cancer incidence was 1.6% in *BRCA1*, 1.4% in *BRCA2* mutation carriers and 0.5% in non-carriers. This compares to 0.06% annualised cancer incidence in the general Australian population.

Conclusions:

Screening was effective at detecting early-stage cancers. The incidence of events in young non-carriers was substantially higher than in the general population. This potentially justifies ongoing management through a specialty clinic although further research to better personalise risk assessment in non-carriers is required.

Keywords

Hereditary breast and ovarian cancer syndrome · *BRCA1* gene · *BRCA2* gene · Breast cancer screening · Early detection of cancer

INTRODUCTION:

Breast cancer screening and preventive measures should ideally be tailored to an individual's risk profile to ensure that the cost/benefit ratio of the selected option is favourable (1).

A family history of breast cancer is the most widely recognized risk factor: approximately 10-15% of breast cancers are assumed to be familial, with 25% of these being associated with a mutation in a high penetrance hereditary breast cancer gene (2, 3). Hence, the majority of women with a substantial family history for breast cancer will test negative for a genetic mutation. Amongst this group, the clinical value of genetic modifiers identified through genome-wide association studies (GWAS) (4) has yet to impact on patient risk assessment and management (5).

An international collaborative study that included Australian women found that the cumulative breast cancer risk by age 80 years was 72% for *BRCA1* and 69% for *BRCA2* mutation carriers. Breast cancer risk for *BRCA* mutation carriers increased rapidly with age in early adulthood, then plateaued to a relatively constant rate. The peak hazard ratio for breast cancer risk occurred in the 30s for *BRCA1* and in the 40s for *BRCA2* mutation carriers (6). Although guidelines vary across countries, *BRCA1/2* mutation carriers (and women with a known hereditary cancer syndrome) are generally encouraged to participate in dedicated high-risk clinics that offer regular breast cancer screening and risk-reducing options. For the larger group of women at high familial risk of breast cancer where no heritable germline mutation has been identified, the optimal approach in managing their cancer risks is unknown (7). Cancer Australia provides a familial risk assessment online tool, FRA-BOC (8), to determine an unaffected woman's risk of developing breast cancer based on her family history that categorises the risk level as 1 (representing general population risk), 2 (moderately increased risk) or 3 (potentially high risk). Category 3 (estimated to approximate to >25% lifetime risk) includes women

1. having two first degree or second degree relatives on one side of the family diagnosed with breast or ovarian cancer plus one or more of the following features on the same side of the family: additional relative(s) with breast or ovarian cancer, breast cancer diagnosed before the age of 40, bilateral breast cancer, breast and ovarian cancer in the same women, Jewish ancestry and/or breast cancer in a male relative,
2. having a family member with a known mutation predisposing to breast cancer,
3. who are at potentially high risk of ovarian cancer.

A detailed description of the FRA-BOC classification is provided in the addendum.

Since February 1st, 2009, breast MRI screening has been subsidised by Medicare Australia for annual surveillance in women under age 50 who are at high risk for breast cancer (9). The Australian Government funds annual breast MRI screening for 'the diagnosis of breast cancer in asymptomatic women with a high risk of developing breast cancer when used as part of an organised surveillance program.' Subsidised access to this test is provided to women under the age of 50 who tested positive for a genetic mutation that predisposes to breast cancer or to mutation-negative women who fit the FRA-BOC Category 3 (10).

The Breast and Ovarian Cancer Risk Management Clinic (BOCRMC) was established in August 2010 at the Royal Melbourne Hospital to centralise the assessment and management of high-risk women. This is conducted in conjunction with the Gynaecological Oncology Service at the Royal Women's Hospital, Melbourne, for ovarian cancer preventive surgery. Initially, referral criteria for the BOCRMC were in accordance with the category 3 FRA-BOC classification as proposed by Cancer Australia and/or with eligibility for Medicare coverage of surveillance MRI. From late 2015, referral criteria were defined as a lifetime risk of developing breast cancer of at least 25% based on the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (11) and/or MRI eligibility as per category 3 of the FRA-BOC. The clinic provides regular breast screening and clinical breast examinations, and informs patients about risk-reducing strategies including bilateral prophylactic mastectomy (BPM) (12), bilateral risk-reducing salpingo-oophorectomy (RRSO) (1), endocrine preventive strategies (1, 13), and lifestyle recommendations (14).

The aim of this study was to evaluate the current approach to patient selection in the BOCRMC, and to investigate whether the reference criteria should be restricted to mutation carriers only, or should remain more broad. Therefore, we assessed the clinical outcomes of high-risk women attending the BOCRMC with regard to breast malignancies detected through the screening services provided and their uptake rate of preventive options, and described these outcomes in both mutation carriers and non-carriers.

METHODS:

A retrospective review was performed using prospectively collected data from women attending the BOCRMC at the Royal Melbourne Hospital between August 3rd, 2010 and July 31st, 2018. These patients were referred from familial cancer centres, public and private breast clinics and general practitioners.

Initially, high-risk was broadly defined as eligibility for Medicare coverage of surveillance MRI and/or category 3 of the FRA-BOC classification. Eligible subjects included both carriers of a pathogenic *BRCA1*, *BRCA2*, *CDH1*, *MSH6*, *TP53*, *PALB2*, *PTEN* or *STK11* mutation and non-carriers.

The BOADICEA tool (11) was introduced in late 2015 to further estimate the lifetime risks of breast cancer in women attending clinic with no known mutation in a cancer predisposing gene.

At the BOCRMC, breast surgeons discuss the available breast cancer risk management options with the patient. A personalised risk management plan is devised based on the mutation status, age, youngest age of cancer diagnosis in the family, and any medical condition that might affect the screening modality. The screening methods utilized in the clinic include yearly clinical breast examination (CBE) and breast ultrasound from age 25 years, yearly breast MRI for women aged between 25 and less than 50 years, and mammogram from age 30 years. Self-funded MRI screening is offered to women aged 50 years or older. In addition, other options are discussed with the patient, including prophylactic surgeries, i.e. bilateral mastectomy and risk-reducing bilateral salpingo-oophorectomy (after child bearing is completed), lifestyle recommendations (weight management, physical activity, diet, smoking, alcohol intake) (15), and, if eligible, risk-reducing medication (16) and clinical trials (e.g. the BRCA-D study) (17).

For this study, de-identified data was extracted from the local clinical database FamBIS (Cancer Council Victoria, version 3.8.1), and entered into a separate study database with institutional ethics approval.

Demographics, personal and family cancer history, genetic test results, screening history and risk reduction data were collected. Within the follow-up period of up to 8 years, data included any new cancers detected within the BOCRMC, including detection modality, tumour size, pathology and therapies, updated information on the uptake of risk-reducing services, and if applicable, date and reason for discharge from the clinic.

The study was approved by the Human Research Ethics Committee of the Royal Melbourne Hospital.

All data were analysed in a descriptive fashion using R version 3.5.2 (<https://www.R-project.org/>).

RESULTS

Between August 2010 to July 2018, a total of 511 women attended the BOCRMC at the Royal Melbourne Hospital for breast cancer surveillance due to the presence of a genetic mutation or strong personal family history.

The patient characteristics are shown in **Table 1**. The median age of the study population was 37 years (range 18-70 years) at the time of their first consultation. The median follow-up time within the clinic was 34 months (range 1-96 months).

Three hundred and five women (59.7%) had no known germline mutation, but had a strong family history of breast and/or ovarian cancer. Of these, 296 women tested negative for a genetic mutation. Based on their family history, these women were offered genetic testing for mutations in the *BRCA1* or *BRCA2* genes from 2010-2012, and panel genetic testing for mutations in *BRCA1*, *BRCA2*, *TP53* and *PTEN* from 2012-2016. The panel was extended by the ATM genes in 2017. 9 patients were not tested for a genetic mutation due to the following reasons: 4 refused to undergo predictive genetic testing after a genetic mutation was detected in a family member, 1 index patient refused genetic testing – consequently, the unaffected patient was not tested, 1 index patient lived in Nepal and did not receive subsidised genetic testing – consequently, the unaffected patient was not tested, the family members of 3 patients were tested positive for a likely benign variant of uncertain significance (VUS) in the *BRCA1* and *BRCA2* genes – no predictive genetic testing for the VUS was offered. As the subgroup of women who did not undergo genetic testing ($n = 9/305$) was negligibly small, we did not treat them separately from the women who tested negative for a deleterious mutation, but included them in the “non-carriers” group. BOADICEA scores for lifetime risk estimates of breast cancer were calculated for 201 of the 305 (65.9%) women. The median BOADICEA lifetime risk of developing breast cancer in this subgroup was 20% (range 10.7-40%). BOADICEA scores were not calculated for the remaining 104 (34.1%) women, mostly (82, 78.8%) because they had been discharged from the clinic before 2016, i.e. before the algorithm was introduced. For this study, we decided to not calculate the BOADICEA scores retrospectively in already discharged patients because it would not have changed their subsequent risk management.

The remaining 206 women (40.3%) were carriers of a pathogenic mutation in breast cancer and/or ovarian cancer predisposition gene. Germline mutations were as follows: *BRCA1* ($n=90$), *BRCA2* ($n=99$), *STK11/LKB1* (Peutz Jeghers Syndrome, $n=6$), *CDH1* ($n=3$), *TP53* (Li-Fraumeni Syndrome, $n=4$), *MSH6* ($n=1$), *PALB2* ($n=2$) and *PTEN* (Cowden Syndrome, $n=1$). The *STK11*, *CDH1* and *MSH6* carriers were also undergoing separate gastrointestinal surveillance.

36 study subjects already had a personal history of cancer when entering the BOCRMC, including 12 breast cancers and 21 ovarian cancers (**Table 1**).

Discharges from the clinic

To date, 210 women have been discharged from the clinic (**Table 2**). Of the women discharged, 55 (26.2%) were discharged due to the completion of risk-reducing surgeries and 53 (25.2%) due to not being at sufficiently high risk after re-evaluation of their family pedigree in subsequent screening rounds (e.g. corrections to the number of cancer cases in the family or the age of disease onset in a family member) or after a negative predictive genetic test result became available. These women were then referred to BreastScreen Australia's recommended screening interval of 2 years. 25 women (11.9%) were discharged from the BOCRMC due to the transfer to oncologic care because of a cancer diagnosis. During the study period, 4 *BRCA1* mutation carriers died from cancer. Two had a recurrent ovarian cancer after 2 and 5 years, respectively, and two developed brain metastases 1.5 and 5 years, respectively, after their breast cancer diagnosis and deceased shortly after. 1 patient self-discharged from the clinic as she decided to opt out of regular surveillance and preventive surgery. The remaining 72 (34.3%) were discharged from the clinic for other reasons (i.e., personal decision not to continue with management in the clinic, missed appointments, managed elsewhere, patient moved interstate or overseas).

Cancer diagnoses

Twenty-two breast malignancies and 2 fallopian tube cancers were detected within the BOCRMC. Outside of the BOCRMC, another five cancers were detected in 3 patients: 1 *in situ* melanoma in a non-carrier, 3 unrelated primary cancers (metastatic uterine leiomyosarcoma, rectal adenocarcinoma and primary lung adenocarcinoma) detected in a *TP53* mutation carrier and 1 metastatic gastric cancer (regular gastroscopies were being conducted with gastroenterologist oversight) detected in a *CDH1* mutation carrier (data not shown).

The pathologic features of the breast cancer cases detected during the study period are detailed in **Table 3**.

The breast cancers included 9 ductal carcinomas *in situ* (DCIS), 12 invasive ductal cancers (IDC), and 1 invasive lobular cancer (ILC). Of the 22 breast malignancies detected in the series, 15 occurred in mutation carriers and 7 in non-carriers. The median BOADICEA lifetime risk for developing breast cancer in the 7 non-carriers was only 14.7% (range: 12.4-26.2%). One *BRCA2* mutation carrier had two metachronous tumours (DCIS diagnosed in 2013 and 2016).

In women aged 25 to 49 years, the annualised breast cancer incidence rate was 1.6% in *BRCA1* and 1.4% in *BRCA2* mutation carriers, compared to 0.5% in non-carriers. Limiting the group of non-carriers to women who were tested negative for a genetic mutation, the annualised breast cancer incidence rate was 0.6% in mutation-negative women between ages 25 to 49 years.

Twenty of the 22 breast cancers were detected during annual screening. All screen-detected cancers were incident cases. The median number of screening rounds at which the breast cancers were detected was 4 in mutation carriers (range: 2-7 rounds) and 4 in non-carriers (range: 2-8 rounds). 13 breast cancers were detected in women before age 50 years, and 9 breast cancers were detected in 8 women aged at least 50 years. In the 13 women diagnosed before age 50 through annual screening, MRI detected 100% (12/12) of the cases and mammogram 72.7% (8/11). Seven out of 9 DCIS were diagnosed in women aged under 50. Of these, all (7/7) DCIS were detected by MRI. Mammography failed to identify DCIS in 1 of these women. In women aged 50 or older, mammogram identified 57.1% (4/7) of breast cancer cases. The remaining 42.9% (3/7) were detected by ultrasound. As no (self-funded) breast MRI scans were undertaken in the patients ≥ 50 years age who developed breast cancer, its sensitivity could not be documented for this group. MRI recall rates have been previously reported at our institution, where we found that recall rates decreased substantially with increasing experience (18).

For the two interval breast cancers, one was detected as an incidental finding in a prophylactic mastectomy specimen in a *BRCA1* mutation carrier and the other *BRCA1* mutation carrier presented as a self-detected axillary lump during pregnancy 10 months after her last screening MRI.

The two fallopian tube cancers were incidental findings made at the time of prophylactic surgery and elective surgery undertaken to treat uterine prolapse. Both cancers were detected at an early stage (1A and 1B).

The median age at breast cancer diagnosis was 45.5 years (range 28-60 years). The median age at diagnosis for the 14 mutation carriers was 45 years (range 28-60 years) and for the 7 non-carriers was 48 years (range 35-60 years).

In 5 cases (22.7% overall), breast conserving surgery was chosen, while the majority (17, 77.3%) of cases proceeded with mastectomy.

The median size of the invasive breast cancers was 11 mm (range 1.5-30 mm). In total, 69.2% of the invasive breast cancers were 15 mm or smaller. The majority (61.5%, 8/13) of these tumours were low to intermediate grade. At time of diagnosis, 3/13 (23.1%) patients with invasive breast cancer had axillary lymph node metastases (1 mutation carrier and 2 non-carriers).

Phenotypic evaluation of the 13 invasive tumours by IHC and HER2 CISH revealed that 3 were triple-negative, basal-like breast cancers (all *BRCA1* mutation carriers), 8 were hormone receptor-positive and HER2 non-amplified (1 *BRCA1*, 2 *BRCA2* mutation carriers, and 5 non-carriers), and 2 were hormone receptor positive and HER2-amplified (non-carriers only).

Although all cases presented as early breast cancer, two patients experienced distant recurrence on long-term follow-up. Patient 1 was first diagnosed with a *BRCA1*-associated, 8 mm Grade 3 triple-negative, node-negative breast cancer. Despite undergoing bilateral mastectomy and adjuvant chemotherapy, she presented with regional axillary node metastasis (10/28 lymph nodes) 2.5 years later, treated by axillary dissection and chemotherapy. She was subsequently diagnosed with brain metastases and died 2 years later. The second patient was first diagnosed with a *BRCA1*-associated 16 mm Grade 3 basal-like triple negative breast cancer during pregnancy, with no involved axillary nodes. She was treated with wide excision, adjuvant radiotherapy and chemotherapy. She developed a second ipsilateral Grade 3 basal-like triple negative tumour 9 months later, presumed to be a local recurrence. She was then treated with bilateral total mastectomies and chemotherapy. She developed bone and brain metastases and died shortly after.

Risk-reducing surgery

12.6% of all unaffected women elected to undergo bilateral prophylactic mastectomies (BPM) and 13.1% risk-reducing bilateral salpingo-oophorectomies (BSO) (**Table 4**). The majority of these were *BRCA1* or *BRCA2* mutation carriers. 37.5% (24/64) of the *BRCA1* mutation carriers underwent BPM at a median age of 39 and 19.2% (15/78) of the *BRCA2* mutation carriers underwent BPM at a median age of 39. Of the *BRCA1* mutation carriers who had BPM, 33.3% (8/24) were 35 years or younger at the time of the procedure. Of all *BRCA2* mutation carriers who underwent BPM, 73.3% (11/15) were ≤45 years old at the time of BPM. 5.7% (16/283) of non-carriers underwent BPM at a median age of 44.5 years.

Out of 65 unaffected patients who were *BRCA1*-positive, 30.8% (20/65) had a BSO at a median age of 46 years. Until age 45 years, 18.5% (10/54) of the unaffected *BRCA1* mutation carriers underwent a BSO. Of all unaffected *BRCA2* mutation carriers, 26.6% (21/79) had a BSO at a median age of 45 years. Until age 45 years, 18.8% (12/64) of the *BRCA2* mutation carriers had a BSO conducted. 5.3% (15/283) of the non-carriers underwent BSO at a median age of 43 years. All non-carriers who proceeded with a BSO had a family history of ovarian cancer.

Endocrine medical prevention

As previously reported, all patients attending the BOCRMC between February 2014 and May 2015 received evidence-based information on endocrine preventive therapy (16). There was a 6.8% collective uptake of tamoxifen (**Table 4**). Among the *BRCA1* mutation carriers, 1.5% (1/65) opted for chemoprevention. Among the *BRCA2* mutation carriers, 8.9% (7/79) decided to initiate chemoprevention. These women went on tamoxifen at a median age of 42 years. Of 283 non-carriers, 7.4% took tamoxifen for chemoprevention at a median age of 44 years. Most patients had a short duration of tamoxifen uptake, i.e. less than a year.

DISCUSSION

While risk management protocols for *BRCA* mutation carriers are well defined (18), the optimal approach to managing the cancer risks of women who have a strong family history, but no known familial mutation for breast cancer, remains uncertain. The impact of intensified screening, prophylactic surgeries and chemoprevention has not been extensively studied (7), meaning that best practice for the care of this population is unclear.

The main goal of a breast cancer screening program is to identify breast cancers at the earliest stage possible due to its association with superior prognosis. DCIS is a non-obligate precursor, with an extremely low breast cancer specific mortality (19). The natural history of untreated DCIS is not fully understood, but almost all high and intermediate grade lesions and a majority of low grade lesions will eventually progress to invasive cancer (20), so prevention of breast cancer by diagnosis and treatment of DCIS is an important objective of a screening program in younger women. Death from breast cancer after a diagnosis of DCIS is substantial for women diagnosed before age 35 years (19).

Therefore, we report on the breast cancer incidence rate including both invasive cancers and DCIS.

Among the general population, the annualised breast cancer incidence rate in women aged 25 to 49 years is approximately 0.06% (21, 22). This compares to 1.6% in *BRCA1* and 1.4% in *BRCA2* mutation carriers and 0.5% in non-carriers at the BOCRMC.

Breast cancer risk assessment

Risk definitions and management practices are highly variable across countries. In Australia, 'high risk' is defined as a lifetime risk of 25% or greater, which is captured by the FRA-BOC category 3 (8), whereas, in contrast, some countries apply other thresholds (e.g., American Cancer Society: lifetime risk $\geq 20\%$; UK: lifetime risk $\geq 30\%$ according to the National Institute of Health Care Excellence) (1).

Furthermore, internationally, neither guideline clearly specifies which empirical model to use to calculate a woman's risk of developing breast cancer; rather, a number of applicable risk models are recommended to estimate a woman's lifetime and age-specific risk of developing breast cancer (23), applying indicators in various detail (family history $\pm$ genetic factors, and sometimes non-genetic factors) and weighing them differently. Internationally, there is no clear consensus on which risk estimation model is the most accurate and reliable, and comparative evaluations of different models showed minimal agreement in the assigned risk estimates (24, 25). Ozanne *et al.* used the BRCAPRO, Claus, and Tyrer-Cuzick calculators to determine a woman's eligibility for breast MRI screening based on a lifetime risk of $\geq 20\%$ (24). The percentage of women identified by the Tyrer-Cuzick model was 5.6%, by BRCAPRO was 0.4% and by the Claus model was 0.9% using data from 10,000 women. Only 0.2% of the study population was found to be eligible by all three methods. Quante *et al.* comparatively evaluated the performance of the risk models IBIS and BOADICEA to determine a woman's eligibility for MRI screening (lifetime risk of $\geq 20\%$) (25). Based on data from 1,764 women, IBIS identified 59.3% of women to be eligible, compared to only 20.1% identified by BOADICEA.

For the selection of patients in Australia, Cancer Australia recommends to use category 3 of the FRA-BOC. While the FRA-BOC is easy to apply in the clinical setting, it is a large category and, therefore, may result in underestimating risk in small sized families with few at-risk female relatives or paternally inherited risk, and overestimating risk in large families with multiple at-risk female relatives. Furthermore, the online tool does not incorporate tumour pathology. BOADICEA has been validated in an Australian population of European ancestry earlier (26), and was introduced to the BOCRCM in late 2015. The BOADICEA risk score was calculated for 201 mutation-negative women. Using BOADICEA, only 22.4% (45/201) would have been classified as high risk using the FRA-BOC threshold of $\geq 25\%$. Based on a lifetime risk of $\geq 20\%$ (as proposed by the American Cancer Society), the proportion of eligible women would equal 50.7% (102/201) using BOADICEA. Thus, a substantial number of mutation-negative women would not have met the inclusion criteria basing breast cancer risk status on BOADICEA only. Although BOADICEA was introduced to tailor breast cancer risk better, 6 out of 7 mutation-negative women who had screen-detected breast cancers met the FRA-BOC criteria, but not the BOADICEA lifetime risk of at least 25%. Of these 6 cases, 4 women were diagnosed with breast cancer (3 x IDC, 1 x DCIS) before age 50 years (median age: 38 years, range: 35-48 years). If BOADICEA is likely to underestimate cancer risk in these individuals, a combination of validated risk models may be useful in reducing misclassification bias as proposed by Park *et al.* (27). In order to help with choosing the right breast cancer risk estimation model, the web-based decision support tool iPrevent uses initial questions to determine whether IBIS or BOADICEA is best to use, thereby providing a more accurate risk assessment at the individual level (28). Mavaddat *et al.* have

recently published a polygenic risk score (PRS) including 313 Single Nucleotide Polymorphisms (SNPs), based on the largest available GWAS dataset (derived from white European populations) and optimized for prediction of ER-positive and ER-negative disease. The polygenic risk score has the potential to improve risk stratification for screening and prevention strategies, and may be incorporated into risk prediction models, e.g. BOADICEA. Clinical translational studies are necessary to evaluate the predictive value of the new PRS_{313} combined with family history and lifestyle risk factors in the context of current screening protocols (29).

Multimodality screening for breast cancer

The addition of MRI to mammography is beneficial in the early detection of breast cancer in high-risk individuals (30-34). MRI has consistently been shown to outperform mammography and ultrasound with regard to sensitivity, at the cost of reduced specificity (30). In this series, MRI was superior to mammography (sensitivity of 100% vs. 72.7%) in the detection of breast cancers in women aged under 50. In line with the EVA trial (35), MRI was superior to mammography for diagnosing DCIS (100% vs. 83.3%) among women less than 50 years of age. Kuhl *et al.* suggest that if the findings of the EVA trial are replicated in empirical studies, it may be conceivable to discontinue mammographic screening in young women who regularly attend quality-assured screening with breast MRI (35). There is some evidence to suggest that this might hold true in *BRCA1* mutation carriers under age 40 (30).

Surgical prevention and chemoprevention

Among *BRCA1/2* mutation carriers, BPM reduces the risk of breast cancer by at least 90% (12), and Ingham *et al.* indicated that any risk-reducing surgery conducted in *BRCA* mutation carriers reduced mortality (36). A simulation study suggested that while there was a substantial mortality benefit of BPM for *BRCA1* mutation carriers at age 25 years, the expected benefit declined rapidly with increasing age at BPM (37). Phillips *et al.* assessed the rate of BPM and BSO in Australian *BRCA* mutation carriers (38). At 3 years follow-up from genetic testing, 5.2% (7/134) had undergone BPM at a mean age of 40 and 16.3% (20/123) had undergone BSO at a mean age of 47 years. Metcalfe *et al.* reported on large differences in the uptake of BPM according to country of residence, with uptake rates varying from 2.7% in Poland to 36.3% in the United States (39). The BPM uptake rate of 27.1% in *BRCA* mutation carriers in our study cohort is comparable to Western European countries (e.g., France: 25%), but is higher than the rate reported by Phillips *et al.*, including Australian women who indicated their uptake of BPM and BSO between 2001 and 2005. Several researchers, e.g. James *et al.* (40), Evans *et al.* (41), and Liede *et al.* (42), have shown that after Angelina Jolie disclosed that

she is a *BRCA1* mutation carrier and opted to have a BPM, there was a significant, long-lasting and global increase in genetic testing and mastectomy rates since 2013. The different analysis periods may have had an impact on the BPM and BSO rates. Considering the reduction in clinical benefit of BPM with increasing age, the fact that 66.7% of the *BRCA1* mutation carriers who underwent BPM at the BOCRMC were older than 35 years at the time of the procedure is of concern.

Evans *et al.* reported on the uptake of risk-reducing surgery among 3,515 women with no known *BRCA1/2* mutation from England (43). After a median follow-up of 8.1 years, 3.2% (112/3,515) opted for BPM. The uptake of BPM was largely dependent on lifetime risk estimates of developing breast cancer using the Tyrer-Cuzick model: 1.8% of women at 25-32% lifetime risk, 2.5% of women at 33-39% lifetime risk, and 6.4% of women at 40-45% lifetime risk underwent BPM ($P < 0.005$). We found an uptake rate of BPM of 5.7% (16/283) in women with no mutation identified.

Tamoxifen treatment for five years will reduce the incidence of oestrogen receptor positive (but not oestrogen receptor negative) breast cancer by 38% (44), with the preventive effect being sustained for at least 5 years (44). According to the IBIS-II trial, anastrozole reduces the incidence of breast cancer in high-risk postmenopausal women by 53% compared to placebo (45). There have not been any primary prevention trials of tamoxifen conducted specifically among *BRCA1* or *BRCA2* mutation carriers, and only limited data from observational studies and secondary analyses are available (46). Yet, as triple-negative cancers predominate in *BRCA1* mutation carriers, selective oestrogen receptor modulators do not seem to substantially reduce the rate of breast cancers in this particular group (47). Although guidelines recommend endocrine preventive therapy for high-risk women, the uptake of chemoprevention remains low, as reported by Skandarajah *et al.* (16). In our updated analysis, only 1.5% of *BRCA1* mutation carriers, 8.9% of *BRCA2* mutation carriers and 7.4% of the non-carriers decided to take tamoxifen for medical prevention.

Strengths, limitations and future directions

This study is of a large number of women being managed in a uniform manner via a dedicated risk management clinic. We had comprehensive data available, and most of the non-carriers had their risk assessed using the BOADICEA program. Adherence to annual screening was high in our centre, with less than 6% choosing to discontinue screening.

The small number of 22 breast cancer cases allowed for a descriptive analysis only. Also, the median follow-up time of 34 months is too short to assess the impact on mortality. Future analyses with a longer follow-up period will allow for a cost-effectiveness analysis of the current management practices at the BOCRMC that will not only account for the numbers of cancers detected within the

clinic, but also for the number of women who benefited from the early breast cancer detection in terms of better survival.

Despite these limitations, our findings highlight the significant implications of centralizing the care of women at high risk for breast cancer with regard to tailor screening advice, early detection, facilitate preventive strategies and provide up access to genetics services and research trials in women at high risk.

Cancers in high risk non-carriers occur at ages that are similar to mutation carriers, and may require MRI to identify them. The multimodal surveillance program in the BOCRMC is effective in detecting early-stage breast cancers and the uptake of preventative strategies mirrors that of other studies.

The FRA-BOC tool provided by Cancer Australia is not optimal in assessing breast cancer risk. BOADICEA was introduced to further estimate the lifetime risks of breast cancer in non-carriers. However, a cut-off of 25% lifetime risk on BOADICEA would make us dismiss 77.6% of the non-carriers, even though a substantial amount of these women seems to be at high risk of developing breast cancer. Moreover, when compared to the FRA-BOC tool, there is a chance that BOADICEA would have defined other women to be at high risk for breast cancer. The introduction of SNP data and other risk factors is likely to improve the ability to identify those who benefit most from intensified surveillance. We need more follow-up data to determine an appropriate cut-off value on BOADICEA before refining referral criteria for non-carriers in Australia.

CONCLUSIONS

Based on our findings, non-carriers at high risk for breast cancer should not be discharged from the BOCRMC. Further understanding of the apparent genetic components in non-carriers are imperative to standardize risk assessment and tailor recommendations for breast cancer screening and risk-reducing measures in *BRCA*-negative women. The growing number of GWAS may bring further insights into personalized risk assessment, ensuring that the limited resources available are used to maximum benefit.

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Conflict of interest

All authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Addendum: Familial Risk Assessment – Breast and Ovarian Cancer (FRA-BOC) (7)

Category 1: at or slightly above average risk	Category 2: moderately increased risk	Category 3: potentially high risk
→95% of the female population	<4% of the female population	<1% of the female population
<ul style="list-style-type: none"> No confirmed family history of breast cancer One 1° relative diagnosed with breast cancer at age 50 or older One 2° relative diagnosed with breast cancer at any age Two 2° relatives on the same side of the family diagnosed with breast cancer at age 50 or older Two 1° or 2° relatives diagnosed with breast cancer, at age 50 or older, but on different sides of the family (i.e. one on each side of the family). 	<ul style="list-style-type: none"> One 1° relative diagnosed with breast cancer before the age of 50 (without the additional features of the potentially high-risk group - see category 3) Two 1° relatives, on the same side of the family, diagnosed with breast cancer (without the additional features of the potentially high-risk group -see category 3) Two 2° relatives, on the same side of the family, diagnosed with breast cancer, at least one before the age of 50, (without the additional features of the potentially high-risk group - see category 3). 	<ul style="list-style-type: none"> Women who are at potentially high risk of ovarian cancer Two 1° or 2° relatives on one side of the family diagnosed with breast or ovarian cancer plus one or more of the following on the same side of the family: <ul style="list-style-type: none"> additional relative(s) with breast or ovarian cancer breast cancer diagnosed before the age of 40 bilateral breast cancer breast and ovarian cancer in the same woman Jewish ancestry breast cancer in a male relative. One 1° or 2° relative diagnosed with breast cancer at age 45 or

		<p>younger plus another 1° or 2° relative on the same side of the family with sarcoma (bone/soft tissue) at age 45 or younger</p> <ul style="list-style-type: none"> • Member of a family in which the presence of a high-risk breast cancer gene mutation has been established.
Risk of breast cancer up to age 75 is between 1 in 4 and 1 in 2. Risk may be more than 3 times the population average. Individual risk may be higher or lower if genetic test results are known.	Risk of breast cancer up to age 75 is between 1 in 8 and 1 in 4. This risk is 1.5 to 3 times the population average.	Risk of breast cancer up to age 75 is between 1 in 4 and 1 in 2. Risk may be more than 3 times the population average. Individual risk may be higher or lower if genetic test results are known.

Table 1. Characteristics of 511 women at the time of their first consultation in the BOCRCM

Median age (range)		
37 years (18-70 years)		
Median follow-up time (range)		
34 months (1-96 months)		
Mutation status	Number of patients	Additional information
<i>BRCA1</i>	90	One subject had a <i>BRCA2</i> variance of unknown significance (VUS) at the same time.
<i>BRCA2</i>	99	One subject had a concomitant pathogenic <i>MSH2</i> mutation.
<i>CDH1</i>	3	
<i>MSH6</i>	1	
<i>STK11</i>	6	
<i>PALB2</i>	2	
<i>PTEN</i>	1	
<i>TP53</i>	4	
None detected	305	Lifetime risk of developing breast cancer in N = 201, based on the risk model BOADICEA, median: 20%, range: 10.7%-40%
Women tested negative for a mutation	296	
Women who did not undergo genetic testing	9	4 refused to undergo predictive genetic testing, 2 index patients did not receive genetic testing (1 refused, 1 lived overseas), 3 family members were tested positive for a likely benign variant of uncertain significance (VUS) in the <i>BRCA1</i> or <i>BRCA2</i> genes – no predictive genetic testing was offered for the

		VUS
Pathology of previously diagnosed cancers in 36 patients	Number of previous cancers	Number of previous cancers by mutation status
Breast cancer	7 x invasive ductal carcinomas (IDC) 1 x invasive lobular carcinoma (ILC) 2 x lobular carcinomas in situ (LCIS) 2 x ductal carcinomas in situ (DCIS)	4 x <i>BRCA1</i> (one had a <i>BRCA2</i> VUS at the same time), 1 x <i>BRCA2</i> , 1 x <i>TP53</i> (bilateral breast cancer) 1 x <i>BRCA2</i> 2 x non-carriers 2 x non-carriers
Ovarian cancer	21	14 x <i>BRCA1</i> 7 x <i>BRCA2</i>
Endometrial cancer	1	1 x <i>PALB2</i>
Multiple myeloma	1	1 x <i>BRCA2</i>
Mucoepidermoid cancer of the lung	1	1 x <i>BRCA2</i>
Cervical cancer	1	1 x non-carrier

Table 2. Reasons for discharge from the clinic (N = 210)

Reason for discharge	Number of patients
Not at high risk	53 (<i>BRCA</i> predictive testing resulted in a negative test result in 10 subjects)
Prophylactic surgeries	55
Managed elsewhere	21
Transfer to oncologic care due to a recent cancer diagnosis	16 x invasive carcinoma 8 x DCIS 1 x LCIS
Deceased (due to cancer)	4
Missed appointments	28
Moved interstate/overseas	19
Self-discharged due to high cancer anxiety	1
To be re-referred	4

Table 3. Characteristics (at time of diagnosis) of the 22 breast malignancies detected in the BOCRCM between August 2010 and July 2018

Cancer type			
	<i>BRCA1</i>	<i>BRCA2</i>	<i>STK11</i>
DCIS (N = 9 in 8 subjects) - 6 high-grade DCIS - 3 intermediate-grade DCIS	2 (one was previously diagnosed with stage IV ovarian cancer)	3 (one had two metachronous diagnoses; one had a <i>MSH2</i> mutation at the same time)	2
IDC (N = 12)	3	3	0
ILC (N = 1)	0	1	0
Grade of invasive cancers (N = 13)			
	<i>BRCA1</i>	<i>BRCA2</i>	
Grade 1	0	0	
Grade 2	2	2	
Grade 3	2	2	
Axillary lymph node involvement			
	<i>BRCA1</i>	<i>BRCA2</i>	
Positive	0	1 Positive nodes/all extirpated nodes: 4/12	
Negative	4	3	
Receptor status of invasive cancers (N = 13)			
	<i>BRCA1</i>	<i>BRCA2</i>	
Triple-negative, basal-like	3	0	
ER positive, PR positive, HER2 negative	1	4	

ER positive, PR negative, HER2 negative	0	0		
ER positive, PR positive, HER2 amplified	0	0		
Surgical treatment				
	BRCA1	BRCA2	STK11	
Lumpectomy only	0	2 (one had two distinct diagnoses of DCIS; one had a MSH2 mutation at the same time)	0	
Mastectomy	5	5	2	
Breast cancer detection methods				
	MRI	Mammogram	Ultrasound	Self-detected
Total numbers of tumours detected by each method	12 (12)	12 (18)	7 (8)	1 (1)
Women aged under 50 years (n = 15 women)	12 (12)	8 (11)		1
Women aged at least 50 years (n = 6 women, 7 cancers)	0	4 (7)	5 (6)	0
Number of screening rounds at which the breast cancer was detected				
	BRCA1	BRCA2	STK11	Non-carrier
Median (range)	3 (2-6)	4 (3-7)	6.5 (6-7)	4 (2-8)

Table 4. Prophylactic surgery and preventive medicine uptake cancer-free women

Prophylactic measurement	Proportion of patients by mutation status			
	<i>BRCA1</i>	<i>BRCA2</i>	<i>PTEN</i>	Non-carrier
Bilateral prophylactic mastectomy (BPM)	36.9% (24/65)	19% (15/79)	100% (1/1)	5.7% (16/283)
Median age (range) in years	39 (27-59)	39 (20-53)	53	44.5 (26-60)
	<i>BRCA1</i>	<i>BRCA2</i>	<i>STK11</i>	Non-carrier
Bilateral risk-reducing salpingo-oophorectomy (BSO)	30.8% (20/65)	26.6% (21/79)	50% (2/4)	5.3% (15/283)
Median age (range) in years	45.5 (37-55)	45 (34-68)	38 (33-43)	43 (39-59)
BSO conducted at age ≤45 years	18.5% (10/54)	18.8% (12/64)	66.7% (2/3)	5.3% (11/209)
	<i>BRCA1</i>	<i>BRCA2</i>	<i>CDH1</i>	Non-carrier
Tamoxifen (1-60 months)	1.5% (1/65)	8.9% (7/79)	50% (1/2)	7.4% (21/283)
Median age (range) in years	42	42 (33-58)	46	43.8 (31-67)

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