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Optimising cancer risk management for women at increased risk of breast cancer

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Master of Philosophy – MDHS (Medicine)

August 2022

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Submitted in total fulfilment for the degree of Master of Philosophy.

i. Abstract

Breast cancer is the most common cancer (after skin cancer) affecting women and is the second most common cause of cancer-related death for Australian women(1). Though breast cancer survival has improved in the last three decades, breast cancer incidence continues to rise and the disease now affects 1 in 7 women in their lifetime(1). In Australia, women are stratified into breast cancer risk categories (high, moderate or low) based on their lifetime risk of breast cancer(2); this categorisation helps guide a personalised approach to screening and breast cancer prevention with the aim of moving away from a “one size fits all” approach and towards precision prevention and screening based on personal risk level

This thesis aims to add to the personalised approach to management of breast cancer risk by: 1) contributing to a better understanding of barriers to effective risk management interventions that are currently available to women at elevated breast cancer risk and 2) reporting on the use of interventions offered to women that are not supported by evidence.

Two studies presented in this thesis address the first aim. The first evaluates the current use of risk-reducing medication in Australia and the potential predictors of use. The second identifies barriers and facilitators to breast cancer risk-reducing medication from the perspectives of women and their clinicians. These studies demonstrate that the use of risk-reducing medication in Australia is very low, even compared to international standards. Novel barriers to risk-reducing medication use were identified, including women not having enough information to make a decision and clinicians being unaware of risk-reducing medications. The application of behavioural change theory to these results suggests the effective interventions to

address these barriers would be: targeted education to clinicians and the public about the role and effectiveness of risk-reducing medications; campaigns to increase awareness of individualised breast cancer risk assessment; and policy change to facilitate routine breast cancer risk assessment.

The second aim was addressed through two studies, the first evaluating the use of ineffective ovarian cancer screening in Australia and the second assessing the effectiveness of clinical breast examination as a component of breast cancer surveillance programs for women who carry a pathogenic variant in *BRCA1* or *BRCA2.*

The first study identified that ovarian cancer screening continues despite strong evidence and national guidelines not supporting its use. The facilitators of screening identified in this study included difficulty discontinuing screening, ordering screening tests for patient peace of mind and the lack of other available screening tests, highlighting the challenges of de-implementation of ineffective screening tests. Linking these identified facilitators with a validated behaviour change model pointed to interventions including education for clinicians and women on the ineffectiveness of ovarian cancer screening and a public campaign illustrating why high-profile women in the community do not screen for ovarian cancer. The second study demonstrated that clinical breast examination in carriers of a pathogenic variant in *BRCA1* and *BRCA2* has a very low clinical yield when used within a screening program that includes breast MRI, suggesting that clinical breast examination may be safely omitted in that setting.

This thesis concludes that effective risk management interventions are underused in Australia, while there is continued widespread use of ineffective screening tests.

Precision prevention for breast cancer requires the harnessing of available effective interventions and not offering tests that are not of benefit. Changes are required in our approach to breast cancer risk reduction to be successful in reducing breast cancer incidence in Australia.

ii. Declaration

This is to certify that

(i) *The thesis comprises only my original work towards the Master of Philosophy – MDHS (Medicine) except where indicated in the Preface;*

(ii) *Due acknowledgment has been made in the text to all other material used;*

(iii) *The thesis is fewer than 40 000 words in length, exclusive of tables, figures, bibliographies and appendices*

Courtney Macdonald, MBChB

iii. Preface

This thesis is comprised of four peer reviewed journal articles. I am lead author on all four of these articles. Several colleagues contributed to these publications as described below.

Study 1 – Chapter 4: *Underutilisation of breast cancer prevention medication in Australia.* This study focused on identifying the use of risk-reducing medication in eligible women in Australia and potential demographic predictors of its use, including parity, number of first-degree relatives with breast cancer, BOADICEA lifetime risk (breast cancer risk from birth to age 80) and education level. I was involved in study design, data interpretation, manuscript writing, revision, and final manuscript approval. Jamie Chamberlain and Roger Milne provided substantial contributions to the study design, data analysis, interpretation of results, manuscript revision and final manuscript approval. Danielle Mazza was involved with the conception of the study, manuscript revision and final approval of the manuscript. Kelly-Anne Phillips assisted with conceptualisation, study design, data interpretation, manuscript review and final manuscript approval.

Study 2 – Chapter 4: *Breast cancer chemoprevention: Use and views of Australian women and their clinicians*. This is a survey-based study, which used the Theoretical Domains Framework to investigate the barriers and facilitators to risk-reducing medication use. Study participants were recruited from the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) cohort that is an Australian based national breast cancer family study. Under the

supervision of Professor Kelly-Anne Phillips, I led this study and was involved in the conceptualisation, design, data analysis and interpretation, manuscript writing and revision. Danielle Mazza was heavily involved in study design, conceptualisation, manuscript revision, editing and final manuscript approval. Christobel Saunders was involved in conceptualisation, manuscript revision and final manuscript approval. Louise Keogh was involved in conceptualisation, data analysis, manuscript revision and final manuscript approval. Morgan Hunter was involved in data analysis, manuscript revision and final manuscript approval. Sue-Anne McLachlan was involved in conceptualisation, manuscript revision, and final manuscript approval. Sandra Jones was involved in conceptualisation, manuscript review, and final manuscript approval. Stephanie Nesci was involved in data acquisition, data analysis, project administration, manuscript review, and final manuscript approval. Michael Friedlander was involved in conceptualisation, manuscript review, editing and final manuscript approval. John Hopper was involved in conceptualisation, manuscript review, editing and final manuscript approval. Jon Emery was involved in conceptualisation, manuscript review, and final manuscript approval. Martha Hickey was involved in conceptualisation, manuscript review, and final manuscript approval. Roger Milne was involved in conceptualisation, study design, data analysis and interpretation, manuscript review and final manuscript approval. Kelly-Anne Phillips was involved in conceptualisation, study design, data interpretation and analysis, supervision, funding acquisition, project administration, manuscript review, and final manuscript approval.

Study 3 – Chapter 5: *Motivators of inappropriate ovarian cancer screening: A survey of women and their clinicians.* This is a survey-based study of Australian women and clinicians that used the Theoretical Domains Framework to identify reasons for use

of ineffective ovarian cancer screening in Australia. Participants for this study were recruited from the kConFab cohort. I led this study with the supervision of Professor Kelly-Anne Phillips and Danielle Mazza and was involved in study design, conceptualisation, data analysis and interpretation, manuscript writing and revision and final manuscript approval. Danielle Mazza was involved in conceptualisation, study design, data interpretation, manuscript revision and final manuscript approval. Martha Hickey was involved in conceptualisation, manuscript revision and final manuscript approval. Morgan Hunter was involved in data analysis, manuscript revision and final manuscript approval. Louise Keogh was involved in conceptualisation, study design, data interpretation, manuscript revision and final manuscript approval. kConFab investigators were involved in data acquisition, manuscript revision and final manuscript approval. Sandra Jones was involved in conceptualisation, manuscript revision and final manuscript approval. Christobel Saunders was involved in conceptualisation, manuscript revision and final manuscript approval. Stephanie Nesci was involved in data acquisition, study design, manuscript writing and final manuscript approval. Roger Milne was involved in conceptualisation, data analysis, supervision, manuscript revision, editing and final manuscript approval. Sue-Anne McLachlan was involved in conceptualisation, manuscript revision and final manuscript approval. John Hopper was involved in conceptualisation, manuscript revision and final manuscript approval. Michael Friedlander was involved in conceptualisation, manuscript revision and final manuscript approval. Jon Emery was involved in conceptualisation, manuscript revision and final manuscript approval. Kelly-Anne Phillips was involved in conceptualisation, study design, data interpretation, manuscript revision, supervision and final manuscript approval.

Study 4 – Chapter 6: *The value of clinical breast examination in a breast cancer surveillance program for women with a germline BRCA1 or BRCA2 pathogenic variant.* This was a retrospective cohort study of women with a *BRCA1* or *BRCA2* pathogenic variant seen at the Peter MacCallum Cancer Centre Breast and Ovarian Risk Management clinic. I led this study and was involved in conceptualisation, study design, data acquisition, data interpretation, manuscript writing, revision and final manuscript approval. Tamara Hettipathirana was involved in study design, data acquisition, manuscript writing and final manuscript approval. Jing Xie assisted with data analysis, manuscript revision and final manuscript approval. Kate Moodie was involved with conceptualization, study design, manuscript revision and final manuscript approval. Chris Michael-Lovatt was involved with data acquisition, data analysis, manuscript review and final manuscript approval. Kelly-Anne Phillips was involved with conceptualization, supervision, study design, data interpretation, manuscript revision and final manuscript approval.

All four studies have been published in peer-reviewed journals.

Study 1: Published in The Breast Journal, August 2021

Study 2: Published in Cancer Prevention Research, October 2020 with an accompanying editorial (appendix 7)

Study 3: Published in Journal of the National Cancer Institute Cancer Spectrum, December 2020

Study 4: Published in the Medical Journal of Australia, September 2021 with an accompanying editorial (appendix 8)

Funding sources

This work within this thesis was supported by Cancer Australia and the National Breast Cancer Foundation (PdCCRS #1100868). kConFab and the kConFab follow up study have received additional funding support from Cancer Australia (809195), the Australian National Breast Cancer Foundation (IF 17), the Australian National Health and Medical Research Council (454508, 288704 and 145684), the National Institute of Health USA (1RO1CA159868), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia.

In addition, this work was funded in part by the Rita Gardner Travelling Scholarship in Medicine for the Highest Overall Mark in the MBChB degree which was awarded to Courtney Macdonald in 2010 by the University of Otago, New Zealand.

iv. Acknowledgements

I would like to thank my supervisors Professor Kelly-Anne Phillips and Professor Roger Milne for their support and guidance during my candidature. In particular, I greatly appreciate their support in allowing me to complete my candidature from New Zealand during the COVID-19 pandemic and following completion of my maternity leave. In addition to supervision for this MPhil, Professor Kelly-Anne Phillips has provided invaluable guidance in my development as a clinician and researcher.

Thank you to my MPhil committee at the Peter MacCallum Cancer Centre for your invaluable feedback on my progress and guidance with the particular direction of my projects. Thank you to my mentor Professor Sarah-Jane Dawson who provided both professional and personal advice that helped me immensely with the change in the work life equilibrium that comes with having a new baby.

Thank you to Sarah O'Connor, Stephanie Nesci, Sandra Picken and Lucy Stanhope for your research support. Thank you to Roger Milne, Jamie Chamberlain, Jing Xie and Julie Bassett, for providing statistical support.

Thank you to all the women who participated in the kConFab study, without whom this research would not be possible. Finally thank you to my wife, Olivia Bupha-Intr and our daughter Lucy, who have supported me through many changes and challenges in the last 3 years.

v. Table of Contents

vi. List of Tables and Figures

vii. List of Abbreviations

Abbreviations	**Term**
ADH	Atypical ductal hyperplasia
ATM	Ataxia-telangiesctasia mutated
BBD	Benign breast disease
BC	Breast cancer
BCRAT	Breast cancer risk assessment tool
BOADICEA	Breast and ovarian analysis of disease incidence and carrier estimation algorithm
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
CAPR	Cancer prevention research
CA125	Cancer antigen 125
CDH1	Cadherin 1
COM-B	Capability, opportunity, motivation behaviour system
DCIS	Ductal carcinoma in-situ
DNA	Deoxyribonucleic acid
ESMO	European society of medical oncology
GP	General practitioner
HER2	Human epidermal growth factor receptor 2
HRT	Hormone replacement therapy
kConFab	Kathleen Cuningham Foundation Consortium for Research into Familial Aspects of Breast Cancer
LCIS	Lobular carcinoma in-situ
MBS	Medical benefits schedule
MRI	Magnetic resonance imaging
NCCN	National comprehensive cancer network
NHS	National health service
NICE	National institute for health and clinical excellence
PALB2	Partner and localiser of *BRCA2*
PARP	Poly adenosine diphosphate-ribose polymerase
PLCO	Prostate, Lung, Colorectal and Ovarian cancer screening trial
PRS	Polygenic risk score
PTEN	Phosphate and TENsin homolog deleted on chromosome 10
RRM	Risk-reducing bilateral mastectomy
RRMed	Risk-reducing medication
RRS	Risk-reducing surgery
RRSO	Risk-reducing salpingo-oophorectomy
RUP	Rapid uptake products

SERM	Selective estrogen receptor modulator
SNP	Single nucleotide polymorphism
STK11	Serine/threonine kinase 11
TP53	Tumor protein 53
TVUS	Trans-vaginal ultrasound

Chapter 1: Thesis overview

Background

Breast cancer is the most common cancer, following skin cancer, affecting women both globally(3) and in Australia(1). Well over half a million women (685,000) died from breast cancer worldwide in 2011(4). There were 19, 535 new cases of breast cancer in Australia in 2019, representing approximately 14% of all new cancer diagnoses. In 2019 3,243 deaths were attributed to breast cancer in Australia(1). Mortality from breast cancer is decreasing due to advances in treatments, in particular targeted treatments(5, 6). However, breast cancer incidence is increasing, and the treatment of breast cancer is a significant undertaking for health systems worldwide.

There are currently two approaches to breast cancer prevention and early detection. The first is population-based, applied to all women regardless of breast cancer risk. Examples of this approach include population-based breast cancer screening with mammography, which is well established in most high-income countries, and educational and policy interventions aimed at risk factor reduction such as limiting alcohol intake and obesity. The benefits of population-based screening, decreasing stage at diagnosis and reduced breast cancer specific mortality, are well described(6). The second approach is precision prevention and screening, which involves accurate estimation of an individual's breast cancer risk and the tailoring of screening and prevention interventions based on degree of risk. Though broad population-based prevention strategies are well established, a more individualised

precision approach to breast cancer prevention and screening is in its infancy. These two approaches are complimentary; the general population approach enhances risk reduction and early detection for all women while the precision approach provides additional, more intensive, screening and risk-reduction strategies for those identified to be at substantially elevated breast cancer risk.

The first step in precision prevention and screening is risk assessment. Validated breast cancer risk assessment models are now widely available and have been refined over the last decade. There are many genetic and non-genetic factors that increase a woman's risk for breast cancer, including age, parity, breastfeeding, body mass index, use of hormone replacement therapy and hormonal contraception, alcohol consumption and being a carrier of a germline pathogenic variant predisposing to breast cancer development. Women with a strong family history of breast and ovarian cancer, or a pathogenic germline variant in cancer predisposition genes such as *BRCA1* or *BRCA2,* also have a substantial increase in ovarian cancer risk. Conversely, women with a strong family history of breast cancer, without a family history of ovarian cancer or a predisposing germline variant, do not have an increased ovarian cancer risk.

Effective options to reduce breast cancer risk in women at elevated risk exist and include risk-reducing medication and surgery. The premise of this thesis is that existing evidence-based risk management strategies for women at increased risk of breast cancer need to be effectively utilised, while avoiding ineffective interventions. This thesis aims to understand the barriers to and facilitators of beneficial and

detrimental interventions aimed at reducing cancer burden in women across the spectrum of breast cancer risk.

In addition to quantifying the problems (extent of use of effective risk management strategies and of ineffective screening tests, such as ovarian cancer screening) and identifying specific barriers and facilitators, this thesis aims to provide focused ways to overcome these barriers by linking with behavioural change theory. Health care behaviours are complex and changing them requires a multifaceted approach. Behavioural change theory helps identify the constructs in which certain health behaviours are founded, and allows identification of interventions aimed at appropriately altering the particular behaviours.

Focus and Structure of this thesis

This thesis focuses on the use of certain risk reducing interventions (both effective and ineffective) in women at different levels of breast cancer risk. There are two study cohorts used in this thesis; the Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer (kConFab) Follow-up Study(7) and a cohort of women who attend the Peter MacCallum Cancer Centre Breast and Ovarian Cancer Risk Management Clinic (see Section: Background Cohorts).
Four research questions were developed:

1) Is risk-reducing medication underutilised in Australia?
2) What are the predictors of, and facilitators and barriers to risk-reducing medication use in women with moderate to high breast cancer risk in Australia?

3) What are the facilitators of use of ineffective ovarian cancer screening in women across the spectrum of cancer risk in Australia?
4) Does clinical breast examination add value to a screening program for *BRCA1* and *BRCA2* pathogenic variant carriers that includes breast MRI?

Chapter 2 reviews the background and key concepts for these research questions including breast cancer risk factors, risk stratification, available risk management interventions and the concept of precision prevention and screening. Chapter 3 provides background on the two main cohorts used for the study settings.

Chapter 4 focuses on answering research questions 1 and 2 and includes two peer-reviewed publications. These demonstrate underutilisation of risk-reducing medication by eligible Australian women and identify common barriers and facilitators from the perspective of both women and their treating clinicians.

Chapter 5 focuses on the issue of ongoing ovarian cancer screening in Australia, despite guidelines no longer recommending screening, as it is ineffective and does not have any impact on mortality from ovarian cancer. This chapter includes a peer-reviewed study that looks at the common facilitators of ovarian cancer screening, again from the perspective of both women and their treating clinicians, shedding light on the work that needs to be done to change this health care behaviour.

Chapter 6 addresses whether clinical breast examination is of benefit to *BRCA1* and *BRCA2* pathogenic variant carriers who already undergo intensive radiological screening that includes breast MRI. This peer-reviewed publication identifies the very

low sensitivity of clinical breast examination in this population and challenges its routine use in clinical practice.

Chapter 7 summarises the implications of the above publications for the implementation of a precision approach to breast cancer prevention and screening. The strengths and limitations of this thesis are also discussed, as well as recommendations for further research, interventions and policy change.

Chapter 2: Background Literature

Breast Cancer Risk Factors

There are several recognised risk factors for breast cancer, and knowledge of new risk factors continues to emerge, particularly with the development of genomic and imaging technologies. Demographic factors of female sex and older age are important risk factors for breast cancer. The ten-year probability of developing breast cancer increases from less than 1.5% at age 40 to over 4% by age 70(8). The average age at diagnosis of a first breast cancer is 61 years and 79% of new cases of breast cancer are in women over the age of 50 years (1). Reproductive factors that predispose women to prolonged exposure to endogenous oestrogen increase breast cancer risk(9). These include early onset of menarche, late menopause, late age at birth of first child, nulliparity and not breastfeeding. Exogenous oestrogen (particularly when combined with progesterone) in hormone replacement therapy (HRT)(10, 11), and hormonal contraceptives are also known to increase risk of breast cancer(12).

Lifestyle factors have become increasingly important in breast cancer development, given the rise in obesity and sedentary lifestyle within society. High body mass index (BMI) is associated with increased post-menopausal breast cancer risk. The Australian Institute of Health and Welfare estimates that in 2011, 22% of the breast cancer burden in women was due to elevated BMI(13, 14). The relative risk for post-menopausal breast cancer, compared with a woman with normal weight ($18.5<BMI<25 kg/m^2$) is around 1.4 for an obese woman ($BMI >30 kg/m^2$) and around 1.6 for a morbidly obese woman ($BMI >35 kg/m^2$)(15). Alcohol consumption is

associated with increased breast cancer risk; for every additional 10g of ethanol consumed daily, breast cancer risk increases by 9%(16). Level of physical activity is also associated with breast cancer risk, independent of BMI. Women in the highest quartile of self-reported physical activity have a 25% relative breast cancer risk reduction than those in the lowest quartile. The benefit of physical activity is seen in pre and post-menopausal women(17). Family history is important, not only for predicting the likelihood of an inherited cancer predisposing germline pathogenic variant, but also to estimate individual risk based on the number of affected first and second-degree relatives and their ages at diagnosis (18).

Specific events within a woman's medical history may influence her breast cancer risk. Women who have had Hodgkin lymphoma and had previous mantle radiation are at elevated breast cancer risk(19). A previous diagnosis of benign breast disease (BBD) is also important to ascertain. Benign breast disease without atypia(20) is associated with a small increase in breast cancer risk. Atypical ductal hyperplasia (ADH) is associated with a modest increase in breast cancer risk(21). DCIS(22) and lobular carcinoma in situ(23) (LCIS) are associated with a much higher risk of breast cancer, with a 7-11% risk of being diagnosed with breast cancer within 10 years(23, 24).

Mammographic density has a strong association with breast cancer risk. Mammographic density refers to the percentage of dense tissue of an entire breast, with a value of 50% or greater defined as high mammographic density. More than 50% of women under the age of 50 in the United States have high mammographic density(25). Breast density relates proportionally to breast cancer risk and is relevant

to both pre and post-menopausal women. Women with over 75% dense tissue have four to six times the risk of breast cancer compared to those with very little to no dense tissue(26). Importantly, several lifestyle and reproductive factors are associated with mammographic density, making it a potentially modifiable risk factor(27).

Around 15-30% of breast cancers are due to genetic factors (28). Pathogenic germline variants in breast cancer susceptibility genes, including *BRCA1, BRCA2, PALB2, ATM* and a range of other genes, explain only 5-10% of breast cancer cases. These genetic pathogenic variants are discussed in detail below (see section *Pathogenic variants*). In an effort to identify the other components of heritable breast cancer risk, there has been much work in identifying single nucleotide polymorphisms (SNPs). SNPs are substitutions of single nucleotides and account for the vast majority of the common variation in the human genome. Some SNPs are associated with generally small increased risk of breast cancer. The joint effect of multiple susceptibility SNPs is associated with greater breast cancer risk than a single SNP. A polygenic risk score (PRS) is a combined measure of the joint effect of multiple SNPs. Recently a PRS comprised of 313 SNPs was shown to be a reliable predictor of breast cancer risk(29) and efforts are underway to incorporate this measure into breast cancer risk assessment. Several studies have evaluated the effect of adding PRS to existing risk prediction models, such as Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), and found that PRS gives the greatest contribution to risk stratification followed by mammographic density (30).

Pathogenic variants

Tracing the heritable contribution of breast cancer dates back to the 1940's when it was observed that breast cancer clustered in particular families with multiple relatives affected. The *BRCA1* gene was discovered on chromosome 17 in 1994(31) and the *BRCA2* gene was discovered in 1995 on chromosome 13(32). Both *BRCA1* and *BRCA2* pathogenic variants demonstrate a highly penetrant autosomal dominant inheritance. Since their discovery, there have been over 1,000 pathogenic variants identified in each gene.

BRCA1 and *BRCA2* are tumour suppressor genes that function in the repair of double-strand DNA breaks, termed homologous recombination repair. When affected by a pathogenic variant, these genes do not function effectively, giving rise to cumulative breaks in the DNA and eventually genomic instability, leading to the development of cancer. *BRCA1* and *BRCA2* account for the majority of breast cancers due to germline variants.

BRCA1 pathogenic variant carriers tend to have an earlier age of onset of breast cancer than non-carriers, with peak relative breast cancer risk occurring between 41 to 50 years of age in *BRCA1* carriers and 51 to 60 years in *BRCA2* carriers (33). Seventy percent of breast cancers arising in a *BRCA1* pathogenic variant carrier are triple-negative (oestrogen receptor-negative, progesterone receptor-negative and human epidermal growth factor receptor 2-negative). The majority of breast cancers in *BRCA2* pathogenic variant carriers are hormone receptor positive with the second most common type of breast cancer being triple negative but this tends to develop within the older age groups. There is a low prevalence of human epidermal growth

factor 2 (HER2) receptor positive breast cancer in *BRCA1* and *BRCA2* pathogenic variant carriers (2.1% *BRCA1* and 6.9% *BRCA2*)(34).

The average cumulative risk of breast cancer to age 80 years is 72% for a *BRCA1* pathogenic variant carrier and 69% for a *BRCA2* pathogenic variant carrier (33). There is also a substantial increase in risk of high-grade serous ovarian, fallopian and primary peritoneal cancers (herewith these three disease entities are referred to as “ovarian cancer” for brevity) in women with *BRCA1* and *BRCA2* pathogenic variants. The average cumulative lifetime risk developing ovarian cancer is around 44% and 17% *BRCA1* and *BRCA2* pathogenic variant carriers, respectively (33). In women with a *BRCA1* or *BRCA2* pathogenic variant, both family history and pathogenic variant position influence breast cancer risk. *BRCA1* and *BRCA2* pathogenic variant carriers with two or more affected relatives have a higher risk of breast cancer than their counterparts who do not have affected relatives(33). *BRCA1* and *BRCA2* pathogenic variants that are located inside the c.2282-c.4071 position and c.2831-c.6401 position, respectively, are associated with lower breast cancer risk than those outside those positions(33). There have also been multiple breast and ovarian cancer cluster regions, within both *BRCA1* and *BRCA2* genes, described in the literature(35).

The prevalence of *BRCA1* and *BRCA2* pathogenic variants in the general population is 0.2-0.3%(36). Certain populations are at greater risk of carrying a pathogenic *BRCA1* or *BRCA2* pathogenic variant. The most well-known example is the Ashkenazi Jewish population, where the prevalence of pathogenic variants in *BRCA1* and *BRCA2* is 2.6%. There are three common founder pathogenic variants

within the Ashkenazi Jewish population: *BRCA1* 185delAG, *BRCA1* 5382insC and *BRCA2* 6174delT which account for the majority of pathogenic variants in this ancestral group(37-39). Women of African or Latin American descent have a higher prevalence of *BRCA1* pathogenic variants compared with women of Western European ancestry(40).

As well as being important for targeting intensified screening and risk reduction strategies, identification of *BRCA1* or *BRCA2* pathogenic variants has important therapeutic consequences and is important in the setting of newly diagnosed breast cancer as it can influence systemic treatment and surgical management decisions. Bilateral mastectomy may be recommended for treatment of breast cancer and prevention of contralateral breast cancer. More recently, the use of the PARP inhibitor, olaparib, as part of adjuvant treatment for breast cancer in *BRCA1* and *BRCA2* pathogenic variant carriers has been shown to significantly extend disease-free survival in patients with early stage, HER2-negative breast cancer(41).

Pathogenic variants in breast cancer susceptibility genes are classified into three groups based on the conferred risk of breast cancer. High-risk variants are associated with a relative risk of breast cancer greater than 4. Moderate risk variants are associated with a relative risk of 2-4 and low risk variants are associated with a relative risk less than 2.0 (42). In addition to *BRCA1* and *BRCA2* other genes with high-risk variants include *TP53*(43), *PTEN*(44), *CDH1*(45), *STK11*(46) and *PALB2*. Genes with moderate risk variants include *ATM*(47), *CHEK2*(48), *RAD51D*(49) and *PALB2*(50). Each of the high and moderate-risk variants have differing

recommendations for surveillance(51) and management, specific to not only breast cancer risk, but also importantly, risk of other associated cancers.

Breast cancer risk stratification

Breast cancer risk can be empirically separated broadly into three categories to guide screening practices and risk management interventions. Cancer Australia defines “at or slightly above average risk of breast cancer” as women with a lifetime risk of cancer to age 75 of less than 1.5 times the population average(2). More than 95% of women fall into this group. Women in the moderately-increased risk group have a lifetime risk of 1.5 to 3 times the population average. The high-risk group is defined as having a lifetime risk of greater than 3 times the population average. Carriers of a high-risk pathogenic variant, women with a personal history of breast cancer or other high-risk breast lesions(21) (lobular carcinoma in situ, atypical ductal hyperplasia) and women who have had high-dose chest radiotherapy, make up the majority of this high-risk group.

Internationally, there are no standardised risk categories and there is heterogeneity in the numerical classification of breast cancer risk. The National Institute for Health and Care Excellence (NICE) guidelines define general population risk as less than 17% lifetime risk, moderate risk 17%-30% and high-risk as 30% or greater lifetime risk of breast cancer(52). The National Comprehensive Cancer Network (NCCN) define average lifetime risk of breast cancer as less than 15%, moderate risk between 15-20% and high risk as greater than 20%(53). There are also differences between the risk prediction models used and whether lifetime or five-year breast cancer risk are used to guide selection for use of risk management interventions.

Breast cancer risk prediction models

With the identification of breast cancer risk factors, there has been an effort to design predictive models that can be used to correctly stratify those at elevated breast cancer risk and offer appropriate preventative strategies. There is wide variation in the risk factors included in the multiple risk prediction models; some include more comprehensive cancer family history, some incorporate different detail about non-familial risk factors and others have evolved to take into account more recently recognised breast cancer risk factors including mammographic density and polygenic risk score (PRS).

The Gail model (also referred to as the Breast Cancer Risk Assessment Tool, BCRAT) was developed in 1989 and was the first model developed for breast cancer risk estimation(54). It has undergone several modifications since then. This model was used in the NSABP P2 trial of tamoxifen and raloxifene as risk-reducing medication(55). In studies of utility, the Gail model has limitations especially in high-risk women with significant family history, as it does not include information on second-degree relatives and lacks accurate individual discrimination. Its generalisability, particularly to different ethnic groups, has also been challenged, as the model was developed using data from a large cohort of white women. This model has been superseded in performance by more comprehensive and generalisable models; however, the Gail model is still widely used internationally.

The International Breast Cancer Intervention Study (IBIS) Breast Cancer Risk Evaluation tool, also known as the Tyrer-Cuzick model, was developed in 2004(56).

This model was used to determine eligibility for the IBIS I prevention trial(57). It includes multiple risk factors including familial, hormonal factors and details of prior breast disease. It includes second-degree relative cancer history, ovarian cancer, age at diagnosis of family members, unaffected status of family members and genetic testing results. An updated version of this model includes information on mammographic density and PRS(58).

The BRCAPRO model was developed in 2002 and calculates breast cancer risk based on the likelihood of being a *BRCA1* or *BRCA2* pathogenic variant carrier(59). It is predominantly used to select women with a strong family history of breast cancer for genetic testing. Data inputs include personal and family history of breast cancer, ovarian cancer and other *BRCA* related cancers. This model does not allow for other unknown, non-*BRCA*, genetic factors and therefore is not suitable for assessment of breast cancer risk in the wider population, outside of women with a strong family history (two affected first-degree relatives or one affected first-degree relative plus two other affected relatives).

The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model was developed in 2002(60). It incorporates the probability of carrying a wider range of less common breast cancer susceptibility gene variants (*BRCA1, BRCA2, PALB2, CHEK2, ATM*). It has further been refined and the most recent version has incorporated mammographic density and PRS in the assessment of risk(30).

There are a wide range of other risk prediction models in use, but the four models described above have been validated and are the most frequently used. A validation study published in 2019 demonstrated that IBIS and BOADICEA have superior ability to predict breast cancer risk when compared with the BCRAT and BRCAPRO models(61).

Risk Management

Screening

Mammographic screening for breast cancer in the general population is well established in most high-income countries and has demonstrated a reduction in breast cancer mortality in women between the age of 40-74 who undergo screening every one to two years(62). In Australia, women are invited for two-yearly mammograms from the age of 50 to 74 years of age(6). Women from age 40 to 49 and those 75 years and older can also access free mammographic breast screening but are not sent invitations The utility of mammographic screening for women under the age of 40 years is limited, due to their generally higher breast density, leading to higher probability of false-positive and false-negative results(63).

Correct breast cancer risk stratification is important in guiding recommended frequency and modality of breast cancer screening. Some younger women are at high-risk of developing early-onset breast cancer and warrant earlier commencement of intensive breast screening. Breast magnetic resonance imaging (MRI) was first shown to be useful in distinguishing abnormal breast tissue from normal breast tissue in the 1980's(64). Breast MRI has a higher sensitivity than mammographic

screening(65-67) and has been shown to detect cancers at an earlier stage(68, 69). No survival benefit has been demonstrated from breast MRI screening compared with mammography(70). In Australia, women at high-risk of breast cancer are offered screening with annual MRI and mammogram from age 30 years, unless there is a familial case of breast cancer diagnosed at an earlier age. From age 50 years, women at high-risk are screened with annual mammography alone. The cost of breast MRI in high-risk women under age 50 years is reimbursed in Australia.

Lifestyle modification

The effect of lifestyle factors on breast cancer development is often not discussed in clinical practice, however minimising alcohol consumption, minimising HRT use, maintaining a healthy body weight, and exercising, are very important in preventing breast cancer. Physical inactivity is a risk factor for breast cancer and several studies have demonstrated that women who regularly undertake moderate to vigorous physical activity have an average breast cancer risk reduction of 25% compared to those who don't (71). Lifestyle changes often receive little attention in cancer risk management initiatives, however, as breast cancer risk is multifactorial, a holistic approach, including a focus on lifestyle measures is important for women at high-risk of breast cancer, especially for those who choose not to have risk-reducing surgery or medication.

Risk-reducing surgery

Bilateral risk-reducing mastectomy

Bilateral risk-reducing mastectomy (RRBM) is considered for women at high lifetime risk of breast cancer. It is the most effective form of breast cancer risk reduction and has been shown to reduce risk by 93% in asymptomatic carriers of the *BRCA1* and *BRCA2* pathogenic variants(72). No mortality benefit has been demonstrated, perhaps due to the lack of long-term prospective data(73).

Use of RRBM in asymptomatic *BRCA1* and *BRCA2* pathogenic variant carriers varies internationally from 2.7% to 44% in reported literature(74, 75). A prospective Australian study evaluated the use of RRBM in *BRCA1* and *BRCA2* pathogenic variant carriers and reported that 21% of pathogenic variant carriers had undergone RRBM, with the median age at the time of surgery being 40 years (76).

The majority of women who elect to undergo RRBM undergo simultaneous reconstruction, though this is associated with a higher incidence of surgical complications then those who do not have reconstruction(77). Though there has been concern about the psychological impact of RRBM, studies have reported that most women experience improved quality of life, diminished level of emotional concern about developing breast cancer and are satisfied with the procedure(78).

International guidelines generally recommend discussion of RRBM with women at high-risk of breast cancer, particularly those who have a predisposing germline pathogenic variant(2, 52, 53). Australian EVIQ guidelines recommend RRBM as the most effective form of risk reduction, with surgery conferring the greatest benefit when performed under the age of 40(79). The United States National Comprehensive Cancer Network guidelines support the discussion of RRBM for

women on a case-by-case basis, acknowledging the high degree of protection against breast cancer(53). ESMO guidelines recommend discussion of RRBM(80), and NICE guidelines recommend RRBM, with an emphasis on pre-surgical counselling and multi-disciplinary support to reduce negative psychosocial outcomes(52).

Bilateral-risk reducing salpingo-oophorectomy

Risk-reducing bilateral salpingo-oophorectomy (RRSO) has been shown to significantly reduce the risk of ovarian cancer in *BRCA1* and *BRCA2* pathogenic variant carriers. The risk reduction is greater than 90%, with the residual risk related to primary peritoneal cancer. RRSO is shown to reduce ovarian cancer specific mortality and all-cause mortality(81-83).

The timing of RRSO requires a careful balance between maximising the reduction in risk of ovarian cancer and minimising the physical consequences of surgery. For *BRCA1* pathogenic variant carriers, the risk of ovarian cancer starts to increase significantly above that of the general population at age 40 years(33). For *BRCA2* pathogenic variant carriers this occurs later, at around age 50 years(33). RRSO before natural menopause is associated with an increase in vasomotor symptoms, decrease in sexual function(84) and a decline in bone mineral density(85). As screening for ovarian cancer is ineffective(86, 87), timely RRSO remains the best method of reducing the risk of ovarian cancer. Women with a *BRCA1* or *BRCA2* pathogenic variant who undergo RRSO report reduced cancer worry and low perceived cancer risk without a significant difference in quality of life compared with women who do not undergo preventative surgery(88).

Previously it was thought that RRSO also reduced breast cancer risk in pre-menopausal *BRCA1* and *BRCA2* pathogenic variant carriers. This was based on the results of four studies published between 2005 and 2010(82, 89-91). However, recent evidence has shown that these results were influenced by significant bias(92). The association between RRSO and breast cancer risk was re-examined using a large prospective cohort of unaffected women, of whom 7.2% were *BRCA1* and *BRCA2* pathogenic variant carriers, and it was found that there was no evidence of breast cancer risk reduction with RRSO(93). Two other prospective cohort studies of unaffected *BRCA1* and *BRCA2* pathogenic variant carriers have also shown through improved study design and minimisation of bias that there is no clear reduction in breast cancer risk in *BRCA1* and *BRCA2* pathogenic variant carriers who undergo RRSO(94, 95). A recently published review outlines the multiple important sources of bias within the historical studies that initially reported reduction in breast cancer risk with RRSO that likely led to overestimation of any risk reduction(96).

In general, use of RRSO in *BRCA1* and *BRCA2* pathogenic variant carriers is higher than that of RRM, likely reflecting the shorter operation, shorter recovery time, lower impact on body image and mortality benefit. Internationally, use of RRSO ranges from 29% to 74% in pathogenic variant carriers(74). In Australia reported rates of RRSO in a study published in 2013 was 38% with a median age of surgery of 44 years. When restricted to women over the age of 50 years who knew their pathogenic variant status before the age of 50 years, use was 66%(76).

International guidelines provide consistent recommendations for RRSO for *BRCA1* and *BRCA2* pathogenic variant carriers at the completion of childbearing(2, 53, 97). A concerning finding that has emerged from previous research is that some women report that the availability of ovarian cancer screening is a reason to delay RRSO, when there is no evidence supporting the efficacy of ovarian cancer screening(98).

Risk-reducing medication

Risk-reducing medication, also known as chemoprevention, significantly reduces breast cancer risk in women who are at moderate or higher lifetime breast cancer risk(99-101).

Tamoxifen, a selective estrogen receptor modulator (SERM) commonly used in the treatment of hormone receptor positive breast cancers, competes with 17_{β}-estradiol (E_2) at the receptor site and also binds to DNA after metabolic activation to inhibit carcinogenesis, though its exact mechanism in breast cancer prevention remains unknown(102). Tamoxifen has demonstrated risk reductions of 32-50% in randomised controlled trials (IBIS1 and NSABP-P1) in pre- and post-menopausal women(55, 57). Raloxifene, another SERM, was initially favoured in post-menopausal women due to its more favourable side-effect profile and reports of equal preventative efficacy with tamoxifen. However, the longer term follow-up of the randomised STAR trial demonstrated that raloxifene was only 76% as effective as tamoxifen at reducing breast cancer risk(103). SERMS are generally well tolerated, however a proportion of women who take these medications in the preventative setting will experience side-effects. For tamoxifen, these are commonly vasomotor symptoms, increased vaginal discharge, a small increase in thromboembolic risk and

a small increase in endometrial cancer risk, which is only seen in post-menopausal women.

Other endocrine therapy agents used in the treatment for breast cancer have been trialled in the preventative setting. The aromatase inhibitors, anastrozole and exemestane, have been trialled in randomised phase III clinical trials and have been shown to be effective in breast cancer prevention in post-menopausal women. Aromatase inhibitors work by inhibiting the aromatase enzyme which catalyses the conversion of androgens to oestrogen. The IBIS-II trial of anastrozole vs placebo demonstrated a 52% reduction in breast cancer risk with a 5-year course(100). The preventative effect of exemestane, taken daily for 5 years, was assessed in the MAP-3 trial which showed a 62% reduction in breast cancer risk, however these study results were limited by a short period of follow up of 35 months(104).

Aromatase inhibitors have a distinct side-effect profile to that of tamoxifen and, because of their mechanism of action, are only effective in the post-menopausal population. The most common side-effects o aromatase inhibitors include vasomotor symptoms, arthralgia and myalgia, vaginal dryness and increased bone density loss. It is important to note that side-effects from both SERMs and aromatase inhibitors differ in the preventative setting compared to the breast cancer treatment setting. This is especially relevant to women at increased risk of breast cancer (who are eligible for RRMed) who may have received information on side-effects from family members who have taken these medications as a component of breast cancer treatment. In the IBIS-1 trial, there were a significantly more vasomotor and gynaecological adverse effects experienced in the tamoxifen arm than the placebo

arm. However, this study also noted a high prevalence of these symptoms in those women who were on placebo (67.7% of women reported gynaecological or vasomotor symptoms), suggesting that in this population pre-existing symptoms may be incorrectly attributed to adverse effects from tamoxifen use(57).

Updated results of the NSABP-P1, IBIS-I and IBIS-II trials has demonstrated ongoing benefit in breast cancer risk reduction after completion of a 5-year preventative course of tamoxifen and anastrozole(99, 101, 105). Following completion of a 5-year course of tamoxifen, there is an ongoing significant breast cancer risk reduction for a further 15 years. For anastrozole, the ongoing risk reduction continues for 5 years following completion of a 5-year course.

Despite the proven effectiveness of risk-reducing medication, the international literature describes very low use in eligible women. A large meta-analysis published in 2016 demonstrated a pooled uptake estimate of 16% of RRMed, with variation across individual studies from 0% to 54%(106). Uptake was higher in trial than non-trial settings (25.2% vs 8.7%). The most commonly identified barrier to RRMed in the literature is the perceived impact of side-effects(107-115). Health professional recommendation is a motivator to RRMed use, however studies have shown that few clinicians have prescribed RRMed, they are often fearful of side-effects for their patients and often present negatively biased presentations of RRMed to patients(115, 116).

Table 1: Summary of breast and ovarian cancer risk management guidelines (as of September 2021)

	NICE *(CG164 Nov 2019)*	**NCCN *(Version 1.2020)***	**Cancer Australia**
Risk-reducing medication	Consider if: • Lifetime risk of BC ≥17%	Consider if: • ≥35 years of age with 5-year BC risk ≥1.7% • LCIS	Consider if: • Women at moderate BC risk and age over 35 years • Women at high BC risk and any age
Risk-reducing salpingo-oophorectomy (RRSO)	*BRCA1* pathogenic variant carriers: • Recommend between 35-40 years of age, upon completion of child bearing *BRCA2* pathogenic variant carriers: • Recommend age 40-45 unless family history warrants earlier consideration	Discussion with women from high-risk families	Recommend to women at high lifetime OC risk
Risk-reducing bilateral mastectomy	*BRCA1* and *BRCA2* pathogenic variant carriers: • Discussion on a case-by-case basis	Discussion recommended in women who carry a pathogenic variant that confers a high risk of BC	Discussion recommended in all women at high BC risk
Ovarian cancer screening	Not recommended in general population *BRCA1* and *BRCA2* pathogenic variant carriers who do not undergo RRSO: • Consider TVUS and CA-125 for screening starting age 30-35 years at clinician discretion (although of uncertain benefit)	Not recommended in any population	Not recommended in any population
Clinical breast examination (CBE)	For *BRCA1* and *BRCA2* pathogenic variant carriers: CBE every 12 months	Recommended every 6-12 months alongside imaging surveillance in those at elevated BC risk	Regular CBE recommended in high-risk women

Precision prevention

The concept of precision medicine has accelerated with advances in technology and an increased understanding of cancer as a genomically driven disease. A precision approach to breast cancer treatment has developed over the last 30 years and has led to a decline in breast cancer mortality. Cancer prevention has failed to progress at the same pace as breast cancer treatment. Rising breast cancer incidence has fuelled renewed interest in developing a precision prevention approach where a prevention plan is customised based on an individual's biology, history and lifestyle.

Our ability to accurately stratify patients into risk groups depending on their risk of breast cancer is a vital first step in precision prevention. Identification of patients with pathogenic germline pathogenic variants that predispose to high risk of breast or ovarian cancer allows tailoring of an individual surveillance and risk management plan for these women, ultimately targeted at preventing the development of cancer in this high-risk group.

Precision prevention requires an understanding of the determinants of breast cancer risk, identification of specific groups that benefit most from interventions, maximising cost effectiveness, minimising toxicities and optimising the timing of interventions. Adding a precision prevention approach to the existing well-established population breast cancer prevention requires a significant shift in the way cancer prevention is viewed.

Determinants of health care behaviours and behaviour change

Understanding health care behaviours requires an understanding of the social and political constructs of health care beyond the physical experience of the individual. Focus on individual-level health determinants and targeting interventions to these is likely to miss the wider determinants of health care behaviours and therefore effective interventions. Implementing effective interventions requires an understanding of the determinants of the specific health care behaviour and application of an evidence-based behaviour change framework for effective interventions. There are multiple behaviour change models and frameworks in existence. Most of these frameworks focus on variables affecting the individual and fail to look more broadly at social and environmental variables, limiting their utility(117). In addition to the lack of coverage of intervention functions, they often fail to link to a model of behaviour(118). In 2011, Michie collaborated with other behavioural scientists and implementation researchers to develop a new behavioural change framework(118) after identifying that existing frameworks(119) failed to capture a wide range of possible interventions and did not link to a model of behaviour. This new model consists of a behaviour system called the capability, opportunity and motivation (COM-B) system, whereby these three factors interact to generate behaviour. The COM-B system forms the centre of the behaviour change wheel which is then linked to nine potential intervention functions and seven policy categories which form the outside of the wheel (Figure 1). The behaviour change system aims to identify the health behaviour, link it with a potential intervention and suggest policy change aiming to change the underlying health behaviour. It was developed with the intention of providing a structured evidence-based approach to

health behaviour research. The studies incorporated into this thesis utilize the COM-B system of behavioural change theory to propose potential interventions.

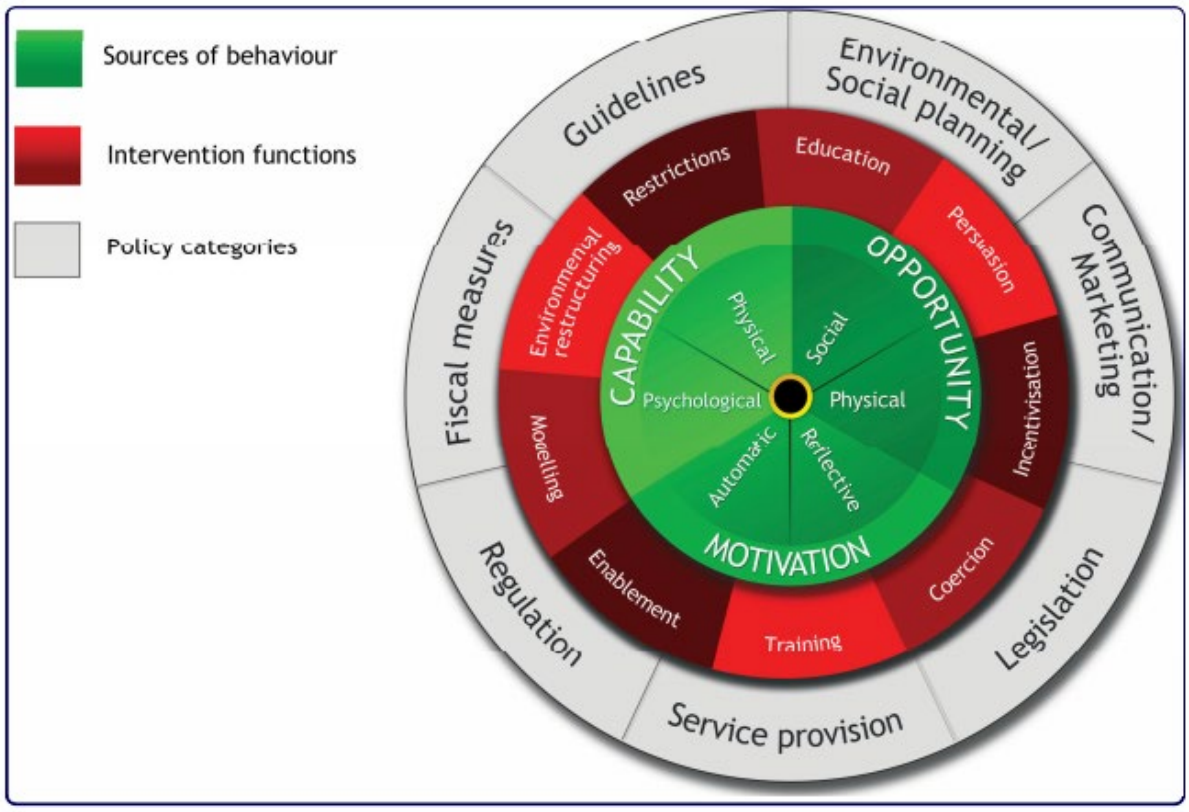

Figure 1. The COM-B model of behaviour change(118)

Summary

Breast cancer incidence has increased over the last four decades. With medical advances, there is a more comprehensive understanding of breast cancer risk factors, including genetic contributions to breast cancer. There are proven, effective risk management strategies that are underutilised in eligible populations. Further understanding the barriers to the implementation of these strategies is vital to overcoming low utilisation and increasing use. In addition to effective interventions,

women at elevated breast cancer risk may also be subject to tests or interventions that do not have proven benefit. Precision approaches centre on minimising ineffective interventions and targeting those at elevated breast cancer risk for more intensive screening and effective prevention interventions.

Chapter 3: Background on cohorts used in this thesis

The studies presented in this thesis utilise an Australasian breast cancer family cohort study, kConFab, in addition to a high-risk clinic cohort based at the Peter MacCallum Cancer Centre.

Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConFab)

Core Resource

kConFab is a collaboration of geneticists, clinicians, community representatives, surgeons, genetic counsellors, psychosocial researchers, pathologists and epidemiologists from Australasia focussed on better understanding familial predisposition to breast cancer. Through the Consortium, the kConFab core resource has been developed. This is a resource of baseline epidemiological data and bio-specimens from multiple-case breast cancer families that can be accessed, for a fee, by researchers world-wide, under ethics approved protocols(76, 120, 121). kConFab started enrolling families with a strong family of breast or ovarian cancer in 1997 and has enrolled over 1,900 breast cancer families. Families are recruited to the study after at least one family member (the proband) attends a familial cancer clinic consultation. Multiple-case breast cancer families are defined as families where a *BRCA1* or *BRCA2* pathogenic variant, or a pathogenic variant in another high- or moderate-risk breast cancer susceptibility gene, had been identified, or families where no predisposing pathogenic variant had been identified but two or more family members on the same side of the family were affected by breast cancer. Following enrolment of the proband, other family members could enrol without attending a

familial cancer clinic. Participants completed a baseline questionnaire at the time of recruitment. Data is collected on family history, clinical and epidemiological factors and diet. Biological specimens, including blood samples, fresh tumour and prophylactic material was collected, along with pathology reports if available. The kConFab clinical follow-up study is a sub-study of the kConFab core resource.

kConFab Clinical Follow-Up Study

The kConFab clinical follow-up study is led by principal investigator Professor Kelly-Anne Phillips(7, 122). The Follow-Up Study collects follow up information every 3 years from women enrolled in kConFab between 2001 and 2011.

To be eligible for the kConFab clinical follow up study participants had to be enrolled in the kConFab core resource between 1997 and November 2008, be aged 18 years or older and be willing to participate in follow-up. Initially both male and female participants were enrolled but follow-up of men ceased in 2007. The kConFab clinical follow-up study commenced in September 2001. Follow-up questionnaires are sent out (by email or by mail) every three years. Questionnaires collect updated information about cancer family history, incident cancer diagnoses (type, date of diagnosis, mode of detection, treatment), breast and ovarian cancer screening behaviours, breast cancer risk factors and breast and ovarian cancer prevention strategies (risk-reducing surgery and medications). An example of a questionnaire can be found as an appendix to this thesis (appendix 1). Self-reported new cancers and surgeries are confirmed by obtaining surgical and pathology reports and details abstracted. Passive, systematic follow-up is also undertaken by linking to the

Australian Cancer Database and National Death Index held by the Australian Institute of Health and Welfare. Non-responders to the questionnaires are followed up by phone every two weeks for a maximum of three attempts. Phone contact with the research team allows participants to ask any questions in the questionnaire and allows research staff to clarify the details of any unclear responses. A response rate of around 70% to the follow-up questionnaires has been maintained (7).

Peter MacCallum Cancer Centre Breast and Ovarian Cancer Risk Management Clinic

The Peter MacCallum Cancer Centre Breast and Ovarian Cancer Risk Management Clinic is a clinical service for women at high familial or genetic risk of breast /or ovarian cancer but who have not personally been affected by cancer(123). All Risk Management Clinic patients have had their breast and ovarian cancer risk formally assessed in a risk assessment clinic (either at the Peter MacCallum or elsewhere) and most have had genetic testing for *BRCA1* and *BRCA2* pathogenic variants. The clinic was founded in 2001, as the first of its kind in Australia, by Professor Kelly-Anne Phillips. Over 550 *BRCA1* and *BRCA2* pathogenic variant carriers have been cared for at the clinic since its inception. The clinic is staffed by breast surgeons, medical oncologists, genetic counsellors and a nurse. Women are seen initially to discuss the implications of their high breast cancer risk or germline pathogenic variant result, and to discuss their screening and prevention options. Women attend clinic every 6-12 months with results of annual screening investigations. Women who develop an invasive cancer or undergo risk-reducing surgeries such that they are no

longer at increased cancer risk are discharged from the clinic back to the care of their oncologist or general practitioner.

Chapter 4: Risk-reducing medication for breast cancer

Low use of RRMed for breast cancer prevention has been consistently demonstrated, both in Australia and elsewhere(76, 106). This continues despite clear guidelines around who RRMed should be discussed with, and offered to(52, 53, 124). Both tamoxifen and anastrozole have existed in clinical practice for the management of hormone receptor positive breast cancers since the 1970's and 1990's, respectively. In 2002, the IBIS-I trial demonstrated that tamoxifen was effective in reducing breast cancer risk in women with an increased risk of breast cancer(57) and in 2014, the IBIS-II trial established anastrozole as a further preventative option(100). Because these medications have had a longstanding role in the management of breast cancer, patents have expired and lower priced generic versions exist. It has been hypothesised that the resultant loss of profit for pharmaceutical companies has led to a lack of impetus to educate and promote these medications for prevention. To counter this, some governmental agencies are developing strategies to increase risk RRMed use. For example, the National Health Service (NHS) in the United Kingdom has listed tamoxifen as part of the Rapid Uptake Products (RUP) programme which aims to increase the awareness and use of proven interventions(125).

The reasons that underpin the low use of RRMed are multifactorial and stem from both women and their clinicians. Previous research has identified that a major barrier to clinicians prescribing RRMed is side-effects(126). Other identified barriers for general practitioners (GPs) has been available time, cost and concern about off-label use of medications, and disagreement about to whom the responsibility of discussing

and prescribing RRMed should fall (107). If a GP has a relative affected by breast cancer, then they are more likely to prescribe RRMed to their patients(127). Other identified motivators for clinicians and women include the women having a strong family history of breast cancer or an abnormal breast biopsy(111). For women, having a higher perceived risk of breast cancer and higher breast cancer anxiety increased the use of RRMed(109, 111, 112). Clinician concern about side-effects has been identified as a major barrier, as has negatively biased physician presentations of the risk and benefits of RRMed(109).

PDF of manuscript 1. Underutilisation of breast cancer prevention medication in Australia

In Australia, very low use of RRMeds has been demonstrated in *BRCA1* and *BRCA2* pathogenic variant carriers. An Australian study published in 2013 demonstrated that of 325 *BRCA1* and *BRCA2* pathogenic variant carriers only 1 woman took RRMeds off trial (<1%) with a further 3% participating in an RRMed trial(76). At the time of that study, discussion of RRMed had been recommended in Australian guidelines since 2011(2) however, the Australian Therapeutic Goods Administration (TGA – similar to the US FDA) had not approved tamoxifen for breast cancer prevention. Thus, use of RRMed at that time was off-label, posing a major barrier to use(107).

The use of RRMed in Australian women at moderate to high-risk of breast cancer has not been addressed. This study aimed to address the use of RRMed in a population of Australian women at elevated risk of breast cancer, given the change in drug access and funding. This study used the kConFab Clinical Follow-up cohort to estimate the use of breast cancer risk-reducing medication in Australia and to

determine potential demographic predictors of use. This study sample was chosen as it included a large number of women from whom data had already been collected using three-yearly self-reported questionnaires. However given these women were from an existing breast cancer family cohort they may have been more likely to use RRMeds and use of RRMed may have been overestimated. This study was published in *The Breast* journal in August 2021. This study demonstrated low use of RRMed by eligible women at elevated risk of breast cancer. Only 70 women (2.4%) had taken RRMed with the majority having taken tamoxifen (n=64, 91%). The most common age to commence RRMed was between 40-49 years. There was no evidence of an association between the use of RRMed and parity or education. Women with a high lifetime risk of breast cancer (≥30% full lifetime risk) had a greater likelihood of using RRMed than those at moderate risk (OR 1.82, CI 1.08-3.07, p = 0.02). There was weak evidence that RRMed use was more likely with an increasing number of first-degree relatives with breast cancer but this was not statistically significant.

Publication citation

Macdonald C, Chamberlain JA, Mazza D, Milne RL, kConFab investigators, Phillips KA. Underutilisation of breast cancer prevention medication in Australia. *Breast.* 2021 Aug 23; 60:35-37.

The Breast 60 (2021) 35–37

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Underutilisation of breast cancer prevention medication in Australia

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ARTICLE INFO

Article history:
Received 7 June 2021
Received in revised form
9 August 2021
Accepted 19 August 2021
Available online 23 August 2021

Keywords:
Breast cancer
Prevention
Chemoprevention
Tamoxifen
Risk

ABSTRACT

Increased implementation of proven prevention strategies is required to combat rising breast cancer incidence. We assessed use of risk reducing medication (RRMed) by Australian women at elevated breast cancer risk. Only 2.4% had ever used RRMed. Higher breast cancer risk was statistically significantly associated with use of RRMed (OR 1.82, 95%CI: 1.08–3.07, p = 0.02 for ≥30% lifetime risk compared with 16%–29% lifetime risk), but parity, education level and family history of breast cancer were not. Breast cancer prevention medications are underutilised. Efforts are needed to incorporate breast cancer risk assessment and risk management discussions into routine health assessments for women.

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1. Introduction

Breast cancer (BC) incidence continues to rise, so implementation of prevention strategies is essential to reverse this trend [1]. Risk-reducing medications (RRMeds), such as tamoxifen and anastrozole, reduce BC risk by up to 50%, with benefit extending for at least 5–15 years after a five-year course [2,3]. In Australia, consideration of RRMed is recommended for women at moderate risk of BC (i.e.16%–29% full lifetime risk) over the age of 35 years, and for women at high BC risk (i.e. ≥30% full lifetime risk) at any age [4]. In 2016, tamoxifen became Australian government-subsidised for the primary prevention of BC for women at elevated risk. This study aimed to describe the uptake of RRMed in Australian women at elevated BC risk and to identify demographic predictors of use.

2. Materials and methods

Participants were women from multiple-case BC families in Australia enrolled in the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer cohort (kConFab) between 1997 and 2008. The probands were recruited from one of fifteen cancer genetics clinics nationwide but family members could be enrolled without clinic attendance or formal risk assessment. Women were mailed a questionnaire at baseline and three yearly thereafter [5] asking about RRMed use, educational level, marital status, pregnancies, breast-feeding, cancer family history, participation in RRMed trials and bilateral mastectomy or cancer diagnoses.

Participants were eligible if, at cohort entry, they were at least 18 years old, had not had a bilateral mastectomy, invasive cancer diagnosis or ductal carcinoma in situ (DCIS) and had at least a moderate lifetime risk of BC (defined as ≥1.5 times population risk,i.e. ≥16% full lifetime risk as calculated by the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation

Abbreviations: RRMed, Risk reducing medication; BC, Breast cancer; kConFab, Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; DCIS, Ductal carcinoma in situ; LCIS, Lobular carcinoma in situ; OR, Odds ratio; CI, Confidence interval.

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https://doi.org/10.1016/j.breast.2021.08.013
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Algorithm: BOADICEA [6]). Participants in RRMed trials were excluded. Consistent with Australian guidelines for RRMed use, moderate-risk women who did not reach age 35 years during their follow-up period were excluded. Because RRmeds are contra-indicated during childbearing, those without a five-year pregnancy- and lactation-free period were also excluded.

Data were obtained from baseline and follow-up questionnaires. BOADICEA full lifetime risk (i.e. from age 1 to 80) was calculated (without polygenic risk scores or mammographic density, which were not available) [6]. Use of RRMed was assessed until the date of any cancer diagnosis, bilateral mastectomy, last follow up or death. Associations with RRMed use were assessed using logistic regression to estimate odds ratios (OR) and associated 95% confidence intervals (CI). The hypothesised demographic predictors of RRMed use, based on existing literature [7–10], were parity, number of first-degree relatives with BC, BOADICEA full lifetime risk, and education level.

3. Results

Of 7549 women enrolled in kConFab between 1997 and 2008, 4654 were excluded due to prior invasive cancer or DCIS (N = 2702), bilateral mastectomy (N = 37), participation in a RRMed trial (N = 79), or being at either average risk of BC or moderate risk and under age 35 (N = 1277), no follow-up (N = 509) and no five-year lactation-and pregnancy-free period (N = 50)). Characteristics of the 2895 eligible participants are shown in Table 1. The median follow-up time was 12.1 years (range 2.8–20 years). The median age at baseline was 43 years. Seventy participants (2.4%) had ever taken RRMed, most commonly tamoxifen (n = 64, 91%). The most common age to commence RRMed was 40–49 years (40%) (Table 1).

We found no evidence of an association between uptake of RRMed and parity or education. BC risk was associated with use; those with a full lifetime risk ≥30% were 82% (OR = 1.82, 95% CI = 1.08–3.07) more likely to take RRMed than those with a 16%–29% risk (Table 2). There was weak evidence that uptake was more likely by women with more affected first-degree relatives (P = 0.06). An exploratory analysis did not suggest that BC risk was associated with adherence to RRMed (Supplement 1).

Table 1
Demographic characteristics.

Characteristic	Number of kConFab women (%)
Age started RRMed (years)	
20-29	1 (1.5)
30-39	10 (14)
40-49	28 (40)
50-59	18 (26)
60-69	8 (11)
70-79	1 (1.5)
Don't know	4 (5.7)
Age at cohort entry	
<20	28 (1)
20-29	364 (12.6)
30-39	793 (27.4)
40-49	698 (24.1)
50-59	607 (21)
60-69	265 (9.1)
70-79	117 (4)
≥80	23 (0.8)
Parity	
Nulliparous	387 (13.4)
1	270 (9.3)
2+	2238 (77.3)
Education	
Pre-tertiary	1990 (68.7)
Tertiary	905 (31.3)
Marital status	
Married/living as married	2048 (70.7)
Other	847 (29.3)
BRCA mutation status	
BRCA1	195 (6.7)
BRCA2	162 (5.6)
No known BRCA1/2 mutation	2538 (87.7)
Affected 1st degree relative (Invasive/DCIS)	
None	288 (9.9)
1	1666 (57.6)
2	650 (22.5)
3	224 (7.7)
≥4	67 (2.3)
Full lifetime breast cancer risk[a]	
16%–29%	2075 (71.7)
≥30%	820 (28.3)
Risk reducing medication	
Yes	70 (2.4)
Tamoxifen	64 (91.4)
Raloxifene	4 (5.7)
Anastrozole	2 (2.9)
No	2825 (97.6)

[a] Lifetime breast cancer risk from age 1 to age 80 as calculated by BOADICEA.

4. Discussion

This study of a large number of women from a familial breast cancer cohort found that use of BC RRMed in Australia is low, compared with that in the international literature, with one meta-analysis reporting a pooled estimated uptake of 16.3% (range 0%–55%) [10]. Use may be even lower for women at increased BC risk in the general Australian population, given our participants likely had greater exposure to information about RRMed due to their enrolment in a familial cohort study. We excluded women who had participated in a placebo-controlled RRMed trial, however if these women were included, still only 5% of women would have used RRMed. Higher lifetime BC risk was associated with use, highlighting the importance of risk stratification and personal knowledge of BC risk. Previous research has shown that higher perceived BC risk in women with elevated objective risk is associated with consideration of RRMed [11].

In a recent survey of a subgroup of the current study sample and their clinicians, for the majority (82%) of women, knowledge of their increased BC risk would facilitate use of RRMed [12]. Although the women in the current study knew they had a family history of BC and that they were therefore at increased risk, a quantitative risk assessment was not provided as part of the kConFab study. Thus the level of knowledge of the women in this study is representative of the "real world" quantitative knowledge about their risk that women obtain from other sources. The study also identified that most family physicians lacked awareness of the existence of RRMeds, and/or lack confidence in providing advice about RRMeds. Thus, taken together, our studies suggest that not knowing one's personal BC risk, and other potentially modifiable clinician and patient factors, act as barriers to the uptake of RRMed in Australia, and that the mostly unmodifiable demographic factors examined in this study are of much less importance. These barriers are not unique to Australia. Tamoxifen was recently listed in the National Health Service Rapid Uptake Products programme [13], which aims to increase uptake of effective health interventions in the UK.

5. Conclusion

Use of breast cancer RRMed by eligible women in Australia is very low. Increasing the use of RRMed requires a precision prevention approach incorporating individualised BC risk assessment and risk management discussions in routine woman's health care.

Table 2
Potential predictors of risk reducing medication use.

Characteristic	Odds ratio	95% confidence interval	P-value
Parity			.17
0	1.0 (reference)	–	
1	0.96	0.34–2.73	
2	1.22	0.55–2.71	
3+	0.90	0.43–1.90	
No. of 1st degree relatives with BC			.06
0	1.0 (reference)	–	
1	2.23	0.68–7.34	
2	3.05	0.88–10.6	
3+	3.11	0.84–11.5	
Education			.48
Pre-tertiary	1.0 (reference)	–	
Tertiary	0.82	0.48–1.42	
BC risk[a]			.02
16–29%	1.0 (reference)	–	
≥30%	1.82	1.08–3.07	

[a] Full Lifetime risk. BC = breast cancer; odds ratios and confidence intervals were calculated from separate logistic regression models with a single categorical predictor. P values for parity and number of first-degree relatives with BC were calculated using a Z-test on the linear term modelling the relevant count variable; P values for education and BC risk were calculated using a Z-test on the coefficient of the relevant indicator variable.

Funding

This research was supported by Cancer Australia and the National Breast Cancer Foundation (PdCCRS #1100868). kConFab and the kConFab Follow-Up Study have received additional funding support from Cancer Australia (809195), the Australian National Breast Cancer Foundation (IF 17), the Australian National Health and Medical Research Council (454508, 288704, 145684), the National Institute of Health U.S.A. (1RO1CA159868), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia.

KAP is an Australian National Health and Medical Research Council Leadership Fellow.

The contents of this manuscript are solely the responsibility of the authors and do not necessarily reflect the views of Cancer Australia.

Ethical approval

The kConFab study is approved by the Peter MacCallum Cancer Centre Human.

Research Ethics Committee. All participants provided written informed consent.

Declaration of competing interest

All authors report no potential conflict of interest.

Acknowledgements

We thank Sandra Picken, Lucy Stanhope, Sarah O'Connor, Stephanie Nesci, Heather Thorne, Eveline Niedermayr, Sharon Guo, the kConFab research nurses and the heads and staff of the Australian Family Cancer Clinics. We thank the women and their families who participated in this research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.08.013.

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PDF of manuscript 2: Breast cancer chemoprevention: Use and views of Australian women and their clinicians

Having identified that use of RRMed remains low in Australia, and that demographic factors did not predict use, this study used the kConFab Clinical Follow-Up Study cohort to identify barriers to, and facilitators of, use from both women's and clinicians' perspectives. A survey, based on the Theoretical Domains Framework, was designed, piloted, revised and then sent to and completed by kConFab women, and the breast surgeons and GPs who cared for them.

The key findings from this study were that 48% of women were aware of medications to reduce breast cancer risk and only 1.4% of women had ever taken risk-reducing medication. The main barriers for kConFab women to RRMed use were the fear of side-effects, not having enough information to make an informed decision, preference for a healthy lifestyle and seeing family or friends experience side-effects when taking medications. Facilitators that women identified would make it easier to take RRMed were that RRMed can reduce breast cancer risk for up to 20 years, that taking RRMed will improve the chance they will stay healthy for their family, knowledge of having high breast cancer risk and having an abnormal biopsy that increases breast cancer risk. The majority of clinicians (breast surgeons and GPs) had heard of RRMed but a minority of GPs had discussed or prescribed RRMed and most reported lacking confidence discussing RRMed. GPs identified that lack of knowledge of RRMed, lack of confidence in providing advice of RRMed, difficulty identifying suitable patients and medication side-effects as strong barriers. For breast surgeons, strong barriers were medication side-effects, difficulty accessing information for patients and lack of consultation time as main barriers. Both clinician

groups identified clear guidelines and recommendations as a strong facilitator and if the patient had a strong family history of breast cancer. Application of the theoretical domains framework allowed us to suggest potential interventions to the identified barriers to RRMed use.

The findings from this study were presented at the European Breast Cancer conference in 2020 as an oral presentation in the proffered papers session and published in *Cancer Prevention Research* (CAPR). The publication was accompanied by a spotlight editorial by Victor Vogel titled Implementation of risk reducing strategies for breast cancer is long overdue (Appendix 7)(128). The manuscript was selected for inclusion in the implementation science section of the CAPR must-read 2021 collection of six publications that represent key areas in cancer prevention.

Publication citation

Macdonald C, Saunders C, Keogh LA, Hunter M, Mazza D, McLachlan SA, Jones SC, Nesci S, Friedlander ML, Hopper JL, Emery J, Hickey M, Milne RL, Phillips KA & Kathleen Cuningham Consortium for Research into Familial Breast Cancer. Breast cancer chemoprevention: Use and views of Australian women and their clinicians. *Cancer Prevention Research*, 14(1), 131-144. 2021.

Breast Cancer Chemoprevention: Use and Views of Australian Women and Their Clinicians

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ABSTRACT

Guidelines endorse the use of chemoprevention for breast cancer risk reduction. This study examined the barriers and facilitators to chemoprevention use for Australian women at increased risk of breast cancer, and their clinicians. Surveys, based on the Theoretical Domains Framework, were mailed to 1,113 women at ≥16% lifetime risk of breast cancer who were enrolled in the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer cohort study (kConFab), and their 524 treating clinicians. Seven hundred twenty-five women (65%) and 221 (42%) clinicians responded. Only 10 (1.4%) kConFab women had ever taken chemoprevention. Three hundred seventy-eight (52%) kConFab women, two (3%) breast surgeons, and 51 (35%) family physicians were not aware of chemoprevention. For women, the strongest barriers to chemoprevention were side effects (31%) and inadequate information (23%), which operate in the Theoretical Domains Framework domains of "beliefs about consequences" and "knowledge," respectively. Strongest facilitators related to tamoxifen's long-term efficacy (35%, "knowledge," "beliefs about consequences," and "goals" domains), staying healthy for family (13%, "social role" and "goals" domains), and abnormal breast biopsy (13%, "environmental context" domain). The strongest barrier for family physicians was insufficient knowledge (45%, "knowledge" domain) and for breast surgeons was medication side effects (40%, "beliefs about consequences" domain). The strongest facilitators for both clinician groups related to clear guidelines, strong family history, and better tools to select patients ("environmental context and resources" domain). Clinician knowledge and resources, and beliefs about the side-effect consequences of chemoprevention, are key domains that could be targeted to potentially enhance uptake.

Prevention Relevance: Despite its efficacy in reducing breast cancer incidence, chemoprevention is underutilised. This survey study of Australian women and their clinicians used behavioural change theory to identify modifiable barriers to chemoprevention uptake, and to suggest interventions such as policy change, educational resources and public campaigns, that may increase awareness and use.

See related Spotlight by Vogel, p. 1

Introduction

Although breast cancer mortality has improved, incidence continues to rise, presenting a major burden for health services worldwide (1). Better implementation of evidence-based breast cancer prevention interventions, such as chemoprevention (also known as risk-reducing medication) in women at increased risk, could reduce this burden (2).

Selective estrogen receptor modulators (tamoxifen and raloxifene) and aromatase inhibitors (anastrozole and exemestane),

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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Cancer Prev Res 2021;14:131–44

doi: 10.1158/1940-6207.CAPR-20-0369

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taken daily for 5 years, reduce breast cancer risk by one-third to one-half in women at increased risk (3–8). For tamoxifen and anastrozole, the preventive benefit continues for at least 15 and 5 years, respectively, after completion (9, 10). Low-dose tamoxifen for only 3 years may also be an efficacious, low side-effect option for women who do not tolerate the standard 20-mg daily dose, although long-term efficacy for this shorter duration, lower dose regimen is unknown (11, 12).

Guidelines recommend consideration of risk-reducing medication for women at elevated breast cancer risk (12–15). Despite this, risk-reducing medication is underutilized. A meta-analysis, including data from 21,423 women, reported a pooled risk-reducing medication uptake estimate of 16% (16), although in individual studies, uptake ranged from 0% to 55%. Uptake was higher in trial (25%) compared with non-trial (8.7%) settings, suggesting it may be more difficult for clinicians to implement risk-reducing medication within routine practice.

Reasons for low use of risk-reducing medication are multifactorial, including patient- and physician-related factors. Concern about side effects is a well-described barrier to use (17–23). Physician recommendation, family history of breast cancer, abnormal breast biopsy, higher perceived breast cancer risk, and higher cancer-specific anxiety are associated with risk-reducing medication use (21, 24).

Tamoxifen became government subsidized for primary breast cancer prevention in Australia in 2016, but national guidelines have recommended doctors consider it for women with a lifetime risk of breast cancer at least 1.5 times population risk (i.e., ≥ 16%) since 2010 (https://www.canceraustralia.gov.au/publications-and-resources/cancer-australia-publications/advice-about-familial-aspects-breast-cancer-and-epithelial-ovarian-cancer). This study aimed to determine the past or current use of risk-reducing medication by Australian women at increased risk of breast cancer and to examine barriers and facilitators to the use of risk-reducing medication.

Materials and Methods

Setting

Participants were women (and their clinicians) from multiple-case breast cancer families recruited to the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer cohort (kConFab) between 1997 and 2008 (https://www.kconfab.org/). Multiple-case breast cancer families were defined as families where a *BRCA1* or *BRCA2* mutation, or a mutation in another breast cancer susceptibility gene, had been identified, or families where no predisposing mutation had been identified but two or more family members on the same side of the family were affected by breast cancer. The proband was recruited after a clinic consultation in any of 15 Australian genetics clinics. Other family members were not required to attend a genetics clinic to enroll. kConFab women were mailed follow-up questionnaires every 3 years (25) asking questions regarding doctors involved in their care, use of risk-reducing medication, educational level, parity, pregnancy, breastfeeding, marital status, family history, participation in clinical trials of risk-reducing medication, and details of any bilateral mastectomy or cancer diagnoses. In addition to follow-up questionnaires, all kConFab women eligible for the study reported here were sent a survey on risk-reducing medication in late 2018 (see surveys of kConFab women section below). This study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent and the kConFab cohort study has Human Research Ethics Committee approval at all participating sites, and this survey study has Human Research Ethics Committee approval at the Peter MacCallum Cancer Centre.

Surveys of kConFab women and clinicians

Understanding the behavioral determinants of use of risk-reducing medication for both clinicians and patients is the first step in implementing practice change to increase use of risk-reducing medication. We used the Theoretical Domains Framework (26) to guide the development of survey questions. The Theoretical Domains Framework was developed to identify the cognitive, affective, social, and environmental influences on health professional and patient behavior related to implementation of evidence-based recommendations. It consists of 84 theoretical constructs grouped into 14 domains and maps directly to the COM-B (capability, opportunity, motivation, behavior) behavioral change model (27), to suggest intervention functions and relevant policy categories to guide pathways to behavioral change.

kConFab women

A 68-item survey (Supplementary data 1) was developed based on a literature review and semi-structured interviews with 62 kConFab women from different geographical locations, socioeconomic status, and ethnicities to identify barriers and facilitators to using risk-reducing medication. Survey questions, based on the Theoretical Domains Framework (**Tables 1** and **2**), were developed by the research team, including experts in health sociology, qualitative research, breast surgery, and primary care. The survey was piloted for usability with nine kConFab women in face-to-face cognitive interviews and refined. kConFab women were eligible if, at the time of survey, they were aged between 25 and 70 years, resided in Australia, and had a BOADICEA (28) lifetime breast cancer risk of ≥16% but had not had bilateral mastectomy, previous breast cancer ever, or other invasive cancer in the previous 6 years. Women who had participated in the IBIS prevention trials (3, 6) or the survey pilot study were also excluded. The survey was mailed or emailed, and non-responders were followed up three times.

Clinicians

In Australia, family physicians and breast surgeons primarily undertake breast cancer prevention. Medical oncologists do not have a primary role in discussion of risk-reducing medication. A literature review and focus group interviews were undertaken with family physicians and breast surgeons to inform survey development (29, 30). The 49-item clinician survey (Supplementary Data 2) was developed using the Theoretical Domains

Table 1. Barriers: relationship between survey statement, Theoretical Domains Framework domain, and COM-B source of behavior and intervention function.

TDF domain	Domain description	Statement (barrier)		COM-B source of behavior	Intervention function
		kConFab women	Clinicians		
Social/professional role and identity	A coherent set of behaviors and displayed personal qualities of an individual in a social or work setting	Not applicable	It is not my role to discuss RRM		
Goals	Mental representations of outcomes or end states that an individual wants to achieve	I have another medical condition that outweighs my BC concerns	There are other things I wish to achieve in most consultations that interfere with my ability to discuss RRMs		Education
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use	I have trouble remembering to take a daily tablet	Patients don't ask me about RRMs I am not confident in providing advice/ information to pts about RRMs I have inadequate training and confidence in BC risk assessment I have difficultly explaining to pts the pros and cons of RRMs	Reflective motivation	Persuasion Incentivization Coercion
Optimism	The confidence that things will happen for the best or that desired goals will be attained	I'm too old to bother trying to prevent BC If cancer is going to happen it will happen, I do not believe you can change your own risk I don't believe RRMs would reduce my risk of BC at all I don't believe RRMs would reduce my risk of BC enough to make it worthwhile	Not applicable		
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behavior in a given situation	I am concerned about drug interactions I am worried my family/friends would assume I have been diagnosed with BC or may ask questions about our family history I wouldn't know whether RRMs were actually working My risk of BC is not high enough to justify taking RRMs Possible side effects I've seen family/friends experience side effects when taking medicines like this, so I am likely to experience the same If cancer is going to happen it will happen, I do not believe you can change your own risk I don't believe RRMs would reduce my risk of BC at all I don't believe RRMs would reduce my risk of BC enough to make it worthwhile	There is no evidence that they reduce mortality Medication side effects I don't believe they decrease the risk of BC I'm concerned I might increase the patient's worry about BC		

(Continued on the following page)

Table 1. Barriers: relationship between survey statement, Theoretical Domains Framework domain, and COM-B source of behavior and intervention function. (Cont'd)

TDF domain	Domain description	Statement (barrier)		COM-B source of behavior	Intervention function
		kConFab women	Clinicians		
Intentions	A conscious decision to perform a behavior or a resolve to act in a certain way	I prefer healthy lifestyle choices alone to medications I don't believe in taking medicines for prevention, only for illness RRMs are unnatural	I don't routinely assess BC risk with my pts		
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus	Not applicable	There are no incentives/rewards for discussing RRMs with pts		Persuasion
Emotion	A complex reaction pattern, involving experiential, behavioral, and physiologic elements, by which the individual attempts to deal with a personally significant matter or event	It would be a reminder of family members or friends cancer experiences Taking a daily tablet for 5 years would be a daily reminder of my cancer risk	I feel uncomfortable prescribing a "cancer drug" to healthy women I'm concerned I might increase the pt's worry about BC	Automatic motivation	Incentivization Coercion Environmental restructuring Modeling Enablement
Memory, attention, and decision processes	The ability to retain information, focus selectively on aspects of the environment, and choose between two or more alternatives	I would prefer to have both breasts removed rather than take the medication I would prefer BC screening (e.g., mammograms) alone, rather than screening and taking RRMs I have trouble remembering to take a daily tablet	I forget to discuss RRMs with pts	Psychological capability	Education Training Enablement
Knowledge	An awareness of the existence of something	I don't know what my BC risk is I don't know how much they cost I think of these as medicines to treat BC, not prevent it I don't have enough information about RRMs to make an informed decision	I have insufficient knowledge of RRMs		
Behavioral regulation	Anything aimed at managing or changing objectively observed or measured actions	My doctor doesn't talk to me enough about RRMs	There are no procedures (e.g., a checklist that facilitates discussion) that encourage me to discuss RRMs		
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behavior	I am already taking too many medications The inconvenience of taking a daily tablet Taking them would mean I couldn't take the OCP Taking them would mean I would have to delay becoming pregnant	It is difficult to measure whether the medication is working I find it hard to access tools/resources to help me estimate patients BC risk I find it hard to access good information/ resources for my pts, e.g., pt information sheets Lack of time during consultations	Physical opportunity	Restriction Environmental restructuring Enablement

(Continued on the following page)

Table 1. Barriers: relationship between survey statement, Theoretical Domains Framework domain, and COM-B source of behavior and intervention function. (Cont'd)

TDF domain	Domain description	Statement (barrier)		COM-B source of behavior	Intervention function
		kConFab women	Clinicians		
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviors	If family/friends did not think taking RRM was a good idea	I don't think pts want to discuss taking medications for prevention of BC	Social opportunity	Restriction Environmental restructuring Enablement
Skills	An ability or proficiency acquired through practice	Not applicable	I have difficulty identifying pts suitable for RRM I have inadequate training and confidence in BC risk assessment I have difficulty explaining to pts the pros and cons of RRMs	Physical capability	Training Enablement

Abbreviations: BC, breast cancer; COM-B system, capability, opportunity and motivation behavior system; TDF, Theoretical Domains Framework; OCP, oral contraceptive pill; RRM, risk reducing medication.

Framework (**Tables 1** and **2**). Eligible clinicians were family physicians or breast surgeons involved in the care of kConFab women and practicing in Australia with a valid address. Non-responders to the mailed questionnaire were followed up.

The survey responses for both clinicians and kConFab women were analyzed using descriptive statistics (numbers and percentages) in R-version 3.6.1 (R Core Team (2015; ref. 31).

Results

Survey of kConFab women

Demographics

Of the 5,231 women unaffected with breast cancer when enrolled in kConFab between 1997 and 2008, 1,097 declined follow-up, 332 died during follow-up, and 2,689 were excluded based on their characteristics at the time of survey (previous breast cancer (1,045), not aged between 25 to 70 years (499), not residing in Australia or invalid address (294), participation in pilot study (9), invasive cancer in last 6 years (61), bilateral mastectomy (191), <16% lifetime breast cancer risk (537), or participation in IBIS trials (53)). Of 1,113 eligible women, 725 (65%) responded to the survey. **Table 3** describes responder characteristics. A minority (7%) were *BRCA1* or *BRCA2* mutation carriers. Only 16% had a high lifetime breast cancer risk (≥ 30%) but 30% of respondents had high perceived breast cancer risk.

Risk-reducing medication awareness, use, and side-effect concerns

Approximately half (48%) of respondents were aware of medications to reduce breast cancer risk. Few (1.4%) had ever taken risk-reducing medication (**Table 3**).

kConFab women were asked to rank side effects of risk-reducing medication from most to least important to them. The side effects most frequently ranked as most important were endometrial cancer (45%) and blood clots (36%; **Fig. 1**). Of the 322 women who ranked endometrial cancer as most important, 201 (62%) were under age 50 years. Only 21 (3%) women ranked vasomotor symptoms as most important.

Barriers to and facilitators of use of risk-reducing medication

kConFab women ($n = 715$) who had not taken risk-reducing medication were asked to identify the strongest of 29 possible barriers to taking it (Supplementary Data 3) and to rate the strength of each barrier (**Fig. 2**). The barriers most frequently identified as the strongest were side effects (31%) and side-effect experiences of family or friends when taking similar medications (4%; both map to the "beliefs about consequences" in the Theoretical Domains Framework), as well as inadequate information to make a decision (23%, Theoretical Domains Framework "knowledge" domain) and preferring healthy lifestyle choices to medication (6%, Theoretical Domains Framework "intentions" domain).

The information ranked most important by women before deciding whether to take risk-reducing medication

Table 2. Facilitators: relationship between survey statement, TDF domain, and COM-B source of behavior, and intervention function.

TDF domain	Domain description	Statement (facilitator)		COM-B source of behavior	Intervention function
		kConFab women	Clinicians		
Social/professional role and identity	A coherent set of behaviors and displayed personal qualities of an individual in a social or work setting	If I thought RRMs would improve the chance I will stay healthy for my family	If it were endorsed as part of my professional role by the relevant college or other peak body		
Goals	Mental representations of outcomes or end states that an individual wants to achieve	Taking RRMs can reduce BC risk for up to 20 years If I thought RRMs would improve the chance I will stay healthy for my family	The beneficial effects of RRMs, e.g., better blood lipid profile and improvements in bone density with tamoxifen		Education Persuasion
Beliefs about capabilities	Acceptance of the truth, reality or validity about an ability, talent or facility that a person can put to constructive use	Not applicable	Not applicable	Reflective motivation	Incentivization Coercion
Optimism	The confidence that things will happen for the best or that desired goals will be attained	Not applicable	I expect positive outcomes for women who take RRMs		
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behavior in a given situation	Taking RRMs can reduce BC risk for up to 20 years	I expect positive outcomes for women who take RRMS		
Intentions	A conscious decision to perform a behavior or a resolve to act in a certain way	Not applicable	Not applicable		
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus	If family/friends were supportive of me taking RRMs	Not applicable		Persuasion
Emotion	A complex reaction pattern, involving experiential, behavioral, and physiologic elements, by which the individual attempts to deal with a personally significant matter or event	Because they would reduce my stress and worry about BC	Sometimes it is easier to discuss RRMs than bilateral mastectomy	Automatic motivation	Incentivization Coercion Environmental restructuring Modeling Enablement
Memory, attention, and decision processes	The ability to retain information, focus selectively on aspects of the environment, and choose between two or more alternatives	Taking a daily tablet to reduce my BC risk would make me feel more in control of my health	If my medical software prompted me to discuss RRMs		
Knowledge	An awareness of the existence of something	Taking RRMs can reduce BC risk for up to 20 years Knowing RRMs can be taken prior to risk-reducing surgery Knowing I have high breast cancer risk Once I stop taking RRMs any side-effects will diminish	Knowing some RRMs are PBS funded	Psychological capability	Education Training Enablement

(Continued on the following page)

Table 2. Facilitators: relationship between survey statement, TDF domain, and COM-B source of behavior, and intervention function. (Cont'd)

TDF domain	Domain description	Statement (facilitator)		COM-B source of behavior	Intervention function
		kConFab women	Clinicians		
Behavioral regulation	Anything aimed at managing or changing objectively observed or measured actions	Taking a daily tablet to reduce my BC would reassure me			
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behavior	Having an abnormal biopsy that increased my risk of developing BC Knowing that some of these medicines help prevent or treat osteoporosis Knowing some of these medicines reduce cholesterol levels Having a family history of BC	If the patient is diagnosed with atypical hyperplasia that increases their risk of BC If the patient is diagnosed with LCIS that increases their risk of BC If a patient has a strong family history of BC If I had better tools to help me identify patients who were suitable Clear guidelines/recommendations e.g., RACGP and Cancer Australia guidelines Support from specialists Support from peers	Physical opportunity	Restriction Environmental restructuring Enablement
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviors	If my family/friends recommended taking RRMs If my doctor recommend taking RRMs	If I knew my colleagues discuss it with their pts	Social opportunity	Restriction Environmental restructuring Enablement
Skills	An ability or proficiency acquired through practice	Not applicable	Not applicable	Physical capability	Training Enablement

Abbreviations: BC, breast cancer; COM-B system, capability, opportunity, and motivation behavior system; LCIS, lobular carcinoma *in situ*; pts, patients; RACGP, Royal Australian College of General Practitioners; RRM, risk-reducing medication; TDF, Theoretical Domains Framework.

Table 3. Characteristics of survey respondents.

Characteristic	kConFab women *n* (%)	Family physicians *n* (%)	Breast surgeons *n* (%)
Age[a]			
18–29	1 (0)	0	0
30–39	83 (12)	5 (3)	1 (1)
40–49	186 (26)	21 (14)	21 (28)
50–59	235 (32)	66 (45)	30 (41)
60+	220 (30)	55 (38)	21 (28)
Not disclosed	0	0	1 (1)
Gender			
Female	725 (100)	99 (67)	30 (41)
Male	0	48 (33)	43 (58)
Not disclosed	0	0	1 (1)
BRCA mutation status[a]			
BRCA1	21 (3)	n/a	n/a
BRCA2	27 (4)	n/a	n/a
No known mutation	677 (93)	n/a	n/a
Number of first- and second-degree relatives with breast cancer			
0	128 (17)	n/a	n/a
1	280 (39)	n/a	n/a
2	216 (30)	n/a	n/a
≥ 3	101 (14)	n/a	n/a
BOADICEA lifetime risk[a]			
16 – 29%	608 (84)	n/a	n/a
≥ 30%	117 (16)	n/a	n/a
Perceived breast cancer risk[b]			
Low	10 (1)	n/a	n/a
Average	173 (24)	n/a	n/a
Moderately increased	302 (42)	n/a	n/a
High	219 (30)	n/a	n/a
Don't know	21 (3)	n/a	n/a
Marital status[a]			
Married/living as married	547 (75)	n/a	n/a
Other	178 (25)	n/a	n/a
Parity[a]			
0	127 (18)	n/a	n/a
1	190 (26)	n/a	n/a
2+	408 (56)	n/a	n/a
Educational status[a]			
Tertiary	328 (45)	n/a	n/a
Less than tertiary	397 (55)	n/a	n/a
Annual screening[c]			
Yes	418 (58)	n/a	n/a
No	198 (27)	n/a	n/a
Unknown	11 (2)	n/a	n/a
Not applicable	98 (13)	n/a	n/a
Awareness of risk-reducing medication			
Yes	347 (48)	96 (65)	72 (97)
No	378 (52)	51 (35)	2 (3)
Source of information[d]			
Family/friends	223 (64)	n/a	n/a
Cancer genetics clinic	70 (20)	n/a	n/a
Family physician	52 (15)	n/a	n/a
Breast surgeon	46 (13)	n/a	n/a
Other	46 (13)	n/a	n/a
TV	43 (12)	n/a	n/a
Internet	37 (11)	n/a	n/a
Magazines	26 (7)	n/a	n/a
Radio	13 (4)	n/a	n/a
Gynecologist	10 (3)	n/a	n/a
Risk-reducing medication use			
Yes	10 (1)	n/a	n/a
No	715 (99)	n/a	n/a

[a]At the time of survey.
[b]Response options were: "Low—lower than most other women," "Average—about the same as most other women," "Moderately increased—about 2 or 3 times that of most other women," "High—more than 3 times that of most other women."
[c]Annual screening with mammogram, magnetic resonance imaging, or both reported in the 9 years prior to being sent the risk-reducing medication survey. Not applicable for 98 women as they were at moderate risk of breast cancer and under the age of 40 at the time of the survey ($n = 98$).
[d]Multiple responses allowed.
n/a: not asked.

pertained to side effects (33%) and extent of breast cancer risk reduction (31%).

Respondents also identified the strongest of 16 facilitators for taking risk-reducing medication (Supplementary Data 3) and rated the strength of each facilitator (**Fig. 2**). The strongest facilitator was that taking risk-reducing medication can reduce breast cancer risk for up to 20 years (35%, Theoretical Domains Framework "knowledge", "beliefs about consequences", and "goals" domains). Additional strong facilitators were knowledge of being at high risk of breast cancer (11%, Theoretical Domains Framework "knowledge" domain), if risk-reducing medications would improve the chance of staying healthy for family (13%, Theoretical Domains Framework "social role/identity" and "goals" domains), and having an abnormal biopsy that increases breast cancer risk (13%, Theoretical Domains Framework "environmental context and resources" domain). Doctor's recommendation was the strongest facilitator for 10% of women, but family or friend recommendation only for 1%. Cholesterol reduction (with tamoxifen) and reduced osteoporosis (with tamoxifen or raloxifene in postmenopausal women) were infrequently identified as the strongest facilitators (1% and 4%, respectively) but most women did identify them as facilitators (55% and 79%, respectively).

Clinician survey

Demographics

Of 554 breast surgeons and family physicians identified by women as involved in their care, 30 were excluded (13 not currently practicing and 17 invalid address). Of 524 eligible clinicians (394 family physicians and 130 breast surgeons) mailed the survey, 221 (42%) responded (57% of breast surgeons and 37% of family physicians). Clinician characteristics are shown in **Table 3**.

Risk-reducing medication awareness, confidence, and roles

Most (76%) clinicians had heard of risk-reducing medication (97% of breast surgeons and 65% of family physicians). Few (3%) family physicians were "very confident" in providing

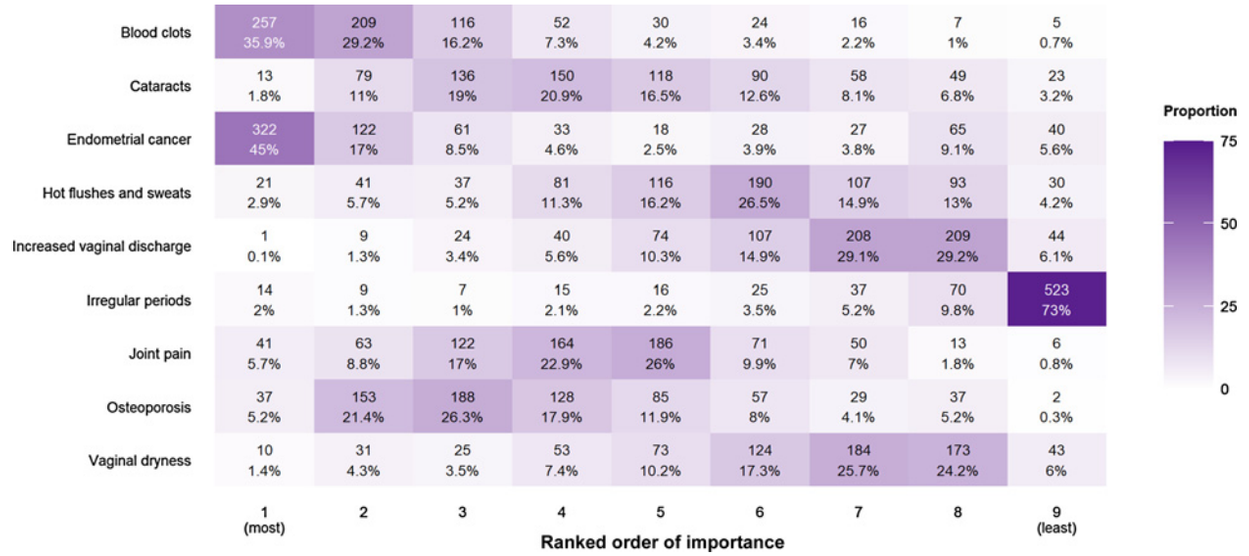

Figure 1.

Heat map of the importance of potential risk-reducing medication side effects as ranked by kConFab women ($n = 716$). Women were asked to rank each potential side effect from most (1) to least (9) important to them when considering taking risk-reducing medication. Numbers and proportions of women who endorsed each level of ranking for each side effect are indicated. Proportions are also indicated by shading, with darker shading representing higher proportions of women endorsing that ranking compared with lighter shading. Data are missing for 9 women who did not answer this question.

information about risk-reducing medication, compared with 56% of breast surgeons. Many family physicians (32%) were "not at all confident" compared with 1% of breast surgeons. Approximately one third (29%) of family physicians had never discussed or prescribed cancer risk-reducing medication, although most (75%) responded it was their role to initiate such discussions and 98% that it was their role to write ongoing prescriptions. Only three (4%) surgeons had never discussed or prescribed risk-reducing medications. Most surgeons perceived their role as initiating discussion and writing first prescriptions (89% and 81%, respectively). Almost half of breast surgeons (47%) but only 10% of family physicians had heard of the iPrevent tool, an Australian tool for women and clinicians to assess and manage breast cancer risk (https://www.canceraustralia.gov.au/affected-cancer/check-your-cancer-risk-online; refs. 32, 33).

Clinician barriers to and facilitators of discussing or prescribing risk-reducing medication

Clinicians who had heard of risk-reducing medication (168) were asked to identify the strongest of 22 barriers to discussing or prescribing risk-reducing medication (Supplementary Data 4) and to rate the strength of individual barriers (**Fig. 3**). The strongest barriers for family physicians were insufficient knowledge (45%, Theoretical Domains Framework "knowledge" domain), lack of confidence in providing advice about risk-reducing medications, and inadequate training and confidence in breast cancer risk assessment (9% and 6%, respectively, Theoretical Domains Framework "beliefs about capabilities" and "skills" domains), medication side effects (7%, Theoretical Domains Framework "beliefs about consequences" domain), difficulty identifying suitable patients (7%, Theoretical Domains Framework "skills" domain), and wanting to achieve other things during a consultation (6%, Theoretical Domains Framework "goals" domain). For breast surgeons, the strongest barriers were medication side effects (40%, Theoretical Domains Framework "beliefs about consequences" domain) and lack of time during a consultation (14%), lack of surrogate markers of medication efficacy (7%), difficulty accessing good patient information (7%), and difficulty finding resources to estimate a patients risk (5%), all operating within the "environmental context and resources" domain of the Theoretical Domains Framework.

Of 14 facilitators, the strongest for family physicians was clear guidelines and recommendations (50%), better tools to identify suitable patients (12%), strong family history of breast cancer (10%), and specialist support (9%), all of which operate within the "environmental context and resources" domain of the Theoretical Domains Framework. For surgeons the strongest facilitators were strong family history (28%), clear guidelines and recommendations (22%), and patients with lobular carcinoma *in situ* (20%), all of which operate in the "environmental context and resources" domain of the Theoretical Domains Framework, as well as expecting positive outcomes for women who take risk-reducing medications (11%, "optimism" and "beliefs about consequences" domains).

Discussion

This Australia-wide study of women at increased risk of breast cancer, and their clinicians, demonstrates very low use of risk-reducing medication (1.4%) by international

Figure 2.
Strength of individual barriers and facilitators to risk-reducing medication for kConFab women (n = 715). Charts show the percentage of kConFab women who identified each barrier or facilitator to risk-reducing medication use as strong, somewhat, not a barrier/facilitator and not applicable. RRM, risk-reducing medication; BC, breast cancer.

Figure 3.
Strength of individual barriers and facilitators to risk-reducing medication for family physicians (n = 96) and breast surgeons (n = 72). Charts show the percentage of clinicians who identified each barrier or facilitator to risk-reducing medication use as strong, somewhat, not a barrier/facilitator and not applicable. BC, breast cancer; RRM, risk-reducing medication.

standards (16). Women in our study may have had greater exposure to information about risk-reducing medication due to their involvement in kConFab, so use of this efficacious prevention intervention could be lower still in other Australian women at increased risk of breast cancer. This study is unique in assessing the views of both women and their clinicians regarding risk-reducing medication. The response rate was high compared with some other survey studies (20); however, the views of nonresponders may differ from those reported here. Regardless, this study has identified several important factors that influence the use of risk-reducing medication, and the behavioral domains in which they operate.

Deficiencies in the "knowledge" domain for both clinicians and women were a prominent barrier to risk-reducing medication use. Unexpectedly, 25% of women in this study perceived their breast cancer risk as low (1%) or average (24%), and this important subset of our study sample is unlikely to have considered use of risk-reducing medication. The reasons for their inappropriately low risk perception are unclear and require further research. Consistent with other studies (34), half of kConFab women and a third of their family physicians had never heard of risk-reducing medication, thus expecting those clinicians to prescribe risk-reducing medication, and women to ask for them, is unrealistic. The potential reasons why a large number of women were unaware of risk-reducing medication was not addressed by this study but would be important to address in future research. Only half of breast surgeons felt very confident in providing information on risk-reducing medications. A clear framework is required in order to improve knowledge, and consequently uptake, of risk-reducing medication. Application of the COM-B behavior change wheel (27) suggests that interventions focused on education, training, and enablement (**Table 1**) may be effective. Risk-reducing medications are all off patent; thus, no commercial incentive exists for pharmaceutical companies to educate clinicians or women about these older generic prevention medicines. In Australia, peak bodies, policymakers, and consumer organizations such as The Royal Australian College of General Practitioners, Cancer Australia, Breast Cancer Network Australia, and BreastSurgANZ could take on this role.

Breast cancer risk assessment is encouraged in Australian primary care guidelines (35). Family physicians identified barriers and facilitators within the domains of "environmental context and resources" (difficulty selecting suitable patients and need for better tools to identify suitable patients) and "skills" (inadequate confidence in breast cancer risk assessment). This is consistent with previous research demonstrating that family physicians lack confidence in personalized medicine, knowledge of risk, and risk perception (36). These findings point to environmental restructuring interventions, such as development of national guidelines mandating routine breast cancer risk assessment, and incorporating prompts into family physician software to assess breast cancer risk and to discuss risk-reducing medication if criteria are met (which has been shown to be effective in other health promotion settings (37)). They also point to the importance of training to impart skills to clinicians in breast cancer risk assessment. Active education strategies such as workshops focusing on assessment and discussion of breast cancer risk and appropriate risk-reducing strategies may improve family physician confidence in discussing risk-reducing medication. Tools to enhance informed decision-making about risk-reducing medication, which present the benefits and potential harms of these medications, could support discussions in primary care (38). Use of iPrevent (an Australian online breast cancer risk assessment and risk management decision support tool for women and clinicians that is endorsed by Cancer Australia; https://www.canceraustralia.gov.au/affected-cancer/check-your-cancer-risk-online) may improve breast cancer risk assessment in primary care and provide easy-to-access, personalized information on the benefits of risk-reducing medication (32, 33, 39). For women, a public campaign around knowing your breast cancer risk and available interventions may increase awareness of risk-reducing medication. Breast cancer screening programs may provide a convenient platform to roll out education about risk-reducing medication. It has been demonstrated in a large study embedded in a screening program in the Manchester area of the UK, that the majority of women want to know their breast cancer risk, and that providing personalized risk information in this setting does not cause psychological harms (40), and results in engagement in prevention programs (41). One Australian state, Western Australia, has mandated that women receive information on their mammographic density from the free breast cancer screening program (similar to several jurisdictions in the United States), but a personalized risk estimate is not provided, nor is this linked to specific prevention information or programs.

Abnormal breast biopsy was identified as a strong facilitator to clinicians to discuss or prescribe risk-reducing medication. Atypical hyperplasia and lobular carcinoma *in situ* are associated with a significant increase in breast cancer risk, and risk-reducing medication reduces risk of invasive breast cancer in these conditions (6, 11, 42). Women with atypical hyperplasia have low uptake of risk-reducing medication and often underestimate their breast cancer risk (43). Environmental restructuring with mandated routine discussion of women with atypical hyperplasia or lobular carcinoma *in situ* at multidisciplinary meetings, after their surgery or biopsy, could help prompt consideration of risk-reducing medication. Automatic prompts in clinician software may also be helpful.

Consistent with previous research, the strongest barrier to risk-reducing medication identified by women and breast surgeons was side effects (18, 22). Seeing family and friends experience side effects from similar medications was also a strong barrier. In our familial breast cancer cohort setting, these experiences are likely to have been in relatives receiving these medications for cancer treatment. Experience of side effects differs when used for breast cancer treatment compared with prevention, because side effects of endocrine therapies

are often confused with chemotherapy toxicities (22). This needs to be carefully outlined when discussing options to prevent overestimation of side effects. Fear of side effects in our study was mainly focused on endometrial cancer and venous thromboembolism. Aromatase inhibitors and raloxifene do not increase endometrial cancer risk, and tamoxifen only increases it in postmenopausal women where the risk is approximately 1 in 250 over 5 years (resolving on completion; ref. 44). Most (62%) women in our study who ranked endometrial cancer risk as most important to them were under the age 50 years, despite tamoxifen conferring no increased risk of endometrial cancer in premenopausal women; this emphasizes the importance of personalized discussions and education to address these misconceptions. Aromatase inhibitors do not increase incidence of venous thromboembolism, and in women on tamoxifen or raloxifene, the absolute risk is generally small (1 in 250 over 5 years of use; ref. 44).

The nocebo effect has the potential to influence patient acceptability of treatments and compliance (45). This is supported by the IBIS prevention trials, which demonstrated similar rates of adverse reactions in both intervention and placebo groups (3, 6). For example in the IBIS II trial, 57% of those in the intervention arm and 49% in the placebo arm experienced vasomotor symptoms, suggesting that only about 1 woman in 12 will experience these symptoms due to risk-reducing medication. Online tools, such as iPrevent (32), can help clinicians provide personalized estimates of the absolute risk reduction, as well as the absolute risk of serious side effects with risk-reducing medication. Considering a short trial of therapy to assess side-effect profile, before a 5-year course, may be a useful approach (2). Low-dose tamoxifen (5 mg daily for 3 years) may be a useful alternative for women who do experience side effects on the standard dose (11). Behavioral change theory (27) also points to incentivization as a possible strategy to address barriers that operate in the Theoretical Domains Framework "beliefs about consequences" domain, as does concern about side effects of risk-reducing medication. Highlighting the potential beneficial effects of risk-reducing medication may be important. Over half of women in our study identified that reduction in cholesterol and the potential prevention of osteoporosis would make it easier to take risk-reducing medication.

It is important to note that for a small number of women we were unable to identify the barriers and facilitators to risk-reducing medication, indicating that there may be other barriers and facilitators that we did not elucidate.

Despite many lacking awareness and confidence, the majority of family physicians (75%) viewed initial discussion of risk-reducing medication as part of their role. Fewer (31%) felt that writing the first prescription was appropriate but 98% were happy to provide ongoing prescriptions. This is consistent with other studies (46) but is potentially a major hurdle, as optimal implementation of risk-reducing medication may require family physicians to prescribe the first dose.

Reducing breast cancer incidence requires a clear strategy that incorporates routine breast cancer risk assessment with implementation of evidence-based risk reduction strategies, including risk-reducing medication. We have identified a significant knowledge and resource gap for both women and clinicians. Application of a behavioral change model suggests that both an individual and a system-based approach, including interventions in education, training, incentivization, and environmental restructuring, could be instrumental in increasing uptake of risk-reducing medication.

Authors' Disclosures

L.A. Keogh reports grants from NHMRC during the conduct of the study. S.C. Jones reports grants from Cancer Australia and grants from National Breast Cancer Foundation during the conduct of the study. M.L. Friedlander reports grants, personal fees, and other from AstraZeneca, personal fees from MSD, Lilly, Takeda, and GSK, and grants and personal fees from Novartis outside the submitted work. R.L. Milne reports grants from NHMRC during the conduct of the study. K.-A. Phillips reports grants from Cancer Australia, the National Breast Cancer Foundation, National Health and Medical Research Council, National Institutes of Health, Cancer Councils, Queensland Cancer Fund, and Cancer Foundation Western Australia during the conduct of the study; in addition, Dr Phillips has a patent for System Process for Cancer Risk Estimation, Australian Innovation Patent No. 2012101273 issued. No disclosures were reported by the other authors.

Authors' Contributions

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Acknowledgments

We thank Sandra Picken, Lucy Stanhope, Sarah O'Connor, Gerda Evans, Leslie Gilham, Heather Thorne, Eveline Niedermayr, Sharon Guo, the kConFab research nurses and the heads and staff of the Family Cancer Clinics. We thank the women, their families, and the clinicians that participated in this research. This research was supported by Cancer Australia and the National Breast Cancer Foundation (PdCCRS #1100868). kConFab and the kConFab Follow-Up Study have received additional funding support from Cancer Australia (809195), the Australian National Breast Cancer Foundation (IF 17), the Australian National Health

and Medical Research Council (454508, 288704, and 145684), the National Institute of Health USA (1RO1CA159868), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia. K.-A. Phillips is an Australian National Breast Cancer Foundation Fellow (PRAC17–004). The contents of this manuscript are solely the responsibility of the authors and do not necessarily reflect the views of Cancer Australia.

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Received July 9, 2020; revised August 27, 2020; accepted October 15, 2020; published first October 28, 2020.

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Chapter 5: Ovarian Cancer Screening

Inappropriate Ovarian Cancer Screening

Screening for ovarian cancer has previously been recommended and has consisted of annual testing of the serum tumor marker CA-125 and trans-vaginal ultrasound (TVUS). Two large randomised controlled trials of women at population risk of ovarian cancer have failed to demonstrate reduction in ovarian cancer mortality(86, 87, 129). A meta-analysis in 2013, and a subsequent systematic review published in 2018, also demonstrated no reduction in mortality with regular ovarian cancer screening(130, 131). In fact, these studies demonstrated the potential harms of ovarian cancer screening. TVUS resulted in a mean of 38 surgeries per ovarian cancer detected and surgery was associated with complications in 6% of women. Women with false-positive results suffered from increased cancer-specific distress and anxiety.

Whether women at high-risk of ovarian cancer benefit from ovarian cancer screening was addressed in a study published into 2017, which used the risk of ovarian cancer algorithm (ROCA) to direct screening frequency with CA-125 in women at increased familial risk of ovarian cancer. This study demonstrated a higher sensitivity of CA-125 for detection of ovarian cancer with application of the algorithm but did not demonstrate a reduction in mortality(132). RRBO remains the most effective form of risk reduction for women with a *BRCA1* and *BRCA2* pathogenic variant. Australian guidelines were changed in 2009 to no longer recommend ovarian cancer screening for women at any level of risk, due to the proven lack of mortality benefit and potential harms(133). International guidelines also do not recommend screening for

ovarian cancer(97, 134) with the exception of the NCCN guidelines(53), which state that screening may be considered in *BRCA1* and *BRCA2* pathogenic variant carriers who do not chose to undergo RRBO.

Despite guidelines recommending against ovarian cancer screening, women continue to screen. A retrospective study of the screening practices of women in the United States with a strong family history of breast or ovarian cancer reported that 20% of women had had at least one CA-125 screening test and 31% had had a TVUS for screening(135). Those women who had a close relative affected by ovarian cancer were more likely to screen for ovarian cancer. Studies from Norway and the US have reported that 21% to 58% of clinicians recommend screening for ovarian cancer to women at average risk of the disease(136-138) and over a third of US physicians who worked in women's health believed that TVUS or CA-125 is an effective screening test for ovarian cancer(136). Previous research into why clinicians continue to order these ineffective screening tests identified patient expectations, fear of litigation and the incorrect belief of improving disease-specific mortality with testing as facilitators of screening(139).

PDF of manuscript 3 Motivators of Inappropriate Ovarian Cancer Screening: A survey of women and their clinicians

This study used the kConFab clinical follow-up study cohort to evaluate the use of ineffective ovarian cancer screening in Australia, and to identify what motivates screening from both clinicians' and women's perspectives. This study sample was chosen, as it is a pre-existing large prospective breast cancer family cohort study of Australian women, including a large number of women with elevated risk of breast

cancer. A survey, based on the Theoretical Domains Framework (TDF), was designed, piloted, revised and then sent to, and completed by, kConFab women, and the gynaecologists/gynaecologic oncologists and GPs who care for them. The TDF was chosen as it provides a comprehensive framework that covers a large range of potential barriers to behaviour change and includes a wide range of suggested interventions(140, 141). The TDF was developed by experts in implementation and behavioural science and has been used widely in healthcare settings(142-145). A key strength of the TDF that it links directly with the Capability, Motivation and Behaviour (COM-B) model, a behaviour change model, which links theoretical domains to potential interventions and policy change to target the desired behaviour change(118, 146). Other frameworks were considered but these lacked validation in multiple healthcare settings (physicians and patients), comprehensive coverage of barriers and did not link to behavioural change models(147, 148).

This study showed that 15% of women in our study continue to undergo ovarian cancer screening with 80% stating that they would continue ovarian cancer screening even if their doctor told them it was ineffective. The majority of women (74%) reported that ovarian cancer screening was effective for ovarian cancer detection and 42% disagreed with the statement that ovarian cancer screening can lead to unnecessary tests and surgery. Motivators for ongoing screening for women were “these tests might improve the change I will stay healthy for my family”, “these tests are easy enough to have” and “there are no other screening options available and it is better than doing nothing”. Few gynaecologists and GPs reported that ovarian cancer screening was useful for early detection, though 64% of GPs and

50% of gynaecologists had ordered ovarian cancer screening in the last two years. Motivators of screening for GPs were “women ask for these tests”, “there is a chance these tests will detect cancer early and lead to more successful patient outcomes” and “I order these tests for patient peace of mind”. For gynaecologists strong motivators were “there are currently no other options available for ovarian cancer screening”, “I order these tests for patient peace of mind” and “It is hard to discontinue these tests in women who have been having ovarian cancer screening for years”. Application of the TDF and linking with the COM-B behaviour change model allowed us to make suggestions for interventions to reduce ovarian cancer screening. These included targeting educational resources for clinicians and patients, communication workshops for clinicians focusing on stopping interventions, understanding how clinicians are accessing ovarian cancer screening tests and potential for a public campaign illustrating why high profile women don’t screen for ovarian cancer. The findings from this study were presented at the Medical Oncology Group of Australia 2020 Abstract and poster programme for Australian medical oncology trainees and young oncologists and at the Familial Aspects of Cancer Research and Practice conference in September 2021. This study was published in the *Journal of the National Cancer Institute – Cancer Spectrum* (JNCI-CS) in December 2020.

Publication citation

Macdonald C, Mazza D, Hickey M, Hunter M, Keogh LA, kConFab investigators, Jones SC, Saunders C, Nesci S, Milne RL, McLachlan SA, Hopper JL, Friedlander ML, Emery J, Phillips KA: Motivators of Inappropriate Ovarian Cancer Screening: A

Survey of Women and Their Clinicians. *JNCI Cancer Spectrum*. Volume 5, Issue 1, February 2021, pkaa110.

JNCI Cancer Spectrum (2021) 5(1): pkaa110

doi: 10.1093/jncics/pkaa110
First published online 8 December 2020
Article

Motivators of Inappropriate Ovarian Cancer Screening: A Survey of Women and Their Clinicians

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Abstract

Background: This study examined why women and doctors screen for ovarian cancer (OC) contrary to guidelines. **Methods:** Surveys, based on the Theoretical Domains Framework, were sent to women in the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer and family physicians and gynecologists who organized their screening. **Results:** Of 1264 Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer women, 832 (65.8%) responded. In the past 2 years, 126 (15.1%) had screened. Most of these (n = 101, 80.2%) would continue even if their doctor told them it is ineffective. For women, key OC screening motivators operated in the domains of social role and goals (staying healthy for family, 93.9%), emotion and reinforcement (peace of mind, 93.1%), and beliefs about capabilities (tests are easy to have, 91.9%). Of 531 clinicians 252 (47.5%) responded; a minority (family physicians 45.8%, gynecologists 16.7%) thought OC screening was useful. For gynecologists, the main motivators of OC screening operated in the domains of environmental context (lack of other screening options, 27.6%), and emotion (patient peace of mind, 17.2%; difficulty discontinuing screening, 13.8%). For family physicians,, the strongest motivators were in the domains of social influence (women ask for these tests, 20.7%), goals (a chance these tests will detect cancer early, 16.4%), emotion (patient peace of mind, 13.8%), and environmental context (no other OC screening options, 11.2%). **Conclusion:** Reasons for OC screening are mostly patient driven. Clinician knowledge and practice are discordant. Motivators of OC screening encompass several domains, which could be targeted in interventions to reduce inappropriate OC screening.

Evidence does not support ovarian cancer (OC) screening in population-risk women. Randomized controlled trials have failed to demonstrate an improvement in survival with annual screening using transvaginal ultrasound (ultrasound) and cancer antigen 125 (CA125) in women at population risk of OC (1,2). In 2013, a meta-analysis (3) showed that screening did not improve survival and led to false-positive results requiring further investigation. Ultrasound resulted in a mean of 38 surgeries

Received: 24 June 2020; **Revised:** 22 September 2020; **Accepted:** 8 October 2020

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per OC detected, and 6% of women experienced surgical complications. Women with false-positive results experienced increased cancer-specific distress. These results are consistent with the most recent US Preventative Services Task Force statement, which recommends against screening for OC in average-risk women (4).

Despite the absence of survival benefit, women continue to undergo OC screening. Data from Norway and the United States suggest 21% to 58% of clinicians recommend screening to average-risk women (5-8). Previous research has demonstrated that clinicians who perform OC screening are driven by patient expectations, fear of litigation, and belief that OC screening reduces mortality (7). Women commonly overestimate their personal risk of OC (9), and most believe that screening improves survival (10).

BRCA1 and *BRCA2* mutation carriers are considered high-risk for OC, with average lifetime risks of 44% and 17%, respectively (11). Bilateral salpingo-oophorectomy is associated with improved survival and is recommended as optimal risk reduction for this group (12-15). A prospective, nonrandomized trial in women at elevated risk suggested that use of an algorithm based on absolute level and rate of increase in CA125 had higher sensitivity for detection of early-stage OC than 6 monthly CA125 with a fixed cut point (16). Confirmatory studies are needed, and there is no evidence that OC screening in high-risk women improves survival.

International guidelines do not recommend OC screening for average and high-risk women. US National Comprehensive Cancer Network guidelines state that ultrasound combined with CA125 testing in *BRCA1* and *BRCA2* mutation carriers who do not undergo salpingo-oophorectomy can be considered at the clinician's discretion from age 30-35 years; however, the benefit is uncertain (17). The UK guidelines recommend against OC screening outside a clinical trial (18,19). Australian guidelines state that there is no evidence to support OC screening in any population (20).

This study aimed to determine the prevalence of OC screening by Australian women enrolled in a familial breast cancer cohort, including women at average and elevated risk of OC. It examined knowledge and motivators of OC screening for women and the clinicians who organized their screening.

Methods

Setting

Participants were women (and their clinicians) from multiple-case breast cancer families who were recruited to the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) cohort between 1997 and 2008 (21,22). The proband was recruited after consultation in 1 of 15 Australian genetics clinics. Other family members could enroll in the cohort study without attending a genetics clinic. Women ranged from average to high risk of OC based on their family history and germline mutation status. Women are mailed follow-up questionnaires every 3 years (23) to update demographics (educational level, parity, and marital status), doctors involved in their care, cancer family history, cancer screening undertaken, risk reduction interventions, and cancer diagnoses (the latter 2 confirmed from pathology and surgical records). Clinician characteristics were obtained from the Australian Health Practitioner Regulation Agency website (24). All participants provided written informed consent, and kConFab and this survey study have human research ethics committee approval.

Surveys of kConFab Women and Clinicians

Understanding the factors that influence use of OC screening for both clinicians and patients is the first step in implementing practice change to reduce OC screening. The Theoretical Domains Framework (TDF) (25,26) was developed to identify the cognitive, affective, social, and environmental influences on health professionals and patient behavior related to implementation of evidence-based recommendations. It consists of 84 theoretical constructs grouped into 14 domains, and maps directly to the capability, opportunity, motivation and behavior (COM-B) model (27), to suggest intervention functions and policy categories to guide potential pathways to behavioral change.

A 33-item survey (Supplementary Materials, available online) was developed based on a literature review and semistructured interviews with 62 kConFab women from different geographical locations, socioeconomic status, and ethnicities to identify possible motivators for OC screening. Survey questions based on the TDF (Table 1) (25) were developed by the research team, which included experts in health sociology, qualitative research, gynecology, and primary care. The survey was piloted for usability with 9 kConFab women in face-to-face cognitive interviews and further refined. kConFab women were eligible for the survey if they were aged between 25 and 70 years, resided in Australia, had no previous bilateral oophorectomy or breast cancer and no invasive cancer in the past 6 years, and had not participated in the pilot. The survey was sent to kConFab women, and nonresponders were followed up 3 times.

The 28-item survey (Supplementary Materials, available online) was developed by the research team, following a literature review and using the TDF (Table 1). Eligible clinicians were family physicians (FPs) or gynecologists identified by kConFab women as having ordered their screening tests and who were currently practicing in Australia with valid address. Nonresponders to the mailed questionnaire were followed up 3 times.

Statistical Analysis

The survey responses for both clinicians and kConFab women were analyzed using descriptive statistics in R version 3.6.1 [R Core Team (2015) (28)]. Missing data were not imputed. For all numeric data, the mean (standard deviation), median (range), and interquartile range are provided. For categorical data, the count, percentages, and 95% confidence intervals are provided. The *t* tests and exact χ^2 tests were calculated to examine whether there was evidence of a difference between responders and nonresponders for continuous and categorical variables, respectively. Tests were 2-tailed, and *P* values less than .05 were considered statistically significant.

Results

kConFab Women Survey

Of 4982 women unaffected with breast cancer when enrolled in kConFab between 1997 and 2008, 1097 declined follow-up. Of the remaining 3885 women, 332 died during follow-up, and 2289 were excluded (previous breast cancer [n = 1045], younger than age 25 years or older than age 70 years [n = 499], not residing in

Table 1. Relationship of TDF domain, COM-B system source of behavior, and intervention function[a]

TDF domain	Domain description	Statement		COM-B source of behavior	Intervention function
		kConFab women	Clinicians		
Social/professional role and identity	A coherent set of behaviors and displayed personal qualities of an individual in a social or work setting	These tests might improve the chance I will stay healthy for my family.	I would not want to conflict with the provided by another clinician.	Reflective motivation	Education Persuasion Incentivization Coercion
Goals	Mental representations of outcomes or end states that an individual wants to achieve	These tests might improve the chance I will stay healthy for my family.	There is a chance these tests will detect cancer early and lead to more successful patient outcomes.		
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use	These tests are easy enough to have.	Sometimes it is too hard to talk women out of it.		
Optimism	The confidence that things will happen for the best or that desired goals will be attained	I believe these tests might pick up ovarian cancer early.	I am optimistic that these tests will detect ovarian cancer at an early and potentially curable stage.		
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behavior in a given situation	I believe these tests might pick up ovarian cancer early.	It is better than doing nothing at all. I am concerned if my patient develops ovarian cancer she may take legal action.		
Intentions	A conscious decision to perform a behavior or a resolve to act in a certain way	Not applicable.	Not applicable.		
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus	Normal test results provide reassurance and peace of mind that I do not have ovarian cancer.	There are no adverse consequences for me when ordering these tests. I have no way of knowing if my approach to ovarian cancer screening is similar to other clinicians.	Automatic motivation	Persuasion Incentivization Coercion Environmental restructuring Modeling Enablement
Emotion	A complex reaction pattern, involving experiential, behavioral, and physiological elements, by which the individual attempts to deal with a personally significant matter or event	Normal test results provide reassurance and peace of mind that I do not have ovarian cancer.	I order these tests for patients' peace of mind. It is hard to discontinue these tests in asymptomatic women who have been having ovarian cancer screening for several years. I am worried I might miss an ovarian cancer diagnosis.		
Memory, attention, and decision processes	The ability to retain information, focus selectively on aspects of the environment, and choose between 2 or more alternatives	There are currently no other screening options available and it is better than doing nothing. The other option is to have my ovaries removed, and I don't want that at the moment.	Not applicable.	Psychological capability	Education Training Enablement

(continued)

Table 1. (continued)

TDF domain	Domain description	Statement		COM-B source of behavior	Intervention function
		kConFab women	Clinicians		
Knowledge	An awareness of the existence of something	There is no reliable way to detect ovarian cancer at an early and potentially curable stage. Screening for ovarian cancer can lead to unnecessary tests and surgery.	There is no reliable way to detect ovarian cancer at an early and potentially curable stage in asymptomatic women. CA125 blood tests and ovarian ultrasound scans can lead to unnecessary tests and surgery in asymptomatic women.		
Behavioral regulation	Anything aimed at managing or changing objectively observed or measured actions	Not applicable.	There are no adverse consequences for me when ordering these tests. I have no way of knowing if my approach to ovarian cancer screening is similar to other clinicians.		
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behavior	There are currently no other screening options available, and it is better than doing nothing. It is affordable. Healthcare professionals change their mind all the time about the best tests/guidelines. I don't trust my health professional's . I have previously had ovarian cancer symptoms.	There are currently no other options available for ovarian cancer screening. A CA125 blood test is a simple test. An ovarian ultrasound is a simple test.	Physical opportunity	Restriction Environmental restructuring Enablement
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviors	My family/friends encourage me to have these tests. My family/friends ovarian cancer was detected through screening.	Women ask for these tests.	Social opportunity	Restriction Environmental restructuring Enablement
Skills	An ability or proficiency acquired through practice	Not applicable.	I am confident talking about ovarian cancer screening with my patients.	Physical capability	Training Enablement

[a]COM-B system= capability, opportunity, and motivation behavior system; TDF = Theoretical Domains Framework.

Australia or invalid address [n = 294], participation in pilot [n = 9], invasive cancer in the past 6 years [n = 61], or bilateral oophorectomy [n = 381]). Of 1264 eligible women, 832 (65.8%) responded. Table 2 describes the characteristics of responders and nonresponders. Responders were statistically significantly more likely to have a tertiary education compared with nonresponders (48.1% vs 34.5%; $P < .001$). There were no other statistically significant differences between respondents and nonrespondents. Only 34 (4.1%) of respondents were *BRCA1* or *BRCA2* mutation carriers. A quarter of women (n = 210) perceived their OC risk as high (5.4%) or moderately increased (19.8%). Of these 210, 51 had a *BRCA1* or *BRCA2* mutation and/or a first-degree relative with OC.

The majority of kConFab women (74.0%) reported that the use of CA125 and ultrasound in combination was either "highly likely" or "likely" to detect early-stage OC (46.1% highly likely, 27.9% likely). All respondents reported their level of agreement with statements about OC screening and

Table 2. Characteristics of responders and nonresponders (60 responders, 82 nonresponders)

Characteristics	kConFab women			Family physicians		Gynecologists	
	Responders No. (%)	Non-responders No. (%)	*P*	Responders No. (%)	Non-responders No. (%)	Responders No. (%)	Non-responders No. (%)
Age, years							
18-29	2 (0.2)	1 (0.2)	.05[a]	n/a	n/a	n/a	n/a
30-39	112 (13.5)	47 (10.9)		n/a	n/a	n/a	n/a
40-49	243 (29.2)	161 (37.3)		n/a	n/a	n/a	n/a
50-59	253 (30.4)	125 (28.9)		n/a	n/a	n/a	n/a
≥ 60	222 (26.7)	98 (22.7)		n/a	n/a	n/a	n/a
Year of first medical registration[c]							
1960-1969	n/a	n/a	n/a	2 (1.0)	2 (1.0)	3 (5.1)	4 (5.0)
1970-1979	n/a	n/a		30 (15.6)	33 (17.0)	7 (11.9)	13 (16.3)
1980-1989	n/a	n/a		66 (34.4)	53 (27.3)	22 (37.3)	22 (27.5)
1990-1999	n/a	n/a		49 (25.5)	50 (25.8)	14 (23.7)	19 (23.7)
≥ 2000	n/a	n/a		45 (23.4)	56 (28.9)	13 (22.0)	22 (27.5)
Missing	n/a	n/a		0	3	1	2
Sex[c]							
Female	832 (100)	432 (100)	n/a	134 (69.8)	127 (64.5)	22 (36.7)	23 (28.0)
Male	0	0		58 (30.2)	70 (35.5)	38 (63.3)	59 (72.0)
BRCA mutation status							
BRCA1 or *BRCA2*	34 (4.1)	27 (6.2)	.10[a]	n/a	n/a	n/a	n/a
No mutation	798 (95.9)	405 (93.8)		n/a	n/a	n/a	n/a
1st degree relative affected with OC							
Yes	52 (6.2)	26 (6.0)	.90[b]	n/a	n/a	n/a	n/a
No	780 (93.8)	406 (94.0)		n/a	n/a	n/a	n/a
Marital Status							
Married/Living as married	628 (75.5)	313 (72.9)	.35[a]	n/a	n/a	n/a	n/a
Other	204 (24.5)	116 (27.1)		n/a	n/a	n/a	n/a
Missing	1	3		n/a	n/a	n/a	n/a
Parity							
Nulliparous	154(18.5)	69 (16.0)	.45[a]	n/a	n/a	n/a	n/a
1	212 (25.5)	107 (24.8)		n/a	n/a	n/a	n/a
≥ 2	466 (56.0)	256 (59.2)		n/a	n/a	n/a	n/a
Educational level							
Less than tertiary	431 (51.9)	285 (65.5)	<.01[a]	n/a	n/a	n/a	n/a
Tertiary	400 (48.1)	147 (34.5)		n/a	n/a	n/a	n/a
Missing	1	0		n/a	n/a	n/a	n/a
Perceived risk[d]							
High	45 (5.4)	n/a	n/a	n/a	n/a	n/a	n/a
Moderately increased	165 (19.8)	n/a		n/a	n/a	n/a	n/a
Average	520 (62.5)	n/a		n/a	n/a	n/a	n/a
Low	40 (4.8)	n/a		n/a	n/a	n/a	n/a
Don't know	62 (7.5)	n/a		n/a	n/a	n/a	n/a

[a]Two-sided χ^2 test. CI = confidence interval; kConFab = Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; N/A = not asked/not applicable.
[b]2-sided Fisher exact test.
[c]Year of medical registration and sex were not statistically significantly different between clinician responders and nonresponders.
[d]High: more than 3 times that of most other women. Moderately increased: about 2 or 3 times that of most other women. Average: about the same as most other women. Low: lower than most other women.

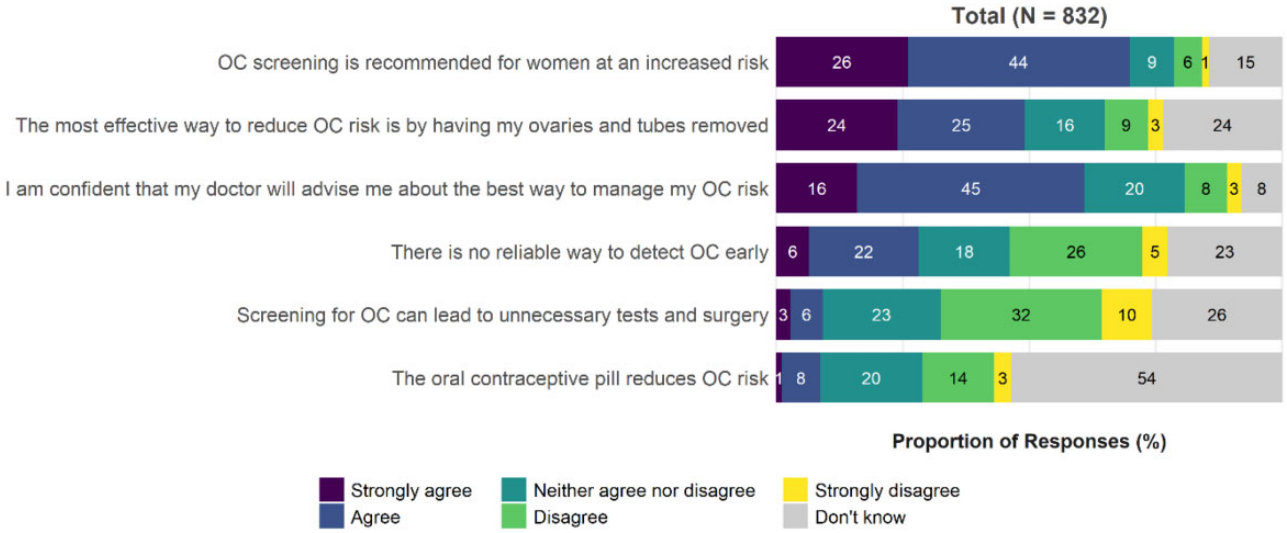

Figure 1. kConFab women: knowledge about ovarian cancer (OC) screening and risk reduction. kConFab = Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer.

risk reduction (Figure 1; Supplementary Table 1, available online). Many (41.9%) disagreed with the statement that OC screening can lead to unnecessary tests and surgery. Most (69.9%) agreed with the statement that OC screening is recommended for women at increased risk (26.0% strongly agreed, 43.9% agreed).

A minority of women (n = 126, 15.1%) had undergone screening in the past 2 years, with 103 (12.4%) having had an ultrasound, most (n = 85, 82.5%) arranged by FPs. More than one-third of *BRCA1* or *BRCA2* mutation carriers (n = 13, 38.2%) had undergone an ultrasound for screening compared with 11.3% (n = 90) of those who did not have a known *BRCA1* or *BRCA2* mutation. A minority of women (n = 53, 6.4%) had CA125 testing for OC screening in the past 2 years, including 4 (11.8%) *BRCA1* and *BRCA2* mutation carriers. The majority were arranged by FPs (n = 44, 83.0%) or gynecologists (n = 6, 11.3%).

Of the 45 (5.4%) women who perceived their OC risk as high, 18 (40.0%) had an ultrasound, 6 (13.3%) had CA125, and 4 (8.8%) had both. Almost half (n = 20, 44.4%) had undergone some form of OC screening compared with 24.8% of those who perceived their risk as moderate and 10.8% of those who thought their risk was average or below.

The majority (n = 101, 80.2%) of women who had undergone OC screening in the past 2 years responded that they would continue screening even if their doctor advised that there was no test that detects OC when it is early and potentially curable.

Those women who indicated they would continue screening despite being told it is ineffective were asked their level of agreement with 12 potential reasons to continue screening (Figure 2; Supplementary Table 2, available online). The most frequently endorsed reason mapped to the social role and goals domain of the TDF ("these tests might improve the chance I will stay healthy for my family," 93.9% [35.7% strongly agreed, 58.2% agreed]). This was followed by "normal test results provide reassurance and peace of mind" (93.1% [24.8% strongly agreed, 68.3% agreed]) in the emotion and reinforcement domains and "these tests are easy enough to have" (91.9% [30.3% strongly agreed, 61.6% agreed]) in the beliefs about capabilities domain. Two-thirds of women (65.6%) agreed that affordability of the tests was a reason to continue screening.

Clinician Survey

Of 399 FPs identified by kConFab women, 10 were excluded (not practicing [n = 5]; invalid address [n = 5]). Of 148 gynecologists identified, 6 were excluded (not practicing [n = 3]; invalid address [n = 3]). Overall, 252 clinicians of 531 (192 FPs, 60 gynecologists) responded to the survey (response rate = 47.4%, FPs = 49.3%, gynecologists = 42.2%). Clinician characteristics are shown in Table 1. There were no statistically significant differences between clinician responders and nonresponders in terms of sex and date of first medical registration ($P = .06$ and .36, respectively).

A minority of clinicians (FPs = 45.8%, gynecologists = 16.7%) thought OC screening was useful. More than one-third of FPs (n = 77, 40.1%) had ordered ultrasound screening, and 92 (47.9%) had ordered CA125 in the past 2 years. Half of gynecologists (n = 30, 50.0%) had ordered ultrasound screening and 25 (41.6%) CA125.

Clinicians were asked to rate their level of agreement with statements about OC screening and risk reduction (Figure 3; Supplementary Table 3, available online). The majority of clinicians agreed there is no reliable way to detect OC at an early stage (72.9% FPs, 90.0% gynecologists) and that CA125 and ultrasound can lead to unnecessary tests and surgery (77.1% FPs, 95.0% gynecologists). However, about half of clinicians (51.6% FPs, 48.3% gynecologists) agreed that they would usually order a CA125 and ultrasound at patient request.

Clinicians who had ordered OC screening in the past 2 years were asked to identify the strongest motivators for ordering these tests and their level of agreement with each motivator (Figure 4; Supplementary Table 4, available online). The most frequently identified motivators for FPs were "women ask for these tests" (20.7%, TDF social influence domain), the chance these tests will detect OC early and lead to more successful patient outcomes (16.4%, goals domain), for patients' peace of

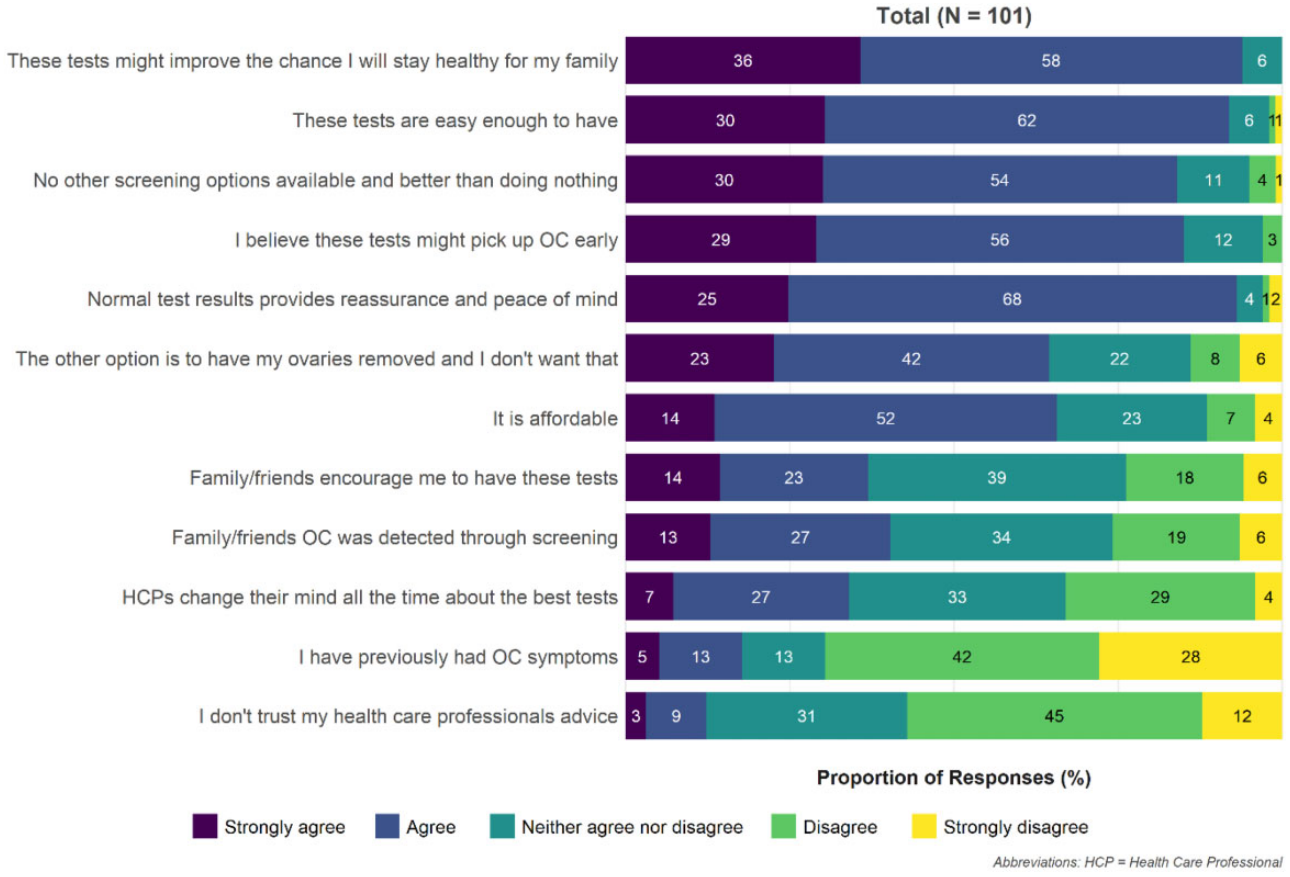

Figure 2. kConFab women: reasons to continue ovarian cancer (OC) screening. HCP = healthcare professionals; kConFab = Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer.

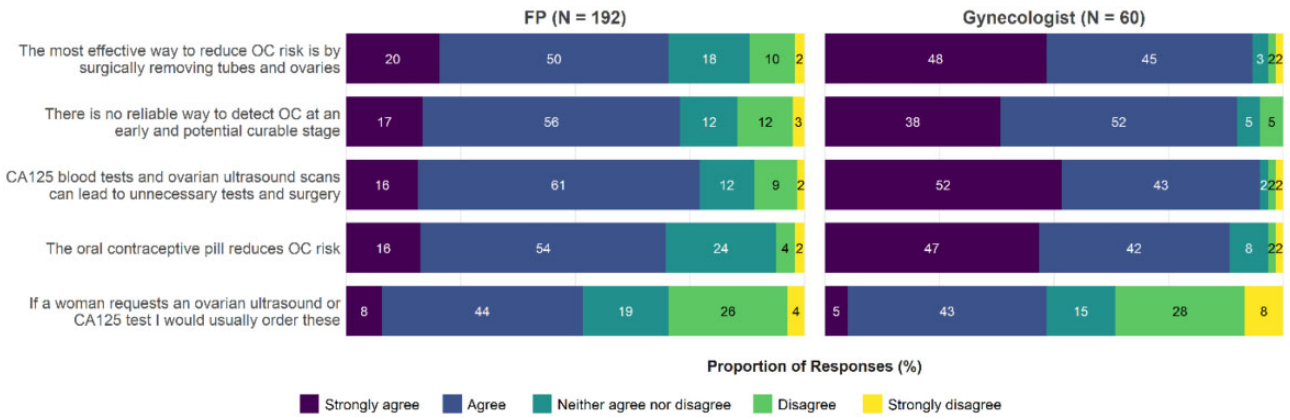

Figure 3. Clinician knowledge about ovarian cancer (OC) screening and risk reduction. CA125 = cancer antigen 125; FP = family physician.

mind (13.8%, emotion domain), and no other available screening options (11.2%, environmental context and resources domain). For gynecologists, the strongest reasons were no other available screening options (27.6%, TDF environmental context and resource domain), for patients' peace of mind (17.2%, emotion domain), and difficulty discontinuing tests in women having OC screening (13.8%, emotion domain). Concern about legal action was never the strongest facilitator (0%), but 31.1% of FPs and 23.3% of gynecologists endorsed it as a reason for ordering OC screening.

Discussion

This Australia-wide study of a large number of women enrolled in a breast cancer cohort, and the clinicians who order their screening, has demonstrated that some women screen for OC despite national guidelines that do not recommend it. Further, we have identified motivators of OC screening, for both women and clinicians, and the behavioral domains in which they operate.

Our study has a number of strengths including a high response rate compared with some others in the literature (6,29)

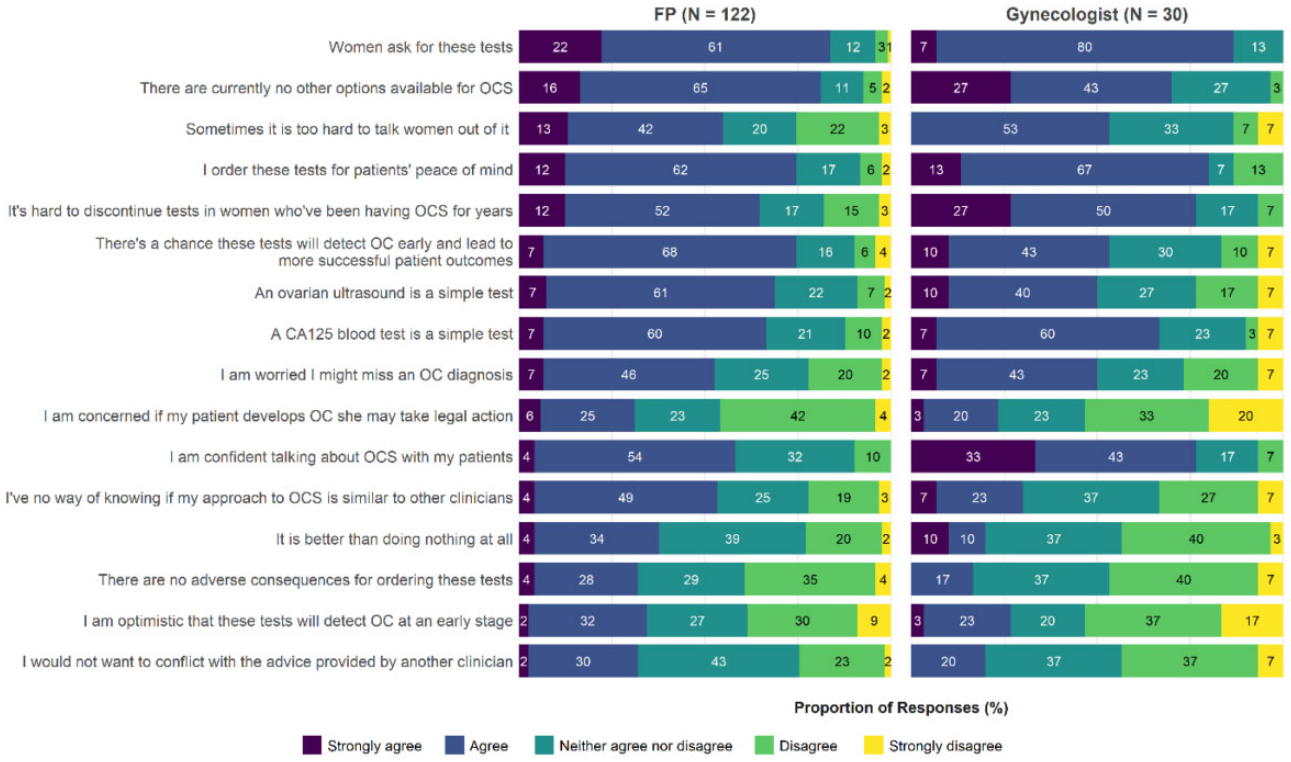

Figure 4. Clinicians: reasons for ordering ovarian cancer screening (OCS). CA125 = cancer antigen 125; FP = family physician.

and the administration of surveys developed using an implementation research framework. However, our study had several limitations. The views of nonresponders may differ from those reported: kConFab women who responded were more likely to have a tertiary education, but there were no statistically significant differences between clinician responders and nonresponders for the limited factors measured. It is possible that the screening behaviors of kConFab women differ from the general population, because these long-term cohort study participants may have been exposed to more information about OC screening. We also did not attempt to confirm survey responses using medical record or administrative data.

OC screening does not improve survival and is not recommended by international guidelines. Previous studies have shown that one-third to half of US clinicians order OC screening for average risk women, and those with nonprofessional exposure to OC are more likely to order screening tests (7,30). We deliberately sampled clinicians who identified women as having ordered screening tests for them, so our data do not enable us to generalize about the proportion of clinicians who order OC screening in Australia. Studies have shown that some clinicians consider OC screening to be effective (6,31), and this is consistent with our study, with one-third of clinicians reporting that ultrasound is effective for OC screening. A small proportion of our study sample had objectively increased OC risk. Previous research demonstrated screening uptake between 17% and 31% in high-risk women (29,32). Other studies on beliefs and attitudes of women toward OC screening have focused on average-risk women and excluded women at elevated risk (9,10).

Most clinicians in our study agreed with "there is a chance these tests will detect cancer early and lead to more successful patient outcomes." This facilitator operates within the goals domain of the TDF and, using the COM-B behavior change wheel (27,33), suggests interventions focused on education, persuasion, and coercion may be effective (Table 1). For example, developing educational resources that explain data from screening trials, illustrating lack of benefit vs harms of screening may prevent misinterpretation of screening efficacy. In addition, communication directed at clinicians by respected experts in each field, outlining the expert's rationale for not ordering OC screening may be effective in modifying clinician behaviors.

Compared with FPs, the majority (70%) of gynecologists surveyed knew that ultrasound and CA125 testing are not effective for early detection of OC. Despite this, almost half of both FPs and gynecologists had ordered screening in the past 2 years. This demonstrates a discordance of practice among gynecologists: Despite knowledge of ineffectiveness, they continue to order these tests. The strongest motivators for gynecologists (no other options available for OC screening—environmental context and resources) and FPs (women ask for these tests—social influence) map to the intervention functions of restriction, and environmental restructuring in the COM-B behavior wheel. Thus, legislation and regulation of the availability of funded access to OC screening tests are policy categories that should be considered to reduce OC screening. Both clinician groups identified strong motivators within the TDF emotion domain (patient peace of mind and difficulty discontinuing tests). Interventions focused on modeling, enablement, and persuasion are important to modify this automatic motivation. This may be achieved through the type of communication campaign already described above (ie, using a respected leader in the field). Active educational interventions such as workshops on persuasive communication and approaching discontinuing tests with patients may also be effective in equipping clinicians for difficult conversations about ceasing screening.

Patient expectations strongly influence ordering screening (7), and patient request is a strong predictor of nonadherence to OC screening guidelines. In one study, a quarter of clinicians who did not believe OC screening to be effective at least sometimes ordered tests at patient request (5). Thus, although clinician knowledge is important, pressure and expectations from women may continue to result in clinicians ordering OC screening. Targeting the motivators for women to ask for screening tests will be important in reducing OC screening.

kConFab women identified strong motivators for OC screening within the TDF domains of social role (staying healthy for family), emotion (tests provide peace of mind), and beliefs about capabilities (tests are easy enough to have). Lack of knowledge among surveyed women was prominent, suggesting that education illustrating the lack of efficacy and the harms of screening could be central. To target the emotion domain, the COM-B behavioral change theory suggests that persuasion—for example by high-profile women who do not screen because it is potentially harmful—might be useful. Reducing access to screening tests should be considered, especially because 66% of women identified the affordability of tests as a reason to continue screening. This is interesting given that, in Australia, there is no provision for funded ultrasound or CA125 screening. Further research might consider whether women are paying for these tests or accessing them through funded routes (eg, using a symptomatic rather than screening indication) and whether this is in the private or public health setting.

Developing effective interventions to eradicate OC screening in Australia will be challenging. Fear often drives patient behaviors, and removing the sense of control from "doing something" without a replacement intervention will be difficult. Research exploring practical ways to address patient fear in this setting may be beneficial. Passive education, in isolation, rarely results in sustained behavior change and thus needs to be combined with effective system-focused strategies (34). The clinician–patient relationship is complex, and patient expectations can be difficult to modify in this context. A parallel example is the unnecessary prescribing of antibiotics for uncomplicated respiratory tract infections by FPs, which is strongly influenced by patient expectations (35). Research has shown that educational interventions have limited benefit, but system approaches using electronic-based decision support tools and regulatory processes are more effective (36,37). Therefore, implementation of effective interventions to reduce OC screening is likely to require a multifaceted individual and system-based approach addressing the behavioral domains that we have identified as facilitating inappropriate screening (34).

Funding

This research was supported by Cancer Australia and the National Breast Cancer Foundation (PdCCRS #1100868). kConFab and the kConFab Follow-Up Study have received additional funding support from Cancer Australia (809195), the Australian National Breast Cancer Foundation (IF 17), the Australian National Health and Medical Research Council (454508, 288704, 145684), the National Institute of Health USA (1RO1CA159868), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia.

KAP is an Australian National Breast Cancer Foundation Fellow (PRAC17-004).

Notes

Role of the funder: The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Disclosures: The authors declare no conflicts of interest.

Disclaimer: The contents of this manuscript are solely the responsibility of the authors and do not necessarily reflect the views of Cancer Australia or the Australian National Breast Cancer Foundation.

Acknowledgements: We thank Sandra Picken, Lucy Stanhope, Sarah O'Connor, Gerda Evans, Leslie Gilham, Heather Thorne, Eveline Niedermayr, Sharon Guo, the kConFab research nurses, and the heads and staff of the Family Cancer Clinics. We thank the women, their families, and the clinicians who participated in this research.

Author contributions: All authors of this research paper have directly participated in the planning, execution, and/or analysis of this study. Courtney Macdonald: formal analysis, project administration, visualization, writing – original draft, writing – review and editing. Danielle Mazza: methodology, supervision, validation, writing – review and editing. Martha Hickey: supervision, writing – review and editing. Morgan Hunter: formal analysis, investigation, software. Louise A. Keogh: methodology, supervision, writing – review and editing. kConFab Investigators: data curation, resources, writing – review and editing. Sandra C. Jones: supervision, writing – review and editing. Christobel Saunders: supervision, writing – review and editing. Stephanie Nesci: data curation, funding acquisition, project administration, resources, software. Roger L. Milne: conceptualization, formal analysis, supervision, writing – review and editing. Sue-Anne McLachlan: supervision, writing – review and editing. John L. Hopper: supervision, writing – review and editing. Michael L. Friedlander: supervision, writing – review and editing. Jon Emery: supervision, writing – review and editing. Kelly-Anne Phillips: conceptualization, funding acquisition, formal analysis, investigation, project administration, supervision, writing – original draft, writing – review and editing.

Data Availability

The data from this study cannot be shared publicly because of ethical and privacy reasons. The data are available on reasonable request to the corresponding author.

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Chapter 6: Clinical Breast Examination in *BRCA1* and *BRCA2* pathogenic variant carriers

Utility of clinical breast examination

Clinical breast examination is defined as the inspection and palpation of both breasts and axilla to detect any abnormalities that may signal pre-malignant or malignant change. In women at population risk of breast cancer in countries with routine radiologic screening, clinical breast examination has not demonstrated utility as a screening tool as it does not reduce breast cancer related mortality and false-positive results lead to increased use of biopsies(149). In low and middle-income countries with no regular mammographic screening program, screening for breast cancer with clinical breast examination remains a useful tool, particularly in older women(150). In women at high-risk of breast cancer, clinical breast examination has variable reported sensitivity. A recent study demonstrated that, of 385 surveillance clinical breast examinations in high-risk women, none detected cancer but there was a recall rate for further imaging of 6.2%(151). A surveillance cohort study of 529 women that were suspected to carry a germline pathogenic variant in 2005 showed that none of 43 breast cancers were detected by clinical breast examination alone(69). This surveillance program included breast MRI screening. Two studies have looked at confirmed *BRCA1* and *BRCA2* pathogenic variant carriers, both included breast MRI as part of the surveillance program and both showed very low sensitivities of breast examination, 0% and 9.1%(152, 153). As breast MRI is the radiological modality that demonstrates the highest sensitivity for breast cancer, it can be hypothesised that clinical breast examination will demonstrate lower sensitivity in populations who are undergoing concomitant breast MRI screening. A single-centre prospective study of

women with a lifetime breast cancer risk of greater than 15% demonstrated a sensitivity of clinical breast examination of 64.1%, however this study did not include breast MRI screening as part of surveillance(154). In Australia, annual breast MRI for women who are at high familial risk of breast cancer and are under the age of 50 years was funded in 2009. International guidelines such as the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) continue to include clinical breast examination as a part of breast cancer surveillance in high-risk women(51, 80). Local Australian guidelines (EVIQ) removed the inclusion of clinical breast examination in surveillance of *BRCA1* and *BRCA2* pathogenic variant carriers in 2015 due to the lack of evidence(79). The Australian guidelines for preventative activities in general practice continue to recommend that inclusion of clinical breast examination in breast cancer surveillance for high-risk women is considered(155). The present study was performed to obtain more evidence on the utility of clinical breast examination in *BRCA1* and *BRCA2* pathogenic variant carriers who partake in an intensive surveillance program that includes regular breast MRI and breast mammography.

PDF of manuscript4: The value of clinical breast examination in a breast cancer surveillance program for women with germline *BRCA1* or *BRCA2* mutations

This chapter features a study designed to determine the clinical utility of breast examination in women with a *BRCA1* or *BRCA2* pathogenic variant who partake in surveillance through the Peter MacCallum Cancer Centre Breast and Ovarian Risk Management Clinic. This study sample was chosen as this clinic provides breast cancer surveillance and risk management counselling to over 500 *BRCA1* and

BRCA2 pathogenic variant carriers in Victoria, Australia. Women are seen on an annual basis and the results of breast examination findings, screening investigations and discussions are documented in a tick-box clinic proforma. The advantages of this study sample are the large number of pathogenic variant carriers and the systematic annual follow up. Potential limitations is that the sample is from a single centre and may not be representative of other Australian states and territories. Clinical breast examination results were only recorded if they were performed in the clinic and this may have missed breast examinations performed in primary care. This study was co-first authored with medical student, Tamara Hettipathirana. This study was included as a component of this thesis as I supervised Tamara Hettipathirana and had significant input in all processes of this research from conceptualisation through to publication.

The key findings of this study was that clinical breast examination had a very low sensitivity for breast cancer detection (sensitivity 6%) in *BRCA1* or *BRCA2* pathogenic variant carriers who are undergoing intensive radiologic surveillance with annual mammogram and, in women under the age of 50, breast MRI. Only 2 of 35 breast cancers were diagnosed by clinical breast examination alone, including a women under the age of 50 who was diagnosed with breast cancer in 2006 and was not undergoing annual breast MRI (as this was only funded in Australia for women at high breast cancer risk in 2009). These findings suggest that clinical breast examination can be omitted in this group, potentially facilitating telehealth reviews and more equitable access to sub-specialist care.

This study was published in the Medical Journal of Australia in September 2021 with an accompanying editorial titled “Is it time to abandon clinical breast examination?” (Appendix 8).

Publication citation

Hettipathirana T, **Macdonald C**, Xie J, Moodie K, Michael C, Phillips KA: The value of clinical breast examination in a breast cancer surveillance program for women with germline *BRCA1* or *BRCA2* mutations. *Medical Journal of Australia* 2021: 10.5694. Published online 13 September 2021.

The value of clinical breast examination in a breast cancer surveillance program for women with germline *BRCA1* or *BRCA2* mutations

Tamara Hettipathirana[1,2], Courtney Macdonald[2], Jing Xie[2], Kate Moodie[2], Chris Michael[2], Kelly-Anne Phillips[1,2]

The known: Reflecting the uncertain evidence base, guidelines offer conflicting advice about the value of clinical breast examination for breast cancer surveillance of women with *BRCA1/2* mutations.

The new: We found that the sensitivity of clinical breast examination for detecting cancers was very low. It is not useful for the surveillance of women with *BRCA1/2* mutations undergoing routine MRI screening.

The implications: Clinical breast examination can safely be omitted from breast cancer screening of women with *BRCA1/2* mutations. This could reduce consultation times and facilitate the use of telehealth.

Abstract

Objective: To assess the sensitivity and specificity of clinical breast examination for detecting breast cancer in asymptomatic women with predisposing germline mutations enrolled in a cancer risk management program that includes radiologic screening.

Design, setting: Retrospective, longitudinal cohort study of women with *BRCA1/2* mutations who attended the Breast and Ovarian Cancer Risk Management Clinic at the Peter MacCallum Cancer Centre, a tertiary referral centre in Melbourne, during 1 September 2001 – 31 December 2019.

Participants: Consecutive women with *BRCA1/2* mutations who did not have personal histories of cancer and had not undergone bilateral risk-reducing mastectomy, and who had visited the clinic at least twice during the study period. Participants had generally undergone breast examination at 6- or 12-month intervals, and annual breast imaging (mammography; and magnetic resonance imaging [MRI] for women aged 50 years or younger).

Main outcome measures: Sensitivity (proportion of all biopsy-confirmed breast cancers detected by breast examination alone) and specificity of breast examination for detecting breast cancer.

Results: Of 414 eligible women (mean age, 35.5 years; SD, 11.2 years), 35 were diagnosed with breast cancer during 1761 woman-years of follow-up. Only two were diagnosed based on breast examination alone (ie, without radiologic evidence), neither of whom was undergoing MRI screening. The sensitivity of breast examination was 6% (95% CI, 1–19%), the specificity 97% (95% CI, 95–98%); the positive predictive value was 14% (95% CI, 2–43%), the negative predictive value 92% (95% CI, 89–94%).

Conclusion: Clinical breast examination did not increase the number of breast cancers detected in MRI-screened women with *BRCA1/2* mutations. Removing breast examination from surveillance programs that include MRI may be reasonable for these women.

In 2020, more than 19 000 women in Australia were diagnosed with breast cancer.[1] The lifetime risk of breast cancer for women with mutations in the breast cancer predisposition genes *BRCA1* and *BRCA2* is about 70%, compared with 14% for the general population.[2] These women are offered several strategies to reduce their risk, including risk-reducing bilateral mastectomy, risk-reducing medications, and management of lifestyle factors. Women who opt not to have risk-reducing bilateral mastectomy are offered an intensive surveillance program with the aim of early detection of any breast cancer.[3]

In Australia, radiologic surveillance of women at high risk generally involves annual mammography and, for women under 50 years of age, magnetic resonance imaging (MRI).[3] Clinical breast examination has not been included in Australian cancer management guidelines on the eviQ website since 2015,[3] but the Royal Australian College of General Practitioners guidelines recommend an individualised screening program that can include breast examination.[4]

The reported performance of breast examination for detecting breast cancer is highly variable; in women at high risk, sensitivity ranges between 0 and 64.1% and specificity between 95.9% and 99.3%.[5-16] Its reported sensitivity in women with *BRCA1/2* mutations is 0–13%.[5-8]

Several factors may explain the variation in sensitivity of breast examination for detecting breast cancer. Firstly, test-related variation (ie, the level of skill of the clinician performing the breast examination) can affect sensitivity and specificity. Secondly, the utility of breast examination is probably influenced by the results of concurrent radiologic screening; breast examination may detect fewer cancers in women undergoing regular MRI screening, as most would be detected by MRI while impalpable.[7-11] The highest reported sensitivity for breast examination (64.1%) was associated with a screening program that did not include MRI.[15]

It is important to know whether adding breast examination to routine radiologic screening improves cancer detection. Breast examination can be uncomfortable for women, and requires a longer consultation and review in person rather than a telehealth appointment. We therefore estimated the sensitivity and specificity of breast examination, and the number of breast cancers detected by breast examination alone in women with *BRCA1/2* mutations participating in a screening program that includes mammography for all screened women and (since the introduction of a Medicare rebate in 2009) MRI for those under 50 years of age.[17] We hypothesised that few breast cancers would be detected in this setting by breast examination alone.

Methods

Women without a personal history of cancer, but with a high familial or genetic risk of breast or ovarian cancer, can attend the Breast and Ovarian Cancer Risk Management Clinic at the Peter MacCallum Cancer Centre in Melbourne at intervals of 6 to 12 months.[18] We undertook a retrospective study of data for consecutive women with pathogenic *BRCA1/2* gene mutations who had attended the clinic at least twice between its opening on 1

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September 2001 and 31 December 2019. Women were excluded if they had undergone risk-reducing bilateral mastectomy prior to their second clinic visit.

Data collection

All data were extracted from personal medical records and managed with REDCap 9.5 electronic data capture tools; the REDCap database is hosted at the University of Melbourne.

Breast examination includes inspection and palpation of both breasts and axillary lymph nodes. Women attending the risk management clinic undergo breast examination at intervals of 6 to 12 months by medical oncologists or breast surgeons, who may be aware of the results of concurrent imaging. For some women, their general practitioner performed breast examinations outside the clinic at alternating six-monthly intervals; only breast examinations during routine risk management clinic visits were included in our analysis. If women presented to the clinic because of imaging evidence of an abnormality, the breast examination result was excluded from our analysis. Information on adverse events related to breast examination was not collected.

The standard screening protocol at the risk management clinic has changed over time, but since 2009 MRI has normally been performed annually from age 25–30 years (depending on family history) until age 50 years. A baseline mammogram is generally performed when a woman is 30 years old to assess breast density; if high, annual mammography is commenced at a later age because of its low sensitivity in women with dense breasts. Some women underwent ultrasound screening while pregnant or breast-feeding. Most imaging modalities were performed at the Peter MacCallum Cancer Centre and interpreted by specialist radiologists.

A tick-box template included in MacCallum Cancer Centre medical records is used to document the screening investigations (breast examination, mammogram, MRI) performed and their results (normal, abnormal) (Supporting Information, figure). We also extracted radiologic screening results from radiologist reports. If abnormal, any additional investigations (early interval imaging, ultrasound, biopsy) are also recorded. The reference standard for breast cancer diagnosis was histopathological confirmation of breast cancer on biopsy. Pathologists were not blinded to clinical history or screening results.

Outcomes

The primary endpoint was a breast cancer diagnosis (either ductal carcinoma in situ or invasive breast cancer). Secondary endpoints were breast examination false positive results and the stage and phenotype of breast cancers detected by breast examination.

Statistical analysis

We included data for all women who met our eligibility criteria. Participant data were censored at the earliest date for bilateral risk-reducing mastectomy, breast cancer diagnosis, final clinic visit, or death. Patient demographic and baseline characteristics and treatment details, and data for cancers detected by breast examination, are summarised as means with standard deviations (SDs) or medians with interquartile ranges (IQRs) and ranges for continuous variables, and as numbers and proportions for categorical variables. Clinic visits with inadequate documentation of breast examination were excluded from our analysis. Indeterminate reference standard results were treated as negative results, as only positive results lead to breast cancer diagnoses. We calculated the rate of breast cancer diagnosis based on breast examination (95% confidence interval [CI]), and sensitivity, specificity, positive and negative predictive values, and false positive rates for breast examination on a per patient basis. Sensitivity of breast examination was defined as the proportion of all breast cancers diagnosed during the study period, regardless of diagnostic pathway, that were detected by breast examination alone (ie, the results of any radiologic screening were normal). Statistical analyses were performed in R 3.6.3 (R Foundation for Statistical Computing).

Ethics approval

The study was approved by the Peter MacCallum Cancer Centre Human Research Ethics Committee (HREC 19/230R), which waived the requirement for individual participant consent. The approved study protocol is available from the corresponding author.

Results

Of the 558 women with *BRCA1* and *BRCA2* mutations who attended the risk management clinic during 2001–2019, 414 met the eligibility criteria (Box 1); 186 women with *BRCA1* mutations and 228 with *BRCA2* mutations underwent 1761 woman-years of follow-up (Box 2; Supporting Information, table). The mean age at the first clinic visit was 35.5 years (SD, 11.2 years). A total of 2723 risk management clinic visits were recorded, for 2552 of which screening breast examinations were documented (94%; median number of visits per woman: five; IQR, 3–9 visits).

Breast events

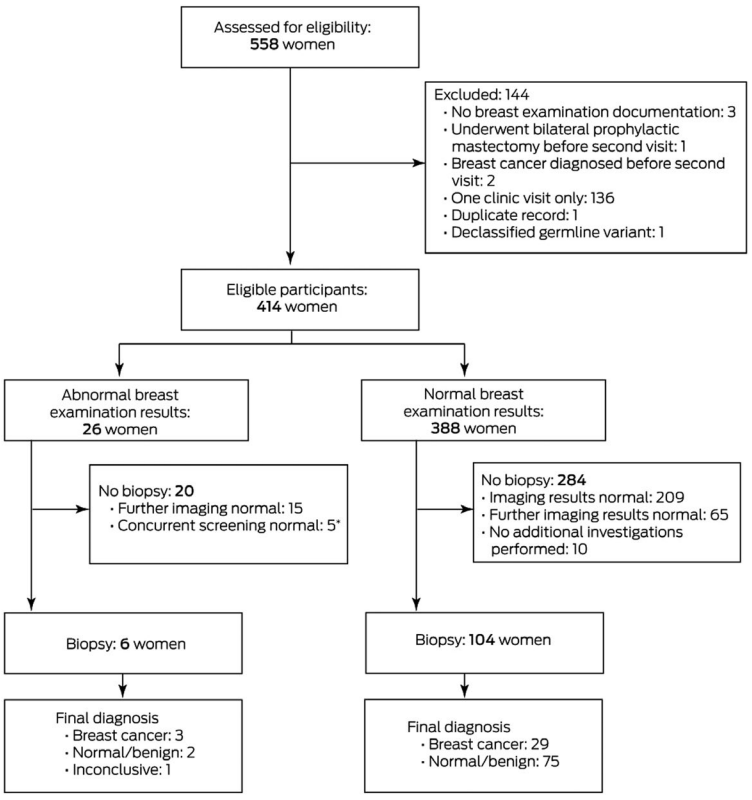
Data for 98 women were censored at the time of bilateral risk-reducing mastectomy (24%). A total of 35 women (19 with *BRCA1*, 16 with *BRCA2* mutations) were diagnosed with breast cancer; 27 were screen-detected, eight were interval cancers. Thirteen ductal carcinomas in situ and 20 invasive cancers were identified; details were unavailable in two cases, as treatment was undertaken at another institution (Box 3).

Seven of the eight women with interval cancers had presented with self-detected breast lumps between clinic visits, each less than two months before their next scheduled radiologic and breast examination screenings. One of these women had given birth five months earlier, was breastfeeding, and had not resumed regular screening. The eighth woman was also deemed to have an interval cancer because her ductal carcinoma in situ (35 mm) was histopathologically confirmed at bilateral risk-reducing mastectomy, although MRI screening one month earlier had indicated the possibility of ductal carcinoma in situ. Seven of the women with interval cancers had *BRCA1* mutations, and most of the cancers were aggressive, invasive, high grade, and hormone receptor-negative.

Performance of clinical breast examination

Twenty-eight abnormal breast examination results were reported for 26 women, and six of these results were followed by biopsies; the median time between breast examination and biopsy was 13.5 days (IQR, 6.8–18.0 days; range, 0–29 days). The biopsy results indicated breast cancer in three women, normal breast tissue in one, and a benign abnormality in one; one result was non-diagnostic. Concurrent imaging did not identify features suggesting malignancy in the woman with the non-diagnostic

1 Selection of women for study inclusion and their assessment pathways



* Three women were diagnosed with breast cancer after resuming routine surveillance following abnormal breast examination results; for two of these women, the abnormal results were related to fibrocystic disease (determined by concurrent imaging). One of these two women was diagnosed with breast cancer one month later (on the basis of concurrent MRI); her abnormal breast examination result was related to fibrocystic disease in a different quadrant. The second woman was diagnosed with an interval breast cancer in the contralateral breast (self-palpated) four months after breast examination. The third woman was diagnosed with breast cancer six years after the abnormal breast examination result; the intervening breast examinations and imaging had been normal. ◆

result or in the 20 women (22 abnormal breast examination results) without biopsies (Box 1).

In the three women diagnosed with breast cancer, one cancer was also detected by concurrent screening mammography; that is, two of 35 breast cancers were detected by breast examination alone (sensitivity, 6%; 95% CI, 1–19%). The specificity of clinical breast examination was 97% (95% CI, 95–98%), the positive predictive value 14% (95% CI, 2–43%), and the negative predictive value 92% (95% CI, 89–94%) (Box 4). The true positive rate for breast examination was 14% (2 of 14; 95% CI, 2–43%) and the false positive rate was 3.2% (12 of 367; 95% CI, 2–55%).

Women with breast cancers detected by clinical examination alone

A 36-year-old woman with a *BRCA1* mutation was diagnosed with breast cancer in 2006 during her breast examination at the risk management clinic between two annual mammography screens. She had not undergone MRI screening, as it was not subsidised by Medicare until 2009; she was found to have clinically abnormal axillary nodes and further imaging detected a primary breast cancer. Annual MRI screening would now be recommended for a woman of this age with a *BRCA1* mutation. A 65-year-old woman with a *BRCA2* mutation was similarly diagnosed with breast cancer in 2007 during a risk management clinic visit between two annual mammography screens. Annual MRI screening would not be offered to this woman, as it is not subsidised for those over 50 years of age.

Discussion

In our study of 414 women with *BRCA1/2* mutations undergoing surveillance at the Peter MacCallum Cancer Centre risk management clinic, 35 breast cancers were detected. Only two were detected by breast examination alone; in neither case was the woman undergoing routine MRI screening. The sensitivity of breast examination alone was 6% (95% CI, 1–19%) and its specificity was 97% (95% CI, 95–98%). While an ideal screening test would be both 100% sensitive and 100% specific, there is no consensus about minimum acceptable values.[19] Given its low sensitivity, however, we conclude that breast examination alone is not an acceptable test for screening women with *BRCA1/2* mutations.

Eight of the 35 breast cancers diagnosed in our study were interval cancers (23%). Their characteristics and those of the women in whom they were identified were consistent with other reports.[5,7-9,11,12]

The specificity of breast examination in our study was consistent with other reports (range, 95.9–99.3%.[8,9,12,13]), as was the sensitivity of breast examination in women with *BRCA1/2* mutations (range, 0 to 13%[5-8]). Few studies have concluded that clinical breast examination should remain part of screening programs; those that did recommend it[14,15] did not include women undergoing MRI screening.

Nevertheless, some guidelines still recommend breast examination for women at high risk. Unlike imaging, it is relatively inexpensive. An English study estimated that breast examination (and any subsequent investigations) cost about $26 000 per quality-adjusted life year.[6] In the cited study, nurses performed the breast examinations, the utility of which was higher because routine MRI screening was not undertaken in the study population. As neither of these factors applies in Australia, the cost is likely to be higher here.

Although non-invasive, breast examination can be intrusive. However, surveys have found that it causes anxiety or embarrassment in fewer than 10% of women at high risk.[20,21] In fact, 94% of women believed that screening breast examinations were important for early detection, and 70% were reassured by normal results; even after being informed of its limited utility, 93% wanted screening breast examinations.[21] Breast examination is not appropriate for relieving cancer-specific anxiety in women, but it can be difficult to discontinue unnecessary but ingrained health behaviours. If breast examination remains a part of screening for some women, it is important to counsel them about its limited effectiveness, particularly when intensive radiological screening is undertaken, and about the possibility of false positive results.

Models of health care delivery are changing rapidly. Providing remote health care, especially in large countries such as Australia, is important for improving access. Patient satisfaction with telehealth

2 Characteristics of the 414 women with *BRCA1* and *BRCA2* mutations included in the study

Characteristic	Value
Age at first clinic visit (years)	
Mean (SD)	35.5 (11.2)
Range	19.2–74.8
Length of clinical follow-up (years)	
Median (IQR)	3.6 (1.8–6.5)
Range	0.1–17.9
Mutation type	
BRCA1 mutation	186 (45%)
BRCA2 mutation	228 (55%)
Breast events	
Bilateral risk-reducing mastectomy	98 (24%)
Breast cancer diagnosis	35 (8.5%)
Screen-detected cancer	*27*
Interval cancer	*8*

IQR = interquartile range; SD = standard deviation. ◆

consultations is generally high, as they provide greater accessibility to health care and reduce time commitment and costs.[22,23] Breast examination requires in person review, and its omission from screening would allow telehealth consultations as an acceptable alternative to many breast cancer risk management visits.

Limitations

We evaluated the performance of breast examination alone in a large sample of women with mutations predisposing them to breast cancer, and our study is one of the few undertaken in women for whom routine screening generally included MRI. Nevertheless, our reliance on data retrospectively extracted from clinic notes was a limitation. However, consistent routine reporting of breast examination results using the tick-box template for clinical documentation at each clinic visit mitigated this problem. Clinicians undertaking breast examinations were aware of recent imaging results, and this may have influenced their assessments. Despite a relatively large sample size, the number of breast cancers detected was small and the confidence intervals for our sensitivity analysis were broad. Death is the standard endpoint for breast cancer screening studies,[24] but we used breast cancer diagnosis because of the limits imposed by our sample size and follow-up times. We undertook a single centre study in a dedicated cancer clinic in which breast examination is performed by experienced breast specialists; in less specialised health care settings, the yield of breast examination would probably be even lower.

Conclusion

Our findings indicate that, for women with predisposing germline mutations, omitting clinical breast examination from screening programs that include MRI would be reasonable. If MRI cannot be offered or circumstances prevent its use (eg, in breastfeeding women), breast examination may be a worthwhile surveillance tool. The removal of breast examination from clinical practice

3 Characteristics of the breast cancers identified in 35 women

Characteristic	Number
Mutation type	
BRCA1	19
BRCA2	16
Breast cancer type	
Ductal carcinoma in situ	13
Invasive carcinoma, no special type	14
Invasive carcinoma, no special type, with medullary features	5
Invasive lobular carcinoma	1
Missing data	2
Estrogen receptor (ER) status	
Positive	9
Negative	25
Missing data	1
Progesterone receptor (PR) status	
Positive	9
Negative	25
Missing data	1
Human epidermal growth factor receptor 2 (HER2) status	
Positive	3
Negative	31
Missing data	1
Focality	
Multifocal	3
Single lesion	31
Missing data	1
Largest invasive breast cancer (mm) (*N* = 18)	
Mean (SD)	14.3 (7.0)
Median (IQR)	15 (8.0–22)
Range	5.0–25
Size of breast cancer (mm)	
< 20	22
20–50	11
Missing data	2
Axillary node involvement	
Yes	4
1–3	*3*
4–9	*1*
No	23
Unknown (axillary surgery not performed)	7
Missing data	1
Metastatic disease present	
No	34
Missing data	1

IQR = interquartile range; SD = standard deviation. ◆

4 Performance of clinical breast examination for the 414 women included in the study

Breast examination result abnormal, imaging results normal	Breast cancer diagnosis: Yes	Breast cancer diagnosis: No	
Yes	2*	12	Positive predictive value: 14%
No	33	367	Negative predictive value: 92%
	Sensitivity: 6%	Specificity: 97%	

* Results of imaging tests at follow-up visit were normal. ◆

could reduce anxiety and consultation times for screened women, and allow the choice of in person or telehealth consultations for many risk management visits.

Acknowledgements: Kelly-Anne Phillips is a National Health and Medical Research Council of Australia Leadership Fellow. We thank the women whose data were analysed in this study. We also thank Michael Henderson and Paul James for their critical review of an earlier version of this manuscript.

Competing interests: No relevant disclosures. ■

Received 14 December 2020, accepted 7 May 2021

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Supporting Information

Additional Supporting Information is included with the online version of this article.

Chapter 7: Discussion

Summary of findings and implications for future research

The key findings from this body of research are that:

- Use of RRMed in Australian women at increased risk of BC is very low and many of the identified clinician and patient barriers are modifiable
- Ovarian cancer screening continues in Australia despite its ineffectiveness and potential harms. De-implementation of screening practices needs a multifaceted approach included policy change, restriction of ordering screening tests and education.
- Clinical breast examination has limited utility in *BRCA1* and *BRCA2* pathogenic variant carriers who are undergoing intensive radiologic surveillance with MRI and mammograms.

Establishing routine breast cancer risk assessment and management in primary care

A consistent theme through this research was the importance of knowledge of individual breast cancer risk. The first step in precision prevention and screening is imparting individualised risk information, as women cannot be expected to act on their breast cancer risk if they are not aware that they are at elevated risk. In Australia, women who are at high risk of breast cancer are managed in a familial cancer clinic. However, a greater number of women are at moderate risk of breast cancer and are managed in primary care. If breast cancer risk assessment is not prioritised and performed routinely then these women will not be aware of their breast cancer risk and therefore cannot be expected to take preventive action, such as use of risk reducing medication. Our research in manuscript 2 demonstrated that for 84% of women, knowing they had high breast cancer risk would facilitate a decision to take risk-reducing medication. In addition, 11% of women identified that

risk was a predictor of RRMed use, with women at high breast cancer risk being statistically significantly more likely to use RRMed. All of this underlines the importance of routine breast cancer risk assessment and communication of this risk to the individual, which may in turn provide opportunity for wider awareness in the community due to discussion of breast cancer risk among friends and family networks.

Women have often established valuable long-term therapeutic relationships and trust in their GPs. The primary care service is familiar with risk assessment and management, for example with routine cardiovascular risk assessment. An Australian focus group study demonstrated that GPs are familiar with routine cardiovascular risk assessment, have the necessary infrastructure to support it and view it as an intrinsic part of their role. This compared unfavourably with breast cancer risk assessment, where GPs felt that this was outside the scope of primary care and was often patient initiated instead of routine(156). Instead of opportunistic risk assessment, mandated frequency of assessment with a re-call or prompt system within primary care software would ensure more women have their breast cancer risk assessed and may increase GP confidence in risk assessment. Risk assessment could be coordinated with other preventative women's health activities, for example cervical screening.

Development of a policy on systematic routine breast cancer risk assessment in primary care with specific guidance on age at commencing risk assessment and frequency of risk re-assessment, as well as appropriate online tools for assessing risk, could guide GPs. In Australia, the national organisation that provides policy guidance on cancer prevention is Cancer Australia. Engaging both Cancer Australia

and the Royal Australian College of General Practitioners to create breast cancer risk assessment guidelines for primary care, and piloting a formal risk assessment programme, could be important in more widespread assessment of breast cancer risk. Incorporation of guidelines into primary care software, with a re-call system or alert when a woman is due for breast cancer risk assessment (similar to a re-call for cervical cancer screening), could help move towards a standardised approach. As breast cancer risk assessment is often raised by patients, increasing awareness of breast cancer risk within the general public will also help women be more aware of the need for breast cancer risk assessment. Public campaigns, such as the "*An invitation that could save your life*" campaign for BreastScreen Australia, have been effective at increasing awareness and public confidence in breast cancer screening(157). A campaign focused on the roll out of regular breast cancer risk assessment may increase the uptake of breast cancer risk assessments in primary care.

The provision of additional services in primary care is often limited by financing, staff shortages, available support from specialists and adequate training(158). Development of a Medicare item number with funding allocated for breast cancer risk assessment in primary care might facilitate regular assessment. Medicare item numbers already exist for some health assessment scenarios including, for a health assessment for people aged 45-49 years who are at risk of developing a chronic disease. The funding allocation is for comprehensive information collection, examination, initiating interventions and providing a preventative health care management plan. A similar structure could be provided for a women's breast cancer risk assessment item. Within a primary care practice, specialist practice nurses could

be trained in risk assessment, and this could assist with the additional workload on primary care.

In our RRMed survey study (manuscript 2), 75% of GPs agreed that initiating RRMed should be their role and 98% reported that it was their role to write ongoing prescriptions for RRMed. This demonstrates that while GPs are open to being involved in the ongoing provision of RRMed, they think that initial assessment should be within a more specialist role. Despite the majority of GPs acknowledging that discussing and initiating RRMed was within their role, only 3% were very confident in providing information on RRMed. One third reported that they were “not at all confident” and 29% had never discussed or prescribed RRMed. This presents a major barrier to the roll-out of risk assessment and risk management discussion in primary care. In addition, 72% of GPs reported that they had inadequate training and confidence in breast cancer risk assessment and that this was a barrier to prescription of RRMed. Nearly all GPs reported that having better tools to identify suitable patients would be a facilitator for prescribing RRMed. Accurate breast cancer risk assessment tools have been developed and are available for use(61, 159, 160). In addition, tools that combine risk assessment and risk management decision support have been developed for use, such as the Australian designed iPrevent tool(159, 160). iPrevent is designed for both clinicians and women to use and aims to standardise breast cancer risk assessment and increase clinician confidence in having discussions with women about prevention and screening. Assessing the acceptability of breast cancer risk assessment tools in primary care will be pivotal to their success. A pilot study of the acceptability of iPrevent in a small number of GPs and women reported an above-average usability score in 68% of

GPs and 76% of surveyed patients(161). This study was limited by low response rates and results may be less generalisable to the population due to the high educational level of those women who responded. A further pilot study involving primary care practices in rural and regional areas may be useful to determine the barriers and acceptability of the iPrevent tool in the real-world setting.

Increasing confidence and familiarity with preventative medicine concepts such as risk assessment and risk reduction needs to start in early medical training, as a large proportion of undergraduate students will go into primary care. Preventative medicine makes up a minority of most medical school curriculums and its importance is often overshadowed by learnings around management of acute medical problems. If these concepts are taught early and regularly, and students are offered training in risk assessment and how to discuss concepts such as cancer risk and interventions with patients, they may be more comfortable having these discussions with patients later in their careers. Incorporation of a clinical preventative medicine module, focusing on communication of risk information, and active educational sessions on counselling patients on risk management interventions, could be valuable.

De-implementation of ineffective, potentially harmful health care interventions

In manuscript 3 15% of asymptomatic Australian women surveyed had screened for ovarian cancer in the prior two years, despite local guidelines recommending against ovarian cancer screening since 2009. The majority of clinicians (both GPs and gynaecologists) correctly reported that ovarian cancer screening is not effective, but a significant proportion of both clinician groups continued to order screening, suggesting a discordance between knowledge and practice. From a systems perspective, further research to identify how clinicians are accessing these tests for

patients will be important. Linking the commonly identified facilitators for ovarian cancer screening to behaviour change theory suggested restriction (the use of rules to reduce the opportunity to engage in the specific behaviour) and environmental restructuring (changing the physical or social context) as potential interventions. At present there is no funded indication (MBS item number) for ordering ovarian cancer screening tests. Further surveys of the clinicians who reported ordering ovarian cancer screening, to identify the ways which they access these tests, is required to determine where effective interventions could be targeted. However, it may be difficult to restrict ordering, especially if clinicians are ordering screening tests through a symptomatic indication, and importance will still need to be placed on education, reinforcing the lack of benefit and empowering clinicians to have discussions with patients who request screening.

The findings from manuscript 3 suggest a degree of expectation that comes from women to order or continue to order ovarian cancer screening. In healthcare, patients often have the expectation that “doing something” is better than doing nothing. Given ovarian cancer screening was once recommended in guidelines, there will be a proportion of women who have been receiving regular screening, and it can be difficult to discuss stopping screening in women who have been doing it for years. De-implementation of a medical procedure or intervention is inherently challenging. Clinicians often feel that stopping testing and raising these discussions can have a negative impact on the patient-clinician relationship. This is reflected in the data from the United States where litigation is a well-established concern and often a driver for clinicians to continue to order ineffective ovarian cancer screening. Further qualitative research, and in particular, focus groups with clinicians who have

reported the difficulty discontinuing screening, to look at effective ways to support clinicians to have these discussions. Incorporation of these findings into clinician training sessions will help give clinicians the tools to approach these conversations with patients requesting screening. Both the RACGP and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) have issued statements updating its members on the lack of efficacy of ovarian cancer screening and reinforcing the recommendation against screening. Educational sessions targeted to college members could also feature emphasis on the lack of evidence behind ovarian cancer screening and provide tools to clinicians on how to discuss stopping screening with their patients.

Manuscript 3 reported that 80% of women who screened for ovarian cancer would continue to do so even if their doctor told them that it was ineffective. This points to the need to not only focus on upskilling the clinician to have these conversations, but also to educate the public about the harms of ovarian cancer screening and the lack of benefit, as women are often the drivers of screening. Information is available for patients on websites such as those of Choosing Wisely Australia and Cancer Council Australia, but these are often not heavily trafficked by patients seeking information(162, 163). Utilising more visible patient-based websites such as Pink Hope may reduce misinformation about screening(164). To increase exposure to correct information, a public campaign featuring women and the reasons they no longer screen for ovarian cancer may increase awareness. Offering support and affective-based strategies (strategies for emotion management for example breathing techniques and progressive relaxation) for managing the anxiety related to

no longer having testing and the fear of a missed diagnosis may also need to be considered.

As ovarian cancer often presents at a late stage and has poor outcomes, there is further work to be done to develop an effective screening test for early detection. As 15% of ovarian cancer occurs in *BRCA1* and *BRCA2* pathogenic variant carriers(165), focusing on early detection and establishing effective biomarkers in this population is a start. In this population in particular, an effective screening test would be helpful in allowing women to delay their RRSO until after menopause, thus minimising many of the longer-term adverse effects of the procedure, such as coronary heart disease, cognitive impairment, osteoporosis and sexual dysfunction. Research suggests that a p53 mutation is a required step for early carcinogenesis in *BRCA1* and *BRCA2* pathogenic variant carriers(166, 167). A substantial proportion of ovarian cancers originate from precursor lesions in the fallopian tube epithelium, referred to as serous tubal intraepithelial carcinomas (STIC)(168). STICs are in-situ, precursor lesions which harbour p53 mutations(169). Potential use of ctDNA to detect early development of p53 mutations may lead to early detection of ovarian cancer and improved outcomes. Early studies of the use of ctDNA for p53 mutations to detect recurrent ovarian cancer has demonstrated promise, with ctDNA rising much earlier than CA-125 in women with recurrence(170). Whether or not this improves outcomes and survival in this setting is not known. A small retrospective trial demonstrated that in 64% of women with ovarian cancer, TP53 clonal variants were able to be detected in DNA purified from Papanicolaou smear tests performed up to 6 years prior to ovarian cancer diagnosis(171). Bringing trials of testing for p53 mutations earlier into the screening setting for a high-risk population should be

considered; however, large prospective trials are needed to demonstrate mortality benefit. In addition to research focused on screening techniques, there are also promising clinical trials in the area of ovarian cancer prevention. Acetylsalicylic acid (ASA) has demonstrated multiple potential anti-oncogenic mechanisms of action in pre-clinical settings and is being trialled in a randomised Phase II trial in *BRCA1* and *BRCA2* pathogenic variant carriers where longitudinal collection of ctDNA is included. Preliminary data from the OlympiA study(41) suggest that the PARP inhibitor, olaparib, may reduce the risk of ovarian cancer in carriers of pathogenic variants in *BRCA1* and *BRCA2(*172*).*

Re-framing health information and communication of risk

A consistent theme identified throughout our four research studies is the importance of effective communication of health information. Informed, shared decision-making relies on the patient having a robust understanding of the relevant risk and benefits, presented in different ways depending on their health literacy and background. This also assumes that the clinician is able to interpret medical evidence correctly and communicate this in ways that the patient can understand. Nearly half of GPs (46%) and 17% of gynecologists in the study reported in manuscript 3 endorsed that ovarian cancer screening is useful, despite randomised controlled trial evidence suggesting otherwise. A survey study of US gynaecologists five years after the release of the PLCO (prostate, lung, colorectal and ovarian cancer screening trial) findings, which did not show a mortality benefit from ovarian cancer screening, demonstrated similar findings; over half of gynaecologists in that study reported they still believed that screening reduced ovarian cancer mortality(138). This discordance with evidence and beliefs may suggest that clinicians do not correctly interpret

clinical trial results or are not up to date with current research in their field, highlighting the importance of continuing medical education.

Focusing on intensive training in the interpretation of medical evidence, starting with medical school curriculums, may mean that future clinicians have more familiarity with critically appraising evidence and interpreting data. A requirement for inclusion of a summary box of clinical trials, summarising the pertinent evidence, may help emphasise the key points for clinicians, especially those who practice broadly, for example in primary care.

Tools exist, that can be used in clinical practice that present the absolute benefits and risks of breast cancer risk management interventions and present the data in an easy to read, visual manner. Incorporation of these into primary care software will reduce the misinterpretation of evidence and the negatively-biased framing of side-effects. This is especially relevant, given our findings that side-effects of risk-reducing medication is a major barrier for GPs, gynaecologists and women. The findings from manuscript 2 demonstrate that women are most concerned about the serious but rare side-effects of risk-reducing medication. In some instances, the side-effect of most concern was not relevant to the population concerned about it (e.g. pre-menopausal women concerned about increased endometrial cancer risk with use of tamoxifen). This underlines the importance of presenting individualised risks and absolute risk estimates. Public facing websites that women may visit with questions about risk management interventions should have succinct educational resources with visual depictions on the benefits and risks of interventions.

Presenting information on breast cancer risk to women is also important to support them in making an informed decision based on their individual risk. Breaking down

risk across a woman's lifetime may be easier to comprehend and more actionable than a single lifetime risk estimate. Time-dependant risk information is likely to be most helpful for women when deciding on the optimal timing of risk-reducing interventions. For example, for a *BRCA1* pathogenic variant carrier in her early twenties, knowledge of an annual breast cancer risk of 1% may be more useful in making risk management decisions than a lifetime breast cancer risk to age 80 of 69%.(174),(175)

Strengths and limitations of this thesis

Utilising the kConFab clinical follow up study for three of the four published articles, ensured that women were included from across Australasia and represent the population of Australasian women at higher risk of breast cancer as much as possible. Effort was made to include women from across all states and territories of Australia, across a wide range of demographic characteristics including age, socioeconomic status, and educational level. However, as identified in each individual study, the enrolment of subjects in a familial breast cancer study may have meant that women have more baseline knowledge of breast cancer prevention, and different attitudes to breast cancer prevention, than the general population. This selection bias could have impacted the results of our research.

As the studies included in this thesis were set in Australia, a high income, developed country, the ability to generalise these findings to low- and middle-income countries with different healthcare structures is limited. The impact of breast cancer in low- and middle-income countries is a significant burden, and further research into prevention approaches in these settings would be important in reducing breast cancer incidence globally.

Some of our studies are limited by their small sample size. The study of clinical breast examination included 414 Victorian *BRCA1* and *BRCA2* pathogenic variant carriers, but the number of diagnosed breast cancers in this group was low (n=35).

This thesis describes and identifies notable barriers and facilitators to the use of certain interventions. However, it was beyond the scope of this research to evaluate strategies to increase the use of certain beneficial interventions or de-implementation

strategies for ineffective interventions. By linking findings with behaviour change theory, suggestions have been made on which further research could be based.

Conclusion

The work reported in this thesis has added considerably to the existing knowledge of obstacles to the establishment of a precision approach to breast cancer prevention and screening. The findings, suggest potential strategies to move the area of breast cancer prevention forward. These include targeted, practical recommendations for primary care services in Australia, potential health policy changes and suggestions for further research to advance this area. The findings presented in this thesis have the potential to improve breast cancer prevention and ultimately reduce breast cancer incidence in Australia.

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ix. Appendices

Appendix 1: kConFab three yearly follow up questionnaire

Kathleen Cuningham Foundation **kConFab** CONsortium for research into FAmilial Breast cancer

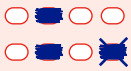
FEMALE FOLLOW-UP QUESTIONNAIRE

Thank you for taking the time to complete this questionnaire. It does look long, however, there will be questions and in some cases, entire sections that do not apply to you. When this occurs you will be instructed which question number to turn to next.

Most questions require you to mark only one answer but there are some questions that require you to "mark all that apply". In some instances you will be asked to supply further written information in your answer.

INSTRUCTIONS

- Please use black/blue pen or pencil.
- Do not use red or green pen or felt tip pens.
- Do not fold or bend the questionnaire.
- Please mark like this only:
- Cross out any mistakes:



- Do not fill in "OFFICE USE ONLY" grids. Simply write your answer on the lines provided.
- Please print when completing questions that require a written answer.
- Please return the completed questionnaire in the reply-paid envelope provided.

We would appreciate it if you could provide us with contact details in case we need to clarify any of the information you provide to us.

TELEPHONE NUMBER ( ) Mobile .....

Best times to contact you: (i.e. 9.00am – 5.00pm; after 6.00pm; Tuesdays; etc)

.....

EMAIL ADDRESS .....

A kConFab research assistant is available on our toll-free number **1800 111 581*** to help you with any questions or problems you may be having completing this questionnaire. Please don't hesitate to give us a call. ** Charges will apply if calling from a mobile phone*

What is your date of birth?

..... / ..... / .....
Day Month Year

What is today's date?

..... / ..... / .....
Day Month Year

OFFICE USE ONLY

D	0	1	2	3	4	5	6	7	8	9
D	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
Y Y	19									
Y	0	1	2	3	4	5	6	7	8	9
Y	0	1	2	3	4	5	6	7	8	9

OFFICE USE ONLY

D	0	1	2	3	4	5	6	7	8	9
D	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
Y Y	20									
Y	0	1	2	3	4	5	6	7	8	9
Y	0	1	2	3	4	5	6	7	8	9

OFFICE USE ONLY

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A. BACKGROUND INFORMATION

The first section asks some general background questions.

A1 During the last **3 years**, have you undertaken any further education?

○ Yes ○ No → SKIP TO A3

A2 I have undertaken this type of education:

○ vocational training (e.g. TAFE)
→ ○ completed ○ still studying

○ university
→ ○ graduated ○ still studying

○ other, *please specify*:

.....

A3 During the last **3 years**, has your marital status changed?

○ Yes → If **YES**, I am currently...
- ○ married
- ○ living as married/living with a partner
- ○ widowed
- ○ separated from spouse/ partner
- ○ divorced
- ○ other, *please specify*:

○ No
○ Don't know

A4 What is your current weight?

..... ○ kilograms ○ stones ○ stones & pounds ○ Don't know

OFFICE USE ONLY
kilos

A5 What is your appropriate household income (before tax)?

ANNUALLY $ ..... OR FORTNIGHTLY $ .....

○ I would rather not say

○ Don't know

OFFICE USE ONLY
fortnightly $

A6 Has anyone in your family (blood relations only) **ever** been told they carry a cancer gene mutation?

○ Yes ○ No ○ Don't know

A7 Have you personally **ever** been tested for a cancer gene mutation?

○ Yes ○ No ○ Don't know → SKIP TO B1

A8 Did you receive results?

○ Yes → If **YES**, when did you receive your result? Month ... / Year ... ○ Don't know
○ No
○ Don't know → SKIP TO B1

OFFICE USE ONLY
M M Y Y Y Y

A9 Were you found to carry a cancer gene mutation?

○ Yes ○ No ○ Don't know → SKIP TO B1

A10 In which gene was the mutation found? *(mark all that apply)*

○ BRCA1 ○ p53
○ BRCA2 ○ CHEK2
○ ATM ○ PALB2
○ Other, *please specify*:

.....

○ Don't know

A11 When was the last time you personally attended a Family Cancer Clinic (FCC) / Genetics Clinic?

○ I attended → Month ... / Year ... ○ Don't know

Name of clinic:

.....

○ I have never attended a Family Cancer Clinic (FCC) / Genetics Clinic

○ Don't know

→ SKIP TO B1

OFFICE USE ONLY
M M Y Y Y Y

B. MEDICAL HISTORY

This section asks about your relevant medical history in the last **3 years**.

B1 During the last **3 years**, has a doctor told you that you had benign breast disease, such as a non-cancerous cyst or breast lump?

- ○ Yes → If **YES**, the date when I was told about this was: Month / Year ○ Don't know
- ○ No
- ○ Don't know

OFFICE USE ONLY

M	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
Y	Y	20								
Y	0	1	2	3	4	5	6	7	8	9
Y	0	1	2	3	4	5	6	7	8	9

B2 During the last **3 years**, has a doctor told you that you have a new cancer, leukaemia, lymphoma, or a malignant/cancerous tumour or growth? *Please only answer "yes" if you have had a new cancer diagnosed. If you have had a recurrence of a cancer that you had previously told us about, answer "no".*

- ○ Yes → If **YES**, I was told I had a: ..... on: Month / Year
- ○ No
- ○ Don't know

OFFICE USE ONLY

M	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
Y	Y	20								
Y	0	1	2	3	4	5	6	7	8	9
Y	0	1	2	3	4	5	6	7	8	9

Name and address of treating doctor:

.....

.....

.....

B3 During the last **3 years**, have you had your right breast completely removed?

- ○ Yes → If **YES**, the date when my right breast was removed was: Month / Year ○ Don't know
- ○ No → SKIP TO B8

OFFICE USE ONLY

M	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
Y	Y	20								
Y	0	1	2	3	4	5	6	7	8	9
Y	0	1	2	3	4	5	6	7	8	9

B4 Why was your right breast removed?

- ○ To remove a cancer
- ○ To try to prevent breast cancer (prophylactic mastectomy)
- ○ Other, *specify reason:*

.....

- ○ Don't know

B5 Was cancer found in your right breast when it was removed?

- ○ Yes
- ○ No
- ○ Don't know

B6 Who performed the surgery to remove your right breast?

Name of doctor:

.....

- ○ Don't know

B. MEDICAL HISTORY (continued)

B7 Where was the surgery to remove your right breast performed?

Name of hospital:

.....

Address:

.....

.....

○ Don't know

B8 During the last **3 years**, have you had your left breast completely removed?

○ Yes → If **YES**, the date when my left breast was removed was:

Month / Year ○ Don't know

○ No

SKIP TO B13

OFFICE USE ONLY

M	0 1 2 3 4 5 6 7 8 9
M	0 1 2 3 4 5 6 7 8 9
Y Y	20
Y	0 1 2 3 4 5 6 7 8 9
Y	0 1 2 3 4 5 6 7 8 9

B9 Why was your left breast removed?

○ To remove a cancer
○ To try to prevent breast cancer (prophylactic mastectomy)
○ Other, *specify reason:*

.....

○ Don't know

B10 Was cancer found in your left breast when it was removed?

○ Yes
○ No
○ Don't know

B11 Who performed the surgery to remove your left breast?

Name of doctor:

.....

○ Same doctor as named in **B6**
○ Don't know

B12 Where was the surgery to remove your left breast performed?

Name of hospital:

.....

Address:

.....

.....

○ Same hospital as named in **B7**
○ Don't know

B13 In the last **3 years**, have you had a breast reconstruction or breast implant on the right side?

○ Yes → If **YES**, the date when my right breast reconstruction was performed was:

Month / Year ○ Don't know

○ No

○ Don't know

OFFICE USE ONLY

M	0 1 2 3 4 5 6 7 8 9
M	0 1 2 3 4 5 6 7 8 9
Y Y	20
Y	0 1 2 3 4 5 6 7 8 9
Y	0 1 2 3 4 5 6 7 8 9

B14 In the last **3 years**, have you had a breast reconstruction or breast implant on the left side?

○ Yes → If **YES**, the date when my left breast reconstruction was performed was:

Month / Year ○ Don't know

○ No

○ Don't know

OFFICE USE ONLY

M	0 1 2 3 4 5 6 7 8 9
M	0 1 2 3 4 5 6 7 8 9
Y Y	20
Y	0 1 2 3 4 5 6 7 8 9
Y	0 1 2 3 4 5 6 7 8 9

B15 During the last **3 years**, have you had your right ovary completely removed?

- ○ Yes → If **YES**, the date when my right ovary was removed was: Month / Year ○ Don't know
- ○ No
- ○ Don't know

SKIP TO B20

OFFICE USE ONLY

M	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
Y	Y	20								
Y	0	1	2	3	4	5	6	7	8	9
Y	0	1	2	3	4	5	6	7	8	9

B16 Why was your right ovary removed? *(mark all that apply)*

- ○ To remove a cancer
- ○ To try to prevent ovarian cancer (prophylactic oophorectomy)
- ○ As part of treatment for breast cancer
- ○ Other, *specify reason:*

.....

.....

- ○ Don't know

B17 Was cancer found in your right ovary when it was removed?

- ○ Yes
- ○ No
- ○ Don't know

B18 Who performed the surgery to remove your right ovary?

Name of doctor:

.....

- ○ Don't know

B19 Where was the surgery to remove your right ovary performed?

Name of hospital:

.....

Address:

.....

.....

- ○ Don't know

B20 During the last **3 years**, have you had your left ovary completely removed?

- ○ Yes → If **YES**, the date when my left ovary was removed was: Month / Year ○ Don't know
- ○ No
- ○ Don't know

SKIP TO B25

OFFICE USE ONLY

M	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
Y	Y	20								
Y	0	1	2	3	4	5	6	7	8	9
Y	0	1	2	3	4	5	6	7	8	9

B21 Why was your left ovary removed? *(mark all that apply)*

- ○ To remove a cancer
- ○ To try to prevent ovarian cancer (prophylactic oophorectomy)
- ○ As part of treatment for breast cancer
- ○ Other, *specify reason:*

.....

.....

- ○ Don't know

B22 Was cancer found in your left ovary when it was removed?

- ○ Yes
- ○ No
- ○ Don't know

B23 Who performed the surgery to remove your left ovary?

Name of doctor:

.....

- ○ Same doctor as named in **B18**
- ○ Don't know

B24 Where was the surgery to remove your left ovary performed?

Name of hospital:

.....

Address:

.....

.....

- ○ Same hospital as named in **B19**
- ○ Don't know

B. MEDICAL HISTORY (continued)

B25 During the last **3 years**, have you had your womb/uterus removed (hysterectomy)?

- ○ Yes → If **YES**, the date when I had my uterus removed was: Month / Year ○ Don't know
- ○ No
- ○ Don't know

SKIP TO B30

OFFICE USE ONLY

M	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
YY	20									
Y	0	1	2	3	4	5	6	7	8	9
Y	0	1	2	3	4	5	6	7	8	9

B26 Why was your uterus removed? *(mark all that apply)*

- ○ To remove a cancer in the lining of the uterus (endometrial cancer)
- ○ To prevent cancer of the uterus (cancer of the womb)
- ○ To remove a cancer in the cervix (cervical cancer)
- ○ As part of treatment for ovarian cancer
- ○ Other, *specify reason:*

.....

.....

- ○ Don't know

B27 Was cancer found in your uterus when it was removed?

- ○ Yes
- ○ No
- ○ Don't know

B28 Who performed the surgery to remove your uterus?

Name of doctor:

.....

- ○ Don't know

B29 Where was the surgery to remove your uterus performed?

Name and address of hospital: .....

.....

.....

- ○ Don't know

B30 In the last **3 years**, have you had your tubes tied/clipped (tubal ligation)?

- ○ Yes → 'If **YES**, the date when I had my tubes tied was: Month / Year ○ Don't know
- ○ No
- ○ Don't know

OFFICE USE ONLY

M	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
YY	19	20								
Y	0	1	2	3	4	5	6	7	8	9
Y	0	1	2	3	4	5	6	7	8	9

B31 Have you **ever** had one or both of your fallopian tubes removed?

- ○ Yes → If **YES**, ○ one tube removed ○ both tubes removed
  If both tubes removed on different dates please record date second tube was removed.
  If **YES**, the date I had my fallopian tube/s removed was Month / Year ○ Don't know
- ○ No
- ○ Don't know

SKIP TO B32

OFFICE USE ONLY

M	0	1	2	3	4	5	6	7	8	9
M	0	1	2	3	4	5	6	7	8	9
YY	19	20								
Y	0	1	2	3	4	5	6	7	8	9
Y	0	1	2	3	4	5	6	7	8	9

If **YES**, reason tube/s removed? *(mark all that apply)*

If both tubes removed on different dates, please record reason second tube was removed.

- ○ To prevent cancer
- ○ To treat a cancer (ovarian, uterine, fallopian tube, etc.)
- ○ To treat a non-cancer condition (endometriosis, ovarian cyst, etc.)
- ○ Ectopic pregnancy
- ○ Contraception
- ○ Other, *specify reason:* .....

.....

B31a Who performed the surgery to remove your fallopian tube/s, and where was it done?

Name of doctor:

.....

Hospital name and address:

.....

.....

○ Don't know

B32 How long ago was your last menstrual period? *(Indicate the number of weeks/months/years since your last period.)*

.....

○ weeks
○ months
○ years

○ More than 10 years ago
○ I have never had a period
○ Don't know

OFFICE USE ONLY

weeks
0 1 2 3 4 5 6 7 8 9
0 1 2 3 4 5 6 7 8 9
0 1 2 3 4 5 6 7 8 9
>10 Years ○

B33 Was your last menstrual period **more than 1 year ago**?

○ Yes → If **YES**, indicate why your period stopped: *(mark all that apply)*

- ○ Natural menopause
- ○ Pregnancy / breastfeeding
- ○ Medication that stopped periods, i.e. chemotherapy, tamoxifen, Zoladex
- ○ Hormonal contraception i.e. the pill, implants, injections
- ○ Removal of both ovaries
- ○ Removal of uterus (hysterectomy)
- ○ IUD with hormones (e.g. Mirena)
- ○ Other, *please specify:*

.....

○ No
○ Don't know

B34 Do you consider yourself to be postmenopausal?

○ Yes
○ No
○ Don't know

Breast cancers diagnosed in the last 3 years

B35 In the last **3 years**, have you been diagnosed with a new breast cancer? (Not a recurrence of a previous cancer.)

○ Yes → If **YES**, my cancer was diagnosed on:

Month ____ / Year ____ ○ Don't know

○ No
○ Don't know

SKIP TO B55

OFFICE USE ONLY

M 0 1 2 3 4 5 6 7 8 9
M 0 1 2 3 4 5 6 7 8 9
Y Y 20
Y 0 1 2 3 4 5 6 7 8 9
Y 0 1 2 3 4 5 6 7 8 9

B36 How was this breast cancer first found? *(mark all that apply)*

- ○ routine mammogram
- ○ routine doctor's examination
- ○ breast self examination (you found the lump yourself)
- ○ nipple discharge or changes to the breast appearance
- ○ routine breast ultrasound
- ○ prophylactic surgery – i.e. breasts were removed and then cancer was found
- ○ other, *please specify:*

.....

.....

○ Don't know

B37 When you were first diagnosed with this breast cancer, which areas of your body did it involve? *(mark all that apply)*

- ○ left breast
- ○ right breast
- ○ both breasts
- ○ the lymph nodes (glands) under the arm
- ○ other areas, *specify below:*

.....

.....

○ Don't know

B. MEDICAL HISTORY (continued)

B38 Did you have surgery for this breast cancer?

- ○ Yes → If **YES**, my surgery was performed on: Month / Year ○ Don't know
- ○ No
- ○ Don't know

SKIP TO B42

OFFICE USE ONLY

M	0 1 2 3 4 5 6 7 8 9
M	0 1 2 3 4 5 6 7 8 9
Y Y	20
Y	0 1 2 3 4 5 6 7 8 9
Y	0 1 2 3 4 5 6 7 8 9

B39 What type of surgery did you have? *(mark all that apply)*

- ○ lumpectomy (removal of just the cancer)
- ○ mastectomy (removal of the entire breast)
- ○ removal of lymph nodes (glands) under the arm
- ○ other, *specify:*

.....

- ○ Don't know

B40 Who was the doctor who performed this surgery?

Name of doctor:

.....

- ○ Don't know

B41 Where was/were the operation(s) performed?

Name of hospital:

.....

Address:

.....

.....

- ○ Don't know

B42 Did you have radiation treatment (radiotherapy) within 12 months of the diagnosis of this breast cancer?

- ○ Yes → If **YES**, my radiation treatment started on: Month / Year ○ Don't know
- ○ No
- ○ Don't know

SKIP TO B46

OFFICE USE ONLY

M	0 1 2 3 4 5 6 7 8 9
M	0 1 2 3 4 5 6 7 8 9
Y Y	20
Y	0 1 2 3 4 5 6 7 8 9
Y	0 1 2 3 4 5 6 7 8 9

B43 What areas of your body received radiation treatment? *(mark all that apply)*

- ○ breast after lumpectomy (removal of just the cancer)
- ○ chest after mastectomy (removal of the entire breast)
- ○ lymph nodes (glands) under the arm
- ○ other, *specify:*

.....

- ○ Don't know

B44 Who was the doctor who supervised your radiation treatment?

Name of radiation doctor:

.....

- ○ Don't know

B45 Where was the radiation treatment given?

Name of hospital:

.....

Address:

.....

.....

- ○ Don't know

B46 Did you have chemotherapy that was started within the first 6 months of the diagnosis of this breast cancer?

- ○ Yes → If **YES**, I started my chemotherapy on: Month / Year ○ Don't know
- ○ No
- ○ Don't know

→ SKIP TO B50

OFFICE USE ONLY

M	0 1 2 3 4 5 6 7 8 9
M	0 1 2 3 4 5 6 7 8 9
Y Y	20
Y	0 1 2 3 4 5 6 7 8 9
Y	0 1 2 3 4 5 6 7 8 9

B47 What type of chemotherapy did you have? *(mark all that apply)*

- ○ Adriamycin (Doxorubicin)
- ○ Carboplatin
- ○ Capecitabine (Xeloda)
- ○ Cyclophosphamide
- ○ Docetaxel (Taxotere)
- ○ Epirubicin
- ○ Fluorouracil
- ○ Gemcitabine (Gemzar)
- ○ Lapatinib (Tykerb/Tyverb)
- ○ Methotrexate
- ○ Paclitaxel (Taxol)
- ○ Pertuzumab (Perjeta)
- ○ Trastuzumab (Herceptin)
- ○ Vinorelbine (Navelbine)
- ○ Other, *please specify:* .....

.....

.....

- ○ Don't know

Examples of chemotherapy combinations:
AC - Adriamycin (Doxorubicin) and Cyclophosphamide
AC-T - Adriamycin and Cyclophosphamide, followed by Paclitaxel (Taxol)
AC-TH - Adriamycin and Cyclophosphamide, followed by Paclitaxel (Taxol) and Trastuzumab (Herceptin)
CMF - Cyclophosphamide, Methotrexate and Fluorouracil
EC - Epirubicin and Cyclophosphamide
FEC - Fluorouracil, Epirubicin and Cyclophosphamide
FAC - Fluorouracil, Adriamycin and Cyclophosphamide
TAC – Taxotere, Adriamycin and Cyclophosphamide

B48 Who was the doctor who prescribed your chemotherapy?

Name of chemotherapy doctor:

.....

- ○ Don't know

B49 Where was the chemotherapy given?

Name and address of hospital :

.....

.....

.....

- ○ Don't know

B50 Did you have anti-hormone treatment that was started within 12 months of the diagnosis of this breast cancer?

- ○ Yes → If **YES**, I started taking anti-hormone treatment on: Month / Year ○ Don't know
- ○ No
- ○ Don't know

→ SKIP TO B54

OFFICE USE ONLY

M	0 1 2 3 4 5 6 7 8 9
M	0 1 2 3 4 5 6 7 8 9
Y Y	20
Y	0 1 2 3 4 5 6 7 8 9
Y	0 1 2 3 4 5 6 7 8 9

B51 What type of anti-hormone treatment did/do you use? *(mark all that apply)*

- ○ Tamoxifen (Nolvadex, Genox, Tamoxen, Tamosin)
- ○ Anastrozole (Anastrol, Arimidex, Anzole, Arianna)
- ○ Letrozole (Femara, Femolet, Fera, Letara, Lezole)
- ○ Goserelin (Zoladex), Triptorelin
- ○ Exemestane (Aromasin, Exaccord)
- ○ Other, *specify:*

.....

- ○ Don't know what type

B52 Are you still using this anti-hormone treatment?

- ○ Yes
- ○ No → If **NO**, I stopped taking anti-hormone treatment on: Month / Year ○ Don't know
- ○ Don't know

OFFICE USE ONLY

M	0 1 2 3 4 5 6 7 8 9
M	0 1 2 3 4 5 6 7 8 9
Y Y	20
Y	0 1 2 3 4 5 6 7 8 9
Y	0 1 2 3 4 5 6 7 8 9

B. MEDICAL HISTORY (continued)

B53 Who was the doctor who prescribed this anti-hormone treatment?

Name of doctor:

.....

Address:

.....

.....

○ Don't know

B54 Did you take a bone strengthener/ bisphosphonate (e.g. Zometa or Alendronate) or denosumab (e.g. Prolia)?

○ Yes ○ No ○ Don't know

All previous cancers

B55 In the last **3 years**, have you had a recurrence of your cancer?

○ Yes → If **YES**, the date my cancer returned was: Month / Year ○ Don't know

○ No

○ Don't know

SKIP TO B57

OFFICE USE ONLY

M M Y Y Y Y

B56 Where in your body did the cancer come back? *(mark all that apply)*

○ same breast/chest wall on same side
○ lymph nodes under the arm on the same side as the breast cancer
○ other lymph nodes, *specify:*

.....

○ skin/subcutaneous
○ bone
○ liver
○ lung
○ brain
○ other, *specify:*

.....

○ opposite breast
○ don't know where

Name and address of treating doctor:

.....

.....

.....

B57 What is the current situation with your cancer?

○ It is in remission – there is no cancer that the doctors can find
○ It is still present
○ Don't know

B58 In the last **3 years**, have you taken any of the following medications? *(mark all that apply)*

○ Yes → ○ Tamoxifen (Nolvadex, Genox, Tamoxen, Tamosin)
○ Anastrozole (Anastrol, Arimidex, Anzole, Arianna)
○ Letrozole (Femara, Femolet, Fera, Letara, Lezole)
○ Goserelin (Zoladex), Triptorelin
○ Exemestane (Aromasin, Exaccord)

○ No

○ Don't know

SKIP TO B60

B59 If **YES**, please estimate the total amount of time that you took this medication in the last 3 years:

○ years
○ months

months

OFFICE USE ONLY

B60 Are there any other doctors, apart from those you have already mentioned on this questionnaire, whom you see for follow-up of your cancer? *(We may need to get information from them about the treatment of your cancer.)*

○ Yes ○ No ○ Don't know

If **YES**, I am also followed up by:

1. Name of doctor: .....

Type of doctor: .....

Address where followed up: .....

.....

2. Name of doctor: .....

Type of doctor: .....

Address where followed up: .....

.....

C. FAMILY HISTORY

This section asks questions about any changes in your family history during the last **3 years**.

C1 During the last **3 years**, has anyone in the family, ***who is related to you by blood***, been diagnosed with a new cancer of any type?

- ○ Yes
- ○ No
- ○ Don't know

If **YES**, please specify their name, date of birth, relationship to you, and the type of cancer:

	Name *(e.g. Karen Smith)*	Date of Birth	Relationship *(e.g. Aunt, father's side)*	Cancer Type *(e.g. Bowel)*
1.				
2.				
3.				
4.				

OFFICE USE ONLY Breast / Ovary ○

C2 Has anyone in the family died during the last **3 years**?

- ○ Yes
- ○ No
- ○ Don't know

If **YES**, please specify their name, date of birth, relationship to you, and what they died from:

	Name *(e.g. John Brown)*	Date of Birth	Relationship *(e.g. Cousin, mother's side)*	Cause of Death *(e.g. Stroke)*	Date of Death
1.					
2.					
3.					
4.					

OFFICE USE ONLY **D** **HORMONAL FORMS OF CONTRACEPTION:**

	Age (when first used)	Age (when last used)	Total time taken
Combined OCP	○○	○○	○○
Progesterone only pill – Mini pill	○○	○○	○○
Injectable Progesterone	○○	○○	○○
Progesterone implants	○○	○○	○○
Mirena IUD	○○	○○	○○
Other	○○	○○	○○

OFFICE USE ONLY

E1 ( ) 0 1 2 3 4 5 6 7 8 9 *pregnancy(ies)*

E2 **(i)**

Date	Weeks	Sex	Breastfed
D D: Don't know day; Don't know month			weeks / months
JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC			OR
Y Y Y Y: 19 20			
		boys 1 2 3 4	
		girls 1 2 3 4	

E3 **(ii)**

Date	Weeks	Sex	Breastfed
D D: Don't know day; Don't know month			weeks / months
JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC			OR
Y Y Y Y: 19 20			
		boys 1 2 3 4	
		girls 1 2 3 4	

F HORMONE REPLACEMENT THERAPY

	Age (when first used)	Age (when last used)	Total time taken
Oestrogen only vaginal creams	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9
Oestrogen only tablets, patches	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9
Combined progesterone and oestrogen	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9
IUD with oestrogen only tablet or patch	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9
Synthetic oestrogen, progesterone and androgen (testosterone)	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9
Other	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9	0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9

D. HORMONAL FORMS OF CONTRACEPTION

This section asks about your use of hormonal contraception in the **last 3 years**.

D1 In the **last 3 years**, have you used any form of hormonal contraception? *(i.e. oral contraceptive pills, progesterone only pills, hormone implants, injectable contraceptives such as Depo Provera)*

- ○ Yes → If **YES, complete the table below**
- ○ No
- ○ Don't know

→ SKIP TO Section E

Type of Hormonal Contraceptive	In the **last 3 years**, have you taken this form of hormonal contraception?	In the **last 3 years**, did you use this form of contraception for the first time?	Are you currently using this form of contraception?	Please estimate the total amount of time you used this form of contraception in the **last 3 years**.
Combined oral contraceptive pill (such as Brenda, Brevinor, Diane, Levlen, Microgynon 30/50, Nordette, Triquilar, Triphasil etc)	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of contraception was ____ years ○ No	○ Yes ○ No – my age when I last used this form of contraception was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know
Progesterone only pill – Mini pill (such as Microlut, Micronor, Microval, Noriday 28)	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of contraception was ____ years ○ No	○ Yes ○ No – my age when I last used this form of contraception was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know
Injectable Progesterone (such as Depo Provera)	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of contraception was ____ years ○ No	○ Yes ○ No – my age when I last used this form of contraception was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know
Progesterone implants (such as Implanon)	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of contraception was ____ years ○ No	○ Yes ○ No – my age when I last used this form of contraception was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know
Mirena IUD (slow release progesterone IUD)	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of contraception was ____ years ○ No	○ Yes ○ No – my age when I last used this form of contraception was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know
Other: *Specify*	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of contraception was ____ years ○ No	○ Yes ○ No – my age when I last used this form of contraception was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know

Please specify the brands you have used: _____

D2 Have you had a full-term pregnancy in the last 3 years?

- ○ Yes
- ○ No → SKIP TO Section E

D3 Was this your first full-term pregnancy?

- ○ Yes
- ○ No → SKIP TO Section E

D4 Estimate how long <u>in total</u> you used hormonal contraception before your first full-term pregnancy?

____

- ○ Months
- ○ Years
- ○ Not taken before first pregnancy

OFFICE USE ONLY

unit ____ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ____ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨

E. PREGNANCIES

This section asks about all pregnancies you've had since we last interviewed you, including all live births, stillbirths, miscarriages, current pregnancies and other outcomes.

E1 During the **last 3 years**, have you been, or are you currently, pregnant?

- ○ Yes → If **YES**, how many pregnancies have you had in the **last 3 years**, including live births, stillbirths, miscarriages, current pregnancies and other outcomes?
  ____ pregnancies ○ Don't know
- ○ No
- ○ Don't know

SKIP TO Section F

E2 The following questions are for your most recent pregnancy.

What date did this pregnancy end?	What was the outcome of this pregnancy?	Did this pregnancy go for the usual 9 months (40 weeks)	IF LIVE BIRTH OR STILLBIRTH: What was the sex of the child (or children if twins or triplets) produced by this pregnancy?	IF LIVE BIRTH: Did you breast-feed the child(ren) from this pregnancy?	IF BREASTFED: For how many weeks/ months did you breast-feed the child(ren) from this pregnancy?
/ / **OR** ○ Currently pregnant SKIP TO E3	○ Single live birth ○ Multiple birth ○ Stillbirth ○ Miscarriage ○ Ectopic pregnancy ○ Induced termination ○ Don't know	○ Yes ○ No → Specify no. of weeks ____ ○ Don't know	Number of boys: ____ Number of girls: ____ ○ Don't know	○ Yes ○ No ○ Don't know	Weeks: ____ **OR** Months: ____ ○ Currently breastfeeding

If this is the only pregnancy you've had during the last 3 years → SKIP TO Section F

E3 Please complete this section if you have had ANY OTHER pregnancies during the last **3 years**.

What date did this pregnancy end?	What was the outcome of this pregnancy?	Did this pregnancy go for the usual 9 months (40 weeks)	IF LIVE BIRTH OR STILLBIRTH: What was the sex of the child (or children if twins or triplets) produced by this pregnancy?	IF LIVE BIRTH: Did you breast-feed the child(ren) from this pregnancy?	IF BREASTFED: For how many weeks/ months did you breast-feed the child(ren) from this pregnancy?
2nd last pregnancy ended on: / /	○ Single live birth ○ Multiple birth ○ Stillbirth ○ Miscarriage ○ Ectopic pregnancy ○ Induced termination ○ Don't know	○ Yes ○ No → Specify no. of weeks ____ ○ Don't know	Number of boys: ____ Number of girls: ____ ○ Don't know	○ Yes ○ No ○ Don't know	Weeks: ____ **OR** Months: ____
3rd last pregnancy ended on: / /	○ Single live birth ○ Multiple birth ○ Stillbirth ○ Miscarriage ○ Ectopic pregnancy ○ Induced termination ○ Don't know	○ Yes ○ No → Specify no. of weeks ____ ○ Don't know	Number of boys: ____ Number of girls: ____ ○ Don't know	○ Yes ○ No ○ Don't know	Weeks: ____ **OR** Months: ____
4th last pregnancy ended on: / /	○ Single live birth ○ Multiple birth ○ Stillbirth ○ Miscarriage ○ Ectopic pregnancy ○ Induced termination ○ Don't know	○ Yes ○ No → Specify no. of weeks ____ ○ Don't know	Number of boys: ____ Number of girls: ____ ○ Don't know	○ Yes ○ No ○ Don't know	Weeks: ____ **OR** Months: ____

F. HORMONE REPLACEMENT THERAPY

This section asks questions about your use of Hormone Replacement Therapy **in the last 3 years**. This does not include the use of herbal preparations for menopausal symptoms.

Type of Hormone Replacement Therapy (HRT)	In the last **3 years**, have you taken this form of HRT?	In the last **3 years**, did you use this form of HRT for the first time?	Are you currently using this form of hormone replacement therapy?	Please estimate the total amount of time you used this form of HRT in the last **3 years**.
Oestrogen only vaginal creams/pessaries Such as Vagifem & Ovestin.	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of HRT was ____ years ○ No	○ Yes ○ No – my age when I last used this form of HRT was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know
Oestrogen only tablets, patches Such as Premarin, Estraderm, Progynova, Zumenon, Estrofem, Climara, Estradot & Ovestin tablets.	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of HRT was ____ years ○ No	○ Yes ○ No – my age when I last used this form of HRT was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know
Combined progesterone and oestrogen Kliovance, Kliogest, Estralis, Trisequens, Angeliq & Provera with oestrogen tablet or patch.	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of HRT was ____ years ○ No	○ Yes ○ No – my age when I last used this form of HRT was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know
IUD with oestrogen only tablet or patch Such as Mirena with Premarin.	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of HRT was ____ years ○ No	○ Yes ○ No – my age when I last used this form of HRT was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know
Synthetic oestrogen, progesterone and androgen (testosterone) Such as Tibolone: Livial, Xyvion.	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of HRT was ____ years ○ No	○ Yes ○ No – my age when I last used this form of HRT was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know
Other: *Specify*	○ Yes → ○ No ○ Don't know	○ Yes – my age when I first used this form of HRT was ____ years ○ No	○ Yes ○ No – my age when I last used this form of HRT was ____ years ○ Don't know age	____ ○ months ○ years ○ Don't know

G. SMOKING

This section asks questions about cigarettes that you may have smoked.

G1 During the last **3 years**, has there been a time when you smoked regularly, i.e. at least one cigarette per day, for at least 3 months?

○ Yes → If **YES**, during the last **3 years**, I estimate that I smoked regularly for... ____ ○ months ○ years

○ No

○ Don't know

SKIP TO Section H

months OFFICE USE ONLY [0 1 2 3 4 5 6 7 8 9] [0 1 2 3 4 5 6 7 8 9]

G2 Over the time when you smoked regularly during the last **3 years**, how many cigarettes did you smoke in a day?

____ *cigarettes*

○ Don't know

cigs OFFICE USE ONLY [0 1 2 3 4 5 6 7 8 9] [0 1 2 3 4 5 6 7 8 9]

G3 Are you currently smoking at least one cigarette per day?

○ Yes

○ No

age OFFICE USE ONLY [0 1 2 3 4 5 6 7 8 9] [0 1 2 3 4 5 6 7 8 9]

If **NO**, my age when I stopped smoking at least one cigarette per day was: ____ years of age ○ Don't know

H. ALCOHOL

This section asks questions about alcoholic beverages that you may have consumed during the last **3 years**.

H1 During the last **3 years**, did you drink any alcoholic beverages such as beer, wine or spirits regularly, i.e. at least once a week, for a period of 6 months or longer?

- ○ Yes → If **YES**, during the last **3 years**, I estimate that I drank regularly for: ____ ○ months ○ years
- ○ No
- ○ Don't know

SKIP TO Section I

OFFICE USE ONLY — months: 0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9

H2 During the period in which you drank alcohol regularly, specify how many standard drinks you consumed daily, weekly or monthly. *(Refer to the table below for definitions of standard drinks.)*

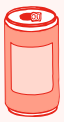
STANDARD DRINKS	Never	Less than once a month	1–3 per month	1 per week	2–4 per week	5–6 per week	1 per day	2–3 per day	4–5 per day	More than 5 per day	Don't know
LIGHT BEER	○	○	○	○	○	○	○	○	○	○	○
BEER	○	○	○	○	○	○	○	○	○	○	○
WINE	○	○	○	○	○	○	○	○	○	○	○
SPIRITS	○	○	○	○	○	○	○	○	○	○	○
ALCOHOLIC SODA	○	○	○	○	○	○	○	○	○	○	○

*Definitions of **STANDARD DRINKS** (Each of these drinks is approximately equal to ONE STANDARD DRINK.)*

Low alcohol beer (3.5%) — 1.6 pots, total volume 375ml

Table wine (12%) — 1 small glass, 100ml

Mixed drinks — 1 glass, 30ml of spirits (40%) plus mixer



Low alcohol beer (3.5%) — 1 can, 375ml

Regular beer (4.9%) — 1 pot, 285ml

Alcoholic soda (5.5%) — 3/4 of a 330ml bottle

Spirits or liqueurs (40%) — 1 nip, 30ml

Regular beer (4.9%) — 3/4 of a stubby

H3 Are you currently drinking alcohol at least once per week?

- ○ Yes
- ○ No → If **NO**, my age when I stopped drinking alcohol at least once per week was: ____ years of age ○ Don't know

OFFICE USE ONLY — age: 0 1 2 3 4 5 6 7 8 9 / 0 1 2 3 4 5 6 7 8 9

I. OTHER COMMENTS

Do you have any comments, or is there any other information that you think we could have asked about?

Thank you for completing this questionnaire.

Remember that if you have problems with any of the questions, please call the toll-free telephone number

1800 111 581*

and a kConFab research assistant will be able to help you. * *Charges will apply if calling from a mobile phone*

Appendix 2: Risk reducing medication survey kConFab women

UPN: _ _ . _ _ _ . _ _ _ _
OFFICE USE ONLY

Kathleen Cuningham Foundation **kConFab** CONsortium for research into FAmilial Breast cancer
CLINICAL FOLLOW-UP PROJECT

Translating Evidence into Practice

Optimising and Facilitating Prevention and Screening in Women with a Strong Family History of Breast Cancer

1. Would you like to participate in this research survey?

Yes ○

2. Please enter your 9 digit unique identifier (UPN) provided to you in the letter:

		.				.				

3. Please enter your date of birth

		/			/				

4. Have you ever been diagnosed with breast or any other cancer, not including skin cancers, in the last 6 years?

Yes ○ Go to Q4a
No ○ Skip to Q5

4a. What type of cancer were you diagnosed with?

_____

_____

4b. The date I was diagnosed with cancer was:

	/	
Month		Year

If you don't know, please leave blank.

5. Have you had both breasts removed?

Yes ○ →
No ○

If **YES**, the date I had my breasts removed was:

	/	
Month		Year

If you don't know, please leave blank.

If you answered **YES** to questions **4 OR 5** (you have been diagnosed with breast or another cancer in the last 6 years **OR** you have had both breasts removed), unfortunately your responses have made you ineligible for the remainder of the survey.

Thank you for your interest and time.
We would appreciate it if you could please return your questionnaire in the supplied, reply-paid envelope.

6. I think my risk of getting breast cancer sometime in my life is: (select one)

○	**Low**	Lower than most other women
○	**Average**	About the same as most other women
○	**Moderately increased**	About 2 or 3 times that of most other women
○	**High**	More than 3 times that of most other women
○	**Don't know**	

7. What comes to mind when you read the words 'risk-reducing medicines'?

_____

_____

Definition of risk-reducing medicines

Medicines that reduce the risk of breast cancer may be considered by women who are at an increased risk. They are called 'risk-reducing medicines'. The most common risk-reducing medicine is tamoxifen.

Other risk-reducing medicines include raloxifene, anastrazole and exemestane. These tablets are taken once a day, usually for 5 years.

8. Before this survey, did you know that there were medications that could reduce your risk of getting breast cancer?

Yes ○ Go to Q8a

No ○ Skip to Q9

8a. Where did you hear about these medications? Select all that apply.

○	GP/Family doctor
○	Gynaecologist
○	Breast surgeon
○	Doctor or Genetic Counsellor at FCC
○	Family/friends
○	TV
○	Radio
○	Magazines
○	Internet
○	Other

If you selected Other, please specify:

_____

9. Have you ever participated in a breast cancer prevention drug trial (IBIS I or IBIS II)?

Yes ○ → If you selected Yes, go to Q20

No ○

10. Please choose one of the following:

○	a. I have heard of risk-reducing medicines but I have not discussed them with my healthcare professional
○	b. I have discussed risk-reducing medicines with my healthcare professional but decided not to take them
○	c. I have taken risk-reducing medicines but stopped taking them
○	d. I am currently taking risk-reducing medicines

If you selected:
'a' please skip to question 14
'b' please skip to question 13
'c' please answer questions 11 – 14, then skip to question 19
'd' please answer questions 12 – 14, then skip to question 19

11. Why did you stop taking risk reducing medicines?

I finished the 5 year course ○

Other (please specify) ○

12. Please specify which medicine/s you were or are currently taking and for how long?

	Medicine	Total Time Taken
○	Tamoxifen (Nolvadex, Gebox, Tamoxen, Tamosin)	• _____Months • _____Years Don't know
○	Raloxifene (Evista)	• _____Months • _____Years Don't know
○	Anastrozole (Anastrol, Arimidex, Anzole, Arianna)	• _____Months • _____Years Don't know
○	Letrozole (Femara, Femolet, Fera, Letara, Lezole)	• _____Months • _____Years Don't know
○	Exemestane (Aromasin, Exaccord)	• _____Months • _____Years Don't know
○	Other (please specify)	• _____Months • _____Years Don't know

13. Which healthcare professional/s discussed risk-reducing medicines with you? For each professional you select below as YES, please indicate how confident you were in the advice/information you received about risk-reducing medicines.

GP/Family doctor:

Yes ○ →

No ○

If no, please go to next health professional

Very confident	Somewhat confident	Not too confident	Not at all confident	Unsure
○	○	○	○	○

If you selected 'not too confident' or 'not at all confident', what would have made you more confident?

_____

Gynaecologist:

Yes ○ →

No ○

If no, please go to next health professional

Very confident	Somewhat confident	Not too confident	Not at all confident	Unsure
○	○	○	○	○

If you selected 'not too confident' or 'not at all confident', what would have made you more confident?

_____

Breast Surgeon:

Yes ○ →

No ○

If no, please go to next health professional

Very confident	Somewhat confident	Not too confident	Not at all confident	Unsure
○	○	○	○	○

If you selected 'not too confident' or 'not at all confident', what would have made you more confident?

_____

Doctor or Genetic Counsellor at Familial Cancer Clinic:

Yes ○ →

No ○

If no, please go to next health professional

Very confident	Somewhat confident	Not too confident	Not at all confident	Unsure
○	○	○	○	○

If you selected 'not too confident' or 'not at all confident', what would have made you more confident?

_____

Other (please specify)**:**

_____

_____

Yes ○ →

No ○

Very confident	Somewhat confident	Not too confident	Not at all confident	Unsure
○	○	○	○	○

If you selected 'not too confident' or 'not at all confident', what would have made you more confident?

_____

14. What 3 key pieces of information would you want to know if deciding whether to take risk-reducing medicines? Please rank top 3 in order of preference (with 1 being the most important), by entering numbers 1 – 3 in the boxes below.

Information Options	Rank (top 3)
Will they interfere with other medicines I take	
Will they affect my other health conditions	
How much will they decrease my risk of breast cancer	
Do they have other health benefits	
How do they work	
How do they compare with other ways of reducing risk	
How do they affect my plans for pregnancy/breastfeeding	
What are the side effects	
How long would I need to take them	
How would I know that the medicine was working	
What is the cost	
Does my doctor recommend them	
Do trustworthy organisations (e.g. Cancer Australia) recommend them	

15. Please rank in order of preference from 1 (most) to 5 (least) who you would like to provide you with information about risk reducing medicines?

Information Provider	Rank (1 – 5)
GP/Family doctor	
Gynaecologist	
Breast surgeon	
Doctor or Genetic Counsellor at Familial Cancer Clinic	
Trustworthy website (e.g. Cancer Australia)	

16a. To what extent are the following a barrier for you to take a risk-reducing medicine?

	These things would be a barrier for me to take a risk reducing medicine		Strong barrier	Somewhat a barrier	Not a barrier at all	Not applicable
1	The inconvenience of taking a daily tablet	*This would be a barrier for me to take a risk-reducing medicine*	○	○	○	○
2	I am already taking too many medications		○	○	○	○
3	Taking a daily tablet for 5 years would be a daily reminder of my cancer risk		○	○	○	○
4	I don't believe risk-reducing medicines would reduce my rick of breast cancer at all		○	○	○	○
5	I don't believe risk-reducing medicines would reduce my risk of breast cancer enough to make it worthwhile		○	○	○	○

16b. To what extent are the following a barrier for you to take a risk-reducing medicine?

	These things would be a barrier for me to take a risk reducing medicine		Strong barrier	Somewhat a barrier	Not a barrier at all	Not applicable
6	I am concerned about drug interactions	*This would be a barrier for me to take a risk-reducing medicine*	○	○	○	○
7	I am worried my family/friends would assume I have been diagnosed with breast cancer or may ask questions about our family history of breast cancer		○	○	○	○
8	It would be a reminder of family members' or friends' cancer experiences		○	○	○	○
9	My doctor doesn't talk to me enough about risk-reducing medicines		○	○	○	○
10	I think of these as medicines to treat breast cancer, not to prevent it		○	○	○	○

16c. To what extent are the following a barrier for you to take a risk-reducing medicine?

	These things would be a barrier for me to take a risk reducing medicine		Strong barrier	Somewhat a barrier	Not a barrier at all	Not applicable
11	I don't believe in taking medicines for prevention, only for illness	*This would be a barrier for me to take a risk-reducing medicine*	○	○	○	○
12	Risk-reducing medicines are unnatural		○	○	○	○
13	I wouldn't know whether risk-reducing medicines were actually working		○	○	○	○
14	I don't have enough information about risk-reducing medicines to make an informed decision		○	○	○	○
15	I would prefer to have both breasts removed rather than take medication		○	○	○	○

16d. To what extent are the following a <u>barrier for you</u> to take a risk-reducing medicine?

	These things would be a barrier for me to take a risk reducing medicine		Strong barrier	Somewhat a barrier	Not a barrier at all	Not applicable
16	I would prefer breast cancer screening (e.g. mammograms) alone, rather than screening and taking risk-reducing medicines	*This would be a barrier for me to take a risk-reducing medicine*	○	○	○	○
17	My risk of breast cancer is not high enough to justify taking risk-reducing medicines		○	○	○	○
18	I don't know what my breast cancer risk is		○	○	○	○
19	I don't know how much they cost		○	○	○	○
20	Taking them would mean I couldn't take the oral contraceptive pill		○	○	○	○

16e. To what extent are the following a <u>barrier for you</u> to take a risk-reducing medicine?

	These things would be a barrier for me to take a risk reducing medicine		Strong barrier	Somewhat a barrier	Not a barrier at all	Not applicable
21	Taking them would mean I would have to delay becoming pregnant	*This would be a barrier for me to take a risk-reducing medicine*	○	○	○	○
22	I'm too old to bother trying to prevent breast cancer		○	○	○	○
23	I have another medical condition that outweighs my breast cancer concerns		○	○	○	○
24	I prefer healthy lifestyle choices alone to medications		○	○	○	○
25	Possible side effects		○	○	○	○

16f. To what extent are the following a <u>barrier for you</u> to take a risk-reducing medicine?

	These things would be a barrier for me to take a risk reducing medicine		Strong barrier	Somewhat a barrier	Not a barrier at all	Not applicable
26	If family/ friends didn't think taking risk-reducing medicine was a good idea	*This would be a barrier for me to take a risk-reducing medicine*	○	○	○	○
27	I've seen family/friends experience side effects when taking medicines like this, so I will be likely to experience the same		○	○	○	○
28	If cancer is going to happen it will happen, I do not believe you can change your own risk		○	○	○	○
29	I have trouble remembering to take a daily tablet		○	○	○	○

16g. Which one of these factors (1 – 29) is the strongest barrier? If none of the above are a barrier, please leave blank.

_____

16h. Are there any other barriers that are not listed above? If no, please leave blank.

_____

17. Do the following make it <u>easier for you</u> to take a risk-reducing medicine?

	These things would make it easier for me to take risk-reducing medicines		Much easier	Somewhat easier	Not at all easier	Not applicable
1	Knowing some of these medicines reduce cholesterol levels	*This would make it easier for me to take a risk-reducing medicine*	○	○	○	○
2	If my family/friends recommended taking risk-reducing medicines		○	○	○	○
3	If my doctor recommended taking risk-reducing medicines		○	○	○	○
4	Having a family history of breast cancer		○	○	○	○
5	Knowing that some of these medicines help prevent or treat osteoporosis (thinning of bones)		○	○	○	○
6	Because they would reduce my stress and worry about breast cancer		○	○	○	○
7	Having an abnormal breast biopsy that increased my risk of developing breast cancer		○	○	○	○
8	Knowing I have a high breast cancer risk		○	○	○	○

	These things would make it easier for me to take risk-reducing medicines		Much easier	Somewhat easier	Not at all easier	Not applicable
9	If family/friends were supportive of me taking risk-reducing medicines	*This would make it easier for me to take a risk-reducing medicine*	○	○	○	○
10	If I thought risk-reducing medicines would improve the chance I will stay healthy for my family		○	○	○	○
11	Taking a daily tablet to reduce my breast cancer risk would reassure me		○	○	○	○
12	Taking a daily tablet to reduce my breast cancer risk would make me feel more in control of my health		○	○	○	○
13	Knowing risk-reducing medicines can be taken prior to risk-reducing surgery (both breasts removed)		○	○	○	○
14	Once I stop taking risk-reducing medicines any side effects will diminish		○	○	○	○
15	Taking risk-reducing medicines can reduce breast cancer risk for up to 20 years		○	○	○	○

17a. Which one of these factors (1-16) would make it <u>easiest</u> for you to take a risk-reducing medicine? If none of the above would make it easier, please leave blank.

_____

17b. Are there any other factors that would make it easier for you to take a risk-reducing medicine? If no, please leave blank.

_____

_____

18. Below is a list of potential side effects of risk-reducing medicines. It is important to note that many of these side effects are rare and that side effects can vary for each medication type. Please rank the most (1) to least (9) important side effect for you:

Potential side effects	Rank (1 – 9)
Blood clots	
Vaginal dryness	
Cataracts	
Hot flushes and sweats	
Joint pain	
Endometrial cancer (cancer of the womb)	
Increased vaginal discharge	
Osteoporosis (thin bones)	
Irregular periods	

19. How much do you think each of these strategies would reduce your risk of breast cancer?

	Not at all	A bit	A lot
Risk-reducing medicines	○	○	○
Screening (e.g. mammogram, ultrasound, MRI)	○	○	○
Risk-reducing surgery (having both breasts removed)	○	○	○

Appendix 3: Risk reducing medication survey clinicians

UNIQUE CLINICIAN NUMBER

☐☐☐☐

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Translating Evidence into Practice:

Optimising and Facilitating Prevention and Screening in Women with a Strong Family History of Breast Cancer

1. Do you consent to participating in this research?

☐ Yes

2. What is your gender?

☐ Male
☐ Female
☐ Other

3. What is your age?

☐ 20 – 29 ☐ 30 – 39 ☐ 40 – 49
☐ 50 – 59 ☐ 60+

OR ☐ I would rather not say

4. What percentage of your time is spent in the following practice types? Please ensure percentages equal 100%.

☐☐☐ % public
☐☐☐ % private

5. What is your profession?

☐ GP
☐ Breast Surgeon
☐ General Surgeon
☐ Gynaecologist
☐ Gynaecological Oncologist

RISK-REDUCING MEDICATIONS

6. Before this study, had you ever heard of breast cancer risk-reducing medications/chemoprevention? These can be prescribed to women without breast cancer.

- ☐ Yes
- ☐ No → **Please skip to the last page and enter your details for your chance to win an Apple Ipad.**

Definition of risk-reducing medications
Medications that reduce the risk of breast cancer may be considered by women who don't have breast cancer but are at an increased risk. These medicines are also known as chemoprevention. The most common risk-reducing medication is tamoxifen. Other risk-reducing medications include raloxifene, anastrazole and exemestane. These tablets are taken once a day, usually for five years.

7. Have you ever discussed risk-reducing medications with your patients and/or prescribed them to your patients? **Tick all that apply.**

- ☐ I have initiated discussion with patients
- ☐ Patients have initiated discussion with me
- ☐ I have written first prescription
- ☐ I have written ongoing prescriptions
- ☐ I have never discussed or prescribed risk-reducing medications with patients

8. How confident are you in providing advice/information to patients about risk-reducing medications?

- ☐ Very confident
- ☐ Somewhat confident
- ☐ Not too confident → **please answer Question 8a**
- ☐ Not at all confident → **please answer Question 8a**
- ☐ Unsure

8a. If you answered 'Not too confident' or 'Not at all confident' at Q8, why are you not confident providing this advice/information to patients?

9. Thinking about discussing or prescribing risk-reducing medications with your patients, how much of a barrier are each of the following?

	Strong barrier	Somewhat a barrier	Not at all a barrier	Not applicable
1. I have insufficient knowledge of risk-reducing medications	☐	☐	☐	☐
2. It is difficult to measure whether the medication is working	☐	☐	☐	☐
3. I find it hard to access tools/resources to help me estimate patients' breast cancer risk	☐	☐	☐	☐
4. I find it hard to access good information/resources for my patients e.g. patient information sheets	☐	☐	☐	☐
5. There is no evidence that they reduce mortality	☐	☐	☐	☐

	Strong barrier	Somewhat a barrier	Not at all a barrier	Not applicable
6. I have difficulty identifying patients suitable for risk-reducing medication	☐	☐	☐	☐
7. I have inadequate training and confidence in breast cancer risk assessment	☐	☐	☐	☐
8. I have difficulty explaining to patients the pros and cons of risk-reducing medications	☐	☐	☐	☐
9. I am not confident in providing advice/information to patients about risk-reducing medications	☐	☐	☐	☐

	Strong barrier	Somewhat a barrier	Not at all a barrier	Not applicable
10. It is not my role to discuss risk-reducing medications	☐	☐	☐	☐
11. There are no incentives/rewards for discussing risk-reducing medications with patients	☐	☐	☐	☐
12. Lack of time during consultations	☐	☐	☐	☐
13. There are no procedures (e.g. a checklist that facilitates discussion) that encourage me to discuss risk-reducing medications	☐	☐	☐	☐

– continued on page 4 –

	Strong barrier	Somewhat a barrier	Not at all a barrier	Not applicable
14. Medication side effects	☐	☐	☐	☐
15. I don't believe they decrease the risk of breast cancer	☐	☐	☐	☐
16. I'm concerned I might increase the patient's worry about breast cancer	☐	☐	☐	☐
17. I don't think patients want to discuss taking medications for prevention of breast cancer	☐	☐	☐	☐
18. I feel uncomfortable prescribing a 'cancer drug' to healthy women	☐	☐	☐	☐

	Strong barrier	Somewhat a barrier	Not at all a barrier	Not applicable
19. Patients don't ask me about risk-reducing medications	☐	☐	☐	☐
20. I don't routinely assess breast cancer risk with my patients	☐	☐	☐	☐
21. There are other things I wish to achieve in most consultations that interfere with my ability to discuss risk-reducing medications	☐	☐	☐	☐
22. I forget to discuss risk-reducing medications with patients	☐	☐	☐	☐

9a. Which one of these factors (1 to 22) is the greatest barrier? ☐

9b. Are there any other barriers that discourage you from discussing or prescribing risk-reducing medications with patients? If no, please leave blank.

10. Thinking about discussing or prescribing risk-reducing medications with your patients, how much of a facilitator are each of the following?

	Strong facilitator	Somewhat a facilitator	Not at all a facilitator	Not applicable
1. If the patient is diagnosed with atypical hyperplasia that increases their risk of breast cancer	☐	☐	☐	☐
2. If the patient is diagnosed with lobular carcinoma in situ (LCIS) that increases their risk of breast cancer	☐	☐	☐	☐
3. If a patient has a strong family history of breast cancer	☐	☐	☐	☐
4. The beneficial effects of risk-reducing medications e.g. better blood lipid profile and improvements in bone density with tamoxifen	☐	☐	☐	☐
5. If I had better tools to help me identify patients who were suitable	☐	☐	☐	☐
6. Knowing some risk-reducing medications are PBS funded	☐	☐	☐	☐
7. Sometimes it is easier to discuss risk-reducing medications than bilateral mastectomy	☐	☐	☐	☐
8. Support from my peers	☐	☐	☐	☐
9. Support from specialists	☐	☐	☐	☐
10. Clear guidelines/recommendations e.g. RACGP and Cancer Australia guidelines	☐	☐	☐	☐
11. If it were endorsed as part of my professional role by the relevant college or other peak body	☐	☐	☐	☐
12. If my medical software prompted me to discuss risk-reducing medications	☐	☐	☐	☐
13. If I knew my colleagues discuss it with their patients	☐	☐	☐	☐
14. I expect positive outcomes for women who take risk-reducing medications	☐	☐	☐	☐

10a. Which one of these factors (1 – 14) is the greatest facilitator? ☐

10b. Are there any other facilitators that encourage you to discuss risk-reducing medications with patients? If no, please leave blank.

11. What do you think should be the role of each clinician type below with regard to discussing and prescribing risk-reducing medications. **Tick all that apply.**

Clinician type	Initiate discussion of risk-reducing medications	Write first prescription	Write ongoing prescriptions
11a. GP role:	☐	☐	☐
11b. Breast/General Surgeon role:	☐	☐	☐
11c. Familial Cancer Clinic/Genetic Specialist role:	☐	☐	☐

12. In which of these circumstances do you think it is appropriate to discuss risk-reducing medications? **Tick all that apply.**

- ☐ In a consultation where breast cancer risk happens to come up.
- ☐ During a consultation specifically planned to focus on breast cancer risk.
- ☐ During a consultation focused on general preventive healthcare.
- ☐ There is no circumstance under which I would discuss risk-reducing medications.

13. Have you heard of iPrevent, a web-based tool to help clinicians and patients collaboratively assess and manage breast cancer risk? (www.petermac.org/iprevent)

☐ Yes ☐ No

Please enter your details on the last page for your chance to win an Apple iPad.

THIS PAGE IS INTENTIONALLY BLANK

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Thank you for completing the survey.

For your chance to win an Apple iPad please provide your email address:

Please return completed survey in the reply paid envelope.

© New Data Solutions **19665**

Appendix 4: Ovarian cancer screening survey kConFab women

UPN: _ _ . _ _ _ . _ _ _ _

OFFICE USE ONLY

Kathleen Cuningham Foundation **kConFab** CONsortium for research into FAmilial Breast cancer

CLINICAL FOLLOW-UP PROJECT

Translating Evidence into Practice

Optimising and Facilitating Prevention and Screening in Women with a Strong Family History of Breast Cancer

1. Would you like to participate in this research survey?

Yes ○

2. Please enter your 9 digit unique identifier (UPN) provided to you in the letter:

		.				.				

3. Please enter your date of birth

		/			/				

4. Have you ever been diagnosed with breast or any other cancer, not including skin cancers, in the last 6 years?

Yes ○ Go to Q4a

No ○ Skip to Q5

4a. What type of cancer were you diagnosed with?

_____

_____

4b. The date I was diagnosed with cancer was:

	/	
Month		Year

If you don't know, please leave blank.

5. Have you had both breasts removed?

Yes ○ → If **YES**, the date I had my breasts removed was:

	/	
Month		Year

If you don't know, please leave blank.

No ○

If you answered YES to question 4 unfortunately your response has made you ineligible for the remainder of the survey. Thank you for your interest and time. We would appreciate it if you could please return your questionnaire in the supplied, reply-paid envelope.

If you answered YES to question 5 please skip ahead to question 7.

6. I think my risk of getting breast cancer sometime in my life is: (select one)

○	**Low**	Lower than most other women
○	**Average**	About the same as most other women
○	**Moderately increased**	About 2 or 3 times that of most other women
○	**High**	More than 3 times that of most other women
○	**Don't know**	

The next set of questions are about ovarian cancer screening:

7. Have you had both your ovaries removed?

Yes ○ → If **YES**, the date I had my ovaries removed was: [ ] / [ ] Month Year **If you don't know, please leave blank**

No ○

→ If you answered **YES** to question 7 (you have had both ovaries removed), please continue to **END OF SURVEY**.

8. I think my risk of getting ovarian cancer at some time in my life is: (select one)

○	**Low**	Lower than most other women
○	**Average**	About the same as most other women
○	**Moderately increased**	About 2 or 3 times that of most other women
○	**High**	More than 3 times that of most other women
○	**Don't know**	

9. How likely do you think it is that each of these would find ovarian cancer when it was still early and potentially curable?

	Highly unlikely	Unlikely	Neither likely nor unlikely	Likely	Highly likely	Don't know
Ultrasound of the ovaries	○	○	○	○	○	○
CA125 blood test	○	○	○	○	○	○
Ultrasound of the ovaries and CA125 blood test together	○	○	○	○	○	○
Pap smear	○	○	○	○	○	○

10. Below are some statements about ovarian cancer screening. For each item please choose the extent to which you agree or disagree.

Statements	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know
There is no reliable way to detect ovarian cancer at an early and potentially curable stage	○	○	○	○	○	○
Ovarian cancer screening is recommended for women at an increased risk of ovarian cancer	○	○	○	○	○	○
Thinking of the doctor I most trust, I am confident that my doctor will advise me about the best way to manage my ovarian cancer risk	○	○	○	○	○	○
The oral contraceptive pill lowers ovarian cancer risk	○	○	○	○	○	○
The most effective way to reduce ovarian cancer risk is by having my ovaries and tubes removed	○	○	○	○	○	○
Screening for ovarian cancer can lead to unnecessary tests and surgery	○	○	○	○	○	○

11. Have you had an ultrasound of the ovaries specifically for ovarian cancer screening in the last 2 years?

Yes	○	Go to 11a
No	○	Skip to Q12

11a. Which doctor organised/wrote a referral for this ultrasound? Select all that apply.

○	GP/Family doctor
○	Gynaecologist
○	Breast surgeon
○	Familial Cancer Clinic or genetic specialist
○	Other (please specify)

11b. About how often do you have an ultrasound of the ovaries?

○	6 monthly
○	12 monthly
○	Every 2 years
○	I don't have regular ultrasounds of the ovaries

11c. These ultrasounds of the ovaries were for? Select all that apply.

○	Routine ovarian cancer screening (to try and pick up cancer early/ I did not have any symptoms)
○	IVF/Infertility treatment
○	Pregnancy – antenatal/postnatal
○	Heavy bleeding/uterine fibroids
○	Because I had symptoms that might be ovarian cancer
○	Other (please specify)

12. Have you had a CA125 blood test specifically for ovarian cancer screening in the last 2 years?

Yes	○	Go to Q12a
No	○	Skip to Q13

12a. Which doctor organised/wrote a referral for this CA125 blood test?

○	GP/Family doctor
○	Gynaecologist
○	Breast surgeon
○	Familial Cancer Clinic or genetic specialist
○	Other (please specify)

12b. About how often do you have a CA125 blood test?

○	6 monthly
○	12 monthly
○	Every 2 years
○	I don't have regular CA125 blood tests

13. If your doctor advised you that there is no test that detects ovarian cancer when it is still early and potentially curable; would you:

Stop having tests such as ultrasound of the ovaries and CA125 blood tests	○	Skip to **END OF SURVEY**
Continue to have tests such as ultrasound of the ovaries and CA125 blood tests	○	Go to Q14

14. Below are some reasons why women decide to continue to have ovarian cancer screening. Thinking about your own decision, please agree or disagree for each.

Statements	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know
Normal test results provides reassurance and peace of mind that I do not have ovarian cancer	○	○	○	○	○	○
There are currently no other screening options available and it is better than doing nothing	○	○	○	○	○	○
I don't trust my health professionals advice	○	○	○	○	○	○
Healthcare professionals change their mind all the time about the best tests/guidelines	○	○	○	○	○	○
The other option is to have my ovaries removed and I don't want that at the moment	○	○	○	○	○	○
I have previously had ovarian cancer symptoms	○	○	○	○	○	○
These tests are easy enough to have	○	○	○	○	○	○
My family/friends encourage me to have these tests	○	○	○	○	○	○
It is affordable	○	○	○	○	○	○
My family/friends ovarian cancer was detected through screening	○	○	○	○	○	○
These tests might improve the chance I will stay healthy for my family	○	○	○	○	○	○
I believe these tests might pick up ovarian cancer early	○	○	○	○	○	○

14a. Are there any other reasons you can think of why women decide to continue having ovarian cancer screening?

_____

_____

END OF SURVEY

Thank you for your time.

Please note:

Breast cancer

Based on the evidence, screening does not reduce the risk of developing breast cancer but it may detect breast cancer when it is still early and potentially curable.

If you would like to find out more about risk-reducing medicines or more about how to manage your breast cancer risk please consult with your doctor.

You may also find the iPrevent website useful: https://www.petermac.org.au/iprevent

iPrevent estimates your personal risk of breast cancer and explains how it can be reduced.

Ovarian cancer

There is no evidence to support the use of any test (including pelvic examination, CA125 blood tests or other blood tests, ultrasound including transvaginal ultrasound, or a combination of tests) for screening any woman who doesn't have relevant symptoms for ovarian cancer

Appendix 5: Ovarian cancer screening survey clinicians

UNIQUE CLINICIAN NUMBER

☐☐☐☐

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Translating Evidence into Practice:

Optimising and Facilitating Prevention and Screening in Women with a Strong Family History of Breast Cancer

1. Do you consent to participating in this research?

☐ Yes

2. What is your gender?

☐ Male
☐ Female
☐ Other

3. What is your age?

☐ 20 – 29 ☐ 30 – 39 ☐ 40 – 49
☐ 50 – 59 ☐ 60+

OR ☐ I would rather not say

4. What percentage of your time is spent in the following practice types? Please ensure percentages equal 100%.

☐☐☐ % public
☐☐☐ % private

5. What is your profession?

☐ GP
☐ Breast Surgeon
☐ General Surgeon
☐ Gynaecologist
☐ Gynaecological Oncologist

OVARIAN CANCER SCREENING

6. Do you think the tests below are useful for detecting ovarian cancer at an early and potentially curable stage in asymptomatic women?

	Yes	No	Unsure
Ovarian ultrasound	☐	☐	☐
CA125 blood test	☐	☐	☐
Ovarian ultrasound and CA125 blood test together	☐	☐	☐

7. Have you ordered an ovarian ultrasound or a CA125 blood test specifically for ovarian cancer screening in asymptomatic women in the last two years? **Tick all that apply.**

	Yes	No
Ovarian ultrasound	☐	☐
CA125 blood test	☐	☐

→ If you selected No for both tests, please skip to Question 9.

8. Below are some reasons why clinicians order ovarian cancer screening tests for asymptomatic women. Thinking about why you order these tests for asymptomatic women, please agree or disagree with each statement below

Reasons	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
1. I order these tests for patients' peace of mind	☐	☐	☐	☐	☐
2. It is hard to discontinue these tests in asymptomatic women who have been having ovarian cancer screening for several years	☐	☐	☐	☐	☐
3. There are currently no other options available for ovarian cancer screening	☐	☐	☐	☐	☐
4. A CA125 blood test is a simple test	☐	☐	☐	☐	☐
5. An ovarian ultrasound is a simple test	☐	☐	☐	☐	☐
6. Sometimes it is too hard to talk women out of it	☐	☐	☐	☐	☐
7. It is better than doing nothing at all	☐	☐	☐	☐	☐
8. Women ask for these tests	☐	☐	☐	☐	☐
9. I am concerned if my patient develops ovarian cancer she may take legal action	☐	☐	☐	☐	☐
10. I am worried I might miss an ovarian cancer diagnosis	☐	☐	☐	☐	☐
11. I have no way of knowing if my approach to ovarian cancer screening is similar to other clinicians	☐	☐	☐	☐	☐

– continued on page 3 –

Reasons	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
12. There are no adverse consequences for me when ordering these tests	☐	☐	☐	☐	☐
13. I am optimistic that these tests will detect ovarian cancer at an early and potentially curable stage	☐	☐	☐	☐	☐
14. I would not want to conflict with the advice provided by another clinician	☐	☐	☐	☐	☐
15. There is a chance these tests will detect cancer early and lead to more successful patient outcomes	☐	☐	☐	☐	☐
16. I am confident talking about ovarian cancer screening with my patients	☐	☐	☐	☐	☐

8a. Which one of these reasons (1 to 16) is the most important when ordering ovarian cancer screening tests for asymptomatic women? ☐

8b. Are there any other reasons you order ovarian cancer screening tests for asymptomatic women? If no, please leave blank.

9. For each statement below choose how much you agree or disagree.

Statements	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
There is no reliable way to detect ovarian cancer at an early and potentially curable stage in asymptomatic women	☐	☐	☐	☐	☐
If an asymptomatic woman requests an ovarian ultrasound or CA125 for ovarian cancer screening I would usually order these	☐	☐	☐	☐	☐
The oral contraceptive pill reduces ovarian cancer risk	☐	☐	☐	☐	☐
The most effective way to reduce ovarian cancer risk is by surgically removing tubes and ovaries	☐	☐	☐	☐	☐
CA125 blood tests and ovarian ultrasound scans can lead to unnecessary tests and surgery in asymptomatic women	☐	☐	☐	☐	☐

Please enter your details on the last page for your chance to win an Apple iPad.

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Thank you for completing the survey.

For your chance to win an Apple iPad please provide your email address:

Please return completed survey in the reply paid envelope.

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Appendix 6: Peter MacCallum Cancer Centre Breast and Ovarian Risk Management Clinic Template

Appendix 6: Peter MacCallum Cancer Centre Breast and Ovarian risk management clinic template

Peter MacCallum Cancer Centre

The Parkville
Familial Cancer Centre
Tel: +61 3 855 95322 Fax: +61 3 855 95329

URN:

NAME:

DOB:

Dear

Your patient ********** was seen for follow up at the Peter MacCallum Cancer Centre Breast/Ovarian Risk Management Clinic on / / . The following examinations/tests were performed:

☐	Clinical breast examination	☐ Normal ☐ Abnormal, requiring further investigation
☐	Mammogram	☐ Normal ☐ Abnormal, requiring further investigation
☐	MRI	☐ Normal ☐ Abnormal, requiring further investigation

Other Comments

NAME's next appointment at the clinic is in

Yours sincerely

Appendix 7: Cancer Prevention Research commentary; Implementation of Risk-reducing Strategies for Breast Cancer is Long Overdue

Article Citation:

Vogel VG. Implementation of Risk-reducing Strategies for Breast Cancer is Long Overdue. Cancer Prev Res (Phila). 2021 Jan;14(1): 1-4. doi: 10.1158/1940-6207. CAPR-20-0556. Epub 2020 Nov 11. PMID: 33177071.

Implementation of Risk-reducing Strategies for Breast Cancer is Long Overdue

Victor G. Vogel

ABSTRACT

Despite strong evidence that it is efficacious, chemoprevention has been underused in eligible women. Reasons offered not to adopt and initiate strategies to reduce the risk of breast cancer include the fear of adverse effects, medication costs, lack of reasonably accurate and feasible methods for assessing an individual's personal risk, and lack of established risk thresholds that maximize benefit and minimize harms. The article by Macdonald and colleagues remind us that the problem of lack of uptake of risk-reducing medications for breast cancer remains a worldwide clinical challenge despite endorsements from national and international organizations that recommend the use of risk-reducing medications for breast cancer with level I evidence. Several strategies are suggested to improve uptake and utilization of safe and effective chemoprevention medications with high therapeutic indices.

See related article by Macdonald et al., p. 131

Multiple studies have shown that several hormonally targeted agents reduce tumor incidence in women who are at increased risk for breast cancer. In addition, we have several strategies to identify women at increased risk: quantitative risk models (1, 2), increased mammographic density, circulating estrogen levels, and the presence of high-risk benign breast disease, such as atypical hyperplasia and lobular carcinoma *in situ* (3). Some investigators have suggested that absolute risk data should be used in place of models to describe breast cancer risk in this population (4). Guidelines for high-risk women could be updated, for example, to include women with atypical hyperplasia, and MRI screening could be considered an option for them, to be performed in addition to mammography.

The selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene, and the aromatase inhibitor, anastrozole, have been studied prospectively in multiple randomized controlled trials that examined benefits, life-threatening side effects, and quality-of-life outcomes. Estimates of the population benefit of using SERMs for breast cancer risk reduction have been published (5–7), and we have estimates of the cost per year of life saved. Yet, despite the fact that the number of women needed to treat to prevent a case of breast cancer is acceptable with both SERMs and aromatase inhibitors, no drug has been able to tip the clinical utility scale to broad usage within the high-risk population for breast cancer risk reduction.

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Cancer Prev Res 2021;14:1–4

doi: 10.1158/1940-6207.CAPR-20-0556

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Despite strong evidence that it is efficacious, chemoprevention has been underused in eligible women (8). Reasons offered not to adopt and initiate strategies to reduce the risk of breast cancer include the fear of adverse effects, medication costs, lack of reasonably accurate and feasible methods for assessing an individual's personal risk, and lack of established risk thresholds that maximize benefit and minimize harms.

The article by Macdonald and colleagues remind us that the problem of lack of uptake of risk-reducing medications for breast cancer remains a worldwide clinical challenge despite endorsements from national and international organizations that recommend the use of risk-reducing medications for breast cancer with level I evidence. Tamoxifen became government-subsidized for primary breast cancer prevention in Australia in 2016, while national guidelines in Australia have recommended that physicians consider tamoxifen for women with a lifetime risk of breast cancer at least 1.5 times the population risk (≥16%) since 2010.

The NCI estimated almost a decade ago that 2.4 million women with specific age and risk characteristics would benefit from using tamoxifen for reducing risk of breast cancer (9). Nevertheless, some observers have said that when a healthy woman takes an oral medication every day, it serves as a reminder of future risk, and for some women, pill taking may indicate a state of unwellness (10). Many have criticized the published breast cancer risk reduction trials for not showing a mortality reduction, often not recognizing that none of the trials was designed to show such a reduction, and often minimizing the enormous value of avoiding the morbidity associated with a diagnosis of breast cancer. Women fear breast cancer, but it appears that they fear death and not simply morbidity. If they valued avoiding morbidity from breast cancer, the uptake of risk-reducing agents would be greater. It is also possible that women perceive that the use of SERMs or aromatase inhibitors to reduce risk simply trades the morbidity of breast cancer with side effects from drug therapy. These

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unfounded concerns overlook the data from the STAR trial comparing tamoxifen and raloxifene, where there were no significant differences between the two treatment groups in patient-reported outcomes for physical health, mental health, and depression (11–13). The tamoxifen group reported better sexual functioning.

This Australian study is not the first to identify underuse of these medications. A 2002–2004 survey of 350 primary care physicians in the United States, who were members of the American Medical Association, found that only 27% had prescribed tamoxifen for breast cancer risk reduction in the previous year (14). An important predictor of a physician providing a tamoxifen prescription for chemoprevention was the perception that the drug's benefit in preventing breast cancer outweighed the drug's risks: physicians who were unsure of this balance were much less likely to recommend or prescribe tamoxifen. Other surveys also showed that a minority of primary care physicians were prescribing tamoxifen or raloxifene for breast cancer prevention (15). A study in California found that the most frequent barriers to counseling reported by clinicians were "not enough time" (40%) and "insufficiently informed about risk reduction options" (19%). Concerns about serious side effects, including endometrial cancer, also were important barriers, and a perceived weak or unfavorable risk–benefit ratio for an individual patient made taking a SERM for chemoprevention unacceptable.

Absolute Benefit of Risk Reduction

Tamoxifen will prevent 20 invasive and 20 noninvasive breast cancers in each 1,000 women at a 5-year risk of 4% versus causing 2.25 endometrial cancers (in women with an intact uterus at study entry) and 3.3 thromboembolic events in the same group of women over 7 years (16). Similarly, raloxifene will prevent 15 invasive and 16 noninvasive breast cancers over 7 years in 1,000 women at an elevated 5-year risk (4%) versus causing about 2.5 thromboembolic events and no endometrial cancers in the same group over 7 years. For these major effects, tamoxifen causes 40 beneficial versus about five adverse effects (benefit/risk ratio of ∼7:1) and raloxifene causes 31 beneficial versus 2.5 adverse effects (benefit/risk ratio of ∼13:1) over 7 years. These ratios indicate a rather extraordinary net gain for women at a 4% 5-year risk of breast cancer and would improve substantially for women at a 4% or higher risk, who number hundreds of thousands in the United States, Europe, and Australia. SERMs are not the only agents that reduce the risk of breast cancer. The IBIS-II trial demonstrated the efficacy and safety of the aromatase inhibitor, anastrozole, for reduction of breast cancer risk in postmenopausal women who are at high risk of the disease (17).

This Australian study addresses important aspects of global underuse of risk-reducing agents. The study is unique in assessing the views of both women and their clinicians regarding use of risk-reducing medications. The authors point out that clinicians' knowledge and resources are key domains that could be targeted to enhance uptake of chemoprevention medications. The lack of knowledge about the risks and benefits identified in this study occurred despite international recommendations for the use of risk-reducing medications by high-risk women. Importantly, the study found that family practitioners identified barriers and facilitators for use of risk-reducing medications, including a perceived difficulty in selecting suitable patients, the need for better tools to identify suitable patients, and inadequate confidence in their ability to perform quantitative breast cancer risk assessments. Given that half of all women older than 60 years of age can be regarded as being at increased risk on the basis of age alone (5), the Australian authors appropriately recognized that restructuring interventions and providing additional training could change the behavior of both patients and their clinicians.

A significant strength of this study is its use of the Theoretical Domains Framework as the conceptual basis for the questionnaire. Survey questions were developed by experts in sociology, qualitative research, breast surgery, and primary care, and the survey was piloted in face-to-face interviews. These features contribute to the study's generalizability as well.

It is instructive that just half of the women, one-third of the family physicians, and only 3% of breast surgeons were not aware of chemoprevention suggesting that lack of knowledge alone may not explain the widespread underuse of pharmacologic agents to reduce the risk of breast cancer. The study is useful because in that it identified both facilitators and barriers for both patients and clinicians regarding the uptake of risk-reducing medications. Fear of side effects remains an important barrier among both patients and their clinicians. It is reassuring that despite a lack of awareness and confidence in the use of risk-reducing medications, 75% of family practitioners in the Australian study viewed initial discussions of these medications as part of their role. While they did not feel that writing initial prescriptions was part of their role, the study indicated that they agreed with providing ongoing prescription renewals.

Several additional reasons have been put forth to explain why patients may not be willing to adopt a SERM for breast cancer risk reduction (3). Patients (and perhaps their physicians) are confused by the concept of probabilistic risk. Hormone replacement therapy is still widely used by postmenopausal women, but it is contraindicated with concurrent SERM therapy. Patients erroneously perceive the risks of SERM therapy to be greater than its benefits, and they perceive the risks of therapy-related side effects to be greater than their risk of breast cancer. This problem is confounded by the fact that they (and perhaps their physicians) are confused by the concept of probabilistic risk. Finally, they fear endometrial cancer out of proportion to its true tamoxifen-related risk and do not understand that there is no increased risk of uterine malignancy associated with raloxifene.

The authors are correct in stating that they have identified a significant knowledge resource for both women and clinicians in Australia with this study. They conclude correctly that the

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application of a behavioral change model using both an individual- and a system-based approach with education, training, and incentives, along with environmental restructuring, could increase the uptake of risk-reducing medications for breast cancer.

There is a need for better preventive medicine courses in medical schools, and for social-based incentives, such as decreased insurance rates and tax benefits for patients who initiate risk-reducing medications for breast cancer. Information presented at the time of screening mammography can, perhaps, improve uptake of these medications. One possible use of negative incentives would be to target providers with litigation for failure to use risk-reducing medications. The need for the use of social media as an information source also needs to be explored further. The development of a serologic marker to be used as positive feedback incentives for the use of risk-reducing medications would be welcomed, although none is in sight.

Authors' Disclosures

No disclosures were reported.

Received October 21, 2020; revised October 27, 2020; accepted November 3, 2020; published first November 11, 2020.

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Appendix 8: Editorial Medical Journal of Australia. Is it time to abandon clinical breast examination?

Article citation:

Kiely BE, Goodwin A. Is it time to abandon clinical breast examination? Med J Aust. 2021 Nov 15;215(10): 458-459. doi: 10.5694/mja2.51285. Epub 2021 Oct 5. PMID: 34611913.

Check for updates

Is it time to abandon clinical breast examination?

Belinda E Kiely[1,2], Annabel Goodwin[2]

Despite limits to its clinical value, the potential benefits for women should not be overlooked

Women with mutations in breast cancer predisposition genes have a very high risk of developing breast cancer and are offered risk-reducing strategies and intensified surveillance; many are referred to specialist risk management clinics. Because magnetic resonance imaging (MRI) is more sensitive for detecting breast cancer at an early stage than mammography,[1] it is part of most high risk breast cancer screening programs, and in Australia is covered by Medicare for women at high risk under 50 years of age.[2]

In this issue of the *MJA*, Hettipathirana and colleagues question the utility of clinical breast examination in high risk breast cancer screening programs.[3] Their analysis included 414 women with *BRCA1* or *BRCA2* mutations who underwent clinical breast examination every 6 to 12 months at a Melbourne risk management clinic in addition to annual mammography and, from 2009, annual MRI screening (until age 50). Overall, 35 women were diagnosed with breast cancer, including three for whom abnormal clinical breast examinations were recorded. One of these women (aged 51 years) had a concurrent abnormal mammogram, while two women (aged 36 and 65 years) had imaging occult cancers (mammography and ultrasound); none of the three had been screened by MRI. Hettipathirana and her colleagues conclude that clinical breast examination could be safely omitted from a high risk screening program that includes MRI for all women, regardless of age.[3]

Before abandoning clinical breast examination, we should review its role in more detail. Its advantages include the facts that it is non-invasive, does not expose women to radiation or gadolinium, and it is inexpensive. It provides women with reassurance and the opportunity to discuss concerns with their clinicians. Practitioners have the opportunity to educate women about breast awareness and self-examination, and the consultation facilitates discussion of other risk mitigation strategies, such as salpingo-oophorectomy and the management of menopausal symptoms. Disadvantages include the need for clinician time and availability, and for women to travel to a specialist clinic for a face-to-face consultation. As clinical breast examination is difficult to standardise, technique and quality of examination vary markedly between clinicians, particularly outside the controlled environment of a clinical trial. There is also the potential for false positive clinical breast examination findings leading to unnecessary imaging and biopsy.

Clinical breast examination has an important role in assessing women with symptoms and in surveillance after treatment of early breast cancer, when it is recommended to help detect local recurrences and new primary cancers.[4] In the context of breast cancer screening, clinical breast examination is most useful in countries without national screening mammography programs.[5] For example, a cluster randomised trial in India found that a program of two-yearly clinical breast examination combined with cancer awareness education was associated with significant down-staging of breast cancer at diagnosis, and it reduced mortality among women aged 50 years or more by almost 30% compared with women who received a single health education session and no clinical breast examination.[6] In countries with mammography screening programs, however, the evidence does not support regular clinical breast examination as part of a screening program for women at average risk.[7]

In the Dutch MRI Screening Study, 2157 women at high risk (including 599 with predisposition mutations) underwent biennial clinical breast examination as well as annual MRI and mammography screening. Of 97 breast cancers, 78 were detected by imaging, three were detected by clinical breast examination with normal concurrent mammography and MRI, 13 were interval cancers, and six were chance findings at risk-reducing mastectomy.[8] Similar studies of women with *BRCA* mutations undergoing MRI and mammography screening reported that no cancers were detected by clinical breast examination alone.[9,10]

Hettipathirana and colleagues reported that seven of the 35 women diagnosed with cancer presented with self-detected lumps between clinic visits.[3] Given the high rates of incident cancers, particularly in women with *BRCA1* mutations,[3,8] educating those at high risk to be breast-aware and to report any symptoms promptly is probably more useful than performing regular clinical breast examinations.

The evidence favours removing annual clinical breast examination from high risk breast cancer screening programs, provided women remain breast-aware and have access to annual MRI breast screening. Removing clinical breast examination would allow screening consultations to be conducted via telehealth, with less impact on work and other commitments for women. It may be difficult to convince women that clinical breast examination can be safely omitted because, even when educated about its limited

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value, many still want regular breast examinations and are reassured by normal results.[11] Knowing that it provides an opportunity for clinicians to educate and counsel women, and that cancers are detected by clinical breast examination alone (if only very occasionally), is there any harm in retaining clinical breast examination as an optional component of a high risk screening program?

Competing interests: Belinda Kiely has received honoraria from Roche for sitting on an advisory board (2018, 2019), and Annabel Goodwin has received honoraria from AstraZeneca and Pfizer for sitting on advisory boards (2018, 2019).

Provenance: Commissioned; not externally peer reviewed. ■

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