Preventing breast and ovarian cancers in high-risk *BRCA1* and *BRCA2* mutation carriers

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Abstract

Objective: To estimate the prevalence of the use of cancer risk-reducing measures among Australian *BRCA1* and *BRCA2* mutation carriers.

Design, setting and participants: Prospective follow-up of female carriers of *BRCA1* or *BRCA2* mutations who had no personal history of cancer and were enrolled in a multiple-case breast cancer family cohort study (kConFab). Data, including cancer events and uptake of risk-reducing surgery and medication were collected by self-report at cohort entry and 3 yearly thereafter. Surgery was confirmed from pathology and medical records. Women were followed up from enrolment until cancer diagnosis, date of last follow-up, or death. Data were collected from 3 November 1997 to 21 May 2012.

Main outcome measures: Uptake of risk-reducing surgery and/or medication.

Results: Of 175 *BRCA1* and 150 *BRCA2* mutation carriers (median age, 37 years at cohort enrolment), 69 (21%) underwent risk-reducing mastectomy, 125 (38%) underwent risk-reducing bilateral salpingo-oophorectomy and nine (3%) participated in a clinical trial of risk-reducing medication, during 2447 person-years of follow-up (median follow-up, 9 years). Sixty-eight women (21%) reported incident cancers, including 52 breast cancers and nine ovarian cancers (defined in this article as high-grade serous cancers of the ovary, fallopian tube or peritoneum).

Conclusions: There is considerable scope to increase the uptake of cancer risk-reducing measures in Australian *BRCA1* and *BRCA2* mutation carriers. These findings should drive (i) future research into the factors contributing to low uptake in Australia and (ii) changes to policy and practice to help better translate genetic knowledge into reductions in cancer incidence.

Women with a mutation in the cancer predisposition genes *BRCA1* or *BRCA2* have a high lifetime risk of breast cancer and ovarian cancer (defined in this article as high-grade serous cancers of the ovary, fallopian tube or peritoneum). By the age of 70 years, the average risk for *BRCA1* mutation carriers is 65% for breast cancer and 39% for ovarian cancer; these risks are 45% and 11%, respectively, for *BRCA2* mutation carriers.[1] Mutation carriers are at increased risk of breast cancer even in their 30s.[1] By contrast, the risk of ovarian cancer does not increase above that of the general population until around the age of 40 years for *BRCA1* mutation carriers, and about 50 years for *BRCA2* mutation carriers.[1] These cancer risks can be greatly reduced with risk-reducing surgery and medication (Box 1).

Multiple non-randomised studies have shown that risk-reducing mastectomy (RRM) and risk-reducing bilateral salpingo-oophorectomy (RRBSO) are associated with a reduction in risk of over 90% for breast and ovarian cancer, respectively.[3] Furthermore, RRBSO in premenopausal women is associated with up to a 50% reduction in risk of breast cancer.[3] Randomised trials have clearly shown that selective oestrogen receptor modulators (SERMs), such as tamoxifen and raloxifene, given for 5 years, reduce the risk of breast cancer by 38%.[4] While the data for *BRCA1* and *BRCA2* mutation carriers from randomised trials are limited, a recent large non-randomised study showed a similar association between tamoxifen use and reduced breast cancer risk for mutation carriers.[5] Use of the oral contraceptive pill is associated with about a 50% reduction in the risk of ovarian cancer for mutation carriers,[6] although its association with breast cancer risk is unclear. Tubal ligation is also associated with about a 40% reduction in the risk of ovarian cancer for mutation carriers.[7] Breast cancer screening is recommended for mutation carriers.[2] Although screening does not reduce the risk of developing breast cancer, early diagnosis and treatment may improve the chance of cure. By contrast, screening for ovarian cancer is not recommended as it does not detect cancers at an early stage nor reduce mortality.[8]

Several studies have prospectively looked at the uptake of risk-reducing interventions by carriers of the *BRCA1* or *BRCA2* mutation and found wide variation.[9] The only Australian data, published some years ago, showed a low uptake of risk-reducing surgery.[10] Since then, evidence for the efficacy of risk-reducing interventions for mutation carriers has strengthened considerably, so contemporary examination of the uptake of risk-reducing surgery by women with mutations is warranted. In this study, we aimed to estimate the prevalence of risk-reducing surgery and medication in Australian carriers of *BRCA1* and *BRCA2* mutations. We hypothesised that a minority of mutation carriers would have undergone risk-reducing surgery or taken SERMs.

1 Risk management strategies for breast and ovarian* cancers in *BRCA1* and *BRCA2* mutation carriers

Strategy	Relative risk reduction	
	Breast cancer	Ovarian cancer
Risk-reducing mastectomy	> 90%	—
Risk-reducing bilateral salpingo-oophorectomy	Up to 50% (if premenopausal)	> 90%
Risk-reducing medication	38%† (tamoxifen/raloxifene)	About 50%‡ (oral contraceptive pill)
Screening	0 (mammography/MRI)	0 (ultrasound/Ca125)§
Tubal ligation	—	About 40%

* High-grade serous cancers of the ovary, fallopian tube or peritoneum. † Estimate from meta-analysis of multiple randomised controlled trials in high-risk women; limited data suggest a similar benefit in mutation carriers. ‡ The effects of the oral contraceptive pill on breast cancer risk are uncertain. § Ineffective and not recommended.[2] ◆

Methods

Participants were female members of families in which there were multiple cases of breast cancer who were enrolled in the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab). kConFab is a resource of stored biospecimens, epidemiological and clinical data.[11]

Families were recruited into kConFab after an initial member attended a consultation in one of 16 family cancer clinics in Australia and New Zealand. Eligibility criteria included a strong family history of breast cancer and/or ovarian cancer, or being a documented carrier of a *BRCA1* or *BRCA2* mutation.[12]

Blood was drawn for *BRCA1* and *BRCA2* mutation analysis at enrolment into kConFab. When genetic test results became available for a family, all enrolled family members who consented to receive such information were notified that genetic information was available and given the option of attending for genetic counselling and clinical genetic testing (for the family mutation identified under the research protocol), and to then receive their result. All participants provided written informed consent, and the kConFab cohort study has Human Research Ethics Committee approval at all recruiting sites.

Women who were eligible for our analysis had no personal history of cancer (apart from non-melanoma skin cancer) at the time of recruitment into kConFab, carried a pathogenic mutation in *BRCA1* or *BRCA2* and reported that they had tested positive for that mutation when completing at least one 3-yearly follow-up questionnaire.

Demographic information, including age, ethnicity, country of birth, education level, marital status, parity, and family history, were collected at recruitment into kConFab by means of an interviewer-administered questionnaire. Follow-up data were systematically collected by means of a uniform self-reported questionnaire every 3 years after cohort entry;[13] data collected included awareness of the result of the mutation test, date the result was disclosed, uptake of risk-reducing surgery including RRM and RRBSO, use of SERMs, any screening undertaken, hysterectomy, tubal ligation (reason not recorded) and cancer outcomes. Surgical and pathology reports were obtained to verify any reported risk-reducing surgery or new cancer. Data were collected between 3 November 1997 and 21 May 2012.

Statistical analysis

Women's uptake of risk-reducing surgery and/or SERMs was assessed from the time they were enrolled into kConFab until the date of any cancer diagnosis, death or last follow-up. Exact binomial confidence intervals were calculated for proportions, and the Fisher exact test was used to compare them between groups. All statistical analyses were conducted using STATA, version 12.0 (StataCorp).

Results

Of 7112 women enrolled in kConFab at the time of our analysis, 4554 had no personal history of invasive cancer at cohort entry and 1317 of these were from families with a *BRCA1* or *BRCA2* mutation. All of these women had mutation testing; 870 did not carry the family mutation while 447 women were found to have pathogenic mutations and 325 of these women reported being aware of their genetic results. They comprised 175 with a *BRCA1* mutation and 150 with a *BRCA2* mutation. There were 2447 person-years of follow-up with a median of 9 years per woman.

Characteristics of the 325 study participants are summarised in Box 2, and uptake of risk-reducing interventions by these participants is summarised in Box 3. The median time between disclosure of their genetic test results and subsequent risk-reducing interventions was 1 year (range, 0–15 years).

RRM was undertaken by 69 women (21%) at a median age of 40 years (range, 26–67 years), including seven who had RRM before entry into the kConFab cohort. There was no signif-

2 Characteristics of our sample of 325 women who were aware that they carried a *BRCA1* or *BRCA2* mutation

Characteristic	Number	Median age (range)
Mutation		
BRCA1	175 (54%)	
BRCA2	150 (46%)	
Age at cohort entry (years)		37 (18–78)
< 20	4 (1%)	
20–30	84 (26%)	
31–40	109 (34%)	
41–50	68 (21%)	
51–60	39 (12%)	
61–70	16 (5%)	
> 70	5 (2%)	
Age at:		
Disclosure of genetic results (years)		39 (18–78)
Last follow-up (years)		46 (22–86)

3 Uptake of risk-reducing interventions among 325 women who were aware that they carried a *BRCA1* or *BRCA2* mutation

		Age at intervention (years)	
Risk-reducing intervention	Number	Median	Range
RRM*	69 (21%)	40	26–67
RRBSO†	125 (38%)	44	30–77
By age 40‡	16/62		
BRCA1	12/35		
BRCA2	4/27		
By age 50§	29/44		
BRCA1	17/27		
BRCA2	12/17		
Both RRM and RRBSO	38 (12%)	—	—
Risk-reducing medication or placebo (on trial)	9 (3%)	36	35–56
Risk-reducing medication (off trial)	1 (< 1%)	—	—
Tubal ligation¶	71 (22%)	32	20–54

RRBSO = risk-reducing bilateral salpingo-oophorectomy. RRM = risk-reducing mastectomy.
* Seven before cohort entry. † Eight before cohort entry. ‡ Restricted to 62 women who were followed to at least the age of 40 years and knew their genetic result before the age of 40 years. § Restricted to 44 women who were followed to at least the age of 50 years and knew their genetic result before the age of 50 years. ¶ 60 before cohort entry. ◆

icant difference in uptake of, or median age at, RRM between carriers of *BRCA1* and *BRCA2*.

RRBSO was undertaken by 125 women (38%), including eight who had RRBSO before entry into the kConFab cohort. Their median age at the time of RRBSO was 44 years (range, 30–77 years). Separate analyses were performed, first restricted to those who knew their genetic test results before the age of 40 years and were followed up to at least the age of 40 years, and second, applying these same restrictions based on the age of 50 years (Box 3). Of the 62 women included in the first analysis, 16 underwent RRBSO by the age of 40 years, and 10 after the age of 40 years. Of the 44 women in the second analysis, 29 had RRBSO by the age of 50 years, and a further two had RRBSO when they were older than 50 years. There were no statistically significant differences in age of uptake of RRBSO between *BRCA1* and *BRCA2* carriers, although the power to address this was low.

Thirty-eight women (12%) underwent both RRM and RRBSO. Nine women (3%) reported participation in a clinical trial of risk-reducing medication at a median age of 36 years (range, 35–56 years) and one reported taking risk-reducing tamoxifen outside the setting of a clinical trial.

Tubal ligation was reported by 71 women (22%), at a median age of 32 years (range, 20–54 years), including 60 who had tubal ligation before cohort entry. Reasons for tubal ligation were not recorded, so it is uncertain how many of these were for contraception. Of these, 29 subsequently underwent RRBSO, including three who were found to have occult "ovarian" cancers at the time of their RRBSO.

Of the 325 women, 68 (21%) reported incident cancers. These included 52 breast cancers, nine ovarian cancers and three melanomas. A further four women reported bowel cancer, gastric cancer, pancreatic cancer and carcinoma with an unknown primary site, respectively. The median age of these women at cancer diagnosis was 45 years (range, 26–80 years). Six of the 52 women with breast cancer developed it after having had premenopausal RRBSO.

Discussion

We examined uptake of risk-reducing strategies in a large contemporary sample of Australian women who carry a mutation in *BRCA1* or *BRCA2*. Uptake of SERMs was minimal, and only a relatively small proportion (21%) had undergone RRM. Overall, 38% of women had undergone RRBSO which, even accounting for the relatively young median age of our sample, was a lower proportion than expected given that there is no effective screening for ovarian cancers.[8]

This was a multicentre study with several strengths, including a relatively large sample size, long follow-up, prospective and systematic data collection and verification of surgical and pathology reports. Possible limitations include the potential for ascertainment bias and the self-reported nature of some data.

RRM is the most effective strategy for reducing breast cancer risk. It decreases worry about breast cancer for most women[14] without adversely impacting overall quality of life. Potential disadvantages include risks of the surgery and alterations in body image.[14] One study of 593 women who underwent RRM with reconstruction found 52% had unanticipated surgery after their original operation, most often for implant related problems, but also for postoperative complications, including bleeding, infection or haematoma, or aesthetic considerations.[15] An uptake of 21% is consistent with the uptake of 11%–50% reported in other countries.[9] The median age at which women had RRM in our study was 40 years. However, later uptake is associated with a higher risk of developing a breast cancer and a lower likelihood of benefit.[16] Importantly, of the 79% who did not undergo RRM, most underwent breast screening (data not shown).

Wide variation in uptake of RRBSO by carriers has been reported internationally, ranging from 29% to 75%.[9] These studies had heterogeneous samples that included mutation carriers and women with a family history of either breast or ovarian cancer who were untested, and are thus difficult to compare directly. Uptake of RRBSO varies with age,[17] and the age distribution within the study sample influences interpretation. In our study, where the median age at last follow-up was 46 years, 38% of all women had undergone RRBSO, but 66% of those aged 50 years or older at last observation, who knew their genetic results at the time, had undergone RRBSO by the age of 50 years. Most experts strongly recommend RRBSO by the age of 50 years at the latest, to minimise the risk of ovarian cancer, but international guidelines recommend RRBSO as soon as childbearing is complete[18] to maximise breast cancer risk reduction, particularly for *BRCA1* mutation carriers whose ovarian cancer risk is elevated above the general population risk by age 40. Thus 66% uptake of RRBSO by age 50 years could be considered low.

Greater uptake of RRBSO is associated with lower educational level, parity, being married, having a family history of ovarian cancer, perceiving a greater cancer risk and cancer-related anxiety or fear.[19] Fear of the adverse effects of premature menopause may explain the reluctance to undergo RRBSO. Menopausal symptoms are common after premenopausal RRBSO, and there is an increased risk of sexual dysfunction,[20] osteoporosis and cardiovascular disease. Short-term (< 5 years) hormone replacement therapy is often used after premenopausal RRBSO to maintain bone density and ameliorate menopausal symptoms. This does not appear to increase breast cancer risk.[21]

Very few women in our study used SERMS for breast cancer prevention. During the study period, there were only limited data for the efficacy of SERMS for mutation carriers specifically,[22] although there has been level 1 evidence for women at high risk in general for many years. New data suggest that SERMS are likely efficacious for mutation carriers,[5] so uptake by carriers may increase in the future. Concern about potential side effects is a barrier to the use of preventive SERMs,[23] but SERMS are usually well tolerated, and the risk of serious side effects is often overestimated.

Approaches to breast cancer prevention could perhaps be informed by those for cardiovascular disease prevention. Many Australian general

practitioners use an online tool that assesses cardiovascular disease risk and puts the risks and benefits of various prevention strategies into perspective.[24] A similar tool for breast cancer risk might promote greater uptake of SERMs.[25] SERMs are not currently listed on the Pharmaceutical Benefits Scheme for breast cancer prevention, and this is also a barrier to prescribing them for this purpose.[23]

Optimal management of risk for a woman at high risk of breast or ovarian cancer tends to be dynamic over time because of changes in evidence for interventions, and because a woman's age and childbearing status change. Australian family cancer clinics are generally focused on assessing cancer risk, genetic testing and disclosing genetic results. Risk management options are discussed at the time of disclosure, but few family cancer clinics undertake regular ongoing multidisciplinary specialist review. Thus many mutation carriers in our study may have had limited opportunities to further discuss the choices they made initially after learning their mutation status. This could explain the relatively low uptake of some risk-reducing strategies.

Most research has focused on predictors of uptake of prevention strategies, but few qualitative studies have explored the attitudes of women who choose not to opt for risk-reducing surgery or medication. Understanding the views of these women might inform strategies to improve the acceptance of appropriate interventions.

Managing cancer risk in mutation carriers is complex. More widespread use of existing decision-support systems[16] might help both women and clinicians better understand risk management options and the best timing or sequence of these for individual women.

Over the past 20 years, major advances have been made in terms of identifying women with *BRCA1* and *BRCA2* mutations who are at high risk of breast and ovarian cancer, and investigating interventions to reduce risk. There will need to be greater uptake of these interventions to optimise the benefits of genetic testing, and reduce the incidence of potentially preventable cancers in women with *BRCA1* and *BRCA2* mutations.

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