Psychosocial factors and uptake of risk-reducing salpingo-oophorectomy in women at high risk for ovarian cancer

Bettina Meiser PhD¹

Melanie A Price PhD²

Phyllis N Butow PhD²

Janan Karatas PhD¹

Judy Wilson PhD²

Louise Heiniger BPsych(Hons)²

Brandi Baylock BA²

Margaret Charles PhD³

Sue-Anne McLachlan MSc^{4,5}

Kelly-Anne Phillips MD^{5,6,7,8}

kConFab Psychosocial and Clinical Follow-Up groups on behalf of the kConFab Investigators*

¹Psychosocial Research Group, Dept of Medical Oncology, Prince of Wales Hospital Randwick and Prince of Wales Clinical School, University of New South Wales, Dickinson 3, Prince of Wales Hospital, Randwick, NSW 2031, Australia.

²Centre for Medical Psychology and Evidence-based Decision-making, School of Psychology, University of Sydney, NSW 2006, Sydney, Australia

³School of Psychology, University of Sydney, NSW 2006, Sydney, Australia

⁴Oncology Department, St Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy VIC 3065, Australia

⁵University of Melbourne, Dept of Medicine, St Vincent's Hospital, Victoria 3010, Australia

⁶Division of Cancer Medicine, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett Street VIC, Australia 8006

⁷University of Melbourne, School of Population Health, Victoria 3010, Australia

⁸Sir Peter MacCallum Department of Oncology, University of Melbourne, Level 5, 161 Barry Street, Parkville 3010 VIC, Australia

*The kConFab Psychosocial group includes the following in addition to the authors listed above: Department of Medical Oncology, Prince of Wales Hospital, Randwick, Australia (B Bennett); Northern Sydney and Central Coast Area Health Service, Sydney, Australia (C Tennant). The kConFab Clinical Follow-Up group includes the following in addition to authors listed above: Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, School of Population Health, The University of Melbourne, Victoria, Australia (JL Hopper, RL Milne); Division of Cancer Medicine, Peter MacCallum Cancer Centre, Victoria, Australia (P Weideman, L Stanhope,); Department of Medical Oncology, Prince of Wales Hospital, Randwick, Australia (ML Friedlander); Familial Cancer Centre, Department of Medicine, University of Utah, Salt Lake City, Utah (D Goldgar).

Correspondence: Bettina Meiser, Psychosocial Research School, Dickinson 3, Prince of Wales Hospital, Randwick, NSW 2031, Australia. e-mail: b.meiser@unsw.edu.au, phone: 61-2-9382-2628, fax: 61-2-9382-3372.

Abstract

Objective: Bilateral risk-reducing salpingo-oophorectomy (RRSO) has been shown to significantly reduce the risk of ovarian cancer. This study assessed factors predicting uptake of RRSO.

Methods/materials: Women participating in a large multiple-case breast cancer family cohort study who were at increased risk for ovarian and fallopian tube cancer (i.e. *BRCA1* or *BRCA2* mutation carrier or family history including at least one first- or second-degree relative with ovarian or fallopian tube cancer), with no personal history of cancer and with at least one ovary *in situ* at cohort enrolment, were eligible for this study. Women who knew they did not carry the *BRCA1* or *BRCA2* mutation segregating in their family (true negatives) were excluded. Sociodemographic, biological and psychosocial factors, including cancer-specific anxiety, perceived ovarian cancer risk, optimism and social support, were assessed using self-administered questionnaires and interviews at cohort enrolment. RRSO uptake was self-reported every three years during systematic follow-up.

Results: Of 2,859 women, 571 were eligible. Mean age was 43.3 years; 62 women (10.9%) had RRSO a median of two years after cohort entry. Factors predicting RRSO were: being parous (OR 3.3, $p=0.015$); knowing one's mutation positive status (OR 2.9, $p<0.001$) and having a mother and/or sister who died from ovarian cancer (OR 2.5, $p=0.013$). Psychological variables measured at cohort entry were not associated with RRSO.

Discussion: These results suggest that women at high risk for ovarian cancer make decisions about RRSO based on risk and individual socio-demographic characteristics, rather than in response to psychological factors such as anxiety.

Keywords Risk-reducing oophorectomy, prophylactic oophorectomy, ovarian cancer, hereditary breast/ovarian cancer, BRCA1, BRCA2

Abbreviations

RRSO	Risk-reducing salpingo-oophorectomy
HBOC	Hereditary breast/ovarian cancer
kConFab	K athleen Cuninghame Foundation C onsortium for Research into F amilial B reast Cancer
BOADICEA	Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
IES	Impact of Event Scale
LOT	Life Orientation Test
NHMRC	National Health and Medical Research Council

Introduction

Hereditary breast/ovarian cancer (HBOC) syndrome describes the occurrence of breast cancer and ovarian and related gynecologic cancers in multiple family members across several generations. In about 20-30% of families this is due to a germline mutation in the *BRCA1* or *BRCA2* gene. The lifetime risks for ovarian and related gynecologic cancers range from 40% to 60% for carriers of *BRCA1* mutations and 10% to 20% for carriers of *BRCA2* mutations [1]. Bilateral risk-reducing salpingo-oophorectomy (RRSO) has been shown to significantly reduce the risk of ovarian and related gynecologic cancers (hazard ratio of 0.21, 95% CI=0.12 to 0.39) [2], and to approximately halve breast cancer risk if undertaken in pre-menopausal women. Due to the lack of efficacy of screening [3] and the high mortality associated with ovarian and related gynecologic cancers, RRSO is currently considered the optimal risk management strategy for women at high risk [2].

It is now recognized that fallopian tube and primary peritoneal carcinomas are histologically and clinically identical to invasive serous epithelial ovarian cancer and have a common embryological origin, with most now considered to be derived from the fimbria of the fallopian tubes [4]. However for the sake of brevity, this group of cancers will be referred to as ‘ovarian cancer’ hereafter, although arguably the term ‘ovarian cancer’ is misleading and the best terminology is being debated at present.

A growing body of data has become available on the patient and family history characteristics that predict uptake of RRSO. These include being older, e.g. [5, 6], number of children e.g. [6], having a family history of ovarian cancer, e.g. [6, 7], or a personal history of breast cancer, e.g. [8], and being a carrier of a *BRCA1* or *BRCA2* mutation, e.g. [7, 9]. However, almost no empirical evidence is available on the

psychological determinants of the decision to undertake RRSO. Cognitive and affective factors, as well as personal values, are likely to be as important as, if not more important than, the individual woman's actual ovarian cancer risk, as reflected by factors such as age, strength of family history, and carrier status. For example, dispositional optimism may be considered a dimension potentially underlying decisions about RRSO; according to the framework developed by Scheier and Carver [10], optimism is thought to have important behavioral consequences, which derive from a generalized expectancy that good things will happen.

This study fills a gap in the existing literature by assessing the psychological factors associated with uptake of RRSO in a cohort of women at increased risk for ovarian cancer. In accordance with the framework developed by Scheier and Carver [10], we hypothesize that women who are more optimistic, will be less inclined to opt for RRSO. We also hypothesize that women with more social support will be more likely to take up RRSO, consistent with literature showing the strong documented role of social support in promoting positive psychological adjustment [11] and potentially women's ability to implement their decisions about risk management [11]. Furthermore, corresponding to the related literature that explores determinants of uptake of risk-reducing surgery in women at increased risk for breast/ovarian cancer, it is hypothesized that uptake of RRSO will be associated with perceived risk for ovarian cancer [12] and/or breast/ovarian-cancer related anxiety [13] and that these associations may be modified by age, given that recommendations for RRSO are age-specific [3].

Materials and Methods

The Sample

This study was approved by all the required Institutional Review Boards. The sample for this study was drawn from women participating in two prospective sub-studies (the Clinical Follow-up study and the Psychosocial study [14]) of a large genetic, epidemiological, medical and clinical data resource of individuals from multiple-case breast cancer families across Australia and New Zealand (the Kathleen Cuninghame Foundation Consortium for Research into Familial Breast Cancer - kConFab). kConFab is a cohort of multiple-case breast cancer families from Australia and New Zealand [15]. Families are recruited after an initial family member attends a consultation in one of 16 family cancer clinics. Eligibility criteria for families are complex, but include a strong family history of breast cancer and/or ovarian cancer, or a documented *BRCA1* or *BRCA2* mutation [15].

Blood is drawn for potential mutation analysis at the time of enrolment (although only key individuals in each family are actually tested) and an epidemiology and family history questionnaire is completed. Unless the individual has attended a familial cancer clinic, genetic counseling does not take place prior to any research-based genetic testing. When a *BRCA1* or *BRCA2* mutation is found in a family member, all enrolled family members who had previously indicated they would like to receive such information are notified by letter that relevant genetic information has become available and that they now have the option of attending a familial cancer clinic for genetic counseling and clinical genetic testing for the family mutation.

Clinical follow-up data and psychosocial data are collected in parallel using three-yearly self-report questionnaires and a semi-structured interview [14]. All participants provided informed consent at cohort enrolment. Cancer events, risk management practices, epidemiological and lifestyle risk factors, cancer risk perception, psychological variables, personality characteristics, levels of social support and life-event stress are updated every three years.

To be eligible for the current analysis, women had to be ‘unaffected’ with cancer at the time of cohort enrolment (i.e. no personal history of cancer, except non-melanoma skin cancer or cervical intraepithelial neoplasia CIN I-III), have at least one ovary *in situ* at the time of cohort enrolment, be at increased risk for ovarian cancer (i.e. carry a *BRCA1* or *BRCA2* mutation and/or have at least one first- or second-degree relative with ovarian cancer). Women who were found to be ‘true negatives’ (i.e. proven non-carriers of the *BRCA1* or *BRCA2* mutation segregating in their family) and knew their mutation status were excluded from the analyses, as were women who developed ovarian cancer after cohort enrolment. Women who developed breast and cancers other than ovarian cancer after cohort enrolment were included in the analysis.

Measures

Predictor variables

All predictor variables were assessed at cohort entry.

Demographic variables: Data on age, educational level, marital status and parity were collected at interview.

Family history variables: The following family history data were included in the analysis: data on total number of first- and second-degree relatives diagnosed with ovarian cancer, and whether the woman's mother or (at least one of) her sister/s died from ovarian cancer.

Genetic testing results: Actual *BRCA1* and *BRCA2* mutation status was based on kConFab records rather than self-report. Participants' knowledge of their mutation status was determined during the psychosocial interview. Data on whether a woman had attended a familial cancer clinic were collected as part of the Clinical Follow-Up study.

Perceived lifetime risk of developing ovarian cancer: Perceived lifetime risk of developing ovarian cancer was assessed by asking participants to indicate their perceived risk on a numerical differential scale ranging from 0 ('No chance') to 100 ('Definitely').

Actual lifetime risk of developing ovarian cancer: Actual lifetime risk of developing ovarian cancer was calculated using the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), which can be used to estimate the risks of developing ovarian cancer by age 70 [16].

Cancer-specific anxiety: This was assessed using the seven-item Intrusive Thoughts subscale of the Impact of Event Scale (IES) [17]. Intrusion is defined as 'the involuntary entry into awareness of ideas, memories and emotions.' Specifically, participants were asked about the frequency and severity of intrusive thoughts about being at risk of developing breast/ovarian cancer in the past week, ranging from 'Not at all' to 'Often'. Scores range from 0-35, with higher scores indicating more intrusive thoughts.

Life Orientation Test (LOT): The LOT was included to assess dispositional optimism. It is a widely used questionnaire with well-documented psychometric properties [10]. Scores range from 0 to 32, with higher scores indicating more optimism.

Social support: This was assessed by the Duke-UNC Functional Social Support Questionnaire [11]. This 8-item scale is a validated measure of the degree of satisfaction with available support. Scores range from 8 to 40, with higher scores indicating more social support.

Outcome variable

Uptake of risk-reducing salpingo-oophorectomy (RRSO): Data on uptake of RRSO during the follow-up period was taken from the most recent three-yearly Clinical Follow-Up study questionnaire, which was administered at least three years and, in some cases, up to nine years after baseline assessment, depending on time passed since cohort entry.

Statistical analysis

Data were initially explored for normality of distribution. Bivariate analyses were used to assess the associations between predictor variables and uptake of RRSO. None of the continuous variables were normally distributed, and thus Mann Whitney U tests were used in the bivariate analysis of these variables. Categorical variables were assessed using Pearson chi-square analyses. For multivariate analyses, all variables with $p < 0.25$ in bivariate analyses were entered into a logistic regression and then removed progressively using a backward elimination modeling strategy [18],

until only those variables with $p < 0.05$ remained, while adjusting for age as a potential confounding variable. The Hosmer-Lemeshow goodness of fit test was performed and confirmed the appropriateness of tests.

Analyses were also conducted to ascertain whether breast/ovarian cancer-specific anxiety and/or perceived ovarian cancer risk were associated with uptake of RRSO depending on age group (<40 years, 40-49, versus 50+). The corresponding interaction terms were entered (psychological variable by age group), one by one, into the final model. However, none of the interaction terms were significant, and they were, therefore, omitted from the final model. Furthermore, potential interactions between mutation status and a range of demographic, family history and psychological variables (age, parity, total number of first- and second-degree relatives with ovarian cancer, perceived ovarian cancer risk, and cancer-specific anxiety) were assessed but found not to be significant.

Our sample size of 571 women provided 80% power at a 0.05 level of significance to detect a difference of 10% in perceived ovarian cancer lifetime risk between women who had an RRSO (N=62) and those who did not (N=509) did not, based on SD=29.5 and 25.7 respectively, range 0 to 100). This difference corresponds to an effect size difference of 0.4, that is a medium effect size [19]. This difference is based on the smallest effect that would have clear public health significance and provides a sensitive indicator of clinically meaningful differences [20].

Results

Of the entire sample of 2,859 unaffected women included in the kConFab Psychosocial and Clinical Follow-Up study, 805 (28.2%) women were at increased risk for ovarian cancer according to the eligibility criteria for inclusion in the analysis stated above. Of these 805 women, 195 women (23.9%) at increased risk for ovarian cancer had undergone RRSO, 133 (16.3%) had undergone RRSO prior to cohort entry and were therefore not eligible for inclusion in this analysis, and 62 women (7.6%) after cohort entry.

The final sample for this prospective analysis consisted of 571 women, who met all the eligibility criteria for this current analysis. See Figure 1 for a description of how the final sample size was established. Table 1 describes the characteristics of the sample at baseline. The mean age of the sample was 43.3 years (SD 12.8). Seventy-four percent of women were parous. The number of first- and second-degree relatives diagnosed with ovarian cancer ranged from 0 to 12 (median of 1). One hundred and nineteen women (24.6%) reported having been tested and knowing that they were mutation positive, while 452 (75.4%) reported not having been tested or being ineligible for testing because no family-specific mutation had been identified to enable them to have predictive genetic testing. The mean actual life time risk of developing ovarian cancer according to BOADICEA was 9.1%. Forty-nine percent (49.2%) of women reported having attended a familial cancer clinic.

Of the 571 women included in this prospective analysis, 62 (10.9%) reported having RRSO during the follow-up period, a median of two years (range: one month to eight years) following the completion of baseline psychosocial questionnaires. Amongst women included in the prospective analysis, 23 (15.6%) underwent RRSO

before age 40, compared to 21 (13.7%) between ages 40 and 49 years, and 18 (19.8%) after the age of 49 years; uptake was not statistically different between age groups. The mean age of women who underwent RRSO was 43.8 (SD 9.0) and that of those who did not was 43.2 (SD 13.3).

[Insert Figure 1 about here]

[Insert Table 1 about here]

Tables 2 and 3 show the results of bivariate analyses of the categorical and continuous variables respectively, hypothesized to be potentially associated with RRSO. Women who were married or living as married were significantly more likely to have had RRSO, compared to those who were not married (13.0% versus 6.0%, $\chi^2=5.33$, $p=0.021$). Similarly, those with offspring were significantly more likely to have undergone RRSO, compared to those without offspring (13.1% versus 4.7%, $\chi^2=7.95$, $p=0.005$). Furthermore, women who had been tested and informed of their mutation positive result were more likely to have undergone RRSO compared to those who had not been tested or who had been tested but not been informed of the result (20.2% versus 8.7%, $\chi^2=11.44$, $p<0.001$). Finally, women who had a mother or sister(s) who had died from ovarian cancer were more likely to have opted for RRSO than those who had not (17.2% versus 9.7%, $\chi^2=4.32$, $p=0.038$). None of the psychological variables were associated with uptake of RRSO nor was actual ovarian cancer risk as assessed by BOADICEA.

[Insert Tables 2 and 3 about here]

Table 4 describes the final logistic regression model, which shows that women who had offspring (OR 3.26, 95% CI 1.25, 8.48, $p=0.015$), knew that they were mutation positive (OR 2.87, 95% CI 1.53, 5.39, $p<0.001$), and/or had a mother and/or sister who died from ovarian cancer (OR 2.49, 95% CI 1.21, 5.15, $p=0.013$), were more likely to have had an RRSO, having adjusted for age as a potential confounder ($p=0.68$). Relationship status was no longer significantly associated with RRSO in multivariate analyses.

[Insert Table 4 about here]

Discussion

A growing body of literature has become available on the socio-demographic and family history factors predicting uptake of RRSO [21]. However, surprisingly few studies have incorporated an assessment of women's psychological characteristics as potential determinants of decision-making about RRSO. Findings from this small number of studies are somewhat conflicting [6, 12, 22, 23] in terms of the correlates and/or predictors of intention to have, and actual uptake of RRSO. With the exception of one study, which reports on attitudes to, as opposed to actual uptake of, RRSO in the kConFab cohort [23], all of these previous studies involved women recruited through specialist familial cancer clinics or gynecological clinics. Women attending such clinics are self-selected and may be motivated to attend clinics to discuss risk-reducing surgery by high levels of anxiety or perceived risk [23]. By contrast, our study relates to a more broadly recruited cohort of women at high risk for breast/ovarian cancer, half of whom have never attended a familial cancer clinic.

Thus, the findings reported are more likely to be representative of the psychological responses of the larger population of women at increased risk for ovarian cancer.

Previous research shows that women opting for risk-reducing surgery may be motivated by high levels of anxiety about breast/ovarian cancer [6, 24] and/or high levels of perceived risk [12, 22, 23]. The results reported here do not support this previous research. The results reported here suggest that among women in the kConFab cohort decision-making about RRSO is associated with socio-demographic characteristics and knowledge about carrier status, rather than psychological factors such as high levels of anxiety and perceived risk.

Our data also did not confirm our hypothesis of a positive association between social support and uptake of RRSO; although perhaps surprising, this findings is consistent with a recent study of women's decision-making regarding risk-reducing mastectomy, which highlights that many women felt that the decision was ultimately theirs to make despite the influence of friends, family, and the medical team [25].

Our hypothesis of an association between optimism and uptake of RRSO was also not confirmed. It has been argued that successful adaptation to cancer depends on the ability to sustain and modify illusions that buffer present and future threats [26]. Similarly, unrealistic optimism (also referred to as optimism bias) about perceived risk levels of threatening events can be adaptive [27]. However, it can be argued that optimism bias in the context of hereditary cancer is maladaptive, as it is likely to cause women to be less inclined to take up effective measures with proven ability to lower the risk of cancer developing in the future.

Our findings demonstrate that women with offspring are more likely to opt for RRSO; this result is consistent with other studies, which found that not having children was associated with delaying surgery [9, 28]. The observed association

between having offspring and uptake of RRSO is of course not surprising, given that RRSO results in irreversible infertility, and is therefore unlikely to be attractive to women who have not yet had children or those who are parous but are uncertain about whether to have more children. Furthermore, clinical practice guidelines recommend that RRSO is used for women who have completed childbearing [3]. In contrast to previous studies, e.g. [5], increasing age was not associated with uptake of RRSO once parity had been adjusted for in multivariate regression, suggesting that, amongst pre-menopausal women, childbearing plans rather than concerns about menopausal symptoms or sexual side-effects of RRSO may be more important determinants of decision-making about RRSO.

We also found that proven carriers of a *BRCA1* or *BRCA2* mutation were more likely to undergo RRSO, underscoring similar findings reported elsewhere [7]. This result indicates that women may derive a sense of certainty from having their mutation status confirmed, and that women use such personally relevant information to make decisions about RRSO.

Finally, we found that women who had a mother and/or sister who died from ovarian cancer were more likely to opt for RRSO, compared to those who had not. Thus experience of a mother's and/or sister's illness and ultimate death due to ovarian cancer may arouse strong fears and concerns about a woman's own health and life expectancy, and such concerns in turn are likely to motivate women to opt for RRSO, given its proven effectiveness in reducing the risk of ovarian cancer.

Interestingly, uptake of RRSO was not associated with actual risk of developing ovarian cancer, which may in part reflect the fact that about half the sample had never had their risk formally assessed at a familial cancer clinic. On the other hand, our findings do correspond to previous findings in the area of

psychological aspects of genetic testing which show that psychological factors, rather than objective risk, guide interest in genetic testing and psychological adjustment to test results. For example, amongst individuals at risk of developing hereditary breast cancer or hereditary nonpolyposis colorectal cancer, interest in genetic testing is significantly associated with perceived risk but not objective risk [29], and adjustment to results has been found to depend more on pretest psychological adjustment than the test result itself [29].

The limitations of our study should be noted. Our study did not assess physician recommendation for RRSO, which has been shown to be a key factor in determining cancer screening uptake [28] and is likely to also be important in influencing decisions about RRSO. The relatively low RRSO uptake rate in our prospectively assessed sample (10.9%) needs to be considered in the context of this being a non-clinical cohort; almost 60% of the women have had no direct contact with a familial cancer clinic and have thus not necessarily received genetic counseling or specialist risk management advice. Another shortcoming of our study is that psychological variables were assessed in some cases several years prior to RRSO, and these variables might have been different just prior to RRSO. On the other hand, the long follow-up period also represents a strength of the study, given previous studies that show women often take many years to decide to have RRSO [6, 28]. We also acknowledge that our sample is heterogeneous given both women who knew they were mutation positive were included as well as those who did not know their mutation status. On the other hand, the heterogeneity of the sample also represents a strength, in that it reflects current clinical practice, where mutation testing can be offered to a minority of women only and where most women have to make decisions about their ovarian cancer risk management within a context of uncertainty without

the benefit of having been provided with their mutation testing results to clarify their risk. Finally, it is unknown to what extent our findings on the predictors of uptake of RRSO are generalisable to other countries, given the evidence available on the substantial international differences in both attitudes to, and uptake of, RRSO [30]. Such differences are likely to reflect differences in provider [31] and patient attitudes [32], which are at least in part culturally determined.

These results suggest that women at high risk for ovarian cancer make decisions about RRSO based on risk and individual socio-demographic circumstances, rather than in response to psychological factors such as anxiety.

Acknowledgments This study was funded by National Health and Medical Research Council (NHMRC) Project Grants No. 153824, 301930, 457316, 145684, 288704, and 454508 and by a National Breast Cancer Foundation and Cancer Australia Priority Driven Collaborative Cancer Research Grant (#628333). kConFab is supported by grants from the National Breast Cancer Foundation, the NHMRC, the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia. Bettina Meiser receives a Career Development Award from the NHMRC. Phyllis Butow receives a Principal Research Fellowship from NHMRC. Kelly-Anne Phillips is the John Colebatch Clinical Research Fellow of the Cancer Council Victoria. We are very grateful to the many families who contribute to kConFab. We also wish to thank Lucy Stanhope, Kate Birch, Heather Thorne, Eveline Niedermayr, the kConFab research nurses and staff, and the heads and staff of the Family Cancer Clinics. We also thank Dr Adrian Bickerstaff and John Hopper for using the Breast and Ovarian

Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) to calculate actual ovarian cancer risk.

Conflict of interest

The authors have no conflicts of interest to declare.

Fig. 1 Description of sample selection from complete psychosocial database

Table 1 Sociodemographic and family history characteristics (N=571)^a

<i>Characteristics</i>	<i>N (%)</i>
<i>Age in years</i> Mean 43.3, SD 12.8, range 18 to 74 years	
<30	76 (13.3)
30-39	162 (28.4)
40-49	153 (26.8)
50-59	100 (17.5)
60-69	63 (11.0)
70+	14 (3.0)
<i>Marital status</i> Married/living as married Widowed/single/divorced	404 (73.2) 149 (26.8)
<i>Educational level</i> No university education University graduate	449 (79.6) 115 (20.4)
<i>Country of birth</i> Australia New Zealand UK Other	464 (81.3) 53 (9.3) 27 (4.8) 27 (4.8)
<i>Offspring</i> One or more offspring No offspring	421 (73.9) 149 (26.1)
<i>Total number of FDR and SDR with OvCa</i> 0 1 2 3+	110 (19.3) 367 (64.3) 70 (12.3) 24 (4.3)
<i>Research genetic mutation status</i> BRCA1/2 mutation positive BRCA1/2 mutation negative ^b No mutation identified in family	177 (31.1) 169 (29.6) 224 (39.3)
<i>Knowledge of mutation status</i> Individual tested and informed mutation positive Individual either not tested or no mutation identified in family	119 (24.6) 452 (75.4)
<i>Mother or sister/s has died from OvCa</i> Yes No	87 (15.2) 484 (84.8)

OvCa ovarian cancer, FDR first-degree relatives, SDR second-degree relatives

^a Cell frequencies vary due to missing data for some variables

^b These women are true mutation negatives (according to the research genetic testing result) but have chosen not to have clinical testing, so they are unaware they are mutation negative

Table 2 Bivariate analysis of categorical predictor variables related to uptake of RRSO (N=571)

<i>Predictor variables</i>	<i>Had RRSO</i> (N=62)		<i>Did not have RRSO</i> (N=509)		χ^2	<i>p</i>
	N ^a	%	N ^a	%		
<i>Marital status</i>						
Married/living together	53	13.0	355	87.0	5.33	0.021*
Not married/living together	9	6.0	140	94.0		
<i>Offspring</i>						
Has offspring	55	13.1	366	86.9	7.95	0.005*
Does not have offspring	7	4.7	142	95.3		
<i>Education</i>						
Not a university graduate	51	11.4	398	88.6	0.30	0.58
University graduate	11	9.6	104	90.4		
<i>Knowledge of mutation status</i>						
Individual tested and informed mutation positive	24	20.2	95	79.8	11.44	<0.001*
Individual either not tested or not informed	31	8.7	325	91.3		
<i>Family mortality history</i>						
Mother or sister died from ovarian cancer	15	17.2	72	82.8	4.32	0.038*
Mother or sister did not die from ovarian cancer	47	9.7	437	90.3		

RRSO risk-reducing salpingo-oophorectomy

^a Cell frequencies vary due to missing data for some variables χ^2 Pearson chi-square value

* Entered into regression model

Table 3 Bivariate analysis of continuous predictor variables related to uptake of RRSO (N=571)

<i>Predictor variables</i>	<i>Had RRSO (N=62)</i>		<i>Did not have RRSO (N=509)</i>		<i>z</i>	<i>p</i>
	<i>N</i>	<i>Mean (SD)</i>	<i>N</i>	<i>Mean (SD)</i>		
Age	62	43.8 (9.0)	503	43.2 (13.3)	-0.75	0.45
Total no of FDRs and SDRs with OvCa	62	1.4 (1.7)	509	1.2 (0.99)	-0.05	0.96
Perceived ovarian cancer risk	61	45.5 (29.5)	503	40.9 (25.7)	-1.20	0.23*
Actual ovarian cancer risk	61	11.0 (14.5)	499	8.9 (13.4)	-1.28	0.20*
Cancer-specific anxiety	60	6.3 (8.1)	508	7.1 (8.3)	-0.80	0.43
Optimism	62	20.0 (4.9)	507	19.8 (5.7)	-0.24	0.81
Social support	62	30.9 (7.3)	508	30.1 (7.8)	-0.70	0.48

RRSO risk-reducing salpingo-oophorectomy, FDR first-degree relative, SDR second-degree relative, OvCa ovarian cancer

z Mann Whitney U value

*Entered into regression model

Table 4 Final model of logistic regression predicting uptake of RRSO (N=571)

<i>Variable</i>	<i>OR*</i>	<i>95% CI OR</i>	<i>p</i>
<i>Offspring</i>			
Yes	3.26	1.25, 8.48	0.015
No			
<i>Knowledge of mutation status</i>			
Individual tested and informed mutation positive	2.87	1.53, 5.39	<0.001
Individual not tested or not informed of result			
<i>Family mortality history</i>			
Mother or sister died from ovarian cancer	2.49	1.21, 5.15	0.013
Mother or sister did not die from ovarian cancer			
<i>Age**</i>	0.99	0.97, 1.02	0.68

OR odds ratios

Note: Final model -2 Log likelihood 314.53, $\chi^2 = 20.59$, $p=0.009$

* Odds ratio refers to comparisons with the category listed last

** Age was entered as a continuous variable

References

1. Antoniou, A., et al., *Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies*. American Journal of Human Genetics, 2003. **72**(5): p. 1117-1130.
2. Rebbeck, T., N. Kauff, and S. Domchek, *Meta-analysis of Risk Reduction Estimates Associated With Risk-Reducing Salpingoophorectomy in BRCA1 or BRCA2 Mutation Carriers*. Journal of the National Cancer Institute, 2009. **101**: p. 80 – 87.
3. Cancer Australia, *Recommendations for management of women at high risk for ovarian cancer* September 2011, Cancer Australia: Canberra.
4. Debeau, L., *The cell of origin of ovarian epithelial tumours*. Lancet, 2008. **9**: p. 1191-1197.
5. Antill, Y., et al., *Risk-reducing surgery in women with familial susceptibility for breast and/or ovarian cancer*. European Journal of Cancer, 2006. **42**(5): p. 621-8.
6. Julian-Reynier, C., et al., *Time to prophylactic surgery in BRCA1/2 carriers depends on psychological and other characteristics*. Genetics in Medicine, 2010. **12**(12): p. 801-807.
7. Metcalfe, K., et al., *Family history as a predictor of uptake of cancer preventive procedures by women with a BRCA1 or BRCA2 mutation*. Clinical Genetics, 2008. **73**(5): p. 474-479.
8. Madalinska, J.B., et al., *The Impact of Hormone Replacement Therapy on Menopausal Symptoms in Younger High-Risk Women After Prophylactic*

- Salpingo-Oophorectomy*. Journal of Clinical Oncology, 2006. **24**(22): p. 3576-3582.
9. Evans, D., et al., *Uptake of risk-reducing surgery in unaffected women at high risk of breast and ovarian cancer is risk, age, and time dependent*. Cancer Epidemiology, Biomarkers and Prevention 2009. **18**: p. 2318-24.
 10. Scheier, M.F. and C.S. Carver, *Optimism, coping and health: Assessment and implications of generalized outcome expectancies*. Health Psychology, 1985. **4**(3): p. 219-247.
 11. Broadhead, W., et al., *The Duke-UNC Functional Social Support Questionnaire*. Medical Care, 1988. **26**(7): p. 709-722.
 12. Schwartz, M.D., et al., *Bilateral prophylactic oophorectomy and ovarian cancer screening following BRCA1/BRCA2 mutation testing*. Journal of Clinical Oncology, 2003. **21**(21): p. 4034-4041.
 13. Bebbington Hatcher, M., L. Fallowfield, and R. A'Hern, *The psychological impact of prophylactic mastectomy: Prospective study using questionnaires and semistructured interviews*. British Medical Journal, 2001. **322**(322): p. 76-79.
 14. Phillips, K.-A., et al., *Predictors of participation in clinical and psychosocial follow up of the kConFab breast cancer family study*. Familial Cancer, 2005. **4**(2): p. 105-113.
 15. Mann, G., et al., *Analysis of cancer risk and BRCA1 and BRCA2 mutation prevalence in the kConFab familial breast cancer resource*. Breast Cancer Research, 2006. **8**: p. R12.

16. Antoniou, A., et al., *The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions*. British Journal of Cancer, 2008. **98**: p. 1457-1466.
17. Horowitz, M., N. Wilner, and W. Alvarez, *Impact of Events Scale: A measure of subjective stress*. Psychosomatic Medicine, 1979. **41**: p. 209-218.
18. Hosmer, D. and S. Lemeshow, *Applied logistic regression*. 2nd ed. 2000, Toronto: John Wiley and Sons.
19. Cohen, J., *Statistical power analysis for the behavioural sciences*. 2nd Edition ed. 1988, New York: Academic Press.
20. Frost, M., *Symposium on clinical significance of quality of life measures in cancer patients*. Mayo Proceedings 2002:77, 2002. **77**: p. 488-494.
21. Miller, S., et al., *New strategies in risk-reducing salpingo-oophorectomy: Uptake and experience of women at high risk of ovarian cancer who are considering risk-reducing salpingo-oophorectomy*. Clinical Cancer Research, 2010. **16**(21): p. 5094-106.
22. Meiser, B., et al., *Attitudes to prophylactic oophorectomy and screening utilization in women at increased risk of developing hereditary breast/ovarian cancer*. Gynecologic Oncology, 1999. **75**: p. 122-129.
23. Meiser, B., et al., *Attitudes to prophylactic strategies in Australian women at increased risk for breast cancer*. Journal of Women's Health, 2003. **12**(8): p. 769-778.
24. Meiser, B., et al., *Intention to undergo prophylactic mastectomy in women at increased risk of developing hereditary breast cancer*. Journal of Clinical Oncology, 2000. **18**(11): p. 2250-2257.

25. McQuirter, M., et al., *Decision-Making Process of Women Carrying a BRCA1 or BRCA2 Mutation Who Have Chosen Prophylactic Mastectomy*. Oncology Nursing Forum, 2010. **37**(3): p. 313-320.
26. Taylor, S., *Adjustment to threatening events: A theory of cognitive adaptation*. American Psychologist, 1983. **38**(11): p. 1162-1174.
27. Weinstein, N.D., *Optimistic biases about personal risks*. Science, 1989. **246**: p. 1232-1233.
28. Bradbury, A.R., et al., *Uptake and timing of bilateral prophylactic salpingo-oophorectomy among BRCA1 and BRCA2 mutation carriers*. Genetics in Medicine, 2008. **10**(3): p. 161-166.
29. Meiser, B., *Psychological impact of genetic testing for cancer susceptibility: An update of the literature*. Psycho-Oncology, 2005. **14**: p. 1060-1074.
30. Meiser, B., et al., *International perspectives on genetic counseling and testing for breast cancer risk*. . Breast Disease, 2007. **27**: p. 109-125.
31. Julian-Reynier, C., et al., *Physicians' attitudes towards mammography and prophylactic surgery for hereditary breast/ovarian cancer risk and subsequently published guidelines* European Journal of Human Genetics, 2000. **8**: p. 204-208.
32. Julian-Reynier, C.M., et al., *Women's attitudes toward preventive strategies for hereditary breast or ovarian carcinoma differ from one country to another: differences among English, French, and Canadian women*. Cancer, 2001. **92**(4): p. 959-68.