Long-term outcomes of risk-reducing surgery in unaffected women at increased familial risk of breast and/or ovarian cancer

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ABSTRACT

Purpose: To prospectively investigate long-term psychosocial outcomes for women who opted for risk-reducing mastectomy (RRM) and/or risk-reducing salpingo-oophorectomy (RRSO).

Methods: Unaffected women from high-risk breast cancer families who had completed baseline questionnaires for an existing study and subsequently underwent RRM and/or RRSO, completed measures of perceived breast and ovarian cancer risk, anxiety, depression, cancer-related anxiety, body image, sexual functioning, menopausal symptoms, use of hormone replacement therapy and decision regret three years post-surgery. Outcomes were compared to age- and risk-matched controls.

Results: Participants (N=233) were 17 women who had RRM (39 controls), 38 women who had RRSO (94 controls) and 15 women who had RRM+RRSO (30 controls). Women who underwent RRM and those who underwent RRM+RRSO reported reductions in perceived breast cancer risk and perceived breast and ovarian cancer risk respectively, compared to their respective controls. RRM women reported greater reductions in cancer-related anxiety compared with both controls and RRSO women. RRSO women reported more sexual discomfort than controls and more urogenital menopausal symptoms than controls and RRM only women. No differences in general anxiety, depression or body image were observed. Regret was associated with greater reductions in body image since surgery and more sexual discomfort, although overall regret levels were low.

Conclusions: Women who undergo RRM experience psychological benefits associated with reduced breast cancer risk. Although women who undergo RRSO experience some deterioration in sexual and menopausal symptoms, they do not regret their surgery decision. It is vital that women considering these procedures receive detailed information about potential psychosocial consequences.

INTRODUCTION

The identification of mutations in the *BRCA1* and *BRCA2* genes associated with an increased risk of breast and/or ovarian cancer has provided opportunities to greatly reduce an individual's risk of hereditary breast and/or ovarian cancer (HBOC) through risk-reducing surgery (RRS). In families with multiple cases of breast and/or ovarian cancer, risks to age 70 are 72-95% for breast and 28-56% for ovarian cancer for *BRCA1* mutations [1], and 43-95% and 0-47% for breast and ovarian cancer, respectively, for *BRCA2* mutations [2]. Although screening options exist for both breast and ovarian cancer, many at-risk women consider RRS due to the inability of these options to guarantee early detection and consequent cure. Risk-reducing (bilateral) mastectomy (RRM) can reduce the risk of breast cancer by approximately 90%, while risk-reducing (bilateral) salpingo-oophorectomy (RRSO) reduces the risk of ovarian/fallopian tube (hereafter 'ovarian') cancer by approximately 80% and the risk of breast cancer by up to 50% [3].

While the main advantage of undergoing RRS is the substantial reduction in disease risk, the psychological benefits associated with this risk reduction are often cited by women as equally important [4-6]. Indeed, research shows that RRS typically leads to reductions in perceived risk of developing cancer [7,8] and reductions in cancer-related distress [9,6,10]. Nevertheless, these procedures can also have a negative impact on psychosocial, sexual and physical well-being.

Studies have shown that up to half of women who undergo RRM report a negative impact on their sexual relationship [11,12,10], a quarter to one-third report poorer body image and reduced feelings of femininity [12,10], and women are more likely to report feelings of regret related to their surgery when body image and sexual function are adversely affected by RRM [13]. Despite this, few women who undergo RRM report that they regret their surgery decision [14,15,12].

Women who undergo RRSO have reported suboptimal sexual functioning and more menopausal symptoms, particularly bothersome vaginal symptoms [16], compared to age-matched population controls [7]. These symptoms are worse when Hormone Replacement Therapy (HRT) is not used [17]. However, a study that compared at-risk women who underwent RRSO (n=29) to a control group of women who were also at-risk but opted for screening (n=28) found no difference between the groups in sexual functioning, although there was a trend for more menopausal symptoms (p=.06) in the surgery group [18]. Thus if risk matched controls are utilized, the impact of RRSO on menopausal symptoms appears less. However, these retrospective studies are limited by the inherent risk of recall bias and the inability to control for pre-existing differences in psychosocial functioning between women who had undergone RRS and controls [7].

Prospective evidence for deteriorations in sexual functioning and body image after RRM has been mixed. Early studies found no evidence of a negative sexual impact in 79 women who opted for

RRM up to 18 months post-surgery [19] and only minor deteriorations in body image in 76 women who had RRM up to three years prior [20]. In contrast, Brandberg et al. [21] reported significant reductions in body image and sexual pleasure in 90 unaffected women one year after RRM, and more recent findings suggest these negative impacts continue at least up to two years following RRM [15,22].

The short follow-up time periods in most of these studies raise the possibility that psychosocial outcome data may be influenced by the acute effects of surgery and convalescence, and longer-term prospective data are needed. In addition, few studies have compared women who underwent surgery to controls and these have typically not controlled for potential confounders. In summary, although there is strong evidence that women who undergo RRSO experience an increase in menopausal symptoms [7,23], prospective assessment of the long-term psychosocial and psychosexual impact of RRSO is lacking.

The first aim of the current study was to prospectively examine the long-term outcomes (three years post-surgery), both positive and negative, of RRS in unaffected women at increased risk for HBOC, and compare these with outcomes experienced by controls (rigorously matched on age and objective risk of breast cancer) who did not undergo RRS. The outcomes of interest include: a) perceived risk of breast and ovarian cancer; b) psychological well-being (anxiety, depression, cancer-related anxiety); and c) body image, sexual functioning and menopausal symptoms.

It was hypothesized that women who underwent RRS would experience:

1) lower perceived risk of breast and/or ovarian cancer, lower general anxiety and depression and cancer-related distress;
2) less favorable body image and/or impaired sexual functioning.
3) Further, it was hypothesized that women who underwent RRSO would experience more negative menopausal symptoms than women who did not undergo RRSO at 3 year follow-up, controlling for HRT use.

The second aim of the study was to examine whether poorer body image and sexual functioning would be associated with greater decisional regret three years post-surgery in women who underwent RRS. It was hypothesized that this would be the case.

METHODS

Participants

Participants in the current study were recruited from among women participating in the **K**athleen Cuningham **Con**sortium for Research into **Fa**milial **b**reast cancer (kConFab) Psychosocial Study. kConFab is a registry of Australian and New Zealand families with strong family histories of breast

and/or ovarian cancer (www.kconfab.org). The Psychosocial Study recruited unaffected kConFab women to complete psychosocial questionnaires and a life event stress interview every three years, described in detail elsewhere [24]. Data were collected for this sub-study between April 2005 and December 2010. Thus women who underwent RRS three years earlier (April 2002 to December 2007) were invited to participate. The eligibility criteria for the RRS sub-study were:

a) Surgery groups: women who had undergone RRM, RRSO, or both (RRM+RRSO), three months or more after completing the baseline Psychosocial Study questionnaire assessment. Women were excluded if they had these surgeries for other reasons (e.g. cysts) or if they had a second RRS within the two years prior to the follow-up assessment.

b) Control groups: women who had not undergone RRS before or after completing the baseline Psychosocial Study questionnaire assessment. Women who had undergone mastectomy or oophorectomy for non-prophylactic reasons were excluded. Up to three controls were matched to each surgery participant on i) age (+/-5years), ii) objective breast cancer risk (defined below); and iii) date of completing the baseline Psychosocial Study assessment (+/-6months).

Procedure

Eligible kConFab Psychosocial Study participants were invited to participate in the RRS sub-study, which involved separate consent and an additional set of self-report questionnaires three years after the date of surgery (or matched control date). Non-responders were contacted up to two times by telephone to ascertain their consent. The RRS sub-study was approved by The University of Sydney Human Research Ethics Committee and institutional ethics committees at each recruitment site.

Measures

Socio-demographics: Age, marital (partner) status and education level were collected as part of the kConFab Psychosocial Study.

Objective breast cancer risk: The relative risk of developing breast cancer by age 70, calculated using the Tyrer-Cuzick algorithm [25] at recruitment into kConFab [26], was obtained from kConFab. The estimate includes genetic, family history and other clinical and epidemiological risk factor data [27].

Risk-reducing surgery: As part of the Psychosocial Study questionnaire assessment at each time point women answered two questions about RRS: "Would you consider a bilateral prophylactic mastectomy (an operation to remove both healthy breasts to prevent getting cancer)?" and "Would you consider a bilateral prophylactic oophorectomy (an operation to remove both healthy ovaries to prevent getting cancer)?" Response options were 1) Don't know, 2) No, 3) Yes, and 4) Done/in progress. Women who responded 'Done/in progress' were asked if they would be willing to answer

some questions related to having had RRS approximately three years after their surgery. Risk reducing surgery status was verified as part of the Psychosocial Study life event stress interviews, and/or from kConFab registry data. Women who had RRM were asked to indicate whether they had undergone breast reconstruction.

Hormone Replacement Therapy (HRT): HRT use was documented by self-report questionnaire as part of the three year post-surgery assessment (or matched date for controls). Questions about HRT use were: 1) Have you ever taken hormone replacement therapy (HRT)? Y/N, if yes; then 2) What age were you when you first took HRT? (Please estimate) ___ years old; 3) Are you still taking HRT? Y/N; if no, what age were you when you stopped HRT? (estimate is fine): ___ years old; and 4) Did you take HRT consistently (that is, with no breaks) from the time you started it until the time you stopped (or until now if you are still taking it)? Y/N. Responses were dichotomised into never or past use versus current use.

Psychosocial variables (measured at baseline and at three years):

a) Perceived breast and ovarian cancer risk:

Perceived lifetime risks of developing breast and ovarian cancer were assessed on two numerical differential scales ranging from 0 ('No chance') to 100 ('Definitely') [28];

b) Psychological well-being:

Anxiety and depression were measured using the 14-item Hospital Anxiety and Depression Scale [HADS; 29], producing two separate scores ranging between 0-21. Cronbach's alpha (α) was .82 for anxiety and .78 for depression.

Cancer-related anxiety was assessed by the 7-item Intrusive Thoughts subscale of the Impact of Event Scale [IES; 30], reflecting the frequency and severity of intrusive thoughts about 'being at risk of developing breast cancer/ovarian cancer' in the past week, with scores ranging from 0-35 (α=.91).

c) Body image, sexual functioning and menopausal symptoms (at three-year follow-up only):

Body image: The affective aspect of body image was assessed using the 20-item short form of the Situational Inventory of Body Image Dysphoria [SIBID; 31]. This scale addressed the need for a body image scale that is applicable to women who had undergone RRM or RRO, as well as controls, and is suitable for use in the oncology setting as, unlike many other body image measures, it does not include weight-related body image concerns [32]. Scale scores reflect the mean of the 20 items (range 0-4), with higher scores reflecting poorer body image (α=.97).

Sexual functioning: The nine-item Sexual Activity Questionnaire [SAQ; 33] was used to measure sexual functioning. Higher pleasure scores (range=0-18, α=.84) indicate greater desire,

enjoyment and satisfaction; lower discomfort scores (range=0-6, α=.80) reflect less dryness and pain; and the habit score (range=0-3) compares the current level of sexual activity with usual activity (0=much more, 1=somewhat more, 2=about the same, 3=less than usual).

Menopausal symptoms: The Menopause Rating Scale [MRS; 34] evaluates 11 symptoms on a five-point scale (0=no symptoms, 4=severe) at three time points ('before surgery', 'after surgery' and 'in the past month'). Since we focus on long-term outcomes in the current paper, only comparisons for menopause symptoms 'in the past month' are reported. Total MRS scores range between 0 (asymptomatic) and 44 (highest degree of complaints), with subscales for psychological symptoms (range 0-16), somato-vegetative symptoms (range 0-16) and urogenital symptoms (range 0-12, α=.85 for the total [current] scale).

Changes in body image and decision regret (surgery participants only, three years post-surgery)

Decision Regret Scale [DRS; 35]: This five-item scale was used to assess the level of regret associated with the RRS decision. Potential scores range between 0-100 (α=.88), with higher scores reflecting greater regret.

Body Image Scale [BIS; 36]: This 10-item scale was used to assess changes in body image since RRS. The BIS consists of 10 items scored on a 4-point scale (0-3), such that higher scores (range 0-30) represent increasing symptoms/distress (α=.92).

Statistical analysis

Descriptive statistics were used to characterize the sample. T-tests were used to compare RRS and control participants on the matching variables age and relative risk. Means and standard deviations for all outcomes were calculated for each of the groups. To identify potential confounders to be included in the analysis, differences between participants who had RRS and their respective controls in demographic and risk-related variables were analyzed using Chi-square for categorical variables and ANOVA for continuous variables. All subsequent analyses controlled for those variables found to differ between groups: age, objective risk of breast cancer, education and partner status.

Generalized linear models (GLM) were employed to compare women who had had any surgery to controls while accounting for the correlation of responses within a matched cluster. Similarly, contrasts in GLM were constructed to compare each surgery group (RRM, RRSO and RRM+RRSO) to its respective control group, and to compare the surgery groups with each other (RRM vs RRSO; RRM vs RRM+RRSO; RRSO vs RRM+RRSO), while controlling for the correlation of responses within a matched cluster. HRT use (never or past use vs current use) was evaluated in the RRSO and RRM+RRSO groups for the SAQ and MRS outcomes using ANCOVA models. No significant

differences were observed in the SAQ or MRS outcomes according to HRT use (data not reported). Thus HRT was not controlled for in subsequent analyses. Stepwise logistic regression was used to assess whether poorer body image and/or sexual functioning were associated with decision regret in women who underwent surgery, with relative risk, age, partner status and education entered in the first step and scores on the BIS and SAQ subscales entered in the second step. Due to missing data, 53 of the 70 surgery participants were included in this analysis, and as all 53 of these participants were partnered this variable was not included in the regression. Statistical significance was defined as $p<.01$ to account for the multiple pairwise comparisons for each outcome.

RESULTS

Participants

The final sample (N=233) consisted of 17 women who had RRM (and 39 matched controls), 38 women who had RRSO (and 94 matched controls) and 15 women who had RRM+RRSO (and 30 controls). Of 76 eligible unaffected women who had had RRS and were contacted, 70 (92%) participated. Three women declined participation, two were not contactable and one was missed due to an administrative error. Of 233 eligible unaffected women who had NOT had RRS and were invited to participate, 163 (70%) participated. Sixty-three women declined participation and seven were not contactable. A flow diagram of study recruitment is presented in Figure 1. There were no differences between controls who participated versus those who refused on age, education or relative risk of breast cancer (data not shown).

At the time of the follow-up questionnaire, 60 women (26% of the sample) were aged under 40 and 112 (48%) were aged 40 to 49, with the remainder aged 50 or over. The median relative risk of developing breast cancer was 3.7 (SD=10.3, range 0.7[1]-65.7). Sixty percent of the women reported post-secondary education, and 85% were partnered. Demographic characteristics are reported separately for RRS participants and controls in Table 1. Of the 32 women who had RRM, 31 reported that they underwent reconstruction and the response to this item was missing for the other participant.

Main Results

Table 2 shows the means and standard deviations for all outcomes measured at baseline and follow up, including change scores, for the surgery groups and their respective controls, with statistical

[1] Relative risk of one RRS participant was calculated as 0.83 upon entry to kConFab. This participant is not eligible for predictive testing as no deleterious mutation has been identified in the family. Lower age at first child and older age at menarche are associated with relative risks of less than 1 [25].

differences highlighted using * to indicate p<.05 and # to indicate p<.01. Table 3 shows results of statistical comparisons between different pairs of surgery groups.

Women who underwent RRS of any type

With regard to the control matching variables, women who had surgery did not differ from controls in age, but had significantly higher relative risks compared with controls, 10.94 vs 6.88, respectively (t[231]=-2.80, p=.006). Women who subsequently underwent either type of RRS reported significantly greater reductions in both perceived breast (p<.01) and ovarian cancer risk (p<.01) as well as cancer-related anxiety (p<.01) at the three-year follow up compared to the control group (Table 2). Women who had RRS of any type reported significantly higher levels of sexual discomfort (SAQ, p<.01) and more urogenital symptoms (p<.01) compared to controls.

Women who underwent RRM

Women who subsequently underwent RRM reported higher perceived risk of breast cancer at baseline than their non-surgery controls (p<.01, Table 2). Perceived breast cancer risk was significantly reduced at the three-year follow up for women in the RRM group, compared to controls (p<.01, Table 2). At the three-year follow-up, perceived risk of breast cancer was significantly lower in the RRM group, compared with the RRSO group (p<.01, Table 3).

Women who underwent RRM reported higher levels of cancer-related anxiety at baseline (p<.01) and greater reductions in cancer-related anxiety (p<.01) at the three-year follow up, compared to controls (Table 2). Women who underwent RRM also reported a greater reduction in cancer-related anxiety at the three-year follow up, compared to the RRSO group (p<.01, Table 3).

Women in the RRM group reported fewer total menopausal symptoms compared to the RRSO (p<.01) and the RRM+RRSO groups (p<.01) at the three-year follow up. Specifically, both psychological menopausal symptoms (p<.01) and urogenital menopausal symptoms (p<.01) were lower in the RRM compared to the RRSO group (Table 3).

Women who underwent RRSO

Women who subsequently underwent RRSO reported higher perceived ovarian cancer risk at baseline compared with women who subsequently underwent RRM (p<.01, Table 3). Perceived ovarian cancer risk was significantly reduced at the three-year follow up for women who had RRSO compared to controls (p<.01, Table 2). Women who had RRSO also reported larger reductions in perceived ovarian cancer risk from baseline to three-year follow up compared with women who only had RRM (p<.01, Table 3). By contrast, reductions in perceived risk of breast cancer at the three-year

follow-up were significantly lower in the RRSO group, compared with the RRM group (p<.01) and the RRM+RRSO group (p<.01, Table 3).

Women in the RRSO group reported more sexual discomfort (p<.01) and urogenital symptoms (p<.01), compared to controls (p<.01, Table 2). Surprisingly, women who had RRSO did not report significantly more menopausal symptoms overall at the three-year follow up compared with their controls, although these differences approached significance (p=.018, Table 2).

Women who underwent RRM+RRSO

Both perceived breast (p<.01) and ovarian cancer risk (p<.01) were significantly reduced at the three-year follow up for women who had RRM+RRSO, compared to controls (Table 2). At the three-year follow-up, perceived risk of breast cancer was significantly lower in the RRM+RRSO group, compared with the RRSO group (Table 3). Women who had RRM+RRSO reported larger reductions in perceived ovarian cancer risk from baseline to three-year follow up compared with women who only had RRM (p<.01, Table 3).

Women who had RRM+RRSO reported more urogenital symptoms compared to their controls (p<.01, Table 2). Perhaps surprisingly, women who had RRM+RRSO did not report significantly more menopausal symptoms overall at the three-year follow up compared with their controls, although these differences approached significance (p=.011, Table 2).

General anxiety, depression and body image

No differences in baseline or changes scores were observed in levels of anxiety, depression or body image (SIBID) for: 1) any of the surgery groups compared to controls, and 2) between surgery groups. No differences in body image (BIS) scores were observed between surgery groups.

RRS decision regret

As the scores were highly skewed towards no regret, with almost two-thirds (62.9%) of the participants reporting no regret about their RRS decision, scores were dichotomized as no regret (score=0) vs any regret (score=1-100). No differences were observed in decisional regret between the surgery groups (X^2[2, *N*=70]=4.82, p=.09). However, women who reported greater reductions in body image (BIS) following surgery (OR=1.41, 95%CI=1.11-1.78, p<.01) were more likely to report feeling at least some regret. The Hosmer and Lemeshow Test supported the goodness of fit of the model (X^2 [8, *N*=53]=5.64, p=.69), which explained approximately 19% of the variation in decisional regret (Nagelkerke R^2 =.19).

Discussion

This study prospectively compared psychological well-being and risk perceptions of women at increased risk of HBOC who underwent RRS to a group of control participants, matched for age and objective risk. Differences between the groups in sexual functioning, body image and menopausal symptoms were also investigated. The results of this study suggest there are few negative long-term impacts of RRS.

Consistent with past research [7,10,6], women who opted for RRS experienced psychological benefits, namely reductions in perceived risk and cancer-related anxiety, compared with controls. However, cancer-related anxiety was higher in the RRS group at baseline, supporting previous findings that elevated cancer-related anxiety predicts uptake of RRS [6]. At follow up, levels of cancer-related anxiety reported by women who had undergone RRS were not significantly different to controls. This suggests that while RRS may effectively reduce cancer-related anxiety, it only reduces it to a level that is comparable with other at-risk women who have not undergone RRS. In addition, based on the current findings, RRS may only reduce cancer-related, but not general, anxiety. The baseline assessment time point in the current study (at a time of usual functioning, versus before screening when anxiety is usually elevated) may explain why the reductions in general anxiety following RRS that have been reported in previous studies [19,21] were not replicated. Further prospective studies using baseline data that reflects usual functioning are needed to clarify this.

In this study, RRS appeared to have minimal long-term impacts on body image and sexual functioning. Although RRSO has not previously been shown to negatively impact body image [37], past research has concluded that women who undergo RRM report worse body image after surgery [21,10,22]. We considered whether the high rate of reconstruction in our sample may explain these differences; however, 95-100% of participants in these previous studies had also undergone reconstruction.

The discrepancy between those studies and findings of the current study may be explained by the longer follow-up and comparison to a matched sample in the present research. In other words, women's body image may take a few years to adjust following surgery; eventually their actual levels of body image may be similar to those of other high-risk women.

However, there may be limitations associated with the measure used in the current research which resulted in insufficient sensitivity to the concerns of the women in this study. The Body Image Scale assessed changes in body image since surgery retrospectively and it is possible that the retrospective assessment biased women's responses. In addition, the Body Image Scale measured

general body image and a measure of breast-related body image may have yielded different results for the women who underwent RRM.

In a study of long-term outcomes of RRM, den Heijer et al. [38] investigated body image in 36 women prior to risk-reducing mastectomy (T0) then again at six months (T1) and six to nine years (T2) post-surgery. All participants underwent breast reconstruction. These authors found a significant deterioration from T0 to T1 in both general and breast-related body image. They observed a non-significant improvement in general body image scores from T1 to T2, concluding that, overall, general body image was worse in the longer term. However, based on the data presented in the paper, we calculate that the overall (T0 to T2) deterioration in general body image was not significant ($t[35]=-1.39$, $p=.17$). This is consistent with our finding in the present research that women do not experience significant long-term reductions in body image following RRM.

Interestingly, den Heijer et al. [38] reported that, following the initial deterioration in breast-related body image, there was a significant improvement between T1 and T2. However we calculate that the overall deterioration in breast-related body image from T0 to T2 is, in fact, significant ($t[35]=-2.57$, $p=.01$). Thus when a breast-specific measure of body image is used, significant deteriorations in body image can be seen in women who undergo RRM. The use of non-specific measures of body image in the current study can be considered a limitation and future studies should aim to measure breast- and ovary-specific components of body image.

Sexual discomfort and urogenital menopausal symptoms were worse in women who had RRS compared to controls, but subgroup analyses revealed these differences were only present for women who had undergone RRSO or both surgeries, which would be expected to cause menopausal symptoms. These findings are consistent with previous studies [7,16]. However, it is reassuring that the discomfort and urogenital symptoms reported in the present research did not appear to interfere substantially with psychosexual (e.g. pleasure, habit) aspects of sexual functioning. Although there is evidence that sexual dysfunction is associated with satisfaction with RRSO [16], further research is needed to explore specific predictors of sexual functioning following RRS. It is surprising that menopausal symptoms were not affected by HRT use in the current study, but the small subgroups in this comparison may have compromised statistical power in this analysis.

Consistent with past research [13], women who experienced a greater deterioration in body image following surgery were more likely to report some level of regret. Despite the difficulties in sexual function and increased menopausal symptoms following RRSO, the level of regret was low in this sample, and this supports the hypothesis that reductions in perceived risk and cancer-related anxiety outweigh any regret related to adverse outcomes [15]. Nevertheless, the findings of this

study support the need to foster realistic expectations about potential sexual dysfunction and menopausal symptoms in women considering RRSO.

A number of limitations should be considered when interpreting the findings of this study. First, the relatively small sample size resulted in small subgroups and thus limited statistical power to detect differences between the groups. Many women had undergone RRS pre-baseline and were thus not eligible for inclusion in this prospective study. Further, there were few women with high relative risks who had not undergone RRS available for matching to surgery participants and thus matching on relative risk was imperfect. Second, while perceived risk and psychological variables were assessed prospectively, body image, sexual functioning and menopausal symptoms were assessed retrospectively. However the inclusion of matched controls for comparison on these (and other) variables is a significant strength of this study, as is the consistent three-year follow-up period. This is the first long-term, matched-control, prospective study of outcomes of RRS. The findings demonstrate that although menopausal symptoms and sexual discomfort persist three years post-surgery for women who underwent RRSO, the overall psychosocial impact is minimal.

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Appendix

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References

1. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE, Haites N et al. (1994) Risks of cancer in BRCA1-mutation carriers. Lancet 343 (8899):692-695. doi:10.1016/s0140-6736(94)91578-4
2. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P et al. (1998) Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. American Journal of Human Genetics 62 (3):676-689
3. Rebbeck TR, Kauff ND, Domchek SM (2009) Meta-analysis of Risk Reduction Estimates Associated With Risk-Reducing Salpingo-oophorectomy in BRCA1 or BRCA2 Mutation Carriers. J Natl Cancer Inst 101 (2):80-87
4. Hallowell N (2000) A qualitative study of the information needs of high-risk women undergoing prophylactic oophorectomy. Psycho-Oncology 9 (6):486-495
5. Hurley KE, Miller SM, Costalas JW, Gillespie D, Daly MB (2001) Anxiety/uncertainty reduction as a motivation for interest in prophylactic oophorectomy in women with a family history of ovarian cancer. Journal of Womens Health & Gender-Based Medicine 10 (2):189-199
6. Vodermaier A, Bauerfeind I, Nestle-Kramling C (2006) Prophylactic surgery in women at high risk for breast and ovarian cancer. An overview of the international literature on attitudes, uptake and quality of life. Geburtshilfe Und Frauenheilkunde 66 (11):1035-1049. doi:10.1055/s-2006-924303
7. Elit L, Esplen MJ, Butler K, Narod S (2001) Quality of life and psychosexual adjustment after prophylactic oophorectomy for a family history of ovarian cancer. Familial Cancer 1 (3-4):149
8. Metcalfe KA, Narod SA (2002) Breast cancer risk perception among women who have undergone prophylactic bilateral mastectomy. J Natl Cancer Inst 94 (20):1564-1569
9. Bresser PJC, Seynaeve C, Van Gool AR, Niermeijer MF, Duivenvoorden HJ, van Dooren S et al. (2007) The course of distress in women at increased risk of breast and ovarian cancer due to an (identified) genetic susceptibility who opt for prophylactic mastectomy and/or salpingo-oophorectomy. European Journal of Cancer 43 (1):95-103. doi:10.1016/j.ejca.2006.09.009
10. Frost MH, Schaid DJ, Sellers TA, Slezak JM, Arnold PG, Woods JE et al. (2000) Long-term satisfaction and psychological and social function following bilateral prophylactic mastectomy. JAMA: Journal of the American Medical Association 284 (3):319-324
11. Bresser PJC, Seynaeve C, Van Gool AR, Brekelmans CT, Meijers-Heijboer H, van Geel AN et al. (2006) Satisfaction with prophylactic mastectomy and breast reconstruction in genetically predisposed women. Plast Reconstr Surg 117 (6):1675-1682. doi:10.1097/01.prs.0000217383.99038.f5

12. Isern AE, Tengrup I, Loman N, Olsson H, Ringberg A (2008) Aesthetic outcome, patient satisfaction, and health-related quality of life in women at high risk undergoing prophylactic mastectomy and immediate breast reconstruction. Journal of Plastic Reconstructive and Aesthetic Surgery 61 (10):1177-1187. doi:10.1016/j.bjps.2007.08.006
13. Payne DK, Biggs C, Tran KN, Borgen PI, Massie MJ (2000) Women's regrets after bilateral prophylactic mastectomy. Annals of Surgical Oncology 7 (2):150-154
14. Fuller S, Anderson RC (2006) Adjustment issues related to bilateral prophylactic mastectomy in women at elevated risk of developing breast cancer. Plast Surg Nurs 26 (2):60-65
15. Gahm J, Wickman M, Brandberg Y (2010) Bilateral prophylactic mastectomy in women with inherited risk of breast cancer - Prevalence of pain and discomfort, impact on sexuality, quality of life and feelings of regret two years after surgery. Breast 19 (6):462-469. doi:10.1016/j.breast.2010.05.003
16. Robson M, Hensley M, Barakat R, Brown C, Chi D, Poynor E et al. (2003) Quality of life in women at risk for ovarian cancer who have undergone risk-reducing oophorectomy. Gynecologic Oncology 89 (2):281-287
17. Madalinska JB, van Beurden M, Bleiker EMA, Valdimarsdottir HB, Hollenstein J, Massuger LF et al. (2006) The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. Journal of Clinical Oncology 24 (22):3576-3582. doi:10.1200/jco.2005.05.1896
18. Fry A, Busby-Earle C, Rush R, Cull A (2001) Prophylactic oophorectomy versus screening: Psychosocial outcomes in women at increased risk of ovarian cancer. Psycho-Oncology 10 (3):231-241
19. Bebbington Hatcher M, Fallowfield L, A'Hern R (2001) The psychosocial impact of bilateral prophylactic mastectomy: Prospective study using questionnaires and semistructured interviews. BMJ: British Medical Journal 322 (7278):76
20. Hopwood P, Lee A, Shenton A, Baildam A, Brain A, Lalloo F et al. (2000) Clinical follow-up after bilateral risk reducing ('prophylactic') mastectomy: Mental health and body image outcomes. Psycho-Oncology 9 (6):462-472
21. Brandberg Y, Sandelin K, Erikson S, Jurell G, Liljegren A, Lindblom A et al. (2008) Psychological reactions, quality of life, and body image after bilateral prophylactic mastectomy in women at high risk for breast cancer: A prospective 1-year follow-up study Journal of Clinical Oncology 26 (24):3943-3949
22. Gopie JP, Mureau MAM, Seynaeve C, ter Kuile MM, Menke-Pluymers MBE, Timman R et al. (2013) Body image issues after bilateral prophylactic mastectomy with breast reconstruction in

healthy women at risk for hereditary breast cancer. Familial Cancer 12 (3):479-487. doi:10.1007/s10689-012-9588-5

23. Finch A, Metcalfe KA, Chiang JK, Elit L, McLaughlin J, Springate C et al. (2011) The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. Gynecologic Oncology 121 (1):163-168
24. Phillips KA, Butow PN, Stewart AE, Chang JH, Weideman PC, Price MA et al. (2005) Predictors of participation in clinical and psychosocial follow-up of the kConFab breast cancer family cohort. Familial Cancer 4 (2):105-113. doi:10.1007/s10689-004-6129-x
25. Tyrer J, Duffy SW, Cuzick J (2004) A breast cancer prediction model incorporating familial and personal risk factors. Statistics in Medicine 23 (7):1111-1130. doi:10.1002/sim.1668
26. Mann GJ, Thorne H, Balleine RL, Butow PN, Clarke CL, Edkins E et al. (2006) Analysis of cancer risk and BRCA1 and BRCA2 mutation prevalence in the kConFab familial breast cancer resource. Breast Cancer Research 8 (1). doi:10.1186/bcr1377
27. Price MA, Butow PN, Lo SK, Wilson J (2007) Predictors of cancer worry in unaffected women from high risk breast cancer families: risk perception is not the primary issue. Journal of Genetic Counseling 16 (5):635-644
28. Meiser B, Butow P, Barratt A, Friedlander M, Gattas M, Kirk J et al. (1999) Attitudes toward prophylactic oophorectomy and screening utilization in women at increased risk of developing hereditary breast/ovarian cancer. Gynecologic Oncology 75 (1):122-129
29. Zigmond AS, Snaith RP (1983) The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica 67 (6):361-370
30. Horowitz MJ, Wilner N, Alvarez W (1979) Impact of Event Scale: A measure of subjective stress. Psychosomatic Medicine 41 (3):209-218
31. Cash TF (2002) The situational inventory of body-image dysphoria: Psychometric evidence and development of a short form. International Journal of Eating Disorders 32 (3):362-366. doi:10.1002/eat.10100
32. White CA, Hood C (2012) Body image issues in oncology. In: Cash TF, Smolak L (eds) Body Image: A Handbook of Science, Practice, and Prevention. Guilford Publications, pp 333-341
33. Thirlaway K, Fallowfield L, Cuzick J (1996) The sexual activity questionnaire: A measure of women's sexual functioning. Quality of Life Research 5 (1):81-90. doi:10.1007/bf00435972
34. Schneider H, Heinemann L, Rosemeier H-P, Potthoff P, Behre H (2000) The Menopause Rating Scale (MRS): reliability of menopausal complaints. Climacteric 3:59-64
35. Brehaut JC, O'Connor AM, Wood TJ, Hack TF, Siminoff L, Gordon E et al. (2003) Validation of a Decision Regret Scale. Medical Decision Making 23:281-292

36. Hopwood P, Fletcher I, Lee A, Ghazal SA (2001) A body image scale for use with cancer patients. European Journal of Cancer 37 (2):189-197. doi:10.1016/s0959-8049(00)00353-1

37. Fang CY, Cherry C, Devarajan K, Li T, Malick J, Daly MB (2009) A prospective study of quality of life among women undergoing risk-reducing salpingo-oophorectomy versus gynecologic screening for ovarian cancer. Gynecologic Oncology 112 (3):594-600

38. den Heijer M, Seynaeve C, Timman R, Duivenvoorden HJ, Vanheusden K, Tilanus-Linthorst M et al. (2012) Body image and psychological distress after prophylactic mastectomy and breast reconstruction in genetically predisposed women: A prospective long-term follow-up study. European Journal of Cancer 48 (9):1263-1268. doi:10.1016/j.ejca.2011.10.020

Table 1. *Baseline participant characteristics*

	RRS groups *n* = 70 *n* (%)	Control groups *n* = 163 *n* (%)	Whole sample *n* = 233 *n* (%)
Age (years)			
<40	17 (24.3)	43 (26.4)	60 (25.8)
40-49	35 (50.0)	77 (47.2)	112 (48.1)
50-59	12 (17.1)	32 (19.6)	17 (7.3)
60+	6 (8.6)	11 (6.7)	17 (7.3)
Educational level			
High school or less	28 (40.6)	62 (39.2)	90 (39.6)
Post-secondary education	41 (59.4)	96 (60.8)	137 (60.4)
Partner Status			
No partner	8 (11.6)	27 (16.6)	35 (15.1)
Partnered	61 (88.4)	136 (83.4)	197 (84.9)
Carrier status			
Knows is BRCA1/2 positive	19 (27.1)	13 (8.0)	32 (13.7)
BRCA1/2 negative/Inconclusive/Not tested			
Relative Risk (Breast Cancer)			
< 1.5	5 (7.1)	9 (5.5)	14 (6.0)
1.5-3	20 (28.6)	65 (39.9)	85 (36.5)
3-5	12 (17.1)	32 (19.6)	44 (18.9)
5-10	8 (11.4)	30 (18.4)	38 (16.3)
10+	25 (35.7)	27 (16.6)	52 (22.3)
Type of surgery or group controls were matched to			
RRM	17 (24.3)	39 (23.9)	N/A
RRSO	38 (54.3)	94 (57.7)	N/A
RRM&RRSO	15 (21.4)	30 (18.4)	N/A
Perceived risk			
Breast cancer *M(SD)*	60.4 (25.5)	52.5 (26.6)	54.8 (26.5)
Ovarian cancer *M(SD)*)	40.4 (27.3)	32.5 (22.7)	34.8 (24.4)

Table 2. *Comparisons between surgery groups and their respective controls on perceived risk, anxiety, depression, cancer-related anxiety, body image, sexual functioning and menopausal symptoms*

	RRM (n=17)	Controls (n=39)	RRSO (n=38)	Controls (n=94)	RRM+RRSO (n=15)	Controls (n=30)
	M(SD)	*M(SD)*	*M(SD)*	*M(SD)*	*M(SD)*	*M(SD)*
Perceived risk of breast cancer						
Baseline	71.3 (15.9)	52.6 (24.9)#	56.9 (26.1)	53.8 (27.1)	57.3 (30.3)	48.0 (27.6)
Follow-up	13.5 (13.8)	52.8 (26.3)	52.7 (18.8)	53.3 (27.4)	11.3 (14.6)	52.9 (26.5)
Change scores	-57.5 (20.7)	0.3 (20.3)#	-4.2 (27.5)	-0.5 (23.7)	-46.0 (37.9)	2.1 (21.3)#
Perceived risk of ovarian cancer						
Baseline	32.2 (15.6)	32.6 (26.4)	42.0 (29.3)	31.8 (21.7)	45.3 (31.4)	34.3 (21.3)
Follow-up	26.2 (18.3)	34.6 (23.8)	1.2 (3.2)	32.8 (23.5)	10.7 (22.2)	40.4 (25.3)
Change scores	-5.0 (18.9)	2.1 (20.7)	-40.8 (28.8)	0.9 (22.5)#	-34.7 (29.0)	4.3 (22.8)#
HADS-Anxiety						
Baseline	6.6 (3.4)	6.1 (3.3)	6.3 (4.1)	5.8 (3.8)	6.5 (4.6)	5.9 (3.0)
Follow-up	5.6 (3.0)	5.5 (3.8)	5.9 (3.4)	5.8 (3.4)	5.9 (3.5)	5.5 (3.5)
Change scores	-1.1 (2.6)	-0.6 (2.9)	-0.4 (3.6)	-0.1 (3.3)	-0.5 (3.4)	-0.4 (2.6)
HADS-Depression						
Baseline	3.5 (3.0)	3.2 (3.1)	3.6 (2.9)	3.9 (3.4)	4.1 (3.2)	3.5 (2.6)
Follow-up	2.2 (2.2)	3.1 (2.9)	2.9 (2.8)	3.5 (3.4)	3.3 (2.4)	3.0 (2.4)
Change scores	1.2 (2.4)	-0.2 (2.7)	-0.7 (2.4)	-0.4 (3.4)	-0.8 (2.9)	-0.5 (2.5)
Cancer-related anxiety						
Baseline	13.4 (8.3)	4.5 (5.9)#	6.5 (7.1)	4.7 (6.7)	9.2 (10.1)	7.8 (8.2)
Follow-up	6.2 (6.9)	4.1 (6.8)	4.5 (6.8)	4.6 (7.0)	3.0 (5.1)	5.1 (7.1)
Change scores	-7.2 (9.3)	-0.5 (8.0)#	-1.9 (6.4)	-0.1 (6.0)	-6.0 (7.7)	-2.7 (7.2)
Body image (SIBID)	1.3 (1.1)	1.3 (1.0)	1.5 (1.1)	1.4 (0.9)	1.3 (0.7)	1.3 (0.7)
SAQ Pleasure	13.1 (4.1)	12.1 (4.3)	11.5 (4.8)	12.0 (4.1)	9.3 (5.3)	13.3 (2.4)*
SAQ Discomfort	1.1 (1.5)	1.1 (1.7)	2.4 (2.0)	1.0 (1.4)#	2.5 (2.1)	1.4 (1.6)*
SAQ Habit	0.9 (0.4)	0.7 (0.5)	0.9 (0.5)	0.9 (0.6)	0.8 (0.6)	1.1 (0.5)
MRS Total	4.1 (5.5)	6.4 (6.1)	11.3 (8.3)	8.5 (5.5)*	10.4 (5.5)	7.3 (5.2)*
MRS Psychological	1.9 (2.4)	3.3 (3.0)	3.8 (3.4)	3.9 (2.9)	2.9 (2.5)	3.4 (2.8)
MRS Somato-vegetative	1.5 (1.8)	1.7 (2.1)	4.0 (3.3)	3.1 (2.6)	3.4 (2.6)	2.9 (2.2)
MRS Urogenital	0.9 (1.9)	1.3 (1.7)	3.4 (2.7)	1.5 (1.6)#	3.6 (2.1)	0.9 (1.1)#

*p<.05; #p< .01; SIBID=Situational Inventory of Body Image Dysphoria; SAQ=Sexual Activity Questionnaire; MRS=Menopause Rating Scale

Table 3. *Comparisons between surgery groups on perceived risk, anxiety, depression, cancer-related anxiety, body image, sexual functioning, menopausal symptoms and change in body image after surgery*

	RRM (*n* = 17)	RRSO (*n* = 38)	RRM+RRSO (*n* = 15)	Surgery Comparison *p*-values		
	M(SD)	*M(SD)*	*M(SD)*	RRM vs RRSO	RRM vs RRM+RRSO	RRSO vs RRM+RRSO
Perceived risk of breast cancer						
Baseline	71.3 (15.9)	56.9 (26.1)	57.3 (30.3)	.32	.54	.98
Follow-up	13.5 (13. 8)	52.7 (18.8)	11.3 (14.6)	<.01	.01	<.01
Change scores	-57.5 (20.7)	-4.2 (27.5)	-46.0 (37.9)	<.01	.18	<.01
Perceived risk of ovarian cancer						
Baseline	32.2 (15.6)	42.0 (29.3)	45.3 (31.4)	<.01	.02	.76
Follow-up	26.2 (18.3)	1.2 (3.2)	10.7 (22.2)	<.01	.34	.05
Change scores	-5.0 (18.9)	-40.8 (28.8)	-34.7 (29.0)	<.01	<.01	.43
HADS-Anxiety						
Baseline	6.6 (3.4)	6.3 (4.1)	6.5 (4.6)	.80	.90	.93
Follow-up	5.6 (3.0)	5.9 (3.4)	5.9 (3.5)	.33	.36	.88
Change scores	-1.1 (2.6)	-0.4 (3.6)	-0.5 (3.4)	.46	.54	.98
HADS-Depression						
Baseline	3.5 (3.0)	3.6 (2.9)	4.1 (3.2)	.48	.33	.60
Follow-up	2.2 (2.2)	2.9 (2.8)	3.3 (2.4)	.10	.07	.61
Change scores	-1.2 (2.4)	-0.7 (2.4)	-0.8 (2.9)	.52	.71	.91
Cancer-related anxiety						
Baseline	13.4 (8.3)	6.5 (7.1)	9.2 (10.1)	.01	.28	.39
Follow-up	6.2 (6.9)	4.5 (6.8)	3.0 (5.1)	.97	.47	.36
Change scores	-7.2 (9.3)	-1.9 (6.4)	-6.0 (7.7)	<.01	.43	.07
Body image (SIBID)	1.3 (1.1)	1.5 (1.1)	1.3 (0.7)	.30	.56	.58
SAQ Pleasure	13.1 (4.1)	11.5 (4.8)	9.3 (5.3)	.12	.01	.12
SAQ Discomfort	1.1 (1.5)	2.4 (2.0)	2.5 (2.1)	.05	.12	.99
SAQ Habit	0.9 (0.4)	0.9 (0.5)	0.8 (0.6)	.87	.35	.38
MRS Total	4.1 (5.5)	11.3 (8.3)	10.4 (5.5)	<.01	<.01	.56
MRS Psychological	1.9 (2.4)	3.8 (3.4)	2.9 (2.5)	<.01	.10	.26
MRS Somato-vegetative	1.5 (1.8)	4.0 (3.3)	3.4 (2.6)	.02	.16	.39
MRS Urogenital	0.9 (1.9)	3.4 (2.7)	3.6 (2.1)	<.01	<.01	.82
Body image (BIS)	8.2 (8.0)	4.9 (5.9)	8.2 (7.9)	.66	.11	.09

SIBID=Situational Inventory of Body Image Dysphoria; SAQ=Sexual Activity Questionnaire; MRS=Menopause Rating Scale; BIS=Body Image Scale

Figure 1. Surgery and control participation flow diagram