The consequences of risk reducing salpingo-oophorectomy: the case for a coordinated approach to long-term follow up post surgical menopause.

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Abstract

Women with germline mutations in *BRCA1* and *BRCA2* genes have significantly increased lifetime risks of breast and ovarian cancer. To manage both the ovarian and breast cancer risks the current recommendation is undergo a risk reducing salpingo-oophorectomy (RRSO) prior to natural menopause. To date, studies have focussed on quality of life and sexual dysfunction in women who undergo RRSO, but few have reported on the wider physical consequences.

We performed a questionnaire study in women with *BRCA 1* or *2* gene mutations known to the Peter MacCallum Familial Cancer Centre. We gathered information about ovarian surgery, ongoing follow-up, management of risk factors including osteoporosis, and current severity of menopausal symptoms.

Two hundred and nineteen women were surveyed. One hundred and forty-three of 157 responding participants (91%) reported having RRSO. Sixty one were pre-menopausal at RRSO. Post surgical follow-up rates were generally low, and a minority of women reported recent bone density imaging or pharmaceutical prevention or treatment of osteoporosis. Menopausal symptoms appeared generally mild. No significant differences in symptom severity were observed in women who underwent a pre-menopausal RRSO compared to RRSO after natural menopause.

These data indicate that a formalised follow-up protocol is necessary to optimally manage the consequences of a RRSO.

Keywords: salpingo-oophorectomy / *BRCA1* gene / *BRCA2* gene / menopause / osteoporosis / comprehensive health care

Background

Women with a germline *BRCA1* or *BRCA2* gene mutation have between 16–66% and 11–27% lifetime risk of ovarian cancer risk respectively [1-3] which has poor long-term survival [4,5]. Ovarian cancer screening is ineffective in this group [6,7]; risk-reducing salpingo-oophorectomy (RRSO) is the optimal management, reducing ovarian cancer risk by up to 95% [8-11]. Clinical recommendations supporting are successful with approximately 60% of at-risk women having surgery by age 60 years [12,13].

In pre-menopausal women, RRSO leads to an abrupt oestrogen withdrawal causing immediate menopause. While there are known acute and chronic physical and psychological consequences of premature menopause, reports of their frequency and severity are mixed. One study has reported worsened quality-of-life scores and unchanged cancer anxiety, but equivalent rates of sexual dysfunction after the surgery [14] while others have suggested little change in quality-of-life scores and reduced cancer anxiety [15-17]. Hot flashes can be more frequent, and sexual function more affected, in women who were pre-menopausal at the time of RRSO [18]. Fortunately,

many of these symptoms appear to improve over time and by one year post surgery, most women have regained their previous overall quality of life [19].

Though the short-term menopausal and quality of life effects of pre-menopausal RRSO appear manageable, a robust prospective study of the long-term effects of surgical menopause is lacking. Surgical menopause may result in a more rapid decrease in bone density when compared to natural menopause [20], associated with cognitive impairment or dementia [21] and an increased risk of cardiovascular mortality [22]. Prospective cohort studies in mutation carriers show an increase in overall survival after RRSO [23], despite RRSO before age 45 being associated with increased overall mortality in non-carriers [24]. One recent report has highlighted the potential for significant cardiac and bone, non-cancer, morbidity in *BRCA* mutation carriers post RRSO [25]. Similar levels of bone density and rates of cardiovascular disease, hypothyroidism and depression were observed between women who were under or older than 50 years at the time of RRSO. However, due to the 16 year mean age difference between the two groups, it is possible that the younger women at the time of surgery will develop increasing rates of bone and cardiovascular disease as they continue to age, eventually overtaking the older. Oestrogen may have a protective effect on cardiovascular outcomes, with a stronger risk association seen in women not treated with oestrogen after RRSO [22]. Despite the lack of high-quality, prospective long-term outcome data other than overall mortality to guide the decision for RRSO, health care workers emphasise the advantages of a premenopausal RRSO to gain maximum cancer-risk reduction, but it is unknown what additional focus is given to the potential long-term, non cancer, consequences of this surgery and their management.

We hypothesised that there was little formal follow-up of women following pre-menopausal RRSO. We undertook a cross-sectional study of female *BRCA1/2* mutation carriers to provide a “snapshot” of current RRSO-related morbidity in this group and to evaluate the extent and content of long-term follow up post RRSO. The overall aim of this study was to provide pilot data on the long-term consequences and to guide the optimal management requirements following pre-menopausal RRSO.

Methods

Women with a germline *BRCA1* or *BRCA2* mutation were identified from the clinical database of the Jack Brockhoff Familial Cancer Centre at the Peter MacCallum Cancer Centre. Mutation carriers with a prior diagnosis of ovarian cancer were excluded. Women known to have intact ovaries were not contacted but were included in the initial analysis. Eligible women were posted a study pack comprising of an invitation, consent letter and questionnaire (Figure 1). The questionnaire collected data about RRSO, menopausal status at RRSO, osteoporosis risk factors, and patient participation in any post-operative follow-up programs including arrangements to monitor and manage bone density. The study was approved by the institutional Human Research Ethics Committee.

The prevalence of current menopausal symptoms was assessed using the menopause rating scale (MRS) [26,27]. Specific menopausal symptoms were rated from 0 (no

symptoms) to 4 (very severe symptoms), or no response. If more than one level of symptoms was selected, an intermediate value was applied.

Descriptive statistics were calculated. T-test and Chi² testing to compare means and proportions respectively. MRS responses on the linear scale were entered numerically. Demographic variables associated with the MRS score were examined and logistic regression methods used to calculate odds ratios, 95% confidence intervals and p-values.

Results

Three hundred and thirty-three living female *BRCA1* and *BRCA2* mutation carriers without a personal history of ovarian cancer were identified (Figure 1). One hundred and six women were known to have intact ovaries and were not mailed a questionnaire; eight women were excluded from the study for medical reasons or had previously declined research participation. Two hundred and nineteen women received questionnaires between January and April 2009 of which 150 (72%) were completed and returned. One hundred and forty-three (65%) had undergone RRSO and 14 (6%) still had their ovaries *in situ*. Of those with a RRSO, 61 reported being pre-menopausal at time of RRSO. Thirty-one women in this cohort recorded their menopausal status as unknown, due in most cases to a previous hysterectomy.

A number of variables were associated with uptake of RRSO (Table 1); a current age >50 years (OR 28.0, $p < 0.0001$) and a personal history of breast cancer (OR 8.0, $p < 0.0001$) were the strongest predictors. One hundred and thirteen of 163 women over 50 years (70%) had had a RRSO; rising to 92% (113 of 123) if women of unknown menopause status at RRSO were excluded (40 women).

Of the 143 women who reported RRSO, surgery dates ranged between 1977 and March 2009. Six women (4%) reported that the surgical specimen contained pre-cancerous changes, three women (2%) reported cancerous changes, while 128 women reported benign histopathology (90%). For six women this information was not known.

Follow-Up after RRSO: Follow-up was defined as more than one post-operative visit with a managing specialist. No information about follow-up was provided by eight women. Thirty-one (22%) reported ongoing follow-up with their gynaecological surgeon and 104 (73%) reported no ongoing follow-up after their immediate post-surgical review. Of the 61 women who reported being pre-menopausal at time of RRSO only 18 (30%) reported ongoing follow-up.

Seventy-three (51%) of the 143 women with RRSO recalled having at least one bone density scan post surgery, 46 (63%) of which occurred within the last two years. Of the women who reported being pre-menopausal at RRSO, 19 (31%) recalled having a bone density scan within the previous 2 years (Figure 2). Of women who had at least one bone density scan, 26 (36%) reported that the scan showed osteoporosis (13 premenopausal and 13 postmenopausal women) but only six (23%) reported taking bisphosphonate treatment (5 post-menopausal, 1 premenopausal at RRSO).

Only 10 women (6%) without ovaries reported ever using hormone replacement therapy (HRT). The mean age of these women at RRSO was 52 years (range 33 – 63). Seven women who reported using HRT were pre-menopausal at the time of RRSO, but the menopausal status of three women was unknown. Two of the women (aged 59 and 63 years) reported that they had been receiving HRT for over eight years.

Menopause symptoms: One hundred and forty-one women completed the MRS questionnaire at a median of five years after their RRSO (range 0-32 years). The questionnaire was generally well completed by participants, with fewer than 4% of the fields not answered. When scores were compared using menopausal status at RRSO, there were no significant differences in the overall distribution of the severe (3) or very severe (4) MRS scores for any individual category (Figure 3) with the exception of sexual function. In this category, the proportion reporting grade 3 or 4 symptoms was greater in the pre-menopausal RRSO group, 41% versus 25% of post-menopausal ($p=0.021$ for the distribution). Six women did not respond to that question.

A group of women had “persisting severe” menopausal symptoms at the time of questionnaire, which we defined as a severe or very severe score in two or more of the different categories. Persisting severe symptoms appeared more frequent in women pre-menopausal at RRSO, although the trend did not reach statistical significance (OR 1.8, 95% CI 0.9-3.8, Table 2). The association was statistically stronger in women who were under 50 years at RRSO, regardless of menopausal status. Overall the probability that a woman would report “persisting severe” menopausal symptoms showed a strong linear correlation with age at RRSO ($p = 0.002$, Figure 4). The difference between the effect of age and menopausal status was influenced by the 14 women who had RRSO under 50 years but still described themselves as post-menopausal prior to RRSO. These young post-menopausal women had a high frequency of persisting severe symptoms at the time of questionnaire.

Discussion

Risk reducing salpingo-oophorectomy is the optimal risk-management strategy for women with a hereditary ovarian cancer risk as it reduces overall mortality in this group [23]. Our current study shows encouraging uptake of RRSO in women with a germline *BRCA1/2* mutation; over 70% of these women older than 50 years have had surgery. This figure has increased from previous local data, which reported less than half were undergoing RRSO [28].

The MRS results are reassuring, suggesting that the majority of women have relatively mild menopausal symptoms a median of 5 years after RRSO, regardless of their menopausal status at the time of the operation. For all menopausal symptoms, except those relating to sexual intercourse, the symptom frequency and severity were broadly similar in all subgroups in our cohort although the sexual symptoms remain difficult to interpret as we did not ask women about their level of sexual activity. We did find a small, but important, proportion of women who remained strongly symptomatic, with a trend towards more “persisting severe” symptoms in the surgical as opposed to natural menopause group (Table 2). Natural menopause was not

symptom free however, with troublesome symptoms still apparent for some women some years later.

The association of symptom severity was more marked in women who had RRSO at a younger age (<50 years) regardless of menopausal status at surgery. As we do not know the menopause aetiology for those women under 50 years at surgery and reported they were post-menopausal prior to surgery, the interpretation of our observations is speculative. Regardless of aetiology, younger menopausal women are more likely to experience hot flashes and are more affected by the sexual consequences of menopause, possibly because they have a greater level of sexual activity.

These data suggest that when pre-menopausal women are considering RRSO, they can be informed that despite an abrupt menopause, in the medium to long term for most women it carries few additional symptoms to those experienced in natural menopause, which is itself symptomatic. Medium-term prospective studies are essential to clarify more clearly the early time course of menopausal symptoms after RRSO.

Despite data suggesting HRT use does not abrogate the breast cancer risk-reducing effect of RRSO [29], very few of the women in our cohort used HRT. This may reflect the wide-spread public concern of HRT-associated breast cancer risk. However it is a useful agent as many menopausal symptoms can be alleviated by HRT in younger women, although other approaches include treatment with gabapentin or serotonin-reuptake inhibitors (SSRIs) [18,30,31]. HRT may also help mitigate some of the longer-term consequences of premature menopause such as osteoporosis and cardiovascular disease. The limited use of HRT does suggest a need for improved education about safety of HRT in this setting, for both women and their associated healthcare professionals.

Our results are less encouraging with respect to women receiving follow-up care for the potential complications of surgical menopause; 66% of women who were pre-menopausal at time of RRSO could not recall having a bone density scan in the past two years. Fortunately two recent US-based cohorts describe smaller proportions, 26% [32] and 36% [25], without bone density scans post-RRSO. The self-report of outcomes of bone density scans in our study suggest a potentially clinically significant misunderstanding of the scan results with clear discordance between self-reported results and subsequent clinical management. Women specifically reported 'osteoporosis' as opposed to 'bone thinning' (i.e. osteopenia) but few of them were using recognised osteoporosis treatments such as bisphosphonates. Either women did not appreciate the differences between these two conditions and misreported the diagnosis or they had suboptimal osteoporosis management. Further study, including formal review of bone density results, is needed to confirm women's perception of the degree of bone pathology.

In the authors' clinical experience, a large proportion of pre-menopausal women considering this surgery fear the consequences of a surgical menopause and some postpone surgery because of these fears. It is essential that robust data are available to

ensure an informed decision about the optimal timing of a RRSO. Our study may help to inform women about the physical impact of a RRSO and provide reassurance for women and clinicians that symptoms following premenopausal RRSO are generally manageable and comparable to natural menopause. It is clear that women need more information about both the acute and longer term consequences of a RRSO, as well as the importance of follow-up investigations including bone density [33].

The findings from this study support our hypothesis that many women are not receiving formalised support for many of the physical consequences of a premenopausal RRSO. The optimal follow up of these women crosses many specialist disciplines and general practice. These women may ‘fall between the cracks’ of existing support services and importantly many do not have nominated health care professionals providing overall supervision. We suggest that the team providing the long-term genetics follow-up are in an ideal position to coordinate the long-term post-RRSO management in conjunction with general practitioners and/or related specialists and that it is essential that clinical management guidelines outlining optimal post-RRSO management are developed.

Figure 1: Study population

* Excluded from study: one because of intellectual disability, three were overseas, two were too unwell and two had previously indicated they did not want to be contacted for research purposes

Figure 2: Bone health management in premenopausal RRSO cohort

Table 1: Characteristics of Familial Cancer Centre patients with a known mutation in *BRCA1* or *BRCA2* and analysis of the factors associated with uptake of RRSO.

	All	RRSO	No RRSO	Unknown	Predictive OR* (95% CI)	p-value
	333	157	119	57		
Median Age – years	49	53	35	57		
BRCA1	163 (49%)	83 (53%)	49 (41%)	31 (54%)	1.6 (1.0 - 2.59) [†]	0.05
BRCA2	170 (51%)	74 (47%)	70 (59%)	26 (46%)		
Age >50 years	163 (49%)	113 (72%)	10 (8%)	40 (70%)	28.0 (13.4 - 58.4)	<0.0001
PHx Breast Ca	168 (50%)	103 (66%)	23 (19%)	42 (74%)	8.0 (4.5 - 14.0)	<0.0001
FHx Breast Ca	312 (94%)	146 (93%)	115 (97%)	51 (89%)	0.3 (0.1 - 1.3)	Ns
FHx Ovarian Ca	153 (46%)	72 (46%)	57 (48%)	24 (42%)	0.9 (0.6 - 1.5)	Ns
Mutation Known >1yr	277 (83%)	141 (90%)	88 (74%)	48 (84%)	4.8 (2.2 - 10.8)	<0.0001

*Odds ratios for RRSO versus no RRSO, [†]OR for BRCA1 versus BRCA2 mutation

Table 2: Factors predictive of persisting severe menopausal symptoms (MRS grade 3 or 4 in two or more categories) in women following RRSO.

		n (%)	OR*	p-value
All (n=143)				
Severe Symptoms		55 (38%) [†]		
<i>Predictors:</i>				
Pre-menopausal		28 (47%)	1.8 (0.9-3.8)	ns (0.1)
Post-menopausal		22 (34%)		
Age at RRSO	<50 years	41 (75%)	3.0 (1.4-6.3)	0.004
Current Age	<50 years	21 (38%)	2.4 (1.2-5.2)	0.02
Time since RRSO	<2 years	9 (41%)	1.1 (0.4-2.8)	ns
Pre-menopausal (n=59)				
Severe Symptoms		28 (47%) [†]		
<i>Predictors:</i>				
Age at RRSO	<50 years	22 (79%)	0.4 (0.1-1.7)	ns
Current Age	<50 years	16 (57%)	1.8 (0.7-5.2)	ns
Time since RRSO	<2 years	4 (57%)	2.7 (0.6-13.7)	ns
Post- menopausal (n=65)				
Severe Symptoms		22 (34%) [†]		
<i>Predictors:</i>				
Age at RRSO	<50 years	14 (64%)	8.2 (2.5-26.8)	<0.0001
Current Age	<50 years	4 (18%)	0.6 (0.2-1.7)	ns
Time since RRSO	<2 years	4 (33%)	1.0 (0.3-3.7)	ns

*Odds ratios for severely affected versus not severely affected women

[†] The percentage of each group reporting severe or very severe symptoms in 2 or more categories. All other percentages are the proportion of severely affected women with a particular predictive factor within each group.

Figure 3: Persisting Severe Symptoms (MRS grade 3 or 4) according to menopausal status at the time of RRSO.

Figure 4: The probability of reporting persisting severe menopausal symptoms at follow-up according to age at the time of RRSO.

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Conflict of interest statement:

The authors declare that they have no conflict of interest

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