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What Happens after Menopause? (WHAM): Protocol for a prospective multicentre, age-matched cohort trial of risk-reducing bilateral salpingo-oophorectomy in high-risk premenopausal women

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Contributors

MH, AT, SB, MAD, EOK and JW contributed to the conception, design, writing and editing of the protocol. MH drafted the manuscript and all other authors contributed to the final version. SB wrote the statistical methods. MH is the guarantor. All authors read and approved the final manuscript.

Competing interests

None.

Ethics approvals

Country, State	HREC Name	HREC Reference #	Project #	Approval Date
Australia, Victoria	Peter MacCallum Cancer Centre	HREC/12/PMCC/24	12/90	04/12/2012
Australia, Victoria	The Royal Women's Hospital	HREC/12/PMCC/24	12/07	20/12/2012
Australia, Victoria	Melbourne Health	HREC/12/PMCC/24	2013/060	07/10/2013
Australia, NSW	South Eastern Sydney Local Health District (Prince of Wales Hospital)	HREC/13/POWH/61	12/304	23/05/2013
Australia, NSW	Western Sydney Local Health District	HREC/13/POWH/61	SSA/13/ WMEAD/189	28/11/2013
Australia, NSW	South Eastern Sydney Local Health District (Royal Hospital for Women)	HREC/13/POWH/61	14/G/146	29/04/2014
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Abstract

Introduction: Women at high inherited risk of ovarian cancer are advised to undergo risk-reducing bilateral salpingo-oophorectomy (RRBSO) at age 40-45 years or when their families are complete. Most women are premenopausal at this age, so RRBSO will induce surgical menopause. Despite the clear benefits of RRBSO for cancer risk reduction, much less is known about the impact on non-cancer outcomes which contribute to health and wellbeing and inform surveillance and management strategies.

Methods and analysis: This will be a multicentre, prospective cohort study of 105 premenopausal high-risk women undergoing RRBSO and an age-matched comparison group of 105 premenopausal women not planning oophorectomy or pregnancy in the next two years. The aim of this study is to measure the impact of RRBSO on sexual function (primary outcome) at 12 months in high-risk premenopausal women compared to the comparison group. Secondary outcomes include menopausal symptoms and menopause-related quality of

life (QOL), mood, sleep quality, markers of cardiovascular disease and prediabetes, bone density and markers of bone turnover and the impact of hormone replacement therapy (HRT) use on these outcomes. Data analysis methods will include logistic and linear regression using general estimating equations accounting for the repeated outcome measurements within each participant.

Ethics and dissemination: The study has been approved by institutional ethics committees at each participating centre. Findings will be disseminated through peer reviewed publications and conference presentations, national and international networks of centres managing high-risk women and will inform national and international clinical guidelines.

Registration details: The trial is registered (anzctr.org.au, Registration No: ACTRN12615000082505)

Introduction

Ovarian cancer is the fifth most common female cancer and carries a poor prognosis. Around 10-15% of ovarian cancers, and over 20% in women under age 50 are due to germline mutations in the BRCA1 or BRCA2 gene[1]. These women have an elevated lifetime risk of breast (72% and 69% respectively) and ovarian cancer (44% and 17% respectively) [2] compared to the population risk of 1-5% for ovarian cancer. Other germline mutations such the mismatch repair genes responsible for Lynch Syndrome increase ovarian cancer risk to around 9%[3]. The prevalence of germline gene mutations which increase the risk of ovarian cancer is up to 1:400 women and these cancers commonly develop at an earlier age than in the general population[2]. The wider availability of rapid, low-cost sequencing methods and the increasing indications for gene testing mean that more women are being diagnosed with germline mutations which increase their risk of ovarian cancer.

There is currently no effective screening strategy for ovarian cancer and the only intervention proven to reduce risk is bilateral salpingo-oophorectomy. Extensive evidence confirms that RRBSO reduces the risk of ovarian cancer by up to 95% in high-risk women and leads to an overall survival benefit[4]. RRBSO may also detect occult ovarian cancer. Current guidelines advise RRBSO before aged 40 in BRCA1 carriers or before aged 45 for BRCA2 carriers[5].

Despite strong evidence that bilateral salpingo-oophorectomy reduces cancer risk and increases survival in high-risk women, many women decline to undergo risk-reducing surgery. Reported uptake rates vary considerably from around 17%-89%[6]. The reasons why many women decline or defer RRBSO are not well understood, but concerns about early menopause are a factor in premenopausal women[7]. Deleterious gene mutations are commonly identified in premenopausal women, so RRBSO will lead to surgical menopause. Despite the clear benefits for cancer risk reduction in high-risk women, very little is known about the impact of RRBSO on non-cancer outcomes[8] and this is of concern to high-risk women and their health care providers[9]. In the general population, there is growing evidence that early menopause (<45 years), and particularly surgical menopause has significant negative consequences for coronary heart disease[10], cardiovascular death, all cause-mortality, dementia and Parkinson's disease, particularly for those who do not take hormone replacement therapy HRT[11 12]..However, the quality of current evidence is low, and there have been very few prospective studies of surgical menopause in any population.

High-risk women considering RRBSO are faced with complex decision-making, weighing up the potential adverse health implications of bilateral oophorectomy against the known reduction in cancer risk[5]. Most studies of RRBSO have focused exclusively on cancer outcomes, but current evidence suggests that premenopausal women experience a significant worsening of vasomotor symptoms (hot flushes and night sweats), a persistent decline in menopause-related quality of life and sexual function one year after RRBSO [13]. HRT partly mitigates these symptoms, but even in HRT users sexual function and vaginal symptoms do not return to pre-surgical levels[14 15]. Use of HRT is thought to be safe in high-risk women, provided they do not have a personal history of breast cancer, but the proportion of users is unknown and evidence for safety is limited[16].

Bilateral salpingo-oophorectomy leads to infertility, and women may consider undergoing concurrent hysterectomy. Hysterectomy adds to the duration, cost and potential complications of surgery, but avoids the need for combined HRT and removes the risk of endometrial pathology associated with tamoxifen use[17]. More information is needed from prospective studies to inform women and their health care providers considering hysterectomy at the time of RRBSO.

To support informed decision making and to appropriately structure follow-up care there is an unmet need for prospective data on the non-cancer consequences of RRBSO[5]. Having reduced their risks of breast and ovarian cancer, high-risk women should reasonably anticipate a normal QOL and life expectancy. In order to decide whether and when to undergo RRBSO, and how best to optimise health post-operatively, more information is needed about the non-cancer consequences of risk-reducing oophorectomy.

This multicentre, population-based, controlled, cohort study will generate new data to inform decision making around RRBSO and evidence-based follow-up care in the general population following surgical menopause. The primary objective of WHAM is to assess the association between RRBSO and sexual function as measured by the Female Sexual Function Index. The secondary outcomes are menopausal symptoms and menopause-related quality of life, mental health, bone health and turnover, cardiometabolic risk and sleep quality. We hypothesise that RRBSO in premenopausal women will reduce sexual function (primary outcome), increase menopausal symptoms, reduce menopause-related QOL, increase bone turnover, reduce bone density, increase cardiometabolic risk and reduce sleep quality compared to age-matched premenopausal women who retain their ovaries. We do not expect RRBSO to affect mental health[18].

Methods: Participants and Outcomes

Study design and setting

This is a multicentre, cohort study comparing 105 high-risk pre-menopausal women up to 50 years of age who plan to undergo RRBSO with 105 age-matched, premenopausal women who do not plan to undergo oophorectomy or pregnancy in the next two years. Study recruitment commenced in April 2013, enrolling women from 8 public and 4 private hospitals in Australia (Victoria and New South Wales). The projected timeline for recruitment is 3-4 years. All subjects will be followed up for two years from the baseline visit.

Eligibility criteria and recruitment

Eligible women will be premenopausal and age up to 50 years with regular menstrual periods (if intact uterus), no vasomotor symptoms and an FSH (follicular stimulating hormone) level of <15IU/L on day 2-6 of the menstrual cycle. Exclusions include <3 months since pregnancy and lactation, abnormal uterine bleeding, or use of anti-estrogens such as tamoxifen.

Exposed women are defined as those at high inherited risk of ovarian cancer due to confirmed presence of a gene mutation (carriers of BRCA1, BRCA2, BRIP1, RAD51C, Lynch Syndrome) or high familial risk of ovarian cancer and planning to undergo RRBSO. Those with a personal history of breast cancer will be included if they remain premenopausal and are not currently taking endocrine therapy. Participants will be recruited via clinician referrals from familial cancer, high-risk breast cancer and menopause clinics, referrals from public and private gynaecology oncologists and surgeons, and via targeted advertising through mainstream and electronic media (eg. newspaper and television reports, cancer registries, cancer support newsletters and websites). Each referral will be processed upon receipt and eligibility screening and subsequent recruitment will be scheduled to occur within 8 weeks prior to the RRBSO surgery date. The baseline visit will be scheduled for the early follicular phase (days 2-6) of the subject's menstrual cycle prior to RRBSO.

Women in the comparison group are defined as 1:1 individually age-matched (within +/- 5 years), pre-menopausal women who are not planning oophorectomy or pregnancy within the next 2 years. Comparison subjects can be low-risk or relatives of high-risk women who do not carry a gene mutation. The comparison group will be recruited via mainstream and electronic media advertising to the general public (eg. clinical research recruitment websites, hospital and university staff newsletters and websites), and by asking recruited cases to recommend the study to relatives and friends. Recruitment will be scheduled to occur during the early follicular phase (days 2-6) of the subject's menstrual cycle, and within the 8 weeks after eligibility screening. Women in the comparison group withdrawing prior to the 6-month follow-up will be replaced women of similar baseline age.

Participant timeline

A schedule of study assessments and measurements is presented in Table 1. After informed consent and eligibility, baseline data will be collected including obstetric, gynaecological, medical and surgical history, current medications, risk factors for fracture (www.shef.ac.uk/FRAX), risk factors for cardiovascular disease including blood pressure, circulating cholesterol and lipids and C-reactive protein (www.heartfoundation.org.au/SiteCollectionDocuments/austcardiovascular-risk-charts.pdf), tobacco, drug and alcohol use, methods of contraception, methods of breast cancer surveillance, germline mutation type and family cancer history. In those with a history of breast cancer, stage and grade of tumour and treatment history will be recorded. Blood pressure, weight, height and waist-hip ratio will be measured and repeated at selected follow-up visits (see Table 1). A blood sample will be taken after an overnight fast to measure sex steroid concentrations, lipids, and cardiovascular risk factors which will be repeated at 1 and 2 years follow-up. A urine sample will be collected for comparison subjects to exclude pregnancy (see Table 1). Medications used in the 3 months prior to enrolment and throughout the 2 year follow-up period will be recorded and includes those related to bone health (calcium, vitamin D and anti-resorptive agents), depression, anxiety, HRT, non-hormonal treatments for vasomotor symptoms, contraception and insomnia. Adverse events (changes in physical and psychological health from baseline) will be monitored over the 2-year follow-up period. Questionnaires to measure sexual function, menopausal symptoms, menopause-

related QOL, sleep quality, depression and anxiety will be administered at baseline and all post-baseline study visits (see Table 1). All participants will undergo DXA scans within 3 months of RRBSO (baseline) and again at 1 and 2-years post-baseline.

Participants will be free to withdraw at any time, either through formal revocation of consent (patient preference) or via ceased communication with the recruitment site (lost to follow-up). All collected data will be included in the analyses and any discrepancies related to data collected prior to withdrawal will be queried with the subject up to one month after the withdrawal date. In order to minimise missing data, participants who cannot complete all scheduled visits will be invited to continue in the study despite missing visits. Those who withdraw at a scheduled time-point, or who are unable to attend the recruitment site at a scheduled time-point will be offered the opportunity to complete any time-point data that can be captured remotely via telephone and email correspondence, including questionnaire, medications and adverse events data.

Outcomes

The primary outcome is the change in sexual function following RRBSO, as measured by the Female Sexual Function Index (FSFI)[19]. Sexual function was selected because it is a patient priority and in young women and because previous prospective studies suggest that sexual function may be permanently impaired following RRBSO[13-15]. Secondary outcomes include menopause-related QOL, menopausal symptoms, sleep quality, depression and anxiety, markers of cardiovascular disease and prediabetes, bone density and markers of bone turnover. All measures will be collected at baseline (prior to RRBSO in the intervention group) with follow-up measures scheduled as per Table 1.

Measurement of sexual function

Subjects will be asked whether they currently have a sexual partner and whether sexual problems for the partner impact on their sexual activity. We will use standardized and validated questionnaires to measure three aspects of sexual function:

1) The Female Sexual Function Index (FSFI) is a widely-used brief self-report questionnaire that assesses six separate dimension: Desire, arousal, lubrication, orgasm, satisfaction, pain and it also provides a total score[20]. The FSFI has been validated in a large group of women with sexual arousal disorder versus age-matched controls[19] and in cancer survivors[21]. It has demonstrated a high level of acceptability, reliability and validity in both cancer and non-cancer populations[22]. The FSFI has a high internal consistency, test retest reliability and differentiates well between sexually-dysfunctional and non-dysfunctional women and is highly sensitive in discriminating between clinical and non-clinical populations[20]. FSFI scores (primary) will indicate which domains of sexual function are affected by RRBSO. The FSFI takes <5 minutes to complete.

2) The revised Female Sexual Distress Scale (FSDS-R)[23] is a brief (13 item) questionnaire which measures the extent to which reduced sexual desire causes distress in women. Distress is a key feature of hypoactive sexual desire disorder (HSDD). The (FSDS-R) has good discriminant validity, test-retest reliability, and internal consistency in measuring sex-related personal distress in women with

HSDD[24]. The scale also has good content validity (relevance, clarity, comprehensiveness)[25].

3) The Sexual Activity Questionnaire (SAQ) evaluates sexual pleasure (desire, enjoyment and satisfaction), discomfort (vaginal dryness and dyspareunia) and habit (frequency of sexual activity compared to usual activity)[26]. The SAQ has been validated in breast cancer patients and in high-risk women[27]. It is quick and easy to administer and has good face validity discriminating between the sexual functioning of pre- and post-menopausal women[27]

Measurement of circulating testosterone and SHBG

Circulating testosterone concentrations are reduced following RRBSO and this may contribute to sexual function, although findings are conflicting[15]. Circulating concentrations of total testosterone and the testosterone precursors, androstenedione and 5-dehydroepiandrosterone (DHEA) and sex hormone binding globulin (SHBG) will be measured at baseline and follow up, as per Table 1. Fasting blood samples will be immediately centrifuged to isolate plasma, and stored at -80 degrees centigrade. Because conventional radioimmunossays lack sensitivity at low androgen concentrations found after surgical menopause[82] we will use liquid chromatography tandem mass spectrometry (LC-MS/MS), using a Sciex API 5500Q instrument by CPR Pharma Services (Adelaide, SA). The lower limit of measurement is 0.025 ng/mL for testosterone, 0.05 ng/mL for androstenedione, and 0.5 ng/mL for DHEA. The intra-assay coefficients of variation are low (<5%) at 1nM. SHBG concentrations will be measured using a non-competitive liquid-phase RIA (68562, Orion Diagnostica, Finland). We will calculate free testosterone concentrations using measured total testosterone and SHBG concentrations[28].

Measurement of menopausal symptoms and menopause-related quality of life

Menopausal symptoms will be measured using the Greene Climacteric Scale, which measures the frequency and severity of menopausal symptoms in psychological somatic and vasomotor domains[29]. The scale is widely used and has been validated in an Australian population[30].

Menopause-related QOL will be measured using the Menopause-related Quality of Life Intervention (MENQOL-Intervention) questionnaire[31]. The MENQOL-intervention covers four domains; vasomotor, physical, psychosocial and sexual, and includes a global QOL life item. It is widely used internationally and its strength and validity have recently been confirmed in a large population-based sample of midlife women[32] and in breast cancer survivors[33]. The questionnaire tests the impact of an intervention, such as oophorectomy, on symptoms. Each takes less than five minutes to complete. Use of HRT and of non-hormonal medications for vasomotor symptoms will be recorded, and subjects will be asked about decision-making around HRT.

Measurement of sleep quality

Sleep quality will be measured using the Pittsburgh Sleep Quality Index (PSQI)[34], a widely used and validated measure of sleep quality[35]. The questionnaire measures subjective sleep quality, latency, duration, habitual sleep efficiency, sleep disturbances and medications, and daytime dysfunction. The PSQI takes <5 minutes to complete.

Measurements of depression and anxiety

Depression and anxiety will be measured using the Centre for Epidemiologic Studies Depression (CES-D)[36]and the Generalized Anxiety Disorder (GAD-7)[37]scales, respectively. The CES-D measures the frequency of depressive feelings and behaviours experienced in the past week and includes 20 items that are assigned scores ranging from 0-3. The final CES-D score (0 – 60) is the sum of the 20 items and a score of ≥16 points is indicative of depression. The GAD-7 measures the frequency of GAD symptoms in the past fortnight and includes 7 items that are assigned scores ranging from 0-3. The final GAD-7 score (0 – 21) is the sum of the 7 items and a scores of 5-9, 10-14 and 15-21 are indicative of mild, moderate and severe anxiety respectively. Each questionnaire takes <5 minutes to complete.

Measurement of cardiovascular disease risk

Resting blood pressure, weight, height and waist/hip ratio will be measured as per table 1. Fasting blood samples will be analysed for serum insulin, glucose, triglycerides (TG), cholesterol, high density lipoprotein (HDL-C), low density lipoprotein (LDL-C) and high sensitivity C-reactive protein (hs CRP) which predicts CVD in healthy women[38]. These have not previously been prospectively measured in surgical menopause. Homeostasis model assessment (HOMA) will be calculated by fasting insulin (μU/ml) x fasting glucose (mM)]/22.5. Insulin resistance will be defined by a HOMA reading >488. The presence of diabetes or prediabetes will be established by fasting glucose and HbA1c. A HbA1c of >6.5% will be used as a cut-off for the diagnosis of diabetes as recommended by the American Diabetes Association (www.diabetes.org) and carried out in National Association of Testing Authorities (NATA) accredited laboratories using standard equipment.

Measurement of bone density and markers of bone turnover

We will measure fasting serum albumin, creatinine, calcium and phosphate, circulating markers of bone turnover (beta-C-terminal telopeptide of type I collagen (beta CTX) and N-terminal propeptide of type 1 collagen)[39]. We will measure 25-OH vitamin D2 and D3 using LC tandem mass spectrometry and intact parathyroid hormone (PTH) immunoassay. The bone turnover markers are independent predictors of fracture risk and will supplement BMD data. Regional BMD (at the lumbar spine and hip) will be measured using dual-energy X-ray absorptiometry (DXA) within 3 months of RRBSO (baseline). We will also use DXA to measure total body bone mineral content (BMC) which will increase power to detect bone loss[40]. DXA measurement location will be included as a covariate and change from baseline will be used in outcome analyses.

Sample size

We will recruit 105 high-risk pre-menopausal women planning RRBSO and 105 age-matched (± 5 years) women in the comparison group. The primary outcome is sexual dysfunction (FSFI score <26.55)[41] where lower FSFI scores indicate worse sexual function. Based on large population-based surveys, we have assumed that around 24% of premenopausal women will have sexual dysfunction (FSFI below clinical cut off) at baseline[42 43] and that the proportion with sexual dysfunction does not differ between the high-risk women or those in the comparison group, or between age groups, and that it does not change over the 2-year study period in the comparison group. Sample size calculations are based on comparing the proportion of women with sexual dysfunction in the RRBSO group with the comparison

group at 12 months follow-up. A sample size of 89 women per group will provide 80% power at a two-sided 5% level of significance to detect a 21% difference (from 24% in the comparison group to 45% in the RRBSO group), or 105 per group when allowing for 15% loss to follow-up at 2-years. This difference in the proportion of women with sexual dysfunction is clinically significant[44]. For the secondary outcomes, this sample size of 89 per group will also provide 83% power to detect a difference in the proportion of women with a DXA T-score of ≤ -1 at 2 years, from 16% in the comparison group to 36% in the RRBSO group[45] and 92% power to detect a mean difference between groups of 0.5 standard deviation in the MENQOL score

Methods: Data collection, management, and analysis

Data collection methods

Study data are being collected using paper case report forms (CRF), paper self-reported questionnaires, paper recorded phone interviews, and paper copies of biochemical, pathology and bone density imaging reports. These paper documents will be kept by each recruitment site in a locked cabinet accessible to local research staff only. All data will be entered and stored in a de-identified, password-protected electronic study database created with the REDCap© web application (https://projectredcap.org/)[44]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources[46]. Internet access to the REDCap© database will utilise a secure server located at the University of Melbourne, Australia (REDCap© consortium host), and access will be limited to local research staff at each recruitment site. Research staff will only have access to the REDCap© data collected at their local recruitment site, whereas the chief investigator, project manager, data administrator and statistician will have access to all REDCap© data.

Data management

Management of comprehensive and valid paper records will be the responsibility of local research staff at each recruitment site. To ensure a systematic approach to data collection the project manager will provide protocol training and written standard operating procedures to research staff prior to any study visits being performed. Data integrity will be maintained thorough review of all collected data prior to, during and after each study visit. Any time-sensitive data (eg. questionnaires) will be reviewed as soon as they are collected and any identified discrepancies will be resolved within one week of collection. Medications and adverse events data will be reviewed and consolidated at every study visit. All other data discrepancies will be queried with the subject via email or telephone correspondence and resolved within one month of collection. Records of participant screenings and enrolments at each site will be maintained using Microsoft Excel spreadsheets with diary features. These documents will assist research staff to adhere to study timelines and to regularly monitor and report site study progress to the project manager, investigators and the responsible HRECs. Electronic data entry into the REDCap© database will begin no later than 12 months prior to the last participant last visit. Database training of research staff and data entry will be conducted and overseen (respectively) by the project manager.

Data and safety monitoring

We do not anticipate any study-related adverse events (AEs) or serious adverse events (SAEs). The only anticipated AEs include phlebotomy-related site injuries (minor) and vasovagal syncope (rarely), and negative psychological responses to questionnaires and interview discussions. These AEs will be circumvented or managed by providing the subject with appropriate advice and counselling during and after each study visit. Reports of biochemistry, pathology and bone density results will be routinely reviewed by medically-qualified site investigators. Any concerning results will be immediately reviewed and reported to the subject and her GP. All other results will be reviewed within one week of report receipt and any results outside of normal ranges will be reported to the subject's GP within 2 weeks. The project manager will directly monitor all Victorian data within one month of collection, and personally visit other recruitment sites on a 6-monthly basis to perform data monitoring activities. The outcomes will be reported to the chief investigator and all relevant research staff and investigators within one month of each monitoring visit, and any systematic problems with data collection, data management and adverse events monitoring and reporting will be rectified. Questionnaires will be independently scored on two separate occasions prior to data entry into the REDCap© database, and all data entry into REDCap© will be monitored by an independent data administrator. REDCap© data queries will be addressed by the project manager and data administrator using the REDCap© Data Resolution Workflow module.

Statistical methods

The analysis set will consist of all recruited women. Baseline characteristics will be summarised by group. The primary outcome is sexual dysfunction, defined as an FSFI score of <26.55 at 12 months. Changes in FSFI from baseline will also be measured as a continuous variable. Binary secondary outcomes (e.g., PSQI score > 5; CES-D score ≥ 16; GAD-7 ≥ 10, absolute change from baseline in diastolic blood pressure ≥ 5 mmHg, relative change from baseline in HDL:LDL ratio > 2.5, BMD T-score ≤ -1) will be analysed by fitting a generalised linear model with a logistic link function using generalised estimation equations to account for the repeated measurements[47]. Continuous secondary outcomes will be analysed by fitting a linear regression model using generalised estimating equations. Appropriate transformation of a continuous variable may be performed before analyses if the variable is found to be skewed. A directed acyclic graph will be used to explore which covariates to include in the adjusted -model[48 49]. An adjusted model will be fitted to correct for the potential confounding of time-independent covariates (e.g., age at baseline, use of hormonal contraception at baseline, use of antidepressant medication at baseline) and time-dependent covariates (e.g., use of HRT, symptoms of depression and/or anxiety). We anticipate that around 30% will undergo hysterectomy at the time of RRBSO, and 50% will subsequently take HRT. The proportion of women who take HRT/tibolone during the 24-month follow-up period will be compared using logistic regression. The number and proportion of women using specific medication (e.g., HRT, antidepressants) will be summarised by group. Adverse events will be recorded and graded using the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) criteria and the number and proportion of women with at least one AE will be summarised by group. Exploratory subgroup analyses will examine whether the effect differs across the following subgroup categories a) age at

baseline (<45 years vs ≥45 years) and b) use of hormonal contraception at baseline (yes vs no) by adding the subgroup and its interaction with group to the model.

Outcomes and Significance

Growing numbers of women are known to be at high inherited risk of ovarian cancer and are electing to undergo RRBSO. The established reduction in ovarian cancer mortality following RRBSO could be further improved by minimizing the negative non-cancer consequences, which also may contribute to morbidity and all-cause mortality. This can be addressed only when the non-cancer outcomes are known, and this requires prospective data collection. The principal significance is high burden of disease from ovarian cancer and the growing number of high-risk women who would benefit from RRBSO. In addition, because prospective studies of surgical menopause in the general population are very limited, the findings from this study will also inform care of low-risk women undergoing surgical menopause. These data will be used to develop resources to support decision making around RRBSO including the timing of surgery, additional hysterectomy, preoperative risk assessment and counselling and post-operative follow-up including use of HRT. Our studies will directly improve cancer outcomes by impact on clinical practice and policy, through the development of multidisciplinary evidence-based guidelines and screening protocols. Consumers have clearly indicated that they wish to be informed about the consequences of RRBSO and that current information provision and follow-up care are inadequate[50 51]. Decision making and satisfaction are improved when high-risk women are offered dedicated clinical services[52 53]. Our data and guidelines will provide a template for the care of other high-risk women considering RRBSO as new genes are identified. Improved information about the non-cancer consequences of RRBSO is unlikely to dissuade high-risk women from surgery. Despite side effects, most do not regret their choice[18 50]. Improved follow-up care may also improve QOL for high-risk women and contribute to early detection and/or prevention of conditions related to early menopause. This will be the first international multicentre, prospective study of non-cancer outcomes after RRBSO or surgical menopause in any population. Currently, there is no consensus on how high-risk women should be managed following RRBSO. This study will provide new evidence on which to develop evidence-based care for this growing population of women.

Ethics and Dissemination

This is a prospective observational cohort study of high-risk women undergoing RRBSO. No study-related safety concerns are anticipated. The study has been granted ethics approval at each of the participating recruitment centres, including:

- Peter MacCallum Cancer Centre (Victoria, Australia)
- The Royal Women's Hospital (Victoria, Australia)
- The Royal Melbourne Hospital (Victoria, Australia)
- Prince of Wales Hospital (NSW, Australia)
- Westmead Hospital (NSW, Australia)
- Royal Hospital for Women (NSW, Australia)
- Royal Prince Alfred Hospital (NSW, Australia)
- Chris O'Brien Lifehouse (NSW, Australia)

Dissemination will be through peer-reviewed publications, presentations at national and international conferences and existing networks including WISP, National and International Menopause societies and specialist colleges.

Table 1: Schedule of Assessments / Investigations

Study Procedures	Baseline Day 1* (Visit 1)	Month 3 ±6 weeks (Visit 2)	Month 6 ±6 weeks (No Visit)	Month 12 ±6 weeks (Visit 3)	Month 24 ±6 weeks (Visit 4)
Informed Consent and Eligibility	•				
Surgical, Medical, Gynaecological, Obstetric and Menstrual History	•				
Smoking, Drug and Alcohol Use History	•				
Germline Mutation Testing History	•				
Personal and Family Cancer History	•				
Personal Breast Cancer Surveillance, Diagnosis, Treatment Details (if applicable)	•				
Contraceptive Methods	•				
Fracture Risk Assessment *(http://www.shef.ac.uk/FRAX/tool.jsp)*	•				
Height	•				
Weight	•			•	•
Waist-Hip Ratio *(http://bupa.com.au/)*	•			•	•
Blood Pressure	•	•		•	•
Urinary Pregnancy Test (Comparison	•	•		•	•
Medications	•	•	•	•	•
Adverse Events		•	•	•	•
Questionnaires					
FSFI, FSDS-R and SAQ (Sexual function, distress and activity)	•	•	•	•	•
GCS and MENQOL (Menopausal Symptoms and QOL)	•	•	•	•	•
PSQI (Sleep Quality)	•	•	•	•	•
CES-D (Depression) and GAD-7 (Anxiety)	•	•	•	•	•
Blood Tests (Fasting)					
FSH, Estradiol (days 2-6 menstrual cycle)	•				
Total Testosterone, DHEAS, Androstenedione, SHBG	•			•	•
Total Cholesterol, LDL-C, HDL-C, Triglycerides, Insulin, Glucose, HbA1c	•			•	•
Albumin, Creatinine, Calcium, Phosphate, P1NP, BCTX, Parathyroid Hormone	•			•	•
Bone Mineral Density (BMD)					
Baseline DXA Scans of Hip and Lumbar Spine BMD and of Total Body Bone		•		•	•

* The baseline visit will be performed up to 8 weeks prior to RRBSO for the intervention group, or following eligibility screening for controls.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	10

Continued on next page

Results Checklist not applicable – this is a Study Protocol submission

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

What Happens after Menopause? (WHAM): Protocol for a prospective multicentre, age-matched cohort trial of risk-reducing bilateral salpingo-oophorectomy in high-risk premenopausal women

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Keywords:	Menopause, Ovarian cancer, RRBSO

What Happens after Menopause? (WHAM): Protocol for a prospective multicentre, age-matched cohort trial of risk-reducing bilateral salpingo-oophorectomy in high-risk premenopausal women

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Contributors

MH, AT, SB, MAD, EOK and JW contributed to the conception, design, writing and editing of the protocol. MH drafted the manuscript and all other authors contributed to the final version. SB wrote the statistical methods. MH is the guarantor. All authors read and approved the final manuscript.

Competing interests

None.

Ethics approvals

Country, State	HREC Name	HREC Reference #	Project #	Approval Date
Australia, Victoria	Peter MacCallum Cancer Centre	HREC/12/PMCC/24	12/90	04/12/2012
Australia, Victoria	The Royal Women's Hospital	HREC/12/PMCC/24	12/07	20/12/2012
Australia, Victoria	Melbourne Health	HREC/12/PMCC/24	2013/060	07/10/2013
Australia, NSW	South Eastern Sydney Local Health District (Prince of Wales Hospital)	HREC/13/POWH/61	12/304	23/05/2013
Australia, NSW	Western Sydney Local Health District	HREC/13/POWH/61	SSA/13/ WMEAD/189	28/11/2013
Australia, NSW	South Eastern Sydney Local Health District (Royal Hospital for Women)	HREC/13/POWH/61	14/G/146	29/04/2014
Australia, NSW	Sydney Local Health District (Royal Prince Alfred Hospital)	X14-0396	10/21	22/04/2015
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Data sharing statement: It is the intention of the study group that once completed and the research articles stemming from the study have been published, any remaining data that is fully anonymised and not sensitive should be made open access.

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***Conflict of Interest declaration*.** No conflict of interest to declare.

Abstract

Introduction: Women at high inherited risk of ovarian cancer are advised to undergo risk-reducing bilateral salpingo-oophorectomy (RRBSO) at age 40-45 years or when their families are complete. Most women are premenopausal at this age, so RRBSO will induce surgical menopause. Despite the clear benefits of RRBSO for cancer risk reduction, much less is known about the impact on non-cancer outcomes which contribute to health and wellbeing and inform surveillance and management strategies.

Methods and analysis: This will be a multicentre, prospective cohort study of 105 premenopausal high-risk women undergoing RRBSO and an age-matched comparison group of 105 premenopausal women not planning oophorectomy or pregnancy in the next two years. The aim of this study is to measure the impact of RRBSO on sexual function (primary outcome) at 24 months in high-risk premenopausal women compared to the comparison group. Secondary outcomes include menopausal symptoms and menopause-related quality of life (QOL), mood, sleep quality, markers of cardiovascular disease and prediabetes, bone density and markers of bone turnover and the impact of hormone replacement therapy (HRT) use on these outcomes. Data analysis methods will include logistic and linear regression using general estimating equations accounting for the repeated outcome measurements within each participant.

Ethics and dissemination: The study has been approved by institutional ethics committees at each participating centre. Findings will be disseminated through peer reviewed publications and conference presentations, national and international networks of centres managing high-risk women and will inform national and international clinical guidelines.

Registration details: The trial is registered (anzctr.org.au; Registration No: ACTRN12615000082505)

Strengths and Limitations

• Increasing numbers of women are being diagnosed with gene mutations that increase their risk of ovarian cancer. Currently, risk-reducing salpingo-oophorectomy (RRBSO) is the only evidence-based intervention to reduce ovarian cancer risk in this population. Since risk-reducing oophorectomy is recommended before age 45 years it will generally induce surgical menopause.

• Although surgical menopause for risk-reduction and other gynaecological indications is relatively common in clinical practice, there have been very few prospective studies of non-cancer outcomes. This will be the largest prospective study of non-cancer outcomes following surgical menopause internationally and will provide new evidence to inform patient decision making, clinical management and follow-up protocols.

• A strength of this study is the prospective design and the inclusion of an age-matched control population to account for the impact of age on the outcomes to be studied.

• Whilst the study is adequately powered to address the primary outcome of sexual function, it will have less power to determine the impact of hormone replacement therapy (HRT) on the outcomes of interest.

•Further potential limitations are the use of hormonal contraceptives (such as COCP) at baseline in participants and the difficulty in recruiting an age-matched control population. To address this we have included multiple and integrated modes of recruitment across a number of centres.

Introduction

Ovarian cancer is the fifth most common female cancer and carries a poor prognosis. Around 10-15% of ovarian cancers, and over 20% in women under age 50 are due to germline mutations in the BRCA1 or BRCA2 gene[1]. These women have an elevated lifetime risk of breast (72% and 69% respectively) and ovarian cancer (44% and 17% respectively) [2] compared to the population risk of 1-5% for ovarian cancer. Other germline mutations such the mismatch repair genes responsible for Lynch Syndrome increase ovarian cancer risk to around 9%[3]. The prevalence of germline gene mutations which increase the risk of ovarian cancer is up to 1:400 women and these cancers commonly develop at an earlier age than in the general population[2]. The wider availability of rapid, low-cost sequencing methods and the increasing indications for gene testing mean that more women are being diagnosed with germline mutations which increase their risk of ovarian cancer.

There is currently no effective screening strategy for ovarian cancer and the only intervention proven to reduce risk is bilateral salpingo-oophorectomy (RRBSO). Extensive evidence confirms that RRBSO reduces the risk of ovarian cancer by up to 95% in high-risk women and leads to an overall survival benefit[4]. RRBSO may also detect occult ovarian cancer. Current guidelines advise RRBSO before aged 40 in BRCA1 carriers or before aged 45 for BRCA2 carriers[5].

Despite strong evidence that bilateral salpingo-oophorectomy reduces cancer risk and increases survival in high-risk women, many women decline to undergo risk-reducing surgery. Reported uptake rates vary considerably from around 17%-89%[6]. The reasons why many women decline or defer RRBSO are not well understood, but concerns about early menopause are a factor in premenopausal women[7]. Deleterious gene mutations are commonly identified when women are still premenopausal, so RRBSO will lead to surgical menopause. Despite the clear benefits for cancer risk reduction in high-risk women, very little is known about the impact of RRBSO on non-cancer outcomes[8] and this is of concern to high-risk women and their health care providers[9]. In the general population, there is growing evidence that early menopause (<45 years), and particularly surgical menopause has significant negative consequences for coronary heart disease[10], cardiovascular death, all cause-

mortality, dementia and Parkinson's disease, particularly for those who do not take hormone replacement therapy HRT[11 12]..However, the quality of current evidence is low, and there have been very few prospective studies of surgical menopause in any population.

High-risk women considering RRBSO are faced with complex decision-making, weighing up the potential adverse health implications of bilateral oophorectomy against the known reduction in cancer risk[5]. Most studies of RRBSO have focused exclusively on cancer outcomes, but current evidence suggests that premenopausal women experience a significant worsening of vasomotor symptoms (hot flushes and night sweats), a persistent decline in menopause-related quality of life and sexual function one year after RRBSO [13]. HRT partly mitigates these symptoms, but even in HRT users sexual function and vaginal symptoms do not return to pre-surgical levels[14 15]. Use of HRT is thought to be safe in high-risk women, provided they do not have a personal history of breast cancer, but the proportion of users is unknown and evidence for safety is limited[16].

Bilateral salpingo-oophorectomy leads to infertility, and women may consider undergoing concurrent hysterectomy. Hysterectomy adds to the duration, cost and potential complications of surgery, but avoids the need for combined HRT and removes the risk of endometrial pathology associated with tamoxifen use[17]. More information is needed from prospective studies to inform women and their health care providers considering hysterectomy at the time of RRBSO.

To support informed decision making and to appropriately structure follow-up care there is an unmet need for prospective data on the non-cancer consequences of RRBSO[5]. Having reduced their risks of breast and ovarian cancer, high-risk women should reasonably anticipate a normal QOL and life expectancy. In order to decide whether and when to undergo RRBSO, and how best to optimise health post-operatively, more information is needed about the non-cancer consequences of risk-reducing oophorectomy.

This multicentre, population-based, controlled, cohort study will generate new data to inform decision making around RRBSO and evidence-based follow-up care in the general population following surgical menopause. The primary objective of WHAM is to assess the association between RRBSO and sexual function as measured by the Female Sexual Function Index. The secondary outcomes are menopausal symptoms and menopause-related quality of life, mental health, bone health and turnover, cardiometabolic risk and sleep quality. We hypothesise that RRBSO in premenopausal women will reduce sexual function (primary outcome), increase menopausal symptoms, reduce menopause-related QOL, increase bone turnover, reduce bone density, increase cardiometabolic risk and reduce sleep quality compared to age-matched premenopausal women who retain their ovaries. We do not expect RRBSO to affect mental health[18].

Methods: Participants and Outcomes

Study design and setting

This is a multicentre, cohort study comparing 105 high-risk pre-menopausal women up to 50 years of age who plan to undergo RRBSO with 105 age-matched, premenopausal women who do not plan to undergo oophorectomy or pregnancy in the next two years. Study recruitment commenced in April 2013 and is ongoing, enrolling women from 8 public and 4 private hospitals in Australia (Victoria and New South Wales). The projected timeline for recruitment is 3-4 years. All subjects will be followed up for two years from the baseline visit.

Eligibility criteria and recruitment

Eligible women will be premenopausal and age up to 50 years with regular menstrual periods (if intact uterus), no vasomotor symptoms and an FSH (follicular stimulating hormone) level of <15IU/L on day 2-6 of the menstrual cycle. Exclusions include <3 months since pregnancy and lactation, abnormal uterine bleeding, or use of anti-estrogens such as tamoxifen.

Exposed women are defined as those at high inherited risk of ovarian cancer due to confirmed presence of a gene mutation (carriers of BRCA1, BRCA2, BRIP1, RAD51C, Lynch Syndrome) or high familial risk of ovarian cancer and planning to undergo RRBSO. Those with a personal history of breast cancer will be included if they remain premenopausal and are not currently taking endocrine therapy. Participants will be recruited via clinician referrals from familial cancer, high-risk breast cancer and menopause clinics, referrals from public and private gynaecology oncologists and surgeons, and via targeted advertising through mainstream and electronic media (eg. newspaper and television reports, cancer registries, cancer support newsletters and websites). Each referral will be processed upon receipt and eligibility screening and subsequent recruitment will be scheduled to occur within 8 weeks prior to the RRBSO surgery date. The baseline visit will be scheduled for the early follicular phase (days 2-6) of the subject's menstrual cycle prior to RRBSO.

Women in the comparison group are defined as 1:1 individually age-matched (within +/- 5 years), pre-menopausal women who are not planning oophorectomy or pregnancy within the next 2 years. Comparison subjects can be low-risk or relatives of high-risk women who do not carry a gene mutation. The comparison group will be recruited via mainstream and electronic media advertising to the general public (eg. clinical research recruitment websites, hospital and university staff newsletters and websites), and by asking recruited cases to recommend the study to relatives and friends. Recruitment will be scheduled to occur during the early follicular phase (days 2-6) of the subject's menstrual cycle, and within the 8 weeks after eligibility screening. Women in the comparison group withdrawing prior to the 6-month follow-up will be replaced by women of similar baseline age.

Participant timeline

A schedule of study assessments and measurements is presented in Table 1. After informed consent and eligibility, baseline data will be collected including obstetric, gynaecological, medical and surgical history, current medications, risk factors for fracture (www.shef.ac.uk/FRAX), risk factors for cardiovascular disease including blood pressure, circulating cholesterol and lipids and C-reactive protein (www.heartfoundation.org.au/SiteCollectionDocuments/austcardiovascular-risk-charts.pdf), tobacco, drug and alcohol use, methods of contraception, methods of breast cancer surveillance, germline mutation type and family cancer history. In those with a history of breast cancer, stage and grade of tumour and treatment history will be recorded. Blood pressure, weight, height and waist-hip ratio will be measured and repeated at selected follow-up visits (see Table 1). A blood sample will be taken after an overnight fast to measure sex steroid concentrations, lipids, and cardiovascular risk factors which will be repeated at 1 and 2 years follow-up. A urine sample will be collected for comparison subjects to exclude pregnancy (see Table 1). Medications used in the 3 months prior to enrolment and throughout the 2 year follow-up period will be recorded and includes those related to bone health (calcium, vitamin D and anti-resorptive agents), depression, anxiety, HRT, non-hormonal treatments for vasomotor symptoms, contraception and insomnia. Adverse events (changes in physical and psychological health from baseline) will be monitored over the 2-year follow-up period. Questionnaires to measure sexual function, menopausal symptoms, menopause-related QOL, sleep quality, depression and anxiety will be administered at baseline and all post-baseline study visits (see Table 1). All participants will undergo DXA scans within 3 months of RRBSO (baseline) and again at 1 and 2-years post-baseline.

Participants will be free to withdraw at any time, either through formal revocation of consent (patient preference) or via ceased communication with the recruitment site (lost to follow-up). All collected data will be included in the analyses and any discrepancies related to data collected prior to withdrawal will be queried with the subject up to one month after the withdrawal date. In order to minimise missing data, participants who cannot complete all scheduled visits will be invited to continue in the study despite missing visits. Those who withdraw at a scheduled time-point, or who are unable to attend the recruitment site at a scheduled time-point will be offered the opportunity to complete any time-point data that can be captured remotely via telephone and email correspondence, including questionnaire, medications and adverse events data.

Outcomes

The primary outcome is the change in sexual function following RRBSO, as measured by the Female Sexual Function Index (FSFI)[19]. Sexual function was selected because it is a patient priority and in young women and because previous prospective studies suggest that sexual function may be permanently impaired following RRBSO[13-15]. Secondary outcomes include menopause-related QOL, menopausal symptoms, sleep quality, depression and anxiety, markers of cardiovascular disease and prediabetes, bone density and markers of bone turnover. All measures will be collected at baseline (prior to RRBSO in the intervention group) with follow-up measures scheduled as per Table 1.

Measurement of sexual function

Subjects will be asked whether they currently have a sexual partner and whether sexual problems for the partner impact on their sexual activity. We will use standardized and validated questionnaires to measure three aspects of sexual function:

1) The Female Sexual Function Index (FSFI) is a widely-used brief self-report questionnaire that assesses six separate dimension: Desire, arousal, lubrication, orgasm, satisfaction, pain and it also provides a total score[20]. The FSFI has been validated in a large group of women with sexual arousal disorder versus age-matched controls[19] and in cancer survivors[21]. It has demonstrated a high level of acceptability, reliability and validity in both cancer and non-cancer populations[22]. The FSFI has a high internal consistency, test retest reliability and differentiates well between sexually-dysfunctional and non-dysfunctional women and is highly sensitive in discriminating between clinical and non-clinical populations[20]. FSFI scores (primary) will indicate which domains of sexual function are affected by RRBSO. The FSFI takes <5 minutes to complete.

2) The revised Female Sexual Distress Scale (FSDS-R)[23] is a brief (13 item) questionnaire which measures the extent to which reduced sexual desire causes distress in women. Distress is a key feature of hypoactive sexual desire disorder (HSDD). The (FSDS-R) has good discriminant validity, test-retest reliability, and internal consistency in measuring sex-related personal distress in women with HSDD[24]. The scale also has good content validity (relevance, clarity, comprehensiveness)[25].

3) The Sexual Activity Questionnaire (SAQ) evaluates sexual pleasure (desire, enjoyment and satisfaction), discomfort (vaginal dryness and dyspareunia) and habit (frequency of sexual activity compared to usual activity)[26]. The SAQ has been validated in breast cancer patients and in high-risk women[27]. It is quick and easy to administer and has good face validity discriminating between the sexual functioning of pre- and post-menopausal women[27]

Measurement of circulating testosterone and SHBG

Circulating testosterone concentrations are reduced following RRBSO and this may contribute to sexual function, although findings are conflicting[15]. Circulating concentrations of total testosterone and the testosterone precursors, androstenedione and 5-dehydroepiandrosterone (DHEA) and sex hormone binding globulin (SHBG) will be measured at baseline and follow up, as per Table 1. Fasting blood samples will be immediately centrifuged to isolate plasma, and stored at -80 degrees centigrade. Because conventional radioimmunossays lack sensitivity at low androgen concentrations found after surgical menopause[28] we will use liquid chromatography tandem mass spectrometry (LC-MS/MS), using a Sciex API 5500Q instrument by CPR Pharma Services (Adelaide, SA). The lower limit of measurement is 0.025 ng/mL for testosterone, 0.05 ng/mL for androstenedione, and 0.5 ng/mL for DHEA. The intra-assay coefficients of variation are low (<5%) at 1nM. SHBG concentrations will be measured using a non-competitive liquid-phase RIA (68562, Orion Diagnostica, Finland). We will calculate free testosterone concentrations using measured total testosterone and SHBG concentrations[28].

Measurement of menopausal symptoms and menopause-related quality of life

Menopausal symptoms will be measured using the Greene Climacteric Scale, which measures the frequency and severity of menopausal symptoms in psychological somatic and vasomotor domains[29]. The scale is widely used and has been validated in an Australian population[30].

Menopause-related QOL will be measured using the Menopause-related Quality of Life Intervention (MENQOL-Intervention) questionnaire[31]. The MENQOL-intervention covers four domains; vasomotor, physical, psychosocial and sexual, and includes a global QOL life item. It is widely used internationally and its strength and validity have recently been confirmed in a large population-based sample of midlife women[32] and in breast cancer survivors[33]. The questionnaire tests the impact of an intervention, such as oophorectomy, on symptoms. Each takes less than five minutes to complete. Use of HRT and of non-hormonal medications for vasomotor symptoms will be recorded, and subjects will be asked about decision-making around HRT.

Measurement of sleep quality

Sleep quality will be measured using the Pittsburgh Sleep Quality Index (PSQI)[34], a widely used and validated measure of sleep quality[35]. The questionnaire measures subjective sleep quality, latency, duration, habitual sleep efficiency, sleep disturbances and medications, and daytime dysfunction. The PSQI takes <5 minutes to complete.

Measurements of depression and anxiety

Depression and anxiety will be measured using the Centre for Epidemiologic Studies Depression (CES-D)[36]and the Generalized Anxiety Disorder (GAD-7)[37]scales, respectively. The CES-D measures the frequency of depressive feelings and behaviours experienced in the past week and includes 20 items that are assigned scores ranging from 0-3. The final CES-D score (0 – 60) is the sum of the 20 items and a score of ≥16 points is indicative of depression. The GAD-7 measures the frequency of GAD symptoms in the past fortnight and includes 7 items that are assigned scores ranging from 0-3. The final GAD-7 score (0 – 21) is the sum of the 7 items and a scores of 5-9, 10-14 and 15-21 are indicative of mild, moderate and severe anxiety respectively. Each questionnaire takes <5 minutes to complete.

Measurement of cardiovascular disease risk

Resting blood pressure, weight, height and waist/hip ratio will be measured as per table 1. Fasting blood samples will be analysed for serum insulin, glucose, triglycerides (TG), cholesterol, high density lipoprotein (HDL-C), low density lipoprotein (LDL-C) and high sensitivity C-reactive protein (hs CRP) which predicts CVD in healthy women[38]. These have not previously been prospectively measured in surgical menopause. Homeostasis model assessment (HOMA) will be calculated by fasting insulin (μU/ml) x fasting glucose (mM)]/22.5. Insulin resistance will be defined by a HOMA reading >488. The presence of diabetes or prediabetes will be established by fasting glucose and HbA1c. A HbA1c of >6.5% will be used as a cut-off for the diagnosis of diabetes as recommended by the American Diabetes Association (www.diabetes.org) and carried out in National Association of Testing Authorities (NATA) accredited laboratories using standard equipment.

Measurement of bone density and markers of bone turnover

We will measure fasting serum albumin, creatinine, calcium and phosphate, circulating markers of bone turnover (beta-C-terminal telopeptide of type I collagen (beta CTX) and N-terminal propeptide of type 1 collagen)[39]. We will measure 25-OH vitamin D2 and D3 using LC tandem mass spectrometry and intact parathyroid hormone (PTH) immunoassay. The bone turnover markers are independent predictors of fracture risk and will supplement BMD data. Regional BMD (at the lumbar spine and hip) will be measured using dual-energy X-ray absorptiometry (DXA) within 3 months of RRBSO (baseline). We will also use DXA to measure total body bone mineral content (BMC) which will increase power to detect bone loss[40]. DXA measurement location will be included as a covariate and change from baseline will be used in outcome analyses. Fracture risk assessment using a FRAX tool (www.shef.ac.uk/FRAX), will only be applied to women aged over 40 years.

Sample size

We will recruit 105 high-risk pre-menopausal women planning RRBSO and 105 age-matched (± 5 years) women in the comparison group. The primary outcome is sexual dysfunction (FSFI score <26.55)[41] where lower FSFI scores indicate worse sexual function. Based on large population-based surveys, we have assumed that around 24% of premenopausal women will have sexual dysfunction (FSFI below clinical cut off) at baseline[42 43] and that the proportion with sexual dysfunction does not differ between the high-risk women or those in the comparison group, or between age groups, and that it does not change over the 2-year follow-up period in the comparison group. Sample size calculations are based on comparing the proportion of women with sexual dysfunction in the RRBSO group with

the comparison group at the two year follow-up. A sample size of 89 women per group will provide 80% power at a two-sided 5% level of significance to detect a 21% difference (from 24% in the comparison group to 45% in the RRBSO group), or 105 per group when allowing for 15% loss to follow-up at 2-years. This difference in the proportion of women with sexual dysfunction is clinically significant[44]. For the secondary outcomes, this sample size of 89 per group will also provide 83% power to detect a difference in the proportion of women with a DXA T-score of ≤ -1 at 2 years, from 16% in the comparison group to 36% in the RRBSO group[45] and 92% power to detect a mean difference between groups of 0.5 standard deviation in the MENQOL score.

Methods: Data collection, management, and analysis

Data collection methods

Study data are being collected using paper case report forms (CRF), paper self-reported questionnaires, paper recorded phone interviews, and paper copies of biochemical, pathology and bone density imaging reports. These paper documents will be kept by each recruitment site in a locked cabinet accessible to local research staff only. All data will be entered and stored in a de-identified, password-protected electronic study database created with the REDCap© web application (https://projectredcap.org/)[44]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources[46]. Internet access to the REDCap© database will utilise a secure server located at the University of Melbourne, Australia (REDCap© consortium host), and access will be limited to local research staff at each recruitment site. Research staff will only have access to the REDCap© data collected at their local recruitment site, whereas the chief investigator, project manager, data administrator and statistician will have access to all REDCap© data.

Data management

Management of comprehensive and valid paper records will be the responsibility of local research staff at each recruitment site. To ensure a systematic approach to data collection the project manager will provide protocol training and written standard operating procedures to research staff prior to any study visits being performed. Data integrity will be maintained thorough review of all collected data prior to, during and after each study visit. Any time-sensitive data (eg. questionnaires) will be reviewed as soon as they are collected and any identified discrepancies will be resolved within one week of collection. Medications and adverse events data will be reviewed and consolidated at every study visit. All other data discrepancies will be queried with the subject via email or telephone correspondence and resolved within one month of collection. Records of participant screenings and enrolments at each site will be maintained using Microsoft Excel spreadsheets with diary features. These documents will assist research staff to adhere to study timelines and to regularly monitor and report site study progress to the project manager, investigators and the responsible HRECs. Electronic data entry into the REDCap© database will begin no later than 12 months prior to the last participant last visit. Database training of research staff and data entry will be conducted and overseen (respectively) by the project manager.

Data and safety monitoring

We do not anticipate any study-related adverse events (AEs) or serious adverse events (SAEs). The only anticipated AEs include phlebotomy-related site injuries (minor) and vasovagal syncope (rarely), and negative psychological responses to questionnaires and interview discussions. These AEs will be circumvented or managed by providing the subject with appropriate advice and counselling during and after each study visit. Reports of biochemistry, pathology and bone density results will be routinely reviewed by medically-qualified site investigators. Any concerning results will be immediately reviewed and reported to the subject and her GP. All other results will be reviewed

within one week of report receipt and any results outside of normal ranges will be reported to the subject's GP within 2 weeks. The project manager will directly monitor all Victorian data within one month of collection, and personally visit other recruitment sites on a 6-monthly basis to perform data monitoring activities. The outcomes will be reported to the chief investigator and all relevant research staff and investigators within one month of each monitoring visit, and any systematic problems with data collection, data management and adverse events monitoring and reporting will be rectified. Questionnaires will be independently scored on two separate occasions prior to data entry into the REDCap© database, and all data entry into REDCap© will be monitored by an independent data administrator. REDCap© data queries will be addressed by the project manager and data administrator using the REDCap© Data Resolution Workflow module.

Statistical methods

The analysis set will consist of all recruited women. Baseline characteristics will be summarised by group. The primary outcome is sexual dysfunction, defined as an FSFI score of <26.55 at 2 years. The primary outcome and binary secondary outcomes (e.g. PSQI score > 5; CES-D score ≥ 16; GAD-7 ≥ 10, absolute change from baseline in diastolic blood pressure ≥ 5 mmHg, relative change from baseline in HDL:LDL ratio > 2.5, BMD T-score ≤ -1) will be analysed by fitting a generalised linear model with a logistic link function using generalised estimation equations to account for the repeated measurements [47]. Continuous secondary outcomes including FSFI as a continuous outcome will be analysed by fitting a linear regression model using generalised estimating equations. The matching variable age-group will be including in the above models. Appropriate transformation of a continuous variable may be performed before analyses if the variable is found to be skewed. A directed acyclic graph will be used to explore which covariates to include in the adjusted -model[48 49]. An adjusted model will be fitted to correct for the potential confounding of time-independent covariates (e.g. use of hormonal contraception at baseline, use of antidepressant medication at baseline) and time-dependent covariates (e.g. symptoms of depression and/or anxiety). We anticipate that around one third of women will have concurrent hysterectomy at the time of RRBSO, that 40% will take HRT following RRBSO, and that 10% of high-risk women will either have a history of breast cancer or will develop breast cancer over the follow-up period. In addition to the primary comparison of all RRBSO participants with all controls, we will compare outcomes between the three sub-groups (RRBSO ± hysterectomy, ±HRT, ± breast cancer) with all controls.

The number and proportion of women using specific medication (e.g. HRT, antidepressants) will be summarised by group. Adverse events will be recorded and graded using the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) criteria and the number and proportion of women with at least one AE will be summarised by group. Exploratory subgroup analyses will examine whether the effect differs across the following subgroup categories a) age at baseline (<45 years vs ≥45 years) and b) use of hormonal contraception at baseline (yes vs no) by adding the subgroup and its interaction with group to the model.

Outcomes and Significance

Growing numbers of women are known to be at high inherited risk of ovarian cancer and are electing to undergo RRBSO. The established reduction in ovarian cancer mortality following RRBSO could be further improved by minimizing the negative non-cancer consequences, which also may contribute to morbidity and all-cause mortality. This can be addressed only when the non-cancer outcomes are known, and this requires prospective data collection. The principal significance is high burden of disease from ovarian cancer and the growing number of high-risk women who would benefit from RRBSO. In addition, because prospective studies of surgical menopause in the general population are very limited, the findings from this study will also inform care of low-risk women undergoing surgical menopause. These data will be used to develop resources to support decision making around RRBSO including the timing of surgery, additional hysterectomy, preoperative risk assessment and counselling and post-operative follow-up including use of HRT. Our studies will directly improve cancer outcomes by impact on clinical practice and policy, through the development of

multidisciplinary evidence-based guidelines and screening protocols. Consumers have clearly indicated that they wish to be informed about the consequences of RRBSO and that current information provision and follow-up care are inadequate[50 51]. Decision making and satisfaction are improved when high-risk women are offered dedicated clinical services[52 53]. Our data and guidelines will provide a template for the care of other high-risk women considering RRBSO as new genes are identified. Improved information about the non-cancer consequences of RRBSO is unlikely to dissuade high-risk women from surgery. Despite side effects, most do not regret their choice[18 50]. Improved follow-up care may also improve QOL for high-risk women and contribute to early detection and/or prevention of conditions related to early menopause. This will be the first international multicentre, prospective study of non-cancer outcomes after RRBSO or surgical menopause in any population. Currently, there is no consensus on how high-risk women should be managed following RRBSO. This study will provide new evidence on which to develop evidence-based care for this growing population of women.

Ethics and Dissemination

This is a prospective observational cohort study of high-risk women undergoing RRBSO. No study-related safety concerns are anticipated. The study has been granted ethics approval at each of the participating recruitment centres, including:

- Peter MacCallum Cancer Centre (Victoria, Australia)
- The Royal Women's Hospital (Victoria, Australia)
- The Royal Melbourne Hospital (Victoria, Australia)
- Prince of Wales Hospital (NSW, Australia)
- Westmead Hospital (NSW, Australia)
- Royal Hospital for Women (NSW, Australia)
- Royal Prince Alfred Hospital (NSW, Australia)
- Chris O'Brien Lifehouse (NSW, Australia)

Dissemination will be through peer-reviewed publications, presentations at national and international conferences and existing networks including WISP, National and International Menopause societies and specialist colleges.

Table 1: Schedule of Assessments / Investigations

Study Procedures	Baseline Day 1* (Visit 1)	Month 3 ±6 weeks (Visit 2)	Month 6 ±6 weeks (No Visit)	Month 12 ±6 weeks (Visit 3)	Month 24 ±6 weeks (Visit 4)
Informed Consent and Eligibility	•				
Surgical, Medical, Gynaecological, Obstetric and Menstrual History	•				
Smoking, Drug and Alcohol Use History	•				
Germline Mutation Testing History	•				
Personal and Family Cancer History	•				
Personal Breast Cancer Surveillance, Diagnosis, Treatment Details (if applicable)	•				
Contraceptive Methods	•				
Fracture Risk Assessment [#] *(http://www.shef.ac.uk/FRAX/tool.jsp)*	•				
Height	•				
Weight	•			•	•
Waist-Hip Ratio *(http://bupa.com.au/)*	•			•	•
Blood Pressure	•	•		•	•
Urinary Pregnancy Test (Comparisons Only)	•	•		•	•
Medications	•	•	•	•	•
Adverse Events		•	•	•	•
Questionnaires					
FSFI, FSDS-R and SAQ (Sexual function, distress and activity)	•	•	•	•	•
GCS and MENQOL (Menopausal Symptoms and QOL)	•	•	•	•	•
PSQI (Sleep Quality)	•	•	•	•	•
CES-D (Depression) and GAD-7 (Anxiety)	•	•	•	•	•
Blood Tests (Fasting)					
FSH, Estradiol (days 2-6 menstrual cycle)	•				
Total Testosterone, DHEAS, Androstenedione, SHBG	•			•	•
Total Cholesterol, LDL-C, HDL-C, Triglycerides, Insulin, Glucose, HbA1c, CRP	•			•	•
Albumin, Creatinine, Calcium, Phosphate, P1NP, BCTX, Parathyroid Hormone, Vitamin D	•			•	•
Bone Mineral Density (BMD)					
DXA Scans of Hip and Lumbar Spine BMD and of Total Body Bone Mineral Content (BMC)		•		•	•

* The baseline visit will be performed up to 8 weeks prior to RRBSO for the intervention group, or following eligibility screening for controls.

[#] The FRAX tool will only be applied to women aged over 40 years at baseline.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	10

Continued on next page

Results Checklist not applicable – this is a Study Protocol submission

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.