Cochrane Library

Cochrane Database of Systematic Reviews

Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations (Protocol)

Eleje GU, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, Okonkwo OO

Eleje GU, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, Okonkwo OO.
Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations.
Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD012464.
DOI: 10.1002/14651858.CD012464.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations

George U Eleje[1], Ahizechukwu C Eke[2], Ifeanyichukwu U Ezebialu[3], Joseph I Ikechebelu[4], Emmanuel O Ugwu[5], Onyinye O Okonkwo[6]

[1]Effective Care Research Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, PMB 5001, Nnewi, Nigeria. [2]Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Johns Hopkins University School of Medicine, Baltimore, MD, Maryland, USA. [3]Department of Obstetrics and Gynaecology, Faculty of Clinical medicine, College of Medicine, Anambra State University Amaku, Awka, Nigeria. [4]Department of Obstetrics/Gynaecology, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria. [5]Obstetrics and Gynaecology, University of Nigeria Enugu Campus/University of Nigeria Teaching Hospital Ituko-Ozalla, Enugu, Nigeria. [6]Department of Pathology, Tabitha Medical Centre, Abuja, Nigeria

Contact address: George U Eleje, Effective Care Research Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, PMB 5001, Nnewi, Anambra State, Nigeria. georgel21@yahoo.com.

Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: New, published in Issue 12, 2016.

Citation: Eleje GU, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, Okonkwo OO. Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No.: CD012464. DOI: 10.1002/14651858.CD012464.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations.

BACKGROUND

Description of the condition

Ovarian cancer is the fifth most common type of cancer, and the fourth most common cause of cancer mortality, in women (ESMO 2013; Gottschau 2016). Globally approximately 204,000 women are diagnosed with ovarian cancer each year, of whom nearly 115,000 die from their disease, with an incidence rate of 6.1/100,000 and a mortality rate of 3.8/100,000 (IARC 2012; Ozols 2006). There were an estimated 65,540 new diagnoses and 42,700 deaths from this disease in Europe in 2012, and 22,240 new diagnoses and 14,030 deaths in the USA in 2013 (ESMO 2013; NCCN 2014). The estimated lifetime risk for a woman developing ovarian cancer is about 1/54 (ESMO 2013). The incidence of ovarian cancer increases with age and is most prevalent in postmenopausal women with a median age of 63 years at the time of diagnosis (McGuire 2016; NCCN 2014). Patients with early stage disease have few or vague symptoms, which may contribute to their late presentation (Ang 2011; NCCN 2014). More than 70% of patients present with advanced disease, and less than 40% of women with ovarian cancer in the USA survive more than five years following diagnosis (NCCN 2014), but more than 40% survive in European populations (Gottschau 2016).

Studies have shown that the presence of deleterious mutations in the BRCA-1 or BRCA-2 gene has a decisive influence on the development of various types of neoplasms, such as breast, ovarian, tubal and peritoneal cancers (Eccles 2016; Guidozzi 2016; Iavazzo 2016). Approximately, 10% of ovarian cancers and 3% to 5% of breast cancers are due to germline mutations in BRCA1 and BRCA2 genes (ACOG 2009). BRCA1 and BRCA2 are separate genes that map onto two different chromosomes, 17q21 and 13q12.3 respectively (Girolimetti 2014; Staples 2013). They have distinctive primary sequences although interruption of either BRCA gene leads to comparable pathophysiological effects, in addition to similar cancer spectra. BRCA1 and BRCA2 are tumour suppressor genes for DNA repair. In addition to, and as part of, their roles as tumour suppressor genes, BRCA1 and BRCA2 are involved in myriad functions within cells, including homologous DNA repair, genomic stability, transcriptional regulation, protein ubiquitination, chromatin remodeling and cell cycle control (Iodice 2010; Tutt 2002; Venkitaraman 2014). Loss of BRCA function results in development of chromosomal instability (Tutt 2002; Venkitaraman 2014).

BRCA gene mutations only account for a small fraction of the overall breast and ovarian cancers. Approximately 1/300 to 1/800 individuals carry the mutations in the general population (ACOG 2009). In the UK, BRCA1 and BRCA2 mutations were identified in 5.9% of women diagnosed with breast cancer under the age of 36 years, and in 4.1% of women diagnosed with breast cancer between the age of 36 and 45 years (Peto 1999). Two studies found that BRCA1 and BRCA2 mutations represent 10% to 15% of all ovarian cancers (Pal 2005; Risch 2001).

Specific mutations in the BRCA1 or BRCA2 gene occur more frequently in certain populations, including Ashkenazi Jews, French Canadians and Icelanders (Hartge 1999; Lynch 2013). The lifetime risk of ovarian cancer for a woman is 39% to 46% with a BRCA1 mutation and 12% to 20% with a BRCA2 mutation, and the risk of breast cancer for a woman with a BRCA1 or BRCA2 mutation is 65% to 74% (Girolimetti 2014; Meaney-Delman 2013). Specific mutations may be identified in the affected person, through the full sequencing of BRCA1 and BRCA2, and a 'single-site' test could then be offered to other family members (Ford 1998). The result of this could be either (a) a deleterious mutation is identified, or (b) no deleterious mutation is identified, or (c) variants of uncertain significance (VUS) (Girolimetti 2014; Ready 2011). VUS are alterations in the DNA sequence that have unknown effects on the protein function and disease risk, and often constitute a major issue in BRCA diagnostic testing (Girolimetti 2014). Since undetectable BRCA1/2 mutations may be present, those negative results may be uninformative (ACOG 2009).

In women with BRCA1 mutations, less than 2% to 3% of carriers develop ovarian cancer by the age of 40. This increases to 10% to 21% by the age of 50. In women with BRCA2 mutations, less than 3% of carriers develop ovarian cancer by the age of 50. However, 26% to 34% of these women appear to develop breast cancer by the age of 50 (Ford 1998; King 2003; Rebbeck 2002; Satagopan 2002; Struewing 1997). Recommendations have therefore been made that women with BRCA1/2 mutations should be offered risk-reducing salpingo-oophorectomy (RRSO) by the age of 40 or when child-bearing is complete (ACOG 2009). Estimates of the frequency of fallopian tube cancer in BRCA mutation carriers are limited by the lack of precision in the assignment of site of origin for high-grade, metastatic, serous carcinomas at initial presentation (Lengyel 2013). Compared with family history-based testing, population-based genetic testing in Ashkenazi Jews may detect 56% additional BRCA carriers (a high proportion of carriers not identified by cancer family history-based testing), which may increase requests for prophylactic surgery in the general populations (Manchanda 2015a; Manchanda 2015b).

BRCA-positive women with ovarian cancer have a better prognosis than controls in terms of overall survival due to greater chemosensitivity of BRCA-positive tumours (Biglia 2016). The pathology of cancer associated with BRCA1 and BRCA2 mutations is predominantly high grade and of serous and endometrioid type, rather than mucinous or borderline tumours (ACOG 2009). Primary peritoneal cancer is an aggressive malignancy which, due to the absence of a specific screening test, cannot be diagnosed in its early stages (Iavazzo 2016). Recent studies have suggested that many ovarian and primary peritoneal cancers may be of tubal origin, and therefore part of the spectrum of disease associated with these mutations (Callahan 2007; NCCN 2014). Collaborative efforts to devise international guidelines around BRCA1 and BRCA2 testing in ovarian cancer and other cancers to ensure consistent screening practices are needed (Arts-de Jong 2016; Karakasis 2016; Lheureux 2016).

Description of the intervention

Available strategies to reduce the risk of developing BRCA1/2 mutation-associated gynaecological cancers include surveillance, chemoprevention and risk-reducing surgery (Kauff 2002). Prophylactic risk-reducing salpingo-oophorectomy (RRSO) refers to the surgical removal of both fallopian tubes and ovaries as an option for women with BRCA1 or BRCA2 mutations not thought to have cancer before the surgical procedure, but who have a high lifetime ovarian cancer, fallopian tube cancer or breast cancer risk (Rebbeck 2009; Shu 2016). In women at increased risk for ovarian cancer, RRSO is a highly effective tool to lower the risk for both ovarian cancer and breast cancer, although there remains a small risk for developing cancer of the peritoneum (the lining of the abdomen) known as primary peritoneal cancer. The specific protocol for RRSO for high-risk women involves exploring the pelvic organs for any evidence of cancer, performing a peritoneal wash (the pelvis is bathed in saline and fluid collected to look for any cancer cells that may be in the abdomen), and removal of the ovaries and fallopian tubes in their entirety. The 'Intensive' RRSO protocol includes: bilateral salpingo-oophorectomy and removal of entire

length of the fallopian tubes, cytologic examination of peritoneal washings, random peritoneal and omental biopsies (Powell 2011; Powell 2014).

Microscopic (occult) cancer of the ovary or fallopian tube might be identified following RRSO and proportionally more fallopian tube cancers have been detected than ovarian cancers following prophylactic surgery (Powell 2005). A study in 122 BRCA-mutation positive women undergoing RRSO detected occult cancers in 6% at the time of surgery; all of the cancers originated in fallopian tubes (Callahan 2007). This study suggests that much of the 'ovarian' cancer in BRCA carriers may begin in the fallopian tubes. It is therefore important to remove the tubes in BRCA-mutation carriers and to perform 'serial sectioning' of the fallopian tubes to exclude occult cancers or serous intra-epithelial tubal carcinomas (STIC). In the SEE-FIM protocol (Sectioning and Extensively Examining of the Fimbriated end), the greatest surface area of the tube is histologically examined, based on the suggestion that multiple deeper sections should be examined, if the initial haematoxylin and eosin (H&E) sections are negative. This was reinforced in a study involving 300 consecutive bilateral salpingectomies that employed the SEE-FIM protocol and a single-H&E section per block and had identified 68 cases of pelvic serous carcinoma, of which 12 were associated with STIC lesions (Mahe 2013). The sensitivity of a single-H&E section to detect STIC was evaluated and revealed that of the 56 cases initially negative for STIC, four additional cases (three associated with primary ovarian serous carcinoma and one associated with primary peritoneal serous carcinoma) of STIC were detected after examination of multiple deeper sections of the fallopian tubes. The single-H&E section SEE-FIM approach therefore detected only 75% (95% confidence interval (CI) 51% to 90%) of STIC (Mahe 2013). The SEE-FIM protocol should be considered especially in cases of endometrial carcinoma, non-uterine pelvic serous cancers or serous borderline ovarian tumours (Crum 2007; Koc 2016; Leonhardt 2011).

Laparoscopy is the preferred method for performing a RRSO (Blok 2016), due to a lower morbidity than laparotomy. Although hysterectomy is not a part of risk-reducing surgery for BRCA1/2 mutations, it could theoretically reduce risk of cancer in the cornual fallopian tube (Karlan 2004). Hysterectomy may be considered for other potential medical indications, or for women taking tamoxifen to reduce risk of endometrial cancer (ACOG 2009). However, most clinicians view the role of synchronous hysterectomy as controversial (Segev 2013; Shu 2016), as the risk of endometrial cancer in women with hereditary breast and ovarian cancer is not significantly elevated (Segev 2013).

Follow-up will vary based on whether or not a hysterectomy will be performed and whether or not hormone replacement therapy is prescribed. Early surgical menopause may increase some other health risks and many experts recommend long-term follow-up to monitor bone density and heart disease. Chemoprevention with anti-oestrogens, especially in BRCA2 carriers, and breast surveillance may be recommended after RRSO to reduce the risk of breast cancer. In all the placebo-controlled trials in which tamoxifen was studied as a chemopreventive agent, only the National Surgical Adjuvant Breast and Bowel Project P-1 Study showed an increase in endometrial cancer, and the absolute risk was 0.55% over five years (Hartmann 2015). Thus, tamoxifen therapy remains an important option for the reduction of the risk of breast cancer in premenopausal women and in women who cannot take aromatase inhibitors (Hartmann 2016).

Recent data from Shu 2016 found that women with BRCA1 mutations have a higher risk of developing a rare type of endometrial cancer. They enrolled more than 1000 female BRCA1 or BRCA2 mutation carriers who had RRSO, but still had a uterus, and found that BRCA1 mutations were associated with a serous endometrial cancer (Shu 2016). Shu 2016 followed the women (median age of 45.6 years) for several years after RRSO, comparing the incidence of uterine cancer in this group with expected uterine cancer rates, adjusted for age and race, from the Surveillance, Epidemiology, and End Results database. Among the 1083 women enrolled, eight incident uterine cancers were observed (4.3 expected; observed to expected [O:E] ratio, 1.9; 95% CI 0.8 to 3.7; P= 0.09). Although no increased risk for endometrioid endometrial carcinoma or sarcoma was found after stratifying by subtype; five serous or serous-like (serous/serous-like) endometrial carcinomas, or both, were observed (four BRCA1+ and one BRCA2+) 7.2 to 12.9 years after RRSO (BRCA1: 0.18 expected [O:E ratio 22.2, 95% CI 6.1 to 56.9; P<0.001]; BRCA2: 0.16 expected [O:E ratio, 6.4, 95% CI 0.2 to 35.5; P =0.15]) (Shu 2016). Combined RRSO-hysterectomy may become the preferred risk-reducing surgical approach for women with BRCA1 mutations, although may not be appropriate for women who have extensive uterine adhesions, had previous reproductive tract surgery, or may be considering a future pregnancy using assisted-reproductive approaches (Leath 2016; Shu 2016).

The potential adverse effects of RRSO are associated surgical morbidity and premature menopause in younger women. However, the surgery also causes immediate surgical menopause, which can be accompanied by short- and long-term side effects and health consequences (Bober 2015). Apart from significant menopausal symptoms, RRSO could lead to increased risk for bone mineral loss (osteopenia and osteoporosis) and cognitive dysfunction (Guidozzi 2016). Risk for cardiovascular disease is also increased, if the procedure is performed in women less than 50 years of age (Guidozzi 2016). It is important for women who have undergone surgical menopause, or who are considering RRSO, to discuss menopausal symptoms and management with their healthcare team. Studies have found that short-term hormone replacement therapy use does not negate the protective effect of salpingo-oophorectomy on subsequent breast cancer risk in BRCA1/2 mutation carriers until the time of expected natural menopause about age 50 years (Armstrong 2004; Rebbeck 2005).

In women who do not also have risk-reducing mastectomy, there is growing concern regarding the possible adverse effect on the risk

of breast cancer associated with the use of a combination of oestrogen and progesterone, especially among younger women who would use the agents for more than 10 years. Because of the theoretical increased risk of breast cancer associated with combined treatment with oestrogen and progesterone HRT (compared with oestrogen only HRT), the Society of Gynecologic Oncology suggests the use of a progestin-containing intrauterine device to accompany oestrogen replacement and thus avoid the administration of systemic therapy with progestin (Walker 2015). However, performing bilateral risk-reducing mastectomy (BRRM) may lead to highly significant risk reduction of breast cancer in BRCA1 and BRCA2 mutation carriers (De Felice 2015). The risk reduction of breast cancer is estimated to be 94% to 95% when BRRM is performed, nearly 89% in patients who received BRRM plus RRSO, and 46% when RRSO alone is carried out, suggesting that RRSO alone cannot replace the beneficial impact of BRRM in breast cancer occurrence (De Felice 2015). This information may allow clinicians to discuss all the available options with women in order to design individual management strategies.

How the intervention might work

RRSO may reduce the risk for ovarian and fallopian tube cancers by 85% to 90% and for breast cancer by 40% to 70% in women with known BRCA1/2 mutations (ACOG 2009; Finch 2014). Additionally, risk-reducing strategies have been shown to have associations with a gain in life expectancy in BRCA1/2 carriers (Salhab 2010). Previously, ovarian cancers were believed to develop from the lining of the ovary, as a result of the constant rupture and repair process during ovulation. More recent studies suggest that many ovarian cancers in BRCA gene mutation carriers originate in the distal fallopian tube (part of the tube closest to the ovary), causing researchers to question whether salpingectomy alone (removal of the fallopian tubes) might reduce ovarian cancer risk. A candidate precursor to tubal intraepithelial carcinoma, entitled the 'p53 signature', suggests that molecular events associated with serous cancer (p53 mutations) may be detected in benign mucosa (Crum 2007; Leonhardt 2011). Current expert guidelines recommend that women with BRCA mutations should undergo RRSO between the ages of 35 to 40 years or after childbearing is completed. Ovaries secrete the hormones that control the reproductive cycle. Surgical removal of ovaries will substantially reduce the levels of the hormones oestrogen and progesterone that circulate in the body (Finch 2006; Metcalfe 2015; Olivier 2004). Bilateral salpingo-oophorectomy can halt or slow breast cancers that need these hormones to grow (van Verschuer 2014). Some studies have suggested that the level of breast cancer risk reduction may differ between BRCA1 and BRCA2 carriers who choose RRSO (Powell 2011; Powell 2014; van Verschuer 2014). Kauff 2008 reported from a multi-centered study, that women with BRCA2 mutations who had RRSO lowered their risk for breast cancer by 72%. Risk reduction was less (about 29%) for women with BRCA1 mutations. Kauff 2008 suggested that oophorectomy may be more protective for women with BRCA2 mutations, since their breast cancers are more likely to be hormone receptor-positive, while breast cancers in BRCA1 mutation carriers are usually hormone receptor-negative (van Verschuer 2014; Veronesi 2005). This observed mechanism can be attributed to the carcinogenic effect of oestrogen metabolites-DNA adducts (Mitrunen 2003). Overall their risk of dying from breast cancer is reduced by 56% with BRCA1/2 mutation carriers who had oophorectomy (Domchek 2010). Since breast tumours are largely oestrogen-driven, it has been suggested that the hormonal blockade by oophorectomy inhibits the development of breast tumours (Narod 2001). Thus, prophylactic oophorectomy has the advantage of reducing the risk of breast cancer, as well as ovarian cancer. Breast cancer risk reduction surgery in BRCA-mutation carriers who undergo RRSO may extend beyond women under 50 years (the average age of menopause), but some studies have suggested a benefit for breast cancer risk reduction in women who underwent RRSO after the menopause. Barlin 2013 reported that 199 postmenopausal BRCA-mutation carriers who received RRSO postmenopausally had a 57% reduction in breast cancer risk. Barlin 2013 hypothesised that, although the ovaries stop producing oestrogen and progesterone after natural menopause, they continue producing some hormones, including testosterone, which might explain why RRSO after menopause still has protective effects against breast cancer.

Why it is important to do this review

In women at increased risk, due to a family history or confirmed mutation in high penetrance genes, such as BRCA1/2, annual screening with CA125 using a cut-off and transvaginal ultrasound scan (TVS) did not detect early stage cancers (Hermsen 2007; Stirling 2005). This was re-confirmed by the UK Familial Ovarian Cancer Screening Study (UKFOCSS) (Rosenthal 2013a). Between 2002 and 2008, 3563 women underwent annual screening with serum CA125 and transvaginal sonography (TVS). Whilst the sensitivity for detection of incident ovarian cancer/fallopian tube cancer within a year of the last annual screen was high (81.3% to 87.5% depending on whether occult cancers were classified as interval cancers or true positives), only 30.8% of screen-detected ovarian cancer/fallopian tubes were Stage I/II. The preliminary findings led to UK FOCSS Phase II where annual CA125 screening was replaced by four-monthly serum CA125 (Rosenthal 2013b). Whilst the results of the phase II study were encouraging, screening at present cannot be considered a safe alternative to RRSO. Similarly, a large randomised trial (the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial) found that screening did not decrease mortality from ovarian cancer (Pinsky 2013).

Although surveillance for ovarian, peritoneal and fallopian tube cancer has not been proven to be effective, RRSO has been widely adopted as a key component of breast and gynaecological can-

cer risk-reduction in women with BRCA1 or BRCA2 mutations (Girolimetti 2014). The risk of breast cancer can be reduced either with risk-reducing oophorectomy or mastectomy, or both (Maeshima 2016), or non-surgically using effective screening and prevention strategies (Rosenthal 2013b). However, due to the overall lack of effective screening for ovarian cancer, RRSO is usually recommended to BRCA1/2 mutation carriers after completion of childbearing (Rebbeck 2009). Although some authors have shown that fallopian tubes may be the cause of many gynaecological cancers in mutation carriers, researchers caution that there is not enough evidence to suggest that all ovarian cancer cases start in the fallopian tubes (Kramer 2013). Also removing only the fallopian tubes is not likely to lower the risk for breast cancer. More research is needed to completely understand the role of the fallopian tubes in the development of these cancers. Although a previous systematic review (Marchetti 2014), and meta-analysis (Rebbeck 2009), have been conducted on the benefit of RRSO in women with BRCA1 or BRCA2 mutations, its role in reducing the incidence of breast, ovarian, fallopian and other cancers, including other health outcomes are still debatable (Fakkert 2015; Heemskerk-Gerritsen 2015). A Cochrane systematic review is needed to assess the efficacy and adverse effects of RRSO in women with BRCA1 or BRCA2 mutations.

OBJECTIVES

To assess the benefits and harms of risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) are unlikely or possible due to ethical reasons. Therefore we will examine the following types of studies.

- Quasi-randomised trials (studies where participant allocation or enrolment is open to systematic bias/errors, as all participants do not have an equal chance of being in one group or the other).
- Non-randomised trials, prospective and retrospective cohort studies, and case series (all with concurrent comparison groups).
- We will exclude case-control studies and uncontrolled observational studies.

In order to minimise selection bias, we will only include studies that use statistical adjustment for baseline case mix using multivariable analyses.

Types of participants

Adult women, 18 years or older, with known BRCA1/2 mutations. We will include women without a previous or co-existing breast or ovarian or fallopian tube malignancy, as well as women with or without concomitant hysterectomy. We will include women with a mastectomy before, concomitant with, or after risk-reducing salpingo-oophorectomy (RRSO), even if mastectomy has been the focus of another Cochrane review (Lostumbo 2010). We will exclude women with a previous or co-existing breast malignancy and women with unilateral oophorectomy or salpingectomy or salpingo-ophorectomy (both). In addition, we will exclude women with prophylactic salpingectomy with delayed oophorectomy or ovarian conservation (Harmsen 2015).

Types of interventions

Risk-reducing salpingo-oophorectomy (RRSO) (surgery to remove both fallopian tubes and ovaries as an option for women with BRCA1 or BRCA2 mutations not thought to have cancer before the surgical procedure, but who have a high lifetime ovarian cancer, fallopian tube cancer or breast cancer risk) versus no RRSO.

Types of outcome measures

Primary outcomes

- Overall survival: survival until death from all causes. We will assess survival from the time when women were enrolled in the study.
- Ovarian cancer mortality (including fallopian tube cancer and primary peritoneal cancer).
- Breast cancer mortality.

Secondary outcomes

- Ovarian cancer incidence.
- Fallopian tube cancer incidence.
- Serous tubal intraepithelial carcinoma incidence.
- Primary peritoneal cancer incidence.
- Breast cancer incidence.
- Bone fracture incidence.
- Disease-free survival: time from surgical procedure to cancer diagnosis.
- Morbidity:
    - direct surgical morbidity;

- surgically related systemic morbidity e.g. chest/wound/urine infection, venous thromboembolism, premature menopause etc.
- Recovery, readmission
- Quality of life (QoL), measured using a scale that has been validated through reporting of norms in a peer-reviewed publication (Roila 2001; Spitzer 1981).
- Adverse events, classified according to CTCAE 2010: surgery-related complications measured as the proportion of women who develop one or more of the items below (according to the study definition) within 12 weeks. We will classify complications into intraoperative and postoperative complications:
  - intraoperative complications:
    - haemorrhage;
    - bladder injury;
    - gastrointestinal tract injury - small or large bowel;
    - vascular injuryUreteric injury;
    - cardiac or respiratory complications;
    - anaphylaxis;
  - postoperative complications will be classified as either early (before discharge from hospital or within seven days of surgery), late (from seven days to follow-up: within 12 weeks of surgery), or total (early and late):
    - wound breakdown;
    - infection;
    - abscess/haematoma;
    - bowel obstruction/ileus;
    - bowel perforation;
    - primary haemorrhage;
    - secondary haemorrhage;
    - ureteric obstruction;
    - cardiac or respiratory complications;
    - pulmonary embolism;
    - deep vein thrombosis
    - neurological
    - psychiatric/psychosexual problem.

Search methods for identification of studies

We will search for papers in all languages and translate them as necessary.

Electronic searches

We will search the following electronic databases.
- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) (current issue).
- MEDLINE (January 1946 to date).
- Embase (January 1980 to date).

The MEDLINE search strategy is in Appendix 1. For databases other than MEDLINE, we will adapt the search strategy accordingly.
We will identify all relevant articles on PubMed and using the 'related articles' feature and we will perform a further search for newly published articles.

Searching other resources

Unpublished and grey literature

We will search the following for ongoing trials.
- The metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com/rct).
- Physicians Data Query (www.nci.nih.gov).
- USA National Institutes of Health (https://clinicaltrials.gov/ct).
- USA National Cancer Institute (www.cancer.gov/clinicaltrials).
- ISRCTN registry (www.isrctn.com/).
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/).

If ongoing trials that have not been published are identified through these searches, we will approach the principal investigators, and major co-operative groups active in this area, to ask for relevant data.

Handsearching

We will handsearch the citation lists of included studies, key textbooks and previous systematic reviews and contact experts in the field to identify further reports of trials. We will also handsearch the reports of conferences in the following sources.
- Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncologist).
- International Journal of Gynecological Cancer (Annual Meeting of the International Gynecologic Cancer Society).
- British Journal of Cancer.
- British Cancer Research Meeting.
- Annual Meeting of European Society of Medical Oncology (ESMO).
- Annual Meeting of the American Society of Clinical Oncology (ASCO).

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database (EndNote X7), and will remove duplicates. Two review authors (GE and IE) will examine the remaining references independently. We will exclude those studies that clearly do not meet the inclusion criteria and we will obtain full-text copies of potentially relevant references. Two review authors (GE and IE) will independently assess the eligibility of the retrieved reports/publications. We will resolve any disagreement through discussion or, if required, we will consult a third review author (AC). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

For included studies, we will extract the following data.

- Author, year of publication and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design, methodology.
- Study population:
  - total number enrolled;
  - participant characteristics (e.g. BRCA1, BRCA2 or both);
  - age;
  - co-morbidities;
  - other baseline characteristics.
- Intervention details:
  - type of surgery;
  - occult cancer;
  - type of screening test;
  - period of screening test;
  - type of chemoprevention;
  - dose of chemoprevention;
  - course of chemoprevention;
  - type of histology protocol adopted (e.g. the SEE-FIM protocol) as documented in Blok 2016 and Mahe 2013;
  - use of peritoneal washing cytology (Blok 2016);
  - use of oral contraceptives.
- Comparison: we will compare the outcomes for women with adnexa-preserving
- Risk of bias in study (Assessment of risk of bias in included studies).
- Duration of follow-up.
- Outcomes: for each outcome, we will extract the outcome definition and unit of measurement (if relevant). For adjusted estimates, we will record variables adjusted for in analyses.
- Results: we will extract the number of participants allocated to each intervention group, the total number analysed for each outcome, and the missing participants.

We will extract the results as follows.

- For time-to-event data (overall survival and disease-specific survival), we will extract the log of the hazard ratio [log(HR)] and its standard error from trial reports. If these are not reported, we will attempt to estimate the log (HR) and its standard error using the methods described by Parmar 1998.
- For dichotomous outcomes (e.g. adverse events or deaths, if it is not possible to use a HR) we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. quality of life measures), we will extract the final value and standard deviation of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard error.

If reported, we will extract both unadjusted and adjusted statistics. Where possible, all data extracted will be those relevant to an intention-to-treat analysis, in which we will analyse participants in groups to which they were assigned.
We will note the time points at which outcomes were collected and reported.
Two review authors (GE and IE) will extract data independently onto a data abstraction form specially designed for the review. We will resolve differences between review authors by discussion or by appeal to a third review author (AE) if necessary. We will approach the principal investigators of included studies to ask for any missing relevant unpublished data.

Assessment of risk of bias in included studies

We will assess the risk of bias in included studies using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). This will include assessment of the following.

- Selection bias: random sequence generation and allocation concealment.
- Performance bias: blinding of participants and personnel (participants and treatment providers).
- Detection bias: blinding of outcome assessment.
- Attrition bias: incomplete outcome data.
- Reporting bias: selective reporting of outcomes.
- Other possible sources of bias.

Two review authors (GE and IE) will apply the 'Risk of bias' assessment tool independently and we will resolve any differences in opinion by discussion or by appeal to a third review author (AE). We will summarise results in both a 'Risk of bias' graph and a 'Risk

of bias' summary. We will interpret the results of meta-analyses in light of the findings with respect to risk of bias.
We have listed the individual 'Risk of bias' items that we will adapt for our review in Appendix 2.

Measures of treatment effect

We will use the following measures of the effect of treatment.

- For time to event data, we will use the HR, if possible.
- For dichotomous outcomes, we will use the RR.
- For continuous outcomes, we will use the mean difference between treatment arms.

Unit of analysis issues

We do not anticipate unit of analysis issues.

Dealing with missing data

We will not impute missing outcome data for the primary outcomes. If data are missing or the included studies only report imputed data, we will contact trial authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity

We will assess heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by subgroup analyses. If there is evidence of substantial heterogeneity, we will investigate and report the possible reasons for this.

Assessment of reporting biases

When we suspect or there is direct evidence of selective outcome reporting, we will ask the trial authors for additional information. We will examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small study effects, such as publication bias, if we identify a sufficient number of studies.

Data synthesis

If sufficient, clinically similar studies are available we will pool their results in meta-analyses using Review Manager 5 (RevMan 5) (Review Manager 5).

- For time-to-event data, we will pool HRs using the generic inverse variance facility of RevMan 5 (Review Manager 5).
- For any dichotomous outcomes, we will calculate the RR for each study and we will then pool these values.
- For continuous outcomes, will pool the mean differences between the treatment arms at the end of follow-up if all trials measure the outcome on the same scale, otherwise we will pool standardised mean difference values.

If any trials have multiple treatment groups, we will divide the 'shared' comparison group into the number of treatment groups and comparisons between each treatment group and treat the split comparison group as independent comparisons.
We will use the random-effects models with inverse variance weighting for all meta-analyses (DerSimonian 1986).

'Summary of findings' table

We will assess the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, will use GRADEpro software and will present the review results in 'Summary of findings' (SoF) tables. A SoF table (Appendix 3) consists of three parts: information about the review, a summary of the statistical results, and the grade of the quality of evidence. Appendix 3 displays a draft 'Summary of findings' table, which will be prepared to summarise the results of the meta-analysis based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We will present the results of the meta-analysis for the following outcomes as outlined in the Types of outcome measures section.

- Overall survival.
- Ovarian cancer mortality.
- Breast cancer mortality.
- Bone fracture incidence.
- Quality of life
- Adverse events.

We will present the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013). The five factors will be used to judge whether the quality of the collected evidence should be decreased if we are dealing with randomised clinical trials or increased if we are dealing with observational studies. We will create a 'Summary of findings' table based on the methods described by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and using GRADEpro Guideline Development Tool (GDT) (GRADEpro GDT 2014). We will use the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014). We will downgrade the evidence from 'high' quality by one level for serious (or by two for very serious) for each limitation.

- High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

- Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table format, such as that used by Chan 2011.

Subgroup analysis and investigation of heterogeneity

We will subgroup by the BRCA mutations (BRCA1, BRCA2 or both) and the type of surgery.
We will consider factors such as age, obesity, race, reproductive history, ovarian stimulation, menstrual history, use of the oral contraceptives, breastfeeding, estrogens therapy, pelvic inflammatory disease, length of follow-up and risk of bias status in our interpretation of any heterogeneity. We will also consider women with BRCA mutation carriers receiving bilateral prophylactic risk-reducing oophorectomy with or without concomitant breast malignancy, with or without concomitant hysterectomy, and with or without concomitant mastectomy.

Sensitivity analysis

We will perform sensitivity analyses and we will exclude studies at high risk of bias.

ACKNOWLEDGEMENTS

We thank Jo Morrison for clinical and editorial advice, Jane Hayes for designing the search strategy and Gail Quinn and Clare Jess for their contribution to the editorial process.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

Additional references

ACOG 2009
American College of Obstetricians and Gynecologists, ACOG Committee on Practice Bulletins-Gynecology, ACOG Committee on Genetics, Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstetrics and Gynecology* 2009;**113**(4):957–66.

Ang 2011
Ang C, Chan KK, Bryant A, Naik R, Dickinson HO. Ultra-radical (extensive) surgery versus standard surgery for the primary cytoreduction of advanced epithelial ovarian cancer. *Cochrane Database of Systematic Reviews* 2011, Issue 4. [DOI: 10.1002/14651858.CD007697.pub2]

Armstrong 2004
Armstrong K, Schwartz JS, Randall T, Rubin SC, Weber B. Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. *Journal of Clinical Oncology* 2004;**22**(6):1045–54.

Arts-de Jong 2016
Arts-de Jong M, de Bock GH, van Asperen CJ, Mourits MJ, de Hullu JA, Kets CM. Germline BRCA1/2 mutation testing is indicated in every patient with epithelial ovarian cancer: a systematic review. *European Journal of Cancer* 2016;**61**:137–45. [PUBMED: 27209246]

Barlin 2013
Barlin J, Pike M, Otegbeye E, Arnold A, Stadler Z, Robson M, et al. Abstract no 245: Does postmenopausal risk-reducing salpingo-oophorectomy reduce the risk of BRCA-associated breast cancer? Proceedings of the 2013 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer; 2013 March 9-12; Los Angeles (CA). 2013.

Biglia 2016
Biglia N, Sgandurra P, Bounous VE, Maggiorotto F, Piva E, Pivetta E, et al. Ovarian cancer in BRCA1 and BRCA2 gene mutation carriers: analysis of prognostic factors and survival. *Ecancermedicalscience* 2016;**10**:639. [PUBMED: 27350785]

Blok 2016
Blok F, Roes EM, van Leenders GJ, van Beekhuizen HJ. The lack of clinical value of peritoneal washing cytology in high risk patients undergoing risk-reducing salpingo-oophorectomy: a retrospective study and review. *BMC Cancer* 2016;**16**:18. [PUBMED: 26768420]

Bober 2015
Bober SL, Recklitis CJ, Bakan J, Garber JE, Patenaude AF. Addressing sexual dysfunction after risk-reducing salpingo-oophorectomy: effects of a brief, psychosexual intervention. *Journal of Sexual Medicine* 2015;**12**(1):189–97. [PUBMED: 25311333]

Callahan 2007

Callahan MJ, Crum CP, Medeiros F, Kindelberger DW, Elvin JA, Garber JE, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. *Journal of Clinical Oncology* 2007;**25**(25):3985–90. [PUBMED: 17761984]

Chan 2011

Chan RJ, Webster J, Marquart L. Information interventions for orienting patients and their carers to cancer care facilities. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: 10.1002/14651858.CD008273.pub2]

Crum 2007

Crum CP, Drapkin R, Miron A, Ince TA, Muto M, Kindelberger DW, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. *Current Opinion in Obstetrics & Gynecology* 2007;**19**(1):3–9. [PUBMED: 17218844]

CTCAE 2010

National Institutes of Health - National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (accessed 05 December 2016).

De Felice 2015

De Felice F, Marchetti C, Musella A, Palaia I, Perniola G, Musio D, et al. Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis. *Annals of Surgical Oncology* 2015;**22**(9):2876–80. [PUBMED: 25808098]

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. *Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis*. Systematic Reviews in Health Care: Meta-Analysis in Context. London: BMJ Publication Group, 2001.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177–88.

Domchek 2010

Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* 2010;**304**(9):967–75. [PUBMED: 20810374]

Eccles 2016

Eccles DM, Balmaña J, Clune J, Ehlken B, Gohlke A, Hirst C, et al. Selecting patients with ovarian cancer for germline BRCA mutation testing: findings from guidelines and a systematic literature review. *Advances in Therapy* 2016;**33**(2):129–50. [PUBMED: 26809252]

ESMO 2013

Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C: ESMO Guidelines Working Group. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2013;**24**(S6):vi24–32.

Fakkert 2015

Fakkert IE, Abma EM, Westrik IG, Lefrandt JD, Wolffenbuttel BH, Oosterwijk JC, et al. Bone mineral density and fractures after risk-reducing salpingo-oophorectomy in women at increased risk for breast and ovarian cancer. *European Journal of Cancer* 2015;**51**(3):400–8. [PUBMED: 25532426]

Finch 2006

Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 mutation. *JAMA* 2006;**296**(2):185–92. [PUBMED: 16835424]

Finch 2014

Finch AP, Lubinski J, Møller P, Singer CF, Karlan B, Senter L, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. *Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology* 2014;**32**(15):1547–53. [PUBMED: 24567435]

Ford 1998

Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *American Journal of Human Genetics* 1998;**62**(3):676–89.

Girolimetti 2014

Girolimetti G, Perrone AM, Santini D, Barbieri E, Guerra F, Ferrari S, et al. BRCA-associated ovarian cancer: from molecular genetics to risk management. *BioMed Research International* 2014;**2014**:787143. [PUBMED: 25136623]

Gottschau 2016

Gottschau M, Mellemkjaer L, Hannibal CG, Kjaer SK. Ovarian and tubal cancer in Denmark: an update on incidence and survival. *Acta Obstetricia et Gynecologica Scandinavica* 2016;**95**(10):1181–9. [PUBMED: 27454324]

GRADEpro GDT 2014 [Computer program]

GRADE Working Group, McMaster University, Hamilton (ON). GRADEpro Guideline Development Tool (GDT). GRADE Working Group, McMaster University, Hamilton (ON), 2014.

Guidozzi 2016

Guidozzi F. Hormone therapy after prophylactic risk-reducing bilateral salpingo-oophorectomy in women who have BRCA gene mutation. *Climacteric* 2016;**19**(5):419–22. [PUBMED: 27426853]

Harmsen 2015

Harmsen MG, Arts-de Jong M, Hoogerbrugge N, Maas AH, Prins JB, Bulten J, et al. Early salpingectomy (TUbectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers (TUBA study): a prospective non-randomised multicentre study. *BMC Cancer* 2015;**15**:593. [PUBMED: 26286255]

Hartge 1999
Hartge P, Struewing JP, Wacholder S, Brody LC, Tucker MA. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. *American Journal of Human Genetics* 1999;**64**(4):963–70. [PUBMED: 10090881]

Hartmann 2015
Hartmann LC, Degnim AC, Dupont WD. Atypical hyperplasia of the breast. *New England Journal of Medicine* 2015;**372**(13):1271–2. [PUBMED: 25806929]

Hartmann 2016
Hartmann LC, Lindor NM. Risk-reducing surgery in hereditary breast and ovarian cancer. *New England Journal of Medicine* 2016;**374**(24):2404. [PUBMED: 27305204]

Heemskerk-Gerritsen 2015
Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, Ausems MG, Collée JM, van Doorn HC, et al. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. *Journal of the National Cancer Institute* 2015;**107**(5):pii: djv033. [PUBMED: 25788320]

Hermsen 2007
Hermsen BB, Olivier RI, Verheijen RH, van Beurden M, de Hullu JA, Massuger LF, et al. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study. *British Journal of Cancer* 2007;**96**(9):1335–42. [PUBMED: 17426707]

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Higgins 2011
Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

IARC 2012
International Agency for Research on Cancer, World Health Organization. GLOBOCAN 2012: Estimated Cancer Incidence, and Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_population.aspx (accessed 05 December 2016).

Iavazzo 2016
Iavazzo C, Gkegkes ID, Vrachnis N. Primary peritoneal cancer in BRCA carriers after prophylactic bilateral salpingo-oophorectomy. *Journal of the Turkish German Gynecological Association* 2016;**17**(2):73–6. [PUBMED: 27403072]

Iodice 2010
Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B, Radice P, et al. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. *European Journal of Cancer* 2010;**46**(12):2275–84. [PUBMED: 20537530]

Karakasis 2016
Karakasis K, Burnier JV, Bowering V, Oza AM, Lheureux S. Ovarian cancer and BRCA1/2 testing: opportunities to improve clinical care and disease prevention. *Frontiers in Oncology* 2016;**6**:119. [PUBMED: 27242959]

Karlan 2004
Karlan BY. Defining cancer risks for BRCA germline mutation carriers: implications for surgical prophylaxis. *Gynecologic Oncology* 2004;**92**(2):519–20.

Kauff 2002
Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *New England Journal of Medicine* 2002;**346**(21):1609–15. [PUBMED: 12023992]

Kauff 2008
Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, Garber JE, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *Journal of Clinical Oncology* 2008;**26**(8):1331–7. [PUBMED: 18268356]

King 2003
King MC, Marks JH, Mandell JB, New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 2003;**302**(5645):643–6.

Koc 2016
Koc N, Ayas S, Arinkan SA. Comparison of the classical method and SEE-FIM protocol in detecting microscopic lesions in fallopian tubes with gynecological lesions. Journal of Pathology and Translational Medicine 2016 Aug 19 [Epub ahead of print]. [DOI: 10.4132/jptm.2016.06.17; PUBMED: 27539290]

Kramer 2013
Kramer L. Mixed reviews on removing fallopian tubes to prevent ovarian cancer. *Canadian Medical Association Journal* 2013 June 11;**185**(9):E391–2.

Langendam 2013
Langendam MW, Akl EA, Dahm P, Glasziou P, Guyatt G, Schünemann HJ. Assessing and presenting summaries of evidence in Cochrane Reviews. *Systematic Reviews* 2013;**2**:81.

Leath 2016
Leath CA, Huh WK, Alvarez RD. Drawing the line in risk-reducing gynecologic surgery in women with a BRCA mutation. *JAMA Oncology* 2016;**2**(11):1409–11. [PUBMED: 27367041]

Lengyel 2013
Lengyel E, Fleming S, McEwen KA, Montag A, Temkin SM. Serial sectioning of the fallopian tube allows for improved identification of primary fallopian tube carcinoma. *Gynecologic Oncology* 2013;**129**(1):120–3. [PUBMED: 23237768]

Leonhardt 2011
Leonhardt K, Einenkel J, Sohr S, Engeland K, Horn LC. p53 signature and serous tubal in-situ carcinoma in cases of primary tubal and peritoneal carcinomas and serous

borderline tumors of the ovary. *International Journal of Gynecological Pathology* 2011;**30**(5):417–24. [PUBMED: 21804388]

Lheureux 2016

Lheureux S, Karakasis K, Harter P, Scott C, Bacon M, Bryce J, et al. Germline BRCA1/2 testing practices in ovarian cancer: current state and opportunities for new directions. *Gynecologic Oncology* 2016;**140**(1):90–4. [PUBMED: 26475959]

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700.

Lostumbo 2010

Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database of Systematic Reviews* 2010, Issue 11. [DOI: 10.1002/14651858.CD002748.pub3]

Lynch 2013

Lynch HT, Snyder C, Casey MJ. Hereditary ovarian and breast cancer: what have we learned?. *Annals of Oncology* 2013;**24**(Suppl 8):viii83–viii95.

Maeshima 2016

Maeshima Y, Oseto K, Katsuragi R, Yoshimoto Y, Takahara S, Yamauchi A. Experience with bilateral risk-reducing mastectomy for an unaffected BRCA mutation carrier. *Journal of Breast Cancer* 2016;**19**(2):218–21. [PUBMED: 27382401]

Mahe 2013

Mahe E, Tang S, Deb P, Sur M, Lytwyn A, Daya D. Do deeper sections increase the frequency of detection of serous tubal intraepithelial carcinoma (STIC) in the "sectioning and extensively examining the FIMbriated end" (SEE-FIM) protocol?. *International Journal of Gynecological Pathology* 2013;**32**(4):353–7. [PUBMED: 23722507]

Manchanda 2015a

Manchanda R, Legood R, Burnell M, McGuire A, Raikou M, Loggenberg K, et al. Cost-effectiveness of population screening for BRCA mutations in Ashkenazi Jewish women compared with family history-based testing. *Journal of the National Cancer Institute* 2015;**107**(1):380. [PUBMED: 25435542]

Manchanda 2015b

Manchanda R, Loggenberg K, Sanderson S, Burnell M, Wardle J, Gessler S, et al. Population testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish community: a randomized controlled trial. *Journal of the National Cancer Institute* 2015;**107**(1):379. [PUBMED: 25435541]

Marchetti 2014

Marchetti C, De Felice F, Palaia I, Perniola G, Musella A, Musio D, et al. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. *BMC Women's Health* 2014;**14**:150. [PUBMED: 25494812]

McGuire 2016

McGuire V, Hartge P, Liao LM, Sinha R, Bernstein L, Canchola AJ, et al. Parity and oral contraceptive use in relation to ovarian cancer risk in older women. *Cancer Epidemiology, Biomarkers & Prevention* 2016;**25**(7): 1059–63. [PUBMED: 27197274]

Meader 2014

Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. *Systematic Reviews* 2014;**3**:82.

Meaney-Delman 2013

Meaney-Delman D, Bellcross CA. Hereditary breast/ovarian cancer syndrome: a primer for obstetricians/gynaecologists. *Obstetrics and Gynecology Clinics of North America* 2013;**40** (3):475–512.

Metcalfe 2015

Metcalfe K, Lynch HT, Foulkes WD, Tung N, Kim-Sing C, Olopade OI, et al. Effect of oophorectomy on survival after breast cancer in BRCA1 and BRCA2 mutation carriers. *JAMA Oncology* 2015;**1**(3):306–13. [PUBMED: 26181175]

Mitrunen 2003

Mitrunen K, Hirvonen A. Molecular epidemiology of sporadic breast cancer. The role of polymorphic genes involved in oestrogen biosynthesis and metabolism. *Mutation Research* 2003;**544**(1):9–41. [PUBMED: 12888106]

Narod 2001

Narod SA. Hormonal prevention of hereditary breast cancer. *Annals of the New York Academy of Sciences* 2001; **952**:36–43. [PUBMED: 11795442]

NCCN 2014

National Comprehensive Cancer Network. Epithelial ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) Version 3.2014. NCCN Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site (accessed 05 December 2016).

Olivier 2004

Olivier RI, van Beurden M, Lubsen MA, Rookus MA, Mooij TM, van de Vijver MJ, et al. Clinical outcome of prophylactic oophorectomy in BRCA1/BRCA2 mutation carriers and events during follow-up. *British Journal of Cancer* 2004;**90**(8):1492–7. [PUBMED: 15083174]

Ozols 2006

Ozols RF. Challenges for chemotherapy in ovarian cancer. *Annals of Oncology* 2006;**17**(Suppl 5):v181–7.

Pal 2005

Pal T, Permuth-Wey J, Betts JA, Krischer JP, Fiorica J, Arango H, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. *Cancer* 2005;**104**(12):2807–16. [PUBMED: 16284991]

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24): 2815–34.

Peto 1999

Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N, et al. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. *Journal of the National Cancer Institute* 1999;**91**(11):943–9. [PUBMED: 10359546]

Pinsky 2013

Pinsky PF, Zhu C, Skates SJ, Black A, Partridge E, Buys SS, et al. Potential effect of the risk of ovarian cancer algorithm (ROCA) on the mortality outcome of the Prostate, Lung, Colorectal and Ovarian (PLCO) trial. *International Journal of Cancer* 2013;**132**(9):2127–33.

Powell 2005

Powell CB, Kenley E, Chen LM, Crawford B, McLennan J, Zaloudek C, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. *Journal of Clinical Oncology* 2005;**23**(1):127–32.

Powell 2011

Powell CB, Chen LM, McLennan J, Crawford B, Zaloudek C, Rabban JT, et al. Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers: experience with a consecutive series of 111 patients using a standardized surgical-pathological protocol. *International Journal of Gynecological Cancer* 2011;**21**(5):846–51. [PUBMED: 21670699]

Powell 2014

Powell CB. Risk reducing salpingo-oophorectomy for BRCA mutation carriers: twenty years later. *Gynecologic Oncology* 2014;**132**(2):261–3. [PUBMED: 24528542]

Ready 2011

Ready K, Gutierrez-Barrera AM, Amos C, Meric-Bernstam F, Lu K, Hortobagyi G, et al. Cancer risk management decisions of women with BRCA1 or BRCA2 variants of uncertain significance. *Breast Journal* 2011;**17**(2):210–2. [PUBMED: 21294809]

Rebbeck 2002

Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *New England Journal of Medicine* 2002;**346**(21):1616–22.

Rebbeck 2005

Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, et al: PROSE Study Group. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *Journal of Clinical Oncology* 2005;**23**(31):7804–10.

Rebbeck 2009

Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *Journal of the National Cancer Institute* 2009;**101** (2):80–7. [PUBMED: 19141781]

Review Manager 5 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Risch 2001

Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *American Journal of Human Genetics* 2001;**68**(3):700–10. [PUBMED: 11179017]

Roila 2001

Roila F, Cortesi E. Quality of life as a primary end point in oncology. *Annals of Oncology* 2001;**12 Suppl 3**:S3–6. [PUBMED: 11804381]

Rosenthal 2013a

Rosenthal AN, Fraser L, Manchanda R, Badman P, Philpott S, Mozersky J, et al. Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. *Journal of Clinical Oncology* 2013;**31**(1):49–57. [PUBMED: 23213100]

Rosenthal 2013b

Rosenthal AN, Fraser L, Philpott S, Manchanda R, Badman P, Hadwin R, et al. Final results of 4-monthly screening in the UK Familial Ovarian Cancer Screening Study (UKFOCSS Phase 2). 2013 ASCO Annual Meeting. *Journal of Clinical Oncology* 2013;**(Suppl)**:Abstract 5507.

Salhab 2010

Salhab M, Bismohun S, Mokbel K. Risk-reducing strategies for women carrying BRCA1/2 mutations with a focus on prophylactic surgery. *BMC Women's Health* 2010;**10**:28. [PUBMED: 20961453]

Satagopan 2002

Satagopan JM, Boyd J, Kauff ND, Robson M, Scheuer L, Narod S, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Clinical Cancer Research* 2002;**8**(12):3776–81.

Schünemann 2011

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Segev 2013

Segev Y, Iqbal J, Lubinski J, Gronwald J, Lynch HT, Moller P, et al. The incidence of endometrial cancer in women

with BRCA1 and BRCA2 mutations: an international prospective cohort study. *Gynecologic Oncology* 2013;**130**(1):127–31. [PUBMED: 23562522]

Shu 2016
Shu CA, Pike MC, Jotwani AR, Friebel TM, Soslow RA, Levine DA, et al. Uterine cancer after risk-reducing salpingo-oophorectomy without hysterectomy in women with BRCA mutations. *JAMA Oncology* 2016;**2**(11):1434–40. [PUBMED: 27367496]

Spitzer 1981
Spitzer WO, Dobson AJ, Hall J, Chesterman E, Levi J, Shepherd R, et al. Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. *Journal of Chronic Diseases* 1981;**34**(12):585–97. [PUBMED: 7309824]

Staples 2013
Staples J, Goodman A. Chapter 14: PARP inhibitors in ovarian cancer. In: Díaz-Padilla I editor(s). *Ovarian Cancer - A Clinical and Translational Update*. InTech, 2013.

Stirling 2005
Stirling D, Evans DG, Pichert G, Shenton A, Kirk EN, Rimmer S, et al. Screening for familial ovarian cancer: failure of current protocols to detect ovarian cancer at an early stage according to the international Federation of gynecology and obstetrics system. *Journal of Clinical Oncology* 2005;**23**(24):5588–96. [PUBMED: 16110018]

Struewing 1997
Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *New England Journal of Medicine* 1997;**336**(20):1401–8.

Tutt 2002
Tutt A, Ashworth A. The relationship between the roles of BRCA genes in DNA repair and cancer predisposition. *Trends in Molecular Medicine* 2002;**8**(12):571–6. [PUBMED: 12470990]

van Verschuer 2014
van Verschuer VM, Heemskerk-Gerritsen BA, van Deurzen CH, Obdeijn IM, Tilanus-Linthorst MM, Verhoef C, et al. Lower mitotic activity in BRCA1/2-associated primary breast cancers occurring after risk-reducing salpingo-oophorectomy. *Cancer Biology & Therapy* 2014;**15**(4):371–9. [PUBMED: 24423863]

Venkitaraman 2014
Venkitaraman AR. Cancer suppression by the chromosome custodians, BRCA1 and BRCA2. *Science* 2014;**343**(6178):1470–5. [PUBMED: 24675954]

Veronesi 2005
Veronesi A, de Giacomi C, Magri MD, Lombardi D, Zanetti M, Scuderi C, et al. Familial breast cancer: characteristics and outcome of BRCA 1-2 positive and negative cases. *BMC Cancer* 2005;**5**:70. [PUBMED: 15996267]

Walker 2015
Walker JL, Powell CB, Chen LM, Carter J, Bae Jump VL, Parker LP, et al. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. *Cancer* 2015;**121**(13):2108–20. [PUBMED: 25820366]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1 exp Ovarian Neoplasms/
2 Fallopian Tube Neoplasms/
3 Peritoneal Neoplasms/
4 exp Breast Neoplasms/
5 (BRCA1 or BRCA2).mp.
6 ((ovar* or fallopian* or peritone* or breast or mammary) adj5 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*)).mp.
7 1 or 2 or 3 or 4 or 5 or 6
8 Salpingectomy/
9 Ovariectomy/
10 (oophorectom* or salping* or ovariectom* or RRSO*).mp.
11 8 or 9 or 10
12 7 and 11
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.

15 randomized.ab.
16 placebo.ab.
17 clinical trials as topic.sh.
18 randomly.ab.
19 trial.ti.
20 exp cohort studies/
21 (cohort* or prospective* or retrospective*).mp.
22 (case* and series).mp.
23 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 12 and 23
25 exp animals/ not humans.sh.
26 24 not 25
key:
mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
pt=publication type
ab=abstract
ti=title
sh=subject heading

Appendix 2. 'Risk of bias' assessment

Assessment of risk of bias in included randomised studies

- Random sequence generation
    - Low risk of bias e.g. participants assigned to treatments on basis of a computer-generated random sequence or a table of random numbers.
    - High risk of bias e.g. participants assigned to treatments on basis of date of birth, clinic id-number or surname, or no attempt to randomise participants.
    - Unclear risk of bias e.g. not reported, information unavailable.
- Allocation concealment
    - Low risk of bias e.g. where the allocation sequence could not be foretold.
    - High risk of bias e.g. allocation sequence could be foretold by patients, investigators or treatment providers.
    - Unclear risk of bias e.g. not reported.
- Blinding of outcomes assessors
    - Low risk of bias if outcome assessors were adequately blinded.
    - High risk of bias if outcome assessors were not blinded to the intervention that the participant received.
    - Unclear risk of bias if this was not reported or unclear.

Blinding of participants and personnel is usually impossible for surgical interventions.

- Incomplete outcome data

We will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as follows.

- Low risk of bias, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms.
    - High risk of bias, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms.
    - Unclear risk of bias if loss to follow-up was not reported.
- Selective reporting of outcomes
    - Low risk of bias e.g. review reports all outcomes specified in the protocol.
    - High risk of bias e.g. it is suspected that outcomes have been selectively reported.

- Unclear risk of bias e.g. it is unclear whether outcomes had been selectively reported.

- Other bias
  - Low risk of bias if we do not suspect any other source of bias and the trial appears to be methodologically sound.
  - High risk of bias if we suspect that the trial was prone to an additional bias.
  - Unclear risk of bias if we are uncertain whether an additional bias may have been present.

Assessment of risk of bias in included non-randomised studies

We will assess the risk of bias in non-randomised controlled trials in accordance with four additional criteria concerning cohort selection comparability of treatment groups.

- Relevant details of criteria for assignment of patients to treatments
  - Low risk of bias e.g. yes.
  - High risk of bias e.g. no.
  - Unclear risk of bias.

- Representative group of patients who received the experimental intervention
  - Low risk of bias, if representative of women with mutations in BRCA1 or BRCA2.
  - High risk of bias, if groups of patients were selected.
  - Unclear, if selection of group was not described.

- Representative group of patients who received the comparison intervention
  - Low risk of bias, if drawn from the same population as the experimental cohort.
  - High risk of bias, if drawn from a different source.
  - Unclear risk of bias, if selection of group not described.

- No differences between the two groups or differences controlled for, in particular with reference to mutations (BRCA1 or BRCA2 or both), type of surgery, age, obesity, race, reproductive history, ovarian stimulation, menstrual history, use of the oral contraceptives, breastfeeding, estrogens therapy and pelvic inflammatory disease etc.

  - Low risk of bias, if the study authors reported at least six of these characteristics.
  - High risk of bias, if the six of these characteristics differed and differences were not controlled for.
  - Unclear risk of bias, if fewer than six of these characteristics were reported even if there were no other differences between the groups, and other characteristics were controlled for.

Appendix 3. Draft 'Summary of findings' table

Title: Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations

Patient or population: adult women, 18 years or older, with known BRCA1/2 mutations
Settings: hospital
Intervention: risk-reducing salpingo-oophorectomy

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	Number of participants (studies)	Quality of evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
Overall survival (HZ)						

(*Continued*)

Ovarian cancer mortality (n)						
Breast cancer mortality (n)						
Bone fracture incidence (%)						
Quality of life						
Adverse events (n)						

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; HR: hazard ratio; MD: mean difference; RR: risk ratio; OR: odds ratio; n: number of events

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

CONTRIBUTIONS OF AUTHORS

George Eleje, Ahizechukwu Eke, Ifeanyichukwu Ezebialu, Joseph Ikechebelu, Emmanuel Ugwu and Onyinye Okonkwo drafted the protocol. All protocol authors read and approved the final protocol draft.

DECLARATIONS OF INTEREST

George Eleje- None known

Ahizechukwu Eke - None known

Ifeanyichukwu Ezebialu - None known

Joseph Ikechebelu - None known

Emmanuel Ugwu - None known

Onyinye Okonkwo - None known

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group, UK.