Risk reducing early salpingectomy and delayed oophorectomy as a two staged alternative for primary prevention of ovarian cancer in increased risk women: a commentary

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Ovarian cancer (OC) is the leading cause of death from gynaecological malignancies in the UK. Despite considerable funding to develop new treatments, 10-year survival remains poor at ~30%. This translates into 4,271 deaths annually in the UK, 42,700 in Europe and 152,000 deaths annually worldwide. High (e.g.-*BRCA1/BRCA2*) and moderate (e.g.-*RAD51C*/*RAD51D/BRIP1)* penetrance gene-mutations account for most of the known hereditary-risk of OC. At least 10% of women with epithelial-OC carry these germline mutations. *BRCA1/BRCA2* carriers have a 17%-44% risk of OC and 65-72% risk of breast cancer (BC), while *RAD51C*/*RAD51D/BRIP1* carriers have a 6-11% risk of OC. Primary surgical prevention in the form of risk-reducing salpingo-oophorectomy (RRSO) remains the most effective option and gold-standard for OC-risk reduction, particularly given the lack of an effective national OC-screening programme. The role of RRSO for primary surgical prevention has expanded to include not just *BRCA1/BRCA2* carriers but also women at intermediate-risk ($\geq$4-5% lifetime-risk of OC). RRSO reduces OC-risk by 80-96%. Whilst initial data suggested pre-menopausal RRSO reduced BC-risk by half, more recent publications have questioned this.[1] Nevertheless, RRSO reduces all-cause (HR=0.40, 95%CI:0.26-0.61), BC-specific (HR=0.44, 95%CI:0.26-0.76), and OC-specific (HR=0.25, 95%CI:0.08-0.75) mortality.[2]

Limitations of premenopausal RRSO:

Premenopausal RRSO leads to premature surgical menopause which has detrimental long-term health consequences. It is associated with an increased risk of heart-disease, stroke, osteoporosis, vasomotor symptoms, mood changes, sleep disturbance, reduced libido, vaginal dryness, sexual-dysfunction and neurocognitive decline, especially if unable to use hormone-replacement-therapy (HRT). A 3.03% absolute increased-risk of cardiovascular mortality has been reported with premenopausal oophorectomy without HRT (NNH=1:33). *BRCA*-carriers who have estrogen-receptor positive BC cannot take HRT. Additionally, vasomotor symptoms and sexual-dysfunction are not fully alleviated by HRT, with symptom levels remaining above those who retain their ovaries. Consequently many

46 women choose to delay RRSO until after menopause. Furthermore, RRSO has a 1.5-5% complication
47 rate.

48 **Role of fallopian-tube in etiopathogenesis of OC**

49 Following initial observations in *BRCA*-mutation carriers,[3] there is now broad acceptance of the role
50 of the fallopian-tube in the etiopathogenesis of epithelial-OC. Genotoxic injury leads to p53-mutations
51 and loss of p53-function (represented by p53-signatures) in the distal fallopian-tube. High-grade
52 serous ovarian cancers (HGSOC) may develop through further DNA damage from the combined
53 functional loss of p53 and *BRCA* (or related pathways) or through epigenetic reprogramming. A
54 precursor lesion called serous-tubal-intraepithelial-carcinoma (STIC) has been defined which is
55 present as a continuum with early tubal carcinomas, supporting transition from one to another. STICs
56 have been reported in up to 60% of sporadic HGSOC as well and in 92% of cases have identical TP53
57 gene-mutations to concurrent pelvic serous carcinomas. Molecular profiling supports the common
58 origin of STICs/HGSC from the distal tube. Occult STIC/invasive tubal cancers occur in 5-8% of RRSO
59 specimens from *BRCA*-mutation carriers. Around 70% of these lesions were found in the distal-tube
60 and not the ovary.

61 **Risk-reducing early-salpingectomy and delayed oophorectomy (RRESDO)**

62 The acceptance of a central role for the tube in OC etiopathogenesis coupled with the detrimental
63 health sequelae of premature menopause, has led to the attractive proposal of a two-step alternative
64 OC surgical prevention strategy in pre-menopausal women at increased (high/intermediate) OC-risk
65 who have completed their family but decline or wish to delay RRSO. It involves early-salpingectomy
66 (ES) as the first-step followed by delayed-oophorectomy (DO) after menopause. RRESDO has the
67 advantage of providing a level of risk reduction whilst conserving ovarian function and avoiding
68 negative side-effects/health-consequences of premature menopause. We reviewed the literature for
69 ES and DO for OC prevention. Appendix-S1 describes the search strategy and Figure-S1 the flow-chart
70 of results. Searches were performed in MEDLINE, EMBASE, Pubmed, CINAHL, PsychINFO and clinical-

trial registries (ISRCTN, clinicaltrials.gov). Table-1 lists the current studies reporting outcomes of RRESDO.[4-11] The quality of studies were assessed using the MINORS (Methodological Index for Non-Randomized Studies) checklist and CASP (Critical Appraisal Skills Programme) qualitative-research checklist.

Acceptability

Data on putative acceptability of RRESDO amongst women at high-risk of OC are limited to one small questionnaire study and one qualitative study in *BRCA1/BRCA2* carriers.[4, 8] Interest in RRESDO has been reported in 34% of women in a US survey (n=204)[8] and 44% in a Dutch qualitative study (n=39).[4] 35%-44% women were reported as being unsure about RRESDO and 12%-30% as disinterested.[4, 8] A recent non-randomised, prospective cohort, pilot study (n=43) with three study arms (RRESDO, RRSO, screening) found 28% uptake rate for RRESDO.[11] There are no data on acceptability of RRESDO in intermediate OC-risk women eligible for surgical prevention. A multicentre, prospective, UK study is evaluating views of high and intermediate-risk women (ISRCTN12310993). A UK-study found 60% of gynaecological oncologists and geneticists favoured offering RRESDO to pre-menopausal high-risk women declining RRSO, along-with strong support for a clinical-trial and creation of a UK-wide registry with ~80% favouring these options.[5] A Dutch qualitative-study also found high acceptability amongst health professionals for a clinical-trial.[4]

Benefits/facilitators and barriers/risks: RRESDO

The main reason for undergoing RRESDO reported by women at high OC-risk and health professionals is the ability to obtain some OC-risk reduction whilst avoiding detrimental consequences of early menopause.[4, 5, 8] Barriers to participation for patients included surgical complications, potential ovarian damage, family-history, previous BC, surgical costs, seriousness of OC and uncertainty on level of benefit obtained from early salpingectomy (ES) and poor pre-operative counselling of negative side-effects of RRSO.[4] Barriers perceived by health-professionals included need for two operations, lack of precision of OC-risk reduction, ease of decision to undergo RRSO, health-care costs, potential loss of

reduction in BC-risk, need for long-term follow-up with possible attrition from DO. Interestingly potential lack of BC-risk reduction was not raised by patients[4] and this in itself has become uncertain with recent reports finding no benefit of reduction in BC from RRSO. Although RRESDO involves two surgical procedures, preliminary evidence indicates that most women would find two procedures acceptable.[8, 11]

Other Outcomes

Preliminary pilot-data from a small study of 43 BRCA-mutation carriers suggests, RRESDO and RRSO are both associated with decreased cancer worry and RRESDO is associated with reduced anxiety at 12-months follow-up.[11] One study suggests that RRESDO may be cost-effective compared to RRSO for a base-case with a utility-score for RRSO=0.82 and for ES=0.99, level of OC-risk reduction=60% and no attrition from DO. However, more recent data reports a RRSO utility-score of 0.95, the actual disutility for ES is unknown, the precise level of OC-risk reduction is unknown, and potential attrition from DO is missing, which together maintain uncertainty around the comparative cost-effectiveness of RRESDO.

RRESDO should only be offered in a Clinical Trial/Research Study

Lack of clarity on several key issues strengthens the case to currently offer RRESDO within a research setting. The extent of OC-risk reduction and long-term health outcomes with ES remain unclear. While two retrospective population studies found a 35–42% reduction in OC-risk with salpingectomy in low-risk women, these studies were limited by: indication and detection bias, wide confidence-intervals, small number of OC cases in salpingectomy subgroups and lack of adjustment for contraceptive pill use. Besides results from the low-risk population cannot be directly extrapolated to high-risk women. Salpingectomy will not prevent OC arising outside the tube or within tubal epithelium lined inclusion cysts. Residual fimbrial tissue implants may remain on the ovarian surface after salpingectomy in 10% of cases,[12] and could become a potential site for malignant transformation. OC etiopathogenesis is complex and our current understanding of this is incomplete. There are different types of STIC and the

natural history, progression rates, outcomes and rate-limiting step in development of OC associated with each type is unknown. Moreover, STICs may not be precursors to all HGSOC cases. The long-term impact of salpingectomy on ovarian function and premature menopause is unknown. Although short-term data show no detrimental outcome for hormonal levels, blood-flow indices or surgical risks, these correlate more with fertility outcomes, and are not predictive of menopause. No validated hormonal criteria predicting duration of menopausal transition or time of final menstruation exist and only long-term assessments of hormonal levels/menstrual cycles can clarify this.

Concerns exist amongst clinicians regarding attrition from DO. A proportion who do not undergo DO may develop OC. Uncertainties remain around the cost-effectiveness of RRESDO. There is need for standardisation of protocols for management and follow-up of (isolated) STIC lesions both at national and international levels. A suggested management protocol is given in Table-2, Supplementary Figure S2. We reviewed the literature on management of STIC (Table-3) and found a limited evidence base. Isolated STIC was found in 2% (82/4,149) and occult invasive cancers in 2.2% (93/4,149) of women undergoing RRSO. We recommend bilateral salpingo-oophorectomy in isolated STIC with negative-cytology but full staging in those with positive-cytology or an abnormal staging CT-scan. Implementing RRESDO within a research setting would also enable the development of a tissue-&-data bio-resource for translational research and secondary studies.

Research studies offering RRESDO

There are currently five important non-randomised trials investigating aspects of RRESDO being undertaken in France, the Netherlands, US and UK. (Table-4). Randomised studies for surgical prevention are not feasible or ethical in high-risk women. The ongoing studies vary with respect to primary outcomes, design and sample sizes. The French (Fimbriectomy) study is powered on OC/PPC incidence, while the others are powered on menopause-related quality-of-life (Dutch), DO uptake (US) and sexual function (UK, US). The French study does not involve DO. DO is undertaken in the Dutch TUBA (TUbectomy with delayed oophorectomy to improve quality-of-life as alternative for risk-

reducing salpingo-oophorectomy in BRCA1/2 mutation carriers) study at 40-45 years in BRCA1 and 45-50 years in BRCA2 carriers; and in the US PSDO (Prophylactic-Salpingectomy-with-Delayed-Oophorectomy) study three years after ES. DO is undertaken in premenopausal women well before onset of menopause in the US and Dutch studies. In the UK PROTECTOR (Preventing Ovarian Cancer through early Excision of Tubes and late Ovarian Removal) study DO is undertaken at menopause but offered earlier for those women who may choose to do so. Similarly, in the US WISP (Women Choosing Surgical Prevention Trial) study, women are given the choice as to when to undergo DO but are encouraged to have this done between 40-50 years. While the Dutch and the US PSDO-study only include *BRCA*-carriers, the French study also includes women ascertained using FH. The UK study includes high and intermediate risk women: *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* carriers and FH based assessment. The WISP-study in addition offers RRESDO to PALB2/BARD1/MSH2/MSH6/MLH1/PMS2/EPCAM mutation carriers. However mutations in the Lynch syndrome genes are predominantly associated with an increased risk of non-serous epithelial-OC. In addition, there is insufficient evidence (lack of validated data) linking PALB2/BARD1/EPCAM/PMS2 mutations with OC.

Conclusion

RRSO remains the gold-standard for surgical prevention in women at increased risk of OC. RRESDO is an alternative for women who have completed their family and prefer to decline or delay premenopausal RRSO. In the absence of long-term prospective outcome data, and unaddressed knowledge gaps highlighted above, RRESDO should only be offered within the controlled environment of a clinical-trial/research study. It is vital clinicians offer appropriate counselling on the advantages and limitations of salpingectomy versus standard RRSO for informed decision making and consent. Long-term follow-up is essential to minimise attrition from DO. As data from ongoing trials emerge it will help inform national and international guidelines on an early-salpingectomy and delayed-oophorectomy strategy in women at increased risk of OC.

Disclosure of Interests

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Contribution to authorship

Literature search: FG

Preparation of tables and figures: FG, RM

Initial draft of manuscript: FG, RM

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Table-1: Studies reporting RRESDO outcomes

Publication	Country	Sample size (n)	Study design	Population	Intervention	Outcomes	Follow up	Quality of methodology
Arts-de Jong, 2015	The Netherlands	62	Qualitative study	BRCA1/BRCA2 mutation carriers; health professionals[¥]	Focus group interviews; semi-structured in-depth interviews	Putative acceptability, barriers and facilitators	NA	Good[˜]
Chandrasekaran, 2015	UK	173	Prospective cohort survey study	Health professionals[€]	Online questionnaire	Putative acceptability	NA	15/16*
Choi, 2017	South Korea	54	Cross-sectional cohort study	Health professionals[#]	Online/paper questionnaire	Putative acceptability	NA	14/16*
Harmsen, 2015 (study protocol)	The Netherlands	510	Multicentre, prospective, cohort study	BRCA1/BRCA2 mutation carriers, premenopausal, >25 years	RRESDO RRSO	Menopause specific QoL	15 years	21/24*
Holman, 2014	US	204	Prospective cohort survey study	BRCA1/BRCA2 mutation carriers	Online questionnaire	Putative acceptability	NA	15/16*
Kwon, 2013	Canada	2,300	Markov Monte Carlo simulation model	Hypothetical cohort of BRCA1/BRCA2 mutation carriers	RRESDO RRES RRSO	Incremental cost effectiveness ratio per quality adjusted life year	NA	NA
Leblanc, 2011	France	14	Single centre, prospective, cohort study	BRCA1/BRCA2 mutation carriers	Radical fimbriectomy	Optimum surgical technique to minimise complications and ensure high quality specimens for histopathological examination	Not reported	13/16*
Nebgen, 2018	US	43	Multicentre, prospective, cohort, pilot study	BRCA1/BRCA2 mutation carriers, premenopausal, 30-47 years	RRESDO RRSO Screening	Acceptability, surgical outcomes, QoL, cancer specific worry, anxiety, sexual function, body image and menopausal symptoms	12 months	22/24*

RRESDO – risk reducing early salpingectomy and delayed oophorectomy; OC – ovarian cancer; QoL – quality of life; RRSO – risk reducing salpingo-oophorectomy; RRES – risk reducing early salpingectomy

[¥]Gynaecological oncologists; clinical geneticists; breast surveillance practitioners: medical oncologists, surgeons, medical doctors, nurses

[€]Gynaecological oncologists; general obstetricians & gynaecologists; clinical geneticists; genetic counsellors

[#]Members of the Korean Society of Gynecologic Oncology and attendants of the inaugural Hereditary Gynecologic Cancer Symposium in South Korea

[˜]Quality of methodology assessed using the CASP (Critical Appraisal Skills Programme) qualitative research checklist

*Quality of methodology assessed using the MINORS (Methodological Index for Non-Randomized Studies) checklist

Table-2: Suggested management and follow up of STIC[#] lesions (without invasion)

Histopathology and Cytology	Management		
	Staging CT Chest, abdomen, pelvis	**Surgical staging***	**Panel genetic testing** (BRCA1/BRCA2/RAD51C/ RAD51D/BRIP1)**
STIC with positive cytology	☑	☑	☑
STIC with negative cytology	☑	Not indicated unless abnormality on CT suggesting otherwise	☑
STIC with missing cytology	☑	Not indicated unless abnormality on CT suggesting otherwise	☑

[#]All cases of isolated STIC identified at salpingectomy alone (patients undergoing early salpingectomy) should have completion oophorectomy

*Hysterectomy, omentectomy, pelvic/para-aortic lymphadenectomy (excision of all visible disease)

**If not previously undertaken

Table-3: Studies reporting the management of STIC lesions in women at increased risk of ovarian cancer

Publication	Sample size (n)	Median follow up in months (range)	Isolated STIC			Occult invasive cancers	Staging for isolated STIC*			Chemotherapy			STIC recurrence		
			Negative Cytology	Positive cytology	No cytology		Negative Cytology	Positive cytology	No cytology	Negative Cytology	Positive cytology	No cytology	Negative Cytology	Positive cytology	No cytology
Conner, 2014	385	60 (12-96)	6	2	0	17	3	1	0	3	0	0	1[#]	0	0
Manchanda, 2011	308	Not reported	6	3	0	5	0	3	0	0	0	0	0	0	0
Powell, 2013	405	80 (40-150)	14	3	0	15	7	3	0	2	2	0	1[~]	0	0
Finch, 2006	159	Not reported	1	0	0	6	0	0	0	0	0	0	0	0	0
Carcangiu, 2006	50	26.5 (1-145)	2	0	1	3	0	0	0	0	0	0	0	0	0
Lamb, 2006	113	29	3	1	0	3	3	1	0	1	1	0	0	0	0
Medeiros, 2006	13	Not reported	0	1	2	2	0	1	2	0	0	0	0	0	0
Callahan, 2007	122	Not reported	2	1	0	4	0	0	0	2	1	0	0	0	0
Reitsma, 2013	360	60 (0-144)	3	0	0	4	0	0	0	0	0	0	0	0	0
Wethington, 2013	593	28 (16–44)	11	1	0	0	6	1	0	0	0	0	0	0	0
Sherman, 2014	966	Not reported	4	0	0	21	0	0	0	0	0	0	0	0	0
Zakhour, 2016	257	79 (20-138)	9	0	0	4	0	0	0	0	0	0	2[£]	0	0
Poon, 2016	138	79 (45-108)	1	1	1	2	0	0	0	0	0	0	0	0	0
Hirst, 2009	45	Not reported	0	0	1	4	0	0	0	0	0	0	0	0	0
Van der Hoeven, 2018	235	78 (59-96)	0	0	2	3	0	0	0	0	0	0	0	0	1[$]
Total (n)	4,149	-	62	13	7	93	19	10	2	8	4	0	4	0	1
Total (%)	-	-	2.0			2.2	0.7			0.3			0.1		

*No upstaging reported in 31cases of isolated STIC identified at RRSO, where staging was undertaken

[#]Recurrence 48 months after RRSO. No staging/chemotherapy after STIC confirmed. Presented with rising CA125 and ascites.

[~]Recurrence 43 months after RRSO. No staging/chemotherapy after STIC confirmed. Presented with rising CA125 and omental deposits.

[£]Recurrence 32 and 42 months after RRSO. No staging/chemotherapy after STIC confirmed.

[$]Recurrence 36 months after RRSO. No staging/chemotherapy after STIC confirmed.

Timing of recurrence (range 32-48 months) of isolated STIC in the small number of reported cases is not that consistent with a missed metastases that would have necessarily have been identified at staging. One would have expected a missed metastases to present in 12-18 months without further treatment (given what we understand of OC progression through screening and tumour modelling studies), and not a delayed presentation at 3-4 years.

Table-4: Clinical trials investigating risk reducing salpingectomy as an alternative surgical strategy for ovarian cancer prevention in women at increased risk of ovarian cancer

Study	Country	Study design	Population	Sample size	Study arms	Primary outcomes	Secondary outcomes	Follow up	Study Status
PROTECTOR (ISRCTN25173360)	UK	Multicentre, prospective, cohort	BRCA1/BRCA2/RAD51C/RAD51D/BRIP1 mutation carriers or FH of BC-&-OC or OC alone#, premenopausal, ≥30 years,	1000	RRESDO RRSO Controls (no surgery)	Sexual function	Endocrine function/menopause; regret/satisfaction; surgical morbidity; QoL/psychological health; intraepithelial carcinomas; invasive cancers; utility scores for ES; cost-effectiveness	3 years (longer term follow up maintained through establishment of a national register)	Recruiting
TUBA (NCT02321228)	Netherlands	Multicentre, prospective, cohort	BRCA1/BRCA2 mutation carriers, premenopausal, ≥25 years	510	RRESDO RRSO	Menopause specific QoL	QoL; sexual function; cancer worry; satisfaction/regret; surgical complications; intraepithelial carcinomas; invasive cancers; CVD risk factors; incidence of CVD; cost-effectiveness	15 years	Recruiting
Radical Fimbriectomy* for Young BRCA Mutation Carriers (NCT01608074)	France	Multicentre, prospective, cohort	BRCA1/BRCA2 mutation carriers or high-risk FH, premenopausal, ≥35 years	123	Radical fimbriectomy	Number of OC/PPC occurring between fimbriectomy and menopause	Morbidity; incidence of intraepithelial/invasive carcinomas at fimbriectomy; incidence and recurrence of BC; rate of DO	15 years	Closed to recruitment
Prophylactic Salpingectomy With Delayed Oophorectomy (NCT01907789)	US	Multicentre, prospective, cohort	BRCA1/BRCA2 mutation carriers, premenopausal, 30-47 years	80	RRESDO RRSO OC screening	Proportion of participants undergoing DO after ES	Acceptability; surgical outcomes; QoL; cancer specific worry; anxiety; sexual function; body image and menopausal symptoms	RRESDO arm 4 years; RRSO arm 1 year OC screening arm 3 years (longer term follow up maintained through annual telephone follow up)	Closed to recruitment
WISP (NCT02760849)	US	Multicentre, prospective, cohort	BRCA1/BRCA2/BRIP1/PALB2/RAD51C/RAD51D/BARD1/MSH2/MSH6/MLH1/PMS2/EPCAM mutation carriers, premenopausal, 30-50 years	300	RRESDO (ISDO) RRSO	Sexual function	QoL	26 years	Recruiting

PROTECTOR - **Pr**eventing **O**varian Cancer **t**hrough early **Exc**ision of **T**ubes and late **O**varian **R**emoval; TUBA - Early Salpingectomy (Tubectomy) With Delayed Oophorectomy in BRCA1/2 Gene Mutation Carriers; OC – ovarian cancer; BC – breast cancer; RRESDO – risk reducing early salpingectomy with delayed oophorectomy; RRSO – risk reducing salpingo-oophorectomy; QoL – quality of life; PPC – primary peritoneal cancer; ES – early salpingectomy; DO – delayed oophorectomy; FH – family history; CVD – cardiovascular disease; WISP - The **W**omen Choos**i**ng **S**urgical **P**revention Trial, ISDO – Interval Salpingectomy & Delayed Oophorectomy

#Significant family history defined as:- BRCA negative: >2 individuals with ovarian cancer who are first degree relatives, ≥3 ovarian cancer case families; BRCA unknown: ≥2 ovarian cancer case families; Manchester Scoring System (MSS3) ≥15; BOADECIA/BRCAPRO combined BRCA1/BRCA2 probability ≥10%

*Fimbriectomy involves removing the tube, fimbrio-ovarian junction and portion of ovary attached to fimbria (up to one-quarter of ovarian volume is removed).

Appendix-S1: Search strategy for literature search

Objective	To identify published literature on RRESDO for surgical prevention of OC in women at increased risk.
Data sources	A systematic review of articles with the use of MEDLINE (1946 June 2018), EMBASE (1974 to June 2018), Pubmed (1996 to June 2018), CINAHL (1937 to June 2018), PsychINFO (1806 to June 2018)
Search strategy	27 searches were undertaken
1. (BRCA).ti,ab	
2. exp "BRCA"/	
3. (BRCA AND "1 OR 2").ti,ab	
4. exp "BRCA AND 1 OR 2"/	
5. (BRCA AND 1).ti,ab	
6. exp " BRCA AND 1"/	
7. (BRCA AND 2).ti,ab	
8. exp "BRCA AND 2"/	
9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8	
10. (SALPINGECTOMY).ti,ab	
11. exp "SALPINGECTOMY"/	
12. (RISK REDUCING SALPINGECTOMY).ti,ab	
13. exp "RISK REDUCING SALPINGECTOMY"/	
14. (EARLY SALPINGECTOMY).ti,ab	
15. exp "EARLY SALPINGECTOMY"/	
16. 10 OR 11 OR 12 OR 13 OR 15	
17. (DELAYED OOPHORECTOMY).ti,ab	
18. exp "DELAYED OOPHORECTOMY"/	
19. (DELAYED OVARIECTOMY).ti,ab	
20. exp "DELAYED OVARIECTOMY"/	
21. 17 OR 18 OR 19 OR 20	
22. (OVARY CANCER).ti,ab	
23. exp "OVARY CANCER"/	
24. (OVARIAN CARCINOMA).ti,ab	
25. exp "OVARIAN CARCINOMA"/	
26. 22 OR 23 OR 24 OR 25	
27. 9 AND 16 AND 21 AND 26	
Eligibility criteria	Women at increased risk of OC undergoing RRESDO; full articles in English language.
Data extraction	Citation and abstracts reviewed by author FG. Relevant papers reviewed by RM.
Conclusion	RRSO is the current gold standard for OC risk reduction but has limitations including premature menopause. RRESDO is a two staged surgical alternative for premenopausal women wanting to reduce their OC risk but at the same time avoid the detrimental health sequelae of premature menopause. There is a paucity of published data on outcomes of RRESDO.

RRESDO – risk reducing early salpingectomy with delayed oophorectomy; RRSO – risk reducing early salpingectomy; OC - ovarian cancer

Figure-S1: Flowchart of study selection