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Title:

Risk Reducing Salpingectomy and Delayed Oophorectomy in high risk women: views of cancer geneticists, genetic counsellors and gynaecological oncologists in the UK

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ABSTRACT

Background

Risk-reducing-salpingectomy & Delayed-Oophorectomy(RRSDO) is being proposed as a two-staged approach in place of RRSO to reduce the risks associated with premature menopause in high-risk women. We report on the acceptability/attitude of UK health professionals towards RRSDO.

Methods

An anonymised web-based survey was sent to UK Cancer Genetics Group(CGG) and British Gynaecological Cancer Society(BGCS) members to assess attitudes towards RRSDO. Baseline characteristics were described using descriptive statistics. A chi-square test was used to compare categorical, Kendal-tau-b test for ordinal and Mann-Whitney test for continuous variables between two groups.

Results

173/708(24.4%) of invitees responded. 71% respondents (CGG=57%/BGCS=83%, p=0.005) agreed with the tubal hypothesis for OC, 55% (CGG=42%/BGCS=66%, p=0.003) had heard of RRSDO and 48% (CGG=46%/BGCS=50%) felt evidence was not currently strong enough for introduction into clinical practice. However, 60% respondents' (CGG=48%/BGCS=71%, p=0.009) favoured offering RRSDO to high-risk women declining RRSO, 77% only supported RRSDO within a clinical trial (CGG=78%/BGCS=76%) and 81% (CGG=76%/BGCS=86%) advocated a UK-wide registry. Vasomotor symptoms(72%), impact on sexual function(63%), osteoporosis(59%), hormonal-therapy(55%) and subfertility(48%) related to premature menopause influenced their choice of RRSDO. Potential barriers to offering the two-stage procedure included lack of data on precise level of benefit(83%), increased surgical morbidity(79%), loss of breast cancer risk reduction associated with oophorectomy(68%), need for long-term follow-up(61%) and a proportion not undergoing DO(66%). There were variations in perception between

BGCS/CGG members which are probably attributable to differences in clinical focus/expertise between these two groups.

Conclusions

Despite concerns, there is reasonable support amongst UK clinicians to offering RRSDO to premenopausal high-risk women wishing to avoid RRSO, within a prospective clinical trial.

Key Words

Risk reducing salpingectomy, delayed oophorectomy, RRSDO, BRCA, high-risk, ovarian cancer

Introduction:

Ovarian cancer (OC) is the leading cause of death from gynaecological malignancies in the UK.[1] 13%-23% of non-mucinous epithelial OC[2-7] have mutations in the *BRCA1* and *BRCA2* genes, which account for most of the known hereditary risk for OC. Published meta-analyses have found cumulative breast and ovarian cancer risks (until age 70 years) to be: up to 65% and 40% respectively for *BRCA1* carriers, and up to 49% and 18% respectively for *BRCA2* carriers.[8-10] However, higher penetrances have been documented in carriers ascertained from high-risk families with multiple cancer cases.[11-15] Premenopausal risk reducing salpingo-oophorectomy (RRSO) is the mainstay of treatment as effectiveness of ovarian cancer screening in the high risk population is still not established.[16-18] It is the most effective option for preventing tubal/ ovarian cancer, with a hazard ratio (HR) of 0.21 (95%CI 0.12, 0.39)[19] reported in a recent meta-analysis in known *BRCA1* and *BRCA2* carriers. Although, the benefits of RRSO are significant, decision making is a complex process with many women and clinicians concerned over the side effects of premature surgical menopause, such as: a higher risk of cardiovascular disease,[20-22] potential cognitive impairment and Parkinsonism,[23-25] osteoporosis, vasomotor symptoms, and detrimental impact on quality of life.[26, 27] Premature menopause has been shown to have a mortality impact[28] in low risk women. Risks are higher in women who undergo the procedure under the age of 45 and do not take hormone replacement therapy (HRT).[27, 28] This has led to high-risk premenopausal women too, opting to delay RRSO till after the menopause.[29]

The increasing support, acceptance and awareness of the tubal origins of OC,[30] has led to premenopausal risk reducing salpingectomy (RRS) and, subsequently delayed oophorectomy (DO) after the menopause as a two staged approach being put forward as a management option for reducing OC risk in women at high-risk of

familial OC. Based on the supposition that interim RRS provides significant OC risk reduction which outweighs the risks, some clinicians advocate use in clinical practice in high risk women who refuse RRSO for fear of early menopause.[31, 32]

However, the benefit of a two stage 'risk reducing salpingectomy delayed oophorectomy' (RRSDO) approach is unproven. It will not prevent cancers that arise outside the tube. Available evidence does not adequately elucidate the level of risk reduction associated with RRS in this population, the long-term implication of salpingectomy on ovarian function and the cost-effectiveness of such an approach. Concerns have also been raised that despite advice, a proportion of women may delay or not undergo DO following the menopause and it is possible that some of these women may develop OC

Despite current literature leaving many questions unanswered a number of centres have changed clinical protocols to offer RRSDO.[32, 33] We have tried to generate UK wide debate and consensus on this issue by developing a working group and involving members of the Cancer genetics Group (CGG) and British Gynaecological Cancer Society (BGCS). We report results of a survey undertaken to understand UK clinicians' attitudes towards RRSDO in pre-menopausal women at high risk of familial OC and propose a preventative surgical framework/way forward for high risk women in the UK.

Methods:

We sent an anonymised web-based survey to members of the UK Cancer Genetics Group (CGG) and the British Gynaecological Cancer Society (BGCS) between August and September 2014 to assess attitudes towards RRSDO. One reminder email was sent approximately 2 weeks after the initial invitation. Both of these are

UK-wide societies, predominantly comprised of cancer geneticists/genetic counsellors (CGG) and surgical gynaecological oncologists (BGCS) respectively.

The 13-item survey included baseline characteristics regarding the respondent's post, specialty, practice setting, years of experience and the number of high-risk women encountered in clinical practice. Questionnaire items covered: agreement with the tubal hypothesis for the origin of ovarian cancer (5-item Likert scale- strongly agree to strongly disagree); familiarity/awareness with the concept of RRS & DO as a risk reducing strategy ('yes/no' question); the importance of premature menopause in RRSO decision making (5-item Likert scale); the association between oophorectomy and subsequent breast cancer risk; views/awareness of factors influencing RRSO decision making (tick box options); views/awareness of potential barriers to the introduction of RRSDO as a risk reducing strategy based on current literature and the high risk groups in whom they would support introduction of RRSDO ('yes', 'no' and 'not sure' options). Clinicians' attitudes and willingness to offer RRSDO were assessed with a 5-point Likert scale on how strongly they would support introduction of RRS & DO into routine practice, offer this to women declining RRSO, and offer this within the context of a clinical trial/ registry Respondents could recheck all answers and an optional free text box was also provided for further comments.

Questionnaire development

The 13-item survey (Supplementary Table 1) was developed in several stages. An initial draft survey comprising 23 items was developed by the core study team following a literature review. Each question was systematically discussed and debated. This was subsequently reviewed by 8 senior clinicians in the fields of Cancer Genetics and surgical Gynaecological Oncology. They gave each item a relevance score from 1 (least relevant) to 4 (most relevant) based on their knowledge and experience in cancer genetics and working with high risk families. They were

also asked to identify any additional questions which they considered important and may be missing. A second consensus meeting was held to review responses to the initial questionnaire, delete low relevance items and to optimise questionnaire length and facilitate compliance. All the items used in the final survey had scores ≥3.1/4. A second pilot of the web-based survey was carried out for readability, ease of use, and layout. These processes helped ensure content and face validity. The final version was further reviewed/commented on by executive members of the BGCS and CGG resulting in further rationalisation to a 13 item questionnaire (Supplementary table-1). .

Baseline respondent characteristics were described using descriptive statistics. A chi-square test was used to compare categorical variables, Kendal tau-b test to compare ordinal variables and t-Test (parametric)/ Mann-Whitney (non-parametric) tests to compare continuous variables between two groups. Two-sided P-values are reported for all statistical tests. Statistical calculations were performed using SPSS 22.0.

Results

Of the 708 survey invitations sent, 173 responded, giving a response rate of 24.4% (23% (80/348) CGG; 26% (93/360) BGCS). Baseline characteristics of the respondents are tabulated in Table-1. 48% CGG and 87% BGCS respondents were consultants while 44% CGG respondents were genetic counsellors. Of the BGCS respondents 83% worked in surgical Gynaecological Oncology and 11% in general Obstetrics & Gynaecology.

Prior to completing the questionnaire, only 55% (66% BGCS, 42% CGG, p=0.003) respondents had heard of the concept of offering RRSDO in pre-menopausal high-

risk women who have completed their family. Attitudes of CGG and BGCS respondents towards the tubal hypothesis and introduction of RRS & DO are described in Table-2. Overall 71% (57% CGG, 83% BGCS, p=0.005) respondents agreed/strongly agreed with the hypothesis that a significant proportion of high grade serous OC originates from the fallopian tube. 48% respondents agreed that the current body of evidence was not strong enough to introduce RRSDO into routine clinical practice, whilst 38% were undecided. However, 60% of respondents were in favour of offering RRSDO to women who decline RRSO. An overwhelming majority (77%) would only support RRSDO within the context of a clinical trial and 81% agreed/strongly agreed that there should be a UK-wide registry of all women undergoing RRSDO. 44% of CGG and 31% BGCS respondents, disagreed or strongly disagreed, that a significant proportion of high-risk women decline/delay RRSO due to their concerns about the effects of early surgical menopause. Vasomotor symptoms (72%), negative impact on sexual function (63%), osteoporosis (59%), need for hormone replacement therapy (55%) and loss of fertility (48%) ranked as the top five effects of surgical menopause that influence pre-menopausal women considering risk reducing surgery (details in Table-3). Interestingly, there were some differences in perception between CGG and BGCS groups. CGG members felt survival (p=0.001) and loss of fertility (p=0.003) were more important factors while BGCS members believed vasomotor symptoms (p=0.015) to be more significant. Additional free text comments highlighted the importance of 'attachment to female organs/loss of femininity' (n=4) and 'fear of surgery' (n=3). Only 47% BGCS compared with 95% of CGG respondents group (p<0.0001) correctly identified the 50% reduction in breast cancer risk associated with premenopausal RRSO.

Details of risk categories which may receive support for RRSDO are given in Table-4. Overall BGCS members (71%) were significantly more supportive than CGG members (48%) of offering RRSDO to women at high risk of familial ovarian cancer

(p=0.009). The majority of the respondents thought that there are a number of potential barriers to offering RRSDO compared to RRSO (Table-4). Higher surgical morbidity, lack of compliance with DO and paucity of cost-effectiveness data were felt to be significantly greater limitations by CGG than BGCS members. Other free text comments included: lack of awareness of literature (n=5), support for future research but questioning the practicality of long term follow up to elucidate level of benefit in comparison to RRSO (n=3), dissatisfaction with 'lack of evidence on the magnitude of risk reduction with RRSDO' (n=3) and restricting RRSDO to women who declined RRSO (n=2).

DISCUSSION

This paper for the first time highlights the awareness and views of cancer geneticists, genetic counsellors and gynaecological oncologists (clinicians) in the UK regarding RRSDO as a risk reducing strategy in women at high risk of familial OC. Our survey is broad based and covers the major clinical groups (both genetics clinicians and gynaecologists) involved in the management of these women. A small proportion of respondents in the survey are general obstetricians & gynaecologists who are members of the BGCS and hence have a special interest in gynaecological oncology. These include trainees in gynaecological oncology and district general hospital leads for gynaecological oncology. Like surgical gynaecological oncologists they would be involved in undertaking risk reducing surgery and managing high-risk women. We found limited awareness amongst health professionals regarding the concept of RRSDO with 45% being unaware of the procedure at the outset. Interestingly this lack of awareness was greater amongst the genetics community. This figure is also likely to be much higher for general gynaecologists/obstetricians who lack a special interest in gynaecological oncology and general practitioners. This suggests the need to increase awareness amongst UK clinicians and health

professionals, should a trial to explore such an intervention be implemented in the future.

Almost half the respondents reported that there was not enough evidence for introduction of RRSDO into routine clinical practice. This highlights the awareness and importance attached to limitations of this intervention. However, there appeared reasonable support (60%) for offering it to premenopausal women declining the gold standard RRSO. This is consistent with views of clinicians/groups from other countries in favour of providing some form of risk reduction in women who may otherwise get none.[32, 34] It has the added advantage of detecting serous tubal intraepithelial carcinoma (STIC) / occult invasive cancers in some women[33] enabling them to undergo appropriate treatment at an earlier time. The timing of the insult/ trigger for development of cancer or shedding of precancerous cells from the tube is not known. Hence, early RRS can be of potential benefit. However, this should not be undertaken before the family is complete. In addition, the potential long term impact of RRS on ovarian function and onset of menopause is not known and this should be built into the decision making.

There was overwhelming support for offering RRSDO only within the context of a clinical trial (77%) as well as for establishing a UK-wide registry (81%) for all women undergoing RRSDO. This predominant view reflects the recognition of the need for long term follow-up, given the limited prospective data on efficacy, such as level of OC risk reduction, impact on survival, long term ovarian function/menopause and importance of ensuring subsequent DO and monitoring attrition. It also provides the additional benefit of standardised protocols for the procedure including use of positive peritoneal cytology, management of STICs and staging surgery for occult disease, as well as the opportunity for bio-banking for translational research. This is something the authors are also strongly in favour of and recommend.

We found some differences in awareness and attitudes between gynaecological-oncologists and cancer geneticists/genetic counsellors towards RRSDO. The significantly greater support for the tubal hypothesis, the importance of premature menopause in decision making and support for offering RRSDO amongst gynaecological oncologists (Table-2) probably reflects their role in preforming risk reducing procedures, and counselling/consenting women prior to surgery. The differences in perception of factors affecting decision making for risk reducing surgery (Table-3) can also largely be explained by the differences in clinical focus/expertise between the two groups. Overall, the factors underscored as important by UK gynaecologists and geneticists have also been highlighted by clinicians elsewhere.[29, 35] Both gynaecologists and geneticists attached much lower importance to neurological sequelae and cardiovascular risk towards decision making. While data related to neurological consequences are more limited and emerging,[24, 25] the impact on higher risk of heart disease is more substantial and well established.[20-22] Compared to geneticists, gynaecologists were half as aware of the 50% reduction in breast cancer risk with premenopausal RRSO. While a number of analyses in the high-risk[19, 36] women have shown this benefit, a recent Dutch paper published after this survey[37] underlined methodological deficiencies in earlier analyses[36, 38, 39] and reported no benefit of breast cancer risk reduction from premenopausal RRSO. However, a key limitation was the short follow-up of only 3.2 years. It is possible/likely that any benefit of reduction in breast cancer risk will be seen only after a longer period of follow up. Some of the differences found between geneticists and gynaecologists highlight an important issue of potentially conflicting information being given out to patients by different groups of clinicians involved in their care which can make decision making more confusing for them. This is an issue that needs to be addressed. Standardised patient information sheets

approved by both the BGCS and CGG, as well as steps to increase awareness/education amongst all health professionals are needed.

The significantly greater support amongst gynaecological oncologists for RRSDO in all risk categories (Table-4) may be reflective of their experience of treating advanced ovarian cancer patients and therefore greater belief/perception of benefit of risk reducing procedures as well greater awareness of absolute OC risk amongst cancer geneticists and the small absolute risk benefit in some risk categories (Table-5). The absolute risk of developing OC by the age of 50 years has been found to vary from 11% to 22.7% in *BRCA1* carriers and 0.4% to 4% in *BRCA2* carriers, with risks at the higher end of the range reported from families ascertained through genetic clinics and lower level risks reported from meta-analysis correcting for ascertainment bias.[8, 9, 15, 40-42] Most of this risk occurs after the age of 35 years in *BRCA1* and after the age of 45 years in *BRCA2* carriers. In the UK RRSO is available not only to *BRCA1/BRCA2* carriers but also to women of unknown mutation status who have greater than 10% life time risk of ovarian cancer. The absolute benefit to such women will be lower. Table-5 provides the potential benefit of reduction in OC risk for various risk categories assuming 40%/50%/60% risk reduction benefit from RRS. Most clinicians did not feel that RRSDO should be offered to RAD51C/D carriers. This is consistent with limited awareness of newer cancer genes, lack of validated precise estimates of ovarian cancer risk for these mutations and current unavailability of testing for these on the UK National Health Service (NHS). However, the applicability of RRSDO to this cohort may change as more data emerge and testing becomes available in clinical practice.

The barriers to introduction of RRSDO found in our survey are consistent with those recently highlighted by others.[34, 43, 44] The top ranked barrier was lack of evidence of level of risk benefit obtained from RRS. While the tube is an extremely

important piece of the puzzle, it does not explain the entire picture.[45, 46] Around one-third of STIC/occult invasive lesions detected at RRSO in women at high-risk of familial OC occur outside the tube.[47] The precise trigger/rate limiting step for carcinogenesis and the natural history of preinvasive STIC lesions are yet to be established. CGG members expressed significantly greater concern regarding higher surgical morbidity with two procedures and lack of compliance with DO. This may reflect the experience of gynaecological oncologists that RRSO is a minimally invasive procedure with relatively low complication rate and the awareness/concern of cancer geneticists of risk issues including the higher residual ovarian and peritoneal cancer risk without DO. With the availability of RRS some women who would have undergone RRSO may opt for RRS instead, with a proportion subsequently delaying postmenopausal DO or declining to undergo another surgical procedure. These women would remain at higher cumulative risk for OC/PC. Of note, two-thirds of BRCA carriers in a study from the USA found the risks associated with the need for two surgeries, possibility of not lowering ovarian cancer risk, and potential disruption of ovarian blood supply to be acceptable.[44] There is need to understand the views of high risk women in the UK too.

It is interesting that paucity of cost-effectiveness data did not rank high amongst clinicians as a barrier to introduction, though it was more important an issue for CGG members. A study from British Columbia using a base case utility score for RRSO of 0.82 and 0.99 for RRS suggested that RRSDO may remain more cost effective than RRSO if the utility score for RRSO is <0.93.[48] However, more recent data than they used reports the utility score of RRSO alone to be 0.95[49] which may question the comparative cost-effectiveness of RRSDO. In addition the potential impact of some women dropping out or not undergoing DO was not incorporated in the analysis. UK cost-effectiveness data using NHS costs and National Institute for Health and Clinical Excellence (NICE) thresholds which are different from those in North America are

lacking. Further studies on cost-effectiveness are needed which compare RRSDO to RRSO.

The response rate of 24.4% may be considered a limitation of the study. However, similar levels of response have been reported in other questionnaire based surveys,[50, 51] and responses in web/electronic surveys are lower than postal/face-to-face ones.[52, 53] Besides our survey is broadly representative of both gynaecologists and geneticists involved in the care of high risk women in the UK.

Our study highlights reasonable support amongst the UK cancer geneticists/genetic counsellors and gynaecological oncologists for offering RRSDO to premenopausal high-risk women who decline RRSO. In the absence of prospective data on risk/benefit, the general consensus is that it should be provided within the context of a research study rather than recommended for routine clinical use. With rising awareness of this option, there is increasing demand from charities and patient groups (personal communication). Interest amongst *BRCA* carriers in participating in a RRSDO study/trial has been reported.[43, 44] A clinical trial led by LeBlanc[32] is currently underway in France, evaluating Radical Fimbriectomy in *BRCA1/2* carriers (NCT01608074) and one is being initiated at MD Anderson in the USA comparing self selected RRSO and RRSDO and screening, with the primary outcome measure being patient compliance with DO at 3 year follow up (NCT01907789). A randomised trial comparing RRSDO with RRSO does not seem feasible given there is no data to support equipoise in outcomes between the two options. Few high-risk women would be willing to be randomised as the risks/benefits differ in the two arms. A pragmatic way forward would be a prospective UK wide observational cohort study based on a standardized nationally acceptable protocol, with a well-designed patient information sheet (highlighting pros and cons) and comprehensive evaluation of short and long term outcomes. It is important to ensure that pressure to translate preliminary research findings into clinical practice does not impede/prevent collection of evidence

required to decide whether RRSDO is appropriate and to identify the processes and support mechanisms needed to safely deliver such an approach.

Ethical Approval

This project was submitted to the Research Ethics committee at the University College London Hospital Joint R&D office. Under the Research Governance Framework the project was deemed to fall under audit or service development and permission for data collection, analysis and submission for publication was given.

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Contribution to authorship

RM and DC prepared the initial draft of the survey. All authors contributed to the development of the survey. RM, DC and UM were involved in conducting the survey, data collection and analysis. RM and DC prepared the first draft of the manuscript. All authors critically contributed to and revised the manuscript and approved the final version

Disclaimers/ Conflict of interest statement

UM has a financial interest in Abcodia, Ltd, a company formed to develop academic and commercial development of biomarkers for screening and risk prediction.

The other authors declare no conflict of interest.

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Table and Figures

Table 1: Baseline characteristics of survey respondents

	CGG (n=80)	BGCS (n=93)	Total
Response rate			
	23.0%(80/348)	25.8%(93/360)	24.4%(173/708)
Post			
Consultant Geneticist/ Gynaecolgicaloncologist	46.2% (37)	87.0% (80)	68.0% (117)
Genetic Counsellor	43.8% (35)	0	20.3% (35)
Subspecialty fellow	0	9.8% (9)	15.2% (9)
Other	10% (8)	3.3% (3)	11 (6%)
Specialty			
Cancer/Clinical Genetics	92.5% (74)	1.1% (1)	43.4% (75)
Surgical GO	3.8% (3)	82.8% (77)	46.2% (80)
General O&G	0	10.8% (10)	5.8% (10)
Other	4% (3)	5% (5)	4.6% (8)
Years in Specialty			
Mean (SD)	12.9 (6.7)	13.9 (8.9)	13.4 (7.9)
Practice setting			
Tertiary Cancer Centre	10.0% (8)	62.4% (58)	38.2% (66)
Regional Genetics Centre	78.8% (63)	0%	36.4% (63)
University Teaching Hospital	8.8% (7)	17.2% (16)	13.3% (23)
District General Hospital	0	20.4% (19)	11.0% (19)
Other	3% (2)	0	1% (2)
No. of high-risk women/year			
None	2.5% (2)	3.3% (3)	2.9% (5)
<20	15.2% (12)	60.9% (56)	39.8% (68)
21-50	50.6% (40)	27.2% (25)	38.0% (65)
51-100	22.8% (18)	7.6% (7)	14.6% (25)
>100	8.9% (7)	1.1% (1)	4.7% (8)
Missing			1.2% (2)

CGG- Cancer Genetics Group; BGCS- British Gynaecological Cancer Society,

Table-2: Attitudes of CGG and BGCS members towards introduction of Risk reducing salpingectomy and Delayed Oophorectomy (RRSDO)

	Total Cohort (BGCS and CGG) %(n)									
Survey Item	**Strongly disagree**		**Disagree**		**Neither agree or disagree**		**Agree**		**Strongly Agree**	
Current body of evidence strong enough to introduce RRS DO into routine clinical practice*	**11.6% (20)**		**36.6% (63)**		**38.4% (66)**		**12.2% (21)**		**1.2% (2)**	
RRS DO should only be offered within the context of a clinical trial*	**0.6% (1)**		**5.2% (9)**		**17.4% (30)**		**45.9% (79)**		**30.8% (53)**	
	CGG %(n)					**BGCS %(n)**				
Survey Item	**Strongly disagree**	**Disagree**	**Neither agree or disagree**	**Agree**	**Strongly Agree**	**Strongly disagree**	**Disagree**	**Neither agree or disagree**	**Agree**	**Strongly Agree**	**P value (Kendall's tau-b)**
I support the hypothesis that a significant proportion of high grade serous cancers (HGSC) of the ovary probably originate from the fallopian tube?	**0**	**3.8% (3)**	**38.8% (31)**	**46.2% (37)**	**11.3% (9)**	**5.4% (5)**	**1.1% (1)**	**10.9% (10)**	**45.7% (42)**	**37.0% (34)**	**<0.005**
Significant proportion of premenopausal high risk women decline RRSO due to their concerns regarding early menopause.	**5.0% (4)**	**38.8% (31)**	**25.0% (20)**	**23.8% (19)**	**7.5% (6)**	**3.3% (3)**	**27.2% (25)**	**19.6% (18)**	**43.5% (40)**	**6.5% (6)**	**0.03**
I would support offering this proposal to women who decline/wish to delay risk reducing bilateral salpingo-	**2.5% (2)**	**11.4% (9)**	**38.0% (30)**	**45.6% (36)**	**2.5% (2)**	**1.1% (1)**	**12.0% (11)**	**16.3% (15)**	**66.3% (61)**	**4.3% (4)**	**0.009**

oophrectomy (RRSO).											
Premenopausal women with a past history of breast cancer could be offered RRS and DO	**5.1% (4)**	**21.8% (17)**	**46.2% (36)**	**26.9 % (21)**	**0**	**8.7% (8)**	**42.4% (39)**	**23.9% (22)**	**21.7 % (20)**	**3.3% (3)**	**0.033**
There should be a UK wide registry of all women undergoing risk reducing salpingectomy	**0**	**3.8% (3)**	**20.0% (16)**	**47.5 % (38)**	**28.7% (23)**	**0**	**4.3% (4)**	**9.8% (9)**	**41.3 % (38)**	**44.6% (41)**	**0.022**

*Responses of CGG and BGCS groups were not significantly different for these variables

BGCS- British Gynaecological Cancer Society, CGG- Cancer Genetics Group, RRS- Risk Reducing Salpingectomy, RRSDO- Risk Reducing Salpingectomy and Delayed Oophorectomy, RRSO- Risk Reducing Salpingo-oophorectomy,

Table 3- Effects of surgical menopause that influence decision making of pre-menopausal women regarding risk reducing surgery

	Overall (n=172)	CGG (n=80)	BGCS (n=92)	P value (Chi Sq)
Cognitive Decline	19.8% (34)	15.0% (12)	23.9% (22)	0.143
Increased risk of neurological disorders	3.5% (6)	2.5% (2)	4.3% (4)	0.51
Increased cardiovascular risk	19.2% (33)	23.8% (19)	15.2% (14)	0.156
Osteoporosis	59.3% (102)	65.0% (52)	54.3% (50)	0.156
Negative impact on sexual functioning	62.2% (107)	62.5% (50)	62.0% (57)	0.942
Need to take HRT until age 50	55.2% (95)	58.8% (47)	52.2% (48)	0.387
Vasomotor symptoms	71.5% (123)	62.5% (50)	79.3% (73)	0.015
Potential survival impact	27.3% (47)	40.0% (32)	16.3% (15)	0.001
Loss of fertility	47.7% (82)	60.0% (48)	37.0% (34)	0.003

CGG- Cancer Genetics Group; BGCS- British Gynaecological Cancer Society, HRT- hormone replacement therapy

Table 4- Comparison of CGG and BGCS support for RRSDO by risk category and barriers to offering RRSDO

Comparison of CGG and BGCS respondents	Yes % (n)		No % (n)		Not Sure % (n)		P value (Chi Sq)
Support for offering RRS & DO in mutation carriers at high risk of familial ovarian cancer	**CGG**	**BGCS**	**CGG**	**BGCS**	**CGG**	**BGCS**	
BRCA1 (n=168)	31.6% (24/76)	60.9% (56/92)	32.9% (25/76)	25.0% (23/92)	35.5% (27/76)	14.1% (13/92)	<0.0005
BRCA2 (n=166)	34.7% (26/75)	60.5% (55/91)	26.7% (20/75)	24.2% (22/91)	38.7% (29/75)	15.4% (14/91)	0.001
RAD51 (n=161)	9.5% (7/74)	19.5% (17/87)	29.7% (22/74)	16.1% (14/87)	60.8% (45/74)	64.4% (56/87)	0.047
UMS 10% risk (158)	19.4% (14/72)	37.2% (32/86)	23.6% (17/72)	27.9& (24/86)	56.9% (41/72)	34.9% (30/86)	0.012
Potential barriers to offering RRS & DO	**CGG**	**BGCS**	**CGG**	**BGCS**	**CGG**	**BGCS**	
Risk reduction only proven with RRSO (n=171)	77.5% (62/80)	72.5% (66/91)	5.0% (4/80)	12.1% (11/91)	17.5% (14/80)	15.4% (14/91)	0.26
Precise level of risk reduction not established (n=171)	83.8% (67/80)	82.4% (75/91)	6.2% (5/80)	7.7% (7/91)	10.0% (8/80)	9.9% (9/91)	0.934
Long term follow up needed for DO (n=167)	62.3% (48/77)	60% (54/90)	19.5% (15/77)	23.3% (21/90)	18.2% (14/77)	16.7% (15/90)	0.828
Confusion and additional stress for patients (n=168)	70.1% (54/77)	57.1% (52/91)	16.9% (13/77)	26.4% (24/91)	13.0% (10/77)	16.5% (15/91)	0.206
Increased surgical morbidity as 2 procedures needed (n=171)	83.5% (66/79)	75.0% (69/92)	3.8% (3/79)	22.8% (21/92)	12.7% (10/79)	2.2% (2/92)	**<0.0005**
Some patients may not undergo DO (n=167)	76.6% (59/77)	57.8% (52/90)	9.1% (7/77)	25.6% (23/90)	14.3% (11/77)	16.7% (15/90)	**0.013**
Loss of benefit of breast cancer risk reduction (n=167)	65.8% (52/79)	70.5% (62/88)	10.1% (8/79)	21.6% (19/88)	24.1% (19/79)	8.0% (7/88)	**0.005**
Cost effectiveness not known (n=165)	57.9% (44/76)	39.3% (35/89)	19.7% (15/76)	52.8% (47/89)	22.4% (17/76)	7.9% (7/89)	**<0.0005**

CGG- Cancer Genetics Group; BGCS- British Gynaecological Cancer Society, RRSDO- Risk Reducing Salpingectomy and Delayed Oophorectomy, RRSO- Risk Reducing Salpingo-oophorectomy, DO- Delayed Oophorectomy, UMS- unknown mutation status

Table-5: Potential benefit of reduction in OC risk with RRS for various risk categories[8, 9, 15, 40-42]

Risk Category	Total OC Risk	OC Risk to 50 years	Reduction in OC risk till 50 years with 40% benefit of RRS	Reduction in OC risk till 50 years with 50% benefit of RRS	Reduction in OC risk till 50 years with 60% benefit of RRS
BRCA1	**40%-60%**	**11-22.7%**	**4.4-9.1%**	**5.5-11.4%**	**6.6-13.6%**
BRCA2	**18-27%**	**0.4-4%**	**0.16-1.6%**	**0.2-2%**	**0.24-2.4%**
UMS	**10%**	**2.50%**	**1%**	**1.25%**	**1.5**
FDR BRCA1	**20-30%**	**5.5-11.4%**	**2.2-4.6%**	**2.8-5.7%**	**3.3-6.8%**
SDR BRCA1	**10-15%**	**2.8-5.7%**	**1.12-2.3%**	**1.4-2.9%**	**1.7-3.4%**
FDR BRCA2	**9-13.5%**	**0.2-2%**	**0.08-0.8%**	**0.1-1%**	**0.12-1.2%**
SDR BRCA2	**4.5-6.8%**	**0.1-1%**	**0.04-0.4%**	**0.05-0.5%**	**0.06-0.6%**

FDR- first degree relative, SDR- second degree relative, UMS- Unknown mutation status, OC- ovarian cancer, RRS- risk reducing salpingectomy

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