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Surgical decision making in premenopausal *BRCA* carriers considering risk-reducing early salpingectomy or salpingo-oophorectomy: a qualitative study

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ABSTRACT

Background Acceptance of the role of the fallopian tube in 'ovarian' carcinogenesis and the detrimental sequelae of surgical menopause in premenopausal women following risk-reducing salpingo-oophorectomy (RRSO) has resulted in risk-reducing early-salpingectomy with delayed oophorectomy (RRESDO) being proposed as an attractive alternative risk-reducing strategy in women who decline/delay oophorectomy. We present the results of a qualitative study evaluating the decision-making process among *BRCA* carriers considering prophylactic surgeries (RRSO/RRESDO) as part of the multicentre PROTECTOR trial (ISRCTN:25173360).

Methods In-depth semistructured 1:1 interviews conducted using a predeveloped topic-guide (development informed by literature review and expert consultation) until informational saturation reached. Wording and sequencing of questions were left open with probes used to elicit additional information. All interviews were audio-recorded, transcribed verbatim, transcripts analysed using an inductive theoretical framework and data managed using NVIVO-v12.

Results Informational saturation was reached following 24 interviews. Seven interconnected themes integral to surgical decision making were identified: fertility/menopause/cancer risk reduction/surgical choices/surgical complications/sequence of ovarian-and-breast prophylactic surgeries/support/satisfaction. Women for whom maximising ovarian cancer risk reduction was relatively more important than early menopause/quality-of-life preferred RRSO, whereas those more concerned about detrimental impact of menopause chose RRESDO. Women managed in specialist familial cancer clinic settings compared with non-specialist settings felt they received better quality care, improved hormone replacement therapy access and were more satisfied.

Conclusion Multiple contextual factors (medical, physical, psychological, social) influence timing of risk-reducing surgeries. RRESDO offers women delaying/declining premenopausal oophorectomy, particularly those concerned about menopausal effects, a degree of ovarian cancer risk reduction while avoiding early menopause. Care of high-risk women should be centralised to centres with specialist familial gynaecological cancer risk management services to provide a better-quality, streamlined, holistic multidisciplinary approach.

INTRODUCTION

BRCA1/BRCA2 mutation carriers have a ~70% lifetime risk of breast cancer (BC) and ~17%–44% lifetime risk of ovarian cancer (OC).[1] *RAD51C/RAD51D/BRIP1/PALB2* are newer moderate penetrance OC genes, whose risks were recently validated (5%–13% lifetime cumulative OC risk) with *RAD51C/RAD51D/PALB2* also associated with increased BC risk (20%–53%).[2 3] BC risk management options include annual (eg, MRI) breast screening;[4] chemoprevention (eg, Tamoxifen/Anastrazole))[5 6] and surgical prevention (risk-reducing mastectomy (RRM)).[7] Risk-reducing salpingo-oophorectomy (RRSO), usually recommended from 35 to 40 years, is the most effective surgical prevention option for OC-risk reduction, especially given the absence of an effective national (or even approved) high-risk OC-screening programme. However, premenopausal RRSO leads to early surgical menopause which has detrimental long-term health sequelae (increased risk of coronary heart disease, osteoporosis, vasomotor symptoms, sexual dysfunction, neurocognitive decline) particularly in women unable to use hormone replacement therapy (HRT).[8–13] Widespread acceptance of a central role for the fallopian tube in the development of high-grade serous carcinoma (HGSC), the most common type of OC has led to early salpingectomy (ES) followed by delayed oophorectomy (DO) proposed as an attractive alternative two-step OC surgical prevention strategy in premenopausal women who have completed their family but decline/wish to delay RRSO. Epidemiological studies show 70% of occult lesions identified in high-risk women undergoing RRSO occur in the tube and that salpingectomy may reduce ovarian cancer risk in low-risk women by 42%–65%. Thus, it is anticipated that risk-reducing early-salpingectomy with delayed oophorectomy (RRESDO) will provide some level of risk reduction while conserving ovarian function to avoid the negative impact of early menopause.

Three trials in the UK (PROTECTOR), Netherlands (TUBA) and US (WISP) are currently offering RRESDO within a controlled research setting. Absence of prospective data strengthens offering RRESDO currently solely within a research setting. The precise estimate of OC risk reduction and the

long-term health outcomes associated with ES remain unclear. Salpingectomy will not prevent OC arising outside the tube. Residual fimbrial tissue (most HGSC arise from tubal fimbria) may remain implanted on the ovarian surface postsalpingectomy in 9.8% cases[14] and represents a possible site of malignant transformation. The natural history of different types of serous-tubal intraepithelial carcinoma (STIC), the precursor of tubal HGSC and rate-limiting step in OC development remain unknown.[15] STICs may not be precursors to all OC.[16] The long-term impact of salpingectomy on sexual function, endocrine function and menopause onset is unknown. Concerns remain regarding attrition from DO and uncertainties persist around cost effectiveness.[17]

There is a paucity of qualitative data on the decision-making process for RRESDO in *BRCA* carriers.[18] Limited data suggest that the seriousness of OC, family history (FH), previous BC, uncertainty around effect of ES and ease of decision to undergo RRSO are barriers to undergoing RRESDO.[18] The main facilitator is longer preservation of ovarian function.[18] RRESDO appears acceptable particularly to women concerned about sexual dysfunction.[19] Barriers to RRSO include early menopause, sexual dysfunction and loss of fertility; facilitators include FH, fear of dying, concurrent benign gynaecological issues, ineffective screening and physician recommendation.[18 20–22]

Current medical decision making encourages clinicians to respect patients' preferences and be guided by them for treatment decisions.[23] Policy makers and commissioners increasingly use qualitative data to inform guideline development and care pathways, as it enables care provision according to user insights by gaining a better understanding of, and reasons for the choices made. We report on the decision making of high-risk UK women undergoing/considering prophylactic surgery in the PROTECTOR trial (ISRCTN 25173360). This study aims to evaluate the decision-making process among *BRCA* carriers considering prophylactic surgeries. We offer novel insights for healthcare professionals providing decision support to *BRCA* carriers and for development of clinical management pathways for these women.

METHODS

Study design

Qualitative substudy nested within a multicentre, observational cohort trial (PROTECTOR: Preventing Ovarian Cancer through early Excision of Tubes and late Ovarian Removal, ISRCTN:25173360) with three arms: RRESDO; RRSO; no surgery.[24] Premenopausal women (follicle stimulating hormone (FSH) levels<40), >30 years, at increased risk of OC (*BRCA1*/*BRCA2*/*RAD51C*/*RAD51D*/*BRIP1* carriers or due to a strong family history) were recruited to the PROTECTOR trial (www.protector.org.uk) through specialist high-risk familial cancer clinics (FCC), genetics, gynaecology/gynaecological oncology clinics. Exclusion criteria included being postmenopausal, previous bilateral salpingectomy or bilateral oophorectomy, pregnancy, future plan of childbearing (surgical arms only), prior OC/peritoneal malignancy, <12 months from cancer treatment, OC suspicion at baseline. Participants self-selected their chosen study arm following informed counselling.

In-depth semistructured one-to-one telephone interviews were conducted (by FG) using a predeveloped topic-guide (online supplemental material 1). Topic-guide development was informed by a literature review and expert consultation. Wording and sequencing of questions were left open with probes used to elicit more information as appropriate. Questions were refined following a pilot interview, and topics covered included: background (family structure, support network, occupation, hobbies); risk-reducing surgery for OC/BC prevention; health values; satisfaction-and-regret. Following informed consent, interviewees were recruited based on sociodemographics (age, ethnicity, marital status, postcode), parity, BC history, trial arm (RRESDO, RRSO, no surgery) and ascertainment location (high-risk FCC, gynaecology clinic, gynaecological oncology clinic, genetics clinic) to ensure adequate representation across the PROTECTOR cohort. Field notes were made, interviews audio-recorded and transcribed verbatim. Interviews were conducted (before OC prevention surgery) between November 2018 and October 2019 until data saturation was reached.

Data analysis

Transcripts were analysed using a grounded-theory approach and data managed using NVIVO V.12 software. The analysis aimed to directly reflect the views and experiences of participants' and not those predetermined by the researchers. Two researchers (FG, SG) independently coded all transcripts, following a three-step process: open coding, axial coding and selective coding. Meaningful text was labelled starting with a line-by-line analysis (open coding). Open codes were categorised, grouping similar codes, refined and combined into larger themes (axial coding). Through multiple, iterative discussions, we reflected on potential relationships between codes within and across cases and developed an in-depth understanding of themes. Coding disagreements were resolved through discussion with further transcript review until reaching consensus. Transcripts were re-reviewed to ensure themes reflected the data and important ideas/views had not been missed/over-represented. Selective coding involved integrating and refining themes. Analysis was performed in parallel with data collection and finalised once theoretical saturation was reached.

RESULTS

Participant characteristics

Twenty-four women were interviewed, with no interview refusals. Participant characteristics are summarised in table 1. Participants ranged from 34 to 46 years; 22 were Caucasian, 19 married, 4 nulliparous, 4 had previously BC themselves, 9 had undergone RRM, 14 were *BRCA1* carriers, 10 *BRCA2* carriers, 11 self-selected RRESDO, 7 RRSO and 6 no surgery. Interviews lasted 40–70 (mean=55) min.

Themes

Seven themes pertinent to decision making emerged: fertility; menopause; cancer risk reduction: surgical choices; surgical complications; sequence of ovarian and breast prophylactic surgeries; support with decision making; satisfaction with treatment choices. Table 2 summarises the facilitators and table 3 the barriers per-theme and surgical prevention strategy. Figure 1 maps the decision-making options for premenopausal *BRCA* carriers considering risk-reducing surgery.

Fertility

> ID-03 (RRESDO-arm): 'I just think because I know that I've completed my family and I don't want these old tubes anymore anyway, I just see it [surgery] as being something positive that I can do for myself, to hopefully reduce my risk of cancer.'

Fertility was an important consideration for all women. For 18 women choosing surgery (RRESDO/RRSO), 16 completed childbearing and two didn't want children. Once fertility was not a

Table 1 Participant characteristics

ID	Study arm	Age (years)	Ethnicity	Marital status	Parity	Carrier status	Personal history of BC	RRM	Number of relatives with OC	Number of relatives with BC	Ascertainment	Postcode
ID-01	No surgery	40	Caucasian	Single	0	BRCA1	No	Yes	0	1 SDR	High-risk FCC	London
ID-02	RRSO	41	Caucasian	Married	0	BRCA2	No	Yes	0	1 FDR, 1 SDR	High-risk FCC	Essex
ID-03	RRESDO	37	Caucasian	Married	3	BRCA2	No	No	1 SDR	1 FDR, 1 SDR	High-risk FCC	Essex
ID-04	RRSO	46	Caucasian	Married	0	BRCA1	No	No	0	0	High-risk FCC	London
ID-05	RRESDO	43	Caucasian	Single	2	BRCA1	No	No	1 SDR	3 SDR	High-risk FCC	London
ID-06	RRESDO	38	Caucasian	Married	2	BRCA1	No	Yes	0	3 SDR	High-risk FCC	Sussex
ID-07	No-surgery	36	Asian	Single	1	BRCA1	No	No	1 SDR	3 SDR	High-risk FCC	London
ID-08	RRESDO	46	Caucasian	Married	3	BRCA2	No	Yes	0	1 FDR, 1 SDR	High-risk FCC	Cambridge
ID-09	RRESDO	39	Caucasian	Married	2	BRCA1	No	Yes	1 FDR, 1 SDR	1 FDR	High-risk FCC	London
ID-10	No-surgery	39	Caucasian	Married	0	BRCA1	No	No	1 SDR	1 FDR	High-risk FCC	London
ID-11	RRESDO	35	Caucasian	Married	2	BRCA2	No	No	1 FDR	0	High-risk FCC	Hertfordshire
ID-12	No-surgery	36	Caucasian	Married	1	BRCA1	No	No	2 SDR	1 SDR	High-risk FCC	London
ID-13	RRSO	45	Caucasian	Married	1	BRCA2	No	Yes	0	0	General gynaecology clinic	Durham
ID-14	No-surgery	38	Caucasian	Married	1	BRCA1	Yes*	No†	0	0	High-risk FCC	London
ID-15	RRESDO	38	Caucasian	Married	2	BRCA2	No	No	0	0	High-risk FCC	Hertfordshire
ID-16	RRESDO	44	Caucasian	Married	2	BRCA2	No	No	2 SDR	1 SDR	High-risk FCC	Hampshire
ID-17	RRESDO	39	Caucasian	Married	2	BRCA1	Yes‡	No†	0	0	GO clinic	Newport
ID-18	RRESDO	44	Caucasian	Single	2	BRCA2	No	Yes	0	1 FDR, 2 SDR	High-risk FCC	London
ID-19	No surgery	34	Caucasian	Married	2	BRCA1	No	No	0	1 SDR	Genetics clinic	Surrey
ID-20	RRSO	46	Asian	Married	2	BRCA1	No	No	1 FDR, 2 SDR	2 SDR	GO clinic	Aberdeen
ID-21	RRESDO	44	Caucasian	Married	2	BRCA2	Yes*	Yes§	1 FDR	1 FDR, 1 SDR	GO clinic	Devon
ID-22	RRSO	39	Caucasian	Married	2	BRCA2	No	No	0	1 FDR	GO clinic	Liverpool
ID-23	RRSO	40	Caucasian	Single	2	BRCA1	No	No	1 FDR, 1SDR	0	High-risk FCC	Surrey
ID-24	RRSO	40	Caucasian	Married	1	BRCA1	Yes‡	Yes*§	0	2 FDR	General gynaecology clinic	Cleveland

*Oestrogen receptor positive breast cancer.
†Bilateral therapeutic mastectomies.
‡Triple negative breast cancer.
§Unilateral therapeutic mastectomy followed by contralateral risk reducing mastectomy.
BC, breast cancer; FCC, familial cancer clinic; FDR, first degree relative; GO, gynaecological oncology; OC, ovarian cancer; RRESDO, risk-reducing early salpingectomy with delayed oophorectomy; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy; SDR, second degree relative.

Table 2 Thematised facilitators to uptake of risk reducing surgeries

Themes	Facilitators	Quotes
	RRESDO	
Surgical complications; satisfaction with treatment choices	Positive experience with previous surgery	*'…the trade-off between having two surgeries as opposed to one, that does feel absolutely fine to me, and that's maybe because I've had positive experiences with surgery before.'* (ID-18)
Menopause; satisfaction with treatment choices	Flexible timing of delayed oophorectomy	*'I know that there is no guarantee that it prevents ovarian cancer but I see it as being a positive thing I can do for myself for now, at my age and I know that if I had any concerns in the future, even before I hit menopause, that I could come back and approach you about having my ovaries removed, no-one's telling me, "If you have your tubes out, you have to wait X, we won't take your ovaries out for this", so I think everyone's been very open to discussing it and it's been very focused around how I feel and what I want, which is very encouraging.'* (ID-16)
Menopause; satisfaction with treatment choices	Avoiding early menopause	*'…what I was most interested in was the fact that it would be two-step because I feel personally, I'm too young to be put into menopause, I don't want to go down that road.'* (ID-03)
Menopause	Avoiding the need to take HRT	*'I'd rather just have a little surgery and deal with that for a small amount of time than have to take HRT all the time, I'm quite loathed to take drugs really.'* (ID-16) *'I was worried about the financial implications of having to take something for life.'* (ID-18)
Menopause; satisfaction with treatment choices	Concerns HRT may not adequately alleviate menopausal symptoms and improve QoL	*'…HRT perhaps hasn't worked out quite as expected or planned or it's needed a lot of tweaking or maybe they haven't received the level that they've needed to and, they haven't regretted the decision because actually they've reduced their risk but they've actually noticed a significant drop in their quality of life that they didn't actually expect. And, I think it's really important for people to know that that might happen…'* (ID-05)
Cancer risk reduction: surgical choices; satisfaction with treatment choices	To reduce anxiety of doing nothing	*'Sometimes you just have to make a decision between two difficult things, where you don't really want to do either of them and doing something is better than doing nothing…'* (ID-16)
Cancer risk reduction: surgical choices	Empowerment	*'…I just see it as being something positive that I can do for myself, to hopefully reduce my risk of cancer.'* (ID-08)
Cancer risk reduction: surgical choices; sequence of ovarian and breast prophylactic surgeries; satisfaction with treatment choices	Stronger FH of BC than OC	*'There's more breast than ovary cancer in my family, so I'm probably at higher risk of breast cancer.'* (ID-18)
Fertility	Childbearing complete	*'I have finished having children so it was an easy decision to make.'* (ID-06)
	RRSO	
Surgical complications	Single surgery and concerns over future health	*'…I think while you're fit and well, it's the time to have surgery. The longer you wait, who knows what happens when you get older.'* (ID-13)
Surgical complications	Straightforward day case surgery	*'…it (salpingo-oophorectomy)sounds like quite a straightforward minor operation and I can go home the same day…'* (ID-13)
Cancer risk reduction: surgical choices	Wanting maximum OC risk reduction	*'I just want the surgery that will protect me from developing ovarian cancer the most.'* (ID-22)
Menopause	Taking HRT acceptable	*'I don't have any issue taking HRT.'* (ID-20)
Cancer risk reduction: surgical choices	Strong family history of OC	*'So many of my relatives have died from ovarian cancer.'* (ID-23)
Fertility	Childbearing complete	*'I'm finished having children.'* (ID-20)
Cancer risk reduction: surgical choices	No NHS OC screening programme	*'There is no screening on the NHS for ovarian cancer and that means my only other option is to have my ovaries out.'* (ID-20)
Cancer risk reduction: surgical choices	Inability to self-examine ovaries	*'From the very beginning I felt I was more concerned more about the ovarian cancer risk than the breast cancer risk, because I felt like I could effectively examine my own breasts and keep a check on that, but I can't check my ovaries.'* (ID-04)
Cancer risk reduction: surgical choices	Poor OC prognosis	*'…it's very hard to detect ovarian cancer and it has a very poor prognosis, it seemed to make complete sense.'* (ID-04)
Support with decision making; cancer risk reduction: surgical choices; sequence of ovarian and breast prophylactic surgeries	Physician recommendation	*'Counselling from my doctor really helped. She was knowledgeable, supportive and sympathetic of my situation. She recommended surgery as I have had all my kids, am 46 and because my aunt died of ovarian cancer at 45.'* (ID-04)
	RRM	
Cancer risk reduction: surgical choices	BC screening anxiety	*'I never went away thinking, "I've got the all clear", I went away feeling like, "As far as anyone can tell I've got the all clear", and then the anxiety would start to rise again as we headed towards the next five month [screening] mark point when I could see it looming in the diary.'* (ID-13)
Fertility	Completion of childbearing and breast feeding	*'I have finished having kids, so I don't really need them anymore.'* (ID-02)
Cancer risk reduction: surgical choices; sequence of ovarian and breast prophylactic surgeries	Strong FH of BC	*'I know that the risk is greater for cancer in the breast as compared to the ovaries because of my family history.'* (ID-02)
	Combined breast and ovarian cancer prevention surgeries	
Sequence of ovarian and breast prophylactic surgeries	Fewer surgeries	*'Just throw everything at it, and let's just get it all sorted in one.'* (ID-11)
Sequence of ovarian and breast prophylactic surgeries	Less anxiety associated with waiting for individual surgeries	*'It's stressful waiting for all the appointment to see different specialists at different times. I would be happier if I could have got it all sorted in one go.'* (ID-05)
Sequence of ovarian and breast prophylactic surgeries	Fewer hospital appointments	*'The fewer times I need to visit hospital, the better.'* (ID-05)
Sequence of ovarian and breast prophylactic surgeries	Less delays waiting for individual surgeries	*'I guess there's no thinking of delaying one or the other, if I've made a decision to reduce my risk, I think it would make sense to do them both at the same time.'* (ID-22)
Sequence of ovarian and breast prophylactic surgeries; support with decision making	Less time off work	*'I'm self employed, so the less time off work, the better.'* (ID-22)

Continued

Table 2 Continued

Themes	Facilitators	Quotes
	RRESDO	
Sequence of ovarian and breast prophylactic surgeries	Single postoperative recovery	*'I would prefer to recover just once from surgery.'* (ID-18)
Sequence of ovarian and breast prophylactic surgeries; fertility	Childbearing complete	*'Because I'm done having kids, I just want it all out.'* (ID-23)

BC, breast cancer; HRT, hormone replacement therapy; OC, ovarian cancer; QoL, quality of life; RRESDO, risk-reducing early salpingectomy with delayed oophorectomy; RRM, risk-reducing mastectomy; RRSO, risk-reducing-salpingo-oophorectomy.

barrier, deciding to undergo surgery was less complex and a natural next step. Four women had not completed childbearing, wished to delay surgery and joined the control arm. Two control arm women despite completing childbearing delayed surgery. One was undecided what to choose and the second had strong beliefs against removing healthy tissue and any risk-reducing surgery.

Two women opted to conceive through in vitro fertilisation (IVF) and preimplantation genetic diagnosis (PGD). Both acknowledged PGD/IVF was physically and mentally stressful with multiple hospital visits and additional procedures but considered it an acceptable tradeoff to prevent their children being *BRCA* carriers and facing similar difficult decisions. One participant felt she may have not proceeded with a natural conception if IVF/PGD had failed.

Table 3 Thematised barriers to uptake of risk reducing surgeries

Themes	Barriers	Quotes
	RRESDO	
Menopause; satisfaction with treatment choices	Approaching the age of natural menopause	*'I think my age, I think it's the fact that they [surgeries] might have ended up being within two or three years, it just didn't make that much sense to me…'* (ID-20)
Cancer risk reduction; sequence of ovarian and breast prophylactic surgeries	Strong family history of OC	*'I am more concerned about protecting myself from ovarian cancer because I have more relatives with ovarian cancer than breast cancer and so I just want the lot [tubes and ovaries] out.'* (ID-23)
Cancer risk reduction: surgical choices	Two staged surgery	*'To be honest, I think if you're going to go and have it done, have it done in one. Why would I want, in another 10 years, to go and have surgery again?'* (ID-23)
Surgical complications	Concerns over future poor health	*'I don't know what my health would be like in 10 years' time, I might not be up for surgery. I just think get it done, get it over and done with now.'* (ID-20)
Cancer risk reduction: surgical choices; satisfaction with treatment choices	More effective surgery to reduce OC risk	*'…I just want to eliminate as much [risk] as possible…'* (ID-20)
Fertility	Childbearing not complete	*'I have not finished having children…'* (ID-01)
	RRSO	
Fertility	Childbearing not complete	*'I have not finished having children…'* (ID-14)
Fertility	Not wanting to remove healthy tissue	*'It's also quite difficult to decide to go through an operation when there's nothing wrong, so obviously it's preventative but part of you is like "I'm perfectly healthy, why would I do this?"'*(ID-01)
Menopause; satisfaction with treatment choices	Early menopause	*'I was very off put by that [oophorectomy] because I feel I'm too young to be put into the menopause and I'm aware, probably through training as a nurse, the symptoms associated with that, the increased risk of, I would be decreasing my risk obviously of ovarian cancer but then have an increased risk of osteoporosis and all the other things, it was trying to weigh up the best option and I didn't feel that that's something I wanted to think of at this moment in time.'* (ID-01)
	RRM	
Cancer risk reduction: surgical choices	Loss of femininity and self esteem	*'My breasts are my womanhood and loosing them I think would really effect my self esteem and not in a good way.'* (ID-15)
Fertility	Childbearing and breastfeeding not complete	*'I still need my breasts to breastfeed. I've not finished having kids.'* (ID-03)
Surgical complications; satisfaction with treatment choices	Major operation with long recovery	*'…it's a major operation, psychologically and physically with long recovery.'* (ID-03)
Cancer risk reduction: surgical choices	Effective BC screening programme	*'There is such an effective screening programme, I wouldn't want surgery unless there was something picked up on a scan.'* (ID-04)
Cancer risk reduction: surgical choices	Good prognosis from early screen detected BC	*'…breast cancer is quite treatable and has often a good prognosis.'* (ID-04)
	Combined ovarian and breast cancer prevention surgeries	
Sequence of ovarian and breast prophylactic surgeries; satisfaction with treatment choices	Increased duration of postoperative recovery	*'I would be worried that recovery from such a big operation would be really long.' (ID-23)*
Sequence of ovarian and breast prophylactic surgeries; satisfaction with treatment choices	Concerns over increased number of complications	*'…primarily it will be around the additional risk of complications and side effects from the various elements of the two different surgeries…' (ID-23)*
Sequence of ovarian and breast prophylactic surgeries; satisfaction with treatment choices	Psychological distress	*'I don't think I would cope well with going into menopause the same time as losing my breasts and all the implications that would have on me feeling like a woman.' (ID-22)*

BC, breast cancer; HRT, hormone replacement therapy; OC, ovarian cancer; QoL, quality of life; RRESDO, risk-reducing early salpingectomy with delayed oophorectomy; RRSO, risk-reducing salpingo-oophorectomy.

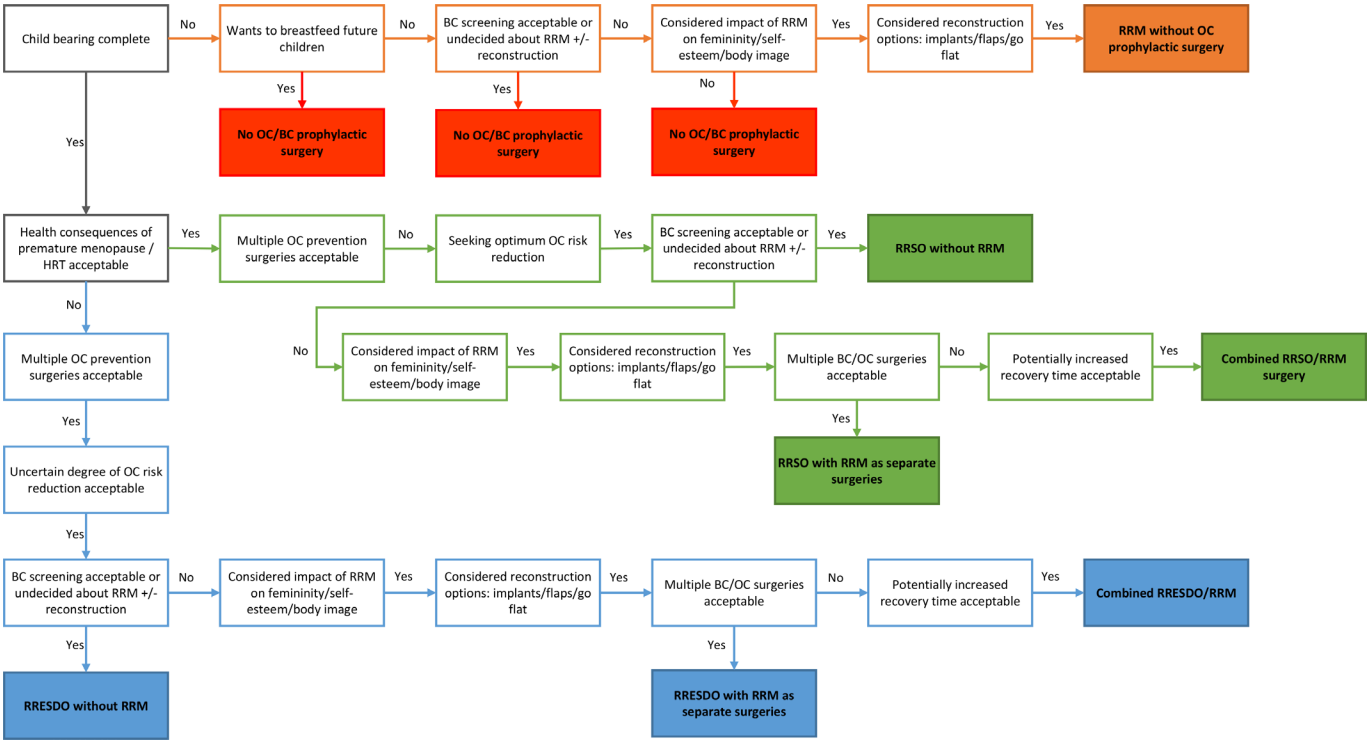

Figure 1 Decision making aid for premenopausal *BRCA* carriers considering risk reducing surgery. BC, breast cancer; HRT, hormone replacement therapy; OC, ovarian cancer; RRESDO, risk reducing early salpingectomy with delayed oophorectomy; RRM, risk reducing mastectomy; RRSO, risk reducing salpingo-oophorectomy.

Menopause

ID-06 (RRESDO-arm): 'I wasn't happy with the impact of going in to menopause straight away and although you obviously have HRT options which might be offered if you go to a good gynaecologist, I just, I wasn't convinced that HRT brings you back up to an even keel or level, the way that I'm feeling right now which is basically very balanced.'

Interviewees who chose RRESDO (n=11) did so because of concerns about detrimental consequences of early menopause following oophorectomy, particularly low mood, sexual dysfunction and poorer QoL. All RRESDO interviewees found the uncertainty regarding long-term health implications (eg, possibility of earlier menopause following ES) an acceptable risk. Interviewees rationalised RRESDO as a preferential strategy to delay early menopause and its long-term consequences while benefiting from some OC risk reduction. Two women would have delayed risk-reducing surgery until they were near/at natural menopause if RRESDO was unavailable, whereas another would have undergone RRSO instead. Two RRESDO women found avoiding need for HRT and repeat prescription costs more appealing. RRESDO interviewees wanted to be in control of choosing the timing of DO (with their clinician) and felt a fixed timing for DO was a barrier to RRESDO uptake. Menopause was a lesser concern to older premenopausal women (nearer the age of natural menopause) self-selecting RRSO because RRESDO would only delay menopause by a few years and require an additional operation.

RRSO women managed outside specialist high-risk clinics reported receiving conflicting advice on HRT safety, lack of information on HRT efficacy for symptom relief and struggling with HRT access. A number of gynaecologists/gynaecological oncologists do not routinely counsel women about health consequences of early menopause, lack awareness of HRT safety and do not offer HRT to *BRCA* carriers undergoing premenopausal RRSO (particularly those near natural menopause age). Women attending *BRCA* support forums felt unsupported without follow-up after surgery and reported persistent menopausal symptoms detrimentally affecting QoL despite HRT. Women managed within a high-risk FCC reported being more reassured with their planned follow-up and access to a menopause specialist post-RRSO.

Cancer risk reduction: surgical choices

Ovarian-cancer risk-reducing surgery

ID-08 (RRESDO-arm): 'It's [RRESDO] acceptable because it's my decision making as well, it's not at the fault of any health professional, no-one is making me do it this way, it's my decision and I'm aware of that.'

Women who prioritised avoiding menopause and preserving QoL selected RRESDO. While, women concerned about the precision of risk reduction and who prioritised maximising OC risk reduction, selected RRSO. Women with a strong FH of OC selected RRSO, and with strong FH of BC preferred RRESDO.

RRESDO interviewees felt comfortable and empowered with the tradeoff between an uncertain degree of OC risk reduction and avoidance of early menopause. They rationalised they were doing '*…something to reduce risk as opposed to nothing…*' while avoiding early menopause and preserving their QoL.

A few interviewees reported being counselled/reading they were at increased endometrial cancer risk and were offered/requested a concomitant hysterectomy.

Breast-cancer risk-reducing surgery

ID-01 (No-surgery-arm): '…it's also quite difficult to decide to go through a major operation when there's nothing wrong, so obviously it's preventative but part of you is like "I'm perfectly healthy, why would I do this?", and there's something quite emotional about the idea of having your

breast removed as well, whereas the ovaries aren't seen, it's about appearance as well and just having implants and things like that.'

Interviewees considered RRM decision making much harder compared with RRSO/RRESDO. Women were conflicted with wanting to optimise BC prevention while preserving breasts for femininity and self-esteem. They preferred delaying RRM until finishing childbearing and breastfeeding.

ID-13 (RRSO-arm): 'I never went away thinking, "I've got the all clear", I went away feeling like, "As far as anyone can tell I've got the all clear", and then the anxiety would start to rise again as we headed towards the next five month mark point when I could see it looming in the diary.'

Some women reported anxiety/stress with breast s

Nine women underwent RRM and five struggled with decision making on reconstruction with flaps or implants; and consideration of nipple-sparing versus non-nipple-sparing surgeries. Two highlighted lack of healthcare professional support for women opting against reconstruction. One interviewee regretted her decision of flap reconstruction due to resultant cosmetic appearance and chronic pain but did not regret RRM.

All BC-affected interviewees selected OC-prevention surgery purely for preventing OC. They felt alternative treatments were available to improve BC survival. Women selecting RRESDO did not consider the potential loss of improved BC-survival from oophorectomy a barrier.

Surgical complications

ID-18 (RRESDO-arm): '…the trade-off between having two surgeries as opposed to one, that does feel absolutely fine to me, and that's maybe because I've had positive experiences with surgery before.'

Women with previous positive surgical experiences (good relationship with surgeon, postoperative care, no complications) and/or good health found two-staged RRESDO acceptable, without concerns for increased surgical complications or hospital appointments. Inspection of pelvis/abdomen for OC at RRES was reassuring for one patient. One RRSO interviewee highlighted concerns of two surgeries as future health may deteriorate with age and increase risks of surgical complications.

Sequence of ovarian and breast prophylactic surgeries

Sequential surgery

ID-16 (RRESDO-arm): 'Because I've never had an operation, I thought it would be better to have a minor operation first, just to kind of prepare me rather than going straight into major surgery, that was one reason but the other was the ovarian cancer prevention felt more pressing because I'm on the breast screening programme and it didn't feel quite so urgent.'

Interviewees reported preferring OC prevention surgery before RRM because of lack of an OC screening programme; poorer prognosis of OC; being a laparoscopic procedure with quick recovery; inability to self-examine ovaries. Women with a stronger FH of OC preferred RRSO first and those with a FH of BC chose undergoing RRM first. Sequence was also dependent on surgical referral and appointment times with some experiencing shorter waiting times for seeing a breast surgeon than a gynaecologist/gynaecological oncologist.

Combined ovarian and breast prophylactic surgery

ID-11 (RRESDO-arm): 'Just throw everything at it, and let's just get it all sorted in one.'

Fifteen women would have preferred a single combined risk-reducing procedure involving RRM±reconstruction along with OC preventative surgery. Reasons included fewer surgeries, less anxiety, less waiting, fewer appointments, less time off work and single surgical recovery. However, nine women expressed concerns over possible increased recovery time and increased psychological distress from early menopause impacted by RRM associated body image issues.

Support with decision making

Clinical support

ID-05 (RRESDO-arm): '…my experience of [gynaecology] appointments is that people just present things to you, and very quickly you have to make a decision, and there isn't a way to just, some of the decisions take a lot of discussion, and coming back to it, and rethinking, and I just feel that there isn't that space for it…'

Interviewees expressed preference for multiple appointments with gynaecologists/gynaecological oncologists for discussing risk-reducing surgery. Decision making was a complex/dynamic process, with one visit being inadequate to absorb/assimilate complex information, and make an informed decision. Interviewees felt more supported with RRM decision making, given access to a psychologist and multiple breast surgical appointments before RRM. Interviewees wished to be routinely offered an 'optional' (not compulsory) consultation with a psychologist prior to OC preventative surgery.

Interviewees who had done personal research (reading literature, speaking to *BRCA* carriers, online support groups (OSGs)) felt their decision was validated following counselling from healthcare professionals. Counselling received aided decision making of women who had not done any personal research. Counselling lacked information on communicating genetic test results to children and complex decisions carriers faced.

Patient support groups

ID-05 (RRESDO-arm): 'I know there are [online] forums, but a lot of it, there's a lot of fearful ideas there, and my cousin was saying that she just had to stop going on those forums.'

Continuous availability/access and anonymity were advantages of online *BRCA* support groups/forums reported by our cohort. However, interviewees also highlighted negative personal experiences (and anxiety) given poor surgical outcomes/negative experiences discussed at these outlets which were not balanced with positive outcomes. Interviewees used online forums for an ad-hoc-specific query rather than for regular support. Clinician-led educational days with experts' talks about management options, opportunities to ask questions, share experiences and meet other *BRCA* carriers appeared preferable.

Lifestyle support

ID-22 (RRSO-arm): 'When I realised that I'd have to go through with a number of operations to help reduce the risk, I made sure that I was in the best possible health beforehand to deal with those and I was really glad that I did.'

RRESDO/RRSO women were eating healthier, losing weight and exercising regularly to minimise postoperative complications and shorten recovery time. Even no-surgery interviewees made healthier choices (smoking cessation, reduced alcohol, exercise, diet) to increase their conception chances.

Satisfaction with treatment choices

ID-16 (RRESDO-arm): 'I'm at peace over the situation, and it's not something that has caused me anxiety, although I don't really like procedures and hospitals as I've said, but I feel that it's something that I can manage.'

Interviewees felt it difficult to state outright satisfaction with their decision to have/not have preventative surgery but rationalised their decision making. Women delaying surgery were concerned about developing cancer. Women undergoing surgery were also concerned about developing cancer along with surgical complications, impact on QoL and psychological health. However surgery reduced OC/BC anxiety.

ID-18 (RRESDO-arm): 'I'd done quite a bit of research myself. I found all of the people that I've met within the team have been fantastic and haven't just treated me like Patient X who doesn't know anything at all.'

Interviewees managed within high-risk multidisciplinary FCC appeared more satisfied than those managed in genetics/gynaecology/gynaecological oncology clinics. Reasons included a more personalised approach, information tailored to the individual's pre-existing knowledge base, same-day consultations with multiple specialists and continuity of care. The combination of specialists supporting FCCs varied but included: geneticists, gynaecologists, breast surgeons, menopause specialists, fertility specialists, psychologists. All seven women previously under the care of non-specialist clinics reported higher satisfaction levels when subsequently managed in the FCC setting.

ID-13 (RRSO-arm): '…it does take time, like relieve yourself of that sense of pressure of having to come to a decision…'

Interviewees would advise fellow *BRCA* carriers to avoid time-pressure with surgical decision making, talk to other *BRCA* carriers, do personal research, ask for second opinions if not satisfied.

No-surgery interviewees would regret their decision to delay/avoid surgery if they developed OC. Women undergoing surgery would regret it if a life-changing surgical complication occurred.

DISCUSSION

We identified seven interconnected themes integral to surgical prevention decision making in *BRCA* carriers. To the best of our knowledge, this is the first qualitative study that has mapped all aspects of the decision-making process of *BRCA* carriers undergoing/considering all ovarian (RRESDO/RRSO)/breast (RRM)/combined risk-reducing surgical options (figure 1). Women for whom maximising OC risk reduction was relatively more important than early menopause/QoL preferred RRSO, whereas those more concerned about impact of menopause chose RRESDO.

While some facilitators/barriers we describe for RRESDO are similar to those reported earlier, we found some differences too.[18 19 25] Unlike a Dutch study reporting a personal history of BC as a barrier, we report that BC-affected *BRCA* carriers found RRESDO acceptable despite potential for improved BC survival afforded by premenopausal oophorectomy. BC-affected and unaffected *BRCA* carriers selecting RRESDO were equally concerned about avoiding early menopause/maintaining QoL. This apparent difference in RRESDO acceptability among UK and Dutch women may be attributed to differences in counselling, risk-management options available, population differences, evolving scientific evidence base, its interpretation by clinicians and patients and changing practices. Oophorectomy may not reduce primary/contralateral BC risk[26–29] and effective adjunct treatments to improve BC outcomes are available including contralateral mastectomy, GnRH analogues, selective estrogen receptor modulators etc.

Approaching the age of natural menopause and concerns over future poor health were new barriers to RRESDO we elicited. Previously unreported RRESDO facilitators identified include avoiding the need for HRT and significant concerns about not adequately alleviating menopausal symptoms or improving QoL. This highlights women's unease and apprehension related to effects of menopause.[30] Premenopausal women concerned about sexual dysfunction are more likely to opt for RRESDO.[19] Despite HRT, symptom levels following premenopausal oophorectomy, particularly for sexual dysfunction, remain above those retaining their ovaries.[31] As part of RRSO decision making all premenopausal women should be involved in formulating an individualised presurgical HRT plan and fully counselled on menopausal issues along with the benefits and limitations of HRT.

Other RRESDO facilitators we identified include positive experience with previous surgery, reducing the anxiety of doing nothing and flexible timing of DO. The Dutch-TUBA,[32] and US-PSDO (Prophylactic Salpingectomy with Delayed Oophorectomy)[33] studies undertake DO well before onset of menopause (without the option to delay until natural menopause). This could have been a barrier for UK women. However, in the UK PROTECTOR, and US WISP (Women Choosing Surgical Prevention)[6] trials, women can choose when to undergo DO but are encouraged to do this by natural menopause. The facilitator and barriers to RRSO/RRM elicited in our cohort are similar to those reported earlier.[22 33–37]

We too found undergoing preventative surgery reduced anxiety.[18 34 35] Although RRM decision making was more complex than OC preventative surgery, women felt more supported in their decision to undergo RRM (than OC prevention) due to psychology input and multiple breast surgical appointments. This reflects the well-established tertiary care BC risk-management pathways in the UK.[38] We found disparities in OC risk management care across the UK. Women managed in high-risk FCC settings were more satisfied with their care and received better support and HRT access. The lower satisfaction in women managed in non-specialist clinics was linked to non-streamlined clinical pathways, need for multiple referrals, delays in seeing different specialists, lack of continuity of care and difficulties in assimilating large volumes of information in a single appointment. Others too have reported low satisfaction with poorly developed care pathways.[36 39] Of particular concern was poor HRT counselling and management, also reported previously.[20] High-risk women need to be supported by a multidisciplinary team comprising geneticists, gynaecologists/gynae-oncologists with a special interest, breast oncologists, oncoplastic surgeons, menopause specialists, fertility specialists, psychologists and specialist nurses. Our findings support centralising care of high-risk women to centres which have specialist high-risk multidisciplinary FCC services and the need to develop more such services/centres with well-defined care pathways.

Our data suggest that women engage concurrently in both OC and BC prevention decision making in contrast to some studies suggesting that women prioritise decisions and make them one at a time.[36 40 41] We identified a demand for combined OC-and-BC prevention surgery. However, only few centres currently offer this, the psychological/QoL effects following combined BC/OC prophylactic surgery are unknown and not all women may be suitable candidates. Combined surgery offers logistical practicality for busy working women with dependent families by limiting the hospital appointments/surgeries/postoperative

recoveries and has high satisfaction.[40] Initial data suggest that a combined approach has lower costs than separate procedures[40] but formal cost-utility analysis including sensitivity analysis is needed. Additionally, RRESDO may be more acceptable than RRSO for combined surgery given the potential for menopausal symptoms while recovering from effects of mastectomy.

Benefits of OSGs[42–44] include fluid informational exchange, continuous availability, greater access/anonymity and were also reported by our cohort. Our cohort reported increasing anxiety with OSGs and a preference for educational support groups (ESGs). ESGs involve face-to-face group activities where participants and clinicians share their experiences and expertise, along with a patient representative acting as the group spokesperson. Women found the opportunity to ask experts questions and meet other *BRCA* carriers face-to-face more helpful than OSGs. Although small randomised controlled trials (RCTs) have shown lower anxiety/depression with OSGs (compared with clinical care) in BC women,[45] these results may not be generalisable to *BRCA* previvors unaffected by cancer. Large, well-designed RCTs comparing OSG with ESG are needed. Another gap we identified was support women needed to communicate to their children genetic test results and the complex decisions they faced. Options to address this may include customised information sheets/decision aids, offering family counselling. While family counselling is established for informing children of a parent's cancer diagnosis,[46] outcome data and pathways for this in a previvor setting are needed.

Strengths of our study include a robust methodological approach using semistructured in-depth interviews until reaching data saturation, independent data analysis by two researchers and a comprehensive three-step coding process. Our sample was broad-based and included women who declined surgery, had a personal history of BC, parous/nulliparous, ascertainment from a variety of outpatient settings and different UK geographical locations. Limitations include that only two interviewees were non-Caucasian and there may be cultural nuances affecting the decision-making process in ethnic minorities. Also, women who had undergone RRM were interviewed retrospectively, ensuing a risk of recall bias.

Medical, physical, psychological and social contextual factors influence the timing of risk-reducing surgeries. RRESDO offers premenopausal women who would otherwise delay/decline premenopausal oophorectomy a degree of OC risk reduction while avoiding the detrimental sequelae of early menopause. The addition of RRESDO as a two-stage surgical alternative to RRSO, adds an additional dimension to an already complex decision-making process, so it is possible it may increase length of time for women to come to a decision regarding OC prevention surgery. Women who prioritise maximising OC risk reduction favour selecting RRSO, whereas those who prioritised maintaining QoL and avoiding menopause preferred RRESDO. Our cohort of women expressed a clear interest in combined breast-and-ovarian prophylactic surgeries. Women managed in specialist FCC settings compared with non-specialist settings received better quality care, better HRT access and were more satisfied. There is need for centralising the care of women at risk of familial gynaecological cancers to centres within specialist-FCC services which are able to provide a more streamlined, holistic multidisciplinary approach.

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Supplementary material 1: Topic Guide for Qualitative Semi-Structured In-depth Interviews

• Introduce self, research study funded by Barts Charity and Rosetrees Trust. • Purpose of the research. • Introduce audio recorder. • Stress all identifiable information will be kept confidential, but anonymised quotes may be published/presented.

- Family composition
  Q: Who lives at home? Tell me about your relationships?
  P: Partner, children, parents, siblings, ages
- Support network
  Q: Tell me about people who are important to you that give you support/advice when you need it.
  P: Friends, family, support groups, religion
- Occupation
  Q: How would you describe your occupation?
  P: Full time, part time, paid, unpaid
- Hobbies
  Q: How do you fill your spare time? What do you do in your spare time?
- How she found out she had a genetic mutation/was found to be at increased risk of ovarian/breast cancer.
  Q: *How did you find out that your chances of developing ovarian/breast cancer was higher than others?*
  P: How long she has known
- Effect on individual and family members.
  Q: *How did you take that news? How did your family take that news?*
  P: Partner, children, extended family, psychological

- Change in lifestyle choices since finding out she is at increased risk of ovarian/breast cancer.
  Q: *What lifestyle changes have you made, if any, since finding out you carry a faulty gene/are at increased risk of developing ovarian cancer? What has changed?*
  P: smoking, drinking, exercise, diet, vitamins, herbal/complementary therapy
- Reason(s) for change in lifestyle choices.
  Q: *Why do you think you made changes?*
  P: *Family, friends, cultural expectations*
- Importance of health to the individual.
  Q: *How important is being healthy to you?*
- Motivations for staying healthy.
  Q: What motivates you to stay healthy? *Why is it important?*
  P: Family, friends, duty to self, cultural expectations

- Previous knowledge of RRESDO/RRSO/RRM/combined surgery.
  Q: *Were you aware of the different types of surgery available to reduce ovarian cancer/breast cancer risk? Where did you get your information from?*
  P: health professionals, reading, attending support group events
- Initial thoughts on hearing about RRESDO/RRSO/RRM.
  Q: *What were your initial thoughts on hearing about this? Why did you feel this way?*
- Reasons RRESDO/RRSO/RRM/combined surgery acceptable
  Q: Why do you think you chose to have RRESDO/RRSO/RRM +/- reconstruction/no surgery?
  P: fertility, premature menopause, surgical risk, ovarian/breast cancer risk reduction, ovarian/breast cancer worry, femininity, self-esteem,

Q: What are your thoughts on combining both ovarian and breast cancer surgery in a single operation?
P: practicality of combined surgery, psychological impact, post-op recovery

- Reasons RRESDO/RRSO/RRM not acceptable
  Q: Talk me through why RRESDO/RRSO/ RRM +/- reconstruction/no surgery was not the right decision for you.
  P: fertility, premature menopause, surgical risk, ovarian/breast cancer risk reduction, ovarian/breast cancer worry
- Does acceptability change with age
  Q: How might your decision have been different if you were older/younger?
- Reaction of family/friends in relation to her having surgery/no surgery.
- Surgery timing for individuals not choosing surgery at present
  Q: *Do you think you may consider surgery in the future to reduce your risk of getting ovarian/breast cancer?*
  P: When, type of surgery, if no surgery why
- Ease of coming to a decision
  Q: *How easy was it to come to a decision?*
  P: what made it easy/difficult
- Satisfaction with decision
  Q: *How satisfied/happy are you with your decision?*
  P: Why satisfied/not satisfied
- Likelihood of future regret
  Q: *How do you think you will feel about your decision in a few months/years? Are there any circumstances which may make you regret your decision?*
  P: reasons for regret

- Overall satisfaction with the counselling process prior to making decision to have/not have risk reducing surgery for ovarian/breast cancer prevention.
  Q: *Overall how satisfied are you with the counselling/information/support you received from health professionals before you made your decision?*
  P: *Did counselling help make a decision, why did it help, what else helped*
- Areas for improvement.
  Q: *Is there anything the clinical team could have done better to help you make your decision? How would you improve the counselling that is provided?*
- Advice she would give to someone trying to make a decision about risk reducing surgery for ovarian/breast cancer prevention.
- Q: *What advice would you give to someone faced with having to make a similar choice as yourself?*

Final steps:
Thank the participant. Check whether they have remaining questions or comments about the topic Reassurance about confidentiality and anonymity PROTECTOR contact details should they want further information

RRSO – risk reducing salpingo-oophorectomy; RRESDO – risk reducing early salpingectomy with delayed oophorectomy; RRM – risk reducing mastectomy