**Setting the threshold for surgical prevention in women at increased risk of ovarian cancer**

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**Abstract**

The number of ovarian cancer cases is predicted to rise by 14% in Europe and 55% worldwide over the next two decades. The current absence of a screening programme, rising drug/treatment costs, and only marginal improvements in survival seen over the last 30 years, suggests the need for maximising primary surgical prevention to reduce the burden of ovarian cancer. Primary surgical prevention through risk-reducing salpingo-oophorectomy (RRSO) is well established as the most effective method for preventing ovarian cancer. In the UK it has traditionally been offered to high risk women (>10% lifetime risk of ovarian cancer) who have completed their family. The cost-effectiveness of RRSO in BRCA1/BRCA2 carriers >35 years is well established. Recently RRSO has been shown to be cost-effective in post-menopausal women at lifetime ovarian cancer risks ≥5% and in premenopausal women at lifetime risks >4%. The acceptability, uptake and satisfaction with RRSO at these intermediate-risk levels remain to be established. Prospective outcome data on risk-reducing salpingectomy and delayed-oophorectomy for preventing ovarian cancer is lacking and hence, this is best offered for primary prevention within the context and safe environment of a clinical trial. An estimated 63% of ovarian cancers occur in women with >4% lifetime-risk and 53% in those with ≥5% lifetime-risk. RRSO can be offered for primary surgical prevention to women at intermediate risk levels (4-5% to 10%). This includes unaffected women who have completed their family and have RAD51C, RAD51D or BRIP1 gene mutations; first-degree relatives of women with invasive epithelial ovarian cancer; BRCA negative women from high-risk breast-&-ovarian cancer or ovarian cancer only families. In those with *BRCA1, RAD51C/RAD51D/MMR* mutations and the ocassional families with history of ovarian cancer in their 40s surgery needs to be considered at <45. In other moderate risk gene mutation carriers and those with polygenic risk, RRSO needs be considered at 50. There is need for establishment/expansion of well-defined pathways to increase clinical access to RRSO. It is time to lower the risk threshold for RRSO to enable introduction of a

targeted primary prevention approach which could significantly impact the future burden of ovarian cancer.

**Setting the threshold for surgical prevention in women at increased risk of ovarian cancer**

The GLOBOCAN project of the International Agency for Research on Cancer (IARC) predicts that by 2035 the number of cases of ovarian cancer will rise by 14% in Europe and 55% worldwide. It also estimates that the number of deaths from ovarian cancer will rise by 22% in Europe and by 67% worldwide over the same time.[1] Advances in treatment strategies have resulted in only a small impact on survival over the last three decades.[2] Both in the low risk UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).[3] and the high risk women United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS) a CA125 based multimodal screening strategy has shown promise with significantly more women being diagnosed with earlier stage disease and lower tumour volume during screening.[4] However in UKCTOCS there is as yet no conclusive mortality benefit. Hence unlike in breast or cervical cancer, screening programmes for ovarian cancer are not recommended. Even if a mortality benefit were proven on extended follow-up in UKCTOCS,[5] primary prevention strategies remain the most proven method in reducing population burden of disease, with immunisation being a prime example. In ovarian cancer this translates into primary surgical prevention. Given the minimal impact observed with alternative strategies, and rising drug/treatment costs, maximising primary surgical prevention needs to be at the core of our efforts to reduce the burden of ovarian cancer in the future. This approach fits well with recent strategic initiatives which emphasise the need for greater focus on cancer prevention, such as the Independent Cancer Task Force, Cancer Strategy for England 2015-2020,[6] and the Obama Precision Medicine initiative.[7]

In the general population, the life time risk of ovarian cancer ranges from 1.3% to 2%.[8, 9] In *BRCA1/BRCA2* mutation carriers lifetime ovarian cancer risks range from 17%-44% and worldwide these women are considered to be at high risk.[10-12] Historically, restricted access to *BRCA* testing in many countries (including the UK) led to women being classified on the basis of family history alone. In the UK we have historically defined women as being high risk if they are estimated to have a life

time risk of ovarian cancer of ≥10% .[4, 13] This was the clinical threshold for screening and prevention

used within the national UKFOCSS trial and followed in many high-risk clinics.[4, 14, 15] This

corresponded to the average estimate of ovarian cancer risk in untested women from high risk

families. However, there was no well-defined scientific basis for this clinical convention. To the best

of our knowledge, there are no 'peer reviewed' 'published' clinical guidelines anywhere which

previously defined the ovarian cancer risk threshold for surgical prevention.

In more recent years, high throughput next generation sequencing technologies and advances in

computational bioinformatics have heralded significant change in this  genomic landscape. Firstly

cheaper testing has led to many of the restrictions around *BRCA* testing to be removed. In the UK,

for example since 2016, women who have never had cancer and are considered to be at a 10% risk

of carrying the *BRCA* gene mutation are being offered testing. Secondly , a number of new moderate

penetrance ovarian cancer gene mutations have been identified, such as *RAD51C* (lifetime ovarian

cancer risk = 11.2%, CI: (5.7%, 21.3%)),[16] *RAD51D* (lifetime ovarian cancer risk = 11.9%, CI: (5.7%,

24.6%)[17] and *BRIP1* (lifetime ovarian cancer risk = 5.8%, CI: (3.65%, 9.1%).[18] Confidence intervals of

these estimates will narrow as more data accrue. Unlike *BRCA1/BRCA2*, mutations in these three

moderate risk genes are not associated with an increased risk of breast cancer. Panel genetic testing

for *RAD51C, RAD51D* and *BRIP1* mutations (along with the traditional *BRCA1/BRCA2* genes) is now

available in clinical practice. Additionally a number of common genetic variants or Single Nucleotide

Polymorphisms (SNPs) which impact ovarian cancer risk have been identified through genome wide

association studies (GWAS).[19, 20] While, the level of risk associated with each individual SNP is small

(odds ratios range from 0.8 to 1.4), a combination of SNPs present together could have a

multiplicative effect on risk in a single individual. The impact of the SNP profile is estimated through

a polygenic risk score. This SNP profile/ polygenic risk score coupled with epidemiological variables

(e.g. parity, age, endometriosis, tubal ligation, first degree relative with ovarian cancer,

contraceptive pill use and BMI) have been incorporated into recently published risk models

developed by consortia like OCAC (Ovarian Cancer Action Consortium). These can predict ovarian cancer risk on a wider population basis.[21, 22] Additionally, further model development work is being undertaken within OCAC and by others. A similar strategy is also being employed by large groups like CIMBA (Consortium of Investigators of Modifiers of *BRCA1/2*) to further improve the precision of risk estimates and enable stratification in high risk women such as *BRCA1/BRCA2* carriers. *BRCA1/BRCA2* mutations are responsible for only 1/4th of the familial relative risk for ovarian cancer. A SNP based polygenic risk driven strategy has been shown to improve risk prediction in BRCA negative women with a strong family history of cancer.[11] Ovarian cancer risk models incorporating epidemiologic factors, high penetrance genes, moderate penetrance genes and common genetic variants are also being developed and validated in the PROMISE (Predicting Risk of Ovarian Malignancy Improved Screening and Early detection) programme.[23] Thus our ability to identify women at varying intermediate ranges of ovarian cancer risk has been significantly boosted. As more sophisticated models are developed and get validated over the coming years, clinical applicability will improve.

In addition to lifetime risk, a critical factor is the age when risk begins to rise. For *BRCA1* the risk begins to rise at 35 years (2% below age 40 rising to 5% if 2 or more first degree relatives with OC)[12] but becomes more significant after the age of 40 years. For *BRCA2* this risk does not begin to rise before 40 years and becomes more significant after the age of 45 years. Hence, RRSO doesn't need to be undertaken before 35-40 years in *BRCA1* and can be delayed till 40-45 years in *BRCA2* carriers. Ovarian cancers not linked to pathogenic mutations are more likely to present after the menopause, with risks beginning to rise after 50 years age. Decision making on whether to undergo RRSO 'or not' is a complex and dynamic process which changes with time.[15] It can be affected by the age of the person, the history of cancer in self or family, presence of a gene mutation, the risks associated with premature menopause and personal preference.

**Risk reducing salpingo-oophorectomy (RRSO)**

Primary surgical prevention through removal of both tubes and ovaries is well established as the most effective method for preventing ovarian cancer. It is routinely offered to high risk women who have completed their family with uptake rates of up to 70%, satisfaction rates of up to 97% and regret rates of ~5%.[15, 24] *BRCA1/BRCA2* carriers undergoing this procedure benefit from a ~80% reduction in ovarian cancer risk,[25] ~79% reduction in ovarian cancer specific mortality[26] and ~60% reduction in all-cause mortality.[26] A 2-4% post-surgical risk of primary peritoneal cancer (PPC) has been reported over 20 years. Average risk women undergoing bilateral salpingo-oophorectomy can also benefit from a ~94% reduction in ovarian cancer risk.[27] This raises the issue of the ovarian cancer risk threshold at which primary surgical prevention should be offered more widely. While cost-effectiveness of RRSO in *BRCA1/BRCA2* carriers who are over 35 and have completed their families is well established,[28] the cost-effectiveness at lower levels of risk was only recently reported. We developed decision analytic models to identify the ovarian cancer risk thresholds which would be appropriate for RRSO based primary surgical prevention in both pre-menopausal[29] and post-menopausal[30] women. Decision modelling provides a logical, quantitative and transparent framework for evaluating costs and consequences (health outcomes) which result from a sequence of events following alternative treatment strategies. Cost-effectiveness analysis has been highlighted by the National Institute of Health and Care Excellence (NICE) as the favoured form of economic assessment to compare relative costs and health outcomes in decision modelling.[31] The model outcome is described in terms of an incremental cost-effectiveness ratio (ICER) / quality adjusted life-year (QALY). This is compared with the standard NICE thresholds for cost-effectiveness of £20,000-30,000/QALY. We found RRSO undertaken at >50 years to be cost-effective in post-menopausal women at a lifetime ovarian cancer risk of ≥5% (ICER = £15247/QALY). In premenopausal women undergoing RRSO at >40 years, the lifetime ovarian cancer risk threshold for RRSO was >4% (ICER = £19536/QALY). The modelling incorporates a detriment for excess deaths from coronary heart/cardiovascular disease reported in the literature.[27] The gains in life expectancy were found to be >42.7 days in premenopausal and >29.2 days in post-menopausal women. These

levels are comparable to life expectancy gains of 11.6-32.4 days reported from other beneficial interventions such as cervical cancer screening.[32] It is important to highlight that these life gains are averaged across the entire population and therefore, for an individual woman in whom an ovarian cancer is prevented, this figure is multiple times higher.

In premenopausal women, surgical menopause is associated with a detrimental impact on cardiovascular disease, sexual function, bone health, vasomotor symptoms and has potential neurological consequences. These side effects are predominantly seen in women who undergo RRSO under 45 years who are not on HRT.[27] Hence two issues are critical – one is age at RRSO in premenopausal women and the second is compliance with HRT use post surgery. It is only in those with *BRCA1, RAD51C/RAD51D* mutations and the ocassional families with history of ovarian cancer in their 40s that surgery needs to be considered below the age of 45. In other moderate risk gene mutation carriers and those with polygenic risk, RRSO needs be considered at 50. More detailed recommendations are listed in Table-1. Short-term HRT in women undergoing premature surgical menopause has not been shown to increase the risk of breast cancer.[33] In premenopausal women who cannot take HRT, the lifetime ovarian cancer risk threshold for cost-effectiveness of RRSO at >40 years is higher at 8.2%.[29]

**Risk Reducing Salpingectomy (RRS)**

There is increasing acceptance of a central role for the tube in the etiopathogenesis of ovarian cancer. Serous tubal intraepithelial carcinoma (STIC) is established as a precursor lesion, present as a continuum with early tubal carcinomas, supporting transition from insitu to invasive cancer. This coupled with the detrimental consequences of premature surgical menopause from RRSO has led to the attractive proposition of premenopausal early salpingectomy and delayed oophorectomy (post-menopausal) as a two-step approach for ovarian cancer prevention in high risk women. This has the advantage of providing reduction in ovarian cancer risk while avoiding the negative consequences of

early menopause. As a result some centres have changed protocols. However, prospective data

showing the benefit of risk reducing salpingectomy in this two stage approach are lacking.

Two large retrospective analyses in low-risk women suggests that salpingectomy offers a 35%-42%

reduction in OC-risk. [34, 35] However, these data are retrospective, suffer from indication and

detection bias and number of OCs are few. A recent systematic review reconfirms the limited and

low-quality of available evidence on level of OC-risk reduction and ovarian function.[36] Additionally

data from the low-risk population cannot be directly extrapolated to higher risk women. We have

recently shown that fimbrial tissue can persist on the ovarian surface despite salpingectomy in 16%

women.[37] The precise level of reduction in risk obtained from salpingectomy alone especially in

women at increased risk is not known. Additionally salpingectomy will not prevent cancers that arise

outside the tube. While 70% occult insitu/invasive cancers discovered at histology in women

undergoing RRSO are tubal in origin, 30% are not.[38] Our understanding of the biology of STICs and

the interplay of the tube and the ovary in the development of ovarian cancer is incomplete. Initial

data from a recent genomic analysis indicates that in cases where STICs co-exist with invasive high

grade serous ovarian cancer (HGSOC), STICs may be precursors of HGSOC in only 50% cases.[39] It has

been suggested that a proportion of STICs may be metastatic to the tube and salpingectomy will not

prevent ovarian cancer in these cases.[40] The long term impact of RRS on ovarian function and onset

of menopause is unknown. Although available short term data show no harmful impact on ovarian

function, these studies have small sample sizes, use surrogate markers, and short duration of follow

up. Short term hormonal function is not predictive of the final menstrual period or onset of

menopause.[41] Only longitudinal long term follow up data can address this question. A significant

concern expressed by many is the attrition from delayed oophorectomy. It is possible some women

may delay or not undergo post-menopausal oophorectomy and some may subsequently develop

ovarian cancer. An additional gap in the literature is the lack of utility scores for salpingectomy.

While one report in the literature suggests that a two-step approach could be cost-effective,[42] the

lack of prospective outcome data and various gaps in knowledge highlighted above preclude our

ability to draw conclusions and maintains significant uncertainty around this issue. The precise risk

thresholds for offering this in routine practice remain to be determined. Hence, risk reducing

salpingectomy (RRS) and delayed oophorectomy is best offered for primary prevention within the

context and safe environment of a clinical trial. There are currently three trials on going – in The

Netherlands (TUBA study NCT02321228),[43] The USA (MD Anderson study NCT01907789) and France

(Radical Fimbriectomy study NCT01608074).[44] We found ~80% support amongst UK clinicians for

such a study.[45] A trial in the UK (PROTECTOR Study) is about to commence later this year.


**Changing the threshold for RRSO**

Data described above support offering RRSO for primary surgical prevention to women at

intermediate levels of ovarian cancer risk, with lifetime risks ranging from 4-5% to 10%. Table-1

summarises recommendations for RRSO based on clinical picture and level of risk. Changing the

threshold for RRSO to these levels could have significant impact on disease burden as an estimated

63% of ovarian cancers occur in women with >4% lifetime risk and 53% in those with a ≥5% lifetime

risk.[11] Modelling suggests that 13% of the female UK population have a >4% lifetime risk of ovarian

cancer, while 9% has a ≥5% lifetime risk.[11] Even without the new risk prediction models in clinical

use, RRSO at these thresholds could immediately be offered to unaffected women who have

completed their family and (a) have *RAD51C, RAD51D* or *BRIP1* gene mutations; (b) are first degree

relatives of women with invasive epithelial ovarian cancer;  or (c) are *BRCA* negative from high risk

breast & ovarian cancer (HBOC) families or high risk ovarian cancer (HOC) families without a known

pathogenic mutation in the family. While for *RAD51C/RAD51D* carriers this would be advised after

the age of 40 years, in BRIP1 carriers as ovarian cancers have not yet been reported below the age of

50 years. The timing of surgery could be delayed till 50 years in the bulk of the intermediate risk

women, thus decreasing the impact of premature menopause.

The acceptability, uptake and satisfaction with RRSO at these intermediate risk levels remain to be established. It is not known if the acceptability, uptake and satisfaction rates in intermediate risk women will be similar to the high levels found in high-risk women. The implementation of such an approach requires establishment or expansion of well-defined pathways to increase clinical access to RRSO. Additionally, it is critical for health professionals and women at risk to understand the importance of HRT following surgical menopause and to act on it to minimise/ ameliorate the potential detrimental long term health consequences. While HRT can ameliorate the negative side effects, it cannot completely alleviate all consequences (e.g. sexual dysfunction). These issues along with a ~3% reported surgical complication rate must form part of the informed decision making process. Patients need to be properly and thoroughly counselled on the benefits, disadvantages and complications of surgery for surgical prevention. Appropriately designed and developed information sheets/decision making materials can help facilitate this. Structures also need to be put in place to safeguard continued availability of HRT prescriptions as well as to monitor compliance and long term health. This could have health service resource and capacity implications. Looking ahead, the development and validation of more complex, state of the art risk models will provide the opportunity to stratify women in the general population by their absolute lifetime risk of ovarian cancer. The feasibility of such an approach is being tested in an ongoing pilot study.[23] Wider implementation of a targeted surgical prevention strategy for women at >4-5% lifetime risk thresholds provides a huge opportunity for cost-effective targeted primary prevention. It is time for us to lower the risk threshold for RRSO to enable introduction of a primary prevention approach which could significantly impact the burden of ovarian cancer.

**Disclosure of Interests**

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**Ethical Approval**

This commentary is not new research and did not require any ethical approval

**Contribution to authorship**

The opinions and conclusions in this commentary are the result of longstanding deliberations between the two authors. RM prepared an initial draft which was critically contributed to by UM. Both approved final version of the manuscript.

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**Table-1: RRSO recommendations**

| Clinical Category | Ovarian Cancer Risk | Recommended age (years) for RRSO*# | Comments | Reference |
|---|---|---|---|---|
| BRCA1 mutation | 44% (range 40-60%)** <br> Risks reported till <40 range from 0.6% - 3.2% <br> Risks between 40-50 years range from 6% - 22% | >35-40* | Risk begins to rise at 35, becomes more significant after 40 | Kuchenbaecker 2017,[12] Chen 2007,[46] Evans 2008[47] Antoniou 2005[48] Eastotn 1995[49] Mavaddat 2013[50] |
| BRCA2 mutation | 17% (range 12- 30%)** <br> Risks reported till <40 range from 0-0.7% <br> Risks between 40-50 years range from 0-4% | >40-45* | Risk begins to rise at 40, becomes more significant after 45 | Kuchenbaecker 2017,[12] Chen 2007,[46] Evans 2008[47] |
| RAD51C or RAD51D mutation | 11-12% | >40-50* | Ovarian cancers have been reproted between ages 40-50 in RAD51C/RAD51D carriers (18% cancers in one series were between 40-50 years). Overall data are however limited and precise risk between 40-50 is not well clarified. No cancers as yet reported at <40 in RAD51C/RAD51D carriers. | Loveday 2012,[16] Loveday 2011[17] |
| BRIP1 mutation | 5.80% | >50* | Overall data are limited and precise risk between 40-50 is not well clarified. Cancer has been reported in the 40-50 age group (7% in a small series) but most occur at >50 years. | Ramus 2015[18] |
| HBOC or HOC (untested) | >7-10% (depends on FH/ pattern of distribution and ages of onset of cancers in the family) | >40-45* | | Jervis 2014,[51] Sutcliffe 2000,[52] Jervis 2015[11] |

| | | | | |
|---|---|---|---|---|
| HBOC/HOC BRCA-Negative | 5-11% (depends on FH/ pattern of distribution and ages of onset of cancers in the family) | >45* | | |
| HBC only family BRCA-Negative | Population level Risk | RRSO Not recommended | Women from breast cancer only families who are BRCA negative on full screen analysis are not at increased risk of ovarian cancer. If the family history changes this risk estimation can change | Ingham 2013 |
| 1 FDR with ovarian cancer (BRCA unknown) | ~5-6% | >50* | FRR ~3 (FRR ~3.6 for serous tumours) | Jervis 2014[51] |
| 2 ovarian cancer case families (BRCA unknown) | ~7-10% | >40-45* | FRR ~4 (FRR~5.1 if exclude early BC families) | Sutcliffe 2000[52] |
| ≥3 ovarian cancer case families (BRCA unknown) | ~12-14% | >40-45* | FRR ~7.45 | Sutcliffe 2000[52] |
| 1 FDR with ovarian cancer (BRCA Negative) | ~3.5-4.5% (5.1% serous) | RRSO could be considered after careful counselling paritcularly for serous histology (>50*) | FRR ~2.25 (FRR is ~2.6 if OC is serous histology) | Jervis 2014[51] |
| 2 ovarian cancer case families (BRCA Negative) | ~5-6% | >50* | FRR ~3 | Sutcliffe 2000[52] |
| ≥3 ovarian cancer case families (BRCA Negative) | ~11% | >40-45* | FRR ~7 | Sutcliffe 2000, estimated[52] |
| Polygenic (SNP) +/- Epidemiological based risk | Model based estimation >4-5% risk | >50* | | Jervis 2015, [11]Pearce 2015[21] |
| Lynch Syndrome: MLH1, MSH2, MSH6 mutations | ~10% (6%-14%) | >40* (combined with hysterectomy for EC risk) | | Barrow 2013[53] |
| Lynch Syndrome: EPCAM deletion | Not high risk for ovarian cancer | RRSO Not recommended | Ovarian cancer risk is not increased. EC risk 16% (Hysterectomy may be considered for increased EC risk) | Kempers 2011[54] |

| Lynch Syndrome: PMS2 mutations | Limited publsihed data to accurately quantify ovarian cancer risk | RRSO not currently recommended (Hysterectomy may be considered for increased EC risk after 50) | Evidence base for ovarian cancer risk is limited, though one paper suggests incresaed OC risk (SIR=12). RRSO is not currenlty recommended. This could change as more evidence accumulates. EC risk =12% (EC risk between 40-50 is <1%) | Senter Gastroenterology 2008;[55] ten Broeke JCO 2014[56] |
| --- | --- | --- | --- | --- |
| Additional risks to consider with Premenopausal oophorectomy | Subfertility, premature menopause, increased sexual dysfunction; increased risk of osteoporosis; increasaed cardiovascular disease. Lack of HRT assocaited with increased cardiovascualr mortality; increased risk of neurological sequelae /cognitive dysfunction | | | |

*Some families may have earlier onset ovarian cancers. RRSO may be undertaken up to 5 years before the earliest age of onset of ovarian cancer in the family.

**higher end estimates are reported from estimates ascertained through high risk families attending cancer genetics clinics. Lower end estimates are from studies correcting for ascertainment.

#Timing of RRSO needs to be decided after thorough counselling of pros and cons including surgical complications and after taking into account patients wishes, including fertility and premature menopause issues along with HRT use (premenopausal women)."

FDR- First degree relative; FRR - familial relative risk; EC- endometrial cancer; HBC- high risk breast cancer only family; HBOC – high risk breast & ovarian cancer family; HOC – high risk ovarian cancer only family; RRSO- risk reducing salpingo-oophorectomy

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