Specifying the ovarian cancer risk threshold of 'premenopausal risk reducing salpingo-oophorectomy' for ovarian cancer prevention: a cost-effectiveness analysis

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Running Title

Risk threshold for surgical prevention of ovarian cancer

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Abstract

Background: Risk-reducing salpingo-oophorectomy (RRSO) is the most effective intervention to prevent ovarian cancer (OC). It is only available to high-risk women with >10% lifetime OC-risk. This threshold has not been formally tested for cost-effectiveness.

Objective: To specify the ovarian cancer risk-thresholds for RRSO being cost-effective for preventing OC in premenopausal women.

Methods:

The costs as well as effects of surgical prevention ('RRSO') were compared over a lifetime with 'no RRSO' using a decision-analysis model. RRSO was undertaken in premenopausal women >40 years. The model was evaluated at lifetime ovarian cancer risk levels: 2%, 4%, 5%, 6%, 8% and 10%. Costs and outcomes are discounted at 3.5%. Uncertainty in the model was assessed using both Deterministic sensitivity analysis and Probabilistic sensitivity analysis (PSA). Outcomes included in the analyses were OC, breast cancer (BC) and additional deaths from coronary heart disease. Total costs-&-effects were estimated in terms of Quality adjusted life years (QALYs); incidence of ovarian and breast cancer; as well as incremental cost-effectiveness ratio (ICER). Data Sources: Published literature, Nurses-Health-Study, BNF, CRUK, NICE guidelines, NHS reference costs. The time-horizon is: Life-time and Perspective: Payer

Results

Pre-menopausal RRSO is cost-effective at 4% OC-risk (life-expectancy gained=42.7 days, ICER= £19536/QALY) with benefits largely driven by reduction in BC-risk. RRSO remains cost-effective at>8.2% OC-risk without hormone replacement therapy (ICER=£29071/QALY, life-expectancy gained=21.8days) or 6% if BC risk-reduction=0 (ICER=£27212/QALY, life-expectancy gained=35.3days). Sensitivity analysis indicated results are not impacted much by costs of surgical prevention, or treatment of ovarian/breast cancer or cardiovascular disease. However results were sensitive to RRSO utility-scores. Additionally, 37%, 61%, 74%, 84%, 96% and 99.5% simulations on PSA are cost-effective for RRSO at the 2%, 4%, 5%, 6%, 8% and 10% levels of OC risk respectively.

Conclusions

Premenopausal RRSO appears to be extremely cost-effective at ≥4% lifetime OC-risk, with ≥42.7days gain in life-expectancy if compliance with HRT is high. Current guidelines should be re-evaluated to reduce the RRSO OC-risk threshold to benefit a number of at risk women who presently cannot access risk-reducing surgery.

INTRODUCTION

Ovarian cancer (OC) remains the top most cause of gynaecological cancer mortality,[1] with 152,000 deaths occurring worldwide annually.[2] The best method for preventing OC in women at high risk of this disease is premenopausal risk-reducing salpingo-oophorectomy (RRSO). This is usually undertaken in in women aged over35 years, who have completed their family. [3] The importance of surgical prevention is further magnified as the effectiveness of OC screening is still not established.[4, 5, 6] RRSO is associated with an OC Hazard ratio (HR) of 0.21(CI: 0.12,0.39)[3] for *BRCA1/2* mutation carriers and 0.06 (CI: 0.02,0.17) for lower-risk populations.[7] RRSO is not currently offered to women at <10% life time risk of OC, but only available to those at 'high-risk', such as *BRCA1/2* carriers, for whom this strategy is found to be cost-effective.[8]

The cost-effectiveness of 'premenopausal RRSO' as a prevention strategy at lower than BRCA1/BRCA2 risk levels remains to be properly assessed. Although we recently addressed this issue in post-menopausal women,[9] the precise 'risk threshold' at which 'Pre-menopausal RRSO' would be cost-effective to prevent OC is yet to be specified. First degree relatives (FDR) of women with epithelial OC have a three-fold higher risk of developing OC.[10] Additionally of late, newer intermediate/moderate risk genes like RAD51C,[11] RAD51D[12] and BRIP1[13] have been identified. Validation data confirming their penetrance estimates have recently been published,[14, 15] and is likely to lead to clinical testing in the near future. A significant proportion of these cancers occur in the pre-menopausal age group. Furthermore, genome wide association studies (GWAS) have led to the discovery of 17 common genetic variants modifying OC risk.).[16, 17] Women carrying multiple risk-variants have a higher OC risk compared to women with a lower polygenic load. Recently we reported an OC risk prediction algorithm[18] which incorporates *BRCA1/2*, as well as common genetic variants and other familial effects thus permitting more accurate risk prediction in BRCA1/2 negative women.

We hypothesise that premenopausal RRSO will turn out to be cost-effective to prevent OC at lower risk levels which are associated with mutations in intermediate/moderate penetrance genes and/or combination of familial/common variant genetic risk factors. Recognised, proven published data are used to illustrate a decision-analysis model[19] comparing 'RRSO' and 'no RRSO' in premenopausal women across a range of ovarian cancer risks (2%-10%) to identify the lifetime risk level(s) for RRSO to be undertaken for OC prevention.

METHODS

A decision-analysis model was built in order to evaluate lifetime costs as well as effects with undertaking 'RRSO' in 40 year old pre-menopausal women by comparing it with 'no RRSO' at varying levels of OC risk ranging from 2-10% within the UK National Health Service (NHS) context. This is consistent with advice from the National Institute of Health and Care Excellence (NICE), who recommend using a cost-effectiveness analysis as the preferred method of economic evaluation to compare the relative health-outcomes and costs of interventions .[20] The model (Figure-1) was programmed in Microsoft Excel and run at varying (2%, 4%, 5%, 6%, 8% and 10%) lifetime risk levels for OC. The baseline breast cancer (BC) risk (12.9%) was obtained from population based data.[21] Screening for OC is not included in the model as a mortality benefit is yet to be demonstrated and it is not available on the NHS.[9] Two large studies [7, 22] have reported an increased mortality associated with premenopausal bilateral oophorectomy. This was seen primarily in those who underwent oophorectomy at ages <45[22]-50[7] years but didn't get hormone replacement therapy (HRT). Following RRSO it is recommended that all pre-menopausal women take HRT till the median age of menopause, 51 years. We assumed that 80% (CI: 76%,83%) of women were compliant[23] and costed/modelled this accordingly.

Figure-1 reflects outcomes of the decision model dependent on whether RRSO is undertaken or not. The upper part depicts outcomes without RRSO. Each point where a decision is made is termed a 'node'. The line stretching out from the 'node' is termed a decision 'branch', which in turn denotes a

mutually exclusive course/outcome. All decisions are assigned a probability and all outcomes were computed accordingly. Costs for identifying/calculating OC risk were not included and were assumed to have been identified through existing algorithms. Outcomes included OC, BC as well as additional deaths due to coronary heart disease (CHD). As recommended by NICE the discounted value used for all outcomes as well as costs was 3.5%.[20]

Probabilities

Probabilities assigned to different pathways in the model are provided in Table-1. It was assumed that short-term HRT following RRSO did not affect BC risk.[24] The reduction in OC and BC risk from RRSO, and the additional CHD deaths were obtained from the Nurses Health Study.[7] They descried an absolute increase in CHD mortality of 3.03% with the number needed to harm (NNH) being 1:33. The probabilities of all paths/branches leading to OC or BC were summed up to estimate cancer incidence. The chance of both BC and OC occurring at the same time is rare and assumed to be close to zero.

Costs

All costs (Table-2) were derived from a health care system (UK NHS) /payer's perspective and reported at 2012 prices.[25] The Hospital and Community Health Service Index was used to convert these costs as needed.[26] As advised by NICE Future healthcare costs which are not related to OC/BC were not included.[20]

Life-years

The time horizon in the study covers life time risks and long term consequences. Office of National Statistics (ONS) life-tables were used to obtain female life expectancy estimates for women who do not get ovarian or breast cancer.[27] The median ages of onset of OC/ BC were 68/ 60 years respectively (from CRUK).[28] Breast and ovarian cancer outcomes were modelled using 10-year survival estimates. The one, five and ten year survival rates for women who develop OC are 72.4% (CI:72.4,72.5); 46.2% (CI:45.9,46.4); and 34.5% (CI:33.8,35.3) respectively.[29] For BC: 1-year survival=96% (CI: 96, 96); 5-year survival rate=86.6% (CI: 86.6, 86.6); 10 year survival=78.4% (CI:

78.3, 78.4).[30] The probability of dying after ten-years survival was presumed to be similar to the rest of the population.

Quality adjusted life years (QALYs)

Quality adjusted life years is recommended by NICE as the most appropriate determinant of health benefit, which reflects mortality and health associated quality-of-life effects.[20] QALY expresses change in life expectancy, which incorporates a potential declining quality-of-life. This necessitates information on utility-weights (also called utility-scores). 'Utility-weights' indicate an individual's choice using a 0-1 scale for particular health states, where '1'implies 'perfect health' while '0'impliesdeath. Utility weight reflects the quality-of-life based adjustment made for different health states included in the model. QALY = (Survival in life-years) x (Utility-weight).[31] for RRSO is reported to have a utility-score estimate of 0.95(SD=0.1, Grann, 2010)[32] and for OC treatment health states were obtained from Havrilesky, 2009.[33] Visual scales which compare health state preferences are intrinsically biased and usually less precise[34] Hence, Time-Trade-Off (TTO) scores were utilised by us. 70% women present with advanced stage newly diagnosed OC,[35, 36] with a lower utility-score= 0.55 (SD=0.29). The utility-score for those with early stage OC is 0.81 (SD= 0.26) and much greater than the utility-score of 0.16(SD= 0.25) for women with OC who are at their end-stage of life (last year of life). The annual recurrence rate for women with early stage OC who survive initial chemotherapy is 10.5%,[37] while the recurrence rate for advanced stage disease is 20.6%.[35] The mean utility-score for women in whom OC recurs is 0.5 (range 0.4-0.61), whereas the score for those in remission it is=0.83(SD=0.25).[31, 33]

One in ten (10%) cases of BC are non-invasive/DCIS and 90% of BC are invasive. Of invasive BC, 95% is early & locally advanced, of which 41% isStage-1, 45% isstage-2, and 9% is stage-3).[21, 38, 39, 40] While 5% of invasive BC is advanced (stage-4).[21, 38, 39] Utility-weights for BC were obtained from NICE guidelines[41, 42] This was assumed to be 0.65 for advanced BC=, 0.71 for early/locally

advanced BC, 0.81 for remission and 0.45 for recurrence. After surviving initial chemotherapy, 35% of early/locally advanced [39] and 66% of advanced BC cases will recur/progress.[43]

Analysis

The path probabilities were multiplied to compute the chance for existing in each of the model branches. The values for each branch in the model were weighted by the probability of being in each branch to calculate overall costs-&-effects from the model described in life-years & QALYs. The incremental cost-effectiveness ratio (ICER) is described as the overall difference in cost divided by the difference in effect . ICER= (Cost of 'RRSO'–Cost of 'No-RRSO')/ (Effect of 'RRSO'–Effect of 'No-RRSO'). The ICER obtained was then compared with the standard cost-effectiveness thresholds of £20000-£30000/QALY recommended by NICE.[31, 44] This was used to determine if undertaking 'Premenopausal-RRSO' is cost-effective in contrast to 'no RRSO' at the different OC-risk thresholds. An extensive sensitivity analysis was undertaken to explore any uncertainty in the results as well as model robustness. Each individual parameter in the model was varied in a deterministic (one-way) sensitivity analysis and the model re-run to evaluate influence on results. Model probabilities/ utility-weights were altered and analysed at extremes of their 95%CI or range, wherever accessible, or by +/-10%,while all costs used in the model were altered by +/-30%.[31] However, model probabilities or parameters are likely to fluctuate simultaneously in parallel and not individually. Hence, additionally as per NICE recommendations, we also performed probabilistic sensitivity analysis (PSA) [20, 45], where uncertainty in the model is explored by varying all variables simultaneously across their distributions. Appropriate distributions were fitted in the PSA such as 'beta' for probabilities, 'gamma' for costs as well as 'log normal' for utilities as suggested in the literature.[46] Results of 1000 simulations was plotted by a cost-effectiveness acceptability curve. It depicted the proportion of simulations showing RRSO was cost-effective at varying 'OC risk' and £20,000 as well as £30,000 'willingness-to-pay' thresholds.

RESULTS

Undiscounted and discounted survival time in terms of life-years/QALYs as well as overall costs and cancer incidence obtained at different OC risk thresholds (2%-10%) are given in Table-3. The overall cost difference as well as gain in life-years/QALYs is smaller following discounting. This is because costs/outcomes that happen in the future are adjusted by discounting and cost savings which are generated through preventing future OC cases are therefore valued less. Pre-menopausal RRSO was highly cost-effective at 4% OC-risk with 42.7 days gain in life expectancy at an ICER= £19536/QALY. At the baseline 2% OC risk, pre-menopausal RRSO is not cost-effective for 30,000£/QALY threshold (ICER= £46480/QALY, 19.9 days gain in life expectancy). These benefits are to a large extent driven by the significant advantage obtained from reduction in BC risk and HRT compliance rate. Modelling shows that cost-effectiveness increases with corresponding rises in thresholds for OC risk.

Deterministic sensitivity analysis (Figure-2) showed the influence of various paramenters on cost-effectiveness falls with a rise in level of lifetime OC risk. Sensitivity analysis indicated model-outcomes are not impacted much by various risk probabilities (Table-1), costs of surgical prevention, or treatment of ovarian/breast cancer or cardiovascular disease. However, results were sensitive to RRSO utility-weights. The one-way sensitivity analysis indicated that the model lacked cost-effectiveness for the lowermost limit of the RRSO utility-weight at the 4% OC risk threshold but became cost-effective at the 8.5% risk threshold, with an ICER= £28532/QALY. Results can also be affected by the HRT compliance rate. If this rate falls beyond the limits of our analysis, the OC risk threshold for cost-effectiveness would rise. If women don't take HRT after RRSO, i.e. p6=0, then at OC-risk=8.2%, the ICER =£29071/QALY for 21.8days increase in life-expectancy. This suggests RRSO will be cost-effective at >8.2% OC risk, without HRT. As a scenario analysis, if we assume 'no reduction' in BC risk, then RRSO at age ≥40 years, is not cost-effective at 4% OC risk but becomes cost-effective at the 6% OC risk threshold (0.1 life-years saved, ICER=£27212/QALY).

Figure-3 shows that when all variables are varied simultaneously in a PSA at 2%, 4%, 5%, 6%, 8% and 10% risk-thresholds, then, 37%, 61%, 74%, 84%, 96% and 99.5% simulations respectively remain cost-effective for the NICE £30,000/QALY 'willingness-to-pay threshold' when RRSO is undertaken in pre-menopausal women . However, at the NICE threshold of £20,000/QALY, then 23%, 46%, 60%, 72%, 91% and 98% simulations will be cost effective if pre-menopausal RRSO is undertaken at 2%, 4%, 5%, 6%, 8% and 10% OC risk levels respectively.

DISCUSSION

We for the first time precisely define the threshold for lifetime OC-risk for recommending 'Premenopausal-RRSO' for OC prevention in the population. Our modelling suggests that RRSO would be extremely cost-effective in pre-menopausal women ≥40 years with lifetime OC risks ≥4% at the £20,000-30,000/QALY WTP threshold ,[44] and equates to >42.7days gain in life expectancy, for an overall ICER= £19536/QALY. This risk threshold is similar though slightly lower than the recently defined threshold in post-menopausal women.[9] This threshold takes into account results of the probabilistic sensitivity analysis. Our results are of major significance for clinical practice and risk management in view of declining genetic testing costs and the improvements in estimating an individual's OC risk. With routine clinical testing for certain moderate penetrance genes around the corner and lack of an effective OC screening programme, these findings are timely as it provides evidence supporting a surgical prevention strategy for 'lower-risk' (lifetime risk <10%) individuals. Such an approach can contribute to decreasing the number of ovarian cancer cases and disease burden within the population. This is a key measure needed for moving towards a predictive, preventive, personalized, and participatory (P4) medicine strategem.

A major driver for the cost-effectiveness of pre-menopausal RRSO has been the beneficial impact on BC risk. Although various initial analyses in the high[3, 47] and low-risk[48] populations suggest a reduction in BC risk following pre-menopausal RRSO, a recent publication[49] from a Dutch group found no reduction in risk of BC in BRCA1/2 women and highlighted some methodological

limitations of earlier reports.[47, 50, 51] . A key limitation of the Dutch paper is the short 3.2 years follow-up duration. It is likely/ plausible that any benefit of decrease in BC cases from early oophorectomy will accrue over a longer period of time. Besides a subsequent re-analysis (conforming to the Dutch methodology) by authors of the earlier analyses reconfirmed their initially observed reduction in BC risk.[52] Our extreme scenario analysis indicates that if there was no reduction in BC risk, RRSO would be cost-effective for higher risk levels for ovarian cancer of ≥7%.

Model outcomes appear to be very sensitive for the lower-limit of utility-weight for bilateral salpingo-oophorectomy. Although pre-menopausal oophorectomy in women is not associated with any difference in generic quality-of-life , it is reported to be associated with poorer sexual functioning as well as post-menopausal symptoms when compared to those who retain their ovaries.[53, 54, 55] HRT use is essential post-RRSO to minimise the detrimental consequences of premature surgical menopause. However, despite HRT, the symptom levels reported (particularly for sexual dysfunction) remain above those who have not undergone premenopausal oophorectomy.[56] This limitation needs to be discussed as part of informed consent for the surgical procedure, and incorporated into RRSO decision making process. In addition, we have assumed 80% compliance based on reports from a small study of 521 low-risk women undergoing premature surgical menopause from a single centre. The true compliance in a larger broad-based population sample remains to be established. Hence, pre-menopausal RRSO should be only offered to women aged >40 who are committed to taking HRT at OC risk levels >4%. Additionally longer/ more intensive follow-up after RRSO may be needed to address cardiovascular, bone health and psychosexual consequences. Of note, the standard deviation for the utility-score in our analysis is large. It is necessary to improve our understanding and precision of RRSO utility-scores, particularly in lower risk women and future research should be directed towards this. Although, pre-menopausal RRSO is undertaken at >35 years for high-penetrance BRCA1/2 carries, the median age of onset for moderate penetrance genes like RAD51C/ RAD51D/ BRIP1 is higher with no cancers as yet reported

at <40 years.[14, 15] 18% of OC in RAD51C/RAD51D carriers[15] and 7% OC in BRIP1 carriers[14] occur between 40-49 years age. Hence, RRSO can be delayed till >40 years in these women.

Our model has numerous strengths and satisfies the several requisites stipulated by NICE for health-economic analyses. It includes excess mortality from coronary events described in the literature.[7] Besides OC risk, it incorporates impact on BC outcomes and any possible decline in QALYs with the intervention. Other advantages include using QALYs for evaluating health-outcomes, using current practice as a comparator, discounting of costs and outcomes by 3.5% and, utilizing well established/proven information from the literature to obtain parameters used in the model.[20] The 'time-horizon' is an important factor in such an analysis. [20] This is suitably long enough to reveal any relevant changes in costs and outcomes from our modelling. Only a limited subset of overall costs for OC and BC diagnosis and treatment have been included in the analysis. Additionally costs for further investigations, management of recurrence or treatment complications were not included. Being conservative in our costs for OC and BC diagnosis and treatment curtails over-estimating the advantages of surgical prevention.[9]

The robustness of our results are enhanced by an extensive sensitivity analyses undertaken. The deterministic one-way sensitivity-analysis enabled careful inspection of model outcomes to highlight/ recognize variables which exert greatest influence. The 95% confidence-limits/range of parameters incorporated in the sensitivity analysis are fairly wide. This further adds to the rigour of the results. It is reassuring that despite probabilities varying widely the model remains largely cost-effective. That 30% variation in costs did not significantly affect outcomes indicates that costs of surgical prevention or treatment costs for OC/BC/cardiovascular events do not have much significance in affecting modelling outcomes. We undertook both PSA and DSA in line with recommendation from authorities like NICE.[20] PSA adds rigour by facilitating all parameter probabilities to be varied concurrently in order to properly characterise model uncertainties and any

impact on final outcomes. The cost-effectiveness of ≥61-74% of PSA simulations at ≥4-5%OC risk reconfirms that premenopausal RRSO for OC prevention is beneficial in health economic terms at these risk thresholds.

The exclusion of increased mortality from lung/colorectal cancer found in the Nurses Health cohort may be considered a weakness of our analysis.[7] However, these additional deaths from cancer which were observed could have been confounded by smoking or other risk related behaviours. Much larger cohort studies have shown smoking per se is linked to menopause,[57, 58] and after stratification by smoking, any increase in lung cancer risk reported following oophorectomy is limited to those who smoke.[57] Furthermore, the EPIC study (337,802 women) reported lack of any significant association of colorectal cancer risk with age or surgical menopause .[59] Even if we do include the impact of all-cause mortality (1:8) found in the Nurses Health Study in our model, the model remains cost-effective at an OC risk ≥7% (ICER= £29128/QALY, 0.1 life-years gained). We did not account for complications from RRSO in our analysis, which have been reported to occur in 1.5-5% of high-risk women.[60, 61, 62] This is an important part of pre-operative surgical consent by the treating clinician, and built into the decision making process.

Our findings indicate that RRSO would be cost-effective even for women with (a) mutations in moderate risk genes like RAD51C,[11] RAD51D,[12] BRIP1;[13] (b) BRCA1/BRCA2 negative women from high-risk families ; and (c) those who have a FDR with OC. We have shown that ~75% of OC familial relative risk is not accounted for by BRCA1/BRCA2 mutations[10] and that if all OC susceptibility alleles are identified then 53% of all OC occur in 8.8% of the population with ≥5%risk and 62.8% OC occur in 13.4% of the population at >4% risk.[18] Unlike earlier models (BOADICEA[63], BRCAPRO[64]) which underestimate OC risks in BRCA1/BRCA2 negative women, a recently published model incorporates the effects of an observed 'polygenic risk score' (PRS) which incorporates all known common genetic variants leading to more accurate risk prediction in

BRCA1/BRCA2 negative women. For example, the lifetime risk of OC in a woman who has two affected FDRs and is found to test negative for a BRCA1/2 mutation is >5% if her PRS score is in the upper half of the PRS distribution.[18]

The shifting landscape resulting from new genetic discoveries, better risk estimation and rapidly changing genetic testing technology has important implications, and offers opportunities for cancer risk management and prevention. SNP profiles in combination with family history[18] data and other epidemiological risk factors[65] provide the ability to discriminate between low (1-2%) and intermediate (>3 to <10%) OC risk individuals and have an increasingly important role to play in personalised OC-risk prediction, with implications for OC prevention. Our findings have significant implications for changing practice and guiding policy for developing a surgical prevention strategy for OC. This fits well with the newly published Independent Cancer Task Force, Cancer Strategy for England 2015-2020,[66] which highlights the need for major emphasis and focus on cancer prevention as well as the Obama Precision Medicine initiative.[67] The significance and need for fresher/novel cost-effective targeted prevention strategies is further heightened by the challenging economic environment, increasing costs of health care as well as rising prices of new OC drugs/ treatment strategies. However, implementation of this approach requires building knowledge, understanding and awareness amongst health professionals and lay people through education, dissemination of information as well as media campaigns, which in turn are associated with additional costs. Given the many side effects of premature menopause, it also requires women to understand the need to take HRT till the age of natural menopause. Additionally, research needs to be directed towards understanding the acceptability, uptake and impact of genetic-testing, risk prediction and RRSO at lower-risk thresholds in the general population. Furthermore, care commissioners, general practitioners, genetics teams and gynaecologists need to develop additional downstream care pathways for these at-risk women for this approach to be successful.

Contribution to authorship

RM, UM, RL developed original concept and design of the study. RM, RL, UM developed the model. All authors (RM, RL, UM, ACA) were involved in the design of the work, and data interpretation of the health-economic and statistical analysis. RM, RL,VD did the health economic analysis and prepared the tables and figures. RM, RL prepared the first draft of the manuscript and all authors contributed to subsequent drafts. All authors critically contributed to and revised the manuscript and approved the final version.

Conflict of interest statement

All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work.
RM, RL, ACA, VD declare no other relationships or activities that could appear to have influenced the submitted work. UM declares a financial interest in Abcodia, Ltd., which has an interest in ovarian cancer screening and biomarkers for screening and risk prediction.

Authors Statement:

All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Copyright Statement

Transparency declaration

The corresponding author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available

Ethical considerations

This analysis uses established published data from the literature. No new data have been collected or used and hence, no formal ethics approval was deemed necessary for this work.

Table 1: Probabilities of pathways in the model

Probability	Value	(CI) [Range]	Description	Source
P1	0.1, 0.08, 0.06, 0.05, 0.04, 0.02		'Lifetime risk' of developing ovarian cancer	Model assumption
P2	0.94	[0.83-0.98]	Reduction in ovarian cancer risk from RRSO	Parker 2013[7]
P3	0.13	[0.065, 0.195]	'Lifetime risk' of developing breast cancer	CRUK[21]
P4	0.38	(0.26-0.47)	Reduction in risk of breast cancer from RRSO alone	Parker 2009[68]
P5	0.03	(0.011-0.046)	Risk of fatal CHD after RRSO and no HRT	Parker 2013[7]
P6	0.80	[0.76-0.83]	Compliance with HRT	Read 2010[23]
CI- confidence interval, RRSO- risk reducing salpingo-oophorectomy, RRM – risk reducing mastectomy, HRT- hormone replacement therapy				
Explanation for Probabilities:				
P1: These are the different lifetime risks of developing ovarian cancer. The model was run and analyses undertakenat these different risk thresholds P2: The level of reduction in ovarian cancer risk following RRSO is obtained from the Nurses Health Study, Parker et al, 2013[7] P3: Lifetime risk of developing breast cancer 12.9% from CRUK[21]. This was varied in the sensitivity analysis by +/- 50% to better reflect the distribution of risks in the population. P4: The reduction in breast cancer risk in pre-menopausal women undergoing RRSO is taken from Parker et al, 2009[68] P5: Risk of a fatal CHD event is 1/33 for women undergoing RRSO and don't take HRT (Parker et al, 2013).[7] This is not seen in women who do take HRT.[7] P6: Compliance with HRT is obtained from a UK cohort of 512 women, Read et al 2010[23]				

CHD- Coronary heart disease, CRUK- Cancer Research UK, HRT- hormone replacement therapy,

RRSO- Risk reducing salpingo-oophorectomy, UK- United Kingdom

Table 2: Costs used in the model (2012 prices)*

Item	Cost (£)	Source
Costs of RSSO	2,165	NHS Reference costs[25]
HRT Costs (for pre-menopausal women)	391	BNF[69]
Osteoprotection Costs	441	BNF[69], NHS Reference costs[25]
Cost of diagnosis and initial treatment of ovarian cancer	16,044	NHS Reference costs,[25] NICE guideline[70]
Annual cost of ovarian cancer treatment and follow-up: years 1-2	639	NHS Reference costs[25], NICE guideline[70]
Annual cost of ovarian cancer treatment and follow-up: years 3-5	274	NHS Reference costs,[25] NICE guideline[70]
Ovarian cancer terminal care costs	15,414	National Audit office[71]
Costs for Breast cancer screening	330	Robertson 2011,[72] NHS reference cost[25]
Breast cancer treatment costs	16,537	NHS Reference costs,[25] NICE guideline Advanced breast cancer[41], NICE guidelines Early and locally advanced breast cancer[73]
Yearly cost of breast cancer follow-up and adjuvant treatment if any (e.g. Tamoxifen): years 1-5	2,003	BNF[69], Robertson 2011[72], NHS Reference costs,[25] NICE guidelines Early and locally advanced breast cancer[73] NICE guideline Advanced breast cancer[41] National Costing report. Implementing NICE guidance 2009[39]
Fatal CHD Costs	3,277	NHS Reference costs[25, 71]
*All costs were varied by +/-30% in one way sensitivity analysis HRT- hormone replacement therapy NHS- National Health Service, NICE-National Institute for Health and Care Excellence, RRSO- risk reducing salpingo-oophorectomy, UK- United Kingdom		
Explanation of Costs: See supplementary table-S1 for a detailed explanation of costs in the model		

BNF- British National Formulary, CHD- Coronary heart disease, HRT- hormone replacement therapy, MRI- Magnetic resonance imaging, NHS- National Health Service, NICE- National Institute of Health and Care Excellence, RRSO- Risk reducing salpingo-oophorectomy

Table-3: Model outcomes for costs, survival (life years) and quality adjusted life years (QALYs), undiscounted and discounted (including benefit of reduction in Breast Cancer risk from premenopausal RRSO)

	Breast cancer incidence	Ovarian cancer incidence	Survival	Discounted survival	Cost	Discounted cost	QALY	Discounted QALY
10% risk								
No RSSO	0.129	0.100	41.5	21.2	6114	2904	41.1	21.1
RRSO	0.080	0.006	42.80	21.46	5705.81	4433.96	42.31	21.36
Difference	0.049	0.094	1.00	0.26	-408	1530	1.21	0.30
ICER (£/QALY)							-338	5031
8% risk								
No RRSO	0.129	0.080	41.68	21.25	5606	2637	41.3	21.1
RRSO	0.080	0.005	42.49	21.46	5675.52	4418.1	42.32	21.37
Difference	0.049	0.075	0.81	0.21	70	1781	1.0	0.2
ICER (£/QALY)							71	7370
6% risk								
No RRSO	0.129	0.060	41.88	21.30	5098	2369	41.6	21.2
RRSO	0.08	0.004	42.50	21.46	5645.23	4402.24	42.34	21.37
Difference	0.049	0.056	0.62	0.16	547	2033	0.8	0.2
ICER (£/QALY)							726	11337
5% risk								
No RRSO	0.1290	0.0500	41.98	21.33	4844	2236	41.70	21.22
RRSO	0.080	0.0183	42.51	21.46	5630	4394	42.35	21.37
Difference	0.0490	0.0317	0.5294	0.136	786	2159	0.6413	0.1481
ICER (£/QALY)							1226	14573
4% risk								
NO RRSO	0.129	0.040	42.08	21.36	4590	2102	41.8	21.3
RRSO	0.080	0.002	42.51	21.47	5614.94	4836.39	42.35	21.37

Difference	0.049	0.038	0.44	0.11	1025	2284	0.5	0.117
ICER (£/QALY)							1940	19536
2% risk								
NO RRSO	0.129	0.020	42.28	21.41	4082	1834	42.1	21.3
RRSO	0.08	0.00	42.53	21.47	5584.64	4370.53	42.37	21.38
Difference	0.049	0.019	0.25	0.06	1503	2536	0.3	0.055
ICER (£/QALY)							4969	46480

ICER- Incremental cost-effectiveness ratio (£/QALY), QALY- quality adjusted life year, RRSO- risk reducing salpingo-oophorectomy

Figure 1: Model Structure

Figure-1: Decision Model Structure. The upper part of the model structure reflects outcomes of not undergoing RRSO and the lower part of the model depicts premenopausal RRSO. This model is run at each of the different thresholds for OC risk (2%, 4%, 5%, 6%, 8%, 10%). Each decision point in the model is called a 'node' and each path extending from a node is called a decision 'branch'. Each branch represents a mutually exclusive course or outcome. Each decision is given a probability (probabilities 'p1 to p6' used in the model are explained in Table1) highlighted in a white box along the decision branch. Values for each outcome are calculated. Cancer incidence was estimated by summing the probabilities of pathways ending in ovarian or breast cancer. Final outcomes (blue boxes on the right of the figure) of each path include development of breast cancer (BC), ovarian cancer (OC), no breast/ovarian cancer (no OC or BC) and excess deaths from coronary heart disease (CHD).

BC- Breast Cancer, CHD- coronary heart disease, HRT- Hormone replacement therapy, OC-Ovarian Cancer; No OC or BC- No Ovarian Cancer or Breast Cancer developed., RRSO –Risk reducing salpingo-oophorectomy; RRM – Risk reducing mastectomy

Figure-2: One way Deterministic Sensitivity Analyses

Figure 2: Deterministic Sensitivity Analyses. One-way sensitivity analysis for all probabilities, costs and utilities in terms of ICER of premenopausal RRSO compared to No RRSO at the different ovarian cancer risk (4%, 5%, 6%, 8%) thresholds. Y-axis: Incremental cost-effectiveness ratio (ICER): Cost (£) per quality adjusted life year (QALY) (discounted). X-axis: Probability, cost and utility parameters in the model. The model is run at both lower and upper values/limits of the 95% confidence interval or range of all probability parameters described in Table-1/methods; and both lower and upper values/limits of the cost and utility-score parameters given in Table 2. Costs are varied by +/- 30%. 'Maximum value' represents outcomes for upper limit and 'minimum value' represents outcomes for lower limit of the parameter.

OC- ovarian cancer, RRSO –Risk reducing salpingo-oophorectomy

Figure 3 Probabilistic sensitivity analyses

Figure-3: Probabilistic sensitivity analyses Cost-effectiveness acceptability curve. Probabilistic sensitivity analysis in which all model parameters/ variables are varied simultaneously across their distributions to further explore model uncertainty. X-axis: Incremental cost-effectiveness ratio (ICER) in terms of Cost (£s)/QALY; Y-axis: Proportion of simulations. The results of 1000 simulations were plotted on a cost-effectiveness acceptability curve showing the proportion of simulations (Y-axis) that indicated that the intervention was cost-effective at different willingness to pay thresholds (X-axis). The first and second dotted line marks the proportion of simulations found to be cost-effective at the £20,000 and £30,000 thresholds used by NICE. 37-99% simulations are cost effective at varying (2-10%) ovarian cancer risk thresholds in this analysis.

RRSO- Risk reducing salpingo-oophorectomy

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