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Defining the risk threshold for risk reducing salpingo-oophorectomy for ovarian cancer prevention in low risk postmenopausal women

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ABSTRACT

Objective:

To define risk thresholds for cost-effectiveness of risk-reducing salpingo-oophorectomy(RRSO) for ovarian cancer(OC) prevention in low/intermediate risk postmenopausal women.

Methods

A decision-analytic model compares lifetime costs-&-effects of offering 'RRSO' with 'no RRSO' to postmenopausal women ≥50years for different lifetime OC-risk thresholds: 2%, 4%, 5%, 6%, 8% and 10%. Well established data from the literature are used to estimate total costs, effects in terms of Quality-Adjusted-Life-Years(QALYs), cancer incidence, incremental cost-effectiveness ratio(ICER) and impact. Costs are reported at 2012 prices; costs/outcomes discounted at 3.5%. Deterministic/Probabilistic sensitivity analysis(PSA) evaluate model uncertainty.

Results

RRSO does not save QALYs and is not cost-effective at the 2% general population lifetime OC-risk. At 4% OC-risk RRSO saves QALYs but is not cost-effective. At risk thresholds ≥5%, RRSO saves more life-years and QALYs and is highly cost-effective. The ICERs for OC-risk levels 5%, 6%, 8% and 10% are £15247, £9958, £4584, and £1864 respectively. The gain in life-years from RRSO equates to 29.2, 40.1, 62.1 and 80.3 days at risk thresholds of 5%, 6%, 8% and 10% respectively. The results are not sensitive to treatment costs of RRSO/OC/cardiovascular events but are sensitive to utility-scores for RRSO. On PSA, 67%, 80%, 84%, 91% and 94% of simulations at risk thresholds of 4%, 5%, 6%, 8% and 10% respectively are cost-effective for RRSO.

Conclusion

RRSO is highly cost-effective in postmenopausal women aged >50 with ≥5% lifetime OC-risk and increases life-expectancy by ≥29.2days. The results could have significant clinical implications given the improvements in risk prediction and falling costs of genotyping.

INTRODUCTION

There are 239,000 new cases and 152,000 deaths from ovarian cancer (OC) worldwide annually.[1] Advances in treatment have led to only small improvements in survival over the last 10-20 years, and it remains the commonest cause of deaths from gynaecological cancer.[2] Screening for OC has not yet been shown to reduce mortality,[3] and the most effective risk-reducing procedure currently available is surgical removal of both tubes and ovaries. Risk reducing salpingo-oophorectomy (RRSO) has been found to have a hazard ratio (HR) being 0.06 (CI:0.02,0.17) in a low-risk population[4] and 0.21 (CI:0.12,0.39) in BRCA1/BRCA2 carriers.[5] However, currently it is only routinely available to women from high-risk families, such as those carrying high penetrance BRCA1/BRCA2 and mismatch-repair gene mutations (lifetime OC risk ≥10%), for whom the cost-effectiveness[6] of such an approach is well established.

In the general (low-risk) population, the OC risk distribution includes women with both higher (but <10%) and lower than the average lifetime risk estimates (1.3%-2%).[2, 7]. A number of lifestyle, reproductive and medical factors such as contraceptive pill use, tubal ligation, parity, endometriosis, subfertility, age and family-history have been shown to be associated with OC risk. In addition 17 common genetic variants influencing OC risk have been identified through genome wide association studies (GWAS) and other large-scale genotyping efforts.[8] Although the risk with each individual variant is small, women who carry multiple risk alleles have a 2-3 fold higher risk estimate than those with a low polygenic load.[9, 10] RRSO has not been formally evaluated as a risk reducing option in these lower risk populations and the 'risk threshold' at which this intervention may become cost-effective for prevention of sporadic OC has not been defined. As the median age of diagnosis of

sporadic OC is >65 years,[11] RRSO could be restricted to postmenopausal women >50 years age.

We hypothesise that in postmenopausal women >50 years age, RRSO may become cost-effective for prevention of sporadic OC at <10% lifetime risk thresholds. We use well established data from the literature to describe a decision analysis model comparing 'RRSO' with 'no RRSO' at different OC risk thresholds. Defining the risk thresholds and circumstances in which RRSO can be offered to lower risk postmenopausal women on a population basis for OC prevention is an important step towards the implementation of predictive, preventive, personalized, and participatory (P4) medicine. The results have immediate implications as currently postmenopausal women in the general population cannot access primary risk reducing salpingo-oophorectomy for OC prevention.

METHODS

A decision-analytic model (Figure-1) was developed to compare the lifetime costs and effects of offering RRSO to women aged 51years for different risk thresholds of developing OC. The model was programmed in Microsoft Excel, and run for the OC risk thresholds: 2%, 4%, 5%, 6%, 8% and 10%. As this analysis concerns prevention of OC not linked to high penetrance genes, the median age of diagnosis of sporadic OC is >65 years and 83% of all OC occurs in women >50 years, we restrict the analysis to post-menopausal women ≥51 years age. OC screening has not been shown to save lives and is not routinely offered in clinical practice. Hence, it is not included in the model.

Figure-1 reflects outcomes based on a decision to perform RRSO or not. 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/outcome. Each decision is given a probability and values for each outcome are calculated. We assume that the risk threshold for the woman has already been identified through existing risk prediction algorithms based on known risk factors and these risk prediction costs are not included. Model outcomes include OC and excess deaths from mainly cardiovascular causes.[4]

In line with guidelines on the reference case for economic evaluation from the National Institute for Health and Care Excellence(NICE), all costs and outcomes were discounted at 3.5%.[12]

Probabilities

All model pathway probabilities are detailed in Table-1. The reduction in risk from salpingo-oophorectomy was taken from a population based cohort.[4] The excess death from cardiovascular mortality was taken from the Nurses Health cohort,[4] that reported 62 (361 if all deaths considered) deaths in 3056 women over 50 years with ovarian conservation compared to 123 (805 if all deaths considered) deaths in 5967 women undergoing BSO. This gives an absolute increase in risk=0.03%% (CI:-0.58%,0.65%) and numbers needed to harm (NNH)=3073 (CI:154,∞). A one-way sensitivity analysis involved rerunning the model at both lower and upper values/limits of the 95%CI or range of all probability parameters (Table-1) used in the model (Figure-2). Cancer incidence was estimated by summing the probabilities of pathways ending in OC.

Costs

All costs are described in Table-2 and are reported at 2012 prices. Where required they have been converted using the Hospital and Community Health Service Index.[13] In line with

NICE recommendations future healthcare costs not associated with OC were not considered.[12]

Life-years

Life expectancy for women who don't develop OC was based on female life tables from Office of National Statistics.[14] Age at onset of postmenopausal OC (median=68 years) was taken from CRUK age of incidence statistics.[11] Ten year survival data (from CRUK) was used to model OC outcomes (1-year survival=72.4% (CI:72.4,72.5); 5-year survival rate=46.2% (CI:45.9,46.4); 10-year survival=34.5% (CI:33.8,35.3)).[15] After ten years survival, the probability of death was assumed to be same as the general population.

Quality adjusted life years (QALYs)

QALY is a measurement which expresses changes in length-of-life, while simultaneously incorporating reductions in quality-of-life. It is calculated using quality-of-life adjustment or utility-weights for each health state in the model. 'Utility-weights' are an indication of an individual's preference for specific health states where '1'=perfect health and '0'=death. QALY=Survival in life-years x Utility-weight. Utility-weight for RRSO=0.95(S.D=0.1) and was obtained from a recent analysis by Grann.[16] Havrilesky[17] reported detailed utility estimates related to various health states following OC treatment using visual analogue scale and time-trade-off (TTO) methods. As visual scales comparing health state preferences have inherent biases and are generally less accurate,[18] we have utilized the TTO scores. We assumed that 70% of women present with OC at advanced stages,[19, 20] with a lower utility-score for a new diagnosis=0.55(S.D=0.29), while the remainder present at early stages with a higher utility-score=0.81(S.D=0.26). The end-stage of life utility-score where OC patients did not survive the next year=0.16(S.D=0.25). Of those who survived initial

chemotherapy the chance of recurrence with early disease was 10.5% annually,[21] and with advanced disease 20.6%.[19] For women with recurrent disease the mean utility-value= 0.5(range:0.4-0.61) and for women in remission the utility-value=0.83(S.D=0.25).[17]

Analysis

The probability of being in a branch of the decision-model was calculated by multiplying together the path probabilities. The total costs and effects in terms of life-years and QALYs were then estimated by weighting the values for each branch by the probability of being in each branch. The incremental cost-effectiveness ratio (ICER) was estimated by dividing the difference in cost by the difference in effect. ICER= (Cost A–Cost B)/(Effect A–Effect B). By comparing this ICER with the £20,000-£30,000/QALY cost-effectiveness threshold used by NICE,[22] we determined whether 'offering RRSO' to women above a certain risk threshold was cost-effective compared with 'no RRSO'. To explore uncertainty in the results and robustness of the model, a one-way (deterministic) sensitivity analysis was undertaken by varying each parameter in the model and then re-running the model to assess the impact on overall results. Probabilities and utility-scores were varied according to their 95% confidence-intervals/range, where available, or by +/-10%, and costs were varied by +/-30%. In addition to the one-way sensitivity results, a probabilistic sensitivity analysis (PSA) was undertaken as recommended by NICE methods guidance.[12, 23] Any variation in model parameters/variables is likely to occur in parallel rather than independently of each other. In the PSA all variables were varied simultaneously across their distributions to further explore model uncertainty. We assigned costs a gamma distribution, probabilities a beta distribution, and utilities a log-normal distribution as suggested in the literature.[24] The results of 1000 simulations were plotted on a cost-effectiveness acceptability curve showing the proportion

of simulations that indicated that the intervention was cost-effective at different willingness to pay thresholds.

RESULTS

The discounted and undiscounted survival (life-years), lifetime costs, and QALYs for each branch in the decision model at the different OC risk thresholds of 2%, 4%, 5%, 6%, 8% and 10% are given in Table-3. Discounted results show a smaller overall gain in life-years/QALYs and overall cost difference, as discounting adjusts costs and outcomes that occur in the future and the cost savings generated through prevention of future OC cases is valued less. At the 2% baseline population OC risk level, routine RRSO does not save more QALYs and is not cost-effective. At a 4% OC risk level, RRSO saves more QALYs but is not cost-effective at the ICER=£25,577, which is above the £20,000 NICE threshold. However, at risk thresholds of ≥5%, RRSO saves more life-years and QALYs and is highly cost-effective for the NICE threshold of £20,000/QALY. The ICERs for risk levels of 5%, 6%, 8% and 10% are £15247, £9958, £4584, and £1864 respectively. The gains in life expectancy from RRSO at the risk thresholds of 5%, 6%, 8% and 10% equate to 29.2, 40.1, 62.1 and 80.3 days respectively.

One-way sensitivity analysis results are given in Figure-2. It suggests that the results are not that sensitive to treatment costs of RRSO, OC or cardiovascular events. Results are however sensitive to excess cardiovascular deaths at the 5% threshold but not that sensitive at the 6% and 8% thresholds. It is also very sensitive to utility-scores for RRSO. The model was not cost-effective at the lower most limit of the utility-score for RRSO. The impact of different variables on cost-effectiveness decreases as the OC risk threshold increases.

The PSA results (Figure-3) shows that at a £20,000 willingness to pay threshold/QALY, 67%, 80%, 84%, 91% and 94% of simulations at risk thresholds of 4%, 5%, 6%, 8% and 10%, respectively are cost-effective for RRSO. If the willingness to pay threshold is increased to £30,000/QALY, then 77%, 84%, 85%, 92% and 94% simulations are cost effective for RRSO at the above risk thresholds, respectively.

DISCUSSION

This is the first analysis that we are aware of that defines precise risk thresholds at which RRSO can be cost-effective for OC prevention on a population basis. Our modelling suggests that in postmenopausal women with lifetime OC risk thresholds of ≥5%, RRSO is highly cost-effective for the NICE threshold of £20,000/QALY[22] and equates to gains in life expectancy of ≥29.2 days. This gain in life-years (range 29.2 to 80.3 days) compares favourably with the gain in life-years from cervical cancer screening which is reported to range between 11.6-32.4 days.[25] Our findings have significant implications for clinical practice given the falling cost of genotyping and increasing ability to better calculate an individual's OC risk. Availability of such an approach could impact on risk management choices of 'low/intermediate risk' (lifetime risk <10%) women especially given the lack of an effective screening strategy for OC. If widely adopted it has the potential to contribute to reducing the OC burden in the population.

Restricting use to women >50 years enables primary surgical prevention to be offered with less side effects. The increased all-cause mortality associated with bilateral oophorectomy reported by the Nurses Health[4] and Olmsted County[26] studies were predominantly in women <45[26]-50[4] years who did not take hormone replacement therapy. The same is true

for cardiovascular, bone and neurological risks.[4, 26, 27] Most sporadic OC (not related to BRCA/mismatch repair gene mutations) occurs at >50 years, with the median age of diagnosis being >65 years[11]. Although precise data on the proportion of OC <50 years in BRCA1/BRCA2/MMR-negative individuals who have a life time OC risk ≥5% risk are not currently available, this risk under 50 is likely to be minimal.

In our analysis, the lifetime OC risk threshold for RRSO in postmenopausal women was ≥5%. This 5% risk threshold is significantly lower than the OC risk (18-40%) in BRCA1/BRCA2 carriers,[28] and also less than the risk of OC in Lynch Syndrome women (6-14%).[29] OC risk prediction is increasingly possible and general population models based on known epidemiological risk and protective factors have recently been published.[30, 31] Recently we quantified the population distribution of lifetime risks of OC by adding common genetic (SNP) risk factors to the known epidemiologic (contraceptive use, parity, tubal ligation, endometriosis, first degree relative with OC) factors.[10] Eight combinations of risk factors gave a life time OC risk ≥5% and 2% of the US population would have a lifetime risk ≥5%.[10] RRSO could be of benefit to all such women. Newer OC SNPs are constantly being identified through large consortia led collaborative work, incorporation of which will further improve performance of such models. Alongside such progress, major advancements in genetic testing technology and falling costs now enables individual SNP information to be made available at a low cost. Additionally, other lifestyle factors including aspirin and menopausal HRT use are being identified through pooled analyses. As models get more sophisticated incorporating additional genetic and epidemiologic data, their ability to predict ovarian cancer risk will improve and their applicability will rise.

Our analysis has several strengths. It incorporates impact on OC risk and fulfils various requirements suggested by NICE for health-economic decision making. We use current

practice as a comparator, QALYs to measure health-outcomes, a 3.5% discount rate on costs and health outcomes and, well established population-based data for parameters in the analysis.[12] Our model includes potential excess deaths from coronary events in the postmenopausal population as reported in the most recent analysis of the Nurses Health Study.[4] This is despite no such adverse association being reported from the Women's Health Initiative cohort.[32] We have also included the potential reduction in QALYs following RRSO. The 'time-horizon' in our analysis is long enough to reflect important differences in costs and outcomes.[12] In order to minimize over-estimating benefits of RRSO, we have been conservative in our use of costs for OC diagnosis and treatment, by including a minimal subset of baseline costs. We have not included all costs for additional investigations, treatment of recurrence or management of complications. Inclusion of these additional costs would further increase cost-effectiveness of the model at a given risk threshold. We have also not included costs of genetic testing in the analysis and this may be a constraint. We have not included the excess mortality due to lung/colorectal cancer reported in the Nurses Health Study. However, this excess cancer mortality may be confounded by cigarette smoking or other risk related behaviours. Smoking itself is associated with early menopause.[33, 34] Data from the 185,017 women NIH-AARP (American Association of Retired Persons) Diet-&-Health Study found that when stratified by smoking status, the increased lung cancer risk associated with bilateral oophorectomy was restricted to smokers, and absent in non-smokers.[33] Additionally, data from 337,802 women in the European Prospective Investigation into Cancer and Nutrition (EPIC) study found no significant association between age at menarche/menopause or type of menopause (surgical/natural) and colorectal cancer risk.[35] We have not accounted for complications related to RRSO. A 1.5-5% complication rate has been reported in high risk women.[36, 37] It is important that this

issue be discussed by the treating clinician at time of consent and be built into the decision making process of whether to undergo surgery or not.

The deterministic sensitivity analysis permitted scrutiny of model outcomes and identification of variables exerting most influence. The 95% confidence-limits for probabilities explored in our sensitivity analysis were quite wide, adding to the strength of the results. The lack of statistically significant effect on outcome despite 30% variation in costs indicates that costs of RRSO, OC or cardiovascular treatment, are less important in influencing overall results. That the model remains largely cost-effective despite probabilities varying widely is reassuring. The reduction in level of impact exerted by different variables at increasing OC risk thresholds is expected and reassuring. It is interesting that the model is highly sensitive to the lower limit of the utility-score for RRSO at all risk levels. This is probably because the standard deviation is large. Hence, there is need for further research on RRSO utility-scores to better understand and improve the precision of its estimate. Of note nearly all published work is on the pre-menopausal population where the impact on quality-of-life is different. Separate utility-scores need to be developed for pre and postmenopausal RRSO.

The PSA undertaken is recommended by decision making bodies and adds to the robustness of our results.[12] It permits simultaneous variation in probabilities of all parameters to fully characterise model uncertainties and its effect on overall results. That 80-94% of simulations on PSA were cost-effective for the risk thresholds ≥5% reconfirms the health-economic benefit of RRSO at these risk levels for OC prevention.

Health economic assessments are crucial for determining the appropriateness of resource allocation for cost intensive population-based interventions. Rising health care costs and ever

increasing price of new OC treatments/drug therapies in a challenging economic environment further magnify the importance of newer cost-effective preventive strategies. Our findings thus have potentially important implications for clinical practice especially for the individual woman and for reducing the burden of OC. A key next step would be assessment of the acceptability of such a surgical intervention to decrease risk in postmenopausal women aged over 50 with lifetime OC risk of >5-<10%. The increasing availability of panel testing, identification newer moderate penetrance genes and common genetic variants and improved risk prediction models has made it possible to identify a number of women who can fall into this risk category. Tools/decision aids to facilitate understanding of risk and informed consent would need to be developed. Implementation of such an approach will necessitate information dissemination for raising health professional/public awareness and education. All these will have an added cost. Close attention will also need to be paid to developing well defined care and patient referral pathways in co-ordination with general practitioners, geneticists, gynaecologists and commissioners of care, as well as implementation studies for collecting long term outcomes.

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Submission declaration and verification

This work described has not been published previously, it is not under consideration for publication elsewhere, and its publication is approved by all authors and tacitly or explicitly

by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere without the written consent of the copyright-holder.

Disclaimers

UM has a financial interest in Abcodia, Ltd, a company formed to develop academic and commercial development of biomarkers for screening and risk prediction. RL reports personal fees from UCL, during the conduct of the study. The other authors declare no conflict of interest.

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Contribution to authorship

RM, UM, RL developed concept and design of the study. RM, RL, UM developed the model. RM, RL, UM, LP were involved in the health-economic and statistical analysis. RM, RL prepared the tables and figures. RM, RL prepared the first draft of the manuscript. All authors critically contributed to and revised the manuscript and approved the final version.

FIGURE LEGENDS

Figure-1: Decision Model Structure

The upper part of the model structure reflects 'no RRSO' for a given OC risk threshold. The lower part of the model depicts the option of RRSO for the same OC risk threshold. This model is run at each of the different thresholds for OC risk (2%, 4%, 5%, 6%, 8% and 10%).Each decision point in the model is a 'node' and each path extending from a node is a decision 'branch'. Each branch represents a mutually exclusive course or outcome. Each decision is given a probability (probabilities used in the model are detailed in Table1) highlighted in a white box along the decision branch. Values for each outcome are calculated. Cancer incidence is estimated by summing the probabilities of pathways ending in ovarian cancer. Final outcomes (blue boxes on the right of the figure) of each path include development of OC, no OC and excess deaths mainly from heart disease (Branch E).
OC-Ovarian Cancer; No OC - No Ovarian Cancer developed, RRSO –Risk reducing salpingo-oophorectomy

Figure 2: One way Deterministic Sensitivity Analyses

One-way sensitivity analysis (at the 8%, 6%, 5% risk thresholds) for all probabilities, costs and utilities in terms of ICER of RRSO compared to No RRSO at the different ovarian cancer risk 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.

382 OC- Ovarian cancer, RRSO –Risk reducing salpingo-oophorectomy

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384 **Figure-3: Probabilistic Sensitivity Analysis**

385 Shows the Cost-effectiveness acceptability curve (for different OC risk thresholds) in which
386 all model parameters/variables are varied simultaneously across their distributions to further
387 explore model uncertainty. X-axis: Incremental cost-effectiveness ratio (ICER) in terms of
388 Cost (£s)/QALY; Y-axis: Proportion of simulations. The results of 1000 simulations were
389 plotted on a cost-effectiveness acceptability curve showing the proportion of simulations (Y-
390 axis) that indicated that the intervention was cost-effective at different willingness to pay
391 thresholds (X-axis). The solid red line marks the proportion of simulations found to be cost-
392 effective at the £20,000 threshold used by NICE. 67-94% simulations are cost effective in
393 this analysis.

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395 OC- Ovarian cancer, RRSO- Risk reducing salpingo-oophorectomy

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FIGURE-1 Decision Model Structure

Figure-1: Decision Model Structure.

The upper part of the model structure reflects 'no RRSO' for a given OC risk threshold. The lower part of the model depicts the option of RRSO for the same OC risk threshold. This model is run at each of the different thresholds for OC risk (2%, 4%, 5%, 6%, 8% and 10%).Each decision point in the model is a 'node' and each path extending from a node is a decision 'branch'. Each branch represents a mutually exclusive course or outcome. Each decision is given a probability (probabilities used in the model are detailed in Table1) highlighted in a white box along the decision branch. Values for each outcome are calculated. Cancer incidence is estimated by summing the probabilities of pathways ending in ovarian cancer. Final outcomes (blue boxes on the right of the figure) of each path include development of OC, no OC and excess deaths mainly from heart disease (Branch E). OC-Ovarian Cancer; No OC - No Ovarian Cancer developed, RRSO –Risk reducing salpingo-oophorectomy

Figure-2 One way Deterministic Sensitivity Analyses

Figure 2: Deterministic Sensitivity Analyses. One-way sensitivity analysis (at the 8%, 6%, 5% risk thresholds) for all probabilities, costs and utilities in terms of ICER of RRSO compared to No RRSO at the different ovarian cancer risk 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 analysis

Figure-3: Probabilistic sensitivity analysis: Shows the Cost-effectiveness acceptability curve (for different OC risk thresholds) 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 solid red line marks the proportion of simulations found to be cost-effective at the £20,000 threshold used by NICE. 67-94% simulations are cost effective in this analysis.

OC- Ovarian cancer, RRSO- Risk reducing salpingo-oophorectomy

TABLES

Table 1: Probabilities of different pathways

Probability	Value	(CI) [Range]	Description	Source
P1	0.10 0.08 0.06 0.04 0.02		Lifetime risk of developing ovarian cancer	Model assumption
P2	0.94	(0.83, 0.98)	Reduction in risk of ovarian cancer from RRSO	Parker et al 2013[4]
P3	0.0003	(0.0078,0)	Excess risk of deaths from heart disease	Parker et al 2013[4]
CI- confidence interval, RRSO- risk reducing salpingo-oophorectomy				
Explanation: P1: Lifetime risk of developing ovarian cancer. The model was run over varying risk thresholds. P1=0.02 represents the baseline population based risk. P2: The reduction in ovarian cancer risk obtained from RRSO is taken from the Nurses Health Study, Parker et al, 2013.[4] P3: The absolute excess risk of deaths from heart disease = 0.03% (-0%, 0.65%). This is taken from the Nurses Health Study.[4] The numbers needed to harm (NNH)= 3073 (CI 154, ∞).				

471 **Table 2: Summary of costs used in model (2012 prices)***

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Item	Cost (£)	Source
Cost of RRSO	2,165	NHS Reference costs
Cost of ovarian cancer diagnosis and initial treatment	16,044	NHS Reference costs[38], NICE guideline[39]
Yearly cost of ovarian cancer treatment and follow-up: years 1-2	639	NHS Reference costs[38], NICE guideline[39]
Yearly cost of ovarian cancer treatment and follow-up: years 3-5	274	NHS Reference costs[38], NICE guideline[39]
Terminal care cost with ovarian cancer	15,414	National Audit office[40]
Cost of CHD death	3277	
*All costs were varied by +/-30% in one way sensitivity analysis NHS- national health service, NICE-national institutes for health and clinical excellence, , RRSO- risk reducing salpingo-oophorectomy,		

Explanation

The cost of RRSO was based on national reference costs for an upper genital tract laparoscopic/endoscopic intermediate procedure.[38]

Costs for ovarian cancer diagnosis and treatment were derived from national reference costs and a recent ovarian cancer guideline developed by NICE.[38, 39] We assumed that the cost of diagnosis to include a pelvic examination, ultrasound scan, CA125 test, CT scan, percutaneous biopsy and peritoneal cytology.

The cost of treatment included the reference cost for a lower and upper genital tract very complex major procedure and administration of chemotherapy based on 6 cycles of carboplatin and paclitaxel treatment. It was assumed that in years-1 and -2 treated survivors would have a further three consultant visits, a CT scan and 4 CA125 tests each year. In years 3 to 5 post-surgery it was assumed that survivors would have 2 consultant visits and 2 CA125 tests. We were conservative in our cost-estimates and did not include costs for additional investigations, treatment of recurrence or management of complications in the analysis.

Costs for terminal care for ovarian cancer were derived from end-of-life costs for cancer patients based on a report from the National Audit Office, UK.[40]

In line with NICE recommendations future healthcare costs not associated with ovarian cancer were not considered.

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Table 3: Model outcomes for costs, survival (life years) and quality adjusted life years (QALYs), undiscounted and discounted

	Ovarian cancer incidence	Survival	Discounted survival	Cost	Discounted cost	QALY	Discounted QALY
10% risk							
NO RSSO	10.0%	31.376	18.518	2475	1866	31.3	18.5
RRSO	0.6%	31.958	18.738	2314	2277	31.9	18.7
Difference	9.4%	0.582	0.220	-161	412	0.6	0.22
ICER						-251	1864
8% risk							
NO RRSO	8.0%	31.501	18.565	1980	1493	31.4	18.5
RRSO	0.5%	31.966	18.741	2285	2255	31.9	18.7
Difference	7.5%	0.465	0.176	304	762	0.5	0.17
ICER						605	4584
6% risk							
NO RRSO	6.0%	31.626	18.613	1485	1119	31.6	18.58
RRSO	0.4%	31.973	18.744	2255	2233	31.9	18.69
Difference	5.6%	0.347	0.131	770	1113	0.4	0.11
ICER						2116	9958
5% risk							
NO RRSO	5.0%	31.69	18.64	1237.72	932.81	31.63	18.61
RRSO	0.3%	31.98	18.75	2239.95	2221.31	31.92	18.69
Difference	4.7%	0.29	0.11	1002.23	1288.49	0.29	0.08
ICER						3409	15247
4% risk							
NO RRSO	4.00%	31.751	18.660	990	746	31.7	18.6
RRSO	0.24%	31.981	18.747	2225	2210	31.9	18.7
Difference	3.76%	0.230	0.087	1235	1464	0.2	0.057
ICER						5505	25577
2% risk							

NO RRSO	2.00%	31.875	18.707	495	373	31.9	18.7
RRSO	0.12%	31.988	18.749	2195	2188	31.9	18.7
Difference	1.88%	0.113	0.043	1700	1815	0.1	0.0
ICER						19999	674656

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

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