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

[1,2,3]Ranjit Manchanda, [4]Rosa Legood, [5]Antonis C. Antoniou, [4]Vladimir Gordeev, [2]Usha Menon

[1]Barts Cancer Institute, Queen Mary University of London, Old Anatomy Building, Charterhouse Square, London, EC1M 6BQ, UK, [2]Gynaecological Cancer Research Centre, Department of Women's Cancer, Institute for Women's Health, University College London, 149 Tottenham Court Road, London, UK, W1T 7DN, [3]Department of Gynaecological Oncology, St Bartholomew's Hospital, London, UK, EC1A 7BE, [4]Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, 15-17 Tavistock Place, London, WC1H 9SH, [5]Centre for Cancer Genetic Epidemiology, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, CB1 8RN, UK.

*Correspondence to:

Dr Ranjit Manchanda

Barts Cancer Institute, Queen Mary University of London,

Old Anatomy Building, Charterhouse Square, London, EC1M 6BQ, UK

Email: r.manchanda@ucl.ac.uk ; Fax- +44(0)2034472129

Professor Usha Menon

Gynaecological Cancer Research Centre, University College London,

149 Tottenham Court Road, London, UK, W1T 7DN

Email: u.menon@ucl.ac.uk ; Fax- +44(0)2034472129

Running Title

Risk threshold for surgical prevention of ovarian cancer

Key Words: Ovarian cancer, surgical prevention, risk reducing salpingo-oophorectomy, risk threshold, cost-effectiveness

Word Count: 3320

1

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=61.7 days, ICER= £11270/QALY) with benefits largely driven by reduction in BC-risk. RRSO remains cost-effective at>7% OC-risk without hormone replacement therapy (ICER=£20071/QALY, life-expectancy gained=27.1days) or if BC risk-reduction=0 (ICER=£19595/QALY, life-expectancy gained=46.7days). 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, 50.8%, 73.9%, 84.5%, 92.9%, 98.6% and 99.8% 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 ≥61.7days

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 only 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 of17 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 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 of0.95(SD= 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 is10.5%,[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 arenon-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 modelwere 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 61.7 days gain in life expectancy at an ICER= £11270/QALY.

At the baseline 2% OC risk, pre-menopausal RRSO becomes cost-effective for 30,000£/QALY but not

the 20,000£/QALY threshold (ICER= £20216/QALY, 38.9 days gain in life expectancy). However,

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 7.5% risk threshold, with an ICER= £19666.8/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=7%, the ICER =£20071/QALY for 27.1d increase in life-expectancy. This suggests RRSO will be

cost-effective at >7% 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

7% OC risk threshold (0.13 life-years saved, ICER=£19595/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, 50.8%, 73.9%, 84.5%, 92.9%, 98.6% and 99.8% simulations respectively remain cost-effective for the NICE £20,000/QALY 'willingness-to-pay threshold' when RRSO is undertaken in pre-menopausal women . Should the NICE threshold increase to £30,000/QALY, then 65.6%, 83.6%, 90.5%, 96.8%, 99.1% and 99.8% 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/QALY WTP threshold ,[44] and equates to 61.7days gain in life expectancy, for an overall ICER= £11270/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

10

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 ≥74% of PSA simulations at ≥4%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 ≥6% (ICER= £18982/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.

Role of Funding Source

The study is not funded by any charity or grant.

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

Proba bility	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	0.62	(0.53-0.74)	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	0.049	0.006	42.60	21.49	4867.12	4055.14	42.47	21.41
Difference	0.080	0.094	1.12	0.30	-1247	1151	1.37	0.36
ICER (£/QALY)							-909	3231
8% risk								
No RRSO	0.129	0.080	41.68	21.25	5606	2637	41.3	21.1
RRSO	0.049	0.005	42.61	21.50	4836.83	4039.29	42.49	21.42
Difference	0.080	0.075	0.94	0.25	-769	1403	1.1	0.3
ICER (£/QALY)							-671	4773
6% risk								
No RRSO	0.129	0.060	41.88	21.30	5098	2369	41.6	21.2
RRSO	0.040	0.004	42.63	21.50	4806.54	4023.43	42.50	21.42
Difference	0.089	0.056	0.75	0.20	-291	1654	0.9	0.2
ICER (£/QALY)							-317	7146
5% risk								
No RRSO	0.1290	0.0500	41.98	21.33	4844	2236	41.70	21.22
RRSO	0.0490	0.0122	42.63	21.50	4791	4015	42.51	21.42
Difference	0.0800	0.0378	0.6547	0.1727	-52	1780	0.8066	0.2003
ICER (£/QALY)							-65	8887
4% risk								
NO RRSO	0.129	0.040	42.08	21.36	4590	2102	41.8	21.3
RRSO	0.049	0.002	42.64	21.50	4776.24	4007.57	42.52	21.43

Difference	0.080	0.038	0.56	0.15	186	1906	0.7	0.169
ICER (£/QALY)							269	11270
2% risk								
NO RRSO	0.129	0.020	42.28	21.41	4082	1834	42.1	21.3
RRSO	0.61	0.61	42.65	21.51	4745.95	3991.71	42.53	21.43
Difference	-0.484	-0.594	0.37	0.10	664	2157	0.5	0.107
ICER (£/QALY)							1420	20216

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 dotted line marks the proportion of simulations found to be cost-effective at the £20,000 threshold used by NICE. 51-99% simulations are cost effective at varying (2-10%) ovarian cancer risk thresholds in this analysis.

RRSO- Risk reducing salpingo-oophorectomy

References

1   CRUK. Ovarian Cancer, Key Stats. *Cancer Statistics,* Nov 2014 ed. CRUK: Cancer Research UK,
        2014:1-2, http://publications.cancerresearchuk.org/downloads/Product/CS_KF_OVARY.pdf

2   Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin D, Forman
        D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC
        CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer,
        2013:Available from: http://globocan.iarc.fr, accessed on 10/03/2015.

3   Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated
        with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl
        Cancer Inst* 2009;**101**(2):80-7.

4   Jacobs I. Screening for familial ovarian cancer: the need for well-designed prospective
        studies. *J Clin Oncol* 2005;**23**(24):5443-5.

5   Evans DG, Gaarenstroom KN, Stirling D, Shenton A, Maehle L, Dorum A, Steel M, Lalloo F,
        Apold J, Porteous ME, Vasen HF, van Asperen CJ, Moller P. Screening for familial ovarian
        cancer: poor survival of BRCA1/2 related cancers. *J Med Genet* 2009;**46**(9):593-7.

6   Hermsen BB, Olivier RI, Verheijen RH, van Beurden M, de Hullu JA, Massuger LF, Burger CW,
        Brekelmans CT, Mourits MJ, de Bock GH, Gaarenstroom KN, van Boven HH, Mooij TM,
        Rookus MA. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an
        observational follow-up study. *Br J Cancer* 2007;**96**(9):1335-42.

7   Parker WH, Feskanich D, Broder MS, Chang E, Shoupe D, Farquhar CM, Berek JS, Manson JE.
        Long-term mortality associated with oophorectomy compared with ovarian conservation in
        the nurses' health study. *Obstet Gynecol* 2013;**121**(4):709-16.

8   Anderson K, Jacobson JS, Heitjan DF, Zivin JG, Hershman D, Neugut AI, Grann VR. Cost-
        effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. *Annals
        of internal medicine* 2006;**144**(6):397-406.

9   Manchanda R, Legood R, Pearce L, Menon U. Defining the risk threshold for risk reducing salpingo-oophorectomy for ovarian cancer prevention in low risk postmenopausal women. *Gynecol Oncol* 2015;**139**(3):487-94.

10   Jervis S, Song H, Lee A, Dicks E, Tyrer J, Harrington P, Easton DF, Jacobs IJ, Pharoah PP, Antoniou AC. Ovarian cancer familial relative risks by tumour subtypes and by known ovarian cancer genetic susceptibility variants. *J Med Genet* 2014;**51**(2):108-13.

11   Loveday C, Turnbull C, Ruark E, Xicola RM, Ramsay E, Hughes D, Warren-Perry M, Snape K, Eccles D, Evans DG, Gore M, Renwick A, Seal S, Antoniou AC, Rahman N. Germline RAD51C mutations confer susceptibility to ovarian cancer. *Nat Genet* 2012;**44**(5):475-6; author reply 6.

12   Loveday C, Turnbull C, Ramsay E, Hughes D, Ruark E, Frankum JR, Bowden G, Kalmyrzaev B, Warren-Perry M, Snape K, Adlard JW, Barwell J, Berg J, Brady AF, Brewer C, Brice G, Chapman C, Cook J, Davidson R, Donaldson A, Douglas F, Greenhalgh L, Henderson A, Izatt L, Kumar A, Lalloo F, Miedzybrodzka Z, Morrison PJ, Paterson J, Porteous M, Rogers MT, Shanley S, Walker L, Eccles D, Evans DG, Renwick A, Seal S, Lord CJ, Ashworth A, Reis-Filho JS, Antoniou AC, Rahman N. Germline mutations in RAD51D confer susceptibility to ovarian cancer. *Nat Genet* 2011;**43**(9):879-82.

13   Rafnar T, Gudbjartsson DF, Sulem P, Jonasdottir A, Sigurdsson A, Besenbacher S, Lundin P, Stacey SN, Gudmundsson J, Magnusson OT, le Roux L, Orlygsdottir G, Helgadottir HT, Johannsdottir H, Gylfason A, Tryggvadottir L, Jonasson JG, de Juan A, Ortega E, Ramon-Cajal JM, Garcia-Prats MD, Mayordomo C, Panadero A, Rivera F, Aben KK, van Altena AM, Massuger LF, Aavikko M, Kujala PM, Staff S, Aaltonen LA, Olafsdottir K, Bjornsson J, Kong A, Salvarsdottir A, Saemundsson H, Olafsson K, Benediktsdottir KR, Gulcher J, Masson G, Kiemeney LA, Mayordomo JI, Thorsteinsdottir U, Stefansson K. Mutations in BRIP1 confer high risk of ovarian cancer. *Nat Genet* 2011;**43**(11):1104-7.

14   Ramus SJ, Song H, Dicks E, Tyrer JP, Rosenthal AN, Intermaggio MP, Fraser L, Gentry-Maharaj

A, Hayward J, Philpott S, Anderson C, Edlund CK, Conti D, Harrington P, Barrowdale D,

Bowtell DD, Alsop K, Mitchell G, Cicek MS, Cunningham JM, Fridley BL, Alsop J, Jimenez-Linan

M, Poblete S, Lele S, Sucheston-Campbell L, Moysich KB, Sieh W, McGuire V, Lester J,

Bogdanova N, Durst M, Hillemanns P, Odunsi K, Whittemore AS, Karlan BY, Dork T, Goode EL,

Menon U, Jacobs IJ, Antoniou AC, Pharoah PD, Gayther SA. Germline Mutations in the BRIP1,

BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. *J Natl Cancer Inst*

2015;**107**(11).

15   Song H, Dicks E, Ramus SJ, Tyrer JP, Intermaggio MP, Hayward J, Edlund CK, Conti D,

Harrington P, Fraser L, Philpott S, Anderson C, Rosenthal A, Gentry-Maharaj A, Bowtell DD,

Alsop K, Cicek MS, Cunningham JM, Fridley BL, Alsop J, Jimenez-Linan M, Hogdall E, Hogdall

CK, Jensen A, Kjaer SK, Lubinski J, Huzarski T, Jakubowska A, Gronwald J, Poblete S, Lele S,

Sucheston-Campbell L, Moysich KB, Odunsi K, Goode EL, Menon U, Jacobs IJ, Gayther SA,

Pharoah PD. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D

Genes to Ovarian Cancer in the Population. *J Clin Oncol* 2015;**33**(26):2901-7.

16   Kuchenbaecker KB, Ramus SJ, Tyrer J, Lee A, Shen HC, Beesley J, Lawrenson K, McGuffog L,

Healey S, Lee JM, Spindler TJ, Lin YG, Pejovic T, Bean Y, Li Q, Coetzee S, Hazelett D, Miron A,

Southey M, Terry MB, Goldgar DE, Buys SS, Janavicius R, Dorfling CM, van Rensburg EJ,

Neuhausen SL, Ding YC, Hansen TV, Jonson L, Gerdes AM, Ejlertsen B, Barrowdale D, Dennis

J, Benitez J, Osorio A, Garcia MJ, Komenaka I, Weitzel JN, Ganschow P, Peterlongo P, Bernard

L, Viel A, Bonanni B, Peissel B, Manoukian S, Radice P, Papi L, Ottini L, Fostira F,

Konstantopoulou I, Garber J, Frost D, Perkins J, Platte R, Ellis S, Godwin AK, Schmutzler RK,

Meindl A, Engel C, Sutter C, Sinilnikova OM, Damiola F, Mazoyer S, Stoppa-Lyonnet D, Claes

K, De Leeneer K, Kirk J, Rodriguez GC, Piedmonte M, O'Malley DM, de la Hoya M, Caldes T,

Aittomaki K, Nevanlinna H, Collee JM, Rookus MA, Oosterwijk JC, Tihomirova L, Tung N,

Hamann U, Isaccs C, Tischkowitz M, Imyanitov EN, Caligo MA, Campbell IG, Hogervorst FB,

Olah E, Diez O, Blanco I, Brunet J, Lazaro C, Pujana MA, Jakubowska A, Gronwald J, Lubinski J, Sukiennicki G, Barkardottir RB, Plante M, Simard J, Soucy P, Montagna M, Tognazzo S, Teixeira MR, Pankratz VS, Wang X, Lindor N, Szabo CI, Kauff N, Vijai J, Aghajanian CA, Pfeiler G, Berger A, Singer CF, Tea MK, Phelan CM, Greene MH, Mai PL, Rennert G, Mulligan AM, Tchatchou S, Andrulis IL, Glendon G, Toland AE, Jensen UB, Kruse TA, Thomassen M, Bojesen A, Zidan J, Friedman E, Laitman Y, Soller M, Liljegren A, Arver B, Einbeigi Z, Stenmark-Askmalm M, Olopade OI, Nussbaum RL, Rebbeck TR, Nathanson KL, Domchek SM, Lu KH, Karlan BY, Walsh C, Lester J, Hein A, Ekici AB, Beckmann MW, Fasching PA, Lambrechts D, Van Nieuwenhuysen E, Vergote I, Lambrechts S, Dicks E, Doherty JA, Wicklund KG, Rossing MA, Rudolph A, Chang-Claude J, Wang-Gohrke S, Eilber U, Moysich KB, Odunsi K, Sucheston L, Lele S, Wilkens LR, Goodman MT, Thompson PJ, Shvetsov YB, Runnebaum IB, Durst M, Hillemanns P, Dork T, Antonenkova N, Bogdanova N, Leminen A, Pelttari LM, Butzow R, Modugno F, Kelley JL, Edwards RP, Ness RB, du Bois A, Heitz F, Schwaab I, Harter P, Matsuo K, Hosono S, Orsulic S, Jensen A, Kjaer SK, Hogdall E, Hasmad HN, Azmi MA, Teo SH, Woo YL, Fridley BL, Goode EL, Cunningham JM, Vierkant RA, Bruinsma F, Giles GG, Liang D, Hildebrandt MA, Wu X, Levine DA, Bisogna M, Berchuck A, Iversen ES, Schildkraut JM, Concannon P, Weber RP, Cramer DW, Terry KL, Poole EM, Tworoger SS, Bandera EV, Orlow I, Olson SH, Krakstad C, Salvesen HB, Tangen IL, Bjorge L, van Altena AM, Aben KK, Kiemeney LA, Massuger LF, Kellar M, Brooks-Wilson A, Kelemen LE, Cook LS, Le ND, Cybulski C, Yang H, Lissowska J, Brinton LA, Wentzensen N, Hogdall C, Lundvall L, Nedergaard L, Baker H, Song H, Eccles D, McNeish I, Paul J, Carty K, Siddiqui N, Glasspool R, Whittemore AS, Rothstein JH, McGuire V, Sieh W, Ji BT, Zheng W, Shu XO, Gao YT, Rosen B, Risch HA, McLaughlin JR, Narod SA, Monteiro AN, Chen A, Lin HY, Permuth-Wey J, Sellers TA, Tsai YY, Chen Z, Ziogas A, Anton-Culver H, Gentry-Maharaj A, Menon U, Harrington P, Lee AW, Wu AH, Pearce CL, Coetzee G, Pike MC, Dansonka-Mieszkowska A, Timorek A, Rzepecka IK, Kupryjanczyk J, Freedman M, Noushmehr H, Easton DF, Offit K, Couch FJ, Gayther S, Pharoah PP, Antoniou

27

AC, Chenevix-Trench G. Identification of six new susceptibility loci for invasive epithelial ovarian cancer. *Nat Genet* 2015;**47**(2):164-71.

17   Song H, Ramus SJ, Tyrer J, Bolton KL, Gentry-Maharaj A, Wozniak E, Anton-Culver H, Chang-Claude J, Cramer DW, DiCioccio R, Dork T, Goode EL, Goodman MT, Schildkraut JM, Sellers T, Baglietto L, Beckmann MW, Beesley J, Blaakaer J, Carney ME, Chanock S, Chen Z, Cunningham JM, Dicks E, Doherty JA, Durst M, Ekici AB, Fenstermacher D, Fridley BL, Giles G, Gore ME, De Vivo I, Hillemanns P, Hogdall C, Hogdall E, Iversen ES, Jacobs IJ, Jakubowska A, Li D, Lissowska J, Lubinski J, Lurie G, McGuire V, McLaughlin J, Medrek K, Moorman PG, Moysich K, Narod S, Phelan C, Pye C, Risch H, Runnebaum IB, Severi G, Southey M, Stram DO, Thiel FC, Terry KL, Tsai YY, Tworoger SS, Van Den Berg DJ, Vierkant RA, Wang-Gohrke S, Webb PM, Wilkens LR, Wu AH, Yang H, Brewster W, Ziogas A, Houlston R, Tomlinson I, Whittemore AS, Rossing MA, Ponder BA, Pearce CL, Ness RB, Menon U, Kjaer SK, Gronwald J, Garcia-Closas M, Fasching PA, Easton DF, Chenevix-Trench G, Berchuck A, Pharoah PD, Gayther SA. A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. *Nat Genet* 2009;**41**(9):996-1000.

18   Jervis S, Song H, Lee A, Dicks E, Harrington P, Baynes C, Manchanda R, Easton DF, Jacobs I, Pharoah PP, Antoniou AC. A risk prediction algorithm for ovarian cancer incorporating BRCA1, BRCA2, common alleles and other familial effects. *J Med Genet* 2015.

19   Petrou S, Gray A. Economic evaluation using decision analytical modelling: design, conduct, analysis, and reporting. *BMJ* 2011;**342**:d1766.

20   NICE. Guide to the methods of technology appraisal. N1618 ed. London: National Institute for Health and Clinical Excellence (NICE), 2008.

21   CRUK. Breast Cancer Incidence Statistics UK 2009-2011. *Breast Cancer (C50), Average Number of New Cases per Year and Age-Specific Incidence Rates, Females, UK, 2009-2011*: Cancer Research UK, 2012.

22   Rivera CM, Grossardt BR, Rhodes DJ, Brown RD, Jr., Roger VL, Melton LJ, 3rd, Rocca WA. Increased cardiovascular mortality after early bilateral oophorectomy. *Menopause* 2009;**16**(1):15-23.

23   Read MD, Edey KA, Hapeshi J, Foy C. Compliance with estrogen hormone replacement therapy after oophorectomy: a prospective study. *Menopause Int* 2010;**16**(2):60-4.

24   Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, Isaacs C, Olopade OI, Neuhausen SL, van 't Veer L, Eeles R, Evans DG, Tomlinson G, Matloff E, Narod SA, Eisen A, Domchek S, Armstrong K, Weber BL. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2005;**23**(31):7804-10.

25   Department of Health. NHS Reference Costs 2012-2013. London: Department of Health, 2013:https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/261154/nhs_reference_costs_2012-13_acc.pdf.

26   Curtis L. Unit Costs of Health and Social Care 2011. Canterbury, Kent: Personal Social Services Research Unit (PSSRU), 2011.

27   Office of National Statistics. Lifetable for females in the UK. Vol 2012: Office of National Statitics, 2011:Office for National Statistics licensed under the Open Government Licence v.1.0. .

28   CRUK. Ovarian Cancer Incidence Statistics: 2011. London, UK: Cancer Research UK, 2014:accessed from http://www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/incidence/uk-ovarian-cancer-incidence-statistics#age , access date 10/03/2015.

29   CRUK. Ovarian Cancer Survival Statistics 2010-2011. London, UK: Cancer Research UK, 2014:accessed from http://www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/survival/ovarian-cancer-survival-statistics (access date 11/03/2015).

30   CRUK. Breast Cancer Survival Statistics. *One-, five-, and ten-year survival*. London: Cancer Research UK, 2011:http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/survival/breast-cancer-survival-statistics.

31   Manchanda R, Legood R, Burnell M, McGuire A, Raikou M, Loggenberg K, Wardle J, Sanderson S, Gessler S, Side L, Balogun N, Desai R, Kumar A, Dorkins H, Wallis Y, Chapman C, Taylor R, Jacobs C, Tomlinson I, Beller U, Menon U, Jacobs I. Cost-effectiveness of population screening for BRCA mutations in Ashkenazi jewish women compared with family history-based testing. *J Natl Cancer Inst* 2015;**107**(1):380.

32   Grann VR, Patel P, Bharthuar A, Jacobson JS, Warner E, Anderson K, Tsai WY, Hill KA, Neugut AI, Hershman D. Breast cancer-related preferences among women with and without BRCA mutations. *Breast Cancer Res Treat* 2010;**119**(1):177-84.

33   Havrilesky LJ, Broadwater G, Davis DM, Nolte KC, Barnett JC, Myers ER, Kulasingam S. Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. *Gynecologic oncology* 2009;**113**(2):216-20.

34   Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. *Methods for the economic evaluation of health care programmes,* Third Edition ed. Oxford Oxford University Press 2005.

35   Armstrong DK. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. *The oncologist* 2002;**7 Suppl 5**:20-8.

36   Yancik R. Ovarian cancer. Age contrasts in incidence, histology, disease stage at diagnosis, and mortality. *Cancer* 1993;**71**(2 Suppl):517-23.

37   Swart A. Long-term follow-up of women enrolled in a randomized trial of adjuvant chemotherapy for early stage ovarian cancer. *ASCO Annual Meeting Proceedings (Part I)*. Vol 25: Journal Clinical Oncology, 2007:18S (June 20 Supplement): 5509.

38   Lyratzopoulos G, Abel GA, Barbiere JM, Brown CH, Rous BA, Greenberg DC. Variation in

advanced stage at diagnosis of lung and female breast cancer in an English region 2006-

2009. *Br J Cancer* 2012;**106**(6):1068-75.

39   NICE. National costing report: Early and locally advanced breast cancer/Advanced breast

cancer. London, UK: National Institute for Health and Clinical Excellence, 2009.

40   ONS. Registrations of cancer diagnosed in 2006, England. *Cancer Statistics Registrations, The

Office for National Statistics,* Series MB1 No. 37 ed. Cardiff, Wales, UK: The Office for

National Statistics, 2008.

41   NICE. Clinical Guideline (CG81) – Advanced breast cancer: diagnosis and treatment. Cardiff,

Wales, UK: National Collaborating Centre for Cancer, National Institute for Health and

Clinical Excellence, 2009.

42   Peasgood T, Ward SE, Brazier J. Health-state utility values in breast cancer. *Expert review of

pharmacoeconomics & outcomes research* 2010;**10**(5):553-66.

43   Gennari A, Conte P, Rosso R, Orlandini C, Bruzzi P. Survival of metastatic breast carcinoma

patients over a 20-year period: a retrospective analysis based on individual patient data

from six consecutive studies. *Cancer* 2005;**104**(8):1742-50.

44   NICE. Social value judgements: principles for the development of NICE guidance. In: (NICE)

NIfHaCE, ed.*,* 2nd ed: National Institute for Health and Clinical Excellence (NICE), 2008.

45   Andronis L, Barton P, Bryan S. Sensitivity analysis in economic evaluation: an audit of NICE

current practice and a review of its use and value in decision-making. *Health technology

assessment* 2009;**13**(29):iii, ix-xi, 1-61.

46   Briggs A. Probabilistic analysis of cost-effectiveness models: statistical representation of

parameter uncertainty. *Value in health : the journal of the International Society for

Pharmacoeconomics and Outcomes Research* 2005;**8**(1):1-2.

47   Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, Garber JE, Neuhausen SL,

Matloff E, Eeles R, Pichert G, Van t'veer L, Tung N, Weitzel JN, Couch FJ, Rubinstein WS, Ganz

PA, Daly MB, Olopade OI, Tomlinson G, Schildkraut J, Blum JL, Rebbeck TR. Association of

risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality.

JAMA : the journal of the American Medical Association 2010;**304**(9):967-75.

48   Parker WH, Jacoby V, Shoupe D, Rocca W. Effect of bilateral oophorectomy on women's

long-term health. *Womens Health (Lond Engl)* 2009;**5**(5):565-76.

49   Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, Ausems MG, Collee JM, van Doorn

HC, Gomez Garcia EB, Kets CM, van Leeuwen FE, Meijers-Heijboer HE, Mourits MJ, van Os

TA, Vasen HF, Verhoef S, Rookus MA, Hooning MJ. Breast cancer risk after salpingo-

oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk

reduction. *J Natl Cancer Inst* 2015;**107**(5).

50   Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, Garber JE, Isaacs C, Evans DG, Lynch

H, Eeles RA, Neuhausen SL, Daly MB, Matloff E, Blum JL, Sabbatini P, Barakat RR, Hudis C,

Norton L, Offit K, Rebbeck TR. Risk-reducing salpingo-oophorectomy for the prevention of

BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective

study. *J Clin Oncol* 2008;**26**(8):1331-7.

51   Eisen A, Lubinski J, Klijn J, Moller P, Lynch HT, Offit K, Weber B, Rebbeck T, Neuhausen SL,

Ghadirian P, Foulkes WD, Gershoni-Baruch R, Friedman E, Rennert G, Wagner T, Isaacs C,

Kim-Sing C, Ainsworth P, Sun P, Narod SA. Breast cancer risk following bilateral

oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. *J

Clin Oncol* 2005;**23**(30):7491-6.

52   Chai X, Domchek S, Kauff N, Rebbeck T, Chen J. RE: Breast Cancer Risk After Salpingo-

Oophorectomy in Healthy BRCA1/2 Mutation Carriers: Revisiting the Evidence for Risk

Reduction. *J Natl Cancer Inst* 2015;**107**(9).

53   Madalinska JB, Hollenstein J, Bleiker E, van Beurden M, Valdimarsdottir HB, Massuger LF,

Gaarenstroom KN, Mourits MJ, Verheijen RH, van Dorst EB, van der Putten H, van der Velden

K, Boonstra H, Aaronson NK. Quality-of-life effects of prophylactic salpingo-oophorectomy

versus gynecologic screening among women at increased risk of hereditary ovarian cancer. *J Clin Oncol* 2005;**23**(28):6890-8.

54   Robson M, Hensley M, Barakat R, Brown C, Chi D, Poynor E, Offit K. Quality of life in women at risk for ovarian cancer who have undergone risk-reducing oophorectomy. *Gynecol Oncol* 2003;**89**(2):281-7.

55   Finch A, Metcalfe KA, Chiang JK, Elit L, McLaughlin J, Springate C, Demsky R, Murphy J, Rosen B, Narod SA. The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. *Gynecologic Oncology* 2011;**121**(1):163-8.

56   Madalinska JB, van Beurden M, Bleiker EM, Valdimarsdottir HB, Hollenstein J, Massuger LF, Gaarenstroom KN, Mourits MJ, Verheijen RH, van Dorst EB, van der Putten H, van der Velden K, Boonstra H, Aaronson NK. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. *J Clin Oncol* 2006;**24**(22):3576-82.

57   Brinton LA, Gierach GL, Andaya A, Park Y, Schatzkin A, Hollenbeck AR, Spitz MR. Reproductive and hormonal factors and lung cancer risk in the NIH-AARP Diet and Health Study cohort. *Cancer Epidemiol Biomarkers Prev* 2011;**20**(5):900-11.

58   Midgette AS, Baron JA. Cigarette smoking and the risk of natural menopause. *Epidemiology* 1990;**1**(6):474-80.

59   Tsilidis KK, Allen NE, Key TJ, Bakken K, Lund E, Berrino F, Fournier A, Olsen A, Tjonneland A, Overvad K, Boutron-Ruault MC, Clavel-Chapelon F, Byrnes G, Chajes V, Rinaldi S, Chang-Claude J, Kaaks R, Bergmann M, Boeing H, Koumantaki Y, Stasinopoulou G, Trichopoulou A, Palli D, Tagliabue G, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HB, van Duijnhoven FJ, van Gils CH, Peeters PH, Rodriguez L, Gonzalez CA, Sanchez MJ, Chirlaque MD, Barricarte A, Dorronsoro M, Borgquist S, Manjer J, van Guelpen B, Hallmans G, Rodwell SA, Khaw KT, Norat T, Romaguera D, Riboli E. Oral contraceptives, reproductive history and risk of

colorectal cancer in the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer* 2010;**103**(11):1755-9.

60   Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, Ellis NA, Boyd J, Borgen PI, Barakat RR, Norton L, Castiel M, Nafa K, Offit K. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med* 2002;**346**(21):1609-15.

61   Manchanda R, Abdelraheim A, Johnson M, Rosenthal AN, Benjamin E, Brunell C, Burnell M, Side L, Gessler S, Saridogan E, Oram D, Jacobs I, Menon U. Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. *BJOG : an international journal of obstetrics and gynaecology* 2011;**118**(7):814-24.

62   Meeuwissen PA, Seynaeve C, Brekelmans CT, Meijers-Heijboer HJ, Klijn JG, Burger CW. Outcome of surveillance and prophylactic salpingo-oophorectomy in asymptomatic women at high risk for ovarian cancer. *Gynecol Oncol* 2005;**97**(2):476-82.

63   Antoniou AC, Pharoah PP, Smith P, Easton DF. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. *Br J Cancer* 2004;**91**(8):1580-90.

64   Berry DA, Iversen ES, Jr., Gudbjartsson DF, Hiller EH, Garber JE, Peshkin BN, Lerman C, Watson P, Lynch HT, Hilsenbeck SG, Rubinstein WS, Hughes KS, Parmigiani G. BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. *J Clin Oncol* 2002;**20**(11):2701-12.

65   Pearce CL, Stram DO, Ness RB, Stram DA, Roman LD, Templeman C, Lee AW, Menon U, Fasching PA, McAlpine JN, Doherty JA, Modugno F, Schildkraut JM, Rossing MA, Huntsman DG, Wu AH, Berchuck A, Pike MC, Pharoah PD. Population distribution of lifetime risk of ovarian cancer in the United States. *Cancer Epidemiol Biomarkers Prev* 2015;**24**(4):671-6.

66   Independent Cancer Task Force. Achieving world-class cancer outcomes: a strategy for England 2015-2020. London, UK: Cancer Research UK,

2015:http://www.cancerresearchuk.org/sites/default/files/achieving_world-class_cancer_outcomes_-_a_strategy_for_england_2015-20.pdf.

67   The White House. Remarks by the President on Precision Medicine. Office of the Press Secretary, The White House, USA, 2015:https://www.whitehouse.gov/the-press-office/2015/01/30/remarks-president-precision-medicine.

68   Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, Shoupe D, Berek JS, Hankinson S, Manson JE. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol* 2009;**113**(5):1027-37.

69   BNF. *British National Formulary 67*. London, UK: BMJ Group, and the Pharmaceutical Press (Royal Pharmaceutical Society of Great Britain) 2014.

70   NICE. Ovarian cancer: the recognition and initial management of ovarian cancer. Vol CG122. London: National Institute for Health and Clinical Excellence (NICE), 2011.

71   NAO. End of life care. In: Burr TCaAG, ed. London: National Audit Office (NAO), House of Commons, 2008.

72   Robertson C, Arcot Ragupathy SK, Boachie C, Dixon JM, Fraser C, Hernandez R, Heys S, Jack W, Kerr GR, Lawrence G, MacLennan G, Maxwell A, McGregor J, Mowatt G, Pinder S, Ternent L, Thomas RE, Vale L, Wilson R, Zhu S, Gilbert FJ. The clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment for primary breast cancer: systematic reviews registry database analyses and economic evaluation. *Health Technol Assess* 2011;**15**(34):v-vi, 1-322.

73   NICE. Early and locally advanced breast cancer: diagnosis and treatment. *NICE Clinical Guideline, CG80*. Cardiff, Wales, UK: National Collaborating Centre for Cancer, National Institute for Health and Clinical Excellence, 2009.

4% OC Risk

5% OC Risk

6% OC Risk

8% OC Risk