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

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1 **Title page**

2 **Defining the risk threshold for risk reducing salpingo-oophorectomy for ovarian cancer**

3 **prevention in low risk postmenopausal women**

4

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28   **Keywords**

29   Cancer prevention, Ovarian neoplasm, Risk reducing salpingo-oophorectomy, QALY, Risk

30   prediction, Cost effectiveness

31

32   **Running Head** -   Defining risk threshold for surgery for ovarian cancer prevention

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37   **ABSTRACT**

38   **Objective**:

39   To define risk thresholds for cost-effectiveness of risk-reducing salpingo-

40   oophorectomy(RRSO) for ovarian cancer(OC) prevention in low/intermediate risk

41   postmenopausal women.

42   **Methods**

43   A decision-analytic model compares lifetime costs-&-effects of offering 'RRSO' with 'no

44   RRSO' to postmenopausal women ≥50years for different lifetime OC-risk thresholds: 2%,

45   4%, 5%, 6%, 8% and 10%. Well established data from the literature are used to estimate total

46   costs, effects in terms of Quality-Adjusted-Life-Years(QALYs), cancer incidence,

47   incremental cost-effectiveness ratio(ICER) and impact. Costs are reported at 2012 prices;

48   costs/outcomes discounted at 3.5%. Deterministic/Probabilistic sensitivity analysis(PSA)

49   evaluate model uncertainty.

50   **Results**

51   RRSO does not save QALYs and is not cost-effective at the 2% general population lifetime

52   OC-risk. At 4% OC-risk RRSO saves QALYs but is not cost-effective. At risk thresholds

53   ≥5%, RRSO saves more life-years and QALYs and is highly cost-effective. The ICERs for

54   OC-risk levels 5%, 6%, 8% and 10% are £15247, £9958, £4584, and £1864 respectively. The

55   gain in life-years from RRSO equates to 29.2, 40.1, 62.1 and 80.3 days at risk thresholds of

56   5%, 6%, 8% and 10% respectively. The results are not sensitive to treatment costs of

57   RRSO/OC/cardiovascular events but are sensitive to utility-scores for RRSO. On PSA, 67%,

58   80%, 84%, 91% and 94% of simulations at risk thresholds of 4%, 5%, 6%, 8% and 10%

59   respectively are cost-effective for RRSO.

60   **Conclusion**

61   RRSO is highly cost-effective in postmenopausal women aged >50 with ≥5% lifetime OC-

62   risk and increases life-expectancy by ≥29.2days. The results could have significant clinical

63   implications given the improvements in risk prediction and falling costs of genotyping.

64

65

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

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

91 years age.

92

93 We hypothesise that in postmenopausal women >50 years age, RRSO may become cost-

94 effective for prevention of sporadic OC at <10% lifetime risk thresholds. We use well

95 established data from the literature to describe a decision analysis model comparing 'RRSO'

96 with 'no RRSO' at different OC risk thresholds. Defining the risk thresholds and

97 circumstances in which RRSO can be offered to lower risk postmenopausal women on a

98 population basis for OC prevention is an important step towards the implementation of

99 predictive, preventive, personalized, and participatory (P4) medicine. The results have

100 immediate implications as currently postmenopausal women in the general population cannot

101 access primary risk reducing salpingo-oophorectomy for OC prevention.

102

103 **METHODS**

104 A decision-analytic model (Figure-1) was developed to compare the lifetime costs and effects

105 of offering RRSO to women aged 51years for different risk thresholds of developing OC. The

106 model was programmed in Microsoft Excel, and run for the OC risk thresholds: 2%, 4%, 5%,

107 6%, 8% and 10%. As this analysis concerns prevention of OC not linked to high penetrance

108 genes, the median age of diagnosis of sporadic OC is >65 years and 83% of all OC occurs in

109 women >50 years, we restrict the analysis to post-menopausal women ≥51 years age. OC

110 screening has not been shown to save lives and is not routinely offered in clinical practice.

111 Hence, it is not included in the model.

112

113 Figure-1 reflects outcomes based on a decision to perform RRSO or not. Each decision point

114 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

7

140 NICE recommendations future healthcare costs not associated with OC were not

141 considered.[12]

142

Life-years

144 Life expectancy for women who don't develop OC was based on female life tables from

145 Office of National Statistics.[14] Age at onset of postmenopausal OC (median=68 years) was

146 taken from CRUK age of incidence statistics.[11] Ten year survival data (from CRUK) was

147 used to model OC outcomes (1-year survival=72.4% (CI:72.4,72.5); 5-year survival

148 rate=46.2% (CI:45.9,46.4); 10-year survival=34.5% (CI:33.8,35.3)).[15] After ten years

149 survival, the probability of death was assumed to be same as the general population.

150

Quality adjusted life years (QALYs)

152 QALY is a measurement which expresses changes in length-of-life, while simultaneously

153 incorporating reductions in quality-of-life. It is calculated using quality-of-life adjustment or

154 utility-weights for each health state in the model. 'Utility-weights' are an indication of an

155 individual's preference for specific health states where '1'=perfect health and '0'=death.

156 QALY=Survival in life-years x Utility-weight. Utility-weight for RRSO=0.95(S.D=0.1) and

157 was obtained from a recent analysis by Grann.[16] Havrilesky[17] reported detailed utility

158 estimates related to various health states following OC treatment using visual analogue scale

159 and time-trade-off (TTO) methods. As visual scales comparing health state preferences have

160 inherent biases and are generally less accurate,[18] we have utilized the TTO scores. We

161 assumed that 70% of women present with OC at advanced stages,[19, 20] with a lower

162 utility-score for a new diagnosis=0.55(S.D=0.29), while the remainder present at early stages

163 with a higher utility-score=0.81(S.D=0.26). The end-stage of life utility-score where OC

164 patients did not survive the next year=0.16(S.D=0.25). Of those who survived initial

165 chemotherapy the chance of recurrence with early disease was 10.5% annually,[21] and with

166 advanced disease 20.6%.[19] For women with recurrent disease the mean utility-value=

167 0.5(range:0.4-0.61) and for women in remission the utility-value=0.83(S.D=0.25).[17]

168

169 **Analysis**

170 The probability of being in a branch of the decision-model was calculated by multiplying

171 together the path probabilities. The total costs and effects in terms of life-years and QALYs

172 were then estimated by weighting the values for each branch by the probability of being in

173 each branch. The incremental cost-effectiveness ratio (ICER) was estimated by dividing the

174 difference in cost by the difference in effect. ICER= (Cost A–Cost B)/(Effect A–Effect B).

175 By comparing this ICER with the £20,000-£30,000/QALY cost-effectiveness threshold used

176 by NICE,[22] we determined whether 'offering RRSO' to women above a certain risk

177 threshold was cost-effective compared with 'no RRSO'. To explore uncertainty in the results

178 and robustness of the model, a one-way (deterministic) sensitivity analysis was undertaken by

179 varying each parameter in the model and then re-running the model to assess the impact on

180 overall results. Probabilities and utility-scores were varied according to their 95%

181 confidence-intervals/range, where available, or by +/-10%, and costs were varied by +/-30%.

182 In addition to the one-way sensitivity results, a probabilistic sensitivity analysis (PSA) was

183 undertaken as recommended by NICE methods guidance.[12, 23] Any variation in model

184 parameters/variables is likely to occur in parallel rather than independently of each other. In

185 the PSA all variables were varied simultaneously across their distributions to further explore

186 model uncertainty. We assigned costs a gamma distribution, probabilities a beta distribution,

187 and utilities a log-normal distribution as suggested in the literature.[24] The results of 1000

188 simulations were plotted on a cost-effectiveness acceptability curve showing the proportion

189   of simulations that indicated that the intervention was cost-effective at different willingness

190   to pay thresholds.

191

192

193   **RESULTS**

194   The discounted and undiscounted survival (life-years), lifetime costs, and QALYs for each

195   branch in the decision model at the different OC risk thresholds of 2%, 4%, 5%, 6%, 8% and

196   10% are given in Table-3. Discounted results show a smaller overall gain in life-

197   years/QALYs and overall cost difference, as discounting adjusts costs and outcomes that

198   occur in the future and the cost savings generated through prevention of future OC cases is

199   valued less. At the 2% baseline population OC risk level, routine RRSO does not save more

200   QALYs and is not cost-effective. At a 4% OC risk level, RRSO saves more QALYs but is

201   not cost-effective at the ICER=£25,577, which is above the £20,000 NICE threshold.

202   However, at risk thresholds of ≥5%, RRSO saves more life-years and QALYs and is highly

203   cost-effective for the NICE threshold of £20,000/QALY. The ICERs for risk levels of 5%,

204   6%, 8% and 10% are £15247, £9958, £4584, and £1864 respectively. The gains in life

205   expectancy from RRSO at the risk thresholds of 5%, 6%, 8% and 10% equate to 29.2, 40.1,

206   62.1 and 80.3 days respectively.

207

208   One-way sensitivity analysis results are given in Figure-2. It suggests that the results are not

209   that sensitive to treatment costs of RRSO, OC or cardiovascular events. Results are however

210   sensitive to excess cardiovascular deaths at the 5% threshold but not that sensitive at the 6%

211   and 8% thresholds. It is also very sensitive to utility-scores for RRSO. The model was not

212   cost-effective at the lower most limit of the utility-score for RRSO. The impact of different

213   variables on cost-effectiveness decreases as the OC risk threshold increases.

214

215 The PSA results (Figure-3) shows that at a £20,000 willingness to pay threshold/QALY,

216 67%, 80%, 84%, 91% and 94% of simulations at risk thresholds of 4%, 5%, 6%, 8% and

217 10%, respectively are cost-effective for RRSO. If the willingness to pay threshold is

218 increased to £30,000/QALY, then 77%, 84%, 85%, 92% and 94% simulations are cost

219 effective for RRSO at the above risk thresholds, respectively.

220

221 **DISCUSSION**

222 This is the first analysis that we are aware of that defines precise risk thresholds at which

223 RRSO can be cost-effective for OC prevention on a population basis. Our modelling suggests

224 that in postmenopausal women with lifetime OC risk thresholds of ≥5%, RRSO is highly

225 cost-effective for the NICE threshold of £20,000/QALY[22] and equates to gains in life

226 expectancy of ≥29.2 days. This gain in life-years (range 29.2 to 80.3 days) compares

227 favourably with the gain in life-years from cervical cancer screening which is reported to

228 range between 11.6-32.4 days.[25] Our findings have significant implications for clinical

229 practice given the falling cost of genotyping and increasing ability to better calculate an

230 individual's OC risk. Availability of such an approach could impact on risk management

231 choices of 'low/intermediate risk' (lifetime risk <10%) women especially given the lack of an

232 effective screening strategy for OC. If widely adopted it has the potential to contribute to

233 reducing the OC burden in the population.

234

235 Restricting use to women >50 years enables primary surgical prevention to be offered with

236 less side effects. The increased all-cause mortality associated with bilateral oophorectomy

237 reported by the Nurses Health[4] and Olmsted County[26] studies were predominantly in

238 women <45[26]-50[4] years who did not take hormone replacement therapy. The same is true

239 for cardiovascular, bone and neurological risks.[4, 26, 27] Most sporadic OC (not related to

240 BRCA/mismatch repair gene mutations) occurs at >50 years, with the median age of

241 diagnosis being >65 years[11]. Although precise data on the proportion of OC <50 years in

242 BRCA1/BRCA2/MMR-negative individuals who have a life time OC risk ≥5% risk are not

243 currently available, this risk under 50 is likely to be minimal.

244 In our analysis, the lifetime OC risk threshold for RRSO in postmenopausal women was

245 ≥5%. This 5% risk threshold is significantly lower than the OC risk (18-40%) in

246 BRCA1/BRCA2 carriers,[28] and also less than the risk of OC in Lynch Syndrome women

247 (6-14%).[29] OC risk prediction is increasingly possible and general population models based

248 on known epidemiological risk and protective factors have recently been published.[30, 31]

249 Recently we quantified the population distribution of lifetime risks of OC by adding common

250 genetic (SNP) risk factors to the known epidemiologic (contraceptive use, parity, tubal

251 ligation, endometriosis, first degree relative with OC) factors.[10] Eight combinations of risk

252 factors gave a life time OC risk ≥5% and 2% of the US population would have a lifetime risk

253 ≥5%.[10] RRSO could be of benefit to all such women. Newer OC SNPs are constantly being

254 identified through large consortia led collaborative work, incorporation of which will further

255 improve performance of such models. Alongside such progress, major advancements in

256 genetic testing technology and falling costs now enables individual SNP information to be

257 made available at a low cost. Additionally, other lifestyle factors including aspirin and

258 menopausal HRT use are being identified through pooled analyses. As models get more

259 sophisticated incorporating additional genetic and epidemiologic data, their ability to predict

260 ovarian cancer risk will improve and their applicability will rise.

261

262 Our analysis has several strengths. It incorporates impact on OC risk and fulfils various

263 requirements suggested by NICE for health-economic decision making. We use current

264   practice as a comparator, QALYs to measure health-outcomes, a 3.5% discount rate on costs

265   and health outcomes and, well established population-based data for parameters in the

266   analysis.[12] Our model includes potential excess deaths from coronary events in the

267   postmenopausal population as reported in the most recent analysis of the Nurses Health

268   Study.[4] This is despite no such adverse association being reported from the Women's

269   Health Initiative cohort.[32] We have also included the potential reduction in QALYs

270   following RRSO. The 'time-horizon' in our analysis is long enough to reflect important

271   differences in costs and outcomes.[12] In order to minimize over-estimating benefits of

272   RRSO, we have been conservative in our use of costs for OC diagnosis and treatment, by

273   including a minimal subset of baseline costs. We have not included all costs for additional

274   investigations, treatment of recurrence or management of complications. Inclusion of these

275   additional costs would further increase cost-effectiveness of the model at a given risk

276   threshold. We have also not included costs of genetic testing in the analysis and this may be a

277   constraint. We have not included the excess mortality due to lung/colorectal cancer reported

278   in the Nurses Health Study. However, this excess cancer mortality may be confounded by

279   cigarette smoking or other risk related behaviours. Smoking itself is associated with early

280   menopause.[33, 34] Data from the 185,017 women NIH-AARP (American Association of

281   Retired Persons) Diet-&-Health Study found that when stratified by smoking status, the

282   increased lung cancer risk associated with bilateral oophorectomy was restricted to smokers,

283   and absent in non-smokers.[33] Additionally, data from 337,802 women in the European

284   Prospective Investigation into Cancer and Nutrition (EPIC) study found no significant

285   association between age at menarche/menopause or type of menopause (surgical/natural) and

286   colorectal cancer risk.[35] We have not accounted for complications related to RRSO. A 1.5-

287   5% complication rate has been reported in high risk women.[36, 37] It is important that this

288   issue be discussed by the treating clinician at time of consent and be built into the decision

289   making process of whether to undergo surgery or not.

290

291   The deterministic sensitivity analysis permitted scrutiny of model outcomes and identification

292   of variables exerting most influence. The 95% confidence-limits for probabilities explored in

293   our sensitivity analysis were quite wide, adding to the strength of the results. The lack of

294   statistically significant effect on outcome despite 30% variation in costs indicates that costs

295   of RRSO, OC or cardiovascular treatment, are less important in influencing overall results.

296   That the model remains largely cost-effective despite probabilities varying widely is

297   reassuring. The reduction in level of impact exerted by different variables at increasing OC

298   risk thresholds is expected and reassuring. It is interesting that the model is highly sensitive to

299   the lower limit of the utility-score for RRSO at all risk levels. This is probably because the

300   standard deviation is large. Hence, there is need for further research on RRSO utility-scores

301   to better understand and improve the precision of its estimate. Of note nearly all published

302   work is on the pre-menopausal population where the impact on quality-of-life is different.

303   Separate utility-scores need to be developed for pre and postmenopausal RRSO.

304

305   The PSA undertaken is recommended by decision making bodies and adds to the robustness

306   of our results.[12] It permits simultaneous variation in probabilities of all parameters to fully

307   characterise model uncertainties and its effect on overall results. That 80-94% of simulations

308   on PSA were cost-effective for the risk thresholds ≥5% reconfirms the health-economic

309   benefit of RRSO at these risk levels for OC prevention.

310

311   Health economic assessments are crucial for determining the appropriateness of resource

312   allocation for cost intensive population-based interventions. Rising health care costs and ever

313 increasing price of new OC treatments/drug therapies in a challenging economic environment

314 further magnify the importance of newer cost-effective preventive strategies. Our findings

315 thus have potentially important implications for clinical practice especially for the individual

316 woman and for reducing the burden of OC. A key next step would be assessment of the

317 acceptability of such a surgical intervention to decrease risk in postmenopausal women aged

318 over 50 with lifetime OC risk of >5-<10%. The increasing availability of panel testing,

319 identification newer moderate penetrance genes and common genetic variants and improved

320 risk prediction models has made it possible to identify a number of women who can fall into

321 this risk category. Tools/decision aids to facilitate understanding of risk and informed consent

322 would need to be developed. Implementation of such an approach will necessitate

323 information dissemination for raising health professional/public awareness and education.

324 All these will have an added cost. Close attention will also need to be paid to developing well

325 defined care and patient referral pathways in co-ordination with general practitioners,

326 geneticists, gynaecologists and commissioners of care, as well as implementation studies for

327 collecting long term outcomes.

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335 **Submission declaration and verification**

336 This work described has not been published previously, it is not under consideration for

337 publication elsewhere, and its publication is approved by all authors and tacitly or explicitly

338 by the responsible authorities where the work was carried out, and that, if accepted, it will not

339 be published elsewhere without the written consent of the copyright-holder.

340

341 Disclaimers

342 UM has a financial interest in Abcodia, Ltd, a company formed to develop academic and

343 commercial development of biomarkers for screening and risk prediction. RL reports

344 personal fees from UCL, during the conduct of the study. The other authors declare no

345 conflict of interest.

346

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349

350 Contribution to authorship

351 RM, UM, RL developed concept and design of the study. RM, RL, UM developed the model.

352 RM, RL, UM, LP were involved in the health-economic and statistical analysis. RM, RL

353 prepared the tables and figures. RM, RL prepared the first draft of the manuscript. All authors

354 critically contributed to and revised the manuscript and approved the final version.

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356

357 **FIGURE LEGENDS**

358 **Figure-1: Decision Model Structure**

359 The upper part of the model structure reflects 'no RRSO' for a given OC risk threshold. The

360 lower part of the model depicts the option of RRSO for the same OC risk threshold. This

361 model is run at each of the different thresholds for OC risk (2%, 4%, 5%, 6%, 8% and

362 10%).Each decision point in the model is a 'node' and each path extending from a node is a

363 decision 'branch'. Each branch represents a mutually exclusive course or outcome. Each

364 decision is given a probability (probabilities used in the model are detailed in Table1)

365 highlighted in a white box along the decision branch. Values for each outcome are calculated.

366 Cancer incidence is estimated by summing the probabilities of pathways ending in ovarian

367 cancer. Final outcomes (blue boxes on the right of the figure) of each path include

368 development of OC, no OC and excess deaths mainly from heart disease (Branch E).

369 OC-Ovarian Cancer; No OC - No Ovarian Cancer developed, RRSO –Risk reducing

370 salpingo-oophorectomy

371

372 **Figure 2: One way Deterministic Sensitivity Analyses**

373 One-way sensitivity analysis (at the 8%, 6%, 5% risk thresholds) for all probabilities, costs

374 and utilities in terms of ICER of RRSO compared to No RRSO at the different ovarian cancer

375 risk thresholds. Y-axis: Incremental cost-effectiveness ratio (ICER): Cost (£) per quality

376 adjusted life year (QALY) (discounted). X-axis: Probability, cost and utility parameters in the

377 model. The model is run at both lower and upper values/limits of the 95% confidence interval

378 or range of all probability parameters described in Table-1/methods; and both lower and

379 upper values/limits of the cost and utility-score parameters given in Table 2. Costs are varied

380 by +/- 30%. Maximum value' represents outcomes for upper limit and 'Minimum value'

381 represents outcomes for lower limit of the parameter.

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

383

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.

394

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

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399 **FIGURE-1 Decision Model Structure**

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405 **Figure-1: Decision Model Structure.**

406 The upper part of the model structure reflects 'no RRSO' for a given OC risk threshold. The lower

407 part of the model depicts the option of RRSO for the same OC risk threshold. This model is run at

408 each of the different thresholds for OC risk (2%, 4%, 5%, 6%, 8% and 10%).Each decision point in the

409 model is a 'node' and each path extending from a node is a decision 'branch'. Each branch

410 represents a mutually exclusive course or outcome. Each decision is given a probability (probabilities

411 used in the model are detailed in Table1) highlighted in a white box along the decision branch.

412 Values for each outcome are calculated. Cancer incidence is estimated by summing the probabilities

413 of pathways ending in ovarian cancer. Final outcomes (blue boxes on the right of the figure) of each

414 path include development of OC, no OC and excess deaths mainly from heart disease (Branch E).

415 OC-Ovarian Cancer; No OC - No Ovarian Cancer developed, RRSO –Risk reducing salpingo-

416 oophorectomy

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

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

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440 **Figure 3: Probabilistic sensitivity analysis**

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446 **Figure-3: Probabilistic sensitivity analysis:** Shows the Cost-effectiveness acceptability curve (for

447 different OC risk thresholds) in which all model parameters/variables are varied simultaneously

448 across their distributions to further explore model uncertainty. X-axis: Incremental cost-

449 effectiveness ratio (ICER) in terms of Cost (£s)/QALY; Y-axis: Proportion of simulations. The results of

450 1000 simulations were plotted on a cost-effectiveness acceptability curve showing the proportion of

451 simulations (Y-axis) that indicated that the intervention was cost-effective at different willingness to

452 pay thresholds (X-axis). The solid red line marks the proportion of simulations found to be cost-

453 effective at the £20,000 threshold used by NICE. 67-94% simulations are cost effective in this

454 analysis.

455

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

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463 **TABLES**

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465 **Table 1: Probabilities of different pathways**

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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, ∞).				

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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

REFERENCES

[1]   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]. In. Lyon, France: International Agency for Research on Cancer; 2013. p. Available from: http://globocan.iarc.fr, accessed on 10/03/2015.

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

[3]   Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, Reding DJ, Greenlee RT, Yokochi LA, Kessel B, Crawford ED, Church TR, Andriole GL, Weissfeld JL, Fouad MN, Chia D, O'Brien B, Ragard LR, Clapp JD, Rathmell JM, Riley TL, Hartge P, Pinsky PF, Zhu CS, Izmirlian G, Kramer BS, Miller AB, Xu JL, Prorok PC, Gohagan JK, Berg CD. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. Jama l2011;305: 2295-303.

[4]   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 l2013;121: 709-16.

[5]   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 l2009;101: 80-7.

[6]   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 l2006;144: 397-406.

[7]   SEER. SEER Cancer Statistics Factsheets: Ovary Cancer. In. Bethesda, MD, USA: National Cancer Institute.; 2014. p. http://seer.cancer.gov/statfacts/html/ovary.html (accessed 10/03/2015).

[8]   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 AC, Chenevix-Trench G. Identification of six new susceptibility loci for invasive epithelial ovarian cancer. Nat Genet l2015;47: 164-71.

[9]   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 l2015.

[10]   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 l2015;24: 671-6.

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

[12]   NICE. Guide to the methods of technology appraisal. In. N1618 ed. London: National Institute for Health and Clinical Excellence (NICE); 2008.

[13]   Curtis L. Unit Costs of Health and Social Care 2011. In. Canterbury, Kent: Personal Social Services Research Unit (PSSRU); 2011.

[14]   Office of National Statistics. Lifetable for females in the UK. In: Office of National Statitics; 2011. p. Office for National Statistics licensed under the Open Government Licence v.1.0. .

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

[16]   Grann VR, Patel PR, Jacobson JS, Warner E, Heitjan DF, Ashby-Thompson M, Hershman DL, Neugut AI. Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. Breast Cancer Res Treat l2011;125: 837-47.

[17]   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 l2009;113: 216-20.

[18]   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.

[19]   Armstrong DK. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. The oncologist l2002;7 Suppl 5: 20-8.

[20]   Yancik R. Ovarian cancer. Age contrasts in incidence, histology, disease stage at diagnosis, and mortality. Cancer l1993;71: 517-23.

[21]   Swart A. Long-term follow-up of women enrolled in a randomized trial of adjuvant chemotherapy for early stage ovarian cancer. In: ASCO Annual Meeting Proceedings (Part I): Journal Clinical Oncology; 2007. p. 18S (June 20 Supplement): 5509.

[22]   NICE. Social value judgements: principles for the development of NICE guidance. In: (NICE) NIfHaCE, editor. 2nd ed: National Institute for Health and Clinical Excellence (NICE); 2008.

[23]   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 l2009;13: iii, ix-xi, 1-61.

[24]   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 l2005;8: 1-2.

[25]   van den Akker-van Marle ME, van Ballegooijen M, van Oortmarssen GJ, Boer R, Habbema JD. Cost-effectiveness of cervical cancer screening: comparison of screening policies. J Natl Cancer Inst l2002;94: 193-204.

[26]   Rivera CM, Grossardt BR, Rhodes DJ, Brown RD, Jr., Roger VL, Melton LJ, 3rd, Rocca WA. Increased cardiovascular mortality after early bilateral oophorectomy. Menopause l2009;16: 15-23.

[27]   Rivera CM, Grossardt BR, Rhodes DJ, Rocca WA. Increased mortality for neurological and mental diseases following early bilateral oophorectomy. Neuroepidemiology l2009;33: 32-40.

[28]   Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol l2007;25: 1329-33.

[29]   Barrow E, Hill J, Evans DG. Cancer risk in Lynch Syndrome. Fam Cancer l2013;12: 229-40.

[30]   Li K, Husing A, Fortner RT, Tjonneland A, Hansen L, Dossus L, Chang-Claude J, Bergmann M, Steffen A, Bamia C, Trichopoulos D, Trichopoulou A, Palli D, Mattiello A, Agnoli C, Tumino R, Onland-Moret NC, Peeters PH, Bueno-de-Mesquita HB, Gram IT, Weiderpass E, Sanchez-Cantalejo E, Chirlaque MD, Duell EJ, Ardanaz E, Idahl A, Lundin E, Khaw KT, Travis RC, Merritt MA, Gunter MJ, Riboli E, Ferrari P, Terry K, Cramer D, Kaaks R. An epidemiologic risk prediction model for ovarian cancer in Europe: the EPIC study. Br J Cancer l2015;112 Suppl: 1257-65.

[31]   Pfeiffer RM, Park Y, Kreimer AR, Lacey JV, Jr., Pee D, Greenlee RT, Buys SS, Hollenbeck A, Rosner B, Gail MH, Hartge P. Risk prediction for breast, endometrial, and ovarian cancer in white women aged 50 y or older: derivation and validation from population-based cohort studies. PLoS Med l2013;10: e1001492.

[32]   Jacoby VL, Grady D, Wactawski-Wende J, Manson JE, Allison MA, Kuppermann M, Sarto GE, Robbins J, Phillips L, Martin LW, O'Sullivan MJ, Jackson R, Rodabough RJ, Stefanick ML. Oophorectomy vs ovarian conservation with hysterectomy: cardiovascular disease, hip fracture, and cancer in the Women's Health Initiative Observational Study. Arch Intern Med l2011;171: 760-8.

[33]   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 l2011;20: 900-11.

[34]   Midgette AS, Baron JA. Cigarette smoking and the risk of natural menopause. Epidemiology l1990;1: 474-80.

[35]   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 l2010;103: 1755-9.

[36]   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 l2002;346: 1609-15.

[37]   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 l2011;118: 814-24.

[38]   Department of Health PbR Team. NHS 2010-11 reference costs publication. In: Department of Health; 2011.

[39]   NICE. Ovarian cancer: the recognition and initial management of ovarian cancer. In. London: National Institute for Health and Clinical Excellence (NICE); 2011.

[40]   NAO. End of life care. In: Burr TCaAG, editor. London: National Audit Office (NAO), House of Commons; 2008.