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Targeted surgical prevention of epithelial ovarian cancer is cost effective and saves money in BRCA mutation carrying family members of women with epithelial ovarian cancer. A Canadian model☆

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HIGHLIGHTS

- Cascade testing of patients for BRCA germline mutation and if positive their family members enables surgical prevention.
- In this model, targeted testing/prevention prevented 59 of 2800 cases per year in Canada and was cost effective/saved money.
- Cost effectiveness/budget savings were most influenced by testing/surgical rates and the cost of treating ovarian cancer.

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ABSTRACT

Objective. Survival but not cure rates have improved for epithelial ovarian cancer (EOC), demonstrating the need for effective prevention. Targeted prevention in BRCA carriers by risk reducing surgery (RRS) prevents 80% of cases but incurs additional up-front costs, compensated for by the potential for long term savings from treatment avoidance. Does prevention represent value for money? In the absence of long-term data from prospective trials, determining the cost effectiveness of a prevention strategy requires economic modelling.

Methods. A patient level simulation was developed comparing outcomes between two groups, using Canadian data. Group 1: no mutation testing with treatment if EOC developed. Group 2: cascade testing (index patient BRCA tested and the first and second-degree relatives tested if index patient or first-degree relative respectively were positive) with RRS in carriers. End points were Incremental Cost-Effectiveness Ratio (ICER) and budget impact.

Results. 2786 women with EOC (1 year incidence) had 766 first and 207 second-degree female relatives. BRCA mutations were present in 390 index cases, 366 first and 49 second-degree relatives. With 100% RRS uptake, 59 EOC were prevented and testing dominated no testing (more effective and less costly; ICER −$8919). The total cost saving over 50 years was $2,904,486 (cost saving of $9,660,381 in treatment costs versus increased cost from cascade testing/RRS of $6,755,895). At a threshold of $100,000 per QALY, prevention was cost effective in all modelled scenarios.

Conclusions. Targeted prevention in BRCA mutation carriers not only prevents EOC but is cost-effective compared to treating EOC if it develops.

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1. Introduction

Epithelial ovarian carcinoma (EOC) is a term that describes a group of biologically different cancers [1]. In the USA and Canada there are 22,240 and 2800 new cases per year with 14,070 and 1800 deaths respectively [2,3]. Canadian 5 year overall survival is 44%, with most deaths occurring within five years. The subsequent 5 year survival rate is 84% [3]. Survival has improved with modern therapy but cure remains unlikely: 10 year survival of 25% if stage III and under 10% if stage IV [4,5]. Given these outcomes, prevention or early detection via screening are important. As yet screening is ineffective [6]. Prevention by risk reducing surgery (RRS) works. There are 2 options. (1) "Opportunistic salpingectomy" in women undergoing pelvic/abdominal surgery for

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another reason and (2) Targeted RRS in the high risk i.e. BRCA mutation carriers, which can potentially prevent 78 to 88% of cases with a compounded value of 81% in a recent meta-analysis [6–8].

Inherited BRCA mutations occur in 15% of women with EOC: BRCA1 representing 60% and BRCA2 40% [9,10]. As inherited mutations can be present in the absence of high risk predictors, current guidelines recommend testing of all women with either high-grade EOC or any type with the exception of low grade mucinous [11–13]. BRCA mutations may truly only occur in the high-grade serous [6]. However, it makes pragmatic sense to continue testing all patients as diagnostic concurrence between pathologists is not 100% and there are reports of mutations in a few non-serous cases [14]. If the index case is BRCA germline mutated, then her first degree family should be tested and then if that individual is positive then the second-degree family members (cascade testing). The future risk of developing EOC by age 80 for a carrier is 50% (range 35–60%) if BRCA1 and 12% (range 12–25%) if BRCA2 [15–17].

In our cost-constrained health care environment, an effective treatment may not be instituted for economic reasons. Two economic analyses of "value for money" can be used. (1) The Incremental Cost Effectiveness Ratio (ICER) provides an estimate of the value for money of two competing options. It is derived from the formula $\Delta C/\Delta E$ where ΔC is the change in cost from using strategy A versus B and ΔE similarly is the efficacy change, most often reported as Quality Adjusted Life Years (QALYs) gained i.e. years of life gained modified negatively by any decrease in its quality due to side effects etc. In N. America, an ICER value of $50,000–$100,000 is considered to represent "value for money" due to sufficient improved health benefits despite increased costs [18,19]. In the UK, the value chosen is lower, £20–30,000 [20]. A treatment/strategy that both costs less and has superior efficacy with a resultant negative ICER values, is called "dominant". The ICER allows for treatment rankings to better inform budgetary decision making. (2) Budget Impact analysis considers the actual costs of providing the service which is relevant to the "payers" ability to pay for it. In the ongoing absence of randomized trials or long term cohort data comparing targeted prevention to treatment, decision analysis modelling using inputs based upon current data can be used to compare strategies from an economic stand-point.

The objective of this study was to evaluate whether such cascade testing with resulting targeted RRS in as yet unaffected carriers represented value for money compared to non-testing/no RRS with treatment of EOC if it developed. The hypothesis was that this BRCA testing/RRS prevention paradigm would be both cost-effective and result in budgetary savings.

2. Methods

The model used in this study was based on an UK economic model of BRCA testing/prevention, described previously [21]. A Canadian healthcare perspective with a 50 year time horizon, all cause mortality and 1.5% discounting was used (i.e. future costs and health benefits are reduced) [22]. If Canadian data was unavailable, data from similar health care systems were used. The model consisted of a patient level simulation developed in Microsoft Excel with yearly updates of their status during their lifespan. An index population of 2786 index patients was assumed, based upon the number of new cases per year in Canada (3). Two strategies were then compared in the first and second degree family members of these index cases: 1) the control arm in which they did not have screening for an inherited BRCA mutation and were treated if EOC developed and 2) the experimental cohort in which there was cascade testing followed by RRS in mutation carriers (second degree relatives only tested if the first-degree relative had a mutation). RRS consisted of laparoscopic bilateral salpingo-oophorectomy. The end points were all cause survival, costs and number of EOC cases avoided. The simulated population of female family members could be in one of 3 health states at the beginning of each annual cycle: 1) no cancer 2) developed EOC and 3) dead. If cured and alive they transitioned from state 2 to state 1. The model does not include the outcomes of the index patients, either in terms of their ovarian cancer or subsequent development of breast cancer. All carriers undergoing RRS were assumed not to have incident cancer: the rate of invasive cancer in a recent study with comprehensive adnexal sampling was <1% [23]. Endometrial cancer outcomes were not included in the model as its occurrence/outcome was assumed to be the same in both cohorts as hysterectomy was not part of RRS.

The following baseline assumptions were used (Table 1 and Supplemental Tables 1–3).

1) 12.46% of the index patients, mean age 50, will have an inherited BRCA mutation, of which 61.58% will be BRCA1 and 38.42 BRCA2 [24,25]. 2) Average number and age of family members are outlined in Supplemental Table 1 [26,27]. 3) The probability of BRCA mutation is 0.5 and 0.25 in first and second degree family members (autosomal dominant inheritance).

4) If the index case had a germline mutation, all first degree female family members in the prevention arm underwent BRCA testing followed by testing of the second degree female relatives if the first-degree relative was positive. 5) All mutation carriers then proceeded to RRS by age of 40 for BRCA1 and 40 to 50 for BRCA2 [13,14]. If they were older than this on model entry they were assumed to have RRS within that year. 6) The risk reduction for developing EOC (secondary to RRS) by age 80 was 84% for BRCA1 and 88% for BRCA2 [6–8,28,29]. Actual number of cases of EOC prevented will lessen with increasing carrier age due to the decreasing risk for future EOC [30]. 7) The overall mortality rate for EOC used was 50% (3). This is a conservative assumption as most BRCA derived EOC are high grade and advanced with much lower survival rates [4,5,31,32]. 8) Survival without relapse for 5 years equates to cure [3]. 9) Sensitivity and specificity of BRCA gene testing was 98%. 10) First and second degree relatives did not have EOC at model entry. 11) RRS was only carried out in mutation carriers. 12) Breast cancer development was not included in the model. 13) There was no difference in rates of cancer development, outcomes or costs for relatives who did not carry a mutation, except for the cost of mutation testing. 14) Only average costs and utility values were used as there is no individualized, real world data.

Model outcomes were expressed as number of cancer cases and deaths, total costs and total QALYs (Quality Adjusted Life Years). A QALY is a measure of life years gained multiplied negatively by any detriment in the quality of that life e.g. l year of life gained but at an 80%

Table 1
Costs included in the model [32–35].

Cost component	Cost	Source
BRCA test	$675	Estimate
Genetic counselling	$300	Estimate
Bilateral salpingo-oophorectomy	$9080	Ontario Case Costing Initiative
Ovarian cancer treatment, with surgery	$40,420	Estimate based on an 'average' cost of treating ovarian cancer
Ovarian cancer treatment, without surgery	$34,412	Estimate based on an 'average' cost of treating ovarian cancer
Ovarian cancer palliative care	$14,687	Hollander et al., inflated to 2016 costs
All-cause mortality palliative care	$14,687	

Table 2
Cost-effectiveness results (discounted).

Base-case – 100% elect for surgery							
	Δ EOC cases	Δ Deaths	Total costs	Δ costs	Total QALYs	Δ QALYs	ICER
No BRCA testing	–	–	$136,767,186	–	9626	–	–
BRCA testing	−59	−25	$133,862,700	−$2,904,486	9951	+326	−$8919

EOC: Epithelial Ovarian Cancer; ICER: Incremental Cost Effectiveness Ratio.
QALYs: Quality Adjusted Life Years; Δ: change in the variable.

quality has a QALY of 0.8. Total QALYs for each patient, representing the number of years of life gained modified by any loss of quality, were calculated based on age at model entry, cancer status, survival duration and utility value reflecting the quality of that life.

Cost (Canadian dollars) and utility values are provided in Table 1 and Supplemental Table 3 [33–36]. Ovarian cancer chemotherapy costs were applied annually due to the high likelihood of retreatment. Palliative care costs were applied in the subject's last year of life. Genetic counselling consisted of one pretest session for all index cases and their family members with a posttest session if a mutation was discovered. In terms of concordance with other jurisdictions, Canadian costs match those in Australia, with its similar health care system [31].

All inputs/costs used in the model were chosen to represent the most conservative end of the range in order to deliberately underestimate potential benefits.

The inputs/assumptions in the model are based on the best available data. However any variation in the values could impact the ICER and budget impact. Accordingly one- way sensitivity analysis was performed in which the baseline inputs were modified to give a range of potential values. Probabilistic Sensitivity Analysis (PSA) was also carried out to assess the impact of varying all inputs simultaneously.

3. Results

In our model there were 2786 index patients, 766 first degree and 207 second degree female relatives. 390 index cases, 366 first degree and 49 second degree relatives had BRCA mutations. Subsequent RRS in all the carriers prevented 59 EOC (91 cases if no cascade testing/RRS and 32 cases with cascade testing/RRS), with 25 fewer all cause deaths.

ICER values and costs are summarized in Tables 2 and 3. Over a 50 year time horizon the base-case ICER (100% testing/RRS) using all-cause mortality was −$8919 per QALY gained i.e. prevention was a dominant strategy. The total 50 year cost within the BRCA testing/RRS arm was $133,862,700 and in the control arm was $136,767,186 i.e. a saving of $2,904,486. With the testing/RRS strategy, there was a cost saving of $9,660,381 from having to treat less EOC but this was countered by the increased cost of up-front counselling, BRCA testing and RRS of $6,755,895.

This base case is for the ideal situation with 100% rates of cascade testing/RRS, unlikely achievable in the real world. Scenario analysis therefore was conducted to vary the proportion receiving RRS in 10% increments from 10 to 90%. The resulting ICERs were dominant at RRS levels of ≥40% and cost effective (ICER < $50,000) at 20% and 30% levels (Table 4). The number of lives saved (all cause mortality over 50 years) at RRS levels of 100%, 50% and 20% were 25, 13 and 7 respectively.

Testing was cost-effective in all 23 one-way scenarios and dominant in 18. Only at RSS rates of 10–30%, age at RRS of >60 years, and an EOC treatment cost of $20,000 was cost effectiveness, which was maintained, no longer dominant (Tables 4 and 5). Cost-effectiveness decreased as the age of the index case was reduced and as the age at RRS increased. The cost of BRCA testing had a minimal impact. Changing the cost of treating EOC had a marked impact. Increasing lifetime non-surgical costs to $40,000, $60,000 and $80,000 resulted in increasing cost-effectiveness with ICERs of −$13,490, −$29,850 and −$46,210 respectively and budget savings of $4,392,990, $9,720,342 and $15,047,695.

To account for uncertainty, a Probabilistic Sensitivity Analysis with 4000 simulations was carried out. All were in the north-east or south-east quadrants of the cost-effectiveness plane, indicating that testing was more effective. The probability that testing was cost-effective vs no testing was 100% using an ICER of <$100,000.

4. Discussion

Most women with EOC die from it, especially so if it is high grade [2–5]. Consequently, affordable, effective prevention is needed. Targeted prevention using BRCA status provides such an opportunity. Cascade germline BRCA testing of index patients with subsequent testing of family members of positive index cases enables oncologists to target a high risk population for RRS (bilateral salpingo-oophorectomy). Such targeted, preventative surgery is estimated to prevent up to 88% of EOC [6–8].

The costs of an intervention are important to its implementation feasibility as all health care systems have monetary constraints. Our study evaluated by modelling, in the ongoing absence of real world data, the economics/value for money of this prevention strategy. Based upon a single year of testing/RRS in Canada (with 100% uptake), 59 fewer cases of EOC would develop with 25 fewer all-cause deaths over 50 years at a cost saving of $2,904,486. The ICER (a measure of relative value for money) showed that testing/RRS dominated no testing (−$8991 per QALY) i.e. it cost less and was more effective. The model inputs, costs of treatment and outcomes used were kept deliberately conservative so as to underestimate the potential economic benefits of prevention, cancers avoided and lives saved. The prevention paradigm resulted in increased up-front costs ($6,755,895) due to increased rates of genetic counselling, BRCA testing and RRS. Over the longer term there was a significant cost reduction from treatment avoidance

Table 3
Base-case costs by category.

Outcome	Index patients			Family members			Overall
	No BRCA testing	BRCA testing	Difference	No BRCA testing	BRCA testing	Difference	Difference
Base-case costs							
Testing and counselling	$0	$2,010,750	$2,010,750	$0	$1,718,664	$1,718,664	$3,729,414
RRS	$0	$0	$0	$0	$3,026,481	$3,026,481	$3,026,481
Cancer treatment	$110,682,242	$110,682,242	$0	$17,245,196	$7,835,502	$9,409,695	−$9,409,695
Palliative care	$5,761,181	$5,761,181	$0	$3,078,566	$2,827,880	−$250,686	−$250,686
Total	$116,443,423	$118,454,173	$2,010,750	$20,323,763	$15,408,527	−$4,915,236	−$2,904,486

RRS: Risk Reducing Surgery.

Table 4
Results of the one-way scenario sensitivity analyses (1).

Scenario	Testing vs no testing				ICER
	Costs	Δ QALYs	EOC cases	Deaths	
Base-case	−$2,904,486	+326	−59	−25	−$8919
RRS uptake: 10%	$3,216,761	+39	−7	−4	$81,747
RRS uptake: 20%	$1,808,729	+82	−16	−7	$22,177
RRS uptake: 30%	$1,259,005	+125	−20	−9	$10,039
RRS uptake: 40%	−$290,457	+185	−29	−12	−$1571
RRS uptake: 50%	−$336,471	+189	−31	−13	−$1776
RRS uptake: 60%	−$783,213	+208	−36	−16	−$3764
RRS uptake: 70%	−$1,102,977	+240	−41	−19	−$4603
RRS uptake: 80%	−$1,330,544	+253	−45	−21	−$5267
RRS uptake: 90%	−$2,129,632	+301	−53	−24	−$7065
Age of RRBSO 35 years	−$3,895,671	+401	−65	−31	−$9705
Age of RRBSO 50 years	−$1,782,442	+236	−50	−16	−$7553
Age of RRBSO 60 years	$2,104,786	+93	−25	−6	$22,738
Mean age of index case 40 years	−$1,469,253	+331	−63	−19	−$4441
Mean age of index case 60 years	−$1,728,984	+258	−56	−27	−$6693

RRS: Risk Reducing Surgery; ICER: Incremental Cost Effectiveness Ratio.
Δ QALYs: change in Quality Adjusted Life Years (+value is improved outcome number).

secondary to prevention (discounted saving of $9,660,3819). These cost savings will only increase as the cost of treatment goes up [37,38]. EOC has been inexpensive to treat, despite multiple lines of chemotherapy, as the drugs are relatively cheap. The introduction of VEGF inhibitors and PARP inhibitors with their high list prices has changed that. The ICER for a PARP inhibitor, list price $9000/month, when used optimally as maintenance post second line chemotherapy was $231,567 [39]. In our model with 100% testing/RRS, the cost savings increased from $934,363 to $15,047,695 as the life-time cost of non-surgical treatment increased from $20,000 to $80,000. The indirect costs to the family/society from lost productivity secondary to EOC, which are similar to the direct costs, were not included in the model i.e. further underestimating the true cost-savings [37].

In practice, uptake rates of all the components of prevention (cascade testing and RRS in carriers) are low [6,39]. A minority of index patients are tested (<20%), unless treated at motivated centres [6]. Rates of testing of first-degree female members range from 15 to 81%, with subsequent rates of RRS of 27–78% [40]. While the cost-savings decreased and ICER increased as RRS rates fell in our model, budget savings were still achieved until RRS rates fell below 30%. However, testing remained cost-effective at the N American threshold of $100,000 per QALY until RRS rates fell below 7%.

All economic models are limited by potential biases arising from any inaccuracies in the inputs used. To allow for this we carried out one-way scenarios varying individual input values and probabilistic sensitivity analyses where all inputs were varied and the overall conclusions remained unchanged.

There are negative consequences associated with BRCA testing and RRS. All abdominal surgery has the potential for morbidity and mortality. There is the time needed to recover from surgery with its potential lost income. There are also the adverse consequences of earlier, rapid onset menopause [6,40]. We were unable to model these costs because reliable estimates are unavailable. Knowledge of BRCA mutation status may have adverse psychological consequences but again with no quantifiable cost data. This is captured to some extent in the model as diminished quality of life is factored in to the efficacy analysis.

The model was designed to include a broad population including mothers of index cases and elderly siblings. The inclusion of these family members adversely impacts cost-effectiveness and budget impact as the risk of developing EOC falls with increasing age even in mutation carriers. Targeted prevention may be better applied to a more limited population.

Our model was set up to understate prevention's benefit. 1) Mortality within the model was measured as all-cause mortality over a 50-year timeframe, rather than EOC-specific mortality, which understates the value of testing/prevention as the number of lives saved from EOC is under-estimated. 2) The biggest impact on the results came from increasing treatment costs. 3) A 50% mortality rate with EOC was utilized to simplify the modelling. It is a reasonable, though conservative estimate which takes into consideration the high cure rates of those with earlier stage disease. However the great majority (70%) are advanced at diagnosis with curability rates below 20%. 4) Sensitivity and specificity of BRCA testing was set at 98% in the model. However, with Next Generation Sequencing, updated bioinformatics, manual review of abnormalities and confirmatory Sanger sequencing, false positive results are less than this in practice. 5) Discounting of costs and utilities at 1.5% as per Canadian guidelines will result in the costs of treatment being discounted as compared to prevention's costs (as prevention costs are incurred up front, treatment's cost is later).

As far as we are aware, there is only one previous cost-effectiveness analysis of prevention in a similar population [21]. This also demonstrated cost-effectiveness with an ICER of £4339 per QALY gained, although testing incurred additional costs compared with no testing. Both this UK analysis and the current analysis used the same model structure and techniques but with certain key differences. The UK model considered both future EOC and breast cancer for family members of index patients with EOC, with bilateral salpingo-oophorectomy (BSO) and risk-reducing mastectomy offered to BRCA carriers. Rates of BSO were lower at 88% than in our model's base case and the costs of cancer treatment were substantially lower (£15,185 for EOC). The current Canadian model did not include breast cancer prevention, inclusion of which would have resulted in increased testing/RRS costs but with better efficacy i.e. increased QALYs associated with avoidance of breast cancer.

In conclusion, most women with EOC have high grade histologies which are often widespread and rarely curable. It is within such patients that inherited BRCA mutations are commonly found. These inheritable mutations present an opportunity for targeted prevention by cascade BRCA testing with subsequent risk reducing surgery. The model presented in this paper demonstrates that this approach is effective, offering economic and clinical value via overall life-time cost savings and avoidance of EOC with resulting mortality reduction. The model demonstrates that to get the greatest patient and societal value from

Table 5
Results of the one-way scenario sensitivity analyses (2).

Scenario	Testing vs no testing				ICER
	Costs	Δ QALYS	EOC cases	Deaths	
Ovarian cancer cost (without surgery) $20,000	$934,363	+326	−59	−25	$2869
Ovarian cancer cost (without surgery) $40,000	−$4,392,990	+326	−59	−25	−$13,490
Ovarian cancer cost (without surgery) $50,000	−$7,056,666	+326	−59	−25	−$21,670
Ovarian cancer cost (without surgery) $60,000	−$9,720,342	+326	−59	−25	−$29,850
Ovarian cancer cost (without surgery) $80,000	−$15,047,695	+326	−59	−25	−$46,210
BRCA test cost: $250	−$3,559,763	+326	−59	−25	−$10,932
BRCA test cost: $1600	−$1,478,294	+326	−59	−25	−$4540

Δ QALY: change in Quality Life Years (+value is improved outcome).
EOC: Epithelial Ovarian Cancer, ICER: Incremental Cost Effectiveness Ratio.

prevention, the highest possible rates of BRCA testing (index patients and their female family members) and subsequent RRS in carriers are needed. Unfortunately in practice we are far from these requirements. Achieving recognition of the value of targeted prevention and its successful implementation will need a concerted effort from all the stakeholders involved i.e. medical practitioners, patients, advocacy groups and especially the payers, who will need to recognize that the long term cost savings far outweigh the initial increase in costs.

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Conflict of interest statement

PH has no conflict, HM and MD are employees of AstraZeneca, MD has shares in AstraZeneca, and AE's employer has contracts with AstraZeneca.

Author contributions

All authors were involved in the conception and design of the study. AE performed the statistical analysis. All authors were involved in the data interpretation and review. PH wrote the first version of the manuscript and all authors participated in the revisions and final approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.01.018.

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