Methods used in Economic Evaluations of Testing and Diagnosis for Ovarian Cancer: a systematic review

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ABSTRACT

Objective: There are multiple tests available which can help diagnose ovarian cancer, and the cost effective analysis of these diagnostic interventions is essential for making well informed decisions regarding resource allocation. There are multiple factors that can impact on the conclusions drawn from economic evaluations including test accuracy, the impact of the testing pathway on patient costs and outcomes, and delays along the ovarian cancer test-treat pathway. The objective of this study was to evaluate how test accuracy, the choice of perspective, and delays along the testing and diagnostic pathway have been incorporated in economic evaluations of testing for ovarian cancer.

Method: A systematic review of published literature was undertaken to identify economic evaluations (e.g. cost-effectiveness, cost-utility analysis) focused on testing and diagnosis for ovarian cancer.

Results: Seven studies met the inclusion criteria. Six studies incorporated test accuracy and its impact on patients to some extent. Four studies adopted a societal perspective, but only one considered the costs incurred by patients on the testing and diagnosis pathway. Where delays on the testing pathway were incorporated into the analysis, these were frequently due to false negative test results leading to delays in patients accessing treatment. Any anxiety that patients might experience as a result of a positive test was not considered in these studies.

Conclusion: The impact on patients of receiving a positive test in terms of anxiety, and the costs incurred by patients having to attend for testing and diagnosis are rarely considered. Delays along the testing and diagnosis pathway can have a major effect on patient outcomes, and it is important that these are acknowledged in economic evaluations focused on testing. Future economic analysis should incorporate these key determinants in order that diagnostic tests for ovarian cancer can be robustly evaluated.

Key Words: Ovarian cancer; systematic review; economic evaluation; diagnostic testing; patient perspective

INTRODUCTION

In the United States ovarian cancer is the fourth highest cause of cancer death amongst women [1]. Most patients with ovarian cancer are diagnosed at an advanced stage, reflecting the challenges with making a diagnosis in a condition that presents with nonspecific symptoms. Symptom triggered testing with biomarkers (cancer antigen) CA125 and sequential ultrasound has recently been recommended by US and UK healthcare systems [2, 3].

Delays in testing women with ovarian cancer can impact on patient outcomes. Women with ovarian cancer may have symptoms for at least six months before the actual diagnosis of the disease, and given its nonspecific symptoms, may be treated initially for other conditions [4, 5]. Outcomes can be affected by delays in referral from primary care (family practitioners), systems delays in hospitals, and inadequate triage to an appropriate gynecological oncologist [4, 6]. Incisive Health-Cancer Research UK [7] add that if these delays can be minimized and earlier diagnosis realized then this can have a positive impact on cost and patient survival. Approximately 36% of women subsequently diagnosed with ovarian cancer present to a general practitioner with symptoms three or more times prior to diagnosis [8]. In the UK the mean time from first symptoms to first presentation is 39 days and the mean time from first presentation to diagnosis is 21 days [9]. Patients with ovarian cancer correctly triaged into cancer centers for surgery by gynecological oncologists have better outcomes than those treated by gynecologists or general surgeons [10]. Patients with benign ovarian masses may be considered for laparoscopic surgery or for fertility preserving surgery.

Test accuracy which incorporates the sensitivity and specificity of a test can also impact on patient outcomes. If a test has a low sensitivity, then women with ovarian cancer may be incorrectly diagnosed as being disease free, while conversely, a low specificity will lead to patients being incorrectly diagnosed as having the disease, and thus being exposed to unnecessary, unpleasant, and expensive treatment.

Resources allocated to health care are becoming increasingly scarce and consequently decision makers have to make more and more difficult decisions regarding the allocation of these resources [11]. To aid this process an economic evaluation is often utilized, which is a comparative analysis of alternative courses of action in terms of cost and consequences [12]. An economic evaluation can take the form of a cost-effectiveness analysis (CEA), cost-benefit analysis (CBA), or a cost-utility analysis (CUA), each of which differs depending on the outcome used to measure the consequences of an intervention. A CEA uses outcomes in natural units, e.g. cases detected, life years gained, a CBA analysis measures the consequences in monetary units, and a CUA uses the

outcome measure of the quality adjusted life year (QALY). Where one QALY is defined as one year lived in perfect health and is a useful measure since it can be used to make comparisons between interventions across different areas of health.

The National Institute for Health and Care Excellence (NICE) a non-departmental public body which provides national guidance advice in England to improve health and social care, has guidance on the implementation of economic evaluations [13]. While this guidance is general and not specific to economic evaluations focused on medical testing, it does include points about defining the decision problem and the comparators, and the methods used in the analysis. One such point is the perspective adopted in an economic evaluation, which informs the costs that should be incorporated in an analysis. NICE adopts a public sector perspective (including the NHS and personal social services, or local government), if this is able to incorporate all major costs and benefits. However, the perspective is flexible, and a societal perspective might be used where appropriate which means that the costs incurred by the wider society including social care givers and patients can also be included. The perspective is important so that like-for-like comparisons can be made between the results obtained from different economic evaluations.

The issues of test inaccuracy, delays on the testing and treatment pathway, and the costs incurred by patients, can potentially have strong ramifications for patient outcomes, and are factors that may have an influence on the results obtained from economic modeling in this setting. The objective of this systematic review was to examine the methods used in economic evaluations that are focused on testing and diagnosis for ovarian cancer, and to assess whether these factors have been incorporated in previous studies.

Materials and Methods

Inclusion Criteria

With the focus being on papers that considered screening or diagnostic testing that resulted in a diagnosis for ovarian cancer, the inclusion/exclusion criteria for studies to be included in this review are shown in Table 1.

Search Strategy

The following electronic databases were searched: MEDLINE; EMBASE; EconLit; CINAHL; NHS Economic Evaluation Database (NHS EED); Cochrane Library; and Health Economic Evaluation Database (HEED). (For the search strategies, see Appendix). While it is acknowledged that NHS EED stopped being updated in March 2015, it is still an excellent source of economic evaluations and thus could not be reasonably overlooked.

Selection of studies

Initial screening of the studies based on their title and abstract based on the population, intervention, comparator, outcome, and study design (PICOS) criteria [14] was conducted to exclude references that were irrelevant to the research topic (Table 1). References were categorized into the groups listed below, which were used to help communication between authors when selecting the final studies for the review.

A Study reports an economic evaluation on testing and diagnosis focused on ovarian cancer

B Study reports an economic evaluation focused on ovarian cancer, but it is unclear whether it is related to testing and diagnosis

C Study is focused on testing and diagnosis for ovarian cancer, but unclear whether it is an economic evaluation

D Generally unsure about the contents

E Study is focused on testing and diagnosis for ovarian cancer, but it is not an economic evaluation

F Study is focused on ovarian cancer but testing and diagnosis is not considered

G Not ovarian cancer related

Papers in groups A-D were considered worthy of further examination, and so the full text for these studies was obtained. Papers that subsequently met the inclusion criteria were included in the final

review. As the focus of this review was on the methods used, none of the studies were rejected for reasons of quality

Results

Search Results

The searches were conducted in November 2014 and led to 2,489 articles being identified. There were 313 duplicates which were removed from the total number of articles for screening. The remaining 2,176 articles were screened based on their titles, abstracts and keywords and placed in one of the 7 categories. Studies in categories A-D (112) were taken forward to check against inclusion/exclusion criteria. Seven studies were identified that met the inclusion criteria (Figure 1).

General Study Characteristics

The seven studies were published between 1997 and 2012, and were all based in the United States. Two studies examined genetic testing for BRCA [15, 16] and four papers considered various combinations of CA125 and transvaginal ultrasound [17-20]. Havrilesky et al [1] did not 'evaluate a specific existing test, but [explored] the impact of various screening intervals, screening strategies, test characteristics and costs, on their potential clinical utility and cost-effectiveness' (p.181).

There were 4 studies that considered screening of the general population, with the remainder focused on monitoring or diagnostic testing amongst patients from high risk groups. Two studies utilized micro-simulation models [17, 19], three employed a Markov model [1, 15, 18] and two used a decision tree approach [16, 20, 21]. Four of the studies were CEA and three were CUA. Four adopted a societal perspective, and three used a healthcare provider perspective (see Table 2).

How are the factors that impact on patients as a result of test inaccuracy incorporated into these studies?

Amongst the seven studies only one did not incorporate test accuracy into the analysis [16]. Only one study considered the impact on the quality of life of patients of receiving a test result [15]. Holland et al., [15] incorporated a reduction in the utility value as a result of a positive diagnosis and a one-time increase in the first cycle as a result of a negative result, in this case patient specific costs were incorporated however productivity losses were not. This meant that the impact on patients of false positive and false negative was incorporated in the analysis both in terms of quality of life, and the costs incurred by patients.

Havrilesky et al., [1] incorporated test accuracy into their study, and conducted extensive sensitivity analysis across a range of sensitivity and specificity values as part of analysis to identify the optimum test characteristics of a hypothetical screening test for ovarian cancer. In their study, following a false positive test it was assumed that a quarter of patients would undergo benign bilateral oophorectomy, with those not subjected to oophorectomy re-entering the well state. In this case false positive test results were assigned an additional cost due to further diagnostic testing. 'Following a false negative test, individuals would experience disease progression, remain in the same disease stage, or have their disease detected clinically' (p.182). However as the authors acknowledge, as indirect costs of screening or treatment, such as lost wages and caregiver costs were not incorporated into the analysis, the frequency of false positive results may overestimate the value of screening. Moreover the impact of a false positive test on patient quality of life was also not considered.

A typical approach in this setting is to assume that a false positive test leads to unnecessary surgery for patients. In addition to Havrilesky et al [1] described above, this approach was also utilised in the study by Drescher et al., [17] who assumed that a false positive screen necessitates laparoscopic bilateral salpingo-oophorectomy even in the absence of epithelial ovarian cancer; Kwon et al., [18] who assumed that an abnormal screen (including false positives) leads to laparatomy, prophylactic hysterectomy with bilateral salpingo-oophorectomy; and Yang et al., [20] who assumed that a false positive test potentially results in an unnecessary hysterectomy and bilateral oophorectomy. While in some cases the impact of receiving surgery on quality of life was considered in the analysis (e.g. Kwon et al., [18]), the impact of receiving a positive test result itself (either true or false positive) on quality of life was not incorporated in any of these studies.

Interestingly Drescher et al., [17] assumed that a positive screen necessitates laparoscopic bilateral salpingo-oophorectomy even in the absence of epithelial ovarian cancer, and consequently in their model, the surgical evaluation of false positive screens could potentially prevent epithelial ovarian cancer in patients that were destined to develop it in the future. This meant that when the authors explored the impact on cost effectiveness of reducing the specificity of transvaginal sonography, this resulted in more false positive test results, and led to a reduction in mortality and improved cost effectiveness. However in this study the impact of a (false) positive test on patient quality of life was not considered. Finally Urban et al., [19] incorporated the impact of false positive tests by assuming a 0.001 probability of death following a laparoscopy among false positives.

Where false negative tests were incorporated into the analyses, these were assumed to lead to delays in patients being identified with disease [15, 18-20]. For example Kwon et al., [18] considered

annual screening with endometrial biopsy, CA 125, and transvaginal ultrasound amongst patients with Lynch syndrome and assumed that when endometrial or ovarian cancer was missed during a screen or test (false negative), then the diagnosis would be made within the next year.

How are the costs incurred by patients on the testing and diagnosis pathway incorporated into these studies?

Three of the studies adopted a healthcare provider perspective [1, 16, 17] which meant that any costs incurred by the patients were not incorporated in the analyses. Four studies utilized a societal perspective however in two of these studies only the costs related to items that would be supplied by a healthcare provider were included [19, 20]. Holland et al., [15] adopted a societal perspective and incorporated the out of pocket costs for ongoing care with and without cancer. However costs incurred by patients along the testing pathway such as travel costs and lost wages were not considered. Only one study considered the costs incurred by patients as a result of screening. Kwon et al., [18] allocated a single patient cost in their analysis for each screen, with these patient costs including the time spent on consultation, transportation to and from a clinic, and time off work (approximately 0.5 days for each screen, and 6 weeks for surgery).

How are the impacts on patients of delays on testing and diagnosis pathways incorporated into these studies?

The most common delay on the testing and diagnosis pathway described in these studies was the delay in getting eligible patients into treatment. This was described in four studies as the result of a false negative test [15, 18-20], and in one study as a result of varying the interval between screens [17]. In all cases this was assumed to lead to unnecessary disease progression amongst the patients. None of the studies considered the possibility that there might be a delay in getting patients into treatment following a positive test result, and it seems to be an unwritten assumption in all these studies that a test result is obtained immediately following a test being administered, thus neglecting the possibility that patients may suffer anxiety while waiting for a test result. Moreover the possibility of patients becoming symptomatic and then experiencing delays in getting access to the necessary testing and treatment was also not considered in any of these studies.

Discussion

This review examined how test accuracy, perspective and delay are incorporated into economic evaluations focused on testing and diagnosis for ovarian cancer. Seven economic evaluations were identified for inclusion in this review.

In terms of test accuracy, this factor was incorporated in all but one of the studies. The studies typically report a sensitivity and specificity value for the diagnostic procedure under consideration, and then false negative tests results are incorporated by assuming that patients experience unnecessary disease progression until the next round of testing, when the disease may or may not be identified. In the case of a false positive test result, it is often assumed that patients are given an unnecessary surgical procedure, typically an oophorectomy. This is of interest as an oophorecctomy can reduce the risk of ovarian cancer by 80-90% [22], and thus reduce the mortality rate of patients. Consequently this issue has to be handled very carefully in modeling studies in this setting. As Havrilesky [1] was able to show, if the adverse effects of a patient receiving a positive test are not properly accounted for by considering the indirect costs of screening or treatment such as lost wages and caregiver costs, as well as the adverse effects on patient quality of life of a positive test, then additional false positive results may overestimate the value of screening. Other screening programmes have shown that there is an anxiety element for patients that receive a false positive test result [23], which can last up to six months following a false positive result [24]. This anxiety may also extend from the individual to family members. Beyond the initial false positive test result this may ultimately lead to a false positive diagnosis, where it has been shown, albeit on a small scale, that patients experience anxiety due to a false positive ovarian cancer diagnosis [25, 26]. Thus the full ramifications of inaccurate test results must be considered, otherwise it is possible that tests that give false positive and negative test results may be shown to overemphasize the value of testing.

Although it was reported in four studies that a societal perspective was used, only two studies considered the costs incurred by patients, with only one of these incorporating costs incurred by patients to access screening. This approach may lead to screening programmes appearing to be more cost-effective than they actually are. As previously noted, in some settings (e.g. England) the advice given when conducting economic evaluations is to use a health care provider perspective, but this is often inadequate for diagnostic testing. Diagnostic tests may be cheap for the health care provider and so the temptation under these circumstances could be to recommend that patients are more frequently tested, or be repeatedly tested in the case of a positive result to overcome the potential impact of a false positive test. While this type of approach can have a positive effect on patient health related outcomes and indeed be cost-effective from the health-care provider perspective, it

will lead to increased costs being incurred by patients through having to attend for testing such as through loss of wages and travel costs. Thus it is proposed here that irrespective of how the research is funded, economic evaluations should at the very least take a societal perspective which incorporates the costs incurred by patients as part of a sensitivity analysis. This approach is relatively straight forward. Patient costs can be informed by using standard approaches such as data collection from the patients, secondary sources, or sensible assumptions can be made.

The most common delays described in studies in this setting are those related to a false negative test result, where patients that are eligible for treatment experience unnecessary disease progression due to their disease status remaining undetected. Delays due to varying the interval between screens were also considered in one study. Interestingly, despite the problem described in the literature of symptomatic ovarian cancer patients experiencing difficulties in being properly diagnosed, none of the studies in this review incorporated this type of delay in their analysis. Delays waiting for results following testing, and delays accessing treatment following a positive test were also not considered in this setting. This is of importance since delays can impact on patient outcomes both in terms of disease progression and anxiety, and their omission may lead to interventions appearing more cost-effective than they are.

This is the first review that has looked at the methodologies adopted in economic evaluations of testing and diagnosis for ovarian cancer focusing specifically on the approaches used to model the key issues on a testing pathway, and thus comparisons with the findings of similar studies on ovarian cancer were not possible. However a previous study that examined some of these issues in economic evaluations of diagnostic testing for chronic kidney disease also showed that test accuracy is often poorly implemented, thus adding strength to the findings here [27].

A particular strength of this review is its methodological rigor. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to guide the systematic methods, and a comprehensive search of seven electronic databases was conducted. However grey literature was not included.

Conclusion

This study has demonstrated the importance of incorporating a wider societal perspective and factoring in the additional costs and outcomes incurred by patients due to the various causes of delay along the testing and diagnostic pathway, as well as test accuracy into economic evaluations of testing and diagnosis for ovarian cancer. It is crucial that the issues that are important to patients are fully incorporated into analyses such as these, since otherwise the potential for interventions

being found to be cost-effective that are not acceptable to patients increases. Thus it is suggested that the following guidelines be adopted to ensure analytical rigor in this field:

- State the test accuracy characteristics of all tests considered in the analysis (e.g. sensitivity, specificity, positive predictive value, etc.)
- Define the patient pathways for each of the possible test results (e.g. true positive, true negative, false positive, false negative)
- State and incorporate the consequences of inaccurate test results into the analysis (e.g. delays accessing treatment, patient anxiety due to a positive test, costs incurred by patients presenting for confirmatory testing, etc.)
- Adopt a societal perspective (either for the base case or during sensitivity analysis) which incorporates the costs incurred by patients (e.g. travel, lost wages, etc.)

By adopting these guidelines this will ensure that better informed decisions regarding resource allocation can be made.

References

1.   Havrilesky, L.J., et al., Reducing ovarian cancer mortality through screening: Is it possible, and can we afford it? Gynecol.Oncol., 2008. **111**(2): p. 179-187.

2.   Moyer, V.A., Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann.Intern.Med., 2012. **157**(12): p. 900-904.

3.   NICE, The recognition and initial management of ovarian cancer, in NICE clinical guideline. 2011: Manchester.

4.   Evans, J., S. Ziebland, and A. McPherson, Minimizing delays in ovarian cancer diagnosis: an expansion of Andersen's model of 'total patient delay'. Fam.Pract., 2007. **24**(1): p. 48-55.

5.   Smith, L.H., et al., Ovarian cancer: can we make the clinical diagnosis earlier? Cancer, 2005. **104**(7): p. 1398-1407.

6.   Barrett, J., et al., Pathways to the diagnosis of ovarian cancer in the UK: a cohort study in primary care. BJOG., 2010. **117**(5): p. 610-614.

7.   Health, I. and C.R. UK, Saving Lives, averting costs - An analysis of the financial implications of achieving earlier diagnosis of colorectal, lung and ovarian cancer. 2014.

8.   Lyratzopoulos, G., et al., Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England. Lancet Oncol., 2012. **13**(4): p. 353-365.

9.   Lyratzopoulos, G., et al., The relative length of the patient and the primary care interval in patients with 28 common and rarer cancers. Br.J Cancer, 2015. **112 Suppl**: p. S35-S40.

10.   Kehoe, S., et al., The influence of the operating surgeon's specialisation on patient survival in ovarian carcinoma. Br.J Cancer, 1994. **70**(5): p. 1014-1017.

11.   Palmer, S. and J. Raftery, Economic Notes: opportunity cost. BMJ, 1999. **318**(7197): p. 1551-1552.

12.   Drummond, M.F., et al., Methods for the Economic Evaluation of Health Care Programmes. Third ed. 2005, Oxford: Oxford University Press.

13.   The Social Care Guidance Manual - Chapter 7: Incorporating Economic Evaluation. 2013. Available at: www.NICE.org.uk. Accessed 26th January 2016

14.   Liberati, A., et al., The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ, 2009. **339**: p. b2700.

15. Holland, M.L., A. Huston, and K. Noyes, Cost-effectiveness of testing for breast cancer susceptibility genes. Value.Health, 2009. **12**(2): p. 207-216.

16. Rubinstein, W.S., et al., Cost-effectiveness of population-based BRCA1/2 testing and ovarian cancer prevention for Ashkenazi Jews: a call for dialogue. Genet.Med., 2009. **11**(9): p. 629-639.

17. Drescher, C.W., et al., Impact of screening test performance and cost on mortality reduction and cost-effectiveness of multimodal ovarian cancer screening. Cancer Prev.Res.(Phila), 2012. **5**(8): p. 1015-1024.

18. Kwon, J.S., et al., Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome. Cancer, 2008. **113**(2): p. 326-335.

19. Urban, N., et al., Use of a stochastic simulation model to identify an efficient protocol for ovarian cancer screening. Control Clin.Trials, 1997. **18**(3): p. 251-270.

20. Yang, K.Y., et al., A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary non-polyposis colorectal cancer (HNPCC) Families. Fam.Cancer, 2011. **10**(3): p. 535-543.

21. Mansueto, M., et al., Positron emission tomography/computed tomography introduction in the clinical management of patients with suspected recurrence of ovarian cancer: a cost-effectiveness analysis. Eur.J Cancer Care (Engl.), 2009. **18**(6): p. 612-619.

22. Arts-de, J.M., et al., Risk-reducing salpingectomy with delayed oophorectomy in BRCA1/2 mutation carriers: Patients' and professionals' perspectives. Gynecol.Oncol., 2015.

23. Jones, M.H., A. Singer, and D. Jenkins, The mildly abnormal cervical smear: patient anxiety and choice of management. J R.Soc.Med., 1996. **89**(5): p. 257-260.

24. Gram, I.T., E. Lund, and S.E. Slenker, Quality of life following a false positive mammogram. Br.J Cancer, 1990. **62**(6): p. 1018-1022.

25. Wardle, F.J., et al., Psychological impact of screening for familial ovarian cancer. J Natl.Cancer Inst., 1993. **85**(8): p. 653-657.

26. Wardle, J., et al., False positive results in ovarian cancer screening: One year follow-up of psychological status. Psychology and Health, 1994. **10**(1): p. 33-40.

27. Sutton, A.J., et al., Methods Used in Economic Evaluations of Chronic Kidney Disease Testing - A Systematic Review. PLoS One, 2015. **10**(10): p. e0140063.

Figure One: Study identification and selection process