A review of recent advances from trials of ovarian cancer screening

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Short synopsis: This is a review into the current progress being made in Ovarian Cancer Screening. There is no established nation-wide screening programme for ovarian cancer to date. Such a programme is very appealing due to the high mortality and suffering caused by the disease. The results from two recent multicentre randomised control trials – the PLCO and UKCTOCS trials – have been summarised in this review.

Introduction

Ovarian cancer remains the deadliest of the gynaecological cancers; deemed the 'silent killer' as it is mostly diagnosed at late, non-curable stages. In 2007 in the UK 4,317 women died from ovarian cancer, accounting for around 6% of all female deaths from cancer. Only about 25% of cases are diagnosed in stage I (potentially curable) disease and the 5 year survival is consistently very poor at 42%[1]. One reason for this is the cancer's elusive symptomatic presentation which is mainly characterised by insidious onset of abdominal pain and bloating. As these symptoms are also features of many more common abdominal diseases, they are often misdiagnosed and therefore diagnosis is delayed . This problem with late diagnosis is also due in part to the anatomical awkwardness of the ovaries, and their direct proximity with bladder and bowel allowing easy seeding to the peritoneum.

Crucially, there is no pre-malignant phase to ovarian cancer which makes the prospect of screening less tangible compared with other cancers. Furthermore, borderline (i.e. non-invasive malignant) tumours, rarely precede invasive epithelial ovarian cancer.

The unfavourable pathology of this malignancy has meant that mortality from ovarian cancer has remained high even in the face of advancing therapeutics. The holy grail of ovarian cancer research therefore, is to establish methods for early detection and prevention. Efforts for prevention have been based on the observation that ovulation inhibition results in a decreased incidence of ovarian cancer - for example through pregnancy, oral contraceptive use, and a shorter ovulatory period (late menarche or early menopause). The use of the oral contraceptive pill for over five year reduces occurrence of ovarian cancer by 50 %. The low complication rate from the pill makes the use of this as a method of prevention appealing, especially in high risk groups[2].

This review will focus on methods for early detection of ovarian cancer. There is currently no effective population wide screening programme. However scientists believe there is potential in this prospect, and there are several ongoing clinical trials and intensive laboratory research in the quest for an effective screening strategy. The results of these efforts to date will be presented.

Implications of the Biology of Ovarian Cancer for Screening

Before attempting to devise a screening programme it is important to consider the potential for its success which largely depends on the biology and epidemiology of the cancer.

In 1968 two scientists Wilson and Jungner published a public health classic, laying down the first framework for successful screening. Wilson and Jungner wanted to establish criteria that would enable the treatment of those with previously undetected disease, whilst avoiding harm to those persons not in need of treatment. Amongst other factors which make a disease suitable for screening, the capacity to detect the disease at an early stage and the availability of an acceptable treatment are important cornerstones of the criteria. Although additions have been made to these guidelines over the last 40 years, they remain essentially unchanged and highly relevant to this date.[3] (See Table 1)

Wilson and Jungner classic screening criteria

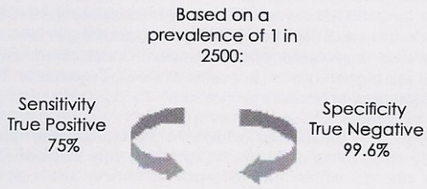
1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically bal anced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Synthesis of emerging screening criteria proposed over the past 40 years

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.

Table 1. Criteria for effective screening

Figure 1. Statistical Standards for effective screening



PPV (positive predictive value) 10%
10 laparotomies per case of ovarian cancer detected would be acceptable

There is evidence to suggest that the majority of ovarian cancer fits these first two requirements[4]. The current UK guidelines do not yet recommend screening for ovarian cancer for anybody that is not in the context of a Medical Research Council randomised control trial (e.g. UKCTOCS, see later). However when considering testing a screening programme, consideration should be given to the following groups:

1. The population in which it is prevalent: post-menopausal women.

2. The population at increased risk: Familial Ovarian Cancer accounts for 10% of Ovarian Cancer. Mutations in repair genes (BRCA1, BRCA2 and mismatch repair) contribute to the greatly increased risk of disease in these families. There is also an overlap with breast cancer risk (also known as the high risk for Breast and Ovarian Cancer syndrome (HBOC)). Paradoxically this group may pose a screening problem whereby early detection may actually be harder. The disease can act more aggressively than sporadic disease; several have p53 mutation at diagnosis indicating high metastatic potential, and 5% of patients who have had prophylactic oophorectomy go on to develop the disease in the peritoneum. It may not be possible to extrapolate data from familial screening programmes for use in sporadic ovarian cancer.

There is not as yet a Familial Ovarian Cancer screening programme in place[5]. Women classed as high risk based on family history are referred to cancer genetic centres - for example, those with 2 or more relatives on the same side of the family diagnosed with ovarian cancer or breast cancer at a young age (before 50 years). If they are found to carry a pre-disposing mutation, or based on history, are classified as HBOC, then they are offered counselling. This includes counselling about risk-reducing prophylactic oophorectomy. Those who don't elect for oophorectomy can receive concurrent transvaginal ultrasound scanning and CA 125 measurements every 6 months from the age of 35 or five-ten years earlier than the earliest diagnosis of ovarian cancer in the family. This screening should only be offered however in the context of a research study designed to gather data on the effectiveness of this screening e.g. the UK Familial Ovarian Cancer Screening Study (UK FOCSS).

3. The Future: Screening for a population to screen: If screening the entire post-menopausal population proves not to be cost effective, another option which could be achieved through research is the identification of a smaller group of people who are at higher than average risk of getting the disease. This could involve genetic analysis – looking for genetic markers associated with increased risk (e.g. single nucleotide polymorphisms) or analysis of life-style risk factors. Following a recent workshop from the National Screening Committee (NSC) it was concluded that there is no evidence so far to support the introduction of a population screening programme to identify high risk women for breast and ovarian cancer based on family history and blood testing for genetic mutations .

1.Population at risk: post-menopausal women
2.High-Risk Groups: Families
3.Screen the population for a smaller group of higher than average riskwomen:-
- genetic analysis
- lifestyle factors

Table 2: Possible Populations to Screen

Methods of Ovarian Cancer Screening

Ultrasonography

Transvaginal ultrasound (TVS) has overtaken transabdominal ultrasound (TAU) as it gives a more precise image of the ovary. it gives a more precise image of the ovary. Several studies have shown that ultrasound has a high sensitivity, probably due to the ability to directly visualise the anatomy. Subjective assessment using pattern recognition, by experienced ultrasonographers can achieve a high specificity. From 3 major trials of TVS alone the PPV was shown to reach 9.9%. The main problem of TVS is that the potential cost: benefit of using TVS to screen the entire post-menopausal population exceeds acceptable limits[6].

Serum Marker CA 125

The most widely investigated serum marker in ovarian cancer is CA 125[7], a heavily glycosylated high molecular weight mucin (MUC16). Serum levels are elevated in 80% of ovarian cancers overall but this value is significantly lower for early stage I cancers. Sensitivity is therefore limited. The CA 125 assay which classifies CA125 >35U/ml as raised, has a specificity of 99%. So CA 125 as an individual value is not specific enough to produce the PPV of 10%. Its limitation lies in the fact that CA 125 is elevated in a host of other benign conditions e.g. menstruation, pregnancy, endometriosis, adenomyosis, benign ovarian cysts & tumours, fibroids. Some individuals have baselines over the 35 U/ml cut off in absence of identifiable benign disease. CA 125 is also raised in other types of cancer e.g. breast and lung.

A recent randomised control trial (MRC/OVO5) assessed the benefit of monitoring CA 125 post-chemotherapy to guide early treatment of recurrence, versus treatment from the onset of clinical symptoms . As serum CA 125 measurements often rise a few months before the onset of clinical symptoms, this study aimed to prove a survival benefit of detecting recurrence using this serum marker. The study however showed no benefit of early treatment based on CA 125 measurements alone.

Combination Strategies for Ovarian Cancer Screening:

These hold the power to increase the specificity and sensitivity of the traditional screening approaches.

Two major approaches have been trialed to date:

1. The Prostate, Lung, Colon and Ovary Screening Trial (PLCO)

2. A concurrent screening trial i.e. TVS and CA 125 measured concurrently.

A randomised control trial carried out across 10 centres in America. Enrolment was between 1993 and 2001, recruiting women aged 55 to 74 years - 37,000 women were randomised to the control arm and 39,115 women randomized to receive screening. The screening arm received CA 125 measurements annually for 6 years and TVS annually for 4 years. Both studies were performed concurrently at entry into the study. The positive predictive value for invasive cancer was 3.7% for an abnormal CA 125, 1.0% for an abnormal TVS, and 23.5% if both tests were abnormal. The predictive values for the individual tests in this trial are therefore quite low. In women where both tests were abnormal the predictive value of the tests combined is high. However if only subjects in which the two tests were abnormal were evaluated 60% of invasive cancers would have been missed[8]. Also, although the number of cancer cases in this trial was small, it was observed that screening, particularly with TVS, might preferentially detect low grade cancers. This produces 'length bias' whereby slow growing cancers are more likely to be detected with screening than rapidly growing ones. This can produce the effect of overdiagnosis i.e. diagnosing cancers that might have gone undetected for the lifetime of the patient and not contribute to mortality.

This is an issue which is already becoming a significant problem in other cancer screening strategies. The detection of ovarian cancers with low malignant potential is unlikely to affect ovarian cancer mortality, since even stage III borderline cancers have a 90% 10-year disease-free survival[9].

The mortality data from the PLCO trial is not yet available as this requires follow-up to be completed. Using mortality as the end point of a screening trial will eliminate the length bias and will be more informative about the effectiveness of this screening on detection and mortality rates. However the data from this trial so far does not permit the recommendation of screening for ovarian cancer with concurrent CA125 and TVS.

UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

A sequential screening trial i.e. CA 125, Risk of Ovarian Cancer (ROC) algorithm then TVS

This is the largest randomised controlled trial of ovarian cancer screening to date, taking place across 13 NHS trusts in the UK. It is also the first trial to assign women to two different screening strategies enabling comparison between the two. Between 2001 and 2005 a total of 202 638 women aged 50-74 years were recruited. The 3 arms which women were randomly assigned to were 1. A control arm 2. A screening arm which received annual CA 125, interpreted with a risk of ovarian cancer algorithm, with TVS as the second line test if risk was raised (this screening is called multi-modal screening/ MMS) 3. A screening arm which received annual screening with TVS alone. Screening lasted 3 years with 7 years follow-up after.

Preliminary evidence from earlier trials of multimodal screening (sequential use of CA 125 then ultrasound) suggests that MMS can produce a survival benefit. In one study a sequential approach using CA 125 then TAU, produced a PPV of 21% and significantly increased median survival in the screened group (72.9 vs 41.8 months, p=0.0112). Refinements to screening made since this study for use in UKCTOCS include the use of TVS as opposed to TAU and the development of a risk of ovarian cancer algorithm to interpret CA 125 results.

Risk of Ovarian Cancer Algorithm (ROCA) –This is a computer algorithm developed to estimate the risk of ovarian cancer being present based on age and serial CA 125 measurement. It is based on the observation that, in benign conditions levels of CA 125 are usually stable even if elevated. Patients with ovarian cancer conversely usually have rising CA 125 values. In prospective studies the ROC algorithm using serial CA 125 measurements was shown to be superior to a fixed cut off for CA 125, mainly by significantly improving sensitivity from 62% to 86%.

Results of the UKCTOCS trial[10]

Mortality data from this trial is not yet available as follow-up is not complete. However data on prevalence of ovarian cancer in the different arms was reported earlier this year . The sensitivity, specificity and PPVs were 89.4%, 99.8% and 43.3% for MMS, and 84.9%, 98.2% and 5.3% for TVS alone, respectively. There was a significant difference in specificity between the two groups (p<0•0001), but no difference in sensitivity (p=0•564).Specificity was higher in the MMS than in the TVS group, resulting in fewer repeat tests and almost nine times fewer operations per cancer detected. This is partly because of the higher rate of detection of benign masses on TVS and more frequent detection of borderline tumours.

The novel design of UKCTOCS in which two different screening approaches are directly compared provides insight into the level of overdiagnosis (discussed above) within the different screening strategies. The results indicate that overdiagnosis of pseudodisease will be less apparent with a serum CA 125 based ovarian cancer screening strategy than with TVS screening. This result is in accordance with the PLCO trial.

Although the prevalence results are promising for these screening strategies, in particular MMS, mortality data needs to be available before the effect of screening on survival from ovarian cancer can be elucidated.

As MMS is speculated, from this data, to be the preferred screening method, a detailed cost analysis is also important and will only be possible to do when the patent on the ROC algorithm expires.

One article by Vergot et al suggested that the instructions over TVS analysis in the UKCTOCS trial lacked clarity, which could indicate a bias towards MMS screening. TVS is inherently more subjective that serial CA 125 measurements. Clinicians received written information about risk of malignancy based on morphological classifications from the International Ovarian Tumour Analysis (IOTA) study. However the information provided did not include subsequent updates of models developed during the IOTA study to distinguish between benign and malignant tumours. Clinicians were also not given clear instructions on the level of conservative management acceptable for probable benign masses. This group suggested that unnecessary interventions in women with benign masses may have been prevented with clearer instructions.

Trial	Number of Women	Screening Method	Results
PLCO Trial	Total: 76 115	CA125 annually for 6 years	PPV 3.7% for CA125 alone, 1.0% for TVS alone, 23.5% for both together.
	Screened: 39 115	TVS annually for 4 years	However only analysing patients when both tests are abnormal misses 60% of cancers
	Control: 37 000		
UKCTOCS	Total: 202 638	1. MMS : CA 125 annually, ROC algorithm, then TVS	PPV 43.3% for MMS, 5.3% for TVS
	Screen arm - MMS: 50 078	Or	Sensitivity similar between two arms, specificity greater in MMS
	Screen arm - TVS: 48 230	2. TVS alone, annually	
	Control: 104 330		
	Screen arm - TVS: 48 230	2. TVS alone, annually	
	Control: 104 330		

Table 3: Results of PLCO and UKCTOCS Trial

The Future: Use of a Panel of Serum Biomarkers

The future of ovarian cancer screening may lie in the identification of new serum biomarkers for the disease. The UKCTOCS trial has set up a serum bank of over 350 000 samples. The PLCO trial also runs the Etiology and Early Marker Study (EEMS). As well as investigating environmental and biological risk factors contributing to ovarian cancer, EEMS is identifying biomarkers for early detection of disease from blood and buccal specimens.
Ovarian cancer is very heterogeneous so it is unlikely that just one biomarker will provide the initial screen. This has lead to the idea of panels of biomarkers which can be assessed simultaneously. This would require advancement in technologies to measure multiple serum markers simultaneously. Gene expression arrays have proven to be powerful tools for biomarker discovery. Promising potential markers discovered so far include HE4, M-CSF, OVX1, Kallikrein, Osteopontin, Mesothelin, prostatin, VEGFB7-H$ and interleukins.

Although none have been validated in a prospective screening trial so far, this is hoped will change in the next few years.

Using multiple markers in an initial screen could improve sensitivity significantly. However this tends to happen at the expense of reduced specificity. One way around this is to use mathematical or statistical tools to maintain specificity.

The biomarkers identified need to be expressed, translated into protein and shed into body fluid which can be easily sampled. Analysis of urinary biomarkers holds potential to provide a more convenient method of screening.

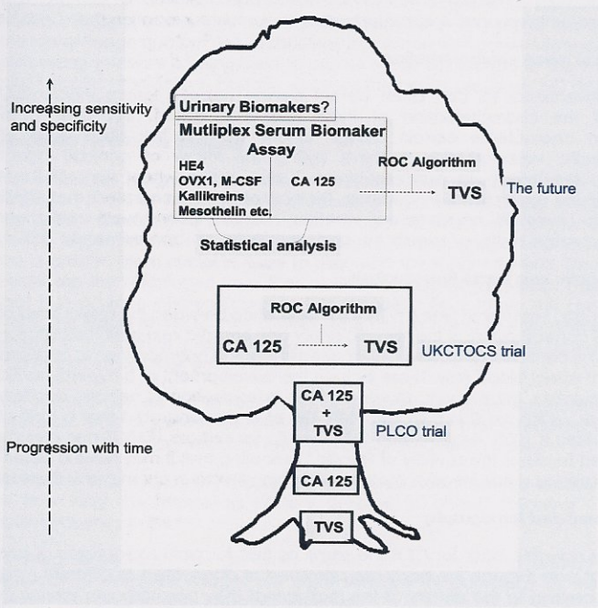


Figure 2. Progress of Screening Methods for Ovarian Cancer
'starting at the roots and progressing to more fruitful methods'

Conclusion

This review has summarised the results of several completed and ongoing trials investigating different methods of screening for ovarian cancer. The two mainstays of ovarian cancer screening – transvaginal ultrasound scanning and CA 125 measurements have proved ineffective alone. Currently, the most promising screening method is Multimodal Screening - incorporating an initial screen of serum biomarkers, analysed statistically, then the application of an algorithm to calculate risk, followed by transvaginal ultrasound scanning based on risk. There is no doubt over the appeal of an effective effective screening programme for such a deadly and agonising disease. However no matter how great the appeal, it is not enough to herald the implementation of a population-wide screening programme. It is necessary to bear in mind the requirements of an effective screening programme in analysis of these trials. Many trials have met their downfall over these requirements. In particular, the need for screening to impact favourably on survival. It will therefore be interesting to await the mortality data from the ambitious UKCTOCS trial.

As well as screening meeting epidemiological and public health requirements, it is important to think of the realities of screening for the women who will be having it. These issues can pose a problem as insurmountable as finding a screening method. If women do not attend for screening there is little point providing it. With regards to ovarian cancer screening we remind ourselves that unlike cervical cancer we are screening for malignancy rather than pre-malignant changes, a much more threatening thought. However caught in stage I 90% can be cured. 'Screening for a population to screen' may help to identify an at risk population. Women from ovarian cancer families are likely to be willing to be screened having watched family members suffer, however it might be considered 'scaremongering' to label an unknowing group of women 'at risk'. Lack of awareness of the disease is another issue. Transvaginal ultrasound is an invasive, potentially embarrassing procedure that could be perceived as painful. Using serum biomarker assays and referring only those with increased risk scores is be more acceptable.

Based on the results of clinical trials to date, presented in this review, a national screening programme for ovarian cancer cannot yet be christened[12]. These trials however have provided hope that through ongoing research such a programme may become a reality in the near future.

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