Ovarian cancer screening

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Ovarian cancer is the fourth commonest cause of cancer deaths in women. Multimodal screening with serum CA125 and transvaginal ultrasonography have been shown to improve survival. However, the results so far do not justify routine screening until the impact of screening on mortality has been assessed in larger randomized trials.

Ovarian cancer is the fourth most common cancer among women in the UK. The majority of ovarian tumours are epithelial in origin. Ovarian cancer is associated with poor prognosis and an overall 5-year survival of only 35% (Office for National Statistics, 1997; Berek, 2000). However, when disease is confined to the ovaries, survival is significantly better and is 76–93% at 5 years (Jacobs et al, 1999). In the UK, as elsewhere, only a quarter of cases are currently diagnosed at such an early stage. This has resulted in a growing interest in screening strategies that might result in early diagnosis and therefore reduced mortality.

Ninety per cent of ovarian cancers occur in females aged >50 years of age, and as a result ovarian cancer screening studies in the general population are limited to older women. It is important to note that even in postmenopausal women ≥50 years of age, the incidence of ovarian cancer is low (approximately 1 in 2000 per year), and therefore to achieve an acceptable positive predictive value, any screening strategy requires a very high specificity. In addition, before it can be implemented as a programme, it is essential that it is definitively established in a randomized control trial that ovarian cancer screening saves lives, is cost effective and is associated with acceptable morbidity in the form of unnecessary operations and complications.

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METHODS OF SCREENING

The existing methods of screening for ovarian cancer are serum CA125 (cancer antigen 125) and pelvic ultrasound. CA125 is a glycoprotein produced by the majority of epithelial ovarian cancers (EOC). In symptomatic patients with clinically diagnosed EOC, CA125 is elevated in 61–96% of cases and in 29–75% of those with stage I disease (Carlson et al, 1994). Cohort studies indicate that raised levels of CA125 may occur many years before diagnosis of the cancer (Zurawski et al, 1987, 1988; Einhorn et al, 1992; Helzlsouer et al, 1993; Hakama et al, 1996). It is estimated that a CA125 level ≥30 U/ml confers a 36-fold increased risk of ovarian cancer (Jacobs et al, 1996). Elevated levels of CA125 also occur in other malignancies, such as advanced endometrial and pancreatic cancer; in benign gynaecological conditions, such as endometriosis, fibroids and pelvic inflammatory disease; and during physiological events like pregnancy and menstruation (Jacobs and Bast, 1989). However, while patients with malignancy demonstrate rising levels of CA125 on serial measurements, elevated levels associated with the non-malignant conditions usually remain stable over time (Zurawski et al, 1990).

Ultrasound is the other test used in screening for ovarian cancer. It has proven to be a safe and effective means of visualizing the ovaries. The early studies focused mainly on ovarian volume measurements. The normal premenopausal ovarian volume was established to be <20 ml, whereas the volume cut-off for postmenopausal ovaries was 8–10 ml (Campbell et al, 1989). With the accumulation of data, the emphasis has shifted to the assessment of ovarian morphology and transabdominal ultrasonography has been replaced by transvaginal ultrasound (TVS) with its better resolution of the ovaries (Sassone et al, 1991; Bourne et al, 1993; Vuento et al, 1995; Kurjak et al, 1996; Misawa et al, 1997). The resulting sensitivity of TVS is 80–100% for the detection of ovarian cancer in asymptomatic women. The main drawback is the low specificity and a high false positive rate, which results partly from the cyclical changes in ovarian size and morphology that occur during the reproductive period and partly from the difficulty in differentiating benign from malignant ovarian lesions.

To address this latter issue, numerous authors have defined a variety of ultrasound criteria to

differentiate benign from malignant ovarian lesions (DePriest et al, 1997; Zalud et al, 1997; Conway et al, 1998) and recommended the use of scoring systems to classify the abnormalities more objectively (Ferrazzi et al, 1997; Merz, 1998). Such morphological scoring systems commonly use combinations of the following ultrasound features: presence of cystic and solid areas in the ovarian/pelvic mass, wall thickness and outline, papillations, presence and structure of septae and internal echoes in the cystic component, echogenicity of the solid component (*Figure 1*), the presence of acoustic shadowing, ascites and presence of distant metastases.

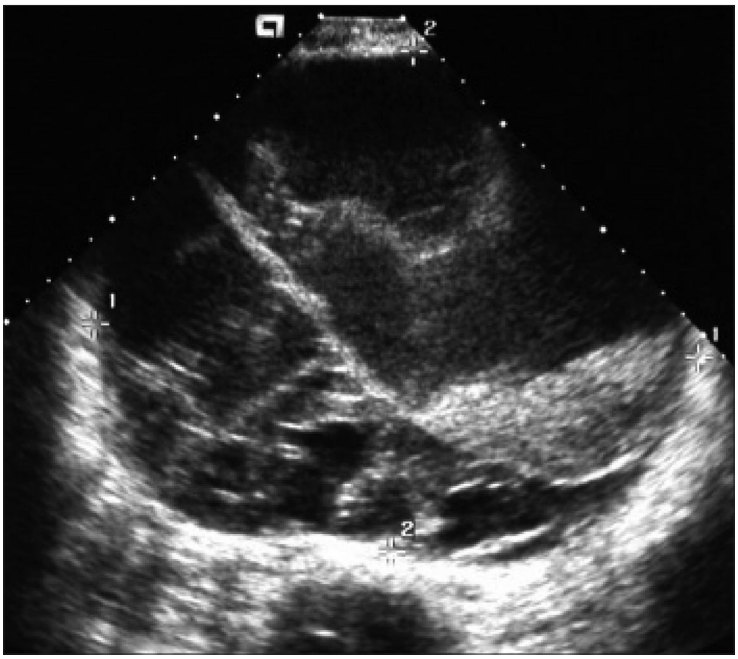

Figure 1. Transvaginal ultrasound image of a multiseptated complex ovarian lesion with thickened wall, papillations and abnormal internal echoes suggestive of malignancy.

AVAILABLE STRATEGIES

Over the past decade, two distinct strategies have emerged for ovarian cancer screening in the general population. The first strategy is entirely ultrasound based. The second, multimodal screening, uses both available screening tests – serum CA125 for primary screening and pelvic ultrasound as a secondary test in women with raised CA125 levels. The assessment of the specificity and feasibility of multimodal screening was first reported by Jacobs et al (1988) in a prospective study of 1010 apparently healthy postmenopausal women. This initial study revealed that multimodal screening can overcome the low specificity and positive predictive value associated with the use of the individual screening tests.

Further studies in this field have demonstrated that high specificity and positive predictive values in excess of 99.7% and 20% respectively can be achieved using the multimodal strategy (Jacobs et al, 1993, 1996; Grover et al, 1995; Adonakis et al, 1996) (*Table 1*). It has been shown that asymptomatic postmenopausal women with an elevated CA125 and an abnormal ultrasound have a 327-fold increased risk of ovarian cancer compared with the entire population (Menon et al, 1999a).

A pilot randomized controlled trial of 22 000 postmenopausal women has shown that multimodal screening can improve ovarian cancer survival in the screened group (Jacobs et al, 1999). Women in the screened arm were offered three annual screens that involved measurement of serum CA125 and pelvic ultrasonography if CA125 was ≥30 U/ml. Ovarian volume of

TABLE 1.
Prospective ovarian cancer screening studies using multimodal approach in the general population

Reference	Main features	Screening strategy	No. screened	No. of invasive EOC detected	No. of positive screens	No. of positive screen/detected
Jacobs et al (1999)	Age ≥45 years postmenopausal (median 56 years)	RCT Serum CA125 and TAS or TVS together	10958	6 (3 stage I)	29	4.8
Jacobs et al (1988), (1993), (1996)	Age ≥45 years postmenopausal (median 56 years)	Serum CA125 and then TAS if CA125 >30 U/ml	22000	11 (4 stage I)	41	3.7
Adonakis et al (1996)	Age ≥45 years (mean 58 years)	Serum CA125 and then TVS if CA125 >30 U/ml	2000	1 (1 stage I)	15	15
Grover et al (1995)	Age ≥40 years (median 51 years) or with family history (3%)	Serum CA125 and then TAS or TVS if CA125 >45 U/ml	2550	1 (0 stage I)	16	16
Total				19(1)	101	5.3

EOC = epithelial ovarian cancer; RCT = randomized controlled trial; TAS = transabdominal ultrasound; TVS = transvaginal ultrasound

≥8.8 ml on ultrasonography was regarded as abnormal, and women were referred for gynaecological opinion. Median survival of women in the screened group was 72.9 months and 41.8 months in the control group (P=0.0112).

Menon et al (1999b) retrospectively analysed the data from the trial to provide the first detailed report on the value of different ultrasound criteria in asymptomatic postmenopausal women with raised serum CA125 levels. A pelvic ultrasound was performed on 741 postmenopausal women with a CA125 level ≥30 U/ml. The ultrasound scans were classified as normal, abnormal (ovarian volume ≥8.8 ml) or equivocal (normal volume with abnormal morphology). Abnormal ovarian morphology was subclassified as simple cyst (single, thin-walled cyst with no septa or papillary projections) or complex (all other abnormalities). During a median follow up of 6.8 years, 17 invasive EOC were diagnosed. The sensitivity for detection of ovarian cancer in this multimodal strategy with different ultrasound criteria was shown to be 100% for abnormal morphology, 89.5% for abnormal volume and 84% for complex morphology. The highest specificity (97%) and positive predictive value (37.2%) were achieved using complex morphology.

Overall, the data suggest that multimodal screening has superior specificity and positive predictive value compared with strategies based on TVS alone. However, ultrasound as a first-line test may offer greater sensitivity for early stage disease. In the largest ultrasound study involving 14 469 asymptomatic women reported from the University of Kentucky, 11 stage I ovarian tumours were detected. The sensitivity for detection of stage I disease was 52% (Van Nagell et al, 2000). It is possible that the increased sensitivity of ultrasound screening may have a greater impact on ovarian cancer mortality. However, the associated lower specificity and positive predictive value of an ultrasound-only strategy will mean a higher rate of surgical intervention and morbidity in the screened group.

KEY POINTS

- Ovarian cancer has very poor 5-year survival of 35% because of its late presentation.
- Current available screening strategies are transvaginal ultrasound only or a combination of transvaginal ultrasound and measurement of CA125 levels.
- The combination of CA125 measurement and transvaginal ultrasound overcomes the low specificity and positive predictive value associated with the use of the individual screening tests and has shown to improve survival.
- An elevated CA125 level ≥30 U/ml confers a 36-fold increased risk of ovarian cancer.
- Asymptomatic postmenopausal women with an elevated CA125 and an abnormal ultrasound have a 327-fold increased risk of ovarian cancer compared with the entire population
- The impact of screening on mortality has not yet been demonstrated in the general population.

ONGOING TRIALS

Currently, there are two ongoing randomized controlled trials aimed at determining the best strategy for screening for ovarian cancer. The first is the Prostate, Lung, Colon, Ovary, (PLCO) trial in USA in which women in the screened group undergo annual serum CA125, TVS and pelvic examination. The second is the United Kingdom Collaborative Trial for Ovarian Cancer Screening (UKCTOCS), which is coordinated by St Bartholomew's Hospital, London. This three-armed randomized control trial has begun recruiting 200 000 postmenopausal women, aged 50–74 years, from around the UK. Participants will be randomized in a 1:1:2 ratio to ultrasound screening, multimodal screening and a control group who will not be screened. In addition to establishing the impact of screening on ovarian cancer mortality, the trial aims to comprehensively tackle the issues of compliance, health economics and physical and psychological morbidity of screening. These trials will also establish the most efficient screening strategy and identify the criteria with the best performance characteristics for ultrasound and serum CA125. HM

Conflict of interest: none.

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