SCREENING IN OVARIAN CANCER

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Ovarian cancer is the leading cause of death from gynaecological cancer in the developed world, comprising 5% of all cancer-related deaths in women. The high mortality rate has been attributed primarily to the difficulty in detecting the disease when it is still confined to the ovary (stage 1). The overall five year survival rate for stage 1 disease is 95%[1], compared with 20% for stage IV disease[2]. However, less than 25% of cases are confined to the ovary at the time of diagnosis. Thus the aim of screening in ovarian cancer has been to detect the disease when still confined to the ovary. However, to date there is no evidence to show an impact on mortality nor is there a test available that predominantly detects early stage disease.

Screening tests in ovarian cancer have until recently relied upon either pelvic ultrasound or the detection of the high molecular weight glycoprotein Ca125 in the serum or a combination of the two modalities (multimodal screening). Transabdominal ultrasound was used in the early screening studies[3-7] but has been replaced by the more sensitive transvaginal ultrasound (TVS) with or without the use of colour Doppler imaging[8]. Problems with utilisation of ultrasound for screening include cost, inter-examination variability leading to decreased sensitivity and specificity and visualisation rates. The latter vary enormously between reports in the literature, depending upon the age of the patient (with visualisation of the ovaries decreasing with age), the skill of the person performing the ultrasound, the presence or absence of a uterus and the presence of bowel gas. Studies to date have based their criteria for malignancy on ovarian volume, outline, the presence of papillary projections and complexity defined by the number of loculations, the cyst wall structure, septa and echogenicity of the cyst fluid. Papillary projections have the highest correlation with a diagnosis of ovarian malignancy and simple cysts and septal thickness have the lowest association with a diagnosis of ovarian malignancy[9]. In terms of operations per cancer detected the figures in the literature range from 9-163, although a systematic review by Bell et al concluded that in annual screening of a population with an incidence of ovarian cancer of 40 per 100,000, if no cancers were missed, between 2.5 and 60 women would undergo surgery for every primary ovarian cancer detected[8].

A number of different molecules detected in the serum of women with ovarian cancer have been investigated. The high molecular weight glycoprotein CA 125 has been the most studied and continues to be the tumour marker used most extensively for screening studies. Bast et al were the first to report an elevated serum Ca125 level in a patient before the diagnosis of ovarian cancer[10]. Since then multiple studies have shown Ca125 to have high sensitivity for ovarian cancer, with the overall sensitivity for all epithelial ovarian cancer in the range of 80% (Urban et al, 2003). Ca125 levels are elevated in greater than 85% of all advanced ovarian cancers but only 50% of early stage disease[1,2]. Elevated levels of Ca125 also occur in 6% of women without ovarian cancer[1] thus reducing specificity. Sensitivity and specificity have been improved by application of

a computerised algorithim based on the Bayes theorem for the interpretation of Ca125 in the place of standard cut-off levels[11]. The algorithm compares an individual's serial Ca125 levels with the pattern seen in ovarian cancer cases where the levels tend to rise and in healthy controls where serial Ca125 levels remain static or decrease over time. The closer the individual's profile is to that seen in known cases of ovarian cancer the greater the risk of malignancy[12]. The combination of Ca125 level in the serum followed by TVS (multimodal screening) has also been utilised. Data from prospective studies of screening for ovarian cancer in postmenopausal women have shown that sequential multimodal screening has improved specificity and positive predictive value compared to TVS alone, although TVS may be more sensitive for detecting early stage disease[13].

Ca125 levels fail to increase early in 20-50% of cases of ovarian cancer[1] so other tumour markers have been investigated. Lysophosphatidic acid (LPA), a bioactive phospholipid, has been reported as a potential discriminating marker for ovarian cancer including early stage disease[14]. High affinity receptors for LPA, Edg4 and Egd7 also have been shown to be increased in ovarian cancer cells[15]. Other molecules that may be potential adjuncts to Ca125 include osteopontin[16], kallikrenins[17] and a panel of markers including OVX1 and M-CSF[18]. Serum inhibin levels may also be a useful adjunct to Ca125 as 80% of mucinous epithelial ovarian cancers and a large proportion of sex cord stromal tumours are associated with increased levels of inhibin[19].

Currently there are two major randomised controlled trials underway to establish the impact of screening on ovarian cancer mortality as well as determining issues of compliance, health economics and physical and psychosocial morbidity. The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) began recruiting postmenopausal women in 2001 and involves 12 centres in the United Kingdom. The aim of the study is to recruit a total of 200,000 women who will be randomised to either control, screening with ultrasound or multimodal screening. The primary end-point is the impact of screening on ovarian cancer mortality and the results are expected in 10 years. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is a two-arm randomised controlled trial involving 74,000 women aged between 55 to 74 who have been randomised to a screening arm (annual screening for ovarian, lung and colon cancer) or to a standard care control arm. Ten centres are involved in this trial which will involve 10 years' average follow-up. Only one screening strategy is being used, namely a combination of TVS and Ca125 performed annually for three years followed by Ca125 alone for two years. The trial has completed enrolment. Clearly the results of both trials will be eagerly awaited although issues pertaining to cost-effectiveness, age at which to begin screening and appropriate screening interval remain unanswered.

The two randomised controlled trials rely upon current technology and run the risk of being out-dated before the data has been analysed. Our understanding of tumour biology would suggest that the progression of a normal cell to a cancer cell involves multiple changes in a number of key pathways in the cell. It would therefore seem logical to question the suitability of single serum markers to identify ovarian cancer. Recent developments in gene expression and more recently in proteomics may well hold the key to new screening tests for ovarian cancer. Petricoin et al have described the use of mass spectroscopy (surface-enhanced laser desorption and ionisation, SELDI) to define a profile associated with sera

derived from patients with ovarian cancer[20]. This profile was able to correctly identify 50 out of 50 cases of ovarian cancer, including 18 cases of stage 1 disease and to identify 63 of 66 cases of non-malignant disease, suggesting that this new technology may be a potential tool for screening. Clearly larger and more discriminatory studies will need to be performed but new technologies such as this may well hold the key to the development of an effective screening test for ovarian cancer.

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