

Screening for ovarian cancer

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EDITORIAL

Screening for Ovarian Cancer

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Screening to prevent disease and death is an integral part of the modern medicine. To ensure that screening was feasible and cost effective certain principles were devised, that ideally should be followed in their entirety. Briefly the recommendations are that the disease burden has major health implications, has a pre-cursor lesion which is treatable and prevents progression and a screening system acceptable to the population and cost effective. Of course exceptions occur – such as in breast cancer screening. Here the identification of a pre-cursor lesion is not the objective, rather detecting disease when of smaller volume and earlier stage, a principle applied to ovarian cancer screening.

Ovarian cancer remains a challenge to treat. In the UK there are about 7000 new cases registered each year, with 4-4500 deaths. The main obstacle remains the fact that 70-75% of women at first presentation will have stage III /IV disease, with 5 year survival patterns at 40% and 5% respectively. In stage I disease survival is at 90% and for stage II close to 70%. Therapeutic intervention is normally primary surgery followed in most cases by platinum based adjuvant chemotherapy, either as single agent or in combination though more recently in some advanced tumours primary chemotherapy may be used with equal efficacy [1].

Understanding the tumour biology is an important pre-requisite for screening. In ovarian cancer, the concept of stage I disease progressing to stage IV disease was unproven, though accepted by many, and for years the confusion lay in translating disease stage I-IV as a surrogate for disease process. Disease stage is but the description of disease spread at surgery and does not mean that the progression from I-IV is inevitable. However, such stepwise progression was assumed at that time of screening. Another element is the more recently accumulating research indicating that the distal portion of the fallopian tube is the origin of many 'ovarian' serous tumours. With careful histological examination, pre-malignant lesions can be identified in tubes removed at prophylactic surgery, and animal models have supported the theory. This information was not available when trials on screening for ovarian cancer commenced.

In 'high risk' populations the value of screening could be identified more rapidly compared to population screening. Approximately 10% of ovarian cancers have an inherited genetic component, the majority related to BRCA 1 and 2 mutations. The life- time risk of developing ovarian cancer is estimated at 50% for BRCA1 and 20-30% for BRCA2 carriers, compared with a lifetime risk of about 2% in the general population.

There are a few randomised trials reported in the literature. Equally there are numerous other reports on the experiences of screening, but it is the RCTs and more structured reports which will form the evidence base should screening be considered within the context of a health strategy.

The earliest report from an RCT was in 1999, where over 22,000 women were invited to be involved in the study, which randomly assigned women to either an observational arm or screening with annual CA125 and trans-vaginal scans. [2] This pilot study reported no difference in the incidence of detected cancers, but interestingly, an improved survival in the screened population. At the same time, and in consideration of a possible trial, work was undertaken compiling all the available

literature on ovarian cancer screening, which revealed a stage shift, with 50% of screen detected cases found to be at stage I/II disease, rather than at 25% in non-screened populations. Such a stage shift could increase cure rates and prevent deaths and randomised studies were commenced.

The largest study called UKCTOCS has recruited over 200,000 women (50-74 years), half of whom form the control population and the remainder screened using either serum CA125 or trans-vaginal scans as the first screen. The final results are expected in late 2015. The US study PLCO (pancreatic, lung, colonic and ovarian cancer study) has already reported. [3]. Over 78,000 women were recruited and randomised to annual serum CA125 and trans-vaginal scans, versus normal clinical care. The incidence of cancers in both arms were equivalent, there was no stage shift noted, and the cumulative ovarian cancer mortality the same. This was the first study to challenge the value of screening. Another RCT by a Japanese group was published in 2008, and over 80,000 women were recruited with similar approach to the PLOC study. Though there were more women in screening arm with stage I disease (64% vs 38%) this was not statistically significant and the overall impact regarding mortality has not yet been reported [4].

With respect to women at high risk of ovarian cancer, based on the detection of BRCA mutations or by family history, another study UKFOCCS, was developed [5]. In the phase I study over 3800 women were enrolled and underwent annual CA125 and scans, the results indicated that to achieve a stage shift, screening with CA125 every 4 months was necessary and a phase II study followed. Some patients from the phase I study was transferred to the phase II, and with further recruitment over 4500 women were recruited. The results, presented at the ASCO meeting (2103) revealed no stage shift, no benefit regarding mortality and concluded that screening in this population was ineffective and prophylactic surgery afforded the best preventative measure. Notably in the study they mention the increased detection of low volume Stage III disease in the screened group, but not reflected in improved overall survival -the studies objective

Thus the present position looks somewhat bleak, though accepting that the largest study has yet to report. Knowing now that the fallopian tube is the primary source of many ovarian cancers and accepting that there are 2 distinct entities low and high grade ovarian cancer, with different carcinogenic pathways, then focusing on the ovary as the organ to screen may have been erroneous. Again, the retrospectoscope remains the most accurate instrument we have. Should the UKCTOCS report a negative outcome, then other screening strategies will need to be considered and developed.

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