Is screening for ovarian cancer worthwhile?

Two papers in this issue of the journal are concerned with screening for cancer of the ovaries.[1,2] Screening for ovarian cancer is indicated for several reasons.

The incidence of ovarian cancer is high – for example, the annual rate in the United Kingdom is 40/100 000, in Denmark 23/100 000, and in the United States there are about 20 000 new cases per year. The cumulative risk over a lifetime in these countries is between 1·3% and 1·7%.

A significant proportion of the mortality from cancer in women is due to ovarian cancer. Mortality in untreated cases is almost 100%. The five year survival rate is much higher (70–90%) after treatment of early stages (localised disease) than after treatment in later stages (generalised disease (20–30% or less)). Available treatment has improved the survival rate only slightly during the last decennium. As primary prevention is not possible at present, secondary prevention is, therefore, needed urgently.

A number of studies have already been carried out with various tests and in various populations and have given valuable, though not conclusive results. In reviewing these articles the nomenclature is a problem. The disease which the screening test aims at detecting may be defined either as ovarian cancer or as all benign and malignant tumours. This affects the false positive and false negative rates. In this review I have used the figures and definitions of the authors. As will be discussed, this is crucial for an evaluation of ovarian cancer screening results.

CA 125

CA 125 is an antigenic determinant expressed in more than 80% of non-mucinous epithelial ovarian cancer. Einhorn *et al* found a specificity of 97% for CA 125 with a cut off value of 30 U/ml for women over 50 years.[3] In the clinical follow up ultrasound and repeat CA 125 determinations were included. Sensitivity could not be defined, but as many (six) ovarian carcinomas were found in the group with normal as with abnormal S-CA 125 concentration.

Transabdominal ultrasound

Andolf *et al* showed in 1986 that transabdominal ultrasound could identify ovarian tumours in a group of patients at risk for ovarian cancer.[4] Campbell *et al* screened 5479 self referred women aged 45–60 with transabdominal ultrasound.[5] The protocol was aiming at three yearly scans, and 77% complied with this schedule. Operations were carried out on 326 women with a positive screening result, and 379 ovarian masses were found. Five of these women had primary ovarian cancer, all stage I, and nine had malignant tumours in the ovaries. It was not possible to identify characteristics unique for the five early malignant tumours. Detection rate was 100% as judged by the follow up information. The so called false positive rate (see below) was 2·3% for the three scanning rounds, specificity was 97·7%, and the positive predictive value was 1·5%.

Transvaginal ultrasound

Transvaginal ultrasound has been shown to be a useful method for screening for ovarian tumours.[6] van Nagell *et al* reported two studies of screening by this method among asymptomatic women. In the first 1000 healthy volunteers aged over 40 were screened.[7] Although no primary ovarian cancers were detected, the false positive rate was 3·1%. In the second study 1300 postmenopausal women were screened.[8] Two primary ovarian cancers were detected, giving a sensitivity of 100% on follow up, a false positive rate of 2·3%, and an odds of being affected given a positive result (OAPR) of 1:15. Bourne *et al* screened 1601 asymptomatic women with a family history of ovarian cancer by means of transvaginal ultrasound.[9] Thirty nine had a laparotomy, and six were found to have primary ovarian cancer (four were stage Ia). The sensitivity, calculated using the results of follow up after two years, was 100%, the false positive rate was 3·5%, and the OAPR 1:9.

CA 125 followed by ultrasound

Jacobs *et al* screened 1010 asymptomatic women with a median age of 54 by a combination of CA 125 and vaginal examination as the initial test and transabdominal ultrasonography as a secondary procedure in selected cases.[10] The specificity was 100% when the three methods were combined. One woman with a positive result at all three examinations had an ovarian cancer stage Ia. Jacobs *et al* developed the multimodal approach further, using CA 125 followed by transabdominal ultrasound.[11] They screened 22 000 women with CA 125 and recalled women with CA 125 $\geqslant$30 U/ml for transabdominal ultrasound. Forty one women had a positive screening result and 11 had ovarian cancer. Of 21 959 women with a negative result, eight developed ovarian cancer. The specificity was 99·9%. Apparent sensitivity, determined by following up screen negative women, was 79% after one year and 58% after two years.

It seems from these papers that the specificity of the various methods, CA 125, transabdominal and transvaginal ultrasound examination, and especially combined CA 125 and ultrasound may be acceptable.

The important issue is that no known non-invasive method alone can distinguish with complete accuracy between benign and malignant processes. Efforts have been made to improve the results of the ultrasound examination. For example, an attempt has been made to improve the detection rate and false positive rate of the ultrasound examination by describing the normal variation of ovarian volume and volume change over time[12,13] and by describing in more detail the morphology of the ovary.[13-15] It may also be expected that the vaginal approach will give better results than the transabdominal approach, because the vaginal approach gives better resolution. Futhermore, the transvaginal ultrasound examination does not demand a full bladder, which makes the examination easier and still acceptable as seen in the two feasibility studies.[1,2]

Adding Doppler flow measurements to the ultrasound examination was expected[16,17] to improve the distinction between benign and malignant tumours of the ovary. Bourne *et al* showed that adding colour Doppler as a secondary screening test after transvaginal ultrasound reduced the false positive rate from 3·5% to 0·9%, and improved the OAPR from 1:9 to 1:25.[18] Other studies have not shown colour Doppler to provide such good results, with values of blood flow measurements in benign and malignant ovarian tumours overlapping.[19-21]

The definition of a false positive result is difficult. Published reports describe women who are operated on for benign ovarian cysts or tumours as false positive cases. It is good clinical practice for gynaecologists to remove even

asymptomatic tumours of the ovaries detected, for example, at regular cervical cytology check up, even if they are thought to be benign. There are reasons to believe that benign ovarian tumours may become malignant (see ref 8 for references). Furthermore, benign tumours may, owing to their size, torsion, or bleeding and infection, produce disease. Until more is known about the natural history of ovarian cancer, defining genuine false positive results will remain a problem in screening for the disease. At one extreme, any lesion with a positive test that is not an ovarian cancer would be considered a false positive, but this may overestimate the disadvantages by ignoring the detection of serious non-cancerous disorders that would benefit from early treatment. At the other extreme, the inclusion of all non-cancerous lesions will overestimate the benefits.

Another important clinical problem is caused by the inevitable investigation of the endometrium when the ovaries are examined. Cancer of the endometrium may be suspected at the ultrasound examination and a number of such cases will be found during screening for ovarian cancer. Such findings demand further investigation. The protocol must include a decision as to whether such a finding should be acted on or not.

There are other theoretical and methodological problems. A large multicentre randomised study must be organised because no single centre can recruit the 100 000 or more volunteers who are needed to show whether or not screening will decrease mortality due to ovarian cancer; this is, of course, the final test of the value of screening. Correct organisation of such a study is important for its success. An obvious difficulty is that members of the control group, preferably not being examined at all, who become aware of their status as controls may go to private gynaecologists for examination. Many women already have regular health check ups, including gynaecological ultrasound scanning; it is therefore urgent to evaluate the effectiveness of screening for ovarian cancer before this becomes more common. The feasibility of the continuing multicentre studies in the United Kingdom and Denmark is therefore an important prognostic factor, and enlargement of the study group is needed and should be made possible. Whether screening for ovarian cancer should be part of a future health service (and eventually paid for by public funds) or not must be evaluated in this study. Society is already paying for this activity but in an unorganised way, which is definitely not effective. A parallel situation exists in screening for cervical cancer,[22] where screening is efficient when organised, but inefficient when unorganised.

In conclusion, it is necessary to evaluate the results and costs of a large scale randomised study (influence on mortality, change of frequency of stages, cost effectiveness) in non-risk populations. The current randomised study is a necessary and urgent experiment because of the frequency and seriousness of ovarian cancer. Hopefully, more centres will be able to join the continuing study.

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