Screening for ovarian cancer

Still controversial, but encouraging

EDITOR,—Maurice J Webb's editorial on screening for ovarian cancer is too negative and may discourage necessary research with currently available techniques.[1] Webb implies that ovarian cancer is too rare to warrant screening and quotes an annual incidence of 15/100 000. In Britain there are over twice as many deaths from ovarian cancer as from cervical cancer, for which screening is established.[2] In women aged 50-69, a possible target age group for screening, the figure was 42/100 000 in 1987.[3]

Webb interprets the study of Thomas H Bourne and colleagues as indicating that transvaginal ultrasonography is not accurate enough as a screening technique.[4] The detection rate of six out of six cases during follow up of 24 months with a false positive rate of 0·9%, though based on small numbers, does not suggest inaccuracy (table). The low false positive rate has been confirmed in a pilot study of screening of the general population in Reading (0·5% based on over 2000 women screened).

Webb cites a study by DePriest *et al* (a paper presented at 24th annual meeting of Society of Gynecologic Oncologists, 1993) to support the inaccuracy of ultrasonography. His conclusion, that screening with transvaginal ultrasonography followed by colour Doppler imaging would yield a high false positive rate, is inappropriate as the study did not include colour Doppler imaging. Colour Doppler imaging as a secondary test would reduce false positive results among women offered a laparotomy (table). Although a secondary test was not offered in DePriest *et al*'s study, a false positive rate of 1·3% and odds of having primary ovarian cancer when the result is positive of 1:14 are encouraging.

Results of screening (with real time ultrasonography and colour Doppler imaging) in study by Bourne and colleagues[4]: 1601 women (mainly premenopausal) were screened

Screening variable	Estimate
Detection rate:	
With follow up of 44 months	6/9 (67%)
With follow up of 24 months	6/6 (100%)
False positive rate:	
Before colour Doppler test	3·5% (55/1592)
After colour Doppler test	0·9% (15/1592)
Odds of being affected, given a positive result:	
Before colour Doppler test	1:9
After colour Doppler test	1:2·5

Webb also questions the potential of assay of serum CA 125 concentration as a screening test. With a two year follow up Ian Jacobs and colleagues detected 11 of 19 cases (58%) with an initial false positive rate of 1·5%, which fell to 0·14% when transabdominal ultrasound examination was used as a secondary screening test.[5] This shows the potential of the CA 125 concentration, given the simplicity of using a biochemical measurement as the initial screening test and the fact that a lower detection rate may be acceptable if the false positive rate is low.

Webb's original estimate, that screening by measuring the CA 125 concentration and then performing transabdominal ultrasonography would cost over $1 million per potentially curable case detected, was too high. The correction (published in the issue of 15 May)—$44 000—may be too low.

Advice to authors

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If the cost of measuring the CA 125 concentration was $20 per person and, as Webb suggests, the cost of each scan was $200, screening 22 000 women would cost $440 000 for the CA 125 test plus $68 000 for an ultrasound scan on 340 women—a total of $508 000. If four stage I or II cancers were detected (as by Jacobs and colleagues) the cost per potentially curable case detected would be $127 000.

Whether early detection will reduce mortality from ovarian cancer and increase expectation of life is not known. The two papers published in the *BMJ*[4,5] indicate the need to resolve the question with a randomised controlled trial of screening for ovarian cancer.

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1 Webb MJ. Screening for ovarian cancer. *BMJ* 1993;**306**:1015-6. (17 April.)
2 Office of Population Censuses and Surveys. *Mortality statistics, 1990.* London: OPCS, 1991. (Series DH2 No 17.)
3 Office of Population Censuses and Surveys. *Cancer statistics—registrations, 1987.* London: OPCS, 1993. (Series MB1 No 20.)
4 Bourne TH, Campbell S, Reynolds KM, Whitehead MI, Hampson J, Royston P, *et al.* Screening for early familial ovarian cancer with transvaginal ultrasonography and colour blood flow imaging. *BMJ* 1993;**306**:1025-9. (17 April.)
5 Jacobs I, Prys Davies A, Bridges J, Stabile I, Fay T, Lower A, *et al.* Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. *BMJ* 1993;**306**:1030-4. (17 April.)

Other chronic diseases affect serum marker

EDITOR,—We wish to comment on Ian Jacobs and colleagues' paper.[1] Raised serum CA 125 concentrations have been reported in liver diseases and other non-malignant conditions.[2,3] In an attempt to study the pathogenesis of a raised concentration in patients with cirrhosis of the liver and ascites we compared the serum CA 125 concentrations in patients with cirrhosis, end stage renal disease treated with continuous ambulatory peritoneal dialysis or haemodialysis, and controls. None of the patients had ovarian cancer or other malignant disease. Serum CA 125 concentration was assayed with a microparticle enzyme immunoassay (Abbott Laboratories, Chicago). The table shows the preliminary results.

Our results show that CA 125 concentrations are raised in 68% of patients with cirrhosis of the liver and ascites and 7-37% of patients receiving dialysis. A substantial proportion of these patients were men. We believe that measurement of CA 125 concentration is not an appropriate initial screening test for ovarian cancer, especially in patients with severe liver and renal disease. Doctors should be aware that a raised serum CA 125 concentration is not uncommonly seen in other, non-malignant conditions.

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1 Jacobs I, Prys Davies A, Bridges J, Stabile I, Fay T, Lower A, *et al.* Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. *BMJ* 1993;**306**:1030-4. (17 April.)
2 Molina R, Filella X, Bruix J, Mengual P, Bosch J, Calvet X, *et al.* Cancer antigen 125 in serum and ascitic fluid of patients with liver diseases. *Clin Chem* 1991;**37**:1379-83.
3 Weaver C, Daoud E. CA 125 concentrations in malignant and non-malignant disease. *Clin Chem* 1991;**37**:1968-74.

Multiple markers may outperform CA 125 alone

EDITOR,—Maurice J Webb correctly points out that there is a long way to go in developing an effective screening test for ovarian cancer.[1] We disagree, however, that the problem of the assay of serum CA 125 concentration as a first line test is its specificity; rather, it is the lack of sensitivity to detect early stage disease. Retrospective analysis of the JANUS serum bank data[2] and anecdotal cases suggest that an increase in CA 125 concentration can occur several years before clinical detection of the disease. Only about half of patients with stage I disease will have an abnormal CA 125 concentration.[3] The specificity of the CA 125 concentration can be improved dramatically by monitoring values over time or by the use of ultrasound to detect disease.[4]

Recent data suggest that use of multiple markers in combination might improve sensitivity without a prohibitive decrease in specificity. When 46 serum samples from patients with stage I epithelial ovarian carcinoma were assayed for CA 125, the mucin determinant OVX1, and macrophage colony stimulating factor at least one of the three markers was raised in 45 of the samples.[5] One of the three markers was raised in 11% of 204 patients who had been screened for ovarian cancer and had not developed malignancy during two years of observation. A specificity of 89% would not be adequate to prompt surgical exploration, but the serum

Serum CA 125 concentrations in patients with cirrhosis of the liver or end stage renal disease and controls

Diagnosis	Sex (M/F)	Mean (SEM) age (years)	Mean (SEM) CA 125 (U/l)	No (%) of patients with CA 125 > 30 U/l
Cirrhosis of liver (n=25)	14/11	61·5 (2·4)	414·1 (110·5)*	17 (68)
End stage renal disease:				
Treated with continuous ambulatory peritoneal dialysis (n=28)	14/14	57·8 (2·5)	17·8 (2·2)*	2 (7)
Treated with haemodialysis (n=27)	14/13	51·6 (2·7)	39·1 (8·1)*	10 (37)
Controls (n=29)	20/9	47·2 (3·0)	9·2 (0·8)	0

*p < 0·001 compared with controls (Student's *t* test).