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A Review of Ovarian Cancer Screening

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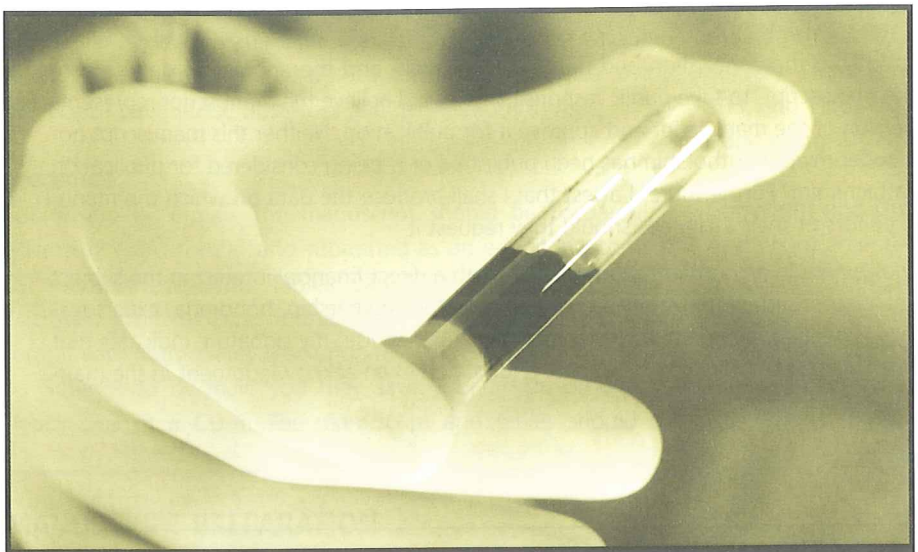

CA125 can be used for the primary screening of ovarian cancer

INTRODUCTION

Ovarian cancer causes more deaths among women in developed countries than all other gynaecological malignancies combined.[1] It has a high mortality rate, and there has been little improvement in patient outcomes despite therapeutic advances. The poor prognosis is mainly attributed to the high proportion of cases presenting at a late stage, as a result of its nonspecific symptoms. Patients are usually not diagnosed until the disease has spread beyond the pelvis or involved other organs to cause significant discomfort.[2] A high survival rate of more than 85% is seen with stage 1 disease.[3] Therefore, efforts are being made to develop ovarian cancer screening (OCS) tools in order to pick up the disease at an early stage. Screening strategies have been reported, with serum CA125 and transvaginal ultrasonography being the most commonly used tools. In this review, we provide an update on the literature regarding OCS.

SCREENING TOOLS

Tumour Markers

CA125 is the most widely studied ovarian tumour marker; it is expressed in about 80% of ovarian epithelial cancers.[4] CA125 has two major antigenic domains, A and B, which bind to monoclonal antibodies OC125 and M11, respectively. Immunoassays quantifying CA125 using both monoclonal antibodies to two distinct sites of the molecule have better specificity and less inter-assay variation than the original assay using monoclonal antibody OC125 alone.[5,6] An upper limit of 35 U/mL, obtained from a group of normal women, has been used arbitrarily as the cutoff. However, this may not be appropriate in postmenopausal women and those who had hysterectomy, in whom the CA125 levels tend to be lower than in the general population.[7] Using elevated CA125 alone to screen for ovarian cancer has been criticized for its low specificity and positive predictive value, because CA125 may also be elevated in other cancers as well as in benign gynaecological conditions, such as pelvic endometriosis and benign ovarian tumours.[8] Einhorn et al reported the use of CA125 alone for OCS.[9] Among women aged 50 years or older, thresholds of 30 and 35 U/mL had a 97% and 98.5% specificity for the CA125 radioimmunoassay, respectively; for those younger than 50 years, the specificity was 91% and 94.5%, respectively. Overall, 29 operations were done for every cancer case detected. In another study by Jacobs et al, a CA125 level of ≥30 U/mL in asymptomatic postmenopausal women was associated with a 36-fold risk of being diagnosed with ovarian cancer in subsequent years.[10] In general, it is agreed that a false-negative elevation of CA125 is less likely to occur in postmenopausal women.[11]

The introduction of the risk of ovarian cancer (ROC) has improved the interpretation of CA125 levels compared with the standard cutoff levels. This was based on studies by Jacobs et al,[10,12] which showed that elevated

CA125 levels in women without ovarian cancer remained stationary or reduced with time, whereas in women with ovarian malignancies they tended to rise. The ROC for an individual is then calculated using a computerized algorithm based on the Bayes's theorem comparing serial CA125 levels between the cases and the controls.[13] The risk calculation is an estimate of the probability of having preclinical ovarian cancer and the result is presented as the individual's estimated risk of ovarian cancer. This approach has been incorporated as part of a multimodal screening strategy used in some ongoing trials.

Apart from CA125, some other tumour markers have been developed for early ovarian cancer detection. Markers such as M-CSF, OVX1, LPA and prostasin have been used alone or in combination with CA125, in an attempt to increase the sensitivity or specificity of the test.[14-17] Use of multiple markers usually increases the sensitivity but at the expense of specificity. Nevertheless, with the advancement in proteomic technologies, it is likely that potential new markers will be identified, which may improve the detection of early ovarian cancer.

Transvaginal Ultrasonography

Transvaginal ultrasonography has been included in all screening strategies, either as the sole screening tool or as a secondary test after screening for serum CA125. The potential use of ultrasound scan in ovarian cancer screening was first proposed in the early 80s.[18] During the past two decades, there have been publications on the use of transvaginal ultrasonography as a primary tool for early detection of ovarian cancer.[19-23] It was shown that primary screening using transvaginal ultrasonography offers a better sensitivity, but a lower specificity and positive predictive value compared with CA125 alone or other combined strategies. Recent studies suggested that the use of Doppler imaging and a morphology index might improve the positive predictive value and reduce costs.[24-26] However, performance varies between different operators and interpreters.

In 2000, Sato et al reported their experience with mass screening for ovarian cancer using transvaginal ultrasonography.[21] A total of 183,034 women who underwent transvaginal ultrasound scan as primary screening were included in the study. Of these women, 5,309 had required a secondary screening, and surgery was performed on 324 women. Twenty-two women were diagnosed with primary ovarian cancer and 17 (77.3%) of them had stage 1 disease. The authors concluded that the use of transvaginal ultrasonography might increase the chance of early diagnosis and decrease mortality from the disease. However, no control group was included in that study and, therefore, a survival benefit could not be demonstrated. On the other hand, 13 operations were performed on women without ovarian cancer for each detected case, which is generally considered unacceptable.

Multimodal Screening

Multimodal screening refers to the incorporation of multiple screening tools such as CA125, ultrasound scan and physical examination in a screening programme.[27] In recent years, this term has been widely used to mean the sequential use of an ultrasound scan in those who have been tested positive with CA125 (level II screen). This multimodal approach improves the positive predictive value and specificity compared with ultrasound scan alone. This is well demonstrated in the series of publications by Jacobs et al.[10,12,27,28] In that series, less than five operations were performed for each case of ovarian cancer detected.

A randomized controlled trial published in 1999 is perhaps the best evidence to date on the use of multimodal screening for ovarian cancer.[12] In that study, 21,935 women were randomized to a control or screening group in a 1:1 ratio. Women receiving screening were offered three annual screens measuring their CA125 level. Level II screening using pelvic ultrasound was performed if the CA125 level was above the cutoff value of 30 U/mL. Women were referred for gynaecological consultation if their ovarian volume was ≥8.8 mL. All women were followed up to detect the development of ovarian or fallopian tube cancers. Of the 468 women who had a raised CA125, 29 were referred for a gynaecological opinion after level II screening. Six were found to have an index cancer and 23 had false-positive screening results. During the seven-year follow-up, 10 further women in the screened group and 20 in the control group were found to have an index cancer. Median survival of women with index cancers in the screened group and the control group was 72.9 months and 41.8 months, respectively (p=0.0112). The author hypothesized that the difference in the median survival may be due to the detection of index cancers at an earlier stage with better differentiation. However, it is still not clear whether the process of ovarian carcinogenesis involves progression from good to poor differentiation. In the study, the number of deaths from an index cancer did not differ significantly between the two groups,

although the screened group had a significantly longer median survival. The authors explained that the primary intention of the trial was to study the feasibility of multimodal screening, not mortality. The pilot study was, therefore, not powered to demonstrate a significant difference in mortality between groups. A large-scale randomized controlled trial has been started in the United Kingdom to address this issue and is discussed below. Table 1 compares the various screening tools and recommendations for their use.

TARGET POPULATION FOR SCREENING

Ovarian cancer is generally detected at an advanced stage and the 5-year survival rate is approximately 30%. The whole purpose of OCS is to pick up the disease at an early stage as survival rate is much higher with stage 1 disease. Because of a low incidence of ovarian cancer in the general population, the positive predictive value of universal screening is low and likely to have a relatively low yield. The majority of women with a positive screening test will not have ovarian cancer. Systematic reviews estimated that 3% to 12% of screened women will need further assessment; this will cause potential distress and anxiety in otherwise healthy women. Even with multimodal screening, which has a positive predictive value as high as 15%, there will still be approximately 0.5% to 1% of women suffering from a significant complication of surgery.[29] Hence, the screening of a general population is probably not cost-effective.

Another approach is to define the target population with a high risk of having ovarian cancer. Ninety percent of ovarian cancer occurs in postmenopausal women older than 50 years, and this represents the largest population who should be studied and considered for future screening programmes. The lifetime risk is higher in those with a family history of ovarian cancer. The presence of one first- or second-degree relative with ovarian cancer increases the RR to 3.1 (95% CI 2.2-4.4); with two or three relatives with ovarian cancer, the RR increases to 4.6 (95% CI, 1.1-18.4).[30] Women who have hereditary risk factors, which account for 5% to 10% of all ovarian cancer cases, are at a higher risk. Those who carry a BRCA1 mutation have a 15% to 60% risk of developing ovarian cancer. Although the risk for BRCA2 carriers is lower (15%-25%), it remains significantly elevated compared with noncarriers.[31] Women included in the UK Familial Cancer Registry are currently being advised to undergo annual screening for ovarian cancer, although none of the potential screening tests have been shown to reduce mortality.[11]

ONGOING STUDIES

Currently, no randomized controlled trial on the screening for ovarian cancer in the general population with mortality outcomes has been completed. Some studies are in progress, including the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS; interested readers are referred to the web site www.ukctocs.org.uk) and the NIH Prostate, Lung, Colon, Ovary (PLCO) trial in the United States.[32]

The UKCTOCS is enrolling 200,000 postmenopausal women aged 50 to 74 years recruited from community registers. Women with familial predisposition are excluded from the study. Subjects are randomized in a 1:1:2 ratio to ultrasound screening, multimodal screening (using ROC to estimate the risk of ovarian cancer and the need for level II screening using transvaginal scan) and control. Women will be tested annually for 6 years and followed up for 7 years, with mortality outcomes obtained through cancer registries and postal questionnaires. Endpoints including quality of life, health economics, morbidity and compliance with screening will also be addressed in this study.

The NIH PLCO trial has recruited women aged 55 to 74 years through mass mailing, with a total of 38,000 women in each arm. Women in the screening group will undergo an annual transvaginal scan for 4 years and annual CA125 testing for 6 years. Women in the control group will receive usual care. A positive result will

Table 1. Comparing different screening tools

Screening Tools	Recommendations
Pelvic examination	• Not useful because it is not sensitive when used alone[27]
CA125	• Rarely used alone but as part of multimodal screening • Interpretation of serial levels is more accurate than using a cutoff value
Transvaginal ultrasonography	• Low specificity and positive predictive value; a lot of operations would be performed for women with false positive results, which is unacceptable
Multimodal screening	• Higher specificity and positive predictive value than transvaginal ultrasonography alone • Potentially useful

initiate a referral to the patients' own primary healthcare provider for further management.

Women with familial predisposition for ovarian cancer represent a distinct group at high risk of developing ovarian cancer at an early age. The UK Familial Ovarian Cancer Screening Study (UKFOCSS) is being conducted in the aim to develop an optimized screening procedure for ovarian cancer in terms of the most appropriate tests, criteria for interpretation of results and screening interval in these high-risk women. The physical morbidity and resource implications associated with OCS will also be assessed.[11,33] Up till now, more than 1,500 subjects are being screened annually with CA125 and ultrasound scan.

CONCLUSIONS

There is insufficient evidence so far to recommend for or against the screening of asymptomatic women at increased risk for developing ovarian cancer. At the moment, OCS should not be performed outside the context of a clinical trial. Although screening is recommended in high-risk populations, the women should be fully counselled about the current lack of evidence to substantiate its efficacy.

Practice Points

- Ovarian cancer is associated with a high mortality rate because of late diagnosis. Survival is much improved if the disease is picked up at an earlier stage.
- CA125 is the most widely used tumour marker in ovarian cancer. It has been used as the primary screening tool in multimodal screening. Evidence shows that interpretation of serial CA125 levels is more accurate than a cutoff in estimating the ROC.
- When used as a primary screening tool, transvaginal ultrasound scan offers a better sensitivity but lower specificity and positive predictive value compared with CA125.
- The multimodal approach has better positive predictive value and specificity than ultrasound scan alone.
- Women in the general population should not be screened outside clinical trials.
- Although screening is recommended in women with a strong family history of ovarian cancer, they should be fully counselled about the current lack of evidence to substantiate its efficacy.
- Large-scale randomized controlled trials on ovarian cancer screening are ongoing to address its impact on patient survival.

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