ORIGINAL ARTICLE

The role of CA125 in clinical practice

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Background: CA125 is a high molecular weight glycoprotein, which is expressed by a large proportion of epithelial ovarian cancers. The sensitivity and specificity of CA125 are poor and there are no guidelines produced by the Royal College of Pathologists or the Association of Clinical Biochemists to aid clinicians and laboratories in its most appropriate use.

Aim: To identify the patient population having a CA125 measurement and to determine its contribution to individual patient management.

Methods: A retrospective case note audit looking at patients who had a CA125 measurement performed between April 2000 and April 2002.

Results: The study comprised 799 patients; 751 (94%) were female and 48 (6%) male; 221 (29%) females and 22 (46%) males had an abnormal result. CA125 was mainly used to investigate a wide range of signs and symptoms, and few tests were for follow up or screening of ovarian cancer. In female patients having a CA125 for suspicion of malignancy/ovarian cancer, only 39 (20%) of the abnormal results were caused by ovarian cancer. False positive results were largely caused by another malignancy (48 cases; 26%), benign ovarian disease (26 cases; 14%), and benign gynaecological conditions, particularly leiomyomas (18 cases; 9%). The specificity of CA125 for ovarian cancer increased with concentrations >1000 kU/litre.

Conclusions: These results confirm the high false positive rate and poor sensitivity and specificity associated with CA125. The substantial inappropriate usage of CA125 has led to results that are useless to the clinician, have cost implications, and add to patient anxiety and clinical uncertainty.

The CA125 antigen is a high molecular weight glycoprotein, which is expressed by a large proportion of epithelial ovarian cancers. It is detected by the OC125 monoclonal antibody, which was first described by Bast *et al* in 1981.[1] Since its discovery, CA125 has become well established as a tumour marker for epithelial ovarian cancer, and has come to have an important role in diagnosis, with its incorporation into the risk of malignancy index.[2] The sensitivity and specificity of CA125 is known to be poor. It is only raised in approximately 50% of stage 1 epithelial ovarian cancers and in 75–90% of patients with advanced disease. False positive results have been noted in many medical disorders, both malignant[3–5] and benign.[6–8] This lack of specificity has been widely investigated and CA125 has now been shown to be an effective marker for many diseases other than ovarian cancer.[9–13] At present, to the best of our knowledge, there are no guidelines produced by the Royal College of Pathologists or the Association of Clinical Biochemists to aid clinicians or laboratories in the most appropriate use of CA125.

> ''CA125 has become well established as a tumour marker for epithelial ovarian cancer, and has come to have an important role in diagnosis''

Requests for CA125 testing are increasing, but there are suggestions that a large proportion of this increase is a result of its use by specialities other than gynaecology or oncology, thus leading to concerns that CA125 is being used by clinicians who are not fully aware of its limitations and its role in ovarian cancer. This may result in missed diagnoses or unnecessary investigation of patients.

Therefore, a retrospective audit was undertaken at Queen's Hospital, Burton upon Trent, UK to investigate the role of CA125 in everyday clinical practice. The principle aim of our study was to identify the patient population having a CA125 measurement, to attempt to determine its contribution to individual patient management, and to improve referral patterns.

METHODS

Our study was a retrospective case note audit using the computerised HISS patient information system, carried out at Queen's Hospital, Burton upon Trent, UK. Every patient who had a CA125 measurement performed between April 2000 and April 2002 was identified and the audit population selected by taking the first 799 chronological hospital unit numbers. Data were collected from pathology, radiology, and laboratory reports and referral, clinic, and discharge letters. Information was collected on population characteristics, including the leading sign or symptom, the index CA125 and other tumour marker results (carcinoembryonic antigen, α fetoprotein (AFP), human chorionic gonadotrophin (HCG), CA19.9, and CA15.3), the mode of ovarian imaging, and the final diagnosis. To determine the indication for a CA125 measurement the patient's leading sign or symptom was categorised into ''suspicion of ovarian cancer'', ''suspicion of malignancy'', ''follow up of ovarian cancer'', ''screening for ovarian cancer'', and patients with a ''known malignancy'' other than ovarian in whom no other malignancy was suspected. A further category was patients in whom it was ''not possible to determine an indication''. Patients presenting with a pelvic mass, ovarian cyst, ascites, or abdominal distension were included in the suspicion of ovarian cancer group, whereas non-specific symptoms—for example, abdominal pain, anaemia, metastatic disease, weight loss, or dermatomyositis—were grouped together in suspicion of malignancy. The CA125 assays were performed in the on site

Abbreviations: AFP, α fetoprotein; HCG, human chorionic gonadotrophin

hospital clinical chemistry laboratory, where an abnormal result was taken to be 30 kU/litre or above. The clinical chemistry department performed no screening of requests and there were no hospital guidelines in place to aid clinicians in the most appropriate use of CA125.

Sensitivity was defined as the proportion of patients with ovarian cancer correctly identified by CA125, and specificity as the proportion of patients without ovarian cancer correctly identified by CA125.

RESULTS

The study comprised 799 patients: 751 female (94%) and 48 male (6%) patients, with 636 (80%) of the patients being over 50 years old. In this population, 221 (29%) of the female and 22 of the 48 male patients had an abnormal result (fig 1).

Because ovarian cancer was not relevant to the male population these patients were excluded from all further analyses. An indication for CA125 use in the female patients was apparent in 672 (89%) of cases (fig 2). A suspicion of ovarian cancer only accounted for 259 (34%) of the CA125 tests performed. A large proportion of CA125 tests—327 (44%)—were undertaken to investigate patients with a wide range of signs and symptoms (table 1).

When the CA125 concentration was correlated with the final diagnosis in patients having a CA125 measurement for suspicion of malignancy/ovarian cancer only 39 (20%) of the abnormal results in the female population were the result of ovarian cancer. The sensitivity of CA125 for ovarian cancer in female patients in this population was 88.6%, but with a specificity of only 72.0%. Patients without ovarian cancer had another malignancy in 48 cases (26%)—such as breast, bowel, or lung—or had benign ovarian pathology (26 cases; 14%), benign gynaecological conditions, particularly leiomyoma (18 cases; 9%), or hepatobiliary disease (12 cases; 6%) (fig 3). When the CA125 results over 1000 kU/litre were analysed the specificity of CA125 increased to 99.1%. Ovarian cancer was diagnosed in 23 of 28 cases, but there were five patients who had a CA125 concentration above 1000 kU/litre in the absence of ovarian cancer. There were three cases of metastatic disease from the breast, gallbladder, and an unknown primary tumour, and there were two cases of cirrhotic liver disease. However, increasing the cut off value to over 1000 kU/litre caused a fall in the sensitivity of CA125 for ovarian cancer to 52.3%.

The radiological investigations performed on the female population being investigated for suspicion of malignancy/ovarian cancer were reviewed (fig 4). Ultrasonography was the most frequently used modality, with 310 patients (53%) having a pelvic ultrasound as their sole investigation and 91 (16%) undergoing this test in conjunction with computerised tomography scanning. Urgent (within two weeks) diagnostic

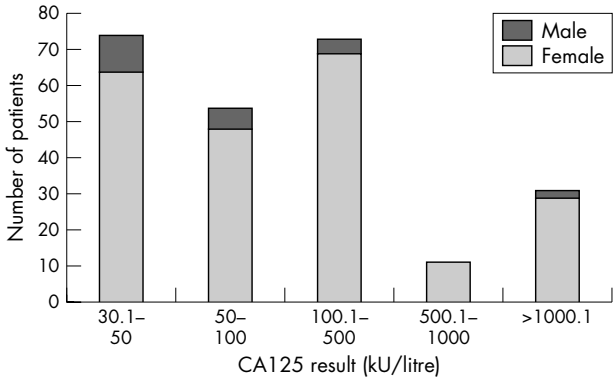

Figure 1 Distribution of abnormal CA125 results (n = 243).

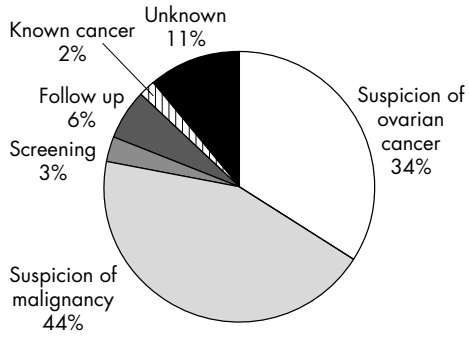

Figure 2 Indication for CA125 measurement in the female population (n = 751).

laparoscopy was performed in seven cases, five of which were preceded by a transvaginal ultrasound scan. One patient was investigated with magnetic resonance imaging. The likelihood of the ovaries being imaged increased with a rising CA125 result, except for patients with a CA125 between 500.1 and 1000 kU/litre. No imaging was performed in 134 (23%) cases; however, 108 (81%) of these had a normal CA125 result.

In this study population, 44 patients were diagnosed with first presentation of a malignant ovarian cancer. In 36 of these, the indication for a CA125 measurement was that they fell into the category of suspicion of ovarian cancer. The CA125 concentrations of these patients were examined and showed a wide distribution of results, with 23 patients having more than 1000 kU/litre but five having less than 30 kU/litre.

Additional serum tumour markers taken at the time of the index CA125 result showed that 422 (56%) of the female population had CA125 taken in isolation, unlike the male population in which the figure was 10 cases (20%). Of the 57 patients who were below 40 years old, only four had an HCG and AFP performed, one patient had AFP alone, and another HCG alone.

Screening for ovarian cancer only accounted for 24 patients in the audit. Ten of the tests were ordered in primary care, with gynaecologists responsible for seven cases and general surgeons for four cases. Imaging of the ovaries with transvaginal ultrasonography was performed in 13 of the 24 patients being screened.

The final analysis concentrated on the departments ordering CA125 measurement. Rheumatology, care of the elderly medicine, and haematology were grouped together as ''other medical specialities'' and orthopaedics and urology as ''other surgical specialities''. Gynaecologists were the most frequent users of CA125, but accounted for only 278 (36%) of all the tests ordered on female patients. Many other specialities, in particular—general surgery (109 tests; 15%), primary care (89 tests; 12%), and general medicine (78 tests; 10%)—were responsible for most of the remainder (fig 5).

In the male population, general medicine and general surgery initiated most of the requests for CA125—16 tests (33%) and 10 tests (21%), respectively.

DISCUSSION

Our audit provides a comprehensive review of the pattern of usage of CA125 measurement in a district general hospital. It shows that CA125 is being widely used as a diagnostic tool throughout the medical specialities for a whole range of signs and symptoms, and is not restricted to patients presenting with the classic picture of ovarian cancer. The use of CA125 as a tumour marker for monitoring treatment response and

Table 1 Clinical indication in female patients for CA125 measurement in the suspicion of malignancy category (n = 327)

Indication	No of patients	Indication	No of patients
Abdominal pain	116	Liver metastases	4
Abnormal vaginal bleeding	15	Lung metastases	1
Altered bowel habit	12	Lymphadenopathy	2
Anaemia	21	Mediastinal mass	2
Back pain	1	Osteomyelitis	1
Bone metastases	5	Peripheral neuropathy	3
Bowel obstruction	4	Pleural effusion	7
Brain metastases	5	Polyarthritis	4
Collapse	1	Postmenopausal bleeding	27
Dermatomyositis	10	Rectal bleeding	5
Fracture	1	Rectovaginal fistula	1
Hyperkalaemia	1	Renal failure	1
Hypercalcaemia	6	Shortness of breath	7
Hypertension	1	Thromboembolic disease	7
Jaundice	7	Weight loss	26
Lethargy	8	Vaginal discharge	2
		None stated	13

disease relapse in patients with known ovarian cancer only accounts for a small proportion of the tests performed.

The population of patients being tested for CA125 reflects the age distribution of ovarian cancer because most patients were female and over 50 years old. Six per cent of the population were male and it was difficult to determine the rationale for CA125 use in these cases; however, 38 of these 48 tests were ordered along with other serum tumour markers and it may be that CA125 was performed as part of a general screening test in the presence of a malignancy of unknown origin. A consequence of this audit is a directive informing clinicians that a CA125 assay is used as a marker for ovarian pathology and that its use in men is limited. A field requiring a mandatory yes/no response to the question "is the patient female?" has been added to the computer ward order entry system, to deter inappropriate testing.

> "A consequence of this audit is a directive informing clinicians that a CA125 assay is used as a marker for ovarian pathology and that its use in men is limited"

The signs and symptoms of ovarian cancer are known to be vague and non-specific in the early stages of the disease. The rationale of dividing the patients into symptoms most often associated with advanced ovarian cancer—namely, abdominal distension, ascites, pelvic mass, or an ovarian cyst[14]—and those with more non-specific symptoms was to attempt to identify patients who were more likely to have ovarian disease. Of the patients in the study population found to have ovarian cancer, 36 of the 44 were in the suspicion of ovarian cancer category and therefore a detailed history and examination would have correctly selected these.

It was apparent that CA125 was mainly being used to investigate a broad range of symptoms and was often not used in conjunction with ovarian imaging. A normal result seems to have been taken as an indication of the absence of ovarian disease in many cases because 27% of patients being investigated had a CA125 within normal limits and had no ovarian imaging. This may be because the suspicion of ovarian malignancy was low or because the clinician involved was not fully aware of the poor sensitivity of CA125. However, Alcazar *et al* and Troiano *et al* showed that transvaginal ultrasonography has a greater sensitivity and specificity than CA125 for diagnosing ovarian cancer,[15 16] and this supports the view that CA125 should be a second line investigation to determine the nature of an ovarian lesion identified on imaging.[17] By confining the population to one with a high clinical suspicion of ovarian cancer—for example, a complex pelvic mass or ascites of unknown origin—both the currently accepted sensitivity and specificity of CA125 in diagnosis would presumably increase. Several patients in our

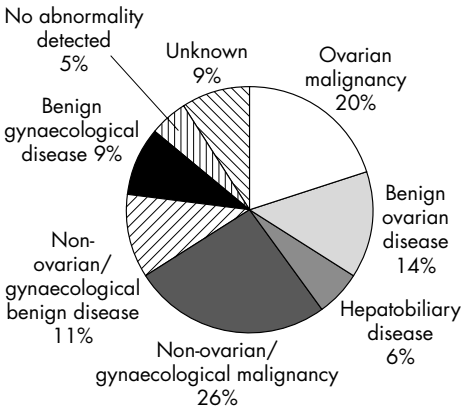

Figure 3 Final diagnosis in women with an abnormal result being investigated with CA125 (n = 191).

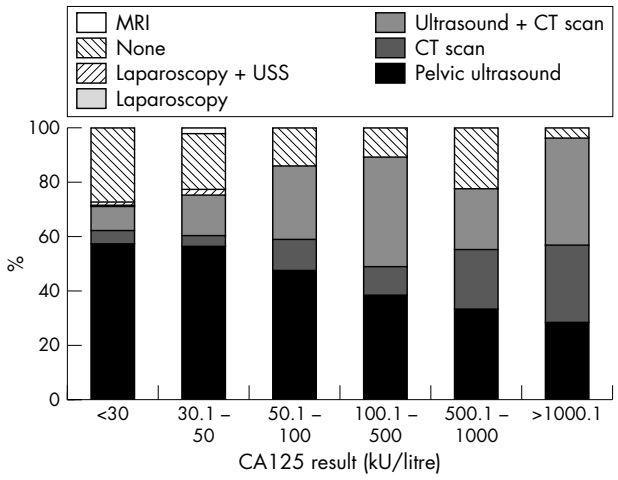

Figure 4 Imaging performed in women under investigation with CA125 (n = 586). CT, computerised tomography; MRI, magnetic resonance imaging; USS, transvaginal ultrasound scan.

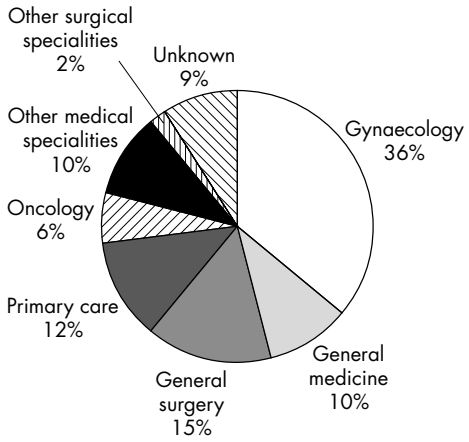

Figure 5 Departments using CA125 in the female population (n = 751).

study were investigated using CA125 for non-ovarian diseases, such as endometriosis, and as monitoring in some cases of leukaemia.

The number and combination of tumour markers performed did not appear to follow a pattern, and was the result of individual clinician choice. There is evidence that a combination of serum tumour markers is superior to CA125 alone in the diagnosis of ovarian cancer[18–20]; however, at present there is no consensus as to the optimum combination, and several of the tumour markers used in these studies are not available in most hospital clinical chemistry laboratories. The low use of AFP and HCG in the under 40 year old population suggests that there is a lack of awareness of ovarian germ cell tumours, which are more frequent in younger women.[21]

Large multicentre ovarian cancer screening trials are currently in progress,[22] and the results are awaited. A small proportion of our population (24 patients) had CA125 measured for screening performed outside clinical trials and on an individual clinical basis. Only 13 of these patients had ovarian imaging, often performed at variable intervals, and therefore not following the widely accepted management comprising a yearly CA125 measurement and a transvaginal ultrasound scan of the ovaries.

The lack of specificity of CA125 was highlighted in the large number of false positive results—80% of the abnormal results in the female audit population undergoing investigation for suspected malignancy/ovarian cancer were not caused by ovarian cancer. Malignancies at other sites, and inflammatory or benign gynaecological disease, were the most common causes for a raised CA125 concentration, as reported previously.[23] The specificity of CA125 increased with rising concentrations, although there were still five false positives with results over 1000 kU/litre, a recognised occurrence.[24–26] Numerous medical disorders are known to be associated with a false positive result; however, many clinicians did not appear to be aware of this, and many patients underwent investigations that may not have been required, possibly generating considerable patient anxiety and stress.

To reduce the number of inappropriate tests many laboratories have introduced screening of requests based on the clinical information accompanying the sample, and thereby enabling obviously unnecessary tests to be excluded—for example, tests on male patients. However, improved education is the best approach to combat CA125 misuse. Consequently, a message detailing the usefulness of CA125 measurement has been added to the computer order entry system at Queen's Hospital. Multidisciplinary teaching, including both hospital and primary care practitioners, may help clinicians to make informed decisions on whether a tumour marker would aid a patient's management and investigation and would therefore reduce the need of the clinical chemistry department to police the service. Guidelines for tumour marker use, as produced by the Association of Clinical Biochemists in Ireland,[27] may be a useful tool in this education process.

The results of this audit confirm the high false positive rate and the poor sensitivity and specificity associated with CA125. There is substantial inappropriate usage of CA125, which has led to results that are of no use to the clinician, have cost implications, and add to patient anxiety and clinical uncertainty.

Take home messages

- We undertook an audit of CA125 usage in a district general hospital and found substantial inappropriate usage of CA125 measurement, leading to results that are of no use to the clinician, have cost implications, and add to patient anxiety and clinical uncertainty
- The results also confirmed the high false positive rate and the poor sensitivity and specificity of CA125 as a marker of ovarian cancer

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