# Combination of cancer antigen 125 and carcinoembryonic antigen can improve ovarian cancer diagnosis

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**ABSTRACT**

**INTRODUCTION:** The purpose of the present study was to evaluate the ability of the tumour marker carcinoembryonic antigen (CEA) in combination with cancer antigen 125 (CA-125) to differentiate between malignant ovarian and malignant non-ovarian disease.

**MATERIAL AND METHODS:** All patients attending the Department of Gynaecology, Herlev Hospital, who underwent an "ovary lab investigation" between 1 January 2006 and 31 December 2008 were included. Among a total of 640 patients, 355 had a malignant diagnosis. Preoperative CEA and CA-125 serum levels and final malignant diagnosis after surgery were extracted from the medical records.

**RESULTS:** Among the patients with CEA levels > 5 ng/ml, 68% had non-ovarian malignancies. This test identified 39% of the non-ovarian cancers correctly. In patients with a CA-125/CEA ratio > 25, an ovarian cancer was found in 82%. The CA-125/CEA test identified 63% of the non-ovarian cancers correctly. The specificity increased to around 85% when the cut-off value of the CA-125/CEA ratio was increased from 25 to 100.

**CONCLUSIONS:** In patients with an undiagnosed tumour in the pelvis, the CA-125/CEA ratio may be used to preoperatively identify a substantial fraction of patients with non-ovarian malignancies. In the study population, the specificity rose to 85% when the cut-off value was increased from 25 to 100, which highlights the usefulness of a higher cut-off level.

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The initial symptoms of ovarian cancer are subtle. Despite careful preoperative examination and a Risk of Malignancy Index (RMI) > 200, patients with a pelvic tumour may prove to have a non-ovarian cancer at surgery [1-4]. The pelvic mass may e.g. be a primary tumour arising from the uterine corpus, the urine bladder or the colon. In other cases, the tumour may be an ovarian metastasis derived from breast, gastric, pancreatic or lung cancer. In such cases, the patient undergoes unnecessary surgery, is exposed to a risk of morbidity and the appropriate treatment is delayed.

Numerous tumour markers have been tested to improve the sensitivity and specificity of preoperative tests in patients suspected of having ovarian cancer. In Denmark, cancer antigen 125 (CA-125) is used routinely as part of the RMI in which ultrasound, menopausal status and serum CA-125 are integrated into one scoring system that helps predict whether an ovarian tumour is benign or malignant [5]. When the RMI is > 200, the tumour is considered malignant and laparotomy is planned. If an ultrasound scan indicates advanced disease, positron emission tomography-computed tomography (PET-CT) is used to assess operability. Conversely, when the RMI is < 200, the probability of ovarian cancer is considered low and the patient is referred to laparoscopic surgery. Further investigations such as radiography of the colon, colonoscopy, cystoscopy, fractionated abrasion and MRI are not performed routinely.

Recently, Yurkovetsky et al [6] developed a multimarker assay for early detection of ovarian cancer, suggesting a panel of CA-125, human epididymis protein 4 (HE4), carcinoembryonic antigen (CEA), and vascular cell adhesion molecule 1 (VCAM-1) in postmenopausal normal-risk women as an initial step in a screening strategy for epithelial ovarian cancer similar to the RMI. The authors concluded that the new findings required additional validation.

Elevated CA-125 levels are found in 82% of patients with ovarian cancer, 28% of patients with non-gynaecological cancers (including pancreatic cancer, breast cancer, and colon cancer), 6% of patients with benign gynecological diseases (including endometriosis, leiomyomas and pelvic inflammatory disease, PID), or other medical conditions (including hepatic cirrhosis and heart failure) – and, furthermore, in 1%of the normal population [7]. For malignant epithelial ovarian tumours, the CA-125 level is related to both the histological subtype and the stage of disease. CA-125 is more often elevated in serous than in mucinous ovarian tumours, and while only 50% of ovarian cancers in stage I and II are associated with elevated CA-125, this is found in 90% of patients at stage IIIC or IV [8, 9].

Carcinoembryonic antigen (CEA) is a glycoprotein that is synthesized in foetal tissues and in some carcinomas. Serum concentrations exceeding 5 ng/ml are

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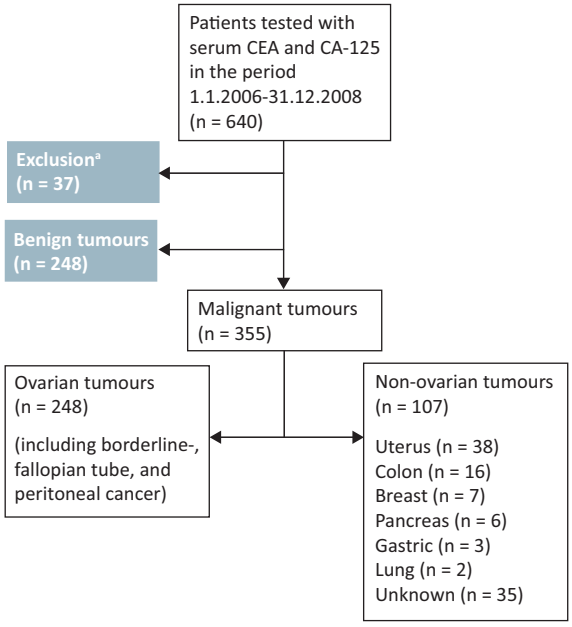
often found in patients with gastrointestinal carcinomas, breast cancer, lung cancer and some types of gynaecological tumours. Furthermore, elevated CEA is correlated with infection, pancreatitis, hepatic cirrhosis and certain benign tumours. In patients with colorectal cancer, the presence of elevated CEA depends on the stage of the disease [10]. However, CEA may still have clinical importance in colorectal cancer, as values above 20 ng/ml are associated with metastatic disease [11]. The marker is now used routinely for monitoring of patients after surgery for colorectal cancer, where a rise in CEA suggests progression. Serum CEA is elevated in approximately 35% of all ovarian cancer patients and occurs more often in mucinous tumours (88%) than in serous tumours (19%) [12-15].

In 1990, Buamah et al published a study based on 155 patients with elevated CA-125: 47 with ovarian cancer, 38 with colorectal cancer, 24 with cervical cancer, 20 with lung cancer, 17 with gastric cancer and nine with pancreatic cancer [16]. In this population, the CA-125/CEA ratio appeared to be excellent for differentiation between ovarian cancer and non-ovarian cancers, since all 47 patients with ovarian cancer had a ratio of more than 25.

In 1992, Yedema et al published a study based on 71 patients: 47 with ovarian cancer and 24 with colorectal cancer, and here the positivity in the test of the CA-125/CEA ratio (value exceeding 25) likewise showed a sensitivity of 91% and a specificity of 100% for detection of ovarian cancer [17].

**FIGURE 1**

Flow chart of patients suspected of having ovarian cancer.




a) Thirty-seven patients were excluded because the testing of CEA and CA-125 was done only because "standard lab investigation" had been performed by mistake. These patients were of no relevance regarding ovarian cancer.

CA 125 = cancer antigen 125; CEA = carcinoembryonic antigen.

In several ovarian cancer trials under the European Organization for Research and Treatment of Cancer (EORTC), the serum CEA has been used as a criterion for further investigation, although there is little evidence of its usefulness. In 2006, routine CEA measurement in patients referred for ovarian cancer was introduced as part of an EORTC project at the Department of Obstetrics and Gynaecology, Herlev Hospital, Denmark.

The purpose of the present study was to determine whether CEA alone or in combination with CA-125 preoperatively can be used to differentiate between malignant ovarian disease and malignant non-ovarian disease in the pelvis, with a view to optimizing the selection for appropriate surgery.

## MATERIAL AND METHODS

The study population consisted of consecutive patients referred to the Department of Obstetrics and Gynaecology, Herlev Hospital, who underwent a standard "ovary lab investigation" including CA-125 and CEA in the period from 1 January 2006 through 31 December 2008. Test results from primary admissions were selected and the CA-125/CEA ratios were calculated. The discharge diagnosis of all patients was obtained from the main hospital database.

In total, 640 patients were blood tested during the study period. Thirty-seven patients with the following diagnoses were excluded – neoplasma malignum cervicis uteri, neoplasma malignum vulva, sterilitas femina, abortus spontanues, enterocele vaginalis, abscessus vulva, prolapsus genitalis femina, or graviditas extrauterina – because in these cases the standard "ovary lab investigation" had no relevance for the present issue. Furthermore, a total of 248 patients had a benign ovarian tumour or other benign disease (e.g. infection or endometriosis) and were therefore excluded from the study population (**Figure 1**).

Since the treatments for ovarian cancer, fallopian tube cancer, primary peritoneal cancer and borderline ovarian tumour were identical, these diagnoses were categorized jointly as ovarian cancer. Moreover, these diseases had no separate diagnostic codes through the entire study period because the coding procedure changed over time. The diagnostic code for suspicion of malignant tumour in the female genital organs was categorized as ovarian cancer and the diagnostic code for suspicion of malignancy was categorized as unknown malignancy.Values of CA-125, CEA and the CA-125/CEA ratio were defined as positives when the values were as expected for ovarian cancer (CA-125 > 35 U/ml, CEA < 5 ng/ml and CA125/CEA > 25). The cut-off level for the CA-125/CEA ratio was 25, as defined in previous studies.

The R Statistics Software (version 2.9.0, 2009; R

TABLE 1

Carcinoembryonic antigen elevation and the cancer antigen 125/carcinoembryonic antigen ratio among ovarian versus non-ovarian cancer patients.

| | Ovarian, n (n = 248) | Non-ovarian, n (n = 107) | Sensitivity, % mean (CI) | Specificity, % mean (CI) | PPV, % mean (CI) | NPV, % mean (CI) | p values |
|---|---|---|---|---|---|---|---|
| CEA < 5 ng/ml | 228 | 65 | 91.9 (87.8-95.0) | 39.3 (30.0-49.2) | 77.8 (72.6-82.4) | 67.7 (54.7-79.1) | < 0.001 |
| CA-125/CEA > 25 | 182 | 40 | 73.4 (67.4-78.8) | 62.6 (52.7-71.8) | 82.0 (76.3-86.8) | 50.4 (41.6-59.2) | < 0.001 |
| CA-125/CEA > 100 | 138 | 17 | 55.6 (49.2-61.9) | 84.1 (75.8-90.5) | 89.0 (83.0-93.5) | 45.0 (38.0-52.2) | < 0.001 |

CA 125 = cancer antigen 125; CEA = carcinoembryonic antigen; CI = 95% confidence interval; NPV = negative predictive value; PPV = positive predictive value.

Foundation for Statistical Computing, Vienna, Austria) and SPSS (PASW Statistics 18, release 18.0.0, 2009, Chicago; SPSS Inc.) were used for all calculations and graphs. Categorical variables were tested using Fisher's exact test. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated by an exact binomial method. All tests were two-sided and p values below 0.05 were considered significant.

*Trial registration:* not relevant.

## RESULTS

Among a total of 355 patients with ovarian cancer and related tumours, 248 patients (70%) had ovarian cancer (214 ovarian cancers, 18 borderline ovarian tumours, 10 fallopian tube cancers and six primary peritoneal cancers) and the remaining 107 patients (30%) had other malignant tumours (38 uterine corpus cancers, 16 colorectal cancers, seven breast cancers, six pancreatic cancers, three gastric cancers, two lung cancers and 35 unknown primary tumours).

CA-125 levels > 35 U/ml were found in 78.6% of ovarian cancer patients and in 50.0% of colon cancer patients. CEA levels > 5 ng/ml were found in 8.1% of ovarian malignancies and in 39.3% of non-ovarian malignancies, most frequently in patients with colon cancer (69.0%).

In patients with CEA levels < 5 ng/ml, 77.8% (95% confidence interval (CI) 72.6-82.4%; p < 0.001) had ovarian cancer (PPV = 77.8%), i.e. non-ovarian malignancies could be excluded with 77.8% certainty when CEA levels were < 5 ng/ml. Among patients with CEA levels > 5 ng/ml, 67.7% (CI 54.7-79.1%; p < 0.001) had a non-ovarian malignancy (NPV = 67.7%). This test identified a total of 39.3% (CI 30.0-49.2%; p < 0.001) of the non-ovarian diagnoses (specificity = 39.3%) (**Table 1**).

Ovarian cancer was predicted in 82.0% (CI 76.3-86.8%; p < 0.001) when the CA-125/CEA ratio was > 25. The NPV was 50.4% (CI 41.6-59.2%; p < 0.001) and the CA-125/CEA test identified a total of 62.6% (CI 52.7-71.8%; p < 0.001) of the non-ovarian diagnoses (specificity = 62.6%) (Table 1, **Figure 2**).

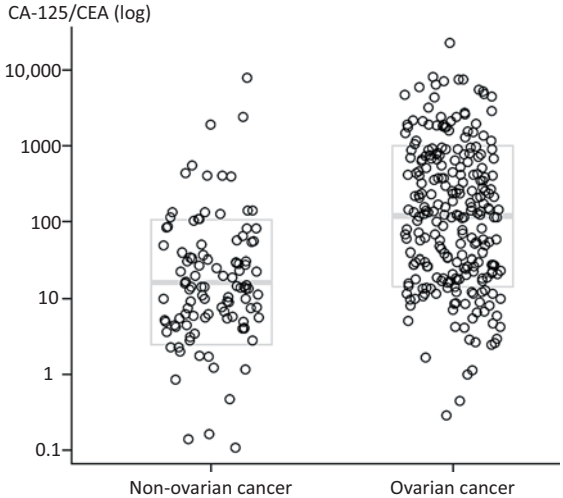
## DISCUSSION

By using the CA-125/CEA ratio rather than CEA alone, a larger proportion of patients with non-ovarian cancers was identified. In this study, the use of the CA-125/CEA ratio would spare 67 out of 107 patients with non-ovarian cancers from a planned unnecessary operation. With a ratio cut-off value of 25, an average of 5.3 patients should be tested further to prevent inappropriate surgery. Measurement of CA-125/CEA was associated with no additional discomfort, since the extra blood samples required can easily be included in the laboratory investigations already planned.

These findings suggest that any patient referred to the hospital with an undiagnosed tumour in the pelvis should – in addition to RMI – be tested by using the CA-125/CEA ratio < 25 as a criterion for further examination such as computed tomography of the abdomen, colonoscopy, mammography, magnetic resonance imaging, etc. Consequently, every ovarian cancer patient with a CA-125/CEA ratio < 25 (false negatives) will go through

FIGURE 2

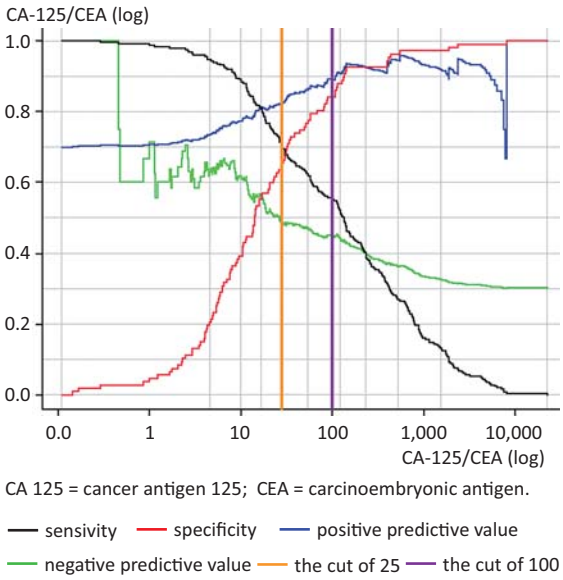
Graphic illustration of the cancer antigen 125/carcinoembryonic antigen ratio in ovarian and non-ovarian cancer patients.




CA 125 = cancer antigen 125; CEA = carcinoembryonic antigen.

FIGURE 3

Increased specificity due to a different cut-off value for the cancer antigen 125/carcinoembryonic antigen ratio.




CA 125 = cancer antigen 125; CEA = carcinoembryonic antigen.

sensivity specificity positive predictive value
negative predictive value the cut of 25 the cut of 100

unnecessary examinations which might delay relevant treatment. Ovarian cancer progresses rapidly and the examination programme should therefore be focused. Furthermore, an investigation such as colonoscopy would (apart from the discomfort) add a risk, although small, of intestinal perforation. On the other hand, non-ovarian cancer patients with a CA-125/CEA ratio > 25 (false positives) would undergo a laparotomy performed by a gynaecologist. Most likely, the operation would be cancelled and instead a new elective operation by a proper specialist (a colorectal surgeon) would be planned. In addition to the risk associated with surgery, the patient would be subjected to further delay in relevant treatment, e.g. a new operation or chemotherapy.

This material is based on a study group in which all patients with benign tumours were excluded; thus, results cannot be generalized to a population of patients referred with an undiagnosed tumour in the pelvis. Most often, patients with benign tumours have normal CEA and CA-125 serum values. In this study, only 12 (4.8%) of 248 patients with benign diseases had CEA levels > 5 ng/ml (median CEA = 1.4 ng/ml). Using the CA-125/CEA ratio on patients with benign tumours seemed irrelevant and therefore this group was excluded.

In previous studies it was found that the CA-125/CEA test had both high sensitivity and specificity with regard to the diagnosis of ovarian cancer [14-16]. All of these studies did, however, include only patients with well-defined diseases, most of them at advanced stages of cancer. The present study was based on patients referred with an undiagnosed tumour in the pelvis, primary weighted as ovarian cancer. The CA-125/CEA calculations were assessed in a clinically relevant situation, namely when the diagnosis was not yet known. Ovarian cancer patients accounted for 65.0% and colon cancer patients for only 4.5% of the study population. The remaining patients had other malignancies such as uterine corpus cancer, breast cancer, pancreatic cancer, gastric cancer, lung cancer and unknown primary tumours. Furthermore, this population included tumours of all stages (including borderline tumours) and the results should therefore be considered more applicable to the clinical situation.

The aim of this study was to evaluate a method for the identification of non-ovarian cancer patients in a clinical group referred with an undiagnosed tumour in the pelvis, so that more patients may be selected for the right treatment before surgery. Most importantly, such a test needs to have a high specificity as well as a high PPV. In our population, when the cut-off ratio was increased from 25 to 100, the specificity and PPV both approached 85% (**Figure 3**). The disadvantage of increasing the cut-off value is that sensitivity decreases. However, this is likely to be less troublesome for ovarian cancer patients who will then undergo further medical tests than for those false-positive cases (patients with colon cancer) who will be exposed to a suboptimal, planned operation.

With a cut-off value of 25, our test misdiagnosed 66 patients with ovarian cancer (false negatives) and 40 patients with non-ovarian cancer (false positives). With a cut-off of 100, a total of 110 ovarian cancer patients (false negatives) would have gone through further examinations, while the number of suboptimal, planned operations would have been reduced to 17 (false positives). The number of non-ovarian cancer patients who were correctly identified would increase to 90, corresponding to 84.1% (Table 1).

## CONCLUSION

In patients with an undiagnosed tumour in the pelvis, the CA-125/CEA ratio may preoperatively identify a substantial fraction of patients with non-ovarian malignancies. These findings support the notion that every patient referred to the hospital with an undiagnosed tumour in the pelvis should be tested – in addition to RMI – by using the CA-125/CEA test as a criterion for further examination. In this population, the specificity increased to almost 85% when the cut-off value was increased from 25 to 100, which justifies the use of a higher cut-off level.

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