

Measuring HE4 alongside CA125 for Ovarian Cancer Diagnosis: A pilot clinical study

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Abstract

[The Instructions to Authors state no abstract is required for a Research Letter but the submission sysem demands one, so this text is included.] In order to assess whether measuring HE4 might add to the performance of CA125 in diagnosing ovarian cancer, we measured both markers in 33 individuals with elevated CA125. We found that HE4 elevated above 150 pmol/l was present in all 9 cases of ovarian cancer and in the single case of pancreatic cancer. HE4 levels below 77pmol/l seen in 16 cases were associated with non-malignant gynaecological conditions and with there being no identified cause for elevated CA125. Two cases with HE4 between 77 and 149 pmol/l had no gynaecological conditions and 2 had no an identifiable cause. Measuring both markers could lead to improved sensitivity and specificity of the initial diagnostic step.

Measuring HE4 alongside CA125 for Ovarian Cancer Diagnosis: A pilot clinical study

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Running title: HE4 alongside CA125 for ovarian cancer diagnosis

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Introduction

In the United Kingdom (UK) the first step in the ovarian cancer diagnostic pathway for patients presenting to their General Practitioner (GP) with relevant symptoms is to measure the CA125 in serum[1]. This

process has a good positive predictive value to trigger the next investigation, a pelvic ultrasound to identify a lesion. Measuring Human Epididymis Protein 4 (HE4) identifies more accurately those pelvic masses that are malignant[2], although this is not in current routine use in the UK. The role of HE4 as a diagnostic test in primary care has recently been evaluated[3]. HE4 performed well in patients aged under 50. The possibility exists that measuring it alongside CA125 would improve the diagnostic performance of the standard pathway. We sought to relate the HE4 results to clinical status in a group of patients with elevated CA125 from whom clinical information was available.

Methods

When a primary care sample with elevated CA125 is identified by the laboratory of this hospital, the biochemist’s report includes advice to consider a pelvic ultrasound scan. We arranged for these ultrasounds to be done in the main hospital radiology department rather than community sites and women were invited to consent to join the study. Serum HE4 was measured as well as CA125 in a new blood sample and medical records were reviewed. In a subsidiary study, women who had an ovarian cancer diagnosis made on a different pathway were invited to consent to having their serum HE4 measured. The analysis was by a chemiluminescent enzyme immunoassay technique using a Fujirebio Lumipulse G600II analyser. Cut-off values for HE4 of 77 and 150 pmol/l are in use[3,4].

The progress of the study was interrupted by the COVID 19 pandemic and it was not possible to arrange for all the subjects to have their ultrasounds undertaken at the hospital. The numbers we recruited were fewer than expected.

Results

There were 33 participants in whom both markers were measured. We found that HE4 elevated above 150 pmol/l was present in all 9 cases of ovarian cancer and in the single case of pancreatic cancer. Other conditions associated with elevated HE4 included hepatic cirrhosis. Normal HE4 levels below 77pmol/l seen in 16 cases were associated with non-malignant gynaecological conditions and with no identified cause for elevated CA125 (See Table). Two cases with HE4 between 77 and 149 pmol/l had no gynaecological conditions and 2 with values in this range had elevated CA125 on 2 occasions without an identifiable cause.

Conclusions

Our findings suggest questions that might be addressed in a larger study. It might be possible to restrict imaging investigation to women who have both markers elevated, thereby saving resources. It also might be possible to explore a lower cut off value for CA125. This would improve the sensitivity of CA125 for ovarian cancer detection if specificity could be maintained when a simultaneous low-range HE4 excluded ovarian malignancy.

References

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	No identifiable cause	Chronic elevation of CA125	Non-malignant gynae	Ovarian/ peritoneal cancer	Other
Age <50	7(0)	3(0)	6(0)	0	0
Age 50+	2(2)*	3(1)	2(0)	9(9)	1(1)

Table: Associations of elevated (>35 u/ml) CA125 in patients studied (Number with HE4 >150 pmol/l in parentheses)

* These women had hepatic cirrhosis

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Contributions to authorship

SMC developed the concept for the study and initiated the protocol.

CE advised on the biochemistry components of the protocol and led the identification of potential recruits.

AS advised on practical points in the protocol and led the recruitment of subjects.

EJC led the department in which CEB conducted the HE4 assays and both contributed to the interpretation of findings.

All authors agreed the text of the manuscript.

The study was approved by Cambridge East Research Ethics Committee 225328, 28 December 2018.