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Letter to the Editor

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Could kidney glomerular filtration impairment represent the "Achilles heel" of HE4 serum marker? A possible further implication

Keywords: bias; biomarkers; He4 serum level; ovarian cancer markers; renal failure; serum dosage.

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To the Editor,

We read with great interest the recently published results of the expert meeting about the analytical and clinical performance of human epididymis protein 4 (HE4) quantitative determination. Recent data on the use of HE4 and the Risk of Ovarian Malignancy Algorithm (ROMA) have supported the utility of this new cancer biomarker for risk stratification, prognosis and monitoring of epithelial ovarian cancer [1].

These conclusions seem to be supported by very recent evidences: the work of Sandri et al. confirms the accuracy of HE4 and the ROMA algorithm in the distinction of ovarian carcinoma from benign disease, thanks to better accuracy of ROMA than CA125 alone [2].

According to HE4 investigation by manual HE4-EIA test (Assay A) in 802 and by Architect-HE4 (Assay B) in 792 healthy Nordic reference population, between all covariates (age, sex, body mass index, smoking habits and creatinine), age emerged as the main determinant of HE4 value in those subjects [3]. Furthermore, the finding of high HE4 levels among 29% of smokers in respect to non-smokers should lead to a reduction of age-dependent influence in defining the cut-off value.

However, the following evidences reported by Moore et al. confirmed the HE4 age-dependent value, with upper 95th percentile of 89 pmol/L for premenopausal women and 128 pmol/L for post-menopausal women [4].

Unexpectedly, a comparison of serum HE4 (assay B) with CA125 in malignant and non-malignant diseases by Escudero et al. identified renal failure as the most important co-factor of HE4 increased values in absence of malignant diseases [5].

Hertlein et al. assessed that the HE4 age-dependent increase (assay B) was higher in women than in men; anyway the highest values registered in presence of kidney failure were not influenced by sex. The association of renal failure with liver cirrhosis, cholestasis, ureteral calculus, prostatitis and benign lung diseases significantly contributed to the highest levels. The authors therefore recommended HE4 not to be used in patients with chronic renal diseases, abnormal serum creatinine levels and undergoing nephrotoxic therapies [6].

Nagy et al. compared HE4 values (assay B) in two cohorts of women without ovarian malignancies, the first with normal GFR values (mL/min/1.73 m^2 - *4v-MDRD formula*) and the second one affected by different stages of chronic kidney disease. They found a strict inverse relation between HE4 increase and eGFR for all stages of renal disease. However, CA125 serum levels were only slightly higher than normal in subjects in stage 3, resulting significantly elevated only in post-menopausal women with stage 4 renal disease [7].

Hellstrom et al. first tested urinary HE4 (assay A) as biomarker for ovarian neoplasms using the normalized ratio HE4(pM)/creatinine (mg/dL). Similar to serum HE4 test, at a specificity of 94.4%, the urinary test was positive for 86.6% of stage I/II and 89% of stage III/IV ovarian cancer (90.5% of serous histotype) leading to

propose it for both diagnosis and follow-up after treatment [8].

Macuks et al. comparing serum and urinary HE4 (assay B) in detecting invasive ovarian cancers reported higher diagnostic accuracy of serum test than urinary one. However, the authors recommended the urinary test in assessing the risk of non-invasive ovarian malignancy, proposing a normalized ratio by eGFR rather than by creatinine [9].

It is now evident that any impairment of renal function may cause a misinterpretation of the ROMA score and the loss of its rationale to provide the clinician an improved distinction between malignant or benign ovarian disease.

No authors, while emphasizing the negative influence of kidney impairment on the value of serum HE4 test, suggested a way to circumvent this limit [5–7].

The attempt by Macuks [9] of correcting the urinary test for eGFR led us to propose a normalization of serum HE4 by the kidney glomerular filtration index in order to avoid as much as possible the falsely increased serum HE4 levels in case of reduced renal function.

In our clinical practice we found high HE4 levels (according to menopausal status) in patients undergoing peritoneal or hemodialysis with consequently increased ROMA scores in the absence of histologically confirmed neoplastic disease.

In the near future a further step is therefore necessary to answer this still open question and to protect the potential of HE4 test in improving the specificity of ROMA score in ovarian cancer detection.

Conflict of interest statement

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