GinPolMedProject ©
4 (50) 2018: 039-043 • REVIEW ARTICLE

Clinical usefulness of HE4 in pathologies other than ovarian carcinoma. A literature review

Andrzej Brenk (AEF), Piotr Bodzek (EF), Mikołaj Baliś (EF), Aleksandra Barbachowska (EF), Iwona Janosz (F), Anita Olejek (AE)

Department of Gynecology, Obstetrics and Gynecologic Oncology in Bytom, Medical University of Silesia in Katowice, Poland

AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection · **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** Funds Collection

SUMMARY

HE4 is a glycoprotein broadly used as a tumor marker in ovarian carcinoma. This article presents a literature review on the clinical usefulness of HE4 concentrations in the diagnosis and treatment of diseases other than ovarian cancer. The authors discuss the role of HE4 in endometrial cancer, vulvar cancer and cervical cancer. Other disorders of the female reproductive system in which the role of HE4 is discussed include endometriosis, uterine fibroids, pelvic inflammatory disease and benign ovarian tumors. Moreover, the authors mention also reports that demonstrate an increase in HE4 concentration in pregnant women, as well as its potential role as a marker of preterm delivery and miscarriage. Finally, the article presents the clinical role of HE4 in patients with lung cancer, chronic kidney disease and colorectal carcinoma.

Key words: HE4 protein; reproductive system cancers; other cancers; non-neoplastic conditions

Address for correspondence: Piotr Bodzek
Department of Gynecology, Obstetrics and Gynecologic Oncology in Bytom
ul. Stefana Batorego 15, 41-902 Bytom, Poland
Tel. +48 32 786 15 40, e-mail: piotr.bodzek@sum.edu.pl

Word count: 2033 **Tables:** 0 **Figures:** 0 **References:** 40

Received: 15.11.2018
Accepted: 27.11.2018
Published: 19.12.2018

INTRODUCTION

Human epididymis protein 4 (HE4) is a glycoprotein broadly used as a tumor marker in ovarian carcinoma. Together with CA-125, it is used in the ROMA algorithm that serves for the differentiation of malignant ovarian tumors from benign ones [1]. Some authors suggest that HE4 is more effective in detecting a relapse or progression of ovarian carcinoma than CA-125 [2]. In some gynecological diseases other than ovarian carcinoma, serum HE4 levels are sometimes elevated as well. Moreover, they also increase with age and in smokers, while HE4 dynamics during pregnancy remains not entirely explained [3–6]. HE4 stimulates cancer cell proliferation, inhibits apoptosis, causes chemotherapy resistance and promotes cell transition from G1 phase to S phase, which maintains cell viability [7]. The usefulness of HE4 in the diagnosis of cancers other than ovarian carcinoma has not been well documented.

ENDOMETRIAL CANCER

Endometrial cancer is the most common cancer of the female genital organs in developed countries. Such a high incidence is attributed to a growing proportion of obese women in the society [8]. The HE4 protein can be potentially used in prognosis as well as in the assessment of a differentiation grade and clinical advancement of this cancer. This entails the selection of appropriate surgical treatment [9,10]. The study of Li et al. [11] indicates that the higher the plasma HE4 level in endometrial cancer patients, the higher the mortality rate, the greater the clinical stage, the lower the differentiation grade and the worse the prognosis. This marker is also higher than in patients with atypical endometrial hyperplasia, who present higher level than healthy women with normal endometrium [11]. Moreover, the study of Australian authors, Brennan et al. [12], has

shown that the higher the HE4 level, the higher the risk of neoplastic infiltration on the external layer of the myometrium, which raises the risk of metastatic foci in lymph nodes considerably. The authors believe that an intraoperative confirmation of high differentiation with HE4 below 70 pmol/L may indicate that lymphadenectomy is redundant as the risk of lymph node metastases is extremely low [12]. Moreover, Abbink et al. [13] suggest that HE4 assays are useful in the detection of distant metastatic foci as its level is significantly higher than that in local relapse. In this case, HE4 is superior to CA-125, which was elevated in only 37% of patients compared with 67% for HE4. Elevated HE4 values heralded relapse 126 days (median) before the occurrence of clinical signs [13]. Combined efforts of Czech and Danish scholars have produced an HE4ren formula, which combines an HE4 value with glomerular filtration. It can be used for a comparison of HE4 values in women with lower glomerular filtration with those of women with normal renal function. In this study, it has been shown that HE4ren is useful for prediction of the depth of myometrial infiltration, which is of prognostic significance in patients with endometrial cancer [14]. A combination of HE4 with CA-125 seems to be an ideal solution allowing to detect endometrial cancer with the greatest sensitivity and specificity, which was confirmed by Dong in 2017 [15]. For the purpose of high-sensitivity clinical FIGO staging, a novel RENT algorithm has been developed. It involves the following parameters: age, BMI, parity, menopausal status, use of contraception and hormonal replacement therapy, hypertension and serum HE4 and CA-125 levels. It helps determine a clinical stage with the sensitivity and specificity of 90% and 76%, respectively. This is relevant for preoperative prognosis and selection of an appropriate therapy, and for estimating the required extent of the surgery [16].

VULVAR CARCINOMA

Vulvar carcinoma is a rare cancer accounting for 3% to 5% of gynecological cancers [17]. A study of Montagnan et al. [18] reveals that the HE4 marker is also increased in this disease (76.8 pmol/L vs 40.3 pmol/L in healthy women). By contrast with HE4 levels, CA-125 does not increase in this cancer and remains within normal ranges [18]. However, a potential use of HE4 in early diagnosis of vulvar carcinoma requires further investigation and testing in larger groups of patients.

CERVICAL CANCER

HE4 levels have also been determined in cervical cancer patients. In cases of normal cervical epithelium and intraepithelial neoplasia, HE4 levels were normal, but elevated in invasive carcinoma [19].

ENDOMETRIOSIS

HE4 may be helpful in the diagnosis of endometriosis. When combined with CA-125, it helps distinguish endometrial cysts from malignant ovarian tumors [20]. In 2016, Zapardiel et al. [21] conducted a multicenter study in which they demonstrated that the use of both these tumor markers helps rule out ovarian carcinoma with a high probability in endometriosis patients as CA-125 is elevated in both endometriosis and ovarian cancer women, while HE4 is elevated only in patients with ovarian carcinoma [21]. Leggieri et al. [22] have examined concentrations of the discussed two markers before and after laparoscopic removal of endometrial cysts. It occurred that HE4 levels do not change, while CA-125 levels markedly fall [22]. Huhtinen et al. [23] have proven that the HE4 marker has a potential ability to distinguish between ovarian tumors, endometrial tumors and ovarian endometrial cysts. It has been shown that the HE4 level is the highest in patients with ovarian carcinoma (1,125.4 pmol/L), in whom it exceeds the upper limit of normal. It is much lower in endometrial cancer (99.2 pmol/L), and the lowest, below the upper limit of normal, in women with ovarian endometrial cysts (46.0 pmol/L) or endometriosis at another site (45.0 pmol/L) [23]. Other authors indicate that HE4 levels may increase significantly (137.6 pmol/L) after chocolate cyst rupture with its contents spread in the pelvic cavity [24].

NON-MALIGNANT LESIONS OF THE FEMALE REPRODUCTIVE ORGANS

Studies of the Polish researchers from the Pomeranian Medical University, conducted in patients with *BRCA1* mutation, confirmed that HE4 levels increase in ovarian carcinoma and endometrial cancer, and remain stable in non-malignant lesions of the female reproductive system, such as uterine fibroids, inflammatory

conditions, endometriosis or benign ovarian tumors. These patients, who did not have any active neoplastic processes, presented low HE4 levels, comparable to those in the healthy population. However, each, even slight increase in the level of this protein was indicative of an active proliferative process within the ovary, fallopian tube or uterine body [25]. Another large study of American authors also seems to confirm this hypothesis. The study involved over a thousand women with various pathologies: ovarian carcinoma, endometrial cancer, ovarian mature teratomas, uterine fibroids, inflammatory diseases in the reproductive system and endometriosis. It occurred that CA-125 levels were elevated in more patients than HE4, and HE4 rose only in ovarian carcinoma and endometrial cancer [26]. Another study that confirms that HE4 is a good marker in the differentiation of pelvic tumors into benign and malignant is the one carried out by Goff et al. [27].

HE4 IN PREGNANCY

Studies on HE4 during pregnancy were initiated by Moore in 2012. He proved that the mean value of this tumor marker is lower in pregnancy, and increases with age irrespective of the menopausal status [4]. This study failed to capture a relationship that has been confirmed in studies addressing this issue later. The analysis conducted in our patients [5] and a study by Lu et al. [6] involving 1,006 pregnant women reveal that HE4 levels are significantly higher in the third trimester of physiological pregnancy than in the first and second trimesters, and that they are higher in each trimester of pregnancy than in non-pregnant women.

Another study has checked whether any serum HE4 fluctuations occur during a physiological menstrual cycle. For this purpose, 74 patients had HE4 serum assays performed five times. It occurred that HE4 levels were relatively stable throughout the menstrual cycle, and a slight increase was noted only during ovulation [28]. HE4 levels have also been investigated during the *in vitro* fertilization procedure. As Hallamaa et al. [29] report, hyperstimulation of ovaries, as preparation for *in vitro* fertilization, does not increase serum HE4 concentrations. It occurs, however, that this marker, particularly when combined with interleukin-13 (IL-13), may help determine the risk of preterm delivery in pregnant patients after *in vitro* fertilization (IVF), as shown by Kanninen et al. [30]. HE4 and IL-13 levels decrease in the case of preterm delivery compared to patients with term pregnancies [30]. This hypothesis seems to be confirmed by Orfanelli et al. [31], who have shown that low HE4 levels on day 28 after IVF herald miscarriage. This study compared HE4 with secretory leukocyte protease inhibitor (SLPI), a low level of which was a predictor of early pregnancy loss [31].

OTHER CANCERS AND NON-NEOPLASTIC DISEASES

It has also been attempted to verify the usefulness of HE4 in diseases that do not emerge from the female reproductive system. A large Chinese study, in which Du et al. [32] evaluated 691 patients, has confirmed that an increase in the level of this protein is an independent risk factor of lung cancer in individuals with pulmonary lesions confirmed in computed tomography. Another study has shown that lung cancer patients present significantly higher HE4 values than patients with a non-neoplastic pathology of the pulmonary parenchyma and healthy persons. It has also been demonstrated that HE4 increases in patients with minor lesions in this organ, which would enable disease detection significantly earlier, and thus at a lower stage [33]. The usefulness of this protein in lung cancer detection is, however, debatable. It occurs that 90.1% of small-cell lung carcinomas show no *WFDC2* expression. A clinically significant expression of this gene in this study was found only for lung adenocarcinoma [34]. This allows to hope for the emergence of a targeted therapy in the case of this subtype of cancer. Yet another study has revealed the usefulness of HE4 in non-small-cell lung carcinoma, in both diagnosis and relapse monitoring [35]. A large meta-analysis has demonstrated that a high HE4 expression in lung cancer patients is a poor prognostic factor [36]. There are also reports about the usefulness of HE4 as a marker in chronic kidney disease (CKD). Chinese researchers have confirmed its efficacy in detecting CKD in women at various ages with normal ovarian function, and found it useful in the evaluation of CKD clinical stage. The diagnostic value was in this case significantly higher than that of serum creatinine, urea or uric acid concentrations [37]. A meta-analysis of numerous studies from 1966–2017 has demonstrated that HE4 may be a marker of renal fibrosis [38]. Moreover, the usefulness of HE4 has also been tested in patients with colorectal carcinoma. A pilot study, which appe-

ared in 2017, showed that this protein may be used in the detection of this cancer. *WFDC2* expression was noted in 28.3% of patients, which was a significantly greater value compared with the control group where the expression of this gene was not observed. A particularly strong increase in HE4 was shown in patients with stage III and IV colorectal cancer and in patients with a high CA19-9 level [39]. However, further investigation in this area is needed as the discussed experiment was conducted in a small group of patients. Furthermore, HE4 concentrations have also been evaluated in pancreatic adenocarcinoma. It turns out that they strongly correlate with the clinical stage of the disease, and are significantly elevated even in early stages [40].

CONCLUSION

HE4 concentrations are increased in various diseases. Currently, HE4 is of the greatest clinical relevance in gynecological cancers, such as ovarian carcinoma and endometrial cancer. However, it also has a huge potential in the differential diagnosis of pelvic lesions. It helps distinguish benign from malignant masses. A correlation with other markers may facilitate the diagnosis of relapse and progression of ovarian cancer and endometrial cancer, or estimate the risk of preterm delivery in patients after *in vitro* fertilization. This protein has been reported to be of vast significance in surgery planning in patients with endometrial cancer as well as in clinical staging and determining the prognosis in this disease. Moreover, it is of substantial importance in detecting local relapses and distant metastases of endometrial cancer. Some hope may be associated with HE4 as a marker predicting preterm delivery in patients after natural fertilization. As for other cancers, the most significant role of HE4 seems to be that of a prognostic factor in non-small-cell lung carcinoma.

REFERENCES

1. **Wang J, Gao J, Yao H et al.** Diagnostic accuracy of serum HE4, CA125 and ROMA in patients with ovarian cancer: A meta-analysis. *Tumor Biol* 2014;35, 6127–6138.
2. **Piovano E, Attamante L, Macchi C et al.** The role of HE4 in ovarian cancer follow-up: A review. *Int J Gynecol Cancer* 2014;24:1359–1365.
3. **Tian Y, Wang C, Cheng L et al.** Determination of reference intervals of serum levels of human epididymis protein 4 (HE4) in Chinese women. *J Ovarian Res* 2015; 8:72.
4. **Moore RG, Miller MC, Eklund EE et al.** Serum levels of the ovarian cancer biomarker HE4 are decreased in pregnancy and increase with age. *Am J Obstet Gynecol* 2012;206: e1–7.
5. **Janosz I, Bodzek P, Partyka R i wsp.** Ocena stężeń białka HE4 w poszczególnych trymestrach ciąży fizjologicznej. *Ginekol Położn/Gynecol Obstet – Med Project* 2017; 1(43): 54-58.
6. **Lu J, Zheng Z, Zhang Q et al.** Measurement of HE4 and CA125 and establishment of reference intervals for the ROMA index in the sera of pregnant women. *J Clin Lab Anal* 2018;32:e22368.
7. **Li J, Chen H, Curcuru JR et al.** Serum HE4 level as a biomarker to predict the recurrence of gynaecologic cancers. *Curr Drug Targets* 2017;18:1158-1164.
8. **Nevadunsky NS, VanArsdale A, Strickler H et al.** Obesity and age at diagnosis of endometrial cancer. *Obstet Gynecol* 2014;124:300–306.
9. **Capriglione S, Plotti F, Miranda A et al.** Utility of tumor marker HE4 as prognostic factor in endometrial cancer: a single-center controlled study. *Tumor Biol* 2015; 36: 4151–4156.
10. **Angioli R, Miranda A, Aloisi A et al.** A critical review on HE4 performance in endometrial cancer: Where are we now? *Tumor Biol* 2014; 35:881–887.
11. **Li X, Gao Y, Tan M et al.** Expression of HE4 in endometrial cancer and its clinical significance. *BioMed Research International,* 2015; article ID 437468, http://dx.doi.org/10.1155/2015/437468.
12. **Brennan DJ, Hackethal A, Metcalf AM et al.** Serum HE4 as a prognostic marker in endometrial cancer - A population based study. *Gynecol Oncol* 2014;132:159–165.
13. **Abbink K, Zusterzeel PLM, Geurts-Moespot AJ et al.** HE4 is superior to CA125 in the detection of recurrent disease in high-risk endometrial cancer patients. *Tumor Biol* 2018; 40, https://doi.org/10.1177/1010428318757103.
14. **Chovanec J, Selingerova I, Greplova K et al.** Adjustment of serum HE4 to reduced glomerular filtration and its use in biomarker-based prediction of deep myometrial invasion in endometrial cancer. *Oncotarget* 2017;8:108213–108222.
15. **Dong C, Liu P, Li C.** Value of HE4 combined with cancer antigen 125 in the diagnosis of endometrial cancer. *Pak J Med Sci* 2017;33:1013–1017.
16. **Vezzoli M, Ravaggi A, Zanotti L et al.** RERT: A novel regression tree approach to predict extrauterine disease in endometrial carcinoma patients. Sci Rep 2017;7:1–10.
17. **Chhabra S, Bhavani M, Deshpande A.** Trends of vulvar cancer. *J Obstet Gynaecol* 2014;34:165–168.
18. **Montagnana M, Lippi G, Danese E at al.** Human epydidimis protein 4 (HE4): could it be useful in the diagnosis of vulvar cancer? *Clin Lab* 2010;56:601–602.
19. **Diniz G, Karadeniz T, Sayhan S et al.** Tissue expression of human epididymal secretory protein 4 may be useful in the differential diagnosis of uterine cervical tumors. *Ginekol Pol* 2017;88:51–55.
20. **Nikolova T, Zivadinovic R, Evtimovska N et al.** Diagnostic performance of human epididymis protein 4 compared to a combination of biophysical and biochemical markers to differentiate ovarian endometriosis from epithelial ovarian cancer in premenopausal women. *J Obstet Gynaecol Res* 2017;43:1870–1879.
21. **Zapardiel I, Gorostidi M, Ravaggi A et al.** Utility serum marker HE4 for the differential diagnosis between endometriosis and adnexal malignancy. *Int J Gynecol Cancer* 2016;26:52–55.
22. **Leggieri C, D'Agostino G, Tommasi L et al.** Is HE4 a useful endometrioma marker? *Eur J Gynaecol Oncol* 2014; 35:438-41.

23. **Huhtinen K, Suvitie P, Hiissa J et al.** Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. *Br J Cancer* 2009;100:1315–1319.
24. **Sükür YE, Taskin S, Simsir C et al.** Highly elevated human epididymis protein 4 (HE4) following endometrioma rupture: a case report. *J Obstet Gynaecol* 2018;38:885-886.
25. **Chudecka-Głaz A, Cymbaluk-Płoska A, Strojna A et al.** HE4 serum levels in patients with BRCA1 gene mutation undergoing prophylactic surgery as well as in other benign and malignant gynecological diseases. *Dis Markers* 2017; 2017: doi: 10.1155/2017/9792756.
26. **Moore RG, Miller MC, Steinhoff MM et al.** Serum HE4 levels are less frequently elevated than CA125 in women with benign gynaecologic disorders. *Am J Obstet Gynecol* 2012;206:e1–8.
27. **Goff BA, Agnew K, Neradilek MB et al.** Combining a symptom index, CA125 and HE4 (triple screen) to detect ovarian cancer in women with a pelvic mass. *Gynecol Oncol* 2017;147:291–295.
28. **Moore RG, Plamnte B, Hartnett E et al.** Assessment of serum HE4 levels throughout the normal menstrual cycle. *Am J Obstet Gynecol* 2017;217:53.e1-53.e9.
29. **Hallamaa M, Huhtinen K, Suvitie P et al.** Serum concentrations of HE4 change little during in vitro fertilization. *Acta Obstet Gynecol Scand* 2014;93:640–646.
30. **Kanninen TT, Sisti G, Ramer I et al.** Predictive biomarkers of preterm delivery in women with ongoing IVF pregnancies. *J Reprod Immunol* 2015;112:58–62.
31. **Orfanelli T, Doulaveris G, Shulman BP et al.** Human epididymis protein 4 (HE4) and secretory leukocyte protease inhibitor (SLPI) are two novel biomarkers predictive of IVF outcome. *Fertil Steril* 2013;100, suppl: S112.
32. **Du Q, Yan C, Wu SG et al.** Development and validation of a novel diagnostic nomogram model based on tumor markers for assessing cancer risk of pulmonary lesions: A multicenter study in Chinese population. *Cancer Lett* 2018;420:236–241.
33. **Choi SI, Jang MA, Jeon BR et al.** Clinical usefulness of human epididymis protein 4 in lung cancer. *Ann Lab Med* 2017;37:526-530.
34. **Celik B, Bulut T.** Human epididymis protein 4 may not be a reliable screening biomarker for detecting lung carcinoma patients. *Biomed Reports* 2017;7:297–300.
35. **Huang W, Wu S, Lin Z et al.** Evaluation of HE4 in the diagnosis and follow up of non-small cell lung cancers. *Clin Lab* 2017;63:461-467.
36. **Zhong H, Qian Y, Fang S et al.** HE4 expression in lung cancer, a meta-analysis. *Clin Chim Acta* 2017;470:109–114.
37. **Yuan T, Li Y.** Human epididymis protein 4 as a potential biomarker of chronic kidney disease in female patients with normal ovarian function. *Lab Med* 2017;48:238–243.
38. **Chen P, Yang Q, Li X et al.** Potential association between elevated serum human epididymis protein 4 and renal fibrosis: A systemic review and meta-analysis. Medicine (Baltimore) 2017; 96: e7824.
39. **Kemal YN, Demirag GN, Bedir AM et al.** Serum human epididymis protein 4 levels in colorectal cancer patients. *Mol Clin Oncol* 2017;7:481–485.
40. **Huang T, Jiang SW, Qin L et al.** Expression and diagnostic value of HE4 in pancreatic adenocarcinoma. *Int J Mol Sci* 2015;16:2956–2970.