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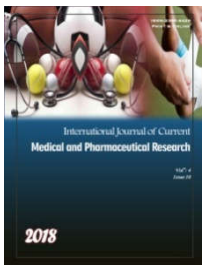

HUMAN EPIDIDYMIS PROTEIN 4 AS A TUMOR MARKER IN OVARIAN CANCER

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ABSTRACT

HE4, Human epididymis protein is a whey acidic domain containing protein. It has serine protease inhibitor activity and also provides immunity against microorganisms. HE4 has emerged as a potential biomarker for the diagnosis of epithelial ovarian cancer. Limited success has been achieved using CA125 (Cancer Antigen 125), which is the only biomarker used for ovarian cancer. CA125 shows low sensitivity and specificity in the diagnosis of early stage ovarian cancer (OC). HE4 has major advantage over CA125 as it helps to distinguish malignant masses from benign one. Several studies have shown the up regulation of serum HE4 values in ovarian cancer. Trials are going on to examine its role as a serological tumor biomarker and as a target for gene based therapy. HE4 has also led to the development of Risk of malignancy algorithm (ROMA) which helps to identify the risk of development of malignancy in an ovarian mass.
In this review, we are going to discuss about the discovery, of HE4, its biological significance and its role as a potential biomarker in the diagnosis of ovarian cancer.

INTRODUCTION

Ovarian cancer (OC) is the most prevalent gynecological malignancy. Its incidence rate increases with age and post-menopausal status (1). Ovarian tumors are classified into three major categories—surface epithelial-stromal tumor, sex cord-stromal tumor and germ cell tumor. Surface epithelial tumors account for approximately 60% of all ovarian tumors and also 90% of malignant ovarian tumors (2). The high death rate of OC is due to its delayed diagnosis and higher tendency of metastasis and recurrence (1).

Methods of screening ovarian cancer

Screening test for OC is neither cost-effective nor practical. Three screening tests are currently used: bimanual pelvic examination, cancer antigen (CA125) and transvaginal ultrasound. The bimanual pelvic examination lacks sensitivity and specificity. It is estimated that physical examination detects only 1 in 10,000 ovarian carcinomas in asymptomatic women. Ultrasound is expensive and also has limited specificity and sensitivity (3). The radioimmunoassay for CA 125, a tumor-specific antigen [CA 125, discovered initially by Bast and colleagues in 1983 (4)] is the only biomarker used for the evaluation of adnexal masses for epithelial ovarian cancer (4-5). CA 125 is elevated in 80% of ovarian carcinomas, but if the tumor is limited to ovary only, the raised value of CA 125 has been seen only in 50% of cases. CA 125 may also be elevated in women with benign ovarian disease and in otherwise healthy women(3).

High serum CA-125 level is seen in conditions like cirrhosis, congestive heart failure, primary liver cancer, especially in cases where ascites is present. Due to such low specificity of CA-125 it cannot be considered a suitable marker of ovarian cancer.

HE4 structure and function

HE4 protein was first identified by Kirchhoff *et al*. in 1991. They characterized HE4 by differential cDNA screening method on human epididymal tissue which demonstrated the localization of HE4 mRNA in the distal region of epididymal duct (8, 9). WFDC2 gene codes for HE4 protein with a WAP (whey acidic protein) domain (15). This domain is characterized by four-disulphide core arrangement of 50 amino acids, including eight cysteines. They are secreted by pro-inflammatory cells and have serine protease inhibitor activity. They play a role in natural defense against microorganisms (10). HE4 plays major role in migration and adhesion of ovarian cancer cells. HE4 knockdown studies have shown tumor growth inhibition (11).

Tissue expression

Drapkin *et al.* studied HE4 expression in ovarian and non-ovarian malignant tissue using immunohistochemistry. He observed diverse HE4 expression in the subtypes of ovarian cancer whereas there was no expression in non-ovarian carcinoma. HE4 was positive in 93% of serous, 100% of endometrioid and in 50% of clear-cell tumors, but no

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expression was observed in mucinous tumor (12). By knowing the expression pattern of HE4, histopathologic diagnosis could be attained. It should be taken into consideration in future studies which examine the role of HE4 as a serological tumor biomarker (13).

HE4 putative marker for ovarian cancer

HE4 has emerged as a valuable biomarker for ovarian cancer after the findings by Hellstrom *et al.* in 2003. They constructed a fusion protein consisting of HE4 fused with mouse or human Ig Fc domains. Mice were immunized with the mouse-derived Ig Fc-HE4 fusion protein and the resultant hybridomas were screened against the human derived Ig Fc-HE4 fusion protein, upon which two monoclonal antibodies2H5 and 3D8 were generated and recognized as HE4 epitopes. These monoclonal antibodies were then used for the construction of a double-determinant (sandwich) ELISA, which has been used for detection of HE4 in serum. Their study demonstrated comparable specificity and sensitivity for HE4 and CA 125 and they also demonstrated that HE4 was less frequently elevated in patients with benign gynecological conditions (14). The molecular weight of HE4 is 25kD, which is below the glomerular filtration cutoff. Due to this HE4 levels have also been found to be higher in the urine of ovarian cancer patients when compared with urine from healthy individual or benign diseases. Consequently, urinary HE4 may serve as a noninvasive method for the diagnosis and monitoring of ovarian cancer (15).

Higher HE4 levels are also associated with conditions like lung cancer (16, 17) chronic kidney disease (18) and kidney fibrosis (19). These conditions must be assessed while interpreting HE4 levels in ovarian cancer (20).

Apart from malignancy there are many other factors that cause increase in serum HE4 level. CA 125 decreases with age whereas HE4 levels increases with age. It was observed that, the upper 95th percentile levels of HE4 was 128 pM in postmenopausal women with respect to premenopausal healthy women which is 89pM. HE4 levels are also affected by pregnancy: pregnant women have low levels of HE4 in comparison to non pregnant premenopausal women (21). Older women with late menarche and smokers have high levels of HE4 when compared with appropriate controls (22). Factors like menstrual cycle, endometriosis, estrogen and progestin contraceptive usage do not alter serum levels of HE4 (23).

Risk of malignancy algorithm (ROMA)

ROMA, risk of malignancy algorithm combines CA 125 and HE4 value along with the menopausal status into a predictive index, which is used to calculate the probability of ovarian cancer in an adnexal mass. ROMA has been approved by FDA for distinguishing malignant from benign pelvic masses for recurrent and progressive disease in 2008 (24).ROMA classifies patients as being at a low or at a high risk for malignant disease using the following algorithms (25).

In Premenopausal women

Predictive index (PI) = -12.0+ 2.38 * LN(HE4) + 0.0626 * LN (CA125)

In Postmenopausal women

Predictive index (PI) = -8.09+ 1.04 * LN (HE4) + 0.732 * LN (CA125)

Predicted probability

(PP)= 100*exp (PI)/ (1+exp(PI))

- Pre-menopausal women:
  - PP ≥ 12.5%= high risk of finding EOC
  - PP < 12.5%= low risk of finding EOC
- Post-menopausal women:
  - PP ≥ 14.4% = high risk of finding EOC
  - PP <14.4% = Low risk of finding EOC

In the premenopausal group, the algorithm had a sensitivity of 92.3% and specificity of 75.0% and in the postmenopausal group, the sensitivity and specificity were 76.5%and 74.8% respectively (24).

Recurrence and Monitoring

Initial studies have shown the role of HE4 in detecting recurrent ovarian cancer. When advanced stage ovarian cancer patients are assessed with the following markers- CA125, HE4, MMP-7, and mesothelin after surgery and chemotherapy. HE4 level increases prior to recurrence with a lead time of 4.5 months. The level of HE4 is elevated prior to the rise of CA125. It has also been observed that some patients, which are negative for both CA125 and imaging, have elevated HE4 level (26). In a recent prospective case control study, HE4 has been found to detect recurrent ovarian cancer with 74% sensitivity and 100% specificity at a cutoff value of HE4 70 pmol/L. Using a combination of HE4 and CA 125 the overall sensitivity increased to 76%. A combination of CA 125 and HE4 may offer better lead times and sensitivity for the detection of recurrent ovarian cancer (27).

HE4 levels may aid in monitoring response to therapy. Serum levels of HE4 obtained at the time of diagnosis of ovarian cancer differed significantly from levels following complete clinical remission (324.1 pMvs 23.3 pM,) indicating a possible role in monitoring response to therapy (28).

CONCLUSION

In the past decade, HE4 has emerged as a novel biomarker for ovarian cancer. Studies have proven superiority of HE4 over CA125 as a biomarker for ovarian cancer. HE4 has this major advantage of distinguishing between benign & malignant tumor over CA 125. HE4 leads to the development of ROMA algorithm that distinguishes benign from malignant pelvic masses. It was also been observed that some patients were negative for both CA125 and imaging studies but they show increased HE4 levels, thereby leading to its role in monitoring the response to therapy and detecting recurrences.

References

1. HE4 as a biomarker for ovarian and endometrial cancer management. - PubMed - NCBI [Internet]. [cited 2018 May 13]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19732003
2. Pathology and classification of ovarian tumors - Chen - 2003 - Cancer - Wiley Online Library. [cited 2018 Aug 19]; Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1002/cncr.11345
3. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. CA Cancer J Clin. 2011 Jun;61(3):183-203.
4. Bast RC, Klug TL, St John E, Jenison E, Niloff JM, Lazarus H, *et al*. A radioimmunoassay using a

monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med. 1983 Oct 13;309(15):883-7.
5. Goonewardene TI, Hall MR, Rustin GJS. Management of asymptomatic patients on follow-up for ovarian cancer with rising CA-125 concentrations. Lancet Oncol. 2007 Sep;8(9):813-21
6. Bast RC, Feeney M, Lazarus H, Nadler LM, Colvin RB, Knapp RC. Reactivity of a monoclonal antibody with human ovarian carcinoma. J Clin Invest. 1981 Nov;68(5):1331-7.
7. Havrilesky LJ, Whitehead CM, Rubatt JM, Cheek RL, Groelke J, He Q, *et al*. Evaluation of biomarker panels for early stage ovarian cancer detection and monitoring for disease recurrence. Gynecol Oncol. 2008 Sep;110(3):374-82.
8. Kirchhoff C, Habben I, Ivell R, Krull N. A major human epididymis-specific cDNA encodes a protein with sequence homology to extracellular proteinase inhibitors. Biol Reprod. 1991 Aug;45(2):350-7.
9. Bingle L, Singleton V, Bingle CD. The putative ovarian tumour marker gene HE4 (WFDC2), is expressed in normal tissues and undergoes complex alternative splicing to yield multiple protein isoforms. Oncogene. 2002 Apr;21(17):2768-73.
10. Sonoda G, Palazzo J, du Manoir S, Godwin AK, Feder M, Yakushiji M, *et al*. Comparative genomic hybridization detects frequent overrepresentation of chromosomal material from 3q26, 8q24, and 20q13 in human ovarian carcinomas. Genes Chromosomes Cancer. 1997 Dec;20(4):320-8.
11. Lu R, Sun X, Xiao R, Zhou L, Gao X, Guo L. Human epididymis protein 4 (HE4) plays a key role in ovarian cancer cell adhesion and motility. Biochem Biophys Res Commun. 2012 Mar 9;419(2):274-80.
12. Drapkin R, von Horsten HH, Lin Y, Mok SC, Crum CP, Welch WR, *et al*. Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. Cancer Res. 2005 Mar 15;65(6):2162-9.
13. Galgano MT, Hampton GM, Frierson HF. Comprehensive analysis of HE4 expression in normal and malignant human tissues. Mod Pathol. 2006 Jun;19(6):847-53.
14. Hellström I, Raycraft J, Hayden-Ledbetter M, Ledbetter JA, Schummer M, McIntosh M, *et al*. The HE4 (WFDC2) protein is a biomarker for ovarian carcinoma. Cancer Res. 2003 Jul 1;63(13):3695-700.
15. Liao JB, Yip YY, Swisher EM, Agnew K, Hellstrom KE, Hellstrom I. Detection of the HE4 protein in urine as a biomarker for ovarian neoplasms: clinical correlates. Gynecol Oncol. 2015 Jun;137(3):430-5.
16. Iwahori K, Suzuki H, Kishi Y, Fujii Y, Uehara R, Okamoto N, *et al*. Serum HE4 as a diagnostic and prognostic marker for lung cancer. Tumour Biol. 2012 Aug;33(4):1141-9.
17. Kamei M, Yamashita S-I, Tokuishi K, Hashioto T, Moroga T, Suehiro S, *et al*. HE4 expression can be associated with lymph node metastases and disease-free survival in breast cancer. Anticancer Res. 2010 Nov;30(11):4779-83.
18. Nagy B, Krasznai ZT, Balla H, Csobán M, Antal-Szalmás P, Hernádi Z, *et al*. Elevated human epididymis protein 4 concentrations in chronic kidney disease. Ann Clin Biochem. 2012 Jul;49(Pt 4):377-80.
19. LeBleu VS, Teng Y, O'Connell JT, Charytan D, Müller GA, Müller CA, *et al*. Identification of human epididymis protein-4 as a fibroblast-derived mediator of fibrosis. Nat Med. 2013 Feb;19(2):227-31.
20. Simmons AR, Baggerly K, Bast RC. The Emerging Role of HE4 in the Evaluation of Advanced Epithelial Ovarian and Endometrial Carcinomas. Oncology (Williston Park). 2013 Jun;27(6):548-56.
21. Moore RG, Miller MC, Eklund EE, Lu KH, Bast RC, Lambert-Messerlian G. Serum levels of the ovarian cancer biomarker HE4 are decreased in pregnancy and increase with age. American Journal of Obstetrics & Gynecology. 2012 Apr 1;206(4):349.e1-349.e7.
22. Lowe KA, Shah C, Wallace E, Anderson G, Paley P, McIntosh M, *et al*. Effects of Personal Characteristics on Serum CA125, Mesothelin, and HE4 Levels in Healthy Postmenopausal Women at High-Risk for Ovarian Cancer. Cancer Epidemiol Biomarkers Prev. 2008 Sep 1;17(9):2480-7.
23. Serum HE4 concentration is not dependent on menstrual cycle or hormonal treatment among endometriosis patients and healthy premenopausal women - Dimensions [Internet]. [cited 2018 Aug 20]. Available from: https://app.dimensions.ai/details/publication/pub.1030231934
24. Simmons AR, Baggerly K, Bast RC. The Emerging Role of HE4 in the Evaluation of Advanced Epithelial Ovarian and Endometrial Carcinomas. Oncology (Williston Park). 2013 Jun;27(6):548-56.
25. Van Gorp T, Cadron I, Despierre E, Daemen A, Leunen K, Amant F, *et al*. HE4 and CA125 as a diagnostic test in ovarian cancer: prospective validation of the Risk of Ovarian Malignancy Algorithm. Br J Cancer. 2011 Mar 1;104(5):863-70.
26. Schummer M, Drescher C, Forrest R, Gough S, Thorpe J, Hellström I, *et al*. Evaluation of ovarian cancer remission markers HE4, MMP7 and Mesothelin by comparison to the established marker CA125. Gynecol Oncol. 2012 Apr;125(1):65-9.
27. Plotti F, Capriglione S, Terranova C, Montera R, Aloisi A, Damiani P, *et al*. Does HE4 have a role as biomarker in the recurrence of ovarian cancer? Tumor Biol. 2012 Dec 1;33(6):2117-23.
28. Chudecka-Głaz A, Rzepka-Górska I, Wojciechowska I. Human epididymal protein 4 (HE4) is a novel biomarker and a promising prognostic factor in ovarian cancer patients. Eur J Gynaecol Oncol. 2012;33(4):382-90.

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