

Recent advances in the biomarkers for epithelial ovarian cancer

Yun Hwan Kim, Seung Cheol Kim

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Ewha Woman's University Mokdong Hospital, Ewha Woman's University School of Medicine, Seoul, Korea

[See accompanying articles on pages 244, 269.](#)

Epithelial ovarian cancer (EOC) is the fourth most common cause of death from cancer in women in the Western world. More than 70% of patients are diagnosed with advanced disease, where 5-year survival rates are less than 30%. Because EOC typically cause few specific symptoms, early detection of EOC has been a challenge to improve clinical outcome.

The triage of women at high risk for EOC before surgery is of critical importance for patient having a pelvic mass. The surgical approach for benign and malignant ovarian tumors differs fundamentally, and preoperative diagnosis allows for careful planning of surgical procedure and referral to high volume centers. In fact, patients with EOC managed by gynecologic oncologists and at high-volume institutions are more likely to undergo complete surgical staging and optimal cytoreductive surgery with fewer complications and better survival than patients managed by less-experienced surgeons [1,2]. Therefore, much effort have been devoted until today for the identification of a simple and effective test that can screen EOC at an early stage and make reliable diagnosis preoperatively.

The serum tumor marker CA-125 was discovered in 1981, and became a milestone in the pathway for the development of a non-invasive and biochemical approach to the diagnosis of EOC. Multimodal screening using annual CA-125 and second-line transvaginal ultrasound scan had showed encouraging results, that is, sensitivity (SN) 89.5%, specificity

(SP) 99.8%, and positive-predictive value 35.1% among post-menopausal women in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) study [3]. However, similar randomized controlled trials performed in the USA, The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening study, recently reported that simultaneous screening CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality in post-menopausal women, and consequent diagnostic evaluation from false positive screening was associated with complications [4]. Although the effect of screening on mortality of the UKCTOCS is pending, the mortality results of PLCO imply that recent screening tools are still unsatisfactory. In fact, measurement of CA-125 has several clinical limitations, because elevation of CA-125 is only observed in less than half of patients with early-stage EOC and in about 80% of all EOC patients. In addition, serum CA-125 concentrations may be affected by common benign gynecologic disorders such as leiomyoma, endometriosis and pelvic inflammatory disease, which are more prevalent in premenopausal women. Therefore, there has been an urgent need for the development of a novel biomarker with higher accuracy.

The human epididymal secretory protein E4 (HE4) was first identified at 1990 on differential cDNA screening of human epididymal tissue. HE4 is one of the most up-regulated genes in EOC based on gene expression profiles, and has been reported to have superiority over CA-125 as a biomarker for EOC. Among various biomarkers including CA-125, CA 72-4, and osteopontin, HE4 had the highest sensitivity for detecting ovarian cancer (SN, 72.9%; SP, 95%), especially for stage I disease [5]. Moreover, recent studies have reported that HE4 is complimentary to CA-125 as it is not falsely increased in

Received Nov 1, 2011, Accepted Nov 16, 2011

Correspondence to Seung Cheol Kim

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Ewha Woman's University Mokdong Hospital, Ewha Woman's University School of Medicine, 911-1 Mok-dong, Yangcheon-gu, Seoul 158-710, Korea.
Tel: 82-2-2650-5996, Fax: 82-2-2647-9860, E-mail: onco@ewha.ac.kr

Copyright © 2011. Asian Society of Gynecologic Oncology, Korean Society of Gynecologic Oncology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

benign gynecologic disorders contrary to CA-125. The combination of CA-125 with HE4 achieved the highest sensitivity for the detection of EOC compared with other biomarkers [5,6], and better diagnostic performance (SN, 92.9%; SP, 95%) between EOC, endometrial cancer, endometriosis, and healthy controls compared with HE4 (SN 78.6%) or CA-125 (SN 78.6%) alone [7]. For these reasons, the risk of ovarian malignancy algorithm (ROMA) was constructed as a predictive index to estimate the risk of EOC in women presenting with a pelvic mass based on the two pilot studies [5,6]. ROMA takes into account the serum concentration of CA-125 and HE4, and the menopausal status. A recent study demonstrated the superiority of ROMA compared with risk of malignancy index (RMI), an algorithm employing ultrasound findings and architectural features of pelvic masses, CA-125 levels and menopausal status (SN 94.3% vs. 84.6% at a set SP of 75%) [8]. Of particular interest, the ROMA showed a higher sensitivity for patients with stage I and II EOC, and for those with tumors grossly confined to the pelvis, or with less than 2 cm disease in the upper abdomen [9]. Nowadays, searching for the optimal multi-marker assay is still ongoing for the early detection of ovarian cancer [10].

In this issue of Journal of Gynecologic Oncology, Partheen et al. [11] evaluated the diagnostic performance of HE4 for the detection of ovarian cancer, compared with CA-125 alone and in combination of the two. HE4 achieved better sensitivity than CA-125 in premenopausal group (80.9% vs. 76.2% at a set SP of 75%), which confirmed the clinical value of HE4, especially in premenopausal women. However, the specificity of HE4 was significantly lower than that of CA-125 in postmenopausal patients (SN 80.6%, SP 75% vs. SN 82.8%, SP 83%), and the sensitivity of HE4 was not superior to that of CA-125 in early stage tumors (SN 59.6%, SP 75% vs. SN 61.7%, SP 80%), which is contradictory to other investigations. Is CA-125 still the best biomarker for the diagnosis of EOC? There are several limitations in the study. Owing to the study design, there may be a possibility of quality problems in the preserved serum. The sample distribution was limited and different from those of other investigations. The cut-off of HE4 is not determined and varies among comparable reports. Indeed, the history of HE4 is relatively short and HE4 is subject to clinical validation. Therefore, both HE4 and CA-125 should be included in more prospective studies in the future.

In another paper in this issue, Kang et al. [12] dealt with the utilization of CA-125 as a predictive marker for recurrence. They collected data from two high-volume institutions and scrutinized the correlation between post-treatment nadir CA-125 and progression free survival in patients with advanced ovarian cancer who had achieved complete remission. An

acknowledgeable finding of this paper is the determination of a reasonable cut-off value of CA-125 that can be used for the identification of high-risk patients. Although there were some limitations including sample size and population, the validated cut-off value of CA-125 may be used reliably to stratify the post-treatment patients or to plan a novel consolidation treatment for the better outcome of the poor prognostic group. In the future, we expect other biomarkers including HE4 could be used for monitoring the response to therapy and the course of the disease as CA-125. Further studies should be performed to provide evidence not only on the diagnostic value of tumor biomarkers but also their potential prognostic or predictive value for the management of EOC patients.

CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Bristow RE, Palis BE, Chi DS, Cliby WA. The National Cancer Database report on advanced-stage epithelial ovarian cancer: impact of hospital surgical case volume on overall survival and surgical treatment paradigm. *Gynecol Oncol* 2010;118:262-7.
2. Mercado C, Zingmond D, Karlan BY, Sekaris E, Gross J, Maggard-Gibbons M, et al. Quality of care in advanced ovarian cancer: the importance of provider specialty. *Gynecol Oncol* 2010;117:18-22.
3. Menon U, Gentry-Maharaj A, Hallett R, Ryan A, Burnell M, Sharma A, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol* 2009;10:327-40.
4. Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA* 2011;305:2295-303.
5. Moore RG, Brown AK, Miller MC, Skates S, Allard WJ, Verch T, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. *Gynecol Oncol* 2008;108:402-8.
6. Moore RG, McMeekin DS, Brown AK, DiSilvestro P, Miller MC, Allard WJ, et al. A novel multiple marker bioassay utilizing

- HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. *Gynecol Oncol* 2009;112:40-6.
7. Huhtinen K, Suvitie P, Hiissa J, Junnila J, Huvila J, Kujari H, et al. Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. *Br J Cancer* 2009;100:1315-9.
 8. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol* 1990;97:922-9.
 9. Moore RG, Jabre-Raughley M, Brown AK, Robison KM, Miller MC, Allard WJ, et al. Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. *Am J Obstet Gynecol* 2010;203:228.e1-6.
 10. Yurkovetsky Z, Skates S, Lomakin A, Nolen B, Pulsipher T, Modugno F, et al. Development of a multimarker assay for early detection of ovarian cancer. *J Clin Oncol* 2010;28:2159-66.
 11. Partheen K, Kristjansdottir B, Sundfeldt K. Evaluation of ovarian cancer biomarkers HE4 and CA-125 in women presenting with a suspicious cystic ovarian mass. *J Gynecol Oncol* 2011;23:244-252.
 12. Kang S, Kim TJ, Seo SS, Kim BG, Bae DS, Park SY. Prediction of a high-risk group based on postoperative nadir CA-125 levels in patients with advanced epithelial ovarian cancer. *J Gynecol Oncol* 2011;23:269-274.