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Original Research Article

Cancer Ovary and Early Diagnosis

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Abstract

Between all of the gynecological cancers, ovarian cancer, despite medical advances and the development of diagnostic tools such as biomarkers and detection techniques, remains a fatal cancer with high progression. Despite this, there is no effective screening strategy or standard treatment for ovarian cancer. If diagnosed during stage I, ovarian cancer has a 90% 5-year survival rate; however, there is usually a masking of symptoms which leads to an often late-stage diagnosis and correspondingly poor survival rate. Current diagnostic methods are invasive and consist of a pelvic examination, transvaginal ultrasonography, and blood tests to detect cancer antigen 125 (CA125). Unfortunately, surgery is often still required to make a positive diagnosis. Epithelial Ovarian Cancer (EOC) is the most common, whereas, stromal and germ cell tumors are of lower abundance. A Risk of Ovarian Malignancy Algorithm (ROMA) classifies patients as being at low or high risk for malignant disease using both the CA125 and HE4 results and a woman's menopausal status. The ROMA index was calculated according to the levels of HE4 and CA-125. HE4 and CA-125 values were input to the ovarian cancer risk assessment software, followed by automatic calculation of the corresponding ROMA index. The premenopausal calculation formula of the ROMA index was: 12+2.38 × LN (HE4) +0.062 6 × LN (CA-125). The postmenopausal calculation formula of the ROMA index was: 8.09+1.04 × LN (HE4) +0.732 × LN (CA-125). Such diagnostic medical methods and biomarkers include vaginal and pelvic examination, diagnostic imaging, serum CA125, and screening tests or a combination used in medical centers, however, it is necessary to find new biomarkers with long-term stability and high specificity and sensitivity to detect Ovarian Ca in early stages of disease.

Keywords: Ovarian Cancer; Serum and genetic Biomarkers; Early diagnosis.

OBJECTIVES

Evaluate the diagnostic accuracy of serum cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) in prediction of malignant ovarian masses.

STUDY DESIGN

This prospective study was performed in Govt. Medical College, Amritsar. The eligibility criteria for inclusion were; consecutive women, at any age ≥18 years, with established diagnosis of ovarian mass based on symptoms, signs, and imaging techniques. All patients underwent personal and medical history taking, preoperative serum CA125 and HE4 (cutoff 35 IU/mL and 150 pmol/L, respectively) assessment then postoperative histopathologic examination of lesions as a reference standard.

RESULTS

Among the included 100 patients, 54 were confirmed to have ovarian malignancy and 46 had benign lesions. Along with 100 healthy individuals accompanying the patients to the hospital were included. Serum CA125 ≥35 IU/mL was associated with ovarian malignancy at sensitivity 91.9%, specificity 53.8% and accuracy 70.7%. Raising its cutoff to 67.5 IU/mL decreased the sensitivity 83.9%, increased the specificity 80.7% with accuracy 82.1%. The combination of HE4 and CA125 showed sensitivity 75.8%, specificity 93.5%, and accuracy 85.7%. Women suffering from both diabetes mellitus and hypertension showed a significant decrease in CA125 concentration $P = 0.02$ with false negative results in (5/11) of them, making its sensitivity 54.5% in this condition. A Risk of Ovarian Malignancy Algorithm (ROMA) classifies patients as being at low or high risk for malignant disease using both the CA125 and HE4 results and a woman's menopausal status. The serum levels of HE4, CA-125 and ROMA index in the ovarian cancer group were significantly higher than those in the benign tumor and healthy control groups, and there was significant difference ($P<0.05$). The expression level of HE4 and ROMA index in the benign tumor group was not

significantly different. The expression level of CA-125 in serum was significantly higher than that in the healthy control group (P<0.05, Table I).

CONCLUSIONS

The performance of CA125 in cancer ovary prediction can be improved by increasing its cutoff or by combining CA125 with HE4. Diabetes mellitus and hypertension can influence CA125 performance while HE4 is independent on these factors. This can be an additional value of the introduction of HE4 in cancer ovary prediction protocols.

INTRODUCTION

Ovarian cancer is the fifth frequency occurring cancer among women and the leading cause of death among gynecological cancers. Malignant epithelial ovarian tumors account for 90% of all malignancies of the ovary and are the fourth most common cause of tumor-related death in women. The empirical lifetime risk of developing ovarian cancer is 1:70 [1], and most women present with advanced disease (FIGO stage III or stage IV), which is rarely curable. Tumor-associated antigens released into the circulation have been described in many diseases. Ideally, a tumor marker should be able to detect subclinical disease (i.e., screening), useful in monitoring the response to treatment, and to identify early recurrence so that further treatment can be instituted. Furthermore, the release of circulating tumor antigen provides an identifiable surface target on the tumor cell that might be used for in vivo diagnosis or antigen directed therapy [11]. No serum tumor marker, with the possible exception of human β chorionic gonadotrophin, meets all these criteria. Nevertheless, measurement of many serum tumor markers has been incorporated into clinical practice. This review will focus on CA125, the most clinically applicable tumor marker for ovarian cancer, and will briefly describe other tumor markers and possible future applications of tumor markers.

Screening and Diagnosis

As early-stage ovarian cancer carries a much more favorable prognosis, there is an urgent need to identify subclinical disease. A satisfactory method of screening subclinical disease for ovarian cancer is needed. Serological markers are theoretically an ideal approach but none have 100% specificity and sensitivity.

Population screening with ultrasonography alone has not proved to be a cost-effective means of detecting ovarian cancer. However, the sensitivity and specificity of this investigation can be increased by transvaginal ultrasonography and transvaginal color Doppler imaging. Serum CA125 measurement in healthy women has been used as a means of selecting women for ultrasonography. This increases the specificity of examination, but the predictive value of screening is about 10%.

The inclusion of other tumor markers may further increase the specificity of screening. *Einhorn et al*. evaluated CA125 concentrations together with those of CA15-3 and TAG-72 in 219 patients undergoing diagnostic laparotomy for pelvic masses. They found that the three tumor markers increased the specificity for detecting ovarian cancer but reduced the sensitivity of the CA125 assay [10]. One such protein is osteopontin, a glycophosphoprotein secreted by activated T lymphocytes, macrophages and leukocytes, found in extracellular matrix, sites of inflammation and body fluids. The gene encoding HE4 is commonly amplified in ovarian tumors. While the exact function of HE4 remains uncharacterized, it is a secreted protein that is absent in normal ovarian surface epithelium, but expressed specifically in 100% of the 16 human endometrioid epithelial ovarian cancers screened and 93% of the 60 serous ovarian carcinomas stained for HE4. VEGF levels have been known to be elevated in ovarian cancer patients, where it contributes to the accumulation of ascites. CA19-9 levels typically have mucinous tumors, whereas CA125 is frequently less elevated in these patients, and therefore, CA19-9 levels could be a useful biomarker for this histotype[4]. However, there have not been enough studies, or studies with enough patients, at present, to determine whether CA19-9 is a reliable biomarker for OC, and these studies still require the invasive collection of patient serum.

Monitoring Response to Therapy

The use of tumor markers to monitor response to treatment is particularly helpful in ovarian cancer where there is often a lack of clinically or radiologically measurable disease. A reduction in the serum CA125 level correlates well with clinical response. Failure of CA125 to fall with chemotherapy indicates drug resistance and identifies a need to change treatment.

Relapse

It has been accepted for a long time that a rise in CA125 into the abnormal range is highly predictive for relapse [3, 5]. However, the lead time to clinical relapse is variable and a clearer definition of relapse is needed if CA125 measurement is to be used as a definition of clinical progression. Measurements of CA125 are frequently taken after the completion of chemotherapy, outside clinical trials. From the results of *Rustin et al*. the predictive power of CA125 follow-up certainly reduces the need for regular abdominopelvic scans [16]. However, while normal levels of CA125 are reassuring for the patient and her doctor, their measurement often evokes a period of anxiety. In approximately 20% of patients, serum CA125 levels are not elevated. The majority of these patients have mucinous tumors. In such cases, other

tumor markers, such as carcinoembryonic antigen or TAG-72,

RESULTS

The serum levels of HE4, CA-125 and ROMA index in the ovarian cancer group were significantly higher than those in the benign tumor and healthy control groups, and there was significant difference ($P<0.05$). The expression level of HE4 and ROMA index in the benign tumor group was not significantly different. The expression level of CA-125 in serum was significantly higher than that in the healthy control group ($P<0.05$, Table I). The patients in the ovarian benign disease and healthy control groups were further divided into the pre- and postmenopausal groups. The patients with ovarian cancer were divided into the pre- and postmenopausal groups. The serum levels of HE4, CA-125 and ROMA index were detected to evaluate the sensitivity, specificity, positive predictive value and negative predictive value of HE4, CA-125 and ROMA standardized with pathological diagnosis (Table II). The ROMA index, and a comparison of the sera levels of CA-125 and HE4 in the diagnosis of ovarian cancer in each group indicated significant differences between the three groups ($P<0.001$, Table III). The AUC of ROC of the ROMA index, HE4 and CA-125 in the diagnosis of ovarian cancer gradually decreased to 0.994, 0.990 and 0.941, respectively.

DISCUSSION

The early diagnosis of ovarian malignancies is one of the key factors for improving the survival rate of patients [9]. CA-125 has been used as a tumor marker for the diagnosis and monitoring of ovarian cancer for 30 years, and is also used for efficacy evaluation and monitoring of recurrence [8]. Data have shown that the serum levels of CA-125, HE4 and ROMA in ovarian cancer patients were significantly higher than those of the patients with ovarian benign disease and healthy women [5]. The specificity and positive predictive value of HE4 for ovarian cancer was the highest, and the sensitivity of ROMA index was the highest. In the present study, the 100 cases were divided into the premenopausal and postmenopausal group to evaluate the three indicators in the diagnostic value of ovarian cancer. The ROMA index demonstrated the highest sensitivity and negative predictive value for ovarian cancer. HE4 had the highest specificity and positive predictive value. The specificity of HE4 for ovarian cancer was higher in the postmenopausal women, as reported elsewhere [12]. The sensitivity, specificity, positive predictive value and negative predictive value of the ROMA index in ovarian cancer were the highest (91.89, 96.97, 97.14 and 91.45%), respectively. CA-125 and HE4 were significantly different from the ROMA index, and the ROMA index was significantly better than CA-125 and HE4 in the diagnosis of ovarian cancer. In addition, the ROC curve drawn in this study for the benign tumor of ovary and healthy control groups identified that the area under the ROC curve of CA-125, HE4 and ROMA index was increased by 0.941, 0.990 and 0.994, respectively. This result confirmed the clinical diagnostic value of the ROMA index [5]. It also showed that detection of ROMA index in the diagnosis of ovarian cancer was higher than CA125 and HE4.

Table-1: Sera levels of he4, ca-125 and roma index of three groups. Sensitivity & specificity of positive & negative predictive values of the$, ca125 and roma & risk of ovarian cancer algorithm

Parameters	Healthy control group	Benign tumor group	Ovarian cancer group
Cases	30	64	64
HE4	39.04±8.38	54.76±42.35	739.03±860.04[a,b]
CA-125	15.08±5.28	49.07±175.61[a]	868.85±1204.08[a,b]
ROMA index	6.18±2.21	10.15±11.98	76.30±28.57[a,b]

Table -2: Diagnostic Values of Ca-125, He4 and Roma in Ovarian Cancer

Characteristics	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
CA-125	85.07 (57/64)	92.31 (84/94)	90.6 (57/67)	89.36 (84/91)
HE4	75 (48/64)	97.87 (92/94)	96 (48/50)	85.19 (92/108)
ROMA index	93.75 (60/64)	92.55 (87/94)	89.55 (60/67)	86.14 (87/101)
CA-125	85.07 (57/64)	92.31 (84/94)	90.6 (57/67)	89.36 (84/91)

Table-3: Depicts premenopausal data

PREMENOPAUSAL	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
CA-125	92.59 (25/27)	CA-125	92.59 (25/27)	CA-125
HE4	70.37 (19/27)	HE4	70.37 (19/27)	HE4
ROMA index	96.3 (26/27)	ROMA index	96.3 (26/27)	ROMA index

Table-4: Depicts postmenopausal data

POSTMENOPAUSAL	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
CA-125	86.49 (32/37)	CA-125	86.49 (32/37)	CA-125
HE4	78.38 (29/37)	96.97 (32/33)	96.67 (29/30)	80.00 (32/40)
ROMA index	91.89 (34/37)	96.97 (32/33)	97.14 (34/35)	91.43 (32/35)

CONCLUSION

HE4 and ROMA index which reference intervals are established according to the menopausal status have important clinical significance in the diagnosis of ovarian cancer. Regular detection of serum HE4, CA125, and ROMA index can help predict postoperative recurrence of ovarian cancer. Serological markers provide a means of monitoring tumor activity at many stages of the disease—diagnosis, therapy, and relapse. However, it is important that they are used appropriately and their significance is understood. Knowledge about raised levels of CA125 often raises questions as well as answers; we need to be able to make use of the information available. Early knowledge about relapse does not necessarily help outcome, as better therapies are needed. Progress in therapy is likely to come from a combination of better drugs and a greater understanding of the biology of the disease. Study of serological and tumor-related surface markers needs to continue. Markers for ovarian cancer, and, in particular, CA125, have led the way for epithelial tumors and provide a valuable model for further studies.

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