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Serum biochemical markers in ovarian cancer – A review

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ABSTRACT

Ovarian cancer is the most frequent cause of death from gynaecological cancers, characterized by few early symptoms, diagnosis at an advanced stage as well as poor prognosis. A number of cell surface antigens and serum proteins are produced by ovarian tumors and can be assayed using monoclonal antibodies. Some of these assays have been applied clinically as markers of disease status and are useful in the diagnosis of recurrent ovarian cancer. CA-125 is currently the serum marker most widely used to monitor therapeutic response and to detect disease recurrence in patients treated for epithelial ovarian cancer. Among the other new tumor markers, M-CSF, HE4, mesotehlin seem to be promising. The serial measurement of complementary serum markers can improve the use of marker screening for epithelial ovarian cancer.

KEYWORDS

Ovarian cancer;
Biochemical markers;
CA-125;
Sensitivity;
Specificity.

INTRODUCTION

Ovarian cancer is the fifth leading cause of death in women. The incidence of this malignancy increases in women over the age of 40[1]. Ovarian cancer is the most frequent cause of death from gynaecological cancers, characterized by few early symptoms, diagnosis at an advanced stage as well as poor prognosis. Ovarian cancer is a malignancy in which the normal ovarian cells begin to grow in an uncontrolled, abnormal manner and produce tumors in one or both ovaries. Epithelial cancers, the most common ovarian cancers (> 80%) develop from cells lining the ovarian surface[2]. The high mortality rate of epithelial ovarian cancers is a consequence of the fact that 70% to 75% of women with epithelial ovarian cancers are diagnosed with stage III or IV disease, which has 5-year survival rates of just 15% to 31%[3-6]. In comparison, 5-year survival rates for stage I epithelial ovarian cancer patients are significantly better, in the range of 90% to 95%[3,7,8]. Despite new therapy options[9,10], the age-adjusted mortality rate for patients with epithelial ovarian cancer has not changed significantly over the past 20 years[3,11]. Early detection, therefore, is a potentially practical approach for controlling epithelial ovarian cancer.

Unfortunately, no single screening test has proven to be effective for this purpose and a valid and feasible program to detect early stage epithelial ovarian cancer in the general population has not yet been devised. Early detection of ovarian cancer requires a strategy with high sensitivity (>75% for stage I disease) and a very high specificity (> 99.6%) to achieve a positive predictive value of 10%.

Diagnosis of an ovarian cancer starts with a physi-

cal examination (including a pelvic examination), a blood test for CA-125 and transvaginal ultrasound. Treatment usually involves chemotherapy and surgery and sometimes radiotherapy[12].

CRITERIA FOR ASSESSING THE DIAGNOSTIC VALUE OF A MARKER

An ideal tumor marker should have 100% sensitivity, specificity and positive predictive value.

Sensitivity

It refers to the percentage of patients with tumor who are correctly identified as a result of a positive test.

Specificity

It refers to the percentage of the population without tumor who are correctly identified as a result of a negative test.

Positive predictive value (PPV)

Refers to the percentage of patients with a positive test that have tumor (true positives).

BIOCHEMICAL MARKERS OF OVARIAN CANCER IN SERUM/PLASMA

A tumour marker is defined as a molecule either produced by the cancer cells or released by the host as various epiphenomena of metabolic changes caused by the presence of malignancy[13]. A number of cell surface antigens and serum proteins are produced by ovarian tumors and can be assayed using monoclonal antibodies. Some of these assays have been applied clinically as markers of disease status and are useful in the diagnosis of recurrent ovarian cancer.

1. Carcinoembryonic antigen (CEA)
2. Cancer antigen-125 (CA-125)
3. Macrophage-colony stimulating factor (M-CSF)
4. LyGDI
5. Human epididymis protein 4 (HE4)
6. Soluble epidermal growth factor receptor (sEGFR)
7. Mesothelin

CEA (Carcinoembryonic antigen)

CEA was detected in 1965 using serum from rabbits immunized with a colon carcinoma[14]. It is an oncofetal antigen found in small amounts in adult colon. Elevated levels are associated with colon and pancreatic carcinoma. Levels are also raised in benign disease of the liver, gastrointestinal tract, and lung and in smokers. Serum CEA levels are elevated in 25% to 50% of women with ovarian cancer. Although there is some correlation with ovarian malignancy, this is less satisfactory than that obtained with the other markers[15].

CA-125

The CA-125 compound was first characterized by Bast et al using the monoclonal antibody OC125[16]. It is a membrane glycoprotein expressed by epithelial cells of different origin and of unknown function[17].

Cancer antigen-125 (CA-125), a heterogeneous cell membrane glycoprotein that ranges in molecular weight from 200 to 500 kDa encoded by the MUC16 gene[18,19] has been studied extensively as a potential screening and diagnostic test of epithelial ovarian cancer[20,21]. This marker was initially described by Dr Robert C Bast and is widely used in clinical practice today. Immunoassay studies have shown that serum CA-125 (>35 units/mL cutoff) levels are elevated in 1.4% of healthy women and 82% of all epithelial ovarian cancer patients, but only 50% of epithelial ovarian cancer patients with stage I disease[22,23]. CA-125 is raised in 50% cases with stage I ovarian carcinoma and is raised in more than 90% of cases with advanced carcinoma. Elevated serum CA-125 levels are not restricted to epithelial ovarian cancer. Notably, serum CA-125 levels are elevated in various normal and pathologic conditions that affect the endometrium, including menstruation[24,25], pregnancy[26,27], endometriosis[28-30], and endometrial cancer[31,32]. Serum CA-125 levels also are elevated in patients with benign and inflammatory diseases of the liver[33,34], pelvis[35], uterus[36], and ovary and in patients with hematologic, bladder, breast, fallopian, gastrointestinal, liver, lung, and pancreatic cancers[37-39]. Despite CA-125's elevation in other diseases, immunoassay studies have documented specificities ranging between 95.4% and 96.7%[40,41].

CA-125 is currently the serum marker most widely used to monitor therapeutic response and to detect disease recurrence in patients treated for epithelial ovarian cancer[42]. The National Comprehensive Cancer Network (NCCN) recommends CA-125 measurement before each treatment cycle for women with elevated pretreatment levels[43]. NCCN also recommends CA-

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125 measurement at each follow-up evaluation if the level was initially elevated. CA-125, however, is not elevated in all patients with epithelial ovarian cancer; thus, other markers have been sought.

M-CSF

Macrophage-colony stimulating factor (M-CSF, CSF-1) receptor is an integral membrane tyrosine kinase encoded by the c-fms proto-oncogene. M-CSF receptor is expressed in monocytes (macrophages and their progenitors) and drives growth and development of this blood cell lineage[44,45]. M-CSF has been found to be measurable in the serum of 68% of patients with clinically detectable disease. Some complimentarity with CA-125 has been documented. M-CSF levels correlate with the clinical status of disease in patients with epithelial ovarian cancer. M-CSF was significantly elevated in the serum of patients with advanced as compared to early stage cancer (stage I) of the ovary ($p< 0.01$), cervix ($p< 0.05$) and endometrium ($p< 0.05$). M-CSF appeared to be a marker with high specificity for ovarian cancer.

HE4

Human epididymis protein 4 (HE4) is a low molecular weight (25 Kd) member of the Whey Acidic Protein family of protease inhibitors. Because it contains two of the 4-disulphide core domains characteristic of this family, it is sometimes referred to as whey acidic protein four disulphide core protein 2, WFDC2[46]. HE4 gene expression is up-regulated in invasive epithelial ovarian cancer as well as adenocarcinomas of the lung. Human epididymis protein 4 (HE4), a relatively new marker for ovarian carcinoma, is the product of the *WFDC2* (*HE4*) gene that is overexpressed in patients with ovarian carcinoma[47,48]. Using an immunoassay, a small study indicated comparable sensitivity for CA 125 and HE4 in postmenopausal women with ovarian cancer[49]. A subsequent and larger study confirmed the sensitivity of HE4[50]. Another study evaluated the utility of HE4 in the follow-up of 80 patients with ovarian cancer. This study indicated serial HE4 levels correlated with clinical status (progression vs no progression) in 70% (247/354) of the samples.

LyGDI

LyGDI is an inhibitor of Rho protein activation by blocking its transformation between guanosine- 5'-diphosphate and guanosine- 5'- triphosphate bound states. LyGDI has significant potential as a markers for detection of ovarian cancer in the patients with ovarian enlargement including detection of early-stage cancers[51].

Soluble EGF receptor

Soluble epidermal growth factor receptor (sEGFR/sErbB1) is a 110-kDa glycoprotein found in human serum that is encoded by a 3.0 kb alternate mRNA transcript of the EGFR gene[52,53]. Immunoassay studies have shown that patients with epithelial ovarian cancer have significantly lower serum p110 sEGFR concentrations than healthy women, and that sEGFR concentrations are inversely associated with serum concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), as well as with age in healthy women[53,54]. Moreover, age and menopausal status modify the association between sEGFR concentrations and epithelial ovarian cancer versus healthy women[72]. Serum sEGFR concentrations were found to have 74% sensitivity to detect epithelial ovarian cancer among premenopausal women, but only 50% sensitivity to detect epithelial ovarian cancer among postmenopausal women. Test sensitivity was lower for detecting stage I/II compared with stage III/IV epithelial ovarian cancer among premenopausal women (64% versus 81%) and postmenopausal women (28% versus 54%). Thus, serum sEGFR concentrations seem to be most useful for detecting epithelial ovarian cancer among younger, premenopausal women.

Mesothelin

Mesothelin is a cell surface protein present on normal mesothelial cells lining the body cavities. It is highly expressed in several cancers, including mesotheliomas, ovarian and pancreatic cancers, and some squamous cell carcinomas[55,56]. Human mesothelin is made as a 69 kDa polypeptide with a hydrophobic sequence at the carboxyl end that is removed and replaced by phosphatidylinositol. This glycosyl-phosphatidylinositol linkage anchors mesothelin to the cell membrane[56,57]. Mesothelin is shed like many other cell membrane proteins[58]. There are soluble mesothelin-related (SMR) protein which are 42 to 44 kDa protein[59,60]. Soluble mesothelin-related peptides are members of the megakaryocyte potentiating factor (MPF) family and have been detected in both the serum and urine of patients with ovarian cancer[61]. A recent study presented evi-

dence that mesothelin binds CA-125 and may, therefore, play a role in the dissemination ovarian cancer in the peritoneal cavity[62].

CONCLUSION

The serial measurement of complementary serum markers can improve the use of marker screening for epithelial ovarian cancer. With the use of several different methods of analysis, it has been shown that this approach improves the sensitivity, specificity, and positive predictive value of serum markers. A procedure that measures complementary serum markers over time can be used as a primary screening technique followed by transvaginal ultrasonography. This could provide a cost-effective means of early detection and could significantly decrease the probability of surgical intervention for false-positive test results.

REFERENCES

[1] T.Malati, K.G.Rajani, B.Yadagiri; Ind.J.Clin. Biochem., **16(2)**, 222-333 **(2001)**.

[2] T.Williams, K.L.Toups, D.A.Saggese, K.R.Kalli, W.A.Cliby, D.C.Muddiman; J.Proteome Res., **6(8)**, 2936-2962 **(2007)**.

[3] A.Jemal, R.C.Tiwari, T.Murray; Cancer J.Clin., **54(1)**, 8-29 **(2004)**.

[4] B.Y.Karlan; J.Cell Biochem., **59(Suppl. 23)**, 227-232 **(1995)**.

[5] R.F.Ozols, S.C.Rubin, G.Thomas, S.Robboy; Epithelial Ovarian Cancer. Principles and Practice of Gynecologic Oncology. Lippincott-Raven Publishers, 919-986 **(1997)**.

[6] I.B.Runnebaum, E.Stickeler; J.Cancer Res.Clin. Oncol., **127(2)**, 73-79 **(2001)**.

[7] R.C.Young, L.A.Walton, S.S.Ellenburg; N.Eng. J.Med., **322(15)**, 1021-1027 **(1990)**.

[8] H.E.Averette, H.N.Nguyen, D.M.Donato, M.A.Penalver, B.U.Sevin, R.Estape, W.A.Little; Cancer, **71(4)**, 1422-1437 **(1993)**.

[9] S.B.Kaye; Eur.J.Cancer, **31(9)**, 19-23 **(2001)**.

[10] S.Wadler; Expert Opin.Investig.Drugs, **10(6)**, 1167-1172 **(2001)**.

[11] K.A.Oriel, E.M.Hartenbach, P.L.Remington; Obstet.Gynaecol., **93(1)**, 30-33 **(1999)**.

[12] N.Chobanian, C.S.Dietrich; Surg.Clin.North Am., **88(2)**, 285-299 **(2008)**.

[13] M.J.Duffy; Crit.Rev.Clin.Lab.Sci., **38(3)**, 225-262 **(2001)**.

[14] P.Gold, S.O.Freedman; J.Exp.Med., **122(3)**, 467 **(1965)**.

[15] M.Onsrud; Scand.J.Clin.Lab.Invest., **51(206)**, 260-270 **(1991)**.

[16] R.C.Bast Jr., T.L.Klug, E.St.John; N.Engl.J.Med., **309(15)**, 883-887 **(1983)**.

[17] S.E.Kabawat, R.C.Bast Jr., A.K.Bhan, W.R.Welch, R.C.Knapp, R.B.Colvin; Int.J.Gyneco.Pathol., **2(3)**, 275- 285 **(1983)**.

[18] T.J.O'Brein, J.B.Beard, L.J.Underwood, R.A.Dennis, A.D.Santin, L.York; Tumour.Biol., **22(6)**, 348-366 **(2001)**.

[19] B.W.T.Yin, K.O.Lloyd; J.Biol.Chem., **276(29)**, 27371-27375 **(2001)**.

[20] I.Jacobs, R.C.Bast Jr.; Hum.Reprod., **4(1)**, 1-12 **(1989)**.

[21] A.N.Rosenthal, I.J.Jacobs; Int.J.Biol.Markers, **13(4)**, 216-220 **(1998)**.

[22] R.C.Bast Jr., T.L.Klug, E.St.John; N.Engl.J.Med., **309(15)**, 883-887 **(1983)**.

[23] I.Zanaboni, F.Vergadoro, M.Presti, P.Galloti, F.Lombardi, G.Bolis; Gynaecol.Oncol., **28(1)**, 61-67 **(1987)**.

[24] W.Mastropaolo, Z.Fernandez, E.L.Miller; Clin. Chem., **32(11)**, 2110-2111 **(1986)**.

[25] P.Lehtovirta, D.Apter, V.H.Stenman; Br.J.Obstet. Gynaecol., **97(10)**, 930-933 **(1990)**.

[26] Y.Touitou, Y.Darbois, A.Bogdan, A.Anzeby, S.Keuzseoglou; Br.J.Cancer., **60(3)**, 419-420 **(1989)**.

[27] J.M.Niloff, R.C.Knapp, E.Schaetzl, C.Reynolds, R.C.Bast Jr.; Obstet.Gynecol., **64(5)**, 703-707 **(1984)**.

[28] L.C.Giudice, A.Jacobs, J.Pineda, C.E.Bell, L.Lippmann; Fertil.Steril., **45(6)**, 876-878 **(1986)**.

[29] K.Takahashi, Y.Yamane, S.Kijima, K.Yoshino, T.Shibukawa, M.Kitao; Gynaecol.Obstet.Invest., **23(4)**, 257-260 **(1987)**.

[30] G.D.Malkasian Jr.; K.C.Podratz, C.R.Stanhope, R.E.Ritts Jr., V.R.Zurawski Jr.; Am.J.Obstet. Gynecol., **155(3)**, 515-518 **(1986)**.

[31] J.M.Niloff, T.L.Klug, E.Schaetzl, V.R.Zurawski Jr., R.C.Knapp, R.C.Bast Jr.; Am.J.Obstet.Gynecol., **148(8)**, 1057-1058 **(1984a)**.

[32] J.W.Duk, J.G.Aalders, G.J.Fleuren, H.W.A.de Bruigh; Am.J.Obstet.Gynaecol., **155(5)**, 1097-1102 **(1986)**.

[33] R.Molina, A.M.Ballesta, E.Casals, G.Borras, M.Eleno, A.Balaue; Protides Biol.Fluids, **32**, 613-616 **(1984)**.

Review

[34] J.Callazos, F.Diaz; Clin.Chem., **38(6)**, 1188-1189 **(1992)**.
[35] J.Mojas, J.A.Castilla, P.Jimena, T.Gil, M.Acebal, A.J.Herruzo; Int.J.Gynaecol.Obstet., **44(1)**, 53-57 **(1994)**.
[36] P.K.Buamah, A.W.Skillen; J.Surg.Oncol., **56(2)**, 71-79 **(1994)**.
[37] R.Molina, X.Filella, J.Bruix; Clin.Chem., **37(8)**, 1379-1389 **(1991)**.
[38] T.Fehm, E.Beck, T.Valerius, M.Gramatzki, W.Jager; Tumor Biol., **19(4)**, 283-289 **(1998)**.
[39] I.Jacobs, R.C.Bast Jr.; Immunodiagnosis of Ovarian Tumors.. Immunodiagnosis of Cancer. Marcel Dekker, Inc. New York, **990**, 323-338 **(1990)**.
[40] V.R.Zurawski Jr., S.F.Broderick, P.Pickens, R.C.Knapp, R.C.Bast Jr.; Obstet.Gynaecol., **69(4)**, 606-611 **(1987)**.
[41] V.R.Zurawski Jr., K.Sjovall, D.A.Schoenfeld; Gynaecol.Oncol., **36(3)**, 299-305 **(1990)**.
[42] M.J.Duffy, J.M.Bonfrer, J.Kulpa; Int.J.Gynecol. Cancer, **15(5)**, 679-691 **(2005)**.
[43] National Comprehensive Cancer Network; Clinical Practice Guidelines in Oncology. Ovarian Cancer. Version1: 30, **(2008)**.
[44] P.V.Byrne, L.J.Guilbert, E.R.Stanley; J.Cell Biol., **91(3)**, 848-853 **(1981)**.
[45] R.P.Bourette, L.R.Rohrschneider; Growth Factors, **17(3)**, 155-166 **(2000)**.
[46] D.Bouchard; Lancet Oncol., **7(2)**, 167-174 **(2006)**.
[47] K.Ono, T.Tanaka, T.Tsunoda; Cancer Res., **60(18)**, 5007-5011 **(2000)**.
[48] J.B.Welsh, P.P.Zarrinkar, L.M.Sapinoso; Proc.Natl. Acad.Sci.USA, **98(3)**, 1176-1181 **(2001)**.
[49] I.Hellstrom, J.Raycraft, M.Hayden-Ledbetter; Cancer Res., **63(13)**, 3695-3700 **(2003)**.
[50] R.G.Moore, A.K.Brown, M.C.Miller; Gynecol. Oncol., **108(2)**, 402-408 **(2008)**.
[51] H.Zhen, S.Yang, H.Wu, S.Wang, L.Ma, X.Zhang; Int.J.Gynecol.Cancer, **20(3)**, 316-322 **(2010)**.
[52] J.L.Reiter, D.W.Threadgill, G.D.Eley; Genomics, **71(1)**, 1-20 **(2001)**.
[53] A.T.Baron, E.M.Cora, J.M.Lafky; Cancer Epidemiol.Biomarkers Prev., **12(2)**, 103-113 **(2003)**.
[54] A.T.Baron, J.M.Lafky, C.H.Boardman; Cancer Epidemiol.Biomarkers Prev., **8(2)**, 129-137 **(1999)**.
[55] K.Chang, I.Pastan, M.Willingham; Int.J.Cancer, **51(4)**, 548-554 **(1992)**.
[56] K.Chang, I.Pastan; Proc.Natl.Acad.Sci., **93(1)**, 136-140 **(1996)**.
[57] R.Hassan, T.Bera, I.Pastan; Clin.Cancer Res., **10**, 3937-3942 **(2004)**.
[58] P.Censullo, M.A.Davitz; Semin.Immunol., **6(2)**, 81-88 **(1994)**.
[59] N.Scholler, N.Fu, Y.Yang; Proc.Natl.Acad.Sci.Usa, **96(20)**, 11531-11536 **(1999)**.
[60] B.S.Robinson, J.Creaney, R.Lake; Lancet, **362(9396)**, 1612-1616 **(2003)**.
[61] A.Rump, Y.Morikawa, M.Tanaka; J.Biol.Chem., **279(10)**, 9190-9198 **(2003)**.