doi: 10.13241/j.cnki.pmb.2018.18.032

血清 HE4、FS、SMRP 及 CA125 在卵巢癌患者中的表达及临床意义 *

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摘要 目的：探讨血清人附睾蛋白 4（HE4）、卵泡抑素（FS）、可溶性间皮素相关蛋白（SMRP）、糖类抗原 125（CA125）在卵巢癌患者中的表达水平及临床意义。**方法：**选取 2014 年 6 月 -2017 年 9 月我院收治的卵巢癌患者 60 例作为卵巢癌组，另选取同期收治的卵巢良性肿瘤患者 32 例作为良性组，选取同期健康体检妇女 40 例作为对照组，检测三组受试者血清 HE4、FS、SMRP、CA125 水平，对比三组 HE4、FS、SMRP、CA125 阳性表达率，并分析血清 HE4、FS、SMRP、CA125 对卵巢癌的诊断价值。**结果：**三组受试者的 HE4、FS、SMRP、CA125 水平整体对比有统计学意义（P<0.05），其中卵巢癌组与良性组 HE4、FS、SMRP、CA125 水平高于对照组，且卵巢癌组高于良性组，差异有统计学意义（P<0.05）。三组受试者的 HE4、FS、SMRP、CA125 阳性表达率整体对比有统计学意义（P<0.05），卵巢癌组与良性组 HE4、FS、SMRP、CA125 阳性表达率高于对照组，且卵巢癌组高于良性组，差异有统计学意义（P<0.05）。联合检测的灵敏度高于 FS、SMRP 单项检测，差异有统计学意义（P<0.05），联合检测的特异度高于 HE4、FS、SMRP、CA125 单项检测，但差异无统计学意义（P>0.05）。**结论：**卵巢癌患者血清 HE4、FS、SMRP、CA125 水平及阳性表达率均较高，四项指标联合检测可提高诊断卵巢癌的灵敏度及特异度。

关键词：卵巢癌；血清人附睾蛋白 -4；卵泡抑素；可溶性间皮素相关蛋白；糖类抗原 125

中图分类号：R737.31 **文献标识码：**A **文章编号：**1673-6273(2018)15-3542-04

The Expression and Clinical Significance of Serum HE4, FS, SMRP and CA125 in Patients with Ovarian Cancer*

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ABSTRACT Objective: To investigate the expression level and clinical significance of serum epididymal protein-4 (HE4), follistatin (FS), soluble mesothelin associated protein (SMRP) and carbohydrate antigen 125 (CA125) in patients with ovarian cancer. **Methods:** 60 cases of ovarian cancer who were treated in our hospital from June 2014 to September 2017 were selected as ovarian cancer group, 32 cases of benign ovarian tumor in the same period were selected as benign group, 40 women in healthy physical examination at the same time as a control group. The serum levels of HE4, FS, SMRP and CA125 were detected in the three groups, the positive rates of HE4, FS, SMRP and CA125 in three groups were compared, the value of serum HE4, FS, SMRP and CA125 in the diagnosis of ovarian cancer were analysed. **Results:** The levels of HE4, FS, SMRP and CA125 in the three groups were statistically significant (P<0.05), among them, the levels of HE4, FS, SMRP and CA125 in the ovarian cancer group and the benign group were higher than those in the control group, the ovarian cancer group was higher than that of the benign group, and the differences were statistically significant (P<0.05). The overall comparison of the positive rates of HE4, FS, SMRP and CA125 in the three groups were statistically significant (P<0.05), the positive expression rate of HE4, FS, SMRP and CA125 in the ovarian cancer group and the benign group were higher than that in the control group, and the ovarian cancer group was higher than the benign group, and the differences were statistically significant (P<0.05). The sensitivity of the combined test was higher than that of FS and SMRP, and the difference was statistically significant (P<0.05), the specificity of the combined test was higher than that of HE4, FS, SMRP and CA125, but the difference was not statistically significant (P>0.05). **Conclusion:** The serum levels of HE4, FS, SMRP, CA125 and positive expression are higher in the patients with ovarian cancer, the combined detection of four indexes could improve the sensitivity and specificity of the diagnosis of ovarian cancer.

Key words: Ovarian cancer; Human epididymal protein-4; Follistatin; Soluble mesothelin related protein; Carbohydrate antigen 125

Chinese Library Classification(CLC): R737.31 Document code: A

Article ID: 1673-6273(2018)18-3542-04

* 基金项目：福建省自然科学基金面上项目（2013D0006）

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（收稿日期：2018-03-05 接受日期：2018-03-29）

前言

卵巢癌是临床常见的妇科恶性肿瘤,其发病率仅次于子宫癌及宫颈癌,且具有较高的病死率[1,2]。据以往临床研究显示,卵巢癌患者若能较早确诊、及时治疗可有效改善患者的预后,延长生存时间[3,4]。但由于卵巢癌患者早期没有典型的临床表现,确诊后约有 75%的患者已发展到晚期,而晚期卵巢癌患者的 5 年生存率仅为 10%-30%,因此卵巢癌患者的早期诊断、早期治疗对延长患者生存期具有重要意义[5-7]。血清人附睾蛋白 4(human epididymal protein 4,HE4)及糖类抗原 125(carbohydrate antigen,CA125)是临床常用于肿瘤筛查的血清肿瘤标志物,卵泡抑素(follistatin,FS)、可溶性间皮素相关蛋白(soluble mesothelin related protein,SMRP)是近几年新发现的卵巢肿瘤标志物,目前临床上对 HE4 及 CA125 用于卵巢癌诊断的研究较多[8-10],但对于联合 FS、SMRP 诊断卵巢癌的研究较少,因此本研究通过探讨血清 HE4、FS、SMRP 以及 CA125 在卵巢癌患者中的表达水平及临床意义,旨在为临床诊治提供数据支持,现整理报道如下。

1 资料与方法

1.1 一般资料

选取 2014 年 6 月 -2017 年 9 月我院收治的卵巢癌患者 60 例作为卵巢癌组,纳入标准:(1)所有患者均符合《中国妇科学分类与诊断标准》第 3 版关于卵巢癌的诊断标准与化疗指征[11];(2)生存期大于 3 个月;(3)自愿参与本次研究,并签署知情同意书,排除标准:(1)合并严重心、肝、肾功能障碍者;(2)伴有其他恶性肿瘤者;(3)近 3 个月接受化疗及放疗治疗者;(4)治疗依从性差者。卵巢癌组患者年龄 27-78 岁,平均(46.92± 3.75)岁,病程 1-4 年,平均病程(2.35± 0.62)年,病理分期:Ⅰ期 5 例、Ⅱ期 8 例、Ⅲ期 25 例、Ⅳ期 22 例,癌症类型:黏液性腺癌 25 例,浆液性腺癌 29 例,子宫内膜样癌 6 例。另选取同期收治的卵巢良性肿瘤患者 32 例作为良性组,良性组患者年龄 24-76 岁,平均(45.64± 4.38)岁,病程 1-4 年,平均(2.72± 0.29)年,其中卵巢囊肿 12 例,畸胎瘤 10 例,纤维瘤 6 例,炎性包块 4 例。选取同期健康体检妇女 40 例作为对照组,对照组年龄 22-78 岁,平均(45.38± 5.12)岁,三组受试者的年龄对比差异无统计学意义(P>0.05),本研究通过医院伦理委员会批准。

1.2 方法

卵巢癌组与良性组患者在入院后抽取清晨空腹静脉血 5 mL,对照组在体检时抽取清晨空腹静脉血 5 mL,应用离心机(美国 Beckman 公司)以 3000 r/min 的转速离心 10 min,离心半径为 10 cm,将血清与血浆分离,收集离心管上层的血清,并放在 -70℃的冰箱中保存待检,HE4、SMRP 的检测采用酶联免疫吸附法,试剂盒由北京方程生物科技有限公司提供,所有操作均严格按照试剂盒说明书进行;FS、CA125 检测采用电化学发光免疫法,试剂盒由瑞士罗氏公司提供,所有操作均严格按照试剂盒说明书进行。各指标诊断卵巢癌阳性范围:HE4≥ 150 pmol/L,FS≥ 1.5 μg/L,SMRP≥ 1.5 nmol/L,CA125≥ 35 U/mL,联合检测时其中任何一项指标达到阳性值均可诊断为阳性。

1.3 观察指标

检测并对比三组受试者血清 HE4、FS、SMRP、CA125 水平,对比三组 HE4、FS、SMRP、CA125 阳性表达率,并分析血清 HE4、FS、SMRP、CA125 对卵巢癌的灵敏度及特异度,其中灵敏度 = 真阳性例数 /(真阳性例数 + 假阴性例数)× 100%,特异度 = 真阴性例数 /(真阴性例数 + 假阳性例数)× 100%。

1.4 统计学方法

采用 SPSS19.0 统计学软件进行统计分析,计量资料以($\bar{x}$± s)的形式表示,组间对比经 t 检验分析,多组间对比经方差分析,计数资料以%的形式表示,组间对比经 x^2 检验分析,以 P<0.05 为差异有统计学意义。

2 结果

2.1 三组受试者 HE4、FS、SMRP、CA125 水平比较

三组受试者的 HE4、FS、SMRP、CA125 水平整体对比有统计学意义(P<0.05),其中卵巢癌组与良性组 HE4、FS、SMRP、CA125 水平高于对照组,且卵巢癌组高于良性组,差异有统计学意义(P<0.05),见表 1。

表 1 三组受试者 HE4、FS、SMRP、CA125 水平比较($\bar{x}$± s)

Table 1 Comparison of the expression levels of HE4, FS, SMRP and CA125 in the three groups($\bar{x}$± s)

Groups	n	HE4(pmol/L)	FS(μg/L)	SMRP(nmol/L)	CA125(U/mL)
Ovarian cancer group	60	250.42± 81.38*#	3.67± 0.62*#	29.27± 7.52*#	201.57± 23.41*#
Benign group	32	23.69± 6.14*	1.34± 0.27*	1.23± 0.33*	26.77± 5.82*
Control group	40	12.49± 3.72	0.53± 0.12	0.14± 0.02	11.73± 3.29
F		10.157	13.186	10.672	9.573
P		0.036	0.012	0.021	0.041

Note: compared with control group, *P<0.05; compared with benign group, #P<0.05.

2.2 三组受试者 HE4、FS、SMRP、CA125 阳性表达率比较

三组受试者的 HE4、FS、SMRP、CA125 阳性表达率整体对比有统计学意义(P<0.05),卵巢癌组与良性组 HE4、FS、SMRP、CA125 阳性表达率高于对照组,且卵巢癌组高于良性组,差异有统计学意义(P<0.05),见表 2。

2.3 血清 HE4、FS、SMRP、CA125 单项检测和联合检测的灵敏度及特异度比较

联合检测的灵敏度高于 FS、SMRP 单项检测,差异有统计学意义(P<0.05),联合检测的特异度高于 HE4、FS、SMRP、CA125 单项检测,但差异无统计学意义(P>0.05),见表 3。

表 2 三组受试者 HE4、FS、SMRP、CA125 阳性表达率比较[n(%)]

Table 2 Comparison of positive rates of HE4, FS, SMRPand CA125 in the three groups [n(%)]

Groups	n	HE4	FS	SMRP	CA125
Ovarian cancer group	60	52(86.67)*#	48(80.00)*#	49(81.67)*#	53(88.33)*#
Benign group	32	6(18.75)*	3(9.38)*	5(15.63)*	4(12.50)*
Control group	40	0(0.00)	0(0.00)	0(0.00)	0(0.00)
x^2		87.376	95.812	86.718	114.932
P		0.000	0.000	0.000	0.000

Note: compared with control group, *P<0.05; compared with benign group, #P<0.05.

表 3 血清 HE4、FS、SMRP、CA125 单项检测和联合检测的灵敏度及特异度比较(%)

Table 3 Comparison of the sensitivity and specificity of serum HE4,FS,SMRPand CA125 in the diagnosis of ovarian cancer(%)

Indexes	True positive(n)	False negative(n)	False positive(n)	True negative(n)	Sensitivity(%)	Specificity(%)
HE4	52	8	6	26	86.67	81.25
FS	48	12	3	29	80.00*	90.63
SMRP	49	11	5	27	81.67*	84.38
CA125	53	7	4	28	88.33	87.50
Combined test	57	3	2	30	95.00	93.75

Note: compared with combined test, *P<0.05.

3 讨论

卵巢癌是临床常见的女性生殖系统恶性肿瘤,发病原因可能与免疫功能、内分泌、遗传、精神等因素有关,饮食营养失调及不良生活习惯也会引起该疾病的发生,围绝经期的妇女是卵巢癌发病的主要群体[12-14]。卵巢癌患者主要临床症状有胀痛、月经不调、消瘦等,但由于发病早期无特异性临床症状,并且在临床上缺乏灵敏度高和特异度强的早期诊断方法,所以多数患者在确诊时已发展到卵巢癌晚期,严重影响卵巢癌患者的预后和生命健康[15-17]。因此寻找诊断卵巢癌灵敏度和特异度高的血清肿瘤标志物,对卵巢癌患者的早期诊断及治疗均具有重要的临床意义。近年来,血清检查肿瘤标记物的诊断方法运用较多,其具有经济、简便、无创等优点受到越来越多的关注,其中血清 HE4、FS、SMRP、CA125 可作为诊断早期卵巢癌的血清肿瘤标志物[18,19]。

本研究结果显示,卵巢癌组与良性组 HE4、FS、SMRP、CA125 水平高于对照组,且卵巢癌组高于良性组(P<0.05),说明 HE4、FS、SMRP、CA125 在卵巢癌及卵巢良性肿瘤患者中的表达水平高于正常妇女,且随着病情的恶化其表达水平升高。可能的原因是 CA125 是一种肿瘤相关抗原,是目前临床上常用于诊断卵巢癌的血清肿瘤标志物,并且有研究报道显示,其在卵巢恶性与良性疾病、肺癌、乳腺癌、肝癌、炎症、子宫内膜异位症等任何刺激腹膜损伤的疾病中均可发生 CA125 表达水平异常升高[20,21]。HE4 是一种新型的肿瘤标志物,属于一种酸性抑制性蛋白,是附睾分泌蛋白 E4 的前体,对机体的免疫功能具有保护作用,在男性附睾上皮、女性生殖道上皮组织及卵巢癌组织中具有较高的表达水平,但在正常的卵巢组织中未能检出 HE4[22-24]。FS 是一种单链糖蛋白,又被称为激活素结合蛋白,有研究显示 FS 参与了机体多种病理生理过程,在细胞分化、胚胎发育和多卵巢综合征中发挥着重要作用[25]。SMRP 是一种可溶性间皮素相关蛋白,是间皮素的异构体,有研究表明[26],SMRP 在卵巢癌患者血清中的表达水平显著升高,在健康人群的血清中则不表达,与本研究结果一致。本研究结果还显示,卵巢癌组与良性组 HE4、FS、SMRP、CA125 阳性表达率高于对照组,且卵巢癌组高于良性组(P<0.05),说明 HE4、FS、SMRP、CA125 在健康孕妇中不会呈阳性表达,在卵巢良性肿瘤与卵巢癌患者中呈阳性表达,所以检测 HE4、FS、SMRP、CA125 可辅助卵巢癌的诊断,主要是因为随着患者病情的发展 HE4、FS、SMRP、CA125 在血清的表达水平逐渐高于阳性临界值[27,28]。另外,联合检测的灵敏度高于 FS、SMRP 单项检测(P<0.05),联合检测的特异度高于 HE4、FS、SMRP、CA125 单项检测,但差异无统计学意义(P>0.05),说明 HE4、FS、SMRP、CA125 联合检测诊断卵巢癌可在一定程度上提高灵敏度及特异度,可能的原因是 HE4、FS、SMRP、CA125 虽然在卵巢癌中的表达水平升高,但是在其他癌症中也可检测到 HE4、FS、SMRP、CA125 高表达,因此较多学者认为单独检测诊断早期卵巢癌存在一定的局限性,联合检测可有效避免因单项检测带来的漏诊或误诊,降低假阳性率,进而提高灵敏度及特异度[29,30]。虽然本研究对 HE4、FS、SMRP、CA125 这这四种血清肿瘤标志物进行检测,但还并未能确诊卵巢癌的发生,所以在今后的临床妇产科重,需寻求更加敏感的肿瘤标志物以提高卵巢癌的确诊率。

综上所述,HE4、FS、SMRP、CA125 在卵巢癌患者血清中具有较高的表达水平,联合检测的灵敏度及特异度高于单项检测,为卵巢癌的早期诊断提供了新的方法和思路。

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