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联合检测血清糖类抗原标志物在女性绝经前后卵巢浆液性癌诊断中的价值 *

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摘要 目的：探讨联合检测血清糖类抗原标志物在女性绝经前后卵巢浆液性癌诊断中的价值。**方法：**采用回顾性研究方法，选择2016年8月到至2018年2月在我院肿瘤科进行检测的绝经前后卵巢浆液性癌患者60例(癌变组)与绝经前后健康体检者60例(健康对照组)，检测其血清癌胚抗原(carcino-embryonic antigen，CEA)、人附睾蛋白4(human epididymis protein 4，HE4)和糖链抗原125(carbohydrate antigen 125，CA125)的水平，并分析其与患者的临床病理特征与随访预后的相关性。**结果：**癌变组血清CEA、HE4、CA125水平及阳性表达率都均显著高于健康对照组(P<0.05)。在癌变组60例患者中，随着病理分期增加、分化程度的减少、淋巴结转移与死亡情况的发生，血清CEA、HE4、CA125的阳性表达率显著升高，对比差异有统计学意义(P<0.05)。同时在120例人群中，联合诊断为卵巢浆液性癌者54例，联合诊断的敏感性与特异性分别为90.0%和100.0%。**结论：**绝经前后女性卵巢浆液性癌患者血清糖类抗原标志物-CEA、HE4、CA12水平均呈现高表达，可能作为绝经前后女性卵巢浆液性癌诊断与预后预测的参考指标。

关键词：癌胚抗原；人附睾蛋白4；糖链抗原125；绝经；卵巢浆液性癌

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The Values of Combined Detection of Serum Carbohydrate Antigen Markers for the Diagnosis of Ovarian serous Carcinoma before and after Menopause in Women*

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ABSTRACT Objective: To investigate the values of combined detection of serum carbohydrate antigen markers in the diagnosis of ovarian serous carcinoma in women before and after menopause. **Methods:** Used a retrospective study, from August 2016 to February 2018 60 patients with ovarian serous carcinoma before and after menopause (canceration group) and 60 healthy subjects before and after menopause (health control group) were selected, the serum levels of CEA, HE4 and CA125 were detected, and their correlation with clinicopathological features and follow-up prognosis was analyzed. **Results:** The levels of serum CEA, HE4, CA125 and positive expression rate in the canceration group were significantly higher than those in the healthy control group (P<0.05). Among the 60 patients in the carcinogenesis group, with the increase of pathological stage, reduction of differentiation, lymph node metastasis and mortality, the positive expression rate of serum CEA, HE4 and CA125 increased significantly, the difference was statistically significant (P<0.05). In the 120 cases, there were 54 cases of ovarian serous carcinoma were combined, the sensitivity and specificity of combined diagnosis were 90.0% and 100.0%, respectively. **Conclusion:** The levels of serum carbohydrate antigen markers CEA, HE4 and CA12 in premenopausal and postmenopausal women with ovarian serous carcinoma were all increased, which may serve as a reference index for the diagnosis and prognosis prediction of ovarian serous carcinoma in premenopausal and postmenopausal women.

Key words: Carcino-embryonic antigen; Human epididymis protein 4; Sugar chain antigen 125; Menopause; Ovarian serous carcinoma

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前言

卵巢浆液性癌是严重威胁女性生命的恶性肿瘤，发病率在妇科恶性肿瘤中一直位居高位，多发病于绝经前后女性[1,2]。卵巢浆液性癌患者发现时多存在腹腔内种植、肝实质和/或胸腔、颅内转移等情况，预后较差[3]。此外，由于卵巢位于盆腔深

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部,卵巢浆液性癌起病隐匿,早期病变难以发现,约 70%的卵巢浆液性癌患者在首次就诊时已属晚期，其生存率不足 30%[4,5]。现代研究表明肿瘤的发生发展过程是一个多步骤、多环节、多阶段、多因素共同交织而调控形成的复杂结局,涉及到原癌基因的激活和抑癌基因的灭活、细胞凋亡与细胞增殖的动态失衡、基因表达的突变、表观遗传学、外在因素的突变等[6,7]。

血清糖类抗原标志物 - 糖链抗原 125(carbohydrate antigen 125,CA125)是诊断恶性肿瘤常见的标志物,已经广泛应用于肺癌、消化道恶性肿瘤、乳腺癌等指标,单独用于诊断恶性肿瘤的诊断敏感性比较高,但是特异性很低,特别是在卵巢癌诊断中可出现许多假阳性，不利于后期诊治 [8,9]。癌胚抗原(carcino-embryonic antigen,CEA)能反映出多种肿瘤的存在,是广谱性肿瘤标志物,其对大肠癌、乳腺癌和肺癌的监测、病情发展、疗效判断和预后估计是一个较好的肿瘤标志物[10]。人附睾蛋白 4 人附睾蛋白 4(human epididymis protein 4,HE4)是近些年来新发现的诊断卵巢癌新型标志物,在卵巢癌患者血清中含量异常升高[11-13]。本研究比较了健康人群组及卵巢浆液性癌组患者血清中 CEA、HE4、CA125 水平，探讨联合检测血清糖类抗原标志物在女性绝经前后卵巢浆液性癌诊断中的价值,现总结报道如下。

1 对象与方法

1.1 研究对象

采用回顾性研究方法,选择 2016 年 8 月到至 2018 年 2 月在我院肿瘤科进行检测的绝经前后卵巢浆液性癌患者 60 例(癌变组)与绝经前后健康体检者 60 例(对照组)。纳入标准:临床病例资料完整;女性;癌变组经病理检查确诊切片证实为卵巢浆液性癌，健康对照组经体检判断为健康无异常；年龄在(45-55)岁之间;纳入前未接受过手术、放疗、化疗或者激素治疗。排除标准:在研究时已进行卵巢手术或进行其他对研究结果有影响的治疗者;合并心、肺、肝、胃等重要脏器的疾病;跟踪随访过程中,患者由于他种疾病死亡者;精神障碍患者;合并其他系统肿瘤病史。

健康对照组中年龄最小 46 岁，最大 54 岁，平均年龄(50.33± 3.11)岁;平均体重指数(22.98± 1.83)kg/m^2。癌变组中年龄最小 45 岁,最大 55 岁,平均年龄(51.11± 2.98)岁;FIGO 手术病理分期:Ⅱ期 34 例,Ⅲ期 20 例,Ⅳ期 6 例;淋巴结转移:无转移 45 例,有转移 15 例;分化程度:低分化 21 例,中分化 19 例,高分化 20 例。两组的年龄、体重指数等资料对比差异均无统计学意义(P>0.05),具有可比性。

1.2 标本采集

采用所有入选者的空腹肘静脉全血 3 mL-5 mL,置于未加抗凝剂的试管中,离心机在 4℃离心 10 min (4000 r/min 离心,离心半径 10 cm),取上层上清,保存在于 -20℃冰箱待检测。

1.3 血清标志物检测

血清 CA125、HE4、CA125 由罗氏电化学发光全自动免疫分析 Cobas e 601、E170 以及配套试剂进行检测。CEA>5 ng/mL 判断为阳性;CA125 参考值为 0-35 U/mL,CA125>35 U/mL判断为阳性;HE4 参考值为 0-150 pmol/L,HE4>150 pmol/L 判断为阳性。联合检测诊断判定标准:CEA、HE4、CA125 中有一项阳性即诊断为卵巢浆液性癌判断为阳性,三者均阴性判断为阴性。HE4 参考值为 0-150 pmol/L,HE4>150 pmol/L 判断为阳性。联合检测诊断判定标准:CEA、HE4、CA125 中有一项阳性即诊断为卵巢浆液性癌判断为阳性,三者均阴性判断为阴性。

1.4 随访方式与内容

随访采用电话、信访相结合的方式,了解癌变组患者的生存情况,随访截止时间为 2018 年 8 月 1 日。

1.5 统计学方法

应用 SPSS 22.00 for windows 软件包进行统计学分析,计量数据以均数± 标准差表示，组间对比采用独立样本 t 检验,计数数据以百分比表示,组间比较采用 x^2 检验等,以 P<0.05 为差异具有统计学意义。

2 结果

2.1 两组血清肿瘤标志物表达水平对比

癌变组血清 CEA、HE4、CA125 水平都均显著高于健康对照组(P<0.05)。见表 1。

表 1 两组血清肿瘤标志物表达水平对比

Table 1 Comparison of the levels of serum tumor markers between two groups

Groups	n	CEA(ng/mL)	HE4(pmol/L)	CA125(U/mL)
Cancerous group	60	11.94± 2.94	294.22± 34.49	735.50± 5.11
Health control group	60	1.50± 9.11	57.01± 22.11	20.14± 8.82
t		4.592	21.855	49.292
P		0.000	0.000	0.000

2.2 两组血清肿瘤标志物表达阳性率对比

癌变组 CEA、HE4、CA125 的阳性表达率分别为 63.3%、55.0%和 70.0%,健康对照组分别为 3.3%、6.7%、和 6.7%,癌变组 CEA、HE4、CA125 的阳性表达率均显著高于健康对照组,差异具有统计学意义(P<0.05),见表 2。

2.3 癌变组患者的预后情况

癌变组患者随访到 2018 年 8 月 1 日,死亡 6 例,存活 54 例,存活率为 90.0%。

2.4 血清肿瘤标志物表达水平与卵巢浆液性癌病理特征和预后的相关性

在癌变组 60 例患者中,随着病理分期增加、分化程度的减少、淋巴结转移与死亡情况的发生,CEA、HE4、CA125 的表达阳性率显著增加,差异有统计学意义(P<0.05),见表 3。

表 2 两组血清肿瘤标志物表达阳性率对比

Table 2 Comparison of the positive rate of serum tumor markers between two groups

Groups	n	CEA	HE4	CA125
Cancerous group	60	38(63.3%)	33(55.0%)	42(70.0%)
Health control group	60	2(3.3%)	4(6.7%)	4(6.7%)
t		84.028	32.862	50.905
P		0.000	0.000	0.000

表 3 血清肿瘤标志物表达水平与卵巢浆液性癌病理特征和预后的相关性(n=60)

Table 3 Correlation between the levels of serum tumor markers and pathological features, prognosis of ovarian serous carcinoma(n=60)

Variable	n	CEA positive rate (n=38)	HE4 positive rate (n=33)	CA125 positive rate (n=42)	P	P
Pathological staging					8.294	0.002
Pathological stage - stage II	34	16(47.1%)	16(47.1%)	22(64.7%)		
Stage Ⅲ	20	16(80.0%)	12(60.0%)	14(70.0%)		
Stage Ⅳ	6	6(100.0%)	5(83.3%)	6(100.0%)		
differentiation grade					6.333	0.012
Well-differentiated	21	10(47.6%)	8(38.1%)	12(57.1%)		
Moderately differentiated	19	12(63.2%)	10(52.6%)	11(57.9%)		
Poorly differentiated	20	16(80.0%)	15(75.0%)	19(95.0%)		
Lymphatic metastasis					7.446	0.009
Without	45	26(57.8%)	20(44.4%)	28(62.2%)		
With	15	12(80.0%)	13(86.7%)	14(93.3%)		
Follow-up outcome					5.200	0.021
Death	6	5(83.3%)	5(83.3%)	6(100.0%)		
Survival	54	33(61.1%)	28(51.9%)	36(66.7%)		

2.5 **联合血清 CEA、HE4、CA125 水平诊断卵巢浆液性癌的价值** 在 120 例人群中，联合诊断为卵巢浆液性癌者 54 例，联合诊断的敏感性与特异性分别为 90.0%和 100.0%。见表 4。

表 4 联合检测血清糖类抗原标志物在女性绝经前后卵巢浆液性癌诊断中的敏感性与特异性(n=120)

Table 4 The sensitivity and specificity of combined detection of serum carbohydrate antigen markers in the diagnosis of ovarian serous carcinoma before and after menopause (n=120)

Pathology	Ovarian serous carcinoma	Non ovarian serous carcinoma	Total
Ovarian serous carcinoma	54	6	60
Non ovarian serous carcinoma	0	60	60
Total	54	66	120

3 讨论

卵巢浆液性癌是目前最常见的女性生殖系统恶性肿瘤之一，死亡率居妇科恶性肿瘤之首。因其早期症状隐匿，缺乏典型临床表现、有效的敏感而特异的早期诊断方法，多数的患者就诊时已是晚期，预后较差[14]。卵巢浆液性癌多发病于绝经前后女性，病因尚不十分清楚，发病机制非常复杂与原癌基因的激活和抑癌基因的灭活、细胞凋亡与细胞增殖的动态失衡、基因表达的突变、表观遗传学、外在因素的突变等均密切相关[15]。

近年来，随着分子遗传学和分子生物学的研究与不断发展，许多学者对卵巢浆液性癌的发生机制进行了越来越深入的研究[16,17]。血清肿瘤标志物含有各种恶性肿瘤的大量生物信息，在临床上的应用较多[18,19]。临床上常常以糖类抗原景点标志物-CA125 联合其他特异性、敏感性都俱佳的血清肿瘤标志物用于卵巢癌的早期诊断，取得了很大的效果，但也存在一定的不足，有研究显示 CA125 对浆液性癌的最高而且是诊断卵巢浆液性癌的首选血清肿瘤标志物[20]。研究表明 CEA 也可作为癌症的标记物，在癌症诊断时特异性不强，但是在女性卵巢上皮肿瘤诊断中灵敏度极高，对卵巢粘液性癌患者的诊断价值高[21]。HE4 在健康组织中主要表达于近端气管、生殖道的上皮中，有

学者提出在卵巢癌时,当其特异性水平为 96%时仍具有 67%的敏感性,显著高于 CA125,尤其是在疾病的早期阶段。本研究显示癌变组血清 CEA、HE4、CA125 水平及阳性表达率都均显著高于健康对照组，提示血清 CEA、HE4、CA125 水平可能作为卵巢粘液性癌的诊断参考指标。

卵巢癌以血清肿瘤标志物是 CA125 作为临床采用检测手段,但受各种因素的影响,少数健康女性与良性卵巢肿瘤患者也会出现 CA125 血清浓度上升情况，其他区域的恶性肿瘤患者也会导致 CA125 升高,单一采用 CA125 进行早期诊断准确度低，特异性不强 [24]。本研究进一步分析了血清 CEA、HE4、CA125 水平与卵巢浆液性癌病理特征和预后的相关性,发现随着病理分期增加、分化程度的减少、淋巴结转移与死亡情况的发生,CEA、HE4、CA125 的表达阳性率显著增加，提示血清 CEA、HE4、CA125 水平与卵巢浆液性癌的进展有关,可能有助于其预后预测[25]。同时在 120 例人群中,联合诊断的敏感性与特异性分别为 90.0%和 100.0%。还有研究显示在卵巢浆液性癌监测体系中纳入血清 HE4 可提高疾病预测的敏感性[26,27];而当恶性肿瘤患者的血清 CA125 浓度 <10 U/mL 时,该病患者的治疗中就呈现出完全缓解状态[28-30]。不过本研究也有一定的不足,研究的样本比较多，所选择的血清糖类抗原标志物也比较少,将在下一步进行完善分析。

总之,联合检测血清糖类抗原标志物 CEA、HE4、CA12 在绝经前后女性卵巢浆液性癌都呈现高表达阳性率情况,与患者的病理特征与随访预后有一定的相关性,有很好的诊断与预测价值。

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