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EGFR 和 KRAS 在上皮性卵巢癌组织中的表达及临床意义

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摘要 目的：探讨表皮生长因子受体（EGFR）和鼠 Kirsten 肉瘤病毒致癌基因（KRAS）蛋白在上皮性卵巢癌组织中的表达水平及临床意义。**方法：**利用免疫组化 SP 法对上皮性卵巢癌组织（病例组，n=57）、卵巢良性肿瘤组织（良性组，n=50）以及正常卵巢组织（对照组，n=50）中的 EGFR、KRAS 蛋白水平进行检测，并分析其在上皮性卵巢癌发生发展中的作用。**结果：**病例组的 EGFR、KRAS 蛋白阳性率高于良性组和对照组（P<0.05），良性组和对照组的 EGFR、KRAS 蛋白阳性率差异无统计学意义（P>0.05）。浆液性腺癌组 EGFR、KRAS 蛋白的阳性表达率高于非浆液性腺癌组，III~IV 期的上皮性卵巢癌组织中 EGFR、KRAS 蛋白阳性表达率高于 I~II 期，中、低分化组中 EGFR、KRAS 蛋白阳性表达率高于高分化组，差异均具有统计学意义（P<0.05）。上皮性卵巢癌组织中 EGFR 与 KRAS 的蛋白的阳性表达率呈正相关关系（r=0.469，P<0.05）。**结论：**EGFR 及 KRAS 蛋白在上皮性卵巢癌组织中的表达水平明显升高，可能参与了上皮性卵巢癌的发生发展过程，且两者之间呈正相关关系，联合检测可作为早期诊断上皮性卵巢癌的重要指标。

关键词：表皮生长因子手受体；鼠 Kirsten 肉瘤病毒致癌基因蛋白；上皮性卵巢癌

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Expression of EGFR and KRAS in Patients with Epithelial Ovarian Cancer and Its Clinical Significance

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ABSTRACT Objective: To explore the expression level and clinical significance of epidermal growth factor receptor(EGFR)and Kirsten rat sarcoma viral proto-oncogene (KRAS)protein in patients with epithelial ovarian cancer. **Methods:** The EGFR and KRAS protein levels of epithelial ovarian cancer tissue (cases group, n=57), benign ovarian tumor tissue (benign group, n=50), and normal ovarian tissue(control group, n=50)were detected by the SP immunohistochemical, and their role in the occurrence and development of epithelial ovarian cancer was analyzed. **Results:** The positive expression rate of EGFR and KRAS protein in cases group were higher than those in benign group and control group (P<0.05). No statistical difference of EGFR and KRAS protein between benign group and control group was found (P>0.05). The positive expression rate of EGFR and KRAS protein in serous adenocarcinoma group were higher than those in non-serous adenocarcinoma group, and the positive expression rate of EGFR and KRAS protein in III-IV epithelial ovarian tissue were higher than those in I-II epithelial ovarian tissue, and the the positive expression rate of EGFR and KRAS protein in medium, low differentiation group were higher than those in high differentiation group, the difference was statistically significant (P<0.05). There was positive relationship of positive expression rate between EGFR and KRAS in patients with epithelial ovarian cancer tissue (r=0.469, P<0.05). **Conclusion:** The expression of EGFR and KRAS in epithelial ovarian cancer tissue is significantly increase, which may participate in the process of occurrence and development of epithelial ovarian cancer. And the positive expression rate is a positive relationship between EGFR and KRAS, combined detection can be helpful to diagnosis of epithelial ovarian cancer.

Key words: Epidermal growth factor receptor; Kirsten rat sarcoma viral proto-oncogene; Epithelial ovarian cancer

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前言

卵巢癌主要表现为上皮性卵巢癌，是女性较为常见的恶性肿瘤，发病率呈逐年上升的趋势，死亡率居各种妇科恶性肿瘤的首位[1]。上皮性卵巢癌无特异性的临床表现，超过 75%的患者在发现时已处于中晚期，因而错过了最佳的治疗时机，以致 5 年存活率仅有 20~30%[2,3]。寻找肿瘤标记物对早期诊断和治疗上皮性卵巢癌，提高患者生存率具有重要意义。研究显示[4]，多种生长因子，如细胞因子，黏附因子、炎症因子等通过介导细胞内的级联信号传导而参与上皮性卵巢癌的发生及发展过程。其中表皮生长因子受体（epidermal growth factor receptor，EGFR）

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作为新生血管生成的调控因子,介导的信号转导对新生血管生成具有重要作用[5]。鼠 Kirsten 肉瘤病毒致癌基因(Kirsten rat sarcoma viral proto-oncogene,KRAS)作为原癌基因,是 EGFR 信号转导通路中的下游信号基因,参与了多种实体性恶性肿瘤的发生发展[6]。本研究主要检测上皮性卵巢癌组织中 EGFR 和 KRAS 蛋白的表达情况,旨在探讨两者在上皮性卵巢癌组织中的临床意义。

1 资料与方法

1.1 一般资料

收集 2015 年 1 月 -2016 年 6 月我院收治的 57 例上皮性卵巢癌患者的手术病理标本作为病例组,纳入标本:① 标本切片均经病理检查证实为上皮性卵巢癌;② 术前未接受任何放化疗治疗及其它可能影响本研究结果的治疗,如激素替代治疗等;③ 不合并有其它内分泌以及免疫性疾病;④ 不合并有其它恶性肿瘤等可能影响本研究结果的疾病。患者年龄 24~73 岁,平均(57.22± 3.41)岁;浆液性腺癌 29 例,子宫内膜样腺癌 11 例,黏液性腺癌 10 例,透明细胞癌 5 例,混合型腺癌 2 例;按照国际妇产科联盟(FIGO)手术病理分期:I~II 期 18 例,III~IV 期 39 例;细胞学分级:高分化 25 例,中分化 19 例,低分化 13 例。并于同期分别选取 50 例卵巢良性肿瘤组织标本作为良性组、50 例正常卵巢组织作为对照组。良性组患者年龄 25~73 岁,平均(56.44± 3.86)岁,正常组年龄 24~71 岁,平均(55.97± 3.25)岁。三组的年龄差异无统计学意义(P>0.05)。本研究所有患者均签署知情同意书,研究经医院伦理委员会批准通过。

1.2 方法

1.2.1 主要仪器及试剂 EGFR 单克隆抗体、KRAS 蛋白单克隆抗体,两种抗体来源于武汉三鹰生物技术公司,SP 法试剂盒及 DAB 显色试剂盒,来源于北京中杉金桥生物技术有限公司。

1.2.2 实验方法 所有的标本均采用浓度为 10%的中性福尔马林液进行固定,石蜡包埋后作成厚度为 4 μm 的连续切片,并进行防脱处理,最后采用免疫组化 SP 法进行检测,严格按照 SP 免疫组化试剂盒上的说明进行相关操作,同时阴性对照以 PBS 磷酸盐缓冲液代替一抗。

1.2.3 结果判断 EGFR 阳性细胞以细胞质和(或)细胞膜上出现的棕黄色的颗粒为标准,KRAS 蛋白阳性细胞则以细胞质中出现的棕黄色的颗粒标准,着色细胞所占比例评分[7]:0 分为未出现阳性细胞,1 分为 1~9%的阳性细胞,2 分为 10~49%的阳性细胞,3 分为 50~74%的阳性细胞,4 分为 75~100%的阳性细胞;染色强度评分:0 分为无色细胞,1 分为淡黄色细胞,2 分为棕黄色细胞,3 分为棕褐色细胞。将以上两种评分分别相乘计算最后得分:0~1 分计为 -,2~3 分计为 +,4~5 分计为 ++,6~7 分计为 +++。

1.3 统计学处理

采用 SPSS21.0 软件录入数据及统计学分析,计量资料以($\bar{x}$± s)表示,采用 t 检验,定性资料以率(%)表示,比较采用 x^2 检验或者 Fisher 确切概率法,EGFR 和 KRAS 之间的相关性采用分类资料的列联表相关性分析,P<0.05 表示差异有统计学意义。

2 结果

2.1 EGFR 及 KRAS 蛋白在三组组织中的表达水平

病例组、良性组、对照组 EGFR 蛋白阳性表达率分别为 75.44%(43/57)、26.00%(13/50)、22.00%(11/50),KRAS 蛋白阳性表达率分别为 87.72%(50/57)、42.00%(21/50)、30.00%(15/50),三组的 EGFR、KRAS 蛋白阳性表达率比较,差异有统计学意义(P<0.05),两两比较,病例组 EGFR、KRAS 蛋白阳性率高于良性组和对照组(P<0.05),良性组和对照组的 EGFR、KRAS 蛋白阳性率差异无统计学意义(P>0.05)。

2.2 EGFR 和 KRAS 蛋白的表达与上皮性卵巢癌临床病理特征的关系

EGFR 和 KRAS 蛋白在不同年龄组的阳性表达率差异无统计学意义(P>0.05),EGFR、KRAS 蛋白的阳性表达率在浆液性腺癌组中高于非浆液性腺癌组,III~IV 期高于 I~II 期,中、低分化组中高于高分化组,差异均具有统计学意义(P<0.05)。见表 1。

表 1 EGFR 和 KRAS 蛋白的表达与上皮性卵巢癌临床病理特征的关系[n(%)]

Table 1 The relationship between expression of EGFR, KRAS and clinicopathologic characteristic among patients with epithelial ovarian cancer[n(%)]

Characteristics	N	EGFR protein		P	KRAS protein		P
		+	-		+	-	
Age(year)							
≤ 60	26	17(65.38)	9(34.62)	0.469	22(84.62)	4(15.38)	0.513
＞60	31	23(74.19)	8(25.81)		28(90.32)	3(9.68)	
Pathologic type							
Serous	29	26(89.66)	3(10.34)	0.011	29(100.00)	0(0.00)	0.005#
Non-serous	28	17(60.71)	11(39.29)		21(75.00)	7(25.00)	
Pathological stage							
I~II stage	18	10(55.56)	8(44.44)	0.018	13(72.22)	5(27.78)	0.027#
III~IV stage	39	33(84.62)	6(15.38)		37(94.87)	2(5.13)	
Cytological classification							
High differentiation	25	15(60.00)	10(40.00)	0.017	19(76.00)	6(24.00)	0.036#
Medium, low differentiation	32	28(87.50)	4(12.50)		31(96.88)	1(3.13)	

Note: #calculated by Fisher exact probability method.

2.3 EGFR、KRAS 蛋白两者之间的相关性分析

上皮性卵巢癌组织中 EGFR 与 KRAS 的阳性表达率呈正相关关系(r=0.469,P<0.05)。

3 讨论

EGFR 是具有酪氨酸激酶活性的表皮生长因子受体家族中的成员,由人 7 号染色体断臂上的原癌基因 c-erbB1 所表达的产物,广泛分布在正常细胞的表面[8]。研究证实[9,10],EGFR 过度表达可使下游的 Ras/PI3K/AKT/mTOR 信号通路以及 Ras/Raf/MAPK 信号通路被激活,从而参与调控肿瘤细胞的增殖、生长、血管生成、侵袭和转移等。同时 EGFR 的过表达还会抑制肿瘤细胞的凋亡[11]。已有研究发现[12,13],在乳腺癌、肺癌、食管癌、卵巢癌等实体恶性肿瘤组织中,能够检测到 EGFR 呈较高水平表达。KRAS 蛋白是处于 EGFR 信号通路下游的原癌基因 RAS 基因的一种形式,当被激活后成为癌基因,KRAS 的表达产物 RAS 的蛋白构型发生突变,使其与 GTP 结合而一直处于活化的状态,引起下游的信号转导持续性的被激活,并影响 Ras/Raf/MEK/ERK/MAPK 细胞转导通路的调控功能[14,15]。而该型号通路途径一旦失去控制,可能引起肿瘤细胞的快速增值、异常的分化以及肿瘤血管的形成,同时抑制恶性肿瘤的凋亡[16]。已有研究表明[17,18],KRAS 基因突变与结肠癌、乳腺癌等多种肿瘤的发生有密切的关联。

本研究通过检测上皮性卵巢癌组织中的 EGFR、KRAS 蛋白水平,旨在探讨其在卵巢癌组织中的表达水平及临床意义。结果显示,病例组的 EGFR、KRAS 蛋白阳性表达水平明显高于良性组和对照组,而良性组和对照组之间的 EGFR 蛋白阳性表达率无明显差异,提示上皮性卵巢癌组织中 EGFR、KRAS 蛋白呈明显的异常表达,可能参与了上皮性卵巢癌的发病过程,与有关研究结果一致[19]。进一步分析显示,浆液性腺癌组织中 EGFR、KRAS 蛋白阳性表达率高于非浆液性腺癌组,III-IV 期的上皮性卵巢癌组织中 EGFR、KRAS 蛋白阳性表达率高于 I-II 期,中低分化组中 EGFR、KRAS 蛋白阳性表达率高于高分化组,临床分期越晚的卵巢癌组织,EGFR、KRAS 蛋白的阳性表达越高,而分化程度越低的卵巢癌组织,EGFR、KRAS 蛋白的阳性表达越高,这一结果与有关研究结果相似[20]。提示 EGFR、KRAS 蛋白参与了卵巢癌的发生发展过程,可能是卵巢癌形成的促使因素,因此两者均可作为临床诊断早期诊断、评估卵巢癌恶性程度的重要指标。此外结果还发现,上皮性卵巢癌组织中的 EGFR、KRAS 蛋白的阳性表达率呈正相关关系,该结果提示联合检测上皮性卵巢癌组织中的 EGFR 与 KRAS 蛋白有助于早期诊断卵巢癌。

综上所述,上皮性卵巢癌的发生发展有多种因素的共同作用,其中 EGFR、KRAS 蛋白在卵巢癌的发生发展过程中有重要的作用,两者联合检测可作为临床早期诊断和评估卵巢癌的重要肿瘤标志物,临床有重要的参考价值。

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来显示其血脂情况，研究结果显示：与对照组比较，实验组患者治疗后以上指标水平明显降低，表明普罗布考联合阿司匹林能有效降低患者的血脂水平。

综上所述，普罗布考联合阿司匹林能有效溶解脑梗死颈内动脉斑块，这可能与其降低血脂水平、改善炎症情况，减轻氧化损伤有关。

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