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上皮性卵巢癌患者组织 P53、Ki67 表达及其临床意义*

青措吉 艾小庆 崔 英 杨晓燕 董 艳

(青海红十字医院妇科 青海 西宁 810000)

摘要 目的:探讨上皮性卵巢癌患者组织 P53、Ki67 表达及其临床意义。**方法:**选择卵巢肿瘤 102 例,其中病理诊断为良性卵巢肿瘤 40 例(良性组)和上皮性卵巢癌 62 例(恶性组),采用免疫组化法检测组织 P53、Ki67 表达水平,调查患者的临床病理特征并进行相关性分析。**结果:**恶性组的 P53、Ki67 表达阳性率为 80.6%和 72.6%,显著高于良性组的 10.0%和 12.5%($P<0.05$)。在恶性组中,不同浸润转移、分化程度、病理分期患者的 P53、Ki67 表达阳性率对比差异有统计学意义($P<0.05$)。直线相关分析显示上皮性卵巢癌患者 P53 表达阳性率与 Ki67 表达阳性率呈现显著正相关性($r=0.872, P=0.000$)。多因素 logistic 回归分析显示浸润转移、分化程度、病理分期都为影响 P53、Ki67 表达阳性率的主要因素($P<0.05$)。**结论:**上皮性卵巢癌患者组织 P53、Ki67 都呈现高表达状况,与患者的临床病理特征显著相关,两者也可互相影响,共同参与上皮性卵巢癌的发生与发展。

关键词:上皮性卵巢癌;P53;Ki67;病理特征;相关性

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Expression of P53 and Ki67 in Patients with Epithelial Ovarian Cancer and Its Clinical Significance*

QING Cuo-ji, AI Xiao-qing, CUI Ying, YANG Xiao-yan, DONG Yan

(Department of Gynecology, Qinghai Red Cross Hospital, Xining, Qinghai, 810000, China)

ABSTRACT Objective: To investigate the expression of P53 and Ki67 in patients with epithelial ovarian cancer and its clinical significance. **Methods:** 102 patients with ovarian tumors were selected and treated, including 40 cases of benign ovarian tumors (benign group) and 62 cases of epithelial ovarian cancer (malignant group). The expression levels of P53 and Ki67 were detected by chemical method, and the clinicopathological features of the patients were investigated and correlation analysis were performed. **Results:** The positive rates of P53 and Ki67 expression in the malignant group were 80.6 % and 72.6 %, which were significantly higher than those in the benign group (10.0 % and 12.5 %)($P<0.05$). In the malignant group, the positive rates of P53 and Ki67 expression in patients with different invasive metastasis, differentiation and pathological stage were statistically significant ($P<0.05$). Linear correlation analysis showed that the positive rate of P53 expression in patients with epithelial ovarian cancer were significantly positively correlated with the positive rate of Ki67 expression ($r=0.872, P=0.000$). Multivariate logistic regression analysis showed that infiltration, differentiation and pathological stage were the main factors affecting the positive rate of P53 and Ki67 expression ($P<0.05$). **Conclusion:** P53 and Ki67 in patients with epithelial ovarian cancer have high expression status, which is significantly correlated with the clinicopathological features of the patients. They can also affect each other and participate in the occurrence and development of epithelial ovarian cancer.

Key words: Epithelial ovarian cancer; P53; Ki67; Pathological characteristics; Correlation

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前言

上皮性卵巢癌是女性常见恶性肿瘤之一,由于卵巢位于盆腔深部,起病隐匿,早期病变难以发现,约 70 %的患者在首次就诊时已属晚期,使得生存率在 30 %以下^[1,2]。已有研究显示上皮性卵巢癌患者早期发现与诊治能显著延长患者的生存率,但是对于晚期患者,5 年生存率低于 30 %^[3,4]。现代研究显示上皮性卵巢癌发生发展是从炎性发展成肿瘤,同时伴有多基因参与、多步骤过程,在此过程中伴随所有癌基因、抑癌基因和生长因子基因等多种基因的改变相关^[5,6]。P53 基因是定位于人染色

体 17p13.1 的一种重要的抑癌基因,其编码产物 P53 蛋白是在细胞分裂和分化过程中发挥重要作用,P53 蛋白正常表达可诱导细胞凋亡与引起细胞周期阻滞,P53 蛋白突变可导致细胞转化和过度增殖而产生肿瘤行为^[7,8]。Ki-67 是目前较为肯定的核增殖标志物,也是预测上皮性卵巢癌发生发展中有重要参考价值的标记物,其表达程度可反映肿瘤细胞的生物学行为^[9,10]。临床上关于宫颈癌的研究颇多并已得出相对可靠的病因,而上皮性卵巢癌的发生目前尚无可靠理论及现实依据,因此,探究与分析上皮性卵巢癌发生发展机制对防治该病具有重要的临床意义。但是 P53、Ki-67 在细胞周期的不同阶段对肿瘤的发生、

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作者简介:青措吉(1982-),女,本科,主治医师,研究方向:妇科,电话:13997483117,E-mail:qing549876464@163.com

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发展起不同程度的作用,因此,联合 P53、Ki-67 评判卵巢癌预后更具有实际的临床意义。本文具体探讨了上皮性卵巢癌患者组织 P53、Ki67 表达及其临床意义,现总结报道如下。

1 资料与方法

1.1 研究对象

本研究获得本院伦理委员会批准。2015 年 8 月至 2019 年 6 月选择在本院诊治的卵巢肿瘤 102 例,其中病理诊断为良性卵巢肿瘤 40 例(良性组)和上皮性卵巢癌 62 例(恶性组),纳入标准:组织病理学确诊为良性卵巢肿瘤或上皮性卵巢癌;病理资料完整;年龄 20-60 岁;入组前未接受放、化疗;单除其他部位恶性肿瘤的转移。排除标准:免疫缺陷者;妊娠与哺乳期妇女;心、肝、肾等重要脏器疾病患者。

1.2 免疫组化方法

鼠抗人 P53 单克隆抗体、鼠抗人 Ki67 单克隆抗体都购自 Santa Cruz Biotechnology 公司;免疫组化通用型染色试剂盒、磷酸缓冲盐缓冲液、氧化二氨基联苯胺显色试剂盒购自北京中山生物技术有限公司。

取所有患者的病理组织样本,进行蜡块连续切片,厚度为 2 μ m,采用二甲苯、乙醇进行透明化与脱水处理。苏木素复染组织切片 15-30 s,使用中性的树脂封片,光学显微镜下观察结果。每张切片均设阳性对照,以上皮性恶性组织为阳性对照,以磷酸缓冲盐代替一抗作为阴性对照。每张切片随机观察 5 个高倍镜视野,P53、Ki67 主要是在细胞核表达阳性,阳性信号均呈棕黄色。由病理医师参照联合评分病理诊断分级标准进行诊断。染色强度阴性为 0 分,染色弱但强于阴性对照为 1 分,染色清晰为 2 分,染色强为 3 分;阳性细胞数 <10%为 0 分,10%

~30%为 1 分,31%~60%为 2 分,>60%为 3 分,上述两种评分相加:0-1 为(-,阴性),2 分为(+,弱阳性),3-4 分为(++ ,中阳性),5-6 分为(+++,强阳性),(+),(++),(+++)为阳性表达。

1.3 调查资料

调查所有患者的年龄、体重、病理类型,重点记录上皮性卵巢癌患者的浸润转移、病理分期、组织学分化程度等。

1.4 统计学方法

应用 SPSS 22.00,计量资料以($\bar{x} \pm s$)表示,计数资料以(%)表示,分别采用 t 检验和 χ^2 检验等,影响因素分析采用多因素 logistic 回归分析,相关性分析采用直线相关分析, $P < 0.05$ 有统计学意义。

2 结果

2.1 一般资料对比

恶性组中浆液性腺癌 32 例,黏液性腺癌 30 例;年龄最小 23 岁,最大 59 岁,平均年龄 45.99 ± 1.38 岁;平均 BMI 22.32 ± 2.91 kg/m²;平均病程 4.29 ± 0.52 年;病理分期:I 期 30 例,II 期 25 例,III 期 7 例;分化程度:低分化 20 例,中分化 25 例,高分化 17 例;浸润转移:无转移 34 例,有转移 28 例。

良性组中卵泡膜纤维瘤 16 例,卵泡膜细胞瘤 10 例,囊性腺纤维瘤 14 例;年龄最小 24 岁,最大 56 岁,平均年龄 45.22 ± 2.19 岁;平均 BMI 22.85 ± 1.49 kg/m²;平均病程 2.49 ± 0.22 年。良性组与恶性组一般资料对比差异无统计学意义($P > 0.05$)。

2.2 P53、Ki67 表达阳性率对比

恶性组的 P53、Ki67 表达阳性率为 80.6%和 72.6%,显著高于良性组的 10.0%和 12.5%,两组对比差异有统计学意义($\chi^2=48.706, \chi^2=35.119, P$ 均 < 0.05)。见表 1。

表 1 两组 P53、Ki67 表达阳性率对比(例,%)

Table 1 Comparison of positive rates of P53 and Ki67 expression between the two groups (n,%)

Groups	n	P53	Ki67
Malicious group	62	50(80.6)*	45(72.6)*
Benign group	40	4(10.0)	5(12.5)

Note: Compared with the benign group, * $P < 0.05$.

2.3 上皮性卵巢癌患者组织 P53、Ki67 表达与临床特征的相关性

在恶性组中,不同浸润转移、分化程度、病理分期患者的

P53、Ki67 表达阳性率对比差异有统计学意义($P < 0.05$)。见表 2。

表 2 上皮性卵巢癌患者组织 P53、Ki67 表达与临床特征的相关性(n=62)

Table 2 Correlation between the expression of P53, Ki67 and clinical characteristics in patients with epithelial ovarian cancer (n=62)

Clinical features	n	P53 positive expression rate (n=50)	F/ χ^2	P	Ki67 positive expression rate (n=45)	F/ χ^2	P
Infiltration and transfer							
-Yes	28	26	4.878	0.027	26	10.548	0.001
-No	34	24			19		
Organizational credit							
-well-differentiated	17	9	11.866	0.00	34	28.340	0.000
-moderately differentiated	25	22			23		
-poorly differentiated	20	19			18		
Pathological staging - I	30	20	7.501	0.024	16	11.216	0.004
-II	25	23			22		
-III	7	7			7		

直线相关分析显示上皮性卵巢癌患者 P53 表达阳性率与 Ki67 表达阳性率呈现显著正相关性($r=0.872, P=0.000$)。

2.4 影响因素分析

在恶性组中,以 P53、Ki67 表达阳性率作为因变量,以浸润

转移、分化程度、病理分期作为自变量,多因素 logistic 回归分析显示浸润转移、分化程度、病理分期都为影响 P53、Ki67 表达阳性率的主要因素($P<0.05$)。见表 3 与表 4。

表 3 影响上皮性卵巢癌患者组织 P53 表达阳性率的因素(n=62)

Table 3 Factors affecting the positive rate of P53 expression in patients with epithelial ovarian cancer (n=62)

Index	β	SE	Wald	P	OR	95%CI
Infiltration and transfer	0.774	0.356	4.678	0.003	2.194	1.098-4.644
Organizational credit	1.883	0.928	4.114	0.004	6.546	2.444-13.573
Pathological staging	1.445	0.876	3.490	0.010	4.294	1.774-23.582

表 4 影响上皮性卵巢癌患者组织 Ki67 表达阳性率的因素(n=62)

Table 4 Factors affecting the positive rate of Ki67 expression in patients with epithelial ovarian cancer (n=62)

Index	β	SE	Wald	P	OR	95%CI
Infiltration and transfer	1.289	0.564	7.729	0.002	3.628	1.209-10.888
Organizational credit	1.278	0.553	5.342	0.006	3.568	1.214-10.472
Pathological staging	0.788	0.378	4.564	0.005	2.119	1.093-4.873

3 讨论

卵巢癌是妇科最常见肿瘤之一,具有较高的死亡率。该病的病因至今尚未完全明了,相关研究表明该病的发生与早婚、性生活紊乱、多产、经济状况、性生活过早、经济状况、种族等因素有关^[11-13]。上皮性卵巢癌多由良性卵巢肿瘤发展而来,因其早期症状表现不特异,在临床上没有敏感、特异检测指标,导致多数患者发现时已为上皮性卵巢癌,患者的存活率降低,为此早期鉴别上皮性卵巢癌具有重要价值^[14-16]。

恶性肿瘤的发生与发展是一个多因素、多基因、多步骤参与的复杂过程^[17]。P53 是一个重要的抑癌基因,在宫颈癌中的作用已被证实,野生型 P53 通过 P53 依赖或 P53 非依赖途径,参与细胞生长、发育、分化等多种功能的调控^[18,19]。P53 能阻断细胞周期,进而抑制细胞增殖、凋亡等^[20]。Ki-67 是核增殖标志物,半衰期短,脱离细胞周期后可迅速降解为检测肿瘤细胞增殖活性的指标。P53 表达增加可导致细胞的增殖加快,使得 Ki-67 表达阳性细胞核增多^[21,22]。本研究显示恶性组的 P53、Ki67 表达阳性率为 80.6 %和 72.6 %,显著高于良性组的 10.0 %和 12.5 %;不同浸润转移、分化程度、病理分期上皮性卵巢癌患者的 P53、Ki67 表达阳性率对比差异有统计学意义,与陈赞^[23]等学者的研究一致,该学者通过分析 P53 蛋白和 Ki-67 在上皮性卵巢癌组织中的表达和预后结果,结果显示 P53 蛋白和 Ki-67 均参与了上皮性卵巢癌发生发展,可作为预测患者预后的独立因素,与本研究不同的是该学者还发现了 P53 和 Ki-67 阳性表达与上皮性卵巢癌患者的总生存时间及无进展生存时间呈反比,预示患者预后不良。国外学者 Adelaida Garcia-Velasco^[24]等人的研究与本研究类似,P53 和 Ki-67 的表达在上皮性卵巢癌中的预后价值,发现 P53 的核表达 $\geq 10\%$,Ki67 核表达 $>30\%$ 可预测晚期卵巢癌。表明上皮性卵巢癌患者多伴随有 P53、Ki67 的高表达,且与患者的临床病理特征具有显著相关性。

侵袭和转移在上皮性卵巢癌中也有重要的意义,P53、Ki67

在侵袭及转移过程中也有重要的功能^[25-29]。P53 能促进肿瘤细胞发生侵袭和转移^[30]。Ki67 的高表达可激活 CDK2/CyclinE 及 Rb 磷酸化,缩短 G1/S 期,由于破坏了细胞的凋亡-增殖的平衡,常被当作癌症患者预后的指标^[31,32]。本研究显示上皮性卵巢癌患者 P53 表达阳性率与 Ki67 表达阳性率呈现显著正相关性;多因素 logistic 回归分析显示浸润转移、分化程度、病理分期都为影响 P53、Ki67 表达阳性率的主要因素。与 Xu^[33]和 Mayora^[34]等学者研究一致,发现 P53、Ki67 蛋白的表达与组织学类型、分化程度、病理分期、淋巴结转移之间有统计学意义,说明浸润转移、分化程度、病理分期都为影响 P53、Ki67 表达阳性率的主要因素。本研究结果提示 P53、Ki67 蛋白共同检测可能有助于诊断和评估上皮性卵巢癌的预后,两种蛋白可能在上皮性卵巢癌的发展过程中共同起作用,有助于成为以后上皮性卵巢癌患者的诊断提供标志物的依据参考,也为上皮性卵巢癌的病理机制和治疗靶点提供研究方向。但是本文没有对患者的总生存时间及无进展生存时间进行与 P53 和 Ki-67 阳性表达相关性进行观察,后续需要深入研究。本研究也有一定的不足,实验病例数较少,相对局限,且没有设置健康人群,研究存在偏倚,将在下一步进行深入分析。

总之,上皮性卵巢癌患者组织 P53、Ki67 都呈现高表达状况,与患者的临床病理特征显著相关,两者也可互相影响,共同参与上皮性卵巢癌的发生与发展。

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