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ER、PR、CA-153、Ki-67的表达与乳腺癌临床病理特征及预后的相关性研究*

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摘要 目的：研究雌激素受体(ER)、孕激素受体(PR)、糖类抗原-153(CA-153)、Ki-67的表达与乳腺癌临床病理特征及预后的相关性。**方法：**选取2015年3月-2017年4月我院收治的乳腺癌患者190例为研究对象。分别采用免疫组化法检测患者ER、PR、Ki-67表达情况，采用酶联免疫吸附法检测CA-153表达情况。分析上述四项指标的表达与临床病理特征的关系，并作指标间的相关性分析。**结果：**有淋巴结转移的乳腺癌组织中ER、PR阳性率明显高于无淋巴结转移，差异有统计学意义(P<0.05)，而年龄、肿瘤大小、TNM分期不同的乳腺癌组织中ER、PR阳性率比较差异均无统计学意义(P>0.05)。肿瘤大小>2cm、TNM分期为Ⅲ-Ⅳ期、有淋巴结转移乳腺癌组织中CA-153阳性率分别高于肿瘤大小≤2cm、TNM分期为Ⅰ-Ⅱ期、无淋巴结转移，差异均有统计学意义(P<0.05)，而年龄不同的乳腺癌组织中CA-153阳性率比较差异无统计学意义(P>0.05)。TNM分期为Ⅲ-Ⅳ期、有淋巴结转移乳腺癌组织中Ki-67阳性率明显高于TNM分期为Ⅰ-Ⅱ期、无淋巴结转移，差异均有统计学意义(P<0.05)，而年龄、肿瘤大小不同的乳腺癌组织中Ki-67阳性率比较差异无统计学意义(P>0.05)。经Pearson相关性分析显示，ER、PR、CA-153、Ki-67在乳腺癌中表达均呈正相关(P<0.05)。**结论：**临床工作中可通过联合检测ER、PR、CA-153、Ki-67的表达情况，从而有效判断乳腺癌患者的病情严重程度以及转移情况，值得临床推广应用。

关键词：乳腺癌；雌激素受体；孕激素受体；糖类抗原-153；Ki-67

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Correlation Between Expression of ER, PR, CA-153, Ki-67 and Clinic Pathological Features and Prognosis of Breast Cancer*

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ABSTRACT Objective: To study the correlation between the expression of estrogen receptor (ER), progesterone receptor (PR), carbohydrate antigen-153 (CA-153), ki-67 and clinic opathological features and prognosis of breast cancer. **Methods:** A total of 190 patients with breast cancer, who were treated in First Affiliated Hospital of Guangxi University of Chinese Medicine from March 2015 to April 2017, were selected as research subjects. The expression of ER, PR and ki-67 were detected by immunohistochemistry; the expression of CA-153 was detected by enzyme-linked immunosorbent assay. The relationship between the expression of the above four indexes and the clinicopathological features was analyzed, and the correlation between the indexes was analyzed. **Results:** The positive rates of ER and PR in breast cancer tissues with lymph node metastasis were significantly higher than those without lymph node metastasis, and the difference was statistically significant (P<0.05). The positive rate of CA-153 in breast cancer tissues with tumor size >2 cm, TNM stage III-IV stage and lymph node metastatic were higher than that with tumor size ≤ 2 cm, TNM stage I-II stage, and without lymph node metastasis, the difference was statistically significant (P<0.05); there was no significant difference in the positive rate of CA-153 in the breast cancer tissues of different ages (P>0.05). The positive rate of Ki-67 in breast cancer tissues with TNM stage III-IV stage and lymph node metastasis was significantly higher than that with TNM stage I-II stage and without lymph node metastasis, the difference was statistically significant (P<0.05); there was no significant difference in the positive rate of Ki-67 in breast cancer tissues of different age and tumor size (P>0.05). The Pearson correlation analysis showed that the expression of ER, PR, CA-153 and Ki-67 were positively correlated in breast cancer (P<0.05). **Conclusion:** In clinical work, combination of detecting the expression of ER, PR, CA-153 and Ki-67 can effectively predict the severity and metastasis of patients with breast cancer, which is worthy of clinical application.

Key words: Breast cancer; Estrogen receptor; Progesterone receptor; Carbohydrate antigen-153; Ki-67

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前言

乳腺癌是全球范围内较为常见的恶性肿瘤疾病，近年来相关数据显示，我国范围内多数地区乳腺癌发病率呈逐年上升趋势，且在女性所有恶性肿瘤疾病中占比较高，严重影响患者的生命健康安全[1-3]。目前，随着分子生物学日益发展，越来越多的研究学者认为，多种病理分子标志物与乳腺癌的临床治疗和预后具有密切的关系 [3-5]。其中雌激素受体（estrogen receptors，ER）、孕激素受体（progesterone receptor，PR）均属于特定功能蛋白，在乳腺癌的生长、分化过程中发挥着调节作用，糖类抗原-153（carbohydrate antigen-153，CA-153）在临床上主要用于监测乳腺癌患者病情的变化，其水平能反映肿瘤的缓解或恶化，Ki-67 属于细胞增殖标志物，目前已成为临床上检测肿瘤细胞增殖的可靠指标[6-8]。由此，本研究通过探讨 ER、PR、CA-153、Ki-67 的表达与乳腺癌临床病理特征及预后的相关性并展开分析，从而为临床乳腺癌的早期诊断、治疗以及预后提供指导作用，现阐述如下。

1 资料与方法

1.1 一般资料

选取 2015 年 3 月 -2017 年 4 月我院收治的乳腺癌患者 190 例为研究对象。纳入标准[9]：（1）所有患者均经临床检查、影像学检查、病理组织检查确诊为乳腺癌；（2）手术病历资料完整者；（3）既往无其他恶性肿瘤疾病者；（4）年龄 >20 岁；（5）入院前未接受任何抗肿瘤治疗者。排除标准：（1）合并心、肝、肾等脏器功能严重障碍者；（2）存在精神系统疾病或交流沟通障碍者；（3）正在参与其它研究者。年龄 42-78 岁，平均年龄（56.23±10.25）岁；肿瘤大小：≤ 2 cm 有 54 例，>2 cm 有 136 例；TNM 分期：Ⅰ-Ⅱ期 120 例，Ⅲ-Ⅳ期 70 例；存在淋巴结转移患者有 108 例，无淋巴结转移患者 82 例。所有患者均知情并签署了同意书，本研究已获得我院伦理委员会批准。

1.2 研究方法

（1）采集患者的乳腺癌组织标本，以浓度为 10%的福尔马林予以固定，常规脱水，随后进行石蜡包埋切片处理，切片厚度为 4 μm，然后予以 HE 染色镜检分析。其中 ER、PR、Ki-67 的表达情况均以免疫组化法进行检测，上述各项指标的单克隆抗体与免疫组化相应试剂盒均为上海基因科技有限公司生产。选取已知阳性切片作为阳性对照，采用 PBS 代替一抗作为阴性对照，相关操作严格遵循试剂盒说明书进行。（2）患者入院后采集清晨空腹静脉血 5 mL，以 3000 r/min 离心 10 min，采用酶联免疫吸附法对 CA-153 水平进行检测，严格根据试剂盒说明书完成具体操作，试剂盒购自北京科美东雅生物技术有限公司。

1.3 判定标准

ER、PR、Ki-67 阳性标准如下：细胞核内有黄色颗粒，且随机选择 5 个高倍视野计算其中阳性细胞数占比情况，若阳性细胞数占比低于 10%记为阴性，阳性细胞数在 10%以上记为阳性[10]。CA-153 阳性判定根据血清表达水平进行评估，即 CA-153 水平 >25 U/mL 为阳性，≤ 25 U/mL 则为阴性[11]。

1.4 观察指标

分析乳腺癌组织中 ER、PR、CA-153、Ki-67 表达与临床病理特征关系，分析 ER、PR、CA-153、Ki-67 在乳腺癌中表达的相关性。

1.5 统计学方法

本研究数据均采用 SPSS20.0 软件进行检测分析，计数资料以[n(%)]表示，采用 x^2 检验，ER、PR、CA-153、Ki-67 在乳腺癌中表达的关系予以 Pearson 相关性分析。P<0.05 表明两组数据对比差异具有统计学意义。

2 结果

2.1 乳腺癌组织中 ER、PR 表达与临床病理特征关系分析

有淋巴结转移的乳腺癌组织中 ER、PR 阳性率明显高于无淋巴结转移，差异有统计学意义（P<0.05），而年龄、肿瘤大小、TNM 分期不同的乳腺癌组织中 ER、PR 阳性率比较差异均无统计学意义（P>0.05）。见表 1。

表 1 乳腺癌组织中 ER、PR 表达与临床病理特征关系分析[n(%)]

Table 1 Analysis of expression of ER, PR and clinicopathological features in breast cancer tissue [n (%)]

Features		n	ER positive rate	x^2	P	PR positive rate	x^2	P
Age(years)	≤ 50	104	57(54.81)	0.019	0.890	49(47.12)	0.786	0.375
	>50	86	48(55.81)			35(40.70)		
Tumor size (cm)	≤ 2	54	32(59.26)	0.487	0.485	22(40.74)	0.368	0.544
	>2	136	73(53.68)			62(45.59)		
TNM stage	Ⅰ-Ⅱ	120	72(60.00)	2.956	0.086	51(42.50)	0.386	0.543
	Ⅲ-Ⅳ	70	33(47.14)			33(47.14)		
Lymph node metastasis	Yes	108	70(64.81)	40.804	0.000	58(53.70)	9.143	0.002
	No	82	15(18.29)			26(31.71)		

2.2 乳腺癌组织中 CA-153、Ki-67 表达与临床病理特征关系分析

肿瘤大小 >2 cm、TNM 分期为Ⅲ-Ⅳ期、有淋巴结转移乳腺癌组织中 CA-153 阳性率分别高于肿瘤大小≤ 2 cm、TNM 分期为Ⅰ-Ⅱ期、无淋巴结转移，差异均有统计学意义（P<0.05），而年龄不同的乳腺癌组织中 CA-153 阳性率比较差异无统计学意义（P>0.05）。TNM 分期为Ⅲ-Ⅳ期、有淋巴结转移乳腺癌组织中 Ki-67 阳性率明显高于 TNM 分期为Ⅰ-Ⅱ期、无淋巴结转移，差

异均有统计学意义(P<0.05),而年龄、肿瘤大小不同的乳腺癌组织中 Ki-67 阳性率比较差异无统计学意义(P>0.05)。见表 2。

表 2 乳腺癌组织中 CA-153、Ki-67 表达与临床病理特征关系分析[n(%)]

Table 2 Analysis of expression of CA-153, Ki-67 and clinicopathological features in breast cancer tissue [n (%)]

Features		n	CA-153 positive rate	x^2	P	Ki-67 positive rate	x^2	P
Age(years)	≤ 50	104	52(50.00)	0.229	0.632	50(48.08)	0.011	0.917
	>50	86	46(53.49)			42(48.84)		
Tumor size (cm)	≤ 2	54	26(48.15)	6.244	0.012	23(42.59)	1.026	0.311
	>2	136	92(67.65)			69(50.74)		
TNM stage	Ⅰ-Ⅱ	120	54(45.00)	40.494	0.000	35(29.17)	48.349	0.000
	Ⅲ-Ⅳ	70	64(91.43)			57(81.43)		
Lymph node metastasis	Yes	108	80(74.07)	15.232	0.000	68(62.96)	21.188	0.000
	No	82	38(46.34)			24(29.27)		

2.3 ER、PR、CA-153、Ki-67 在乳腺癌中表达的相关性分析

经 Pearson 相关性分析可得,ER、PR、CA-153、Ki-67 在乳腺癌中表达均呈正相关(P<0.05),见表 3。

表 3 ER、PR、CA-153、Ki-67 在乳腺癌中表达的相关性分析

Table 3 Correlation analysis of expression of ER, PR, CA-153 and Ki-67 in breast cancer

Indexes	PR		CA-153		Ki-67	
	r	P	r	P	r	P
ER	0.523	0.005	0.491	0.012	0.537	0.001
PR	-	-	0.602	0.000	0.585	0.000
CA-153	-	-	-	-	0.673	0.000

3 讨论

近几年,乳腺癌发病率开始呈逐年递增趋势,其中年轻女性占比日益增多[12]。由于乳腺癌的早期临床症状和体征无特异性,很多患者在确诊时已近中晚期,因此,早期有效诊断乳腺癌患者显得至关重要,并且不同乳腺癌患者的预后亦是截然不同,需在临床治疗过程中需予以个性化的治疗[13-15]。迄今为止,临床上尚且缺乏循证医学以及检测方式的显示,而相关的预后因子也相对缺乏,部分因子的应用效果并不显著[16-18]。既往研究报道证实[19-21],ER、PR 是重要的预后因子,检测 ER、PR 对内分泌治疗具有较高的指导意义,并且乳腺癌组织中 ER、PR 存在明显高表达,而 Ki-67 和染色质及细胞有丝分裂有关,亦是目前临床上应用最为广泛的增殖细胞标志物之一,CA-153 则属于血清肿瘤标志物之一,具有检测方式简便、重复性较好的特点,具有较好的应用前景。所以可通过研究 ER、PR、CA-153、Ki-67 的表达与乳腺癌临床病理特征及预后的相关性,为临床乳腺癌的诊断、治疗以及预后评估提供新的靶点和思路。

本研究结果显示,有淋巴结转移的乳腺癌组织中 ER、PR 阳性率明显高于无淋巴结转移(P<0.05),这与 Panagiotopoulos N 等人的研究报道相符[22],提示了 ER 与 PR 的表达和乳腺癌患者年龄、肿瘤大小、临床分期均无明显关联,但均与淋巴结转移存在密切相关。原因可能与 ER、PR 参与到了乳腺癌的淋巴结转移过程有关。ER、PR 是特定功能蛋白家庭成员之一,两者具有调节乳腺癌生长、分化的作用,临床上可通过对上述两项指标表达情况进行检测,从而有利于内分泌治疗方案的制定以及预后评估[23,24]。但另有研究报道显示乳腺癌组织中 ER 表达与淋巴结转移无明显相关,与本文结果存在差异[25]。分析原因,可能与本研究样本量较少存在一定关系,这也提示了在以后的研究中我们应增加样本量,以获得更加准确、可靠的数据。此外,本研究还发现,肿瘤大小 >2 cm、TNM 分期为Ⅲ-Ⅳ期、有淋巴结转移乳腺癌组织中 CA-153 阳性率分别高于肿瘤大小≤ 2 cm、TNM 分期为Ⅰ-Ⅱ期、无淋巴结转移(P<0.05),这提示了乳腺癌组织中 CA-153 的表达随着肿瘤的增大、临床分期的增加以及淋巴结转移的发生显著上升。原因可能是因为 CA-153 的作用机制或某种信号通路与乳腺癌疾病的进展有关。CA-153 是目前临床上公认的乳腺癌特异性肿瘤标记物之一,其在乳腺癌中过度表达,且随着患者病情不断进展,其表达水平逐渐升高,可作为临床上判断乳腺癌患者疾病严重程度的敏感指标[26,27]。另外,Ki-67 属于临床上应用较为广泛的肿瘤细胞增殖活性评估指标,其有半衰期较短的优势[28-30]。而本研究结果发现,TNM 分期为Ⅲ-Ⅳ期、有淋巴结转移乳腺癌组织中 Ki-67 阳性率明显高于 TNM 分期为Ⅰ-Ⅱ期、无淋巴结转移(P<0.05),这表明了 Ki-67 的阳性表达可能和肿瘤的生长以及浸润存在密切相关,可能成为临床上诊断乳腺癌的指标之一。本研究经 Pearson 相关性分析可得,ER、PR、CA-153、Ki-67 在乳腺癌中表达均呈正相关(P<0.05)。这也再次证实了上述四种指标均与乳腺癌密切相关。分析原因,可能是乳腺癌的发生、发展可能与上述指标的作用机制存在一定的重叠性,亦或是上述四种指标不同程度地

参与到了乳腺癌的发病或进展过程中。

综上所述,ER、PR、CA-153、Ki-67 在乳腺癌组织中均有显著高表达,临床上可联合检测四项指标,从而有利于明确患者病情严重程度,为靶向药物的个体化治疗提供参考依据。

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