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高危型人乳头瘤病毒、P16 和 ki67 在宫颈上皮内瘤变临床意义及相互关系 *

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摘要 目的:探究 P16、ki67 和高危型人乳头瘤病毒(human papillomavirus,HPV)在宫颈上皮内瘤变中诊断临床意义,并就上述指标的相关性进行分析。**方法**:选择 2019 年 1 月至 2019 年 12 月于我院接受治疗的 31 例宫颈炎患者、45 例上皮内瘤变患者(其中 25 例为低级别上皮内瘤变,20 例为高级别上皮内瘤变)为研究对象,分别对上述患者采用免疫组化法检测 P16 和 ki67 的表达,并采用 PCR 法对高危型人乳头瘤病毒的表达进行检测,而后实施组间比对。**结果**:高级别人乳头瘤变组和低级别人乳头瘤变高于宫颈炎组(P<0.05),高级别人乳头瘤病变组感染率高于低级别人乳头瘤变组,但是对比无统计学意义(P>0.05);P16 表达阳性率由高至低为高级别内瘤变组、低级别内瘤变组和宫颈炎组,各组间表达阳性率比对差异具有统计学意义(P<0.05);ki67 表达阳性率由高至低为高级别内瘤变组、低级别内瘤变组和宫颈炎组,各组间表达阳性率比对差异具有统计学意义(P<0.05);P16 和 ki67 表达阳性率与 HPV16/18 感染率呈正相关联系(P<0.05)。**结论**:高危型人乳头瘤病毒、P16 以及 ki67 对宫颈上皮内瘤变具有较好的诊断鉴别价值,可依据上述指标判断患者病程进展程度,对临床治疗具有一定指导意义。

关键词:高危型人乳头瘤病毒;P16;ki67;宫颈上皮内瘤变;临床意义;相互关系

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Clinical Significance and Correlation of High-risk Human Papillomavirus, P16 and ki67 in Cervical Intraepithelial Neoplasia*

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ABSTRACT Objective: To explore the clinical significance of P16, ki67 and high-risk human papillomavirus (HPV) in the diagnosis of cervical intraepithelial neoplasia, and to analyze the correlation of the above indicators. **Methods:** From January 2019 to December 2019, 31 patients with cervicitis and 45 patients with intraepithelial neoplasia (25 cases of low-grade intraepithelial neoplasia and 20 cases of high-grade intraepithelial neoplasia) were treated in our hospital as the research object, the expression of P16 and ki67 was detected by immunohistochemistry in the above patients, and the high-risk human papilloma virus expression was detected by PCR method, and then the group comparison. **Results:** The papillomas in the advanced others and the papillomas in the lower grades were higher than those in the cervicitis group (P<0.05). The infection rate of the papilloma lesions in the high-grade others was higher than that in the low-grade papillomas, but there was no significant difference (P>0.05). The positive rate of P16 expression was changed from high to low to high-grade internal tumorigenic group, low-grade internal tumorigenic group and cervicitis group. The positive expression rate comparison between the groups was statistically significant (P<0.05). ki67 expression positive rate From high to low, there was a high-level intratumoral change group, a low-level intratumoral change group, and a cervicitis group. There was a statistically significant difference in the positive rate comparison between the groups (P<0.05). The positive rate of P16 and ki67 expression was positively correlated with the infection rate of HPV16/18 (P<0.05). **Conclusion:** High-risk human papillomavirus, P16 and ki67 have a good diagnostic value for cervical intraepithelial neoplasia. The above indicators can be used to judge the progress of the patient's disease course and have certain guiding significance for clinical treatment.

Key words: High-risk human papillomavirus; P16; ki67; Cervical intraepithelial neoplasia; Clinical significance; Correlation

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前言

宫颈癌是妇科常见恶性癌症之一，其发病率仅次于乳腺癌,位居女性恶性肿瘤发病率第二位,近些年,随着近些年居民

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生活方式与起居习惯的改变,宫颈癌的发病率呈现逐年上升趋势,统计数据显示,全球每年新增宫颈癌患者约为 50 万例,死亡例数约为 23.1 万例, 我国每年宫颈癌新发病例高达 13.15 万,其发病率与死亡率均位居国内女性恶性肿瘤之首[1-3]。病毒感染、多次分娩、吸烟等因素都可能会诱发宫颈癌,且由于早期宫颈癌临床症状不明显,多数患者在发现时宫颈癌已发展至中后期,现阶段对宫颈癌的治疗主要包括手术治疗、化学治疗与放射治疗等[4,5],早期对宫颈癌的诊断及干预是提高患者预后的重要手段,对制定个体化治疗方案也具有重要意义。宫颈上皮内瘤变是一组与宫颈浸润癌密切相关的癌前病变的统称,主要包括宫颈不典型增生和宫颈原位癌等[6],一般来说宫颈癌的病理变化遵循如下规律: 宫颈不典型增生 - 原位癌 - 早期浸润癌 - 浸润癌, 对宫颈上皮内瘤变的鉴别有助于及早对宫颈疾病实施鉴别和治疗的开展,对改善宫颈癌患者预后具有积极意义[7,8]。P16 是一种新发现的抑癌基因, 临床研究指出当 P16 失活后,细胞会由于失去控制发生恶变,ki67 是一种与增殖细胞相关的核抗原,能够较好的反映细胞增值活性,高危型人乳头瘤病毒感染已被证实是宫颈癌独立危险因素[9-11]。本研究旨在通过分组检测, 就高危型人乳头瘤病毒、P16 和 ki67 在宫颈上皮内瘤变患者中表达临床意义进行探究,以期为宫颈癌的及早干预的治疗提供理论依据,现详述如下。

1 资料与方法

1.1 一般资料

选择 2019 年 1 月至 2019 年 12 月于我院接受治疗的 31 例宫颈炎患者、45 例上皮内瘤变患者 (其中 25 例为低级别上皮内瘤变,20 例为高级别上皮内瘤变)为研究对象,宫颈炎患者年龄 35~69 岁,平均年龄(51.02±4.32)岁,低级别上皮内瘤变患者年龄 36~70 岁,平均年龄(50.98±4.41)岁,高级别上皮内瘤变患者年龄 35~68 岁,平均年龄(51.02±3.99)岁,3 组患者一般临床资料比较差异不具有统计学意义(P>0.05),具有可比性。

纳入标准:(1)意识清晰能够配合进行调研;(2)病例资料齐全;(3)调研经医院伦理学会批准实施;(4)患者或其家属对本次调研过程、方法、原理清楚明白并签署知情同意书;(5)均具有明确的临床诊断。

排除标准:(1) 合并精神疾患者;(2) 妊娠或哺乳期女性;(3)合并严重肝肾功能障碍者;(4)合并其他恶性肿瘤者;(5)既往宫颈病变或宫颈癌病史者;(6)无完整宫颈者;(7)已开展放化疗的宫颈癌患者。

1.2 方法

分别采集宫颈炎组、低级别上皮内瘤变组、高级别上皮内瘤变组和宫颈癌组患者病变组织,制作石蜡切片后使用甲醛固定、石蜡包埋,而后执行切片、染色、比较等步骤,P16 和 ki67 的检测采用免疫组织化学 Elivision 两步法实施检测,检测试剂盒购武汉珈源生物医学工程有限公司,操作严格按照试剂盒说明书进行,每个指标检测 3 次;高危人乳头瘤病毒感染的检测以 HPV16、18 等分型为准,采用 PCR 方法,PCR 仪购自于珠海黑马医学仪器有限公司, 试剂采购自深圳港龙生物技术有限公司,同样操作按照试剂盒说明书实施。

1.3 观察指标及评测标准

1.3.1 **三组患者高危人乳头瘤病毒感染率** 是否感染参照试剂盒说明书进行判断, 组织细胞核内出现蓝色为阳性细胞,未出现蓝色为阴性细胞, 注意三组样本的检测均由同一医师进行,尽量减少误差。

1.3.2 **三组患者 P16 表达阳性率** P16 表达阳性的表现为细胞核或细胞浆内出现棕黄色颗粒,并根据染色细胞染色的深浅和染色细胞占比进行阳性强度的判断,表达阳性的表现为细胞核或细胞浆内出现棕黄色颗粒,并根据染色细胞染色的深浅和染色细胞占比进行阳性强度的判断, 具体参照如下两个标准,细胞染色深浅计分:无染色为 0 分,浅黄色为 1 分,棕黄色为 2 分,黄褐色为 3 分,最终分 0 分为(-),1~4 分为(+),5~8 分为(++),9~12 分为(+++)[12,13]。

1.3.3 **三组患者 ki67 表达阳性率** ki67 表达阳性的具体表现为细胞核内出现棕黄色颗粒,按照 1 个视野内 200 个鳞状上皮全层细胞中阳性细胞的占比来进行表达强度的区分,参照如下标准:<5 %细胞染色为 (-),5 %~25 %细胞染色为 (+),26 %~50 %细胞染色为(++),>50 %细胞染色为(+++)[14]。

1.4 统计学方法

将采集的数据录入至 SPSS 20.0 软件中实施统计学分析,对于计量数据采取($\bar{x}\pm s$)的形式来表示,组间的差异性比较应用 Student's t test 检验,对于计量资料采取[n(%)]的形式表示,组间的差异性比较采用卡方检验, 取 P<0.05 为差异具有统计学意义[13]。

2 结果

2.1 三组患者高危人乳头瘤病毒感染率比较

经检测发现,根据宫颈疾病严重程度的不同,三组患者高危 HPV 感染率也有较大的差异, 三组患者高级别人乳头瘤病变组感染率为 30.00 %, 低级别人乳头瘤病变组感染率为 20.00 %,宫颈炎组感染率仅为 3.23 %,高级别人乳头瘤变组和低级别人乳头瘤变高于宫颈炎组(P<0.05),高级别人乳头瘤病变组感染率高于低级别人乳头瘤变组,但是对比无统计学意义(P>0.05),具体数据如表 1 所示。

表 1 三组患者高危人乳头瘤病毒感染率比较[例(%)]

Table 1 Comparison of high-risk human papillomavirus infection rates in the three groups of patients [n(%)]

Groups	n	Negative	Positive	Infection rate(%)
Cervicitis	31	30	1	3.23
Low-grade intraepithelial neoplasia	25	20	5	20.00*
High-grade intraepithelial neoplasia	20	14	6	30.00*

Note: Compared with the cervicitis group, * P<0.05, compared with the low-grade intraepithelial neoplasia group, $^{\#}P$ <0.05.

2.2 三组患者 P16 表达阳性率比较

经检测发现，宫颈炎组 P16 表达阳性率为 0.00 %，低级别上皮内瘤变组 P16 表达阳性率为 44.00 %，高级别上皮内瘤变组 P16 表达阳性率为 80.00 %，组间比较两两均具有统计学差异（P<0.05），具体数据如表 2 所示。

表 2 三组患者 P16 表达阳性率比较

Table 2 Comparison of positive rates of P16 expression in the three groups of patients

Groups	n	Express results				Positive rate(%)
		-	+	++	+++	
Cervicitis	31	31	0	0	0	0.00
Low-grade intraepithelial neoplasia	25	14	8	3	0	44.00*
High-grade intraepithelial neoplasia	20	4	4	5	7	80.00*#

Note: Compared with the cervicitis group, * P<0.05, compared with the low-grade intraepithelial neoplasia group, #P<0.05.

2.3 三组患者 ki67 表达阳性率比较

经检测发现，宫颈炎组患者 ki67 表达阳性率为 6.45 %，低级别上皮内瘤变组 ki67 表达阳性率为 44.00 %，高级别上皮内瘤变组 ki67 表达阳性率为 80.00 %，各组两两比较 ki67 表达阳性率差异均具有统计学意义（P<0.05），具体如表 3 所示。

表 3 三组患者 ki67 表达阳性率比较

Table 3 Comparison of positive rates of ki67 expression in three groups of patients

Groups	n	Express results				Positive rate(%)
		-	+	++	+++	
Cervicitis	31	29	2	0	0	6.45
Low-grade intraepithelial neoplasia	25	13	9	2	0	44.00*
High-grade intraepithelial neoplasia	20	4	4	5	7	80.00*#

Note: Compared with the cervicitis group, * P<0.05, compared with the low-grade intraepithelial neoplasia group, #P<0.05.

2.4 高危人乳头瘤病毒、P16 与 ki67 表达相关性分析

分别以 P16 和 ki67 作为因变量，以高危人乳头瘤病毒感染为自变量，经相关性分析发现，高危人乳头瘤病毒感染同 P16 和 ki67 阳性表达存在明显的相关性，具体数据如表 4 所示。

表 4 高危人乳头瘤病毒、P16 与 ki67 表达相关性分析

Table 4 Correlation analysis of high-risk human papillomavirus, P16 and ki67 expression

Index	P16		ki67	
	r	P	r	P
High-risk human papillomavirus infection	0.457	<0.05	0.781	<0.05
P16	-	-	0.667	<0.05
ki67	0.817	<0.05	-	-

3 讨论

宫颈癌是发病率仅次于乳腺癌的女性恶性肿瘤，据世界卫生组织国际癌症研究署（IARC）报道，全球每年新发宫颈癌约有 53 万例，占所有癌症发病例数的 5 %，数据显示，美国 2013 年度宫颈癌病例数为 1.2 万例，死亡 4000 例，而发展中国家宫颈癌发病率及死亡率显著高于发展国家[15,16]。调研指出，我国每年约有 13 万例的新发宫颈癌病例，居我国妇女恶性肿瘤第一位，约占全球新发病例数的 30 %，仅次于智利[17,18]。近些年随着居民生活方式的改变及饮食结构的调整，宫颈癌呈现年轻化趋势，给女性身心健康带来较大的威胁，临床实践指出，早期对宫颈癌的诊断和鉴别对后期治疗具有重要意义，因而早期对宫颈癌的排查能够为提高女性生活质量打下良好基础[19,20]。目前宫颈癌早期筛查手段较为多样，包括对宫颈筛查方式较多，包括病理学检测、液基细胞学检测、HPV 分型基因检测、阴道镜检查等，但受患者采样依从性等多种因素影响，均存在一定的不足，因而目前宫颈癌的早期筛查成为临床学者的研究重点方向之一[21,22]。

上皮内瘤变是宫颈癌前期病变类型之一，对上皮内瘤变临床诊断的开展也是鉴别宫颈病变类型的重要途径，当前随着分子生物学的不断发展，越来越多的基因和蛋白指标被应用于宫颈癌的鉴别诊断中，P16 是参与细胞增生调控的重要基因[23,24]，研究指出，P16 即具有调控细胞周期的效果，又具有抑制肿瘤生长的重要作用，P16 蛋白的缺失会增加细胞恶变的几率，而

P16 基因失活则会使肿瘤不断增殖,加速病情的进展[25,26]。本研究中宫颈炎组患者 P16 表达阳性率为 0.00 %,低级别上皮内瘤变患者 P16 表达阳性率 44.00 %,高级别上皮内瘤变患者 P16 表达阳性率 80.00 %,可以发现随着病情加重 P16 表达阳性率逐步升高,这与学者惠霞[20]等的研究结果相一致。该学者的研究结果为宫颈癌患者 P16 表达阳性率 100.00 %,宫颈病变组为 66.67 %,而健康个体表达阳性率为 16.67 %,与本文结果类似,根据该研究结果推断,P16 在上皮内瘤变患者中过表达是一种特征性的改变,可能与宫颈病变的发生发展存在密切联系,可以将 P16 作为上皮内瘤变诊断指标之一。

同理,文中对 ki67 表达阳性率的鉴别与 P16 类似,ki67 是一种非组蛋白抗原,该抗原同哺乳动物细胞周期和细胞分裂增殖存在密切相关性,是一种贯穿表达于增殖细胞中的核抗原[27,28],本文中研究结果显示 ki67 的表达同宫颈病变程度也存在一定的相关性,同时低级别和高级别上皮内瘤变患者 ki67 表达阳性率存在明显的差异性,这提示 ki67 能够作为宫颈癌癌前病变诊断和筛查指标之一,是一种具有较好潜在应用价值的免疫标志物。高危人乳头瘤病毒感染同宫颈癌的相关性已有较多的研究证实,分析其机制可能与高危人乳头瘤病毒感染会对宫颈细胞正常周期产生影响,增加细胞恶变可能,最终诱发宫颈癌变[29,30]。最后高危人乳头瘤病毒感染、P16 和 ki67 表达的相关性分析则指出,上述三种指标在表达上具有一定的关联,佐证了上文中对三种指标能够作为宫颈癌筛查手段的论点。

综上所述,高危型人乳头瘤病毒、P16 以及 ki67 对宫颈上皮内瘤变具有较好的诊断鉴别价值,可依据上述指标判断患者病程进展程度,对临床治疗具有一定指导意义。

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