doi: 10.13241/j.cnki.pmb.2018.16.013

宫颈癌患者人乳头瘤病毒感染分布情况及多重感染与临床病理特征的关系*

李 松 刘君丽 余 超 孙 余 丁春雨

（华中科技大学同济医学院附属协和医院检验科 湖北 武汉 430022）

摘要 目的:研究宫颈癌患者人乳头瘤病毒(HPV)感染的分布情况及多重感染与临床病理特征的关系。**方法:**选择2015年1月-2018年1月期间我院收治的118例宫颈癌患者,根据患者宫颈癌的病变程度分为I期组(n=21)、II期组(n=46)、III期组(n=49)、IV期组(n=2)。所有患者均进行HPV分型检测,比较不同程度的宫颈癌患者的HPV感染情况,分析不同宫颈癌病变程度患者的多重感染和临床病理特征关系。**结果:**118例患者中有97例患者感染了HPV,感染率为82.20%,且II期组、III期组、IV期组患者HPV感染率高于I期组(*P<0.05*)。II期组、III期组、IV期组患者一重感染率低于I期组,IV期组二重感染率低于I期组,II期组、III期组、IV期组患者多重感染率高于I期组,且IV期组多重感染率高于II期组、III期组(*P<0.05*)。多重感染患者类型有多种,其中尤以HPV16+18+53型最多,占比49.05%,其次是HPV16+18+68型感染,占比32.07%,HPV16+53+58型感染,占比13.21%。年龄在50岁以上、分期为III-IV期、鳞癌、淋巴结转移的患者HPV多重感染率更高(*P<0.05*)。**结论:**HPV多重感染与宫颈癌病变程度和临床病理特征均有联系,对年龄较大且HPV多重感染的宫颈癌患者进行筛查,预防病情恶化。

关键词:宫颈癌;人乳头瘤病毒;多重感染;临床病理特征;关系

中图分类号:R737.33 **文献标识码:**A **文章编号:**1673-6273(2018)16-3062-04

The Distribution of Human Papillomavirus Infection and the Relationship between Multiple Infection and Clinicopathological Characteristics in Patients with Cervical Cancer*

LI Song, LIU Jun-li, YU Chao, SUN Yu, DING Chun-yu

(Department of Laboratory Medicine, Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei, 430022, China)

ABSTRACT Objective: To investigate the distribution of human papillomavirus (HPV) and the relationship between multiple infection and clinicopathological characteristics in patients with cervical cancer. **Methods:** 118 cases of cervical cancer who were treated in our hospital from January 2015 to January 2018 were selected. According to the degree of cervical cancer,they were divided into I stage group (n=21), II stage group (n=46), III stage group (n=49), IV stage group (n=2). All patients were detected by HPV typing, the HPV infection of cervical cancer patients in different degrees were compared, the relationship between multiple infections and clinicopathological characteristics of patients with different degrees of cervical cancer were analyzed. **Results:** Among the 118 patients, 97 patients were infected with HPV, the infection rate was 82.20%, the HPV infection rate in II stage group, III stage group and IV stage group was higher than that of I stage group (*P<0.05*). The single infection rate of II stage group, III stage group and IV stage group was lower than that of I stage group, the double infection rate of IV stage group was lower than that of I stage group. The multiple infection rate in II stage group, III stage group and IV stage group were higher than that in I stage group, the multiple infection rate in IV stage group was higher than that in II stage group and III stage group (*P<0.05*). There were many types of multiple infection patients, most of them were HPV16+18+53 type, accounting for 49.05%, the second was type HPV16+18+68 infection, which accounted for 32.07%, type HPV16+53+58 infection, accounting for 13.21%, patients with age over 50 years, stage III-IV, squamous cell carcinoma and lymph node metastasis had higher HPV multiple infection rate (*P<0.05*). **Conclusion:** HPV multiple infection is associated with the degree and clinicopathological features of cervical cancer, screening for patients with older and multiple HPV infections to prevent the deterioration of the disease.

Key words: Cervical cancer; Human papillomavirus; Multiple infection; Clinicopathological characteristics; Relationship

Chinese Library Classification(CLC): R737.33 Document code: A

Article ID: 1673-6273(2018)16-3062-04

* 基金项目:湖北省自然科学基金项目(2014CFB2037)

作者简介:李松(1987-),男,本科,初级检验师,从事检验方面的研究,E-mail: fghbfo@163.com

(收稿日期:2018-04-02 接受日期:2018-04-26)

前言

宫颈癌是妇女疾病中常见的恶性肿瘤之一，其发病率仅次于乳腺癌，是威胁女性健康的第二大癌症杀手[1,2]。我国宫颈癌发病率是发达国家的 6 倍，患病人数占全球的 28%，因此宫颈癌防治刻不容缓[3]。目前有研究认为，宫颈癌的发生是一个多因素、多基因相互协调的漫长的演变过程，其中生物因素是宫颈癌发生的重要因素[4,5]。而高危型人乳头瘤病毒（Human papillomavirus，HPV）持续性感染是宫颈癌发生的主要原因[6]。HPV 亚型较多，根据统计约有 130 多个亚型，但有关研究发现，在目前已知的多种 HPV 亚型中，仅有 30 多种 HPV 亚型与宫颈癌病变发生、发展有直接关系[7-9]。而临床上大部分宫颈癌患者是 HPV 二重感染或者多重感染，但关于 HPV 多重感染是否增加宫颈癌的患病几率仍尚不明确。本研究通过探讨宫颈癌患者 HPV 感染的分布情况及多重感染与临床病理特征的关系，旨在为宫颈癌的防治提供依据，现报道如下。

1 资料和方法

1.1 临床资料

选择 2015 年 1 月 -2018 年 1 月我院收治的 118 例宫颈癌患者作为研究对象，纳入标准：(1)所有患者均符合国际妇产科协会制定的宫颈癌相关诊断标准，经病理学确诊[10]；(2)均行 HPV 分型检测，病例资料完整；(3)患者及家属对研究知情同意。排除标准：(1)HPV 检查前 1 个月内接受过抗菌药物治疗者；(2)拒绝参加研究者；(3)病情较重，预计生存期低于 1 年者。根据国际妇产科协会临床分期将患者分为 I 期组、II 期组，III 期组、IV 期组。其中 I 期组患者 21 例，年龄 23-58 岁，平均（39.91± 3.51）岁；II 期组患者 46 例，年龄 24-56 岁，平均（39.83± 3.48）岁；III 期组患者 49 例，年龄 23-57 岁，平均（39.93± 3.63）岁；IV 期组患者 2 例，年龄 36-42 岁，平均（39.00± 3.04)岁。病理分型：鳞癌 80 例，非鳞癌 38 例；组织分化程度：低分化 83 例，中高分化 35 例；淋巴结转移 41 例，无淋巴结转移 77 例。本次研究已获医院伦理委员会审批，且各组患者一般资料比较差异均无统计学意义（*P>0.05*），具有可比性。

1.2 研究方法

患者处于非月经期时行 HPV 分型检测，检查前 3d 无阴道冲洗或者用药史，检查前 1d 无性生活史，患者的宫颈脱落细胞采集操作如下：采用窥阴器以使宫颈暴露，于宫颈鳞柱交界处采用 HPV 刷采集宫颈上皮脱落细胞；保存好 HPV 刷在 1-2 周内进行 HPV 分型检测（试剂盒来源于中国凯普生物科技有限公司），可检测一下 13 种高危型 HPV：16、18、31、33、35、39、45、51、52、56、58、59、68 型，具体检测方法如下：宫颈细胞液经 14000 r/min 离心 1 min，选择上清液，按照试剂盒说明进行 PCR 扩增，扩增后将 PCR 扩增产物进行导流杂交，芯片显色后进行结果判断。

1.3 观察指标

（1）比较不同宫颈癌病变程度患者的 HPV 感染情况；(2)比较不同宫颈癌病变程度患者 HPV 一重感染、二重感染、多重感染的分布情况；(3)比较不同宫颈癌病变程度 HPV 多重感染患者的 HPV 亚型；(4)分析不同宫颈癌病变程度患者的多重感染和临床病理特征的关系。

1.4 统计学方法

本研究数据均采用 SPSS25.0 软件处理与分析，所有数据均符合正态分布，($\bar{x}\pm s$)代表计量资料，实施 t 检验，[n(%)]代表计数资料，实施 x^2 检验，检验水准α=0.05。

2 结果

2.1 不同宫颈癌病变程度患者的 HPV 感染情况

118 例患者中有 97 例患者感染了 HPV，感染率为 82.20%，且 II 期组、III 期组、IV 期组患者 HPV 感染率高于 I 期组（*P<0.05*），II 期组、III 期组、IV 期组患者 HPV 的感染率比较无统计学差异（*P>0.05*），见表 1。

表 1 不同宫颈癌病变程度患者的 HPV 感染情况对比[n(%)]

Table 1 Comparison of HPV infection among patients with different degrees of cervical cancer[n(%)]

Groups	n	HPV infection
I stage group	21	11(52.38)
IIstage group	46	41(89.13)*
IIIstage group	49	43(87.76)*
IVstage group	2	2(100.00)*
Total	118	97(82.20)

Note: compared with the I stage group,**P<0.05*.

2.2 不同宫颈癌病变程度患者 HPV 一重感染、二重感染、多重感染的分布情况比较

II 期组、III 期组、IV 期组患者一重感染率低于 I 期组，IV 期组二重感染率低于 I 期组，II 期组、III 期组、IV 期组患者多重感染率高于 I 期组，且 IV 期组多重感染率高于 II 期组、III 期组（*P<0.05*），见表 2。

2.3 不同宫颈癌病变程度 HPV 多重感染患者的 HPV 感染类型对比

多重感染患者类型有多种，其中尤以 HPV16+18+53 型最多，占比 49.05%，其次是 HPV16+18+68 型感染，占比 32.07%，HPV16+53+58 型感染，占比 13.21%，见表 3。

2.4 不同宫颈癌病变程度患者的多重感染和临床病理特征关系分析

年龄在 50 岁以上、分期为 III-IV 期、鳞癌、淋巴结转移的患者 HPV 多重感染率更高（*P<0.05*），见表 4。

表 2 不同宫颈癌病变程度患者 HPV 一重感染、二重感染、多重感染的分布情况对比[n(%)]

Table 2 Comparison of the distribution of HPV single infection, double infection and multiple infection in patients with different degrees of cervical cancer

Groups	n	Single infection	Double infection	Multiple infection
I stage group	11	4(36.36)	4(36.36)	3(27.28)
IIstage group	41	6(14.63)*	12(29.27)	23(56.10)*
IIIstage group	43	7(16.28)*	11(25.58)	25(58.14)*
IVstage group	2	0(0.00)*	0(0.00)*	2(100.00)*#&

Note: compared with the I stage group,*P<0.05; compared with the IIstage group, #*P<0.05*; compared with the III stage group, &*P<0.05*.

表 3 不同宫颈癌病变程度 HPV 多重感染患者的 HPV 感染类型对比[n(%)]

Table 3 Comparison of HPV infection types of HPV multiple infection patients with different degrees of cervical cancer[n(%)]

Groups	n	16+18+53	16+18+68	16+53+58	16+31+39+58	16+18+31+58	16+18+53+58
I stage group	3	2(66.67)	1(33.33)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
IIstage group	23	11(47.83)	7(30.43)	5(21.74)	0(0.00)	0(0.00)	0(0.00)
IIIstage group	25	12(48.00)	8(32.00)	2(8.00)	1(4.00)	1(4.00)	1(4.00)
IVstage group	2	1(50.00)	1(50.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Total	53	26(49.05)	17(32.07)	7(13.21)	1(1.89)	1(1.89)	1(1.89)

表 4 不同宫颈癌病变程度患者的多重感染和临床病理特征关系[n(%)]

Table 4 Relationship between multiple infection and clinicopathological characteristics of patients with different degrees of cervical cancer [n (%)]

Related factors		n	Infection rate	x^2	*P*
Age	≥ 50	56	54(96.43)	14.742	0.000
	<50	62	43(69.35)		
Stage	I-II	67	61(91.04)	8.283	0.004
	III-IV	51	36(70.59)		
Pathological classification	Squamous cell carcinoma	80	73(91.25)	13.897	0.000
	Non squamous cell carcinoma	38	24(63.16)		
Tissue differentiation	Poorly differentiated	83	70(84.34)	0.871	0.351
	Middle and high differentiation	35	27(77.14)		
Lymph node metastasis	Yes	41	22(53.66)	34.995	0.000
	No	77	75(97.40)		

3 讨论

HPV 是一种体积较小的环形 DNA 病毒,可促进人体皮肤黏膜的鳞状上皮增殖,临床表现为寻常疣、生殖器疣(尖锐湿疣)等[11,12]。同时高危型 HPV 感染也是宫颈癌发生的危险因素,研究表明,有一半以上的有性生活史的女性曾感染过 HPV,但绝大部分的女性感染的病毒一段时间内可被自身免疫清除,仅有一小部分人群将会出现高危型 HPV 持续感染[13-15]。近年来,随着医学技术的发展和 HPV 基因分型检查的普及,人们发现大部分宫颈癌患者是 HPV 二重感染和多重感染,但对宫颈癌患者 HPV 感染的分布情况及多重感染与临床病理特征的关系仍不完全明确[16-18]。Seminerio I 等报道多重 HPV 感染可以显著增加宫颈癌的发病率 [19]。而 Yuen WWY 等报道宫颈癌患者 HPV 多重感染可能与地区分布和人群分布有关[20]。

本研究对我院收治的 118 例宫颈癌患者分析,结果发现 118 例患者中有 97 例患者感染了 HPV,感染率为 82.20%,且 II 期组、III 期组、IV 期组患者 HPV 感染率显著高于 I 期组(*P*<*0.05*),这可能由于宫颈癌的发生是一个多因素、多基因相互协调的漫长的演变过程,而宫颈癌 II 期、III 期、IV 期患者病变时间较长,往往感染 HPV 时间较长,患者 HPV 的感染率也较高[21-23]。II 期组、III 期组、IV 期组患者一重感染率低于 I 期组,多重感染率高于 I 期组,提示宫颈癌程度越严重患者多重感染发生率更高。其原因可能是 HPV 感染是宫颈癌发生的重要原因,目前已有研究证实当人体感染高危型 HPV 后,HPV 可以将自身的 DNA 整合到机体 DNA 中,通过无限复制导致细胞癌变[24,25],而 HPV 多重感染可能意味着患者 HPV 感染时间更长,细胞癌变时间更长。此外,从 HPV 多重感染患者不同宫颈癌病变程度的 HPV 感染类型对比来看,多重感染患者类型有多种,其

中尤以HPV16+18+53型最多，占比49.05%，其次是HPV16+18+68型感染，占比32.07%，HPV16+53+58型感染，占比13.21%，说明宫颈癌的发病与HPV多重感染有很大关系，且无论是II期、III期、IV期患者，HPV16均是感染的主要类型，临床上应针对HPV感染的常见类型开展重点检查和预防工作，降低HPV多重感染发生率。从不同宫颈癌病变程度患者的多重感染和临床病理特征关系来看，年龄在50岁以上、分期为III-IV期、鳞癌、淋巴结转移的患者HPV多重感染发生更高。这提示了病情相对更重的患者通常具有更高的感染率[26,27]。究其原因，可能是随着患者的年龄的增加，其机体免疫力下降，各项器官功能较年轻人明显降低，体内激素水平变化差别较大，潜伏的HPV病毒较年轻人群更易激发，因此其多重感染率也逐渐升高，临床中应将年龄较大且HPV多重感染的宫颈癌患者作为重点关注对象，以预防宫颈癌病变[28-30]。

综上所述，HPV多重感染与宫颈癌的发生密切相关，且年龄较大、病情严重、淋巴结转移患者的HPV多重感染率更高，临床上应针对以上因素，对高危患者开展宫颈癌病变的检查，以预防宫颈癌病变。

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