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不同检测策略在成都双流地区宫颈癌筛查中的价值研究*

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【摘要】 目的 评估高危HPV（high-risk HPV, hr-HPV）检测和宫颈细胞学（thinprep cytology test, TCT）的不同组合策略在成都双流地区宫颈癌筛查，特别是在高级别宫颈上皮内病变筛查中的临床价值。**方法** 本项目为基于人群的随机临床试验。纳入符合要求的35～65岁的女性。第一年基线筛查中受试者按1∶2随机分配进行细胞学或hr-HPV检测，其中hr-HPV检测呈阳性者被随机分流行细胞学或阴道镜检查。24个月后召回所有受试者，对其均进行细胞学和hr-HPV联合筛查。以上述基线筛查结果阴性且进入第三年随访并完成随访的女性为研究对象。基于上述检查结果，提取相关数据，模拟4种不同的筛查方案：①TCT和hr-HPV联合筛查，任一阳性则转诊阴道镜检查；②TCT和hr-HPV联合筛查，同时阳性则转诊阴道镜检查；③TCT初筛阳性者进行hr-HPV分流，hr-HPV阳性者转诊阴道镜；④hr-HPV初筛阳性者进行TCT分流，TCT阳性者转诊阴道镜。以组织学病检出宫颈高级别鳞状上皮内病变（HSIL$^+$）为终点事件，计算不同筛查方案的敏感性、特异性、阳性预测值和阴性预测值、曲线下面积。**结果** 共筛查3 102人，其中2 967人纳入最终统计。其中，细胞学组979人，hr-HPV组1 988人。初筛细胞学组筛查阳性率为5.6%（55/979），HSIL$^+$检出率为0.2%（2/979）。hr-HPV组筛查阳性率为7.5%（149/1 988），HSIL$^+$病变的检出率为0.9%（18/1 988）。24个月后共计召回2 456名女性，对其同时行宫颈细胞学及hr-HPV检测。其中，细胞学组阳性率为3.2%（78/2 456），hr-HPV组阳性率为8.7%（215/2 456），总的HSIL$^+$检出率为0.69%（17/2 456）。基线hr-HPV阴性的妇女远期HSIL$^+$病变的发生率较低。宫颈细胞学筛查和hr-HPV分流策略是最佳方法，其敏感性为88.9%，特异性为58.3%，阳性预测值为44.4%，阴性预测值为93.3%，曲线下面积为0.736，P=0.039（95%CI：0.555～0.917）。**结论** 本项基于成都双流地区的临床随机试验显示，hr-HPV检测的敏感性优于细胞学，且hr-HPV初筛阴性的女性2年后HISL$^+$患病率低于细胞学初始阴性女性。采用细胞学初筛后再进行hr-HPV分流的筛查方案对HISL$^+$病变的检测更有价值。

【关键词】 宫颈癌筛查 宫颈细胞学 高危HPV 宫颈高级别鳞状上皮内病变 成都双流地区

Effectiveness of Different Testing Strategies Applied for Cervical Cancer Screening in Shuangliu District, Chengdu City

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【Abstract】 Objective To evaluate the clinical value of different combination strategies of high-risk HPV (hr-HPV) testing and Thinprep cytology test (TCT), a cervical cytology test, for cervical cancer screening, especially for high or higher-grade squamous intraepithelial lesion (HSIL$^+$) in Shuangliu District, Chengdu City. **Methods** The study is a population-based randomized clinical trial. Women aged 35 to 65 years meeting the inclusion criteria were enrolled for the study. At the baseline screening conducted in the first year, the participants were randomly assigned to either cytology test or hr-HPV testing at a ratio of 1∶2. If the paticipants had positive results for the baseline hr-HPV test, they would then undergo either cytology test or colposcopy by random assignment. After 24 months, all participants were called back, and combined screening of cytology test and hr-HPV test were performed. Women who had negative results at baseline screening and who entered and completed the third-year follow-up were selected as the subjects of the study. Based on the

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aforementioned testing findings, the related data were extracted and four different screening protocols were simulated: 1) combined TCT and hr-HPV screening, with referral for colposcopy when there was positive results for either one of the two; 2) combined TCT and hr-HPV screening, with referral for colposcopy when both tests had positive results at the same time; 3) TCT was done for preliminary screening and those who were found to be positive would then undergo hr-HPV test for triage purpose, with subsequent referral made for colposcopy if the hr-HPV results were positive; 4) hr-HPV was done for preliminary screening and those who were found to be positive would then undergo TCT, with subsequent referral made for colposcopy if TCT results were positive. With the detection of HSIL$^+$ on histological examination as the endpoint event, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve (*AUC*) of different combination screening models were calculated. **Results**　A total of 3102 women were screened, and 2967 women were included in the statistical analysis in this study. Among the 2967 women, 979 were randomized to cytology and 1988 to hr-HPV genotyping. For prescreening, the positive rate of the cytology group was 5.6% (55/979), with of HSIL$^+$ positive rate being 0.2% (2/979), while the positive rate of the hr-HPV group was 7.5% (149/1988), with HSIL$^+$ positive rate being 0.9% (18/1988). After 24 months, 2456 women were called back and were given cervical cytology test and hr-HPV test at the same time. Among them, the positive rate of the cytology group was 3.2% (78/2456), while the positive rate of hr-HPV group was 8.7% (215/2456). The overall positive rate of HSIL$^+$ was 0.69% (17/2456). Women with a negative baseline hr-HPV had a lower incidence of HSIL$^+$ lesions in the long term. The strategy of cervical cytology screening combined with hr-HPV test for triage purpose is the best method, with a sensitivity of 88.9%, a specificity of 58.3%, a PPV of 44.4%, a NPV of 93.3%, and an *AUC* of 0.736, *P*=0.039 (95% *CI*: 0.555-0.917). **Conclusion**　This randomized clinical trial from Shuangliu District, Chengdu City shows that the sensitivity of hr-HPV testing is better than that of cytology test, and the prevalence of HSIL$^+$ in women with negative baseline hr-HPV results is lower than that of women with negative baseline cytology results. The screening program of TCT for prescreening plus subsequent hr-HPV test for triage purpose shows better value for the detection of HSIL$^+$.

【Key words】　Cervical cancer screening　Cervical cytology　High-risk HPV　High or higher grade squamous intraepithelial lesion (HSIL$^+$)　Shuangliu District, Chengdu City

宫颈癌(cervical cancer, CC)作为全球女性第四大常见的恶性肿瘤,严重危害着女性的生命健康。据世界卫生组织国际癌症研究所(International Agency for Research on Cancer, IARC)数据统计,2020年全球宫颈癌新发病例数约60.41万例,死亡人数约34.18万例,约86%发生在发展中国家[1]。

人乳头瘤病毒(human papillomavirus, HPV)是一种双链脱氧核糖核酸(DNA)病毒,主要通过性途径传播,根据其致癌潜力分为高危型和低危型,持续性高危HPV(high-risk HPV, hr-HPV)感染与宫颈癌前病变及宫颈癌密切相关,其中71%的宫颈癌与HPV 16/18感染有关[2-3]。接种预防性HPV疫苗,可以从源头上预防宫颈癌的发生,但是现有预防性HPV疫苗价格较高,短时间内难以全面推广;且预防性HPV疫苗不包含所有hr-HPV型别,因此,HPV疫苗接种并不能替代宫颈癌筛查[4-5]。从持续性的hr-HPV感染发展为宫颈浸润癌通常需要十数年以上的时间,故有充足的时间在癌症发生前筛查、干预[6-7]。目前,宫颈癌筛查方案主要为单独或者联合使用细胞学检查和hr-HPV分型检测[6]。

子宫颈鳞状上皮内病变(cervical squamous intraepithelial neoplasia, SIL),既往称鳞状上皮内瘤变(cervical intraepithelial neoplasia, CIN),包括低级别鳞状上皮内病变(low-grade squamous intraepithelial lesion, LSIL,对应CIN Ⅰ)、高级别鳞状上皮内病变(high-grade squamous intraepithelial lesion, HSIL,对应CIN Ⅱ、CIN Ⅲ),是一组与宫颈癌相关的癌前病变,是一个连续的过程[8]。

我国自2009年起在农村地区实施“两癌(宫颈癌及乳腺癌)”筛查项目,采用的筛查方法多为巴氏涂片或醋酸/碘染色肉眼观察(visual inspection with acetic acid and with Lugol's iodine, VIA/VILI)[9],但这两种技术在实际筛查应用中结果均不能令人满意,漏诊率较高[10]。2014年,hr-HPV检测首次被引入到国家人群筛查项目中,在部分“两癌”筛查项目点进行试点。本研究为国家卫健委重大公益性行业专项“适合中国农村地区的宫颈癌筛查技术与示范研究”子项目,本项目组与双流区妇幼保健院合作,完成了对双流地区3000余名女性的宫颈癌筛查及随访工作,并模拟组合不同的筛查方案,探讨其对HSIL$^+$的筛查价值。

1　材料与方法

1.1　研究对象

成都双流地区自愿参加宫颈癌筛查的女性,根据宫颈癌筛查研究项目要求,采用方便抽样的方法选择3000

名合格妇女,入组条件如下:①年龄为35~65岁且有性生活史的女性;②无宫颈癌疾病史,宫颈完整;③无临床怀孕可疑症状;④理解研究程序,自愿参加。对计划纳入研究的妇女按1:2比例随机分为细胞学检测组、hr-HPV分型检测组。

1.2 研究方法

1.2.1 *研究方案* 第一年基线筛查中将受试者按1:2比例被随机分配进行细胞学或hr-HPV检测,其中hr-HPV检测呈阳性者被随机分流行细胞学或阴道镜检查。24个月后召回所有受试者,对其均进行细胞学和hr-HPV联合筛查。以上述基线筛查结果阴性且进入第三年随访并完成随访的女性为研究对象。基于上述检查结果,提取相关数据,模拟4种不同的筛查方案:①TCT和hr-HPV联合筛查,任一阳性则转诊阴道镜检查;②TCT和hr-HPV联合筛查,同时阳性则转诊阴道镜检查;③TCT初筛阳性者进行hr-HPV分流,hr-HPV阳性者转诊阴道镜;④hr-HPV初筛阳性者进行TCT分流,TCT阳性者转诊阴道镜。伦理审核由项目组长单位——中国医学科学院北京协和医院牵头完成;中国临床试验注册号:ChiCTR1900022530。

1.2.2 *初筛标本采集与检测* 第一年基线初筛时,在筛查点对拟参与研究的妇女进行宣教,签署知情同意书(无法签字者,由其代理人代替签字);填写宫颈癌筛查调查表,核查无漏项及明显错误后按分组原则完成随机分组,妇科医生根据分组进行取材,并填写临床检查表以及标本采集表。宣教、筛查调查表填写、样本取样、阴道镜检查均由双流区妇幼保健院人员完成(由四川大学华西第二医院医务人员进行质控)。采集所得标本由四川大学华西第二医院细胞学技术人员和HPV检测人员进行相应的检测,并填写诊断结果表。

1.2.3 *细胞学检查* 采用新柏氏(ThinPrep®)薄层液基细胞学(Thinprep cytology test, TCT)代替传统巴氏涂片,按TBS分类系统报告,满意标本的细胞学诊断分类包括:未见上皮内病变和恶性细胞(negative for intraepithelial lesion or malignancy, NILM);未明确诊断意义的非典型鳞状细胞(atypical squamous cells of undetermined significance, ASC-US);不能除外高级别上皮内病变的非典型鳞状细胞(atypical squamous cells, cannot exclude high-grade intraepithelial lesions, ASC-H);不典型腺上皮细胞(atypical glandular cells, AGC);低度鳞状上皮内病变(low-grade squamous intraepithelial lesion, LISL);高度鳞状上皮内病变(high-grade squamous intraepithelial lesion , HISL);鳞状细胞癌(squamous cell carcinoma, SCC);原位腺癌(adenocarcinoma *in situ*, AIS);腺癌(adenocarcinoma, ADC)。

1.2.4 *HPV检测* 采用之江生物(Liferiver®)的高危型人乳头瘤病毒分型核酸测定试剂盒(荧光PCR法)进行HPV检测,对hr-HPV 13种型别(HPV16/18/31/33/35/39/45/51/52/56/58/59/68)的特异性DNA核酸片段进行分型定性检测。

1.2.5 *阴道镜检查* 若阴道镜下可见上皮病变,在病变处直接取活检。若阴道镜满意(转化区及病变的全部边界均可见,没有炎症、药物、损伤的干扰),阴道镜可疑低度病变或高度病变,根据阴道镜指示取活检,若细胞学结果为AGC、ASC-H或≥HSIL,则同时行宫颈管搔刮(endocervical curettage, ECC);若阴道镜检查不满意(转化区及病变的全部边界不完全可见),则行ECC;若阴道镜检查正常,按相应临床管理规范处理。

1.2.6 *初筛阳性处理* 细胞学检测组诊断为≥ASC-US定义为细胞学初筛阳性,直接进行阴道镜检查。HPV检测若为HPV16/18阳性,直接进行阴道镜检查;若为HPV16/18阴性,其他型别阳性,则随机均分为2组,一组直接进行阴道镜检查,另一组进行细胞学分流,如细胞学诊断为ASC-US及以上则进行阴道镜检查,如细胞学诊断为正常则不做阴道镜检查。所有进行阴道镜检查女性,均根据阴道镜结果决定是否做宫颈活检,对有可疑病变者,在可疑部位取宫颈活检,对无可疑病变者,则在宫颈四象限随机活检(活检部位:钟点3°、6°、9°、12°)及ECC,并填写组织学标本采集表。病理切片由四川大学华西第二医院病理科两位具有高级职称的医师独立双盲诊断;如结果不一致时,则由第三位具有高级职称的医师进行复核。病理结果包括:慢性宫颈炎、LSIL、HISL、宫颈浸润癌。对于病理诊断阴性及病检结果LSIL$^+$的女性进入第3年随访,对于病检结果HISL$^+$的女性按临床治疗规范进行治疗。

1.2.7 *随访标本采集与检测* 提前通知需随访女性按时到达复查地点,核对待检女性基本信息,所有女性均进行TCT及hr-HPV检测,并填写复查临床检查记录表。采集所得标本由细胞学技术人员和HPV检测人员进行检测,并填写诊断结果表。

1.2.8 *复查阳性结果处理* 细胞学检测组诊断为ASC-US及以上定义为细胞学复查阳性,HPV组检测任一高危型HPV阳性则定义为HPV复查阳性。受检女性,细胞学和HPV任一阳性则进行阴道镜检查,所有进行阴道镜检查女性,均根据阴道镜结果决定是否做宫颈活检:对有可疑病变者,在可疑部位取宫颈活检;对无可疑病变者,则在宫颈四象限随机活检(活检部位:3°、6°、9°、12°)及

ECC, 并填写组织学标本采集表。阅片诊断流程同前。对于病理诊断阴性及病检结果LSIL的女性嘱其定期随访, 对于病检结果HISL$^+$的女性按临床治疗规范进行治疗。

1.3　统计学方法

对于呈正态分布的计量资料, 采用$\bar{x} \pm s$表示, 两组比较采用成组t检验。对于呈非正态分布的计量资料, 采用M(P_{25} ~ P_{75})表示, 两组比较采用Mann-Whitney U检验。对于计数资料, 采用百分比(%)表示, 两组比较采用χ^2检验或Fisher' s精确概率法, 采用受试者工作特征(ROC)曲线计算曲线下面积(AUC)。所有统计学检验采用双侧检验, P< 0.05为差异有统计学意义。

2　结果

2.1　参加筛查女性的一般情况

本项目初筛入组自然人群妇女3 102人, 其中135人因填报个人信息不完整予以剔除, 剩余2 967人纳入分析。其中细胞学组979人, HPV组1 988人。参加筛查女性的一般情况见表1。细胞学组及HPV组人群基线一般情况差异均无统计学意义。

2.2　细胞学组基线筛查结果

细胞学组初筛阳性率为5.6%(55/979), 其中ASC-US 48例, LISL 5例, HSIL$^+$ 2例。阴道镜检查率为92.7%(51/55, 4例ASC-US失访)。21名女性经阴道镜检查评估后行宫颈活检术, 有2例诊断为HSIL$^+$病变, HSIL$^+$病变的检出率为0.2%(2/979), 其后予以治疗, 剩余977名女性进入随访。基线人群按每5岁划分为一个年龄组, 45 ~ 49岁女性细胞学阳性率最高, 约7.3%(表2)。

2.3　HPV组基线筛查结果

HPV组共纳入1 988名女性, 初筛阳性率为7.5%(149/1 988), 其中HPV16/18阳性者37人(1.9%), HPV其他

表 1　筛查对象一般情况

Table 1　General information of the subjects to be screened

Variable	Total (n=2 967)	HPV group (n=1 988)	Cytology group (n=979)	P
Age/yr., $\bar{x} \pm s$	48.1±7.2	48.4±7.1	48.0±6.9	0.218
Ethnicity/case (%)				
Han	2 900 (97.7)	1 939 (97.5)	961 (98.2)	0.264
Others	67 (2.3)	49 (2.5)	18 (1.8)	
Age at menarche/yr., $\bar{x} \pm s$	14.3±2.1	14.2±2.1	14.3±2.1	0.115
Age at first sexual intercourse/yr., $\bar{x} \pm s$	21.2±2.0	21.3±1.8	21.3±2.0	0.983
Age at first birth/yr., $\bar{x} \pm s$	22.8±2.3	22.8±2.3	22.8±2.2	0.601
Number of sex partners for the last three years/case (%)				
0-1	2 955 (99.6)	1 980 (99.6)	975 (99.6)	0.98
≥2	12 (0.4)	8 (0.4)	4 (0.4)	
Smoking/case (%)				
Yes	29 (0.9)	20 (1.0)	9 (0.9)	0.821
No	2 938 (99.0)	1 968 (98.9)	970 (99.1)	
Bathing before sex/case (%)				
Yes	2 522 (85.0)	1 672 (84.1)	850 (86.8)	0.051
No	445 (14.9)	316 (15.9)	129 (13.2)	
Sexual partners bathing before sex/case (%)				
Yes	2 329 (78.5)	1 546 (77.8)	783 (79.9)	0.168
No	638 (21.5)	442 (22.2)	196 (20.0)	

表 2　不同年龄段基线筛查结果

Table 2　Baseline screening results by age groups

Age/yr.	Cytology screening team			HPV screening team			
	n	TCT positive/ case (%)	HSIL$^+$ positive/ case (%)	n	HPV16/18 positive/ case (%)	Other HPV types positive/ case (%)	HSIL$^+$ positive/ case (%)
35-39	135	8 (5.9)	1 (0.7)	245	5 (2.0)	18 (7.3)	3 (1.2)
40-44	237	14 (5.9)	0 (0)	443	4 (0.9)	22 (4.9)	2 (0.5)
45-49	233	17 (7.3)	1 (0.4)	455	9 (1.9)	23 (5.1)	4 (0.9)
50-54	182	9 (4.9)	0 (0)	371	9 (2.4)	18 (4.9)	4 (1.1)
55-59	98	3 (3.1)	0 (0)	225	5 (2.2)	12 (5.3)	3 (1.3)
≥60	94	4 (4.3)	0 (0)	249	5 (2.0)	19 (7.6)	2 (0.8)
Total	979	55 (5.6)	2 (0.2)	1 988	37 (1.9)	112 (5.6)	18 (0.9)

型别阳性者112人(5.6%)。其他型别HPV阳性妇女中,56人直接转诊阴道镜检查,56例进行TCT分流,TCT分流中结果≥ASC-US者14例,故总共应召回107名女性进行阴道镜检查,实际召回96人,阴道镜召回率为89.7%(96/107)。其中有48人经阴道镜检查评估后行宫颈活检,共检出9例CIN Ⅰ,5例CIN Ⅱ,11例CIN Ⅲ,1例原位腺癌,1例微小浸润癌,其余21例病检结果为阴性,HSIL$^+$病变的检出率为0.9%(18/1 988)。共1 970名女性进入随访。基线人群按每5岁划分为一个年龄组,对不同年龄组分段进行比较,60岁以上年龄组HPV阳性率最高(9.6%)(表2)。

2.4 细胞学组与HPV组的初筛阳性率及CIN Ⅱ$^+$检出率差异

细胞学组与HPV组初筛阳性率分别为5.6%、7.5%,差异无统计学意义;细胞学组与HPV组HSIL$^+$检出率分别为0.2%、0.9%,差异有统计学意义(P<0.05)。

2.5 随访筛查结果

2967人进行第一年初筛,需随访人数为2947人,第三年完成随访人数为2 456人,随访率为83.3%(2 456/2 947)。所有女性均同时再次进行细胞学和HPV检测,任一结果阳性则进行阴道镜检查。细胞学筛查阴性2 378人(96.8%),细胞学筛查阳性78人(3.2%),其中ASC-US 71人,ASC-H 2人,LISL 4人,HISL 1人。HPV筛查阴性2 244人(91.4%),筛查阳性212人(8.6%),其中HPV16/18阳性26人,HPV其他型别阳性186人。

2.6 随访筛查结果组间比较

2 456名筛查女性中,HPV及细胞学筛查均阴性者有2 189人,HPV及细胞学均阳性者有26人,细胞学阴性HPV阳性者有189人,细胞学阳性HPV阴性者有52人。HPV筛查阳性率较细胞学筛查阳性率高(8.75% vs. 3.17%),差异有统计学意义(χ^2=60.9, P<0.001)(表3)。

2.7 随访筛查阴道镜结果

完成阴道镜检查267人。细胞学阳性病例中,阴道镜诊断LSIL 30人、HSIL$^+$ 1人、可疑癌1人。HPV阳性病例中,阴道镜诊断LSIL 68人、HSIL$^+$ 5人、可疑癌1人。

表 3 HPV和细胞学筛查结果比较

Table 3 Comparison of HPV and cytology screening results

Cytology	HPV/case		Total	P
	Negative	Positive		
Negative	2 189	189	2 378	<0.001
Positive	52	26	78	
Total	2 241	215	2 456	

2.8 随访筛查病检结果

进行宫颈活检者共96人,病检结果HSIL$^+$者17人,其中诊断宫颈癌2人,HSIL$^+$的检出率为0.69%(17/2 456)。TCT筛查的敏感性为52.9%(8/17)、特异性为69.6%(55/79),HPV筛查的敏感性为94.1%(16/17)、特异性为19.0%(15/79),两种筛查方法之间差异有统计学意义(χ^2=40.3, P<0.001),但细胞学筛查、HPV筛查的准确性与病检结果比较差异无统计学意义(表4)。

2.9 不同初筛方案的远期筛查效果

完成随访的2 456人中,源自细胞学初筛组839人,源自HPV初筛组1 617人。初筛细胞学阴性者中,随访细胞学阳性率为2.9%,HPV阳性率为8.0%。初筛HPV阴性者中,随访细胞学阳性率为2.8%,HPV阳性率为5.9%。初筛细胞学阴性人群中的LSIL检出率为3.7%,HPV初筛阴性者的LSIL检出率为2.9%。初筛细胞学阴性人群中的HSIL$^+$检出率为1.2%,初筛HPV阴性人群中的HSIL$^+$检出率为0.4%(表5)。

2.10 不同宫颈癌筛查模式的比较

以上述基线筛查结果阴性且进入第三年随访并完成随访的女性为研究对象。基于其检查结果,提取相关数据,模拟组合4种不同的筛查模式。方案一:同时行TCT和HPV检测,任一阳性则定义为阳性,转诊阴道镜检查。方案二:同时进行TCT和HPV检测,TCT和HPV检测同时阳性则定义为阳性,转诊阴道镜检查。方案三:TCT初筛阳性者进行HPV分流,HPV分流阳性则定义为阳性,转诊阴道镜检查。方案四:HPV初筛阳性后TCT分流,TCT分流阳性则定义为阳性,转诊阴道镜检查。

以病检结果为HSIL$^+$定义为病检阳性,综合比较:方

表 4 随访筛查病检结果

Table 4 Pathology results of the follow-ups

Item		TCT results/case		χ^2	P	HPV results/case		χ^2	P	Total
		Negative	Positive			Negative	Positive			
Pathology results	≤LSIL	55	24	3.16	0.076	15	64	0.92*	0.289#	79
	HSIL$^+$	8	9			1	16			17
Total		63	33			16	80			96

* Continuity correction, # Fisher's exact probability test.

表 5　不同初筛方案的远期筛查效果

Table 5　Long-term screening effects by different precreening strategies

Primary sreening	Follow-up screening											
	n	Cytology/case (%)		*P*	HPV/case (%)		*P*	≤LSIL/case (%)		*P*	HSIL$^+$/case (%)		*P*
		Positive	Negative		Positive	Negative		Positive	Negative		Positive	Negative	
Cytology negative	839	24 (2.9)	815 (97.1)	0.912	67 (8.0)	772 (92.0)	0.046	31 (3.7)	808 (96.3)	0.397	10 (1.2)	829 (98.8)	0.031
HPV negative	1 617	45 (2.8)	1 572 (97.2)		95 (5.9)	1 522 (94.1)		48 (2.9)	1 569 (97.0)		7 (0.4)	1 610 (99.6)	

案一敏感性最高, 方案二特异性最高, 方案三*AUC*最大, 即TCT初筛阳性后行HPV分流对HSIL$^+$具有更高的诊断价值(表6)。

表 6　四种筛查方案对HSIL$^+$检测结果综合评价

Table 6　Comprehensive evaluation of HSIL$^+$ test results by the four screening strategies

Screening strategie	Se	Sp	PPV	NPV	*AUC*
Plan 1	100.0%	71.3%	17.9%	100.0%	0.506
Plan 2	47.1%	87.3%	44.4%	88.5%	0.672
Plan 3	88.9%	58.3%	44.4%	93.3%	0.736
Plan 4	50.0%	84.4%	44.4%	87.1%	0.672

Se: Sensitivity; Sp; Specificity; PPV: Positive predictive value; NPV: Negative predictive value; *AUC*: Area under the raw current curves; *CI*: Confidence interval.

3　讨论

本研究采用液基细胞学代替传统巴氏细胞学, 细胞学标本的满意程度更高, 有利于检出高级别病变[11-12]。本研究细胞学筛查的HSIL$^+$检出率为0.2%, 较ZHENG等[13]、CHAN等[14]的研究结果低, 但较2012年我国“两癌”筛查项目的HSIL$^+$检出率(0.12%)略高[15]。本研究的初筛阶段细胞学检测阳性率5.6%, 较我国“两癌”筛查结果(3.93%)及COLDMAN等[16]的研究结果(3.55%)高, 但低于WANG等[17]对山西农村地区4万名妇女的筛查结果(6.76%)。多个研究发现, 随着年龄的增加, 细胞学阳性率呈上升趋势, 本研究中未见明显的年龄趋势。

与细胞学筛查相比, 基于HPV分型的筛查具有更高的敏感性和准确性[18-19]。采用HPV分型检测作为宫颈癌的初筛方法可以有效地延长宫颈癌筛查间隔时间, 并可以达到同细胞学筛查相同的效果, 更具成本效益[20-22], 欧洲及美国的指南也推荐将HPV运用于的宫颈癌初筛[3, 23]。但由于HPV检测具有较高的敏感性, 也造成了HPV检测具有更高的假阳性, 增加了不必要的阴道镜转诊率[21, 24]。本研究中人群的初筛hr-HPV感染率为7.5%, 低于2015–2016年对四川的hr-HPV感染率的调查研究[25]以及其他多个研究报道[14, 26]。本研究发现, hr-HPV感染率在≥60岁年龄段最高, 而35 ~ 39岁年龄段次之, 从35岁到≥60岁, HPV感染率呈现一个先下降后上升的趋势, 类似于其他研究中的“双峰”现象[27-28], 而本研究纳入研究的人群≥35岁, 故未观察到更低年龄的HPV感染情况, 而≥60岁感染率高, 可能与年龄大的女性免疫力低有关[29], 而35 ~ 39岁发病率高, 可能与此年龄段女性的性生活频率较其他年龄段女性更高有关[29]。本研究初筛中利用HPV筛查的HSIL$^+$检出率为0.9%, 与CHAN等[14]的研究结果相似。

本研究随访发现, 成都双流地区总的HSIL$^+$发生率为0.69%, 低于中国其他地区; 本研究中的hr-HPV初筛阴性人群中HSIL$^+$检出率明显低于细胞学筛查初筛阴性人群, 差异有统计学意义。本项目团队认为: 使用HPV分型在成都双流地区作为宫颈癌的初筛方法可以更好的降低远期宫颈癌前病变; 单独以细胞学作为初筛, 其结果阴性者仍可能存在HPV感染, 将增加此类患者远期发生HSIL$^+$的风险。

四种筛查方案中, 筛查方案一对HSIL$^+$的敏感性和阴性预测值最高, 但特异性也最低, 将造成不必要的阴道镜转诊, 增加筛查成本, 但因其检测的高敏感性, 可延长筛查间隔时间, 可抵消部分筛查的花费, 有研究模拟不同筛查筛查模式的经济成本效益, 表明细胞学联合HPV筛查是最具有成本效益的[30], 但需以增加阴道镜检查为代价。方案二对检测HSIL$^+$病变的特异性最高, 但敏感性却最低, 而*AUC*比方案三和方案四也更低, 但初筛成本与方案一相当, 故不推荐方案二作为宫颈癌筛查方案。方案三和方案四可有效地节约筛查成本, 减轻患者的经济负担[30], 并兼顾了敏感性和特异性, *AUC*也较前两种方案大, 初筛成本也较前两者低, 更适合作为宫颈癌筛查的方案。本研究中方案三敏感性及*AUC*均高于方案四, 如以HSIL$^+$为阈值, 方案三更具价值。

本研究显示成都双流城镇地区的hr-HPV的感染率与HSIL$^+$率较国内外其他研究偏低, hr-HPV感染的年龄分布呈“双峰型”(35 ~ 39岁、≥60岁组别感染率高)。与

细胞学筛查相较,以HPV检测作为初筛方案其HSIL$^+$检出率高。细胞学初筛、hr-HPV分流的筛查方案可能对HSIL$^+$的筛查具有更高的诊断价值。

* * *

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