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宫颈癌筛查方法研究进展

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摘　要

宫颈癌是我国最常见的妇科恶性肿瘤，也是一种病因明确且可预防的癌症。宫颈癌筛查在宫颈癌防控中发挥重要作用，随着医疗技术的进步，宫颈癌筛查方法也不断更新发展。宫颈细胞学检查、人乳头瘤病毒检测、阴道镜检查等均为宫颈癌筛查的重要方法，为临床明确病情提供重要参考依据。本文将对目前宫颈癌筛查方法研究进展进行归纳总结，以期为临床工作者的宫颈癌筛查工作提供帮助。

关键词

宫颈癌，筛查方法，研究进展

Progress in the Study of Cervical Cancer Screening Methods

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Abstract

Cervical cancer is the most common gynecological malignant tumor in China, and it is also a kind of cancer with clear etiology and can be prevented. Cervical cancer screening plays an important role in the prevention and control of cervical cancer, and with the advancement of medical technology, cervical cancer screening methods are constantly updated and developed. Cervical cytology, human papillomavirus test, colposcopy, etc. are crucial methods for cervical cancer screening, which provide significant references for clinical clarification of the disease. This article will summarize the current research progress of cervical cancer screening methods, in order to provide help for clinical workers

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in cervical cancer screening.

Keywords

Cervical Cancer, Screening Methods, Research Progress

1. 引言

宫颈癌是女性最常见的妇科恶性肿瘤，发病率及死亡率均位于全球女性癌症的第 4 位[1]。中国国家癌症中心发布的 2022 年中国癌症报告数据显示我国宫颈癌的发病率及死亡率仍在上升，并呈现年轻化趋势[2]。宫颈癌病因明确，主要由高危型人乳头瘤病毒(High-Risk Human Papillomavirus, hrHPV)持续感染引起，但早期往往没有特异性临床表现，因此宫颈癌筛查作为二级预防，在宫颈癌防控中起到至关重要的作用。通过宫颈癌筛查，尽早发现宫颈癌前病变和宫颈癌，对宫颈癌前病变给予及时干预和治疗，阻断其进展，对宫颈癌早期诊断和早期治疗可以明显改善宫颈癌患者预后[3]。本文将对目前宫颈癌筛查方法研究进展进行归纳总结，以期为临床工作者的宫颈癌筛查工作提供帮助。

2. 宫颈细胞学检查

1) 巴氏涂片检查

传统的巴氏涂片检查是宫颈细胞学检查的初始方法，通过收集少量宫颈脱落细胞标本铺在载玻片上，经过巴氏染色后置于显微镜下由专业人员阅片并按巴氏分类法诊断。该方法简单无创，检测费用低，曾是宫颈癌主要筛查方式。但存在宫颈细胞从取样器到载玻片转移不充分、细胞分布不均匀，易受血液和黏液影响，以及受检查者主观判断影响等缺点，多项研究显示其敏感性范围为 50%~75%，导致较高的假阴性率[4] [5]。并且传统巴氏五级分类对宫颈癌前病变分级不够细致，巴氏涂片检查正逐渐被新的筛查方法替代。

2) 液基薄层细胞学检测

液基薄层细胞学检测通过采集宫颈细胞后将宫颈“细胞刷”贮存于标本瓶内，充分摇匀，制作薄层液基细胞涂片，由专业人员读片后采用 TBS (The Bethesda System)分类法进行描述性诊断。该方法弥补了传统巴氏涂片检查的不足，具备细胞结构清晰、背景干净的特点，这使得异常细胞更易于被观察，降低采样不足率[5]，显著提升了宫颈病变上皮细胞的检出灵敏度[6] [7]。2023 年中国子宫颈癌筛查指南(一)提出虽然细胞学检查检出 CIN2+的敏感度较 HPV 检测低，但因其具有较好的特异性，可以评估即时风险。在农村和资源不足的地区，细胞学检查是一种重要的筛查方法[8]。美国癌症协会 2020 年指南提出在接种疫苗的人群中，基于细胞学的筛查效率较低，因为异常细胞学的比例较未接种人群减少，未来的宫颈癌筛查建议可能需要纳入 HPV 疫苗接种状态[9]。

3) 人工智能(AI)辅助细胞学检测

基于机器学习算法或深度神经网络算法，通过大量细胞学图像来训练模型，提取细胞特征并模拟学习，从而能够对新的细胞学图像进行分类，识别正常或异常细胞。使用人工智能辅助可以大大降低加工时间、材料和劳动力成本[10]。Wang 等研究结果表明，AI 辅助细胞学检测具有高灵敏度(90%)和特异度

(100%)，显著优于传统细胞学检查[11]。一项 70 万女性参与的前瞻性队列研究[12]发现，AI 辅助细胞学系统与人工阅片相比，总符合率为 94.7%，灵敏度提高了 5.8%。2024 年一项研究利用 16,056 名参与者组成的多中心、回顾性和前瞻性人群数据集，并进行了随机观察性试验，结果表明 AI 辅助细胞学检测比人工阅片表现出显着更高的特异性和准确性，同时敏感性显着提高了 13.3% [13]。Kurita [14]和 Yang [15]等也同样认为 AI 辅助细胞学检测显著提高效率并减轻病理细胞学家的负担。可见 AI 辅助快速筛查具有巨大的潜力，有望使宫颈癌筛查工作更加准确和高效。

4) DNA 倍体分析

DNA 倍体分析主要是基于细胞内 DNA 含量来进行检测，在细胞癌变过程中 DNA 含量的变化被认为先于细胞形态的改变，精确地测量细胞的 DNA 含量。DNA 倍体分析可实现自动化，具有不受主观因素影响、可重复性好等优势，Guo 等发现 DNA 倍体分析与液基薄层细胞学检测相比，敏感性、特异性、阳性预测值、阴性预测值和漏诊率无显著差异[16]。有学者认为 50 岁以上女性宫颈常有鳞状上皮萎缩，液基细胞学检测具有较高的假阳性，建议对该年龄段女性联合 DNA 倍体分析及 HPV 检测进行初筛[17]。而关春艳等[18]认为倍体分析用颜色深浅反映 DNA 含量容易受到染液、染色技术、标本处理等影响，倍体分析不可单独用于筛查。2024 年发表的一项研究[19]提示 DNA 倍体分析的特异度、阳性预测值、阴性预测值均低于液基细胞学检测，并且 DNA 倍体分析与活检病理诊断结果一致性较差，Kappa 值仅为 0.127。DNA 倍体分析的筛查价值仍存在争议，目前尚无法取代液基细胞学检测，可用于液基细胞学判别困难时辅助筛查。

5) 甲基化检测

甲基化是常见的表观遗传学修饰方式，大量研究发现基因启动子甲基化，尤其是宿主抑癌基因的高甲基化状态导致的抑癌基因表达沉默、转录失活与宫颈癌的发生相关。关于不同基因甲基化的研究正广泛开展见表 1 [20]-[29]。一项纳入 23 项研究的荟萃分析表明甲基化检测研究最多的基因是 CADM1、FAM19A4、MAL 和 miR124-2，其对宫颈上皮内瘤变(cervical intraepithelial neoplasia, CIN) 2+检测的合并敏感度和特异度分别为 0.68%和 0.75% [30]。中国一项前瞻性研究发现 PAX1 和 JAM3 甲基化在检测 CIN3+方面优于液基细胞学，在不影响诊断敏感性的情况下，减少了显著转诊至阴道镜检查的次数[26]。《中国子宫颈癌三级规范化防治蓝皮书》指出，DNA 甲基化检测技术具有客观、高重复性、与信号放大检测等特性，且具有子宫颈癌早筛较高的特异性与精准性，是一种非常有潜力的子宫颈癌筛查和分流手段[31]。此外甲基化研究还有自取样方式、液体活检方式的开展。但不同基因甲基化检测的判读阈值不同，临床应用缺乏统一标准，2025 年中华医学会检验医学分会发布了 PAX1 联合 JAM3 双基因甲基化检测的专家共识[32]，制定了统一检测流程及质控标准，推动宫颈癌甲基化在实验室检测与临床的规范化应用。

6) p16/Ki-67 免疫细胞化学双染检测

Ki-67 是细胞增殖标志物，而 p16 是细胞增殖的负调控因子，如果同时检测到两者表达则表示细胞周期失控和病变[33]。在细胞学初筛为 ASC-US/LSIL (Atypical Squamous Cells of Undetermined Significance/Low-grade Squamous Intraepithelial Lesion, ASC-US/LSIL)的人群分流中，一项前瞻性研究[34]纳入 529 例 ASC-US 病例和 529 例 LSIL 病例比较 p16/Ki-67 双染检测和 HPV 检测分流效果，结果表明 p16/Ki-67 双染检测对 CIN2+病变的灵敏度与 HPV 检测相当或稍低，但特异度更高；同时双染检测在 LSIL 和年龄 < 30 岁的 ASC-US 女性人群中的高级别病变的阳性预测值显著升高。对于 hrHPV 初筛阳性人群的分流，双染比细胞学检查灵敏度高，但特异性低[35]。荷兰一项基于人群的子宫颈癌联合筛查队列研究[36]采用宫颈细胞学与 hrHPV 联合筛查，对 1021 名 HPV 阳性且细胞学阴性的女性采用双染进行分流，并与 HPV 16/18 分型检测的分流方案进行对比，双染显示更高的灵敏度(68.8%比 43.8%)，其特异度稍低(72.8%比 79.4%)。p16/Ki-67 疫细胞化学双染检测展现出良好的分流价值，主要用于初筛液基细胞学异常(ASC-US/LSIL)或 HPV 阳性女性人群的分流。

Table 1. Research on gene methylation in cervical cancer screening
表 1. 基因甲基化在宫颈癌筛查方向的研究

文献	发表年份	基因	例数	样本类型	CIN1及正常	CIN2	CIN3	宫颈癌	研究结果
Vink 等[20]	2023	FAM19A4、miR124-2	1061	宫颈脱落细胞	690	166	204	1	FAM19A4/miR124-2 甲基化在 CIN2、CIN3 及宫颈癌中的阳性率分别为 28%、62%、100%
Kaliff 等[21]	2022	FAM19A4、miR124-2	476	宫颈脱落细胞	415	61			FAM19A4/miR124-2 甲基化阳性率在 CIN2+中为 67%，而在 CIN1 及以下的女性样本中为 28%
Vink 等[22]	2021	FAM19A4、miR124-2	979	宫颈脱落细胞	851		120	8	FAM19A4/miR124-2 甲基化分析的 CIN3+敏感性为 71.3%，特异性为 78.3%
Salta 等[23]	2021	MAL、FAM19A4、hsa-miR124-2	125	宫颈脱落细胞	89	34		2	MAL、FAM19A4、hsa-miR124-2 甲基化分析的 CIN2+敏感性为 61.11%，特异性为 74.16%
Leffers 等[24]	2022	CADM1、MAL	24	血液				24	CADM1 和 MAL 甲基化对宫颈癌的敏感性为 83.3%，特异性为 95.5%
Molano 等[25]	2024	CADM1、MAL、miR124-2	44	自取样宫颈脱落细胞	21	4	19	4	miR124-2/MAL 甲基化对 CIN2+的敏感性和特异性分别为 81.8%和 47.6%，CADM1 的甲基化随病变分级的增加没有显著差异
Chen 等[26]	2024	PAX1、JAM3	1851	宫颈脱落细胞	1522	178	131	20	PAX1、JAM3 甲基化对 CIN2、CIN3 及宫颈癌中的阳性率分别为 62.9%、82.4%、100%
Herzog 等[27]	2022	DPP6、RALYL、GSX1	506	宫颈脱落细胞	355	66	62	23	DPP6、RALYL、GSX1 甲基化分析对宫颈癌和 CIN3 的灵敏度分别为 100%和 78%
Chan 等[28]	2024	PAX1、SOX1	403	宫颈脱落细胞	286	114		3	PAX1、SOX1 甲基化分析对 CIN2+敏感性分别为 73.5%和 41.9%，特异性分别为 70.3%和 83.6%，二者联合效果不如单独 PAX1 甲基化分析
Sha 等[29]	2024	EPB41L3	1396	宫颈脱落细胞/宫颈组织	707	182	281	226	EPB41L3 甲基化检测对 CIN2+的综合敏感度为 67%，特异度为 76%

3. HPV 检测

1) hrHPV DNA 检测

2021 年发布的多中心随机临床试验[37]表明，HPV DNA 检测是一种有效的初步筛查方法，目前我国宫颈癌筛查策略与国际共识/指南均推荐使用 hrHPV DNA 检测作为宫颈癌的初筛方法。hrHPV DNA 检测具有较高敏感度，但假阳性率较高，并且大部分患者 HPV 感染呈一过性，多可自然清除。HPV 假阳性引起 HPV 感染人群过度焦虑和恐惧，造成巨大心理负担，并且引起过度检查和诊断，造成医疗资源的浪费[38]。现急需新的检测技术，进一步细化宫颈病变的分层诊断，优化 hrHPV 阳性患者的分流。

2) HPV E6/E7 mRNA 检测

HPV 感染宫颈细胞后，会分化为游离型和整合型。HPV E6/E7 mRNA 可反映 HPV 的感染状态，检测阳性提示病毒处于活跃期，HPV 已将自身基因整合至宿主细胞中，开始了转录和翻译，是宫颈发生早

期病变的特异性标志物[39] [40]。2022 年一项纳入 2 万 9 千余女性的荟萃分析[41]表明 HPV E6/E7 mRNA 检测对 CIN2+和 CIN3+具有相似的横断面敏感性，特异性略高 HR-HPV DNA 检测。一项纵向前瞻性研究[42]表明 HPV mRNA 对 CIN2+的灵敏度性和特异性分别为 96.9%和 88.0%，阴性预测值和阳性预测值分别为 99.9%和 23.6%。检测 HPV E6/E7 mRNA 的水平能更准确评估病变风险，提高筛查的特异性，降低误诊率，但该检测成本高，时效性差，仍需进一步成本效益分析，评估其卫生经济学效益。

3) HPV E6/E7 蛋白检测

HPV E6/E7 蛋白是 HPV 病毒生命周期的主要蛋白，E6 蛋白作用于 p53，通过影响细胞内多条信号转导通路，使基因突变及外源 DNA 整合到宿主染色体的概率增大，细胞周期失控；E7 蛋白与视网膜母细胞瘤基因蛋白(Retinoblastoma Protein, RB)结合，激活转录因子(Adenovirus E2 Transcription Factor, E2F)，使 RB-E2F 复合体解离，抑制它们的凋亡作用，这些生物学过程导致了肿瘤的发生与发展[43]。2024 年一项荟萃分析[44]表明 HPV E6/E7 蛋白检测的灵敏度和特异度估计范围为 54.2%至 69.5%，特异度范围为 82.8%至 99.1%，E6/E7 蛋白检测的高特异性支持其用于 HPV 阳性女性的分流。然而，其敏感度中等，不建议癌蛋白阴性女性进行常规筛查，需要进一步随访。E6/E7 蛋白检测仍需进行大规模和纵向研究，明确其诊断及预测价值。

4) HPV 病毒载量

多项研究报道[45] [46]，hrHPV DNA 的载量与宫颈癌变程度相关，对 hrHPV DNA 定量检测对预判宫颈病变的发展具有指导意义。Malagón 等[47]则认为 HPV 病毒载量的诊断准确性低于其他 HPV 筛查分流检测的诊断准确性。对于 HPV 病毒载量的诊断价值目前尚存在争议，该检测也尚未获得宫颈癌筛查指南推荐。

5) HPV 自采样检测

女性自己收集阴道样本进行 HPV 检测，称为 HPV 自采样检测。自采样是一种安全且简单的方法，就易用性、便利性、隐私性及身心舒适度而言，多项荟萃分析[48] [49]认为自采样是一种高度可接受的宫颈癌筛查样本采集方法。与由医疗机构专业人员进行样本采集相比，hrHPV 自采样在增加筛查机会、减缓不舒适感等方面更具有优势。一项纳入 72 项研究的荟萃分析关于自采样 HPV 检测接受度研究[48]表明，相较于自采样更喜欢临床医生收集样本的最常见原因是对自采样本缺乏自信。因此人们进行大量研究明确 HPV 自采样的准确性，Arbyn 等[50]认为自身样本的检测与临床医生样本的检测准确性相似；Aarnio 等人[51]通过一项随机研究得出自采样与医生采样 HPV 感染率和组织学中 CIN2+和 CIN3+检出率相同；Polman [52]的研究也得出相同结论。有研究表明[48]最常见的自采样工具是宫颈拭子，在比较不同自采样工具可接受性的研究中，患者更喜欢宫颈拭子而不是灌洗或宫颈刷等其他工具，但这种偏好可能是由于对宫颈拭子更加熟悉。自采样相较于传统医生采样的方式提高了筛查女性的接受度，但仍有部分女性抗拒阴道操作，为了提高此类人群的筛查率，尿液及月经血 HPV 检测被逐步探索。2022 年一项荟萃分析[53]表明自己收集尿液与临床医生收集的样本相比，尿液自采样显示出相似的临床准确性，表明尿液 HPV 检测可能是一种不错的替代筛查工具，用于检测宫颈癌前病变。一项研究通过女性月经血进行 HPV 检测，灵敏度为 97.7%，与 hrHPV DNA 检测的总体一致性为 92.7% [54]，这种无创自我采样 HPV 检测是一种很有前途的替代宫颈癌筛查，可避免耻辱感并提高患者参与意愿。但严格的储存和运输条件是尿液及月经血样本一个不可忽视的缺点，目前有干尿斑、干血斑等技术应用使运输更容易[55] [56]，提高了尿液、月经血样本检测 HPV 的可行性。目前多项国际指南均推荐 HPV 自采样可作为宫颈癌初筛方法，该方法有望在临床进一步广泛应用。

4. 阴道镜检查

1) 光学阴道镜及电子阴道镜

阴道镜检查是宫颈癌筛查异常的重要转诊检查，光学阴道镜主要是利用光学透镜系统来对阴道和宫颈的上皮组织进行放大观察。电子阴道镜是基于电子成像技术，通过一个摄像头来摄取阴道和宫颈的图像，然后将图像信号传输到显示器上进行显示。阴道镜检查由专业人员肉眼观察，或通过醋酸试验、碘染试验来识别下生殖道上皮内病变的大小和位置，进行活检。因此阴道镜检查受检查者主观影响较大，一项回顾性研究[57]以最终宫颈癌手术病理为金标准，评估阴道镜下活检病理的准确性，对 CIN2+漏诊率高达 10.5%。Wei 等[58]研究结果再次证实，阴道镜诊断 HSIL+特异度不高，因此传统阴道镜检查需要结合新的科学技术手段来进一步提高诊断效能。

2) 多光谱成像阴道镜

利用不同波长的光对组织进行照射，获取组织在多个光谱波段的反射和吸收信息，通过光谱分析技术处理这些信息，得到组织的光谱特征图像，从而反映组织的生理和病理状态。提高早期病变检测敏感性和特异性。有研究[59]表明，多光谱阴道镜检查更容易区分病理血管的特征，与传统阴道镜相比，其对检测宫颈病变具有更高的灵敏度和特异性。

3) 人工智能电子阴道镜辅助诊断系统

基于深度学习算法，通过对大量阴道镜图像和病理结果的学习训练，使系统能够自动识别和分析阴道镜图像中的病变特征，为医生提供辅助诊断建议。协助医生快速准确识别病变部位，减少漏诊和误诊，提高诊断效率。已有研究显示其在宫颈病变诊断中有较高准确性和应用价值。如 Miyagi 等[60]研究中，系统检出 CIN2+敏感性为 95.6%，特异性为 83.3%；Hu 等研究[61]中，诊断 CIN2+的 ROC 曲线下面积为 0.91。但仍需大样本、多中心研究进一步验证。

5. 小结

为响应世界卫生组织提出《加速消除宫颈癌全球战略》，宫颈癌筛查在中国已开展多年。HR-HPV DNA 检测因具有较高的灵敏度作为宫颈癌筛查初筛的主要手段，而多数 HPV 感染为一过性，造成 HR-HPV 阳性患者巨大心理及经济负担。现急需准确性更高的新兴筛查方法以及对高危 HPV 感染患者的合理分流策略。分子生物学技术的应用有望进一步提高筛查的准确性和敏感性，例如基因甲基化检测、HPVE6/E7 蛋白检测等。人工智能辅助诊断系统可能在未来的筛查中发挥重要作用，提高诊断效率和一致性。此外，自采样等便捷的筛查方式的推广，将提高筛查的覆盖率，尤其是在偏远地区和医疗资源匮乏的地区。总之，宫颈癌筛查对于早期发现和预防宫颈癌至关重要。选择合适的筛查方法或联合应用多种方法，结合个体情况进行个性化筛查，将有助于提高宫颈癌的检出率，降低宫颈癌的发病率和死亡率。同时，不断探索和发展新的筛查技术，将为宫颈癌的防治带来新的希望。

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