

人乳头瘤病毒疫苗的研究现状与展望

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摘要: 宫颈癌严重危害女性生命健康, 近年来针对宫颈癌的一系列预防手段不断被探索开发, 其中, 疫苗是消除宫颈癌的有效手段。预防性人乳头瘤病毒(human papillomavirus, HPV)疫苗可从根本上阻断 HPV 的传播, 是消除宫颈癌的第一道防线, 目前多个疫苗已上市并被广泛应用。针对逆转 HPV 持续感染和宫颈病变的治疗性 HPV 疫苗的研发及验证研究正在陆续开展。疫苗对于宫颈癌的防治至关重要, 全文综述 HPV 疫苗的研究进展。

关键词: 人乳头瘤病毒; 宫颈癌; 预防性疫苗; 治疗性疫苗

中图分类号: R730.1; R737.3 **文献标识码:** A **文章编号:** 1004-0242(2024)02-0153-08

doi: 10.11735/j.issn.1004-0242.2024.02.A011

The Status Quo and Prospects of Human Papillomavirus Vaccine

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Abstract: Cervical cancer is a serious threat to life and health of women worldwide. A series of approaches for prevention and control of cervical cancer have been explored and developed, among which the vaccine is considered an effective means to prevent the occurrence of cervical cancer. Preventive human papillomavirus (HPV) vaccine can block the transmission of HPV virus, which is the first line of defense to eliminate cervical cancer; and several vaccines have been marketed and widely used. Meanwhile, the development of therapeutic HPV vaccines aimed at reversing persistent HPV infection and cervical lesions is now underway. This paper reviews the research of developments of HPV vaccines for prevention and treatment of cervical cancer.

Key words: human papillomavirus; cervical cancer; preventive vaccine; therapeutic vaccine

人乳头瘤病毒 (human papillomavirus, HPV) 是最常见的通过性传播感染的病毒之一, 可引发宫颈癌、肛门癌、口咽癌等恶性肿瘤。宫颈癌的发病率和死亡率均位居全球女性恶性肿瘤第 4 位, 高危 HPV 病毒持续感染是宫颈癌的主要病因^[1]。2020 年全球

约有 59.8 万例新发病例和 33.88 万例死亡病例, 分别占有女性恶性肿瘤新发病例的 6.5% 和死亡病例的 7.7%^[2]。2020 年世界卫生组织 (World Health Organization, WHO) 提出包括中国在内 194 个国家承诺的《加速消除宫颈癌全球战略》及 2030 年阶段性目标^[3], 其中 90% 15 岁以下女孩接受 HPV 疫苗接种是主要目标之一。疫苗作为一级预防可以直接在源头上阻止 HPV 感染, 从而控制宫颈癌及癌前病

收稿日期: 2023-06-20; 修回日期: 2023-08-08

基金项目: 中国医学科学院医学与健康科技创新工程项目(2021-I2M-1-004); 北京协和医院中央高水平医院临床科研专项项目(2022-PUMCH-D-003)

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HPV 疫苗目前的研究进展进行综述。

1 预防性 HPV 疫苗

1.1 疫苗研发现状

截至 2023 年 5 月,全球上市的预防性 HPV 疫苗共有 6 种,包括 2006 年上市的四价疫苗(Gardasil[®], HPV6/11/16/18,默沙东公司,美国),常规免疫程序为 3 剂次(0/2/6 个月);2007 年上市的二价疫苗(Cervarix[®], HPV16/18,葛兰素史克公司,英国),常规免疫程序为 3 剂次(0/1/6 个月);2014 年上市的九价疫苗(Gardasil[®], HPV6/11/16/18/31/33/45/52/58,默沙东公司,美国),常规免疫程序为 3 剂次(0/2/6 个月);2019 年上市的国产二价疫苗(馨可宁[®]/Cecolin[®], HPV16/18,厦门万泰公司,中国),常规免疫程序为 3 剂次(0/1/6 个月);2022 年上市的二价疫苗(沃泽惠[®], HPV16/18,云南沃森公司,中国),常规免疫程序为 3 剂次(0/2/6 个月);2022 年上市的四价疫苗(Cervavax[®], HPV6/11/16/18,印度血清研究所,印度),常规免疫程序为 3 剂次(0/2/6 个月),其中前 4 种疫苗已经通过了 WHO 的预认证(prequalification, PQ)。中国仍在不断开发新的包括三价、四价、九价以及十五价的预防性疫苗,已有多项进入临床阶段^[4-6]。厦门万泰九价疫苗的 I 期临床试验数据显示出其良好的免疫原性和安全性,高剂量组(270 μg)抗体阳转率可达 100%,不良反应均为轻中度^[7]。重庆博瓦生物制药有限公司开发的四价和九价疫苗的 III 期临床试验也顺利完成,接种疫苗 7 个月后抗体阳转率可达 99%,接种后的不良事件主要是注射部位反应^[4]。

1.2 疫苗免疫原性、有效性及安全性

1.2.1 二价疫苗

二价疫苗可预防 HPV16/18 感染引起的宫颈疾病。距离首个二价疫苗上市已经过去了十多年,多项研究均证明了其有效、安全,保护时效可长达 10 年。有研究证实 10~25 岁女性接种疫苗 10 年后抗体仍呈阳性^[8-10],HPV16 抗体几何平均滴度为 1 589 (ELISA Units, EU)/mL, HPV18 抗体的几何平均滴度为 597.2 EU/mL^[8],疫苗诱导机体产生了高而持续的抗体应答,为机体应对相关感染和病变提供了武器。一项真实世界研究的数据显示,接种疫苗 9 年后

的女性高危 HPV 的感染率(21.3%)低于未接种疫苗的女性(23.7%)^[11]。疫苗对 2 级及以上的宫颈上皮内瘤变(cervical intraepithelial neoplasia grade 2 or worse, CIN2+)预防的有效率为 90.5%~100%^[9-10]。我国国产二价疫苗其 III 期临床试验数据显示,疫苗预防 HPV 持续感染的有效率为 97.3%(95%CI:89.9%~99.7%),预防宫颈病变的有效率高达 100.0%(95%CI:67.2%~100.0%)^[12]。

多项研究均表明疫苗相关的不良反应事件可接受,主要为接种部位局部反应。美国疫苗不良事件报告系统的数据显示,报告中 95.8%为轻度不良反应,常见的为头晕、头痛、恶心和注射部位的反应^[13]。接种二价疫苗的严重不良事件的发生率(0.201/10 000 剂)与接种乙型肝炎病毒疫苗的对照组的发生率(0.204/10 000 剂)相近^[14],其他多项研究同时也表明接种二价疫苗后无疫苗相关的严重不良事件的发生^[8,12,15]。

1.2.2 四价疫苗

四价疫苗可预防 HPV6/11/16/18 感染引起的宫颈疾病和生殖器疣。四价疫苗为最早上市的 HPV 预防性疫苗,已有多项临床及真实世界研究证明其良好的预防相关感染和疾病的效果。各个年龄段接种四价疫苗后都可从中获益,且疫苗接种后的长期效果可观。目前随访时间较长的一项北欧的研究显示,接种四价疫苗后至少可提供长达 14 年的保护,且有效率为 100%(95%CI:94.7%~100%)^[16-17],相关 HPV 抗体阳转率可达 100%^[18]。疫苗在小年龄组人群诱导了更加强烈的免疫反应,接种四价疫苗 7 个月后,9~19 岁女性相关 HPV 抗体几何平均浓度为 20~26 岁女性的 1.39~1.66 倍^[18];17 岁前接种疫苗的女性发病率(0.12)低于 17 岁之后接种疫苗女性的发病率(0.47)^[19]。在年龄较大的人群中,HPV 疫苗也可提供较好的保护,有研究报道在 27~45 岁女性中的抗体反应可持续 10 年^[20],疫苗预防相关感染或宫颈疾病的有效率为 90.5%(95%CI:73.7%~97.5%),预防与 HPV16 和 18 有关的感染或疾病的有效率为 83.1%(95%CI:50.6%~95.8%)^[21]。在一项真实世界研究中,14~19 岁的人群接种四价疫苗后,相关 HPV 感染率从 2003—2006 年的 11.5%下降到 2011—2014 年的 3.3%,20~24 岁的人群接种四价疫苗后感染率从 18.5%下降到 7.2%^[22]。

国内外多项临床及真实世界研究都表明四价疫苗具有良好的安全性。疫苗接种后不良事件的粗报告率约为 2.7/10 000 剂~3.27/10 000 剂,94.2%为轻度不良反应,常见的为头晕、晕厥和接种部位发热/发红/硬化,并且未发现与疫苗相关的严重不良事件^[9,20-21,23]。

1.2.3 九价疫苗

九价疫苗可预防 HPV6/11/16/18/31/33/45/52/58 相关的感染和疾病。由于九价疫苗上市时间相对较晚,针对疫苗接种后的研究尚较少,但现有研究表明九价疫苗有良好的保护效果。接种疫苗后诱导的抗体应答可持续至少 5 年^[24-26],抗体血清阳转率为 77.5%~100%^[24-25],且接种九价疫苗后产生的 HPV6/11/16/18 的抗体浓度不劣于四价疫苗(九价疫苗抗体浓度/四价疫苗抗体浓度:0.80~1.26)^[27-28],疫苗的有效率不低于 90%^[25-26]。

九价疫苗也表现出良好的安全性。疫苗接种后的不良事件的粗报告率为 2.59/10 000 剂~3.12/10 000 剂,报告中 97.4%为轻度不良反应,常见的为头晕、头痛和接种部位发热/发红/硬化^[29],并且未发现与疫苗相关的严重不良事件^[25,30]。

1.3 疫苗应用情况

1.3.1 疫苗覆盖情况及国内推广现状

截至 2023 年 12 月,已经有 137 个国家将 HPV 疫苗接种纳入了免疫规划^[31]。然而,至 2020 年,全球青春期女孩 HPV 疫苗的接种率只有 13%^[32],与 WHO 2030 年阶段性目标的实现还有显著差距。挪威、文莱、墨西哥、卢旺达及土库曼斯坦在 2020 年之前青春期女孩接种率已超过 90%,已提前实现疫苗接种目标,加拿大、英国等一些经济较为发达的国家,疫苗接种率也已经超过 80%^[33]。但是中国的疫苗接种情况不容乐观,2018—2020 年中国 9~45 岁适龄女性估算累计接种率仅为 2.24%^[34],经济较为发达的上海 2017—2019 年青春期女孩的接种率不足 1%^[35]。

中国目前仍尚未有统一的免疫程序和免疫策略^[36]。2020 年内蒙古鄂尔多斯市为 13~18 岁市户籍女性免费接种 HPV 疫苗^[37],这是全国首个政府免费接种 HPV 疫苗的地区。为贯彻落实《健康中国行动(2019—2030 年)》,2021 年全国启动健康城市创新模式试点工作,确定了北京石景山区、天津西青区、

内蒙古鄂尔多斯市、厦门等 15 个地区,先后启动适龄女孩 HPV 疫苗免费接种或补助接种项目。2022 年厦门为 13~14 周岁半学籍在校女生免费接种 HPV 疫苗^[38]。河南新密为初一年级女生免费接种 HPV 疫苗^[39]。福建省对全省 14 周岁女孩免费接种国产二价疫苗^[40],广东省也对初一未接种过 HPV 疫苗的 14 周岁以下的女生免费接种国产二价 HPV 疫苗^[41]。此后云南等其他非试点地区也启动对青春期女孩进行 HPV 疫苗免费接种。目前以政府为主导的地方免疫规划形式多针对小年龄女性 HPV 疫苗接种,这些城市对于 HPV 疫苗接种策略的探索将推进我国将 HPV 疫苗接种纳入国家免疫规划的进程。2023 年初,国家卫生健康委员会同教育部、民政部、财政部等十个部门联合制定印发了《加速消除宫颈癌行动计划(2023—2030 年)》^[42],提出到 2025 年,试点推广适龄女孩 HPV 疫苗接种服务,到 2030 年持续推进,积极响应 WHO“消除宫颈癌”倡议,在政府多部门协作和社会参与下,加快推进我国宫颈癌消除进程。

1.3.2 影响疫苗接种的因素

疫苗的价格、不同地区经济、卫生水平、教育水平和对疫苗的认知等都将影响疫苗的接种情况。美国的一项研究发现,如果疫苗免费,204 名 18~26 岁未接种疫苗的参与者中有 78%愿意接种疫苗;如果疫苗是自费的,则只有 8%的人愿意接种疫苗,若疫苗价格高,自费接种在很大程度上影响人们的接种意愿^[43]。中国的一项调查研究发现,在北京和上海这些经济较为发达地区的疫苗接种率为 7%~9%,远高于低卫生资源地区的接种率(0.5%)^[34]。

此外,提高大众对于 HPV 及 HPV 疫苗的认知也可提高疫苗的接种率。一项问卷调查显示,对 HPV 或 HPV 疫苗比较了解的学生接种疫苗的可能性约是其他学生的 2 倍^[44]。一些父母由于缺乏疫苗相关的正确认识,怀疑 HPV 疫苗的安全性,从而拒绝为他们的孩子接种 HPV 疫苗,或者盲目地等待高价疫苗从而导致孩子错过最佳接种时机^[45-46]。

1.3.3 疫苗的免疫程序

1.3.3.1 疫苗免疫程序进展

2017 年 WHO 及其他国际指南建议 9~14 岁的女孩和男孩接种 2 剂次,15 岁以上人群接种 3 剂次 HPV 疫苗^[47-49]。因为疫苗可及性及供应等问题,为提

高疫苗覆盖率,2022年4月,WHO免疫专家战略咨询小组提出单剂疫苗方案的建议,即9~14岁的女孩及15~20岁的女性均可以选择接种1剂或2剂疫苗^[32]。2022年8月,英国疫苗接种和免疫联合委员会调整了免疫策略,建议将14岁以下女孩的接种程序由2剂变为1剂^[50]。2022年12月,WHO更新了对HPV疫苗的接种建议即9~20岁的女孩和男孩可以选择接种1剂或者2剂疫苗,21岁以上人群可以接种2剂疫苗^[51]。

1.3.3.2 单剂疫苗接种策略

2020年全球肿瘤流行病学统计数据(GLOBOCAN 2020)数据显示,90%的宫颈癌患者都来自中低收入国家。对于经济不发达或低卫生资源的国家和地区,单剂疫苗接种可降低接种成本,简化接种程序,从而增加群体获得疫苗的机会。在发展中国家正在开展一系列关于单剂疫苗接种的前瞻性研究,多项研究结果均证实单剂疫苗接种有效率达80%以上^[52-54],且虽然接种单剂疫苗的抗体浓度低于接种2剂或3剂,但是比未接种疫苗的女性高5~30倍^[55-56],抗体反应可持续10年以上^[52,54-56]。

除此之外,有研究表明单剂疫苗的保护效果与其他剂次相似。在哥斯达黎加和肯尼亚的HPV疫苗临床试验结果均显示,15~25岁的年轻女性接种单剂二价疫苗预防HPV16/18感染的短期和长期有效率均在80%以上^[52]。此外,印度10~18岁女性接种单剂四价疫苗10年后,对预防HPV16/18持续感染的有效率高达95.4%,不低于接种2、3剂疫苗的有效率(93.1%~93.3%)^[54]。单剂九价疫苗也证实可提供较好的保护效果。9~14岁坦桑尼亚女孩在接种单剂九价疫苗后,可产生长达24个月的强烈免疫反应,且HPV16抗体阳性率不劣于接种2剂和3剂疫苗的女孩^[57];15~20岁的肯尼亚女性在接种单剂九价疫苗后18个月内的疫苗有效率为97.5%^[53]。综上,研究证实单剂疫苗特别是对小年龄组女性的保护效果较好,对于卫生资源较低的地区来说可能是一个增加HPV疫苗公平性和可及性,从而降低宫颈癌负担的接种策略^[58]。

虽然现有一些研究表明接种单剂疫苗的效果不劣于其他剂次,但是尚未有优化。虽然单剂疫苗的前期投入是2剂疫苗的一半,但若是考虑更长远的保护,2剂疫苗可能更具成本效益。一项乌干达的预测

模型研究表明,70%的9岁女孩在接种单剂疫苗40年后宫颈癌病例可降低15%~16%,接种2剂疫苗可以降低21%,虽然单剂疫苗接种成本相对更低,但是考虑到后续宫颈癌治疗的费用,2剂疫苗还是较单剂疫苗更符合成本效果,除非单剂疫苗的覆盖率达到90%及以上,否则还是推荐接种2剂疫苗^[59]。我国一项模型研究表明,若对9~14岁的女孩采取单剂接种计划,在接种人群20岁时进行疫苗补接种,其效益将高于常规的单剂接种计划^[60]。目前已有研究表明单剂疫苗的有效性,但是以单剂次接种为主的HPV疫苗接种策略在真实世界应用的临床效果及可行性还需进一步验证。

2 治疗性 HPV 疫苗

预防性HPV疫苗主要是诱导机体产生中和抗体预防HPV感染,然而对于已有的感染HPV预防性疫苗并不能提供有效的治疗。面对越来越多HPV感染或相关病变的患者,恰当有效的治疗已成为重要临床问题。治疗性HPV疫苗创伤小、操作简易,可以避免手术有创操作带来的出血、感染等并发症,是有前景的治疗方法。治疗性疫苗制备的方向有多肽、蛋白质、DNA、RNA及病毒载体等,主要针对的靶抗原基因是HPV E6/E7^[61],E6/E7蛋白是引起宫颈癌的重要转化蛋白质^[62]。接种疫苗后,抗原被呈递给免疫系统,刺激机体产生免疫反应来清除持续的HPV感染和治疗相关病变^[63]。

治疗性HPV疫苗发展较缓,大多处于临床I、II期阶段,目前尚无被批准上市的治疗性疫苗。但是多项临床试验研究结果显示,治疗性HPV疫苗有望抑制HPV持续感染和宫颈癌前病变进展。一项临床II期试验中,72名CIN3的患者接种了针对HPV E6和E7的疫苗7.5个月后,67%的患者宫颈病变消退,77%的患者HPV感染被清除^[64]。在另一项针对HPV E6和E7的疫苗临床II期试验中,CIN2/3患者接种疫苗后,47.62%的患者接种疫苗后宫颈病变消退,42.86%的患者病变得到了改善^[65]。CIN2/3患者接种针对HPV E2的治疗性疫苗后,58.82%的患者病变消退,其他患者病变都得到改善^[66]。

从目前已报道的临床试验结果来看,治疗性疫苗对于清除HPV病毒感染和宫颈病变消退具备一

定的应用前景,但还需大量更强有力的科学证据证实临床应用效果及价值。

3 总结与展望

现有研究表明预防性 HPV 疫苗具有良好的免疫原性、有效性及安全性,是预防宫颈癌的主要措施之一。但在经济、卫生资源、教育水平及认知等因素的影响下,全球预防性疫苗的接种率还是较低^[67-68]。提高大众知晓率,降低疫苗价格,制定适宜的免疫程序或许可以提高疫苗的覆盖率。

目前小年龄组人群接种单剂预防性疫苗对于经济不发达和低卫生资源的国家和地区来说是一个能有效降低宫颈癌负担的接种方案。但单剂疫苗的长期效果仍在进一步验证^[69-70],这些研究可能为单剂疫苗的接种策略提供更多的科学证据。

治疗性 HPV 疫苗有望成为 HPV 感染和宫颈癌变患者治疗的新选择。但是,治疗性 HPV 疫苗现还处于早期研究阶段,距离上市应用于人群还需要较长时间,其免疫原性、长期有效性及安全性有待进一步研究。

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