

亚洲人群 HPV 疫苗免疫原性及安全性的 Meta 分析

胡晓明^{1,2,3}, 孙九峰^{2,3}, 赵 卫¹

(1.南方医科大学公共卫生学院, 广东 广州 510515; 2.广东省公共卫生研究院, 广东 广州 511400;
3.广东省疾病预防控制中心, 广东 广州 511400)

[摘要]目的 评估人乳头状瘤病毒(HPV)疫苗在亚洲人群中接种后的免疫原性和安全性。方法 本研究分别检索英文数据库(PubMed、Embase、Web of Science、Clinical Trails、Cochrane library)和中文数据库(中国知网、万方、维普),自建库至2022年4月,关于亚洲人群进行的 HPV 疫苗安全性和免疫原性临床试验文献。采用主题词与自由词灵活搭配检索并结合纳排标准筛选文献,对最终纳入文献进行质量评价并提取资料,应用 Meta 分析合并评估。结果 最终纳入 16 篇随机对照试验(RCT)研究,累计研究对象 25 485 人。Meta 分析表明对于 HPV 疫苗免疫原性,HPV16 型特异性血清转化率合并效应值 RR 为 43.74 (16.51~115.85), HPV18 型特异性血清转化率合并效应值 RR 为 45.72 (8.78~238.13)。对于 HPV 疫苗安全性,二价与四价 HPV 疫苗接种局部不良事件风险试验组高于对照组, RR 为 1.52 (1.34~1.73) 和 1.38 (1.20~1.59)。二价 HPV 疫苗与四价 HPV 疫苗试验组发生全身性不良事件的风险也高于对照组, RR 分别为 1.21 (1.11~1.32) 和 1.13 (0.99~1.30)。结论 接种亚洲人群 HPV 疫苗后血清抗体阳转率高于未接种者,提示接种 HPV 疫苗可以提高个体特异性抗体水平,接种 HPV 疫苗发生局部和全身性安全事件的风险均高于对照组,提示仍要高度重视 HPV 疫苗的安全性问题。

[关键词]人乳头瘤病毒; HPV 疫苗; Meta 分析; 免疫原性; 安全性

Doi:10.3969/j.issn.1673-5293.2024.01.010

[中图分类号]R173

[文献标识码]A

[文章编号]1673-5293(2024)01-0058-09

Immunogenicity and safety of HPV vaccine in Asia population: a meta-analysis

HU Ximing^{1,2,3}, SUN Jiufeng^{2,3}, ZHAO Wei¹

(1.School of Public Health, Southern Medical University, Guangdong Guangzhou 510515, China;

2.Guangdong Institute of Public Health, Guangdong Guangzhou 511400, China;

3.Guangdong Provincial Center for Disease Control and Prevention, Guangdong Guangzhou 511400, China)

[Abstract] **Objective** To evaluate immunogenicity and safety of human papillomavirus (HPV) vaccine in Asia population. **Methods** English databases such as PubMed, Embase, Web of Science, Clinical trails and Cochrane Library, and Chinese databases such as CNKI and Wan Fang Data were searched from their inception to April 2022 for randomized controlled trials (RCTs) about immunogenicity and safety of HPV vaccine. Using flexible collocation of subject words and free words, the literature were searched and screened according to inclusion and exclusion criteria. Then quality of the literature finally included was assessed and the data were extracted. A meta-analysis was conducted to merge the assessments through Review Manager 5.4 and Stata14.0 software. **Results** 16 RCTs were included, and 25 485 subjects were involved in these studies. Meta-analysis showed that HPV vaccine had good immunogenicity; the RR (relative risk) of HPV16 specific serum conversion rate merged effect value was 43.74 (16.51-115.85) and that of HPV18 specific serum conversion rate merged effect value was 45.72 (8.78-238.13). In safety of HPV vaccine, the risks of local adverse events caused by bivalent HPV vaccine ($RR = 1.52, 95\%CI: 1.34-1.73$) and quadrivalent HPV vaccine ($RR = 1.38, 95\%CI: 1.20-1.59$) in the experimental group were higher than those in the control group. Also, the risks of systemic adverse events caused by bivalent HPV vaccine ($RR = 1.21, 95\%CI: 1.11-1.32$) and quadrivalent HPV vaccine ($RR = 1.13, 95\%CI: 0.99-1.30$) in the experimental group were higher than those in the control group. **Conclusion** In these women population who had been inoculated HPV vaccine, the positive serum antibody conversion rate after inoculation of HPV vaccine for Asian population is higher than that in those women who hadn't been inoculated the HPV vaccine, suggesting that inoculation of HPV vaccine can

[收稿日期]2023-06-19

[作者简介]胡晓明(1997—),男,在读硕士研究生,主要从事传染病学。

[通讯作者]孙九峰,主任技师。

improve individual's specific antibody level. However, the risks of local and systemic safety events caused by HPV vaccines in the experimental group are higher than those in the control group, suggesting that the safety problem of HPV vaccine should be emphasized.

[Key words] human papillomavirus; HPV vaccine; meta-analysis; immunogenicity; safety

宫颈癌是仅次于乳腺癌、结肠直肠癌和肺癌的四大女性常患癌症之一^[1]。据全球癌症研究机构统计,全球每年有约 34.2 万人死于宫颈癌,2020 年新发宫颈癌病例约 60.4 万例,其中 85% 以上新发和死亡病例发生于中低收入国家^[2],且宫颈癌的发病率和死亡率仍在逐年攀升^[3]。亚洲和大洋洲地区宫颈癌病例和死亡人数占全球一半以上,2020 年东南亚宫颈癌发病和死亡病例分别为 6.9 和 3.8 万,预计 2040 年新发和死亡病例将增加 44% 和 63%^[4]。

人乳头瘤病毒(human papilloma virus, HPV)病毒感染是引起宫颈癌的主要危险因素^[5],预防性 HPV 疫苗接种是宫颈癌防控目前公认最为经济的预防性手段,且已广泛获得许可并在全球范围内推广^[6]。截至 2019 年 10 月,全球已有 100 个国家将 HPV 疫苗接种纳入其国家疫苗免疫接种规划,但仅覆盖全球 30% 的人口,中低收入国家 HPV 疫苗的接种率远低于高收入国家^[7]。目前广泛开展的 HPV 疫苗相关临床试验^[8-10]及观察性研究^[11]多在欧洲^[12-14]、加拿大^[15]等西方发达国家,仅少数亚洲国家参与 HPV 疫苗有效性、安全性以及免疫原性的临床试验。因此,了解 HPV 疫苗在亚洲人群接种的免疫原性以及安全性有助于了解和评价疫苗在特定区域人群的预防效果。本研究对疫苗免疫原性及安全性进行荟萃分析,系统探索亚洲地区现有的 HPV 疫苗循证证据。

1 方法

1.1 文献来源及检索策略

本研究分别检索英文数据库(PubMed、Embase、Web of Science、Clinical Trails、Cochrane Library)和中文数据库(中国知网、万方、维普),自建库至 2022 年 4 月,关于亚洲人群进行的 HPV 疫苗安全性和免疫原性临床试验文献。其中英文检索词有 HPV vaccine、human papillomavirus vaccine、HPV-16/18、9/4-valent、quadrivalent human papillomavirus、nine-valent、safety、immunogenicity,中文检索词有人乳头瘤疫苗、二价 HPV 疫苗、四价 HPV 疫苗、

九价 HPV 疫苗、免疫原性、安全性。检索时主题词与自由词灵活搭配检索,PubMed 具体检索式为 #1 HPV vaccine OR human papillomavirus vaccine OR HPV-16/18 OR 9/4-valent OR quadrivalent human papillomavirus OR nine-valent; #2 safety OR immunogenicity; #3 Asia; #4 #1AND#2AND#3。

1.2 纳入排除标准

纳入标准:①在亚洲人群中进行的 HPV 疫苗安全性及免疫原性的随机对照试验(randomized controlled trials, RCT)研究;②研究对象为 9~45 岁的健康人群,不限性别;③结局指标:衡量疫苗免疫原性的指标为血清抗体阳转率,疫苗安全性指标为注射部位不良反应(疼痛、肿胀、红斑)和全身不良反应(关节疼痛、疲劳、头痛、肌肉疼痛、胃肠道症状、皮疹、荨麻疹)。排除标准:①无法获取全文或原始研究数据的文献;②数据重复发表的文献。

1.3 数据提取

通过对纳入的文献进行数据筛选并提取相关数据,系统评估 HPV 疫苗接种后血清抗体转阳率、局部(疼痛、肿胀、红斑)及全身性不良反应(关节疼痛、疲劳、头痛、肌肉疼痛、胃肠道症状、皮疹、荨麻疹)。提取数据包括作者、文献出版年份、国家、受试者性别和年龄、试验组和对照组的样本量等。两名研究员依据纳入与排除标准独立对纳入文献的方法学进行质量评估,评估过程中如有分歧,则通过讨论解决。

1.4 质量评价

两名研究人员使用 Cochrane 偏倚风险工具对每项纳入研究进行质量评估,如遇到分歧,则由第三位研究人员进一步调查和最终决策,使用“低”,“高”和“不清楚”进行偏倚风险分类评估,其中“+”代表偏倚风险低,“-”代表偏倚风险高,“?”代表偏倚风险不明确。

1.5 统计分析

使用 Review Manager5.4 和 Stata14.0 软件进行统计分析,纳入研究的结局均为分类变量,相对危险

度(RR)及 95%可信区间(CI)为效应统计量。对纳入研究进行基于卡方检验的异质性分析,同时结合 I^2 判断异质性大小,如果结果存在明显异质性 ($I^2>50\%$),则使用随机效应模型,并且进行敏感性分析。如果异质性不明显 ($I^2<50\%$),则使用固定效应模型。采用 Egger's 检验评估发表偏倚。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 文献检索结果

剔除重复文献后,各数据库共筛选得到文献

2 213 篇,重复、综述类、数据重复及不完整和研究人群、研究类型等不符合纳入标准文献被剔除,最终纳入 16 篇 RCT 研究文献,见图 1。

2.2 纳入文献的基本特征

纳入文献的研究人群全部为亚洲人群,纳入研究来自中国、马来西亚、日本、韩国、印度和孟加拉国,其中来自中国、日本和韩国的研究分别为 7、3 和 3 篇。纳入文献中二价和四价 HPV 疫苗的研究分别为 11 和 5 篇。二价和四价的 HPV 疫苗使用的疫苗佐剂分别为氢氧化铝佐剂(AS04)和无定形羟基磷酸盐硫酸铝佐剂(AAHS),见表 1。

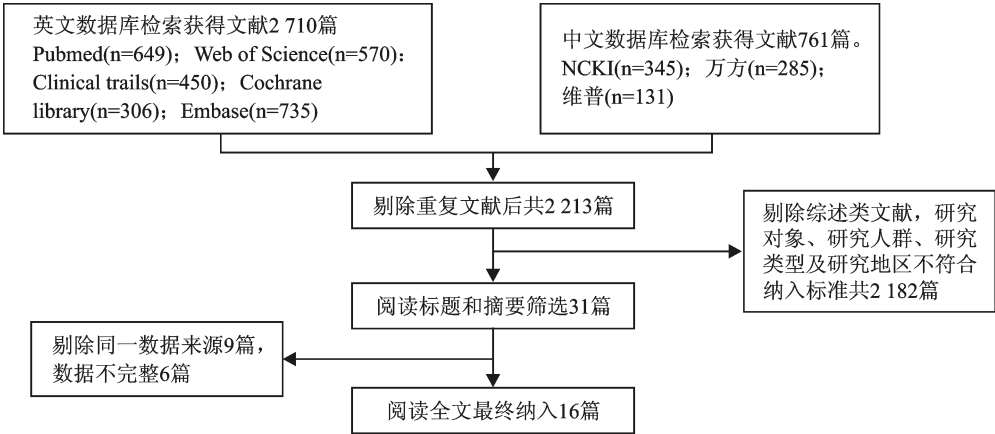


图 1 文献筛选流程图

Fig.1 Flow chart of literature screening

表 1 纳入 RCT 研究的基本特征

Table 1 Basic characteristics of included RCT studies

参考文献	国家	研究人群	人群年龄(岁)	疫苗成分	样本量(试验组/对照组)
Qiao Y L,2020 ^[16]	中国	女性	18~45	HPV16/18	3 689/3 683
Lim B K,2014 ^[17]	马来西亚	女性	18~35	HPV16/18	135/136
Konno R,2010 ^[18]	日本	女性	20~25	HPV16/18	516/519
Kim Y J,2010 ^[19]	韩国	女性	10~14	HPV16/18	160/161
Kim S C,2011 ^[20]	韩国	女性	15~25	HPV16/18	149/76
Khatun S,2012 ^[21]	孟加拉国	女性	9~13	HPV16/18	50/17
Bhatla N,2010 ^[22]	印度	女性	18~35	HPV16/18	176/178
Wu T,2015 ^[23]	中国	女性	18~25	HPV16/18	1 200/400
Ngan H Y,2010 ^[24]	中国	女性	18~35	HPV16/18	150/150
Zhu F,2014(a) ^[25]	中国	女性	9~17	HPV16/18	374/376
Zhu F,2014(b) ^[25]	中国	女性	26~45	HPV16/18	606/606
Zhu F C,2019 ^[26]	中国	女性	9~45	HPV16/18	3 026/3 025
Yoshikawa H,2013 ^[27]	日本	女性	18~26	HPV6/11/16/18	509/512
Chen W,2019 ^[28]	中国	女性	20~45	HPV6/11/16/18	1 503/1 503
Mikamo H,2019 ^[29]	日本	男性	16~26	HPV6/11/16/18	562/562
Li R,2012 ^[30]	中国	男性/女性	9~45	HPV6/11/16/18	302/298
Kang S,2008 ^[31]	韩国	女性	9~23	HPV6/11/16/18	117/59

不良事件的风险。结果显示试验组局部不良事件的发生率高于对照组($RR = 1.52$; $95\%CI: 1.34 \sim 1.73$),试验组发生全身性不良事件的风险也高于对照组($RR = 1.21$; $95\%CI: 1.37 \sim 1.32$),见表 3。对四价 HPV 疫苗进行汇总分析,试验组发生局部不良事件($RR = 1.38$; $95\%CI: 1.20 \sim 1.59$)和全身性不良事件($RR = 1.13$; $95\%CI: 0.99 \sim 1.30$)的风险均高于对照组,见表 4。分别对中国、日本及韩国三个国

家进行汇总分析,显示中国局部不良事件风险($RR = 1.33$; $95\%CI: 1.15 \sim 1.55$)低于日本($RR = 2.08$; $95\%CI: 1.53 \sim 2.82$)及韩国($RR = 1.79$; $95\%CI: 1.15 \sim 2.79$)。中国全身性不良事件风险($RR = 1.13$; $95\%CI: 1.04 \sim 1.23$)低于日本($RR = 1.36$; $95\%CI: 1.03 \sim 1.79$)和韩国($RR = 1.32$; $95\%CI: 1.11 \sim 1.58$)。

表 2 HPV 疫苗接种后特异性抗体转化率合并结果

Table 2 Merge results of specific antibody conversion rate after HPV vaccination

结局指标	疫苗类型	文献数量	研究人数	合并 $RR(95\%CI)$	I^2
HPV16	二价	8	3 157	32.08(11.02~93.44)	94%
	四价	4	3 202	62.47(25.22~154.75)	59%
	汇总	12	6 359	43.74(16.51~115.85)	95%
HPV18	二价	7	2 418	33.53(5.26~213.81)	98%
	四价	4	2 515	73.87(45.41~120.17)	0%
	汇总	11	4 933	45.72(8.78~238.13)	98%
HPV6	四价	4	2 437	67.11(41.57~108.32)	0%
HPV11	四价	4	2 454	119.44(49.21~289.92)	28%

表 3 二价 HPV 疫苗接种后不良事件合并结果

Table 3 Merge results of adverse events after inoculation of bivalent HPV vaccine

汇总项目	结局指标	文献数量	研究人数	合并 $RR(95\%CI)$	I^2
局部不良事件	疼痛	6	9 178	1.20(1.15~1.25)	45%
	红斑	6	9 178	1.67(1.42~1.97)	50%
	肿胀	6	9 178	2.06(1.88~2.26)	0%
	汇总	6	9 178	1.52(1.34~1.73)	94%
全身性不良事件	疲劳	6	8 836	1.10(1.05~1.16)	0%
	胃肠道症状	6	8 814	0.96(0.82~1.13)	41%
	头痛	6	8 814	1.03(0.97~1.11)	1%
	肌肉疼痛	6	8 815	1.63(1.36~1.95)	64%
	关节疼痛	6	8 814	1.54(1.24~1.91)	45%
	皮疹	4	1 777	1.24(0.67~2.32)	46%
	荨麻疹	4	1 777	1.27(0.64~2.53)	0%
	汇总	6	8 836	1.21(1.11~1.32)	76%

表 4 四价 HPV 疫苗接种后不良事件合并结果

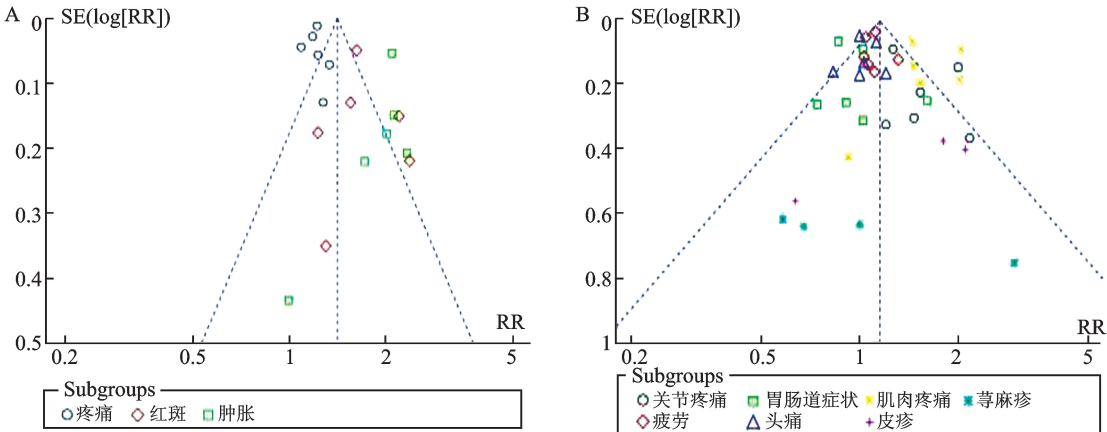
Table 4 Merge results of adverse events after inoculation of quadrivalent HPV vaccine

汇总项目	疫苗类型	文献数量	研究人数	合并 RR(95%CI)	I ²
局部不良事件					
	疼痛	3	4 710	1.28(1.08~1.51)	70%
	红斑	3	4 710	1.22(1.05~1.42)	0%
	肿胀	3	4 710	1.80(1.27~2.56)	59%
	汇总	3	14 130	1.50(1.37~1.64)	45%
全身性不良事件					
	疲劳	2	3 597	1.05(0.72~1.52)	44%
	胃肠道症状	2	3 597	0.94(0.72~1.23)	0%
	头痛	2	3 597	1.11(0.93~1.32)	0%
	肌肉疼痛	2	3 597	1.36(0.96~1.91)	23%
	关节疼痛	6	8 814	1.54(1.24~1.91)	45%
	皮疹	4	1 777	1.24(0.67~2.32)	46%
	荨麻疹	4	1 777	1.27(0.64~2.53)	0%
	汇总	9	14 130	1.13(0.99~1.30)	36%

2.6 发表偏倚

使用 Review manager 软件绘制漏斗图分析潜在发表偏倚,其中局部和全身性不良事件 Egger’s

检验显示 *P* 值分别为 0.534 和 0.191,表明纳入的研究不存在发表偏倚,见图 3。



注:A 图为局部不良事件;B 图为全身性不良事件

图 3 HPV 疫苗接种后不良事件的发表偏倚漏斗图

Fig.3 Funnel plot of publication bias of adverse events after HPV vaccination

3 讨论

3.1 HPV 疫苗接种现状

研究表明,HPV 疫苗接种可以有效预防 HPV 感染、生殖器疣、宫颈癌及癌前病变^[32-33]。截止 2014 年 10 月,北美洲 HPV 疫苗接种率为 53.4%、欧洲地区为 36.4%、大洋洲地区为 41.1%,在整个欧洲地区,所有的欧盟国家都将 HPV 疫苗纳入免疫接种规划^[34]。2021 年底拉丁美洲地区已有 44 个国家和地区将 HPV 疫苗纳入国家免疫接种规划^[35]。

而在亚洲地区,截止 2019 年 10 月,仅有 15 个国家和地区(韩国、日本、新加坡、泰国、孟加拉国、菲律宾等国家)将 HPV 疫苗纳入免疫接种计划^[36]。成本效益分析显示对亚洲地区青春女性实施 HPV 疫苗接种被证明具有明显效益^[36],是减少宫颈癌发生的重要举措。因此,应加快将预防性 HPV 疫苗纳入国家免疫规划。

3.2 HPV 疫苗的免疫原性

预防性二价和四价 HPV 疫苗通过刺激诱导机体产生针对 HPV 16、18 等的特定抗体,预防宫颈癌

和癌前期宫颈疾病。在免疫原性方面,不受受试者的年龄、性别及疫苗接种时间、剂次限制,HPV16、18的血清抗体转阳率均在90%以上,这一结果与在欧洲和美洲地区以及在非洲地区^[37-39]进行的研究一致。其血清抗体转阳率均在90%以上,表明疫苗在亚洲人群中产生的特异性抗体具有高度的免疫原性,受种族、地区的影响较小。一项对基于不同性别的四价HPV疫苗免疫原性Meta分析表明,四价HPV疫苗接种后HPV6/11/16/18的抗体滴度估计值平均能达到6~8^[40]。Li等^[41]通过Meta分析发现HPV疫苗在与其他疫苗同时接种时,HPV疫苗仍具有高度的免疫原性。

3.3 HPV疫苗的安全性

在疫苗安全性方面,二价和四价HPV疫苗对于健康个体比较安全,试验组局部以及全身性AE发生的风险上略高于对照组,接种HPV疫苗在局部以及全身性AE存在较低风险,而且疫苗局部事件以红斑以及肿胀发生更为常见。大多数局部和全身性AE发生为轻度或中度。非洲地区的研究表明注射部位疼痛在疫苗接种者中更常见^[38](疫苗接种组和对照组接种部位疼痛的报告率分别为55.9%和38.7%)。在一项多中心的研究中报道疫苗接种组与对照组注射部位AE的发生率分别为76.7%和46.3%,而疫苗接种组和对照组全身性AE上的发生率分别为39.4%和36.9%^[37],在欧洲和美洲^[39,42-43]进行的研究也表明疫苗接种组在全身性及局部的不良事件发生率略高于对照组。在我们的研究中,试验组局部以及全身性安全事件的发生略高于对照组。在一项对于二价和四价HPV疫苗安全性的Meta分析研究中表明,与安慰剂组相比,接种疫苗组发生局部安全性事件的可能性更高,这一结果与我们的研究一致^[44]。我们的荟萃分析表明,HPV疫苗对于亚洲人群存在局部以及全身性的AE风险,但疫苗接种的安全性处于可接受水平。

3.4 小结

本研究存在一定的局限性。首先,鉴于九价HPV疫苗的相关文献较少,无法开展相关分析。但根据已有的文献资料,本文纳入的文献均为二价或四价疫苗,一项在亚洲地区的亚组分析中表明,在九价HPV疫苗试验组有超过90%的受试者完成特异性血清转换,发生AE的风险程度比四价疫苗略高,

但对于预防HPV31/33/45/52/58持续性感染的有效率为90.4%~100%^[43]。另外在中国进行的一项开放标签的临床试验也表明受试者接种疫苗后完成特异性血清转换超过90%,表明九价疫苗在亚洲人群中接种具有较好的免疫原性^[45]。其次,每一项研究所纳入受试者的年龄各不相同,导致异质性增加,但Skinner等^[39]的研究中将受试者分为26~35岁和36~45岁年龄组,表明HPV疫苗对于预防两年年龄组轻度宫颈癌癌前病变有效性约80%。这表明不同年龄组的受试者接种HPV疫苗均可以产生不错的预防效果。最后,本文纳入的16篇文献来自六个亚洲地区,存在区域差异的风险。

综上所述,本项Meta分析表明在亚洲人群中接种预防性HPV疫苗的高免疫原性,疫苗的安全性可接受,但仍不可忽视,应积极号召民众进行预防性HPV疫苗免疫接种,预防HPV所致宫颈及外生殖器病变的危害。

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[中文编辑:向婉婉;英文编辑:杨周岐]