Review

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HPV-Related Cancer Vaccine Strategies: A Focus on China

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Abstract: Human papillomavirus (HPV) persistent infection is a major pathogenic factor for HPV-related cancers, such as cervical cancer (CC), vaginal cancer, vulvar cancer, anal cancer, penile cancer, and head and neck cancer (HNC). Vaccination against HPV is an effective measure to block the transmission of the virus and to prevent HPV infections and the occurrence of related cancers. Since the introduction of the world's first prophylactic HPV vaccine, there has been a decline in the incidence of HPV infections and associated cancers. Furthermore, there are currently ongoing developments of preventive vaccines that cover more HPV types, as well as the clinical application of therapeutic HPV vaccines. This article reviews the latest literature on the research progress, efficacy, and safety of HPV vaccines for these cancers, providing a reference for HPV vaccination strategy.

Keywords: HPV; vaccine; genital system; head and neck cancer

1. Introduction

In 1976, Harald Zur Hausen proposed that cervical cancer (CC) is related to infection with human papillomavirus (HPV). Over the following decades, extensive research was conducted on genital HPV, leading to the identification of carcinogenic HPV types [1]. HPV infection can lead to various diseases, including genital warts, respiratory papillomatosis, CC, vaginal cancer, vulvar cancer, anal cancer, penile cancer, and head and neck cancer (HNC) [2–4]. Since the first prophylactic HPV vaccine was introduced in 2006, 139 countries have incorporated HPV vaccination into their national immunisation programmes as of September 2024 [5]. However, globally, only 15% of young girls have been vaccinated against HPV [5].

Additionally, HPV vaccination programmes differ across various countries and regions. Addressing obstacles to vaccination, such as vaccine hesitancy and vaccine availability, along with enhancing the preventive and therapeutic efficacy of HPV vaccines, are effective approaches to improve vaccine coverage and the treatment of HPV-related cancers [6]. This article provides a review of HPV characteristics, HPV vaccines, HPV-related cancers, and the current situation and potential future developments for HPV vaccines.

2. Characteristics of HPV

2.1. Structural Composition

HPV is a relatively small, non-enveloped icosahedral virus, with a diameter of approximately 52-55 nm [7]. The viral genome is a single double-stranded circular deoxyribonucleic acid(DNA) molecule, around 8 kilobase pairs (kb) in size [7], capable of encoding six early regulatory proteins (E), two late structural proteins (L), and one non-coding upstream regulatory region (URR) [8]. The early regulatory proteins include E1, E2, E4, E5, E6, and E7[9]. They play important roles in the processes of viral replication, transcription, translation regulation, and cellular transformation, particularly E6 and E7 [9]. The E1 and E2 proteins form a high-affinity hexameric initiation complex that facilitates the unwinding of the double-stranded DNA, thereby initiating viral DNA replication [8]. The E2 protein assists in the integration of viral DNA into the host chromosome [8]. Co-expression

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of E4 and E1 proteins can halt the cell cycle of differentiated cells at the G2 phase [10]. The E5 protein promotes cell proliferation by activating epidermal growth factor receptor (EGFR) signalling and evades host immunity by inhibiting the formation of major soluble complex molecules, including viral peptides, interferon κ (IFN κ), and growth signalling pathways [11,12].

The p53 protein is an oncogene suppressor in human cells; E6 can lead to the degradation of the p53 protein and can also induce the upregulation of human telomerase reverse transcriptase (hTERT) expression and cell cycle dysregulation [13]. The E7 protein is made up of three conserved regions (CR); CR1 and CR2 are responsible for binding to and degrading retinoblastoma protein (pRb) [14]. The CR3 region affects cell cycle and apoptosis [14]. The late structural proteins include L1 and L2 [9], with their corresponding gene regions occupying nearly 40% of the viral genome downstream of the early region [9]. The L1 protein is the major component of the capsid, forming the viral shell and facilitating the binding of the virus to host cells, while the L2 protein assists in the self-assembly of L1 into the capsid and plays a role during the infection process [15,16]. The URR is believed to be the most variable part of the viral genome, containing binding sites for transcription factors and viral E1 and E2 proteins, which control viral replication and gene expression [2].

2.2. HPV Classification

The papillomaviridae family currently encompasses approximately 450 HPV types, with 225 HPV types identified [17]. Based on the homology of the L1 gene nucleotide sequences, HPV is phylogenetically classified into five genera [17]: Alphapapillomavirus (α), Betapapillomavirus (β), Gammapapillomavirus (γ), Mupapillomavirus (μ), and Nupapillomavirus (υ) [17]. Among them, α-HPV (65 types) is isolated from the skin or mucosa of genital and oral lesions and is a cause of many anogenital cancers in humans and primates [18]. The others originate from skin samples, primarily β-HPV (54 types) and γ-HPV (98 types) [18]. α-HPV is further classified into low-risk HPV (LR-HPV) and high-risk HPV (HR-HPV) based on carcinogenic potential [9]. LR-HPV includes HPV 6/11/42/43/44, with HPV 6 and 11 causing benign proliferative diseases in mucosal regions, such as condyloma acuminatum and conjunctival papilloma [9]. HR-HPV includes HPV 16/18/31/33/35/39/45/51/52/56/58/59/68, and approximately 4.5% of global cancers are attributed to persistent HR-HPV infection [2,9].

2.3. History of Epidemics

In most cases, HPV infection is transient and asymptomatic [19]. When the skin or mucosa has minor damage, HPV can infect basal layer cells at the point of injury, utilising the reducing environment of the cell to de-encapsulate and transport DNA into the nucleus, ensuring that the entire lifecycle of HPV remains resistant to cell lysosomal enzymes, thereby reducing clearance by the host [20–22]. Due to its unique molecular virological features and immune evasion mechanisms, HPV spreads widely and has a high prevalence among the population [23]. HPV is primarily transmitted through sexual contact, with infection rates largely dependent on the age and sexual behaviour of the population [20]. Additionally, it can be transmitted via non-sexual contact and mother-to-child transmission, such as direct skin contact with an infected person sharing personal items, or from mother to newborn during childbirth (very rarely) [20].

Approximately 90% of HPV infections are cleared or enter a dormant state within the first one to two years after infection through the host's humoral and cellular immune responses [24]. After the host is infected with HPV, antibodies are produced, but as time passes, these antibodies may no longer be sufficient to resist the virus, leading to reinfection [25]. Young sexually active women have the highest cervical HPV infection rates, with the peak occurring below the age of 25 [26]. The infection rate gradually decreases with age, stabilising in middle age, and slightly increases after the age of 65 [27]. The epidemiology of HPV in men is somewhat different from that in women. Common factors associated with HPV infection in men include human immunodeficiency virus (HIV) infection, number of sexual partners, lack of condom use, race, ethnicity, and circumcision status [6].

3. HPV Vaccine

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3.1. Globally Approved Prophylactic HPV Vaccines

Vaccination against HPV is the most economical and effective means of preventing HPV transmission. HPV vaccines are categorized into prophylactic and therapeutic types, with the former being widely used globally and no therapeutic vaccines currently approved for market [9,28]. There are two main prophylactic HPV vaccines approved worldwide: Cervarix® from GlaxoSmithKline and Gardasil® from Merck, with Gardasil® available in both 4-valent and 9-valent versions [29–31] (see Table 1).

Cervarix® was licensed by the European Medicines Agency (EMA) in 2007 and by the U.S. Food and Drug Administration (FDA) in 2009, becoming the first cervical cancer vaccine approved in Japan that year [32]. According to GlaxoSmithKline, the vaccine has been approved by 107 regulatory agencies, covering 136 countries worldwide [29]. This indicates Cervarix®'s wide acceptance and application globally. Despite its global approval, Cervarix® has been withdrawn from the U.S. market due to low demand [29]. Cervarix® effectively prevents HPV16 and HPV18 infections [30], which cause 70% of cervical cancers [30]. It is suitable for females aged 9-45 [29].

Gardasil®, a 4-valent HPV vaccine, was approved by the FDA and the European Union in 2006. It was the first commercially available HPV vaccine, suitable for females aged 9-45, and prevents diseases caused by HPV infection [33]. Besides HPV16 and 18, Gardasil® also prevents approximately 90% of genital warts caused by HPV6 and 11 infections [34].

Gardasil 9® was licensed by the FDA in 2014 and the European Union in 2015 [32]. It covers five additional HPV types (HPV31/33/45/52/58), providing broader protection [35]. Public information shows that Gardasil 9® has been approved for use in over 70 countries. Initially approved for females aged 9-45 to prevent HPV-related diseases [31], its use has been extended to males in the same age group for preventing HPV-associated diseases such as anal cancer, oropharyngeal cancer, and head and neck cancer [31].

Table 1. Globally approved prophylactic HPV vaccines.

Valency(Brand name/manufacturer)	2vHPV(Cervarix®/GlaxoSmithKline)	4vHPV(Gardasil®/Merck)	9vHPV(Gardasil9®/Merck)
Component content	Per dose contains: HPV 16 L1 protein 20μg, HPV 18 L1 protein 20μg	Per dose contains: HPV 6 L1 protein 20μg, HPV 11 L1 protein 40μg, HPV 16 L1 protein 40μg, HPV 18 L1 protein 20μg.	Per dose contains: HPV 6 L1 protein 30μg, HPV 11 L1 protein 40μg, HPV 16 L1 protein 40μg, HPV 18 L1 protein 40μg, and HPV 31/33/45/52/58 L1 proteins each 20μg.
Expression system	Baculovirus	Saccharomyces cerevisiae	Saccharomyces cerevisiae
Target population	Women aged 9-45	Women aged 9-45	Women and men aged 9-45
Immunisation schedule	Three doses at months 0, 1, and 6 (for girls aged 9-14, two doses at months 0 and 6), each dose being 0.5 ml	Three doses at months 0, 2, and 6, each dose being 0.5 ml	Three doses at months 0, 2, and 6 (for girls aged 9-14, two doses at months 0 and 6), each dose being 0.5 ml
Adjuvant	AS04 [containing 3-O-desacyl-4'-monophosphoryl lipid A, aluminium hydroxide]	Aluminium phosphate sulphate	Aluminium phosphate sulphate
Ingredient	Sodium chloride, disodium dihydrogen	Aluminium (amorphous	Aluminium (amorphous aluminium

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	phosphate dihydrate, water for injection	aluminium hydroxyphosphate sulphate adjuvant), sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injection	hydroxyphosphate sulphate adjuvant), sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injection
Prevented diseases	Cervical pre-cancerous lesions and cervical cancer caused by HPV16/18 infection	Pre-cancerous lesions, cancers, and genital warts caused by HPV6/11/16/18 infection	Pre-cancerous lesions, cancers, and genital warts caused by HPV infection types 6, 11, 16, 18, 31, 33, 45, 52, and 58

Note: HPV, human papillomavirus.

3.2. Vaccines Approved in China

Currently, there are five prophylactic HPV vaccines available in China [5,36–38]. All these vaccines are administered via intramuscular injection, with the deltoid muscle of the upper arm being the preferred site [39]. Cervarix® received approval from the China Food and Drug Administration (CFDA) in 2016, becoming the first HPV vaccine approved to prevent cervical cancer in China [40]. Gardasil's 4-valent and 9-valent versions were approved for the Chinese market in 2017 and 2018, respectively [39]. In late August 2022, Gardasil 9® expanded its age range in China, extending its use from females aged 16-26 to those aged 9-45 [39].

Additionally, two domestically produced prophylactic HPV vaccines have been approved for use in China: Cecolin® from Xiamen Innovax Biotech Co., Ltd. and WalrinVax® from Yunnan Walvax Biotechnology Co., Ltd. Cecolin®, approved in China on December 30, 2019, is the first HPV vaccine developed independently in China [41]. It is suitable for females aged 9-45 and targets HPV16 and 18, preventing cervical cancer and other related diseases caused by these two types [41]. On October 4, 2024, the WHO announced that Cecolin® could be used with a single-dose vaccination schedule [42]. However, China has not yet approved a single-dose immunization program for HPV vaccines. WalrinVax®, approved in China on March 22, 2022, also targets HPV16 and 18, providing more options for cervical cancer prevention [41] (see Table 2). On August 2, 2024, WalrinVax® achieved another significant milestone by receiving WHO prequalification [43].

Table 2. Preventive HPV vaccines produced in China and approved for listing.

Valency(Brand name/manufacturer)	2vHPV(Cecolin®/ Innovax Biotech)	2vHPV(WalrinVax®/ Zerun biotech)
Component content	Per dose contains: HPV 16 L1 protein 40μg, HPV 18 L1 protein 20μg	Per dose contains: HPV 16 L1 protein 40μg, HPV 18 L1 protein 20μg
Expression system	Escherichia coli	Pichia pastoris
Target population	Women aged 9-45	Women aged 9-30
Immunisation schedule	Three doses at months 0, 1, and 6 (for girls aged 9-14, two doses at months 0 and 6), each dose being 0.5 ml	Three doses at months 0, 2, and 6 (for girls aged 9-14, two doses at months 0 and 6), each dose being 0.5 ml
Adjuvant	Aluminium hydroxide	Aluminium phosphate
Ingredient	Sodium chloride, disodium dihydrogen phosphate dihydrate, sodium hydrogen phosphate dihydrate,	Sodium chloride, histidine, polysorbate 80, water for injection

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	polysorbate 80, water for injection	
Prevented diseases	Cervical pre-cancerous lesions and cervical cancer caused by HPV16/18 infection	Cervical pre-cancerous lesions and cervical cancer caused by HPV16/18 infection
Time of approval and listing in China (year)	2019	2022

Note: HPV, human papillomavirus.

3.3. Vaccine Types under Development Globally: Prophylactic and Therapeutic

All licensed prophylactic HPV vaccines contain virus-like particles (VLPs) formed by the self-assembly of the L1 protein from HPV. Since these vaccines do not include viral genomes, they offer a higher safety profile than live attenuated vaccines [44]. Prophylactic vaccines can induce neutralising antibodies in the human body, producing a memory effect that protects against HPV infection [9]. The antibody titres generated post-vaccination are ten times higher than those following natural infection, peaking one month after the last dose and reaching a plateau 18-24 months later [9].

Therapeutic HPV vaccines activate specific cellular immunity by presenting antigens to immune cells, breaking the immune tolerance of chronic infections, and rebuilding or enhancing the patient's immune response mechanisms. This helps eliminate pathogens and cancer cells, thereby blocking the spread and metastasis of cancer [45]. Unlike prophylactic HPV vaccines, therapeutic HPV vaccines aim to induce specific cellular immunity rather than humoral immunity (neutralising antibodies) [46]. Based on the source of tumour antigen expression, therapeutic HPV vaccines can be categorised into four types: nucleic acid vaccines (including DNA and mRNA vaccines), subunit vaccines (including peptide and protein vaccines), recombinant vector vaccines (including bacterial and viral vector vaccines), and dendritic cell vaccines [45]. Currently, the development of new prophylactic and therapeutic HPV vaccines at various clinical stages is summarised in Tables 3 and 4 [41,47,48].

Table 3. Globally in-clinical-stage prophylactic HPV vaccines.

Name	Research and development stage	Antigen information	Research and development unit
AAVLP-HPV	Phase I	L1 protein of HPV 16 and HPV 18	CureVac AG
PANHPVAX	Early Phase I	L1 protein of HPV 16 and HPV 18	Panacea Biotec
VA-HPV	Phase II	L1 protein of HPV 16 and HPV 18	Vaxart, INC.
TheraVax	Some of the studies are in phase I/II clinical trials	The L1 and E7 proteins of HPV	TheraVax, INC.
MVA-HPV	Phase II	L1 protein of HPV 16 and HPV 18	Multiple universities and research institutes worldwide

Note: HPV, human papillomavirus; INC, incorporated.

Table 4. Globally in-clinical-stage therapeutic HPV vaccines.

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Name	Research and development stage	Antigen information	Research and development unit
VGX-3100	Phase III	Two plasmids encoding E6 and E7 protein of HPV16 and 18	Inovio Pharmaceuticals
INO-3112	Phase II	It contains two plasmids, VGX-3100 and INO-9012, INO-9012 expresses IL-12	Inovio Pharmaceuticals
MVA-E2	Phase III	The core antigen is the E2 protein of HPV	The University of Oxford and its partners
BNT113	Phase II	HPV L1 protein and HPV E7 protein	BioNTech
ChAdOx1-HPV+MVA-HPV	Phase II	HPV E6 protein and HPV E7 protein	The University of Oxford and its partners
Ad26. HPV16/18	Phase II	The E7 protein of HPV types 16 and 18	Janssen Pharmaceuticals
SGN-00101	Phase II	HPV E6 and E7 proteins	ADC Therapeutics S.A.
GX-188E	Phase II	HPV E6 and E7 proteins	Genexine,Inc.
GENUINE	Phase II	The E6 and E7 proteins of HPV types 16 and 18	Merck & Co.
TRINITY	Phase II	HPV E6 and E7 proteins	Inovio Pharmaceuticals
ISA101b	Phase II	HPV type 16 E7 protein	ISA Pharmaceuticals
PDS0101	Phase II	The E6 and E7 proteins of HPV types 16 and 18	PDS Biotechnology
HB-201	Phase II	The E6 and E7 proteins of HPV type 16	Gen009
HB-202	Phase II	The E6 and E7 proteins of HPV types 16 and 18	Gen009
DPX-E7 vaccine	Phase II	E7 protein of HPV type 16	ImmuNext
ADXS11-001	Phase II	The E7 protein of HPV types 16 and 18	Advaxis,INC.
TG4001	Phase II	The E6 and E7 proteins of HPV type 16	Transgene
TA-CIN Vaccine	Phase I	L1 protein of HPV	Transgene
pNGVL4aCRTE6E7 L2	Phase I	The E6 and E7 proteins of HPV type 16	Butantan Institute
P16-37-63	Phase I	p16 protein,the E6 and E7 proteins of HPV type 16	CureVac
GTL001	Phase I	HPV E6 and E7 proteins	GlaxoSmithKline
GL-0810	Phase I	HPV 16 E6 and E7 proteins	Genexine, INC.
VB10.16	Phase II	L1 proteins of HPV 16 and 18	VBI Vaccines, INC.
pBI-1101	Phase II	HPV 16 E6 and E7 proteins	Probio Medical
NWRD08	Phase I	E6 and E7 proteins of HPV16 and 18	Novartis

Note: HPV, human papillomavirus; INC, incorporated.

3.4. Vaccine Candidates under Development in China

China continues to develop new prophylactic HPV vaccines, with over 10 domestically produced HPV vaccines currently in various clinical stages [32,49,50] (see Table 5). Due to factors such as the characteristics of HPV, immune evasion, vaccine mechanisms, clinical challenges, and existing treatment methods, there are currently no therapeutic HPV vaccines officially available for use in the population. However, domestic companies have begun researching different therapeutic HPV vaccines [51] (see Table 6).

Table 5. In-clinical-phase preventive HPV vaccines in China.

Name	Development clinical phase	Registration number	Development unit
Recombinant bivalent HPV (types 16/18) vaccine (Hanseniaspora yeast)	Phase I has been completed	CTR20182556	Jiangsu Recbio Technology Co., Ltd.

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Recombinant bivalent HPV (types 6/11) vaccine (Hanseniaspora yeast)	Phase I has been completed	CTR20210109	Jiangsu Recbio Technology Co., Ltd.
Recombinant trivalent HPV (types 16/18/58) vaccine(Escherichia coli)	Phase III	CTR20201795	Beijing Health Guard Biotechnology INC.
Recombinant quadrivalent HPV (types 6/11/16/18) vaccine(Hanseniaspora yeast)	Phase III	CTR20221050	Shanghai Bovax Biotechnology Co., Ltd.
Recombinant quadrivalent HPV (types 16/18/52/58) vaccine(Pichia pastoris)	Phase II has been completed	CTR20190482	Shanghai Institute of Biological Products Co., Ltd.
Recombinant quadrivalent HPV (types 6/11/16/18) vaccine(Hanseniaspora yeast)	Phase III	CTR20171662	Chengdu Institute of Biological Products Co., Ltd.
Recombinant quadrivalent HPV (types 6/11/16/18) vaccine(Hanseniaspora yeast)	Phase III has been completed	CTR20171662	Chengdu Institute of Biological Products Co., Ltd./ Beijing Institute of Biological Products Co., Ltd.
Recombinant nine-valent HPV (types 6/11/16/18/31/33/45/52/58) vaccine(Escherichia coli)	Phase III	CTR20210947	Jiangsu Recbio Technology Co., Ltd.
Recombinant nine-valent HPV (types 6/11/16/18/31/33/45/52/58) vaccine(Escherichia coli)	Phase III (women aged at 9-26year)	CTR20220679	Beijing Health Guard Biotechnology INC.
Recombinant nine-valent HPV (types 6/11/16/18/31/33/45/52/58) vaccine(Escherichia coli)	Recruitment completed (Chinese male participants)	CTR20223306	Beijing Health Guard Biotechnology INC.
Recombinant nine-valent HPV (types 6/11/16/18/31/33/45/52/58) vaccine(Escherichia coli)	Application for market authorization submitted	CXSS2400088and CXSS2400089	Xiamen Innovax Biotech Co., Ltd. / Xiamen University
Recombinant nine-valent HPV (types 6/11/16/18/31/33/45/52/58) vaccine(Hanseniaspora yeast)	Phase III	CTR20242197	Shanghai Bovax Biotechnology Co., Ltd.
Recombinant nine-valent HPV (types 6/11/16/18/31/33/45/52/58) vaccine(Pichia pastoris)	Phase III	CTR20200365	Shanghai Zerun Biotechnology Co., Ltd.
Recombinant 11-valent HPV (types 6/11/16/18/31/33/35/39/45/52/58) vaccine(Hanseniaspora yeast)	Phase III	CTR20221258	Sinopharm Zhongsheng Biotechnology Research Institute Co., Ltd./ Beijing Institute of Biological Products Co., Ltd./ Chengdu Institute of Biological Products Co., Ltd.
Recombinant 14-valent HPV (types 6/11/16/18/31/33/35/39/45/51/52/56/58/59) vaccine (Insect cell)	Phase II	SCT1000	Sinocelltech Group Ltd.
Recombinant 15-valent HPV (types (6/11/16/18/31/33/35/39/45/51/52/56/58/59/68) vaccine(Escherichia coli)	Phase I	CTR20241041	Liaoning Chengda Biotech Co., Ltd./Beijing Health Guard Biotechnology INC.
Recombinant 15-valent HPV (types 6/11/16/18/31/33/35/39/45/51/52/56/58/59/68) vaccine(Hanseniaspora yeast)	Phase I	CTR20242006	Shanghai Bovax Biotechnology Co., Ltd.

Note: HPV, human papillomavirus; CTR, clinical trial registry; CXSS, clinical study summary synopsis; SCT, stem cell therapy; Co., Ltd., company limited; INC, incorporated.

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Table 6. Therapeutic HPV vaccines in development within China.

Product name (registration number)	Vaccine type	Indication	Clinical development stage	Development unit
VGX-3100(CTR20201547)	DNA	HPV16/18 infection-related cervical HSIL	Phase III	Inovio Pharmaceuticals, Inc./Alliance Medical Products INC./Beijing Apollo Saturn Biomedical Technology Co., Ltd.
NWRD08(CTR20240040)	DNA	Cervical HSIL with HPV16 and/or HPV18 positivity	Phase I	Newish Biotechnology (Wuxi) Co., Ltd.
AFN0328(CXSL2400268 and CXSL2400288)	mRNA	Cervical lesions associated with HPV16/18 infection	Clinical trial approval	Hefei Afana Biotechnology Co., Ltd./ Anhui Anke Biotechnology (Group)Co., Ltd.
LY01620(CTR20243545)	mRNA	Treatment of HPV16-related cervical HSIL	Phase I	Nanjing Geneleap Biotech Co., Ltd.
SYS6026(CXSL2300296 and CXSL2300297)	mRNA	Cervical lesions associated with HPV16/18 infection	Clinical trial application	CSPC Megalith Biopharmaceutial Co., Ltd.
ARC01(CXSL2300755)	mRNA	Advanced, unresectable, recurrent or metastatic solid tumours with HPV16 positivity	Phase I	Nanjing Auro Biotechnology Co., Ltd.

Note: HPV, human papillomavirus; CTR, clinical trial registry; CXSL, clinical study summary letter; DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; HSIL, high-grade squamous intraepithelial lesions; Co., Ltd., company limited; INC, incorporated.

4. HPV-Related Cancers

HPV infection is a cause of various cancers, including anogenital cancers (cervical, vaginal, vulvar, penile, and anal cancers) and head and neck cancers (oral cavity, oropharyngeal, and laryngeal cancers) [33]. Research indicates that over 90% of cervical and anal cancers, more than 70% of oropharyngeal cancers, approximately 70% of vulvar and vaginal cancers, and over 60% of penile cancers are associated with HPV infection [52,53]. Currently, for HPV-related cancers, apart from cervical cancer, there have been no proposals for implementing different vaccination programmes and schedules for various tumour types. However, HPV vaccination programmes vary across different countries and regions. The currently administered HPV vaccines cover the major high-risk HPV types, thus addressing HPV-related cancers, and have already achieved some interim results.

4.1. Cervical Cancer(CC)

CC is the fourth leading cause of cancer-related mortality among women globally [3]. In 2022, there were approximately 661,021 new cases of CC worldwide and about 348,189 deaths, with around 90% of cases occurring in low- and middle-income countries [3]. Progress in reducing the burden of CC in these regions has been slow due to several factors, including the slow expansion of HPV vaccination coverage, low rates of CC screening and early diagnosis, the cost of HPV vaccines, adverse reactions from previous vaccinations for other diseases, and political issues [54]. In developed countries, there has been a significant decline in the incidence and mortality rates of CC in recent years, attributed to early screening and HPV vaccination among women [33].

A study from Finland regarding the effectiveness of the 2-valent and 4-valent HPV vaccines found that there were no cases of CC or other HPV-related cancers among the vaccinated population, while the incidence rates in the unvaccinated population were 6.4 per 100,000 and 8.0 per 100,000 for CC and other HPV-related cancers, respectively [55]. A retrospective analysis by Steben et al. [56]

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over the past decade in Canada assessed the impact of the 4-valent HPV vaccine on HPV infection and prevalence, revealing an 86% reduction in the incidence of cervical intraepithelial neoplasia (CIN) among vaccinated individuals. A 2020 study in Sweden showed that women who received at least one dose of the 4-valent HPV vaccine had a 53% lower incidence of CC compared to those who were unvaccinated [57]. A domestic study on HPV vaccination indicated that the efficacy of the HPV vaccine in protecting Chinese women aged 20-45 against persistent cervical HPV infection was 97.5% over 6.5 years [58]. Furthermore, the 9-valent HPV vaccine demonstrated an efficacy of up to 96.7% in preventing infections related to HPV types 31, 33, 45, 52, and 58, as well as a high efficacy of 96.3% in preventing HPV-related CC [59]. This highlights the significant impact of HPV vaccination in preventing CC and reducing its incidence, while the continued development of vaccines covering more HPV types and expanding vaccination coverage remains crucial.

4.2. Vaginal Cancer

Vaginal cancer is relatively rare, accounting for 1% to 2% of all malignancies of the female reproductive system [60,61]. Up to 90% of vaginal cancers are associated with high-risk HPV [62,63]. In 2022, there were 18,800 new cases of vaginal cancer globally, resulting in 8,238 deaths [3].

A study by Bertoli et al. [64] that compared the incidence of vaginal cancer before and after the approval of the HPV vaccine in 2006 found a significant decrease of 15.6% in high-grade squamous intraepithelial lesions (HSIL) among women under 30 years old. The incidence of squamous cell carcinoma (SCC) in the vagina fell from 0.5 per 100,000 (1978-1982) to 0.3 per 100,000 (2013-2017). Jacqueline et al. [65] reported that within 17 years following the introduction of the HPV vaccine in the United States, the incidence of vaginal HSIL decreased by 19.1% annually among females aged 15-19. A study from Denmark [66] established a follow-up cohort of 514,537 women aged 17; it compared the incidence of HSIL of the vulva and vagina, revealing an 84% reduction in vaginal HSIL among the 260,571 (50.6%) women who were vaccinated before age 17, compared to unvaccinated women. This was the first observational study to report the effectiveness of HPV vaccination in preventing vaginal HSIL. Since vaginal cancer is less common than vulvar cancer, further research is needed to evaluate the protective effects of HPV vaccination against vaginal cancer.

4.3. Vulvar Cancer

Vulvar cancer comprises 2% to 5% of all malignancies of the female reproductive system and is more common in postmenopausal women [67]. In 2022, the global incidence of vulvar cancer was 47,342, with 18,579 deaths [3]. The aetiology remains unclear, but it is primarily associated with HPV infection (mainly HPV types 16 and 18), increasing age, immunosuppression, and smoking[63,67].

A study conducted by Garland et al. [68] involving 6,463 women aged 16-24 found that the protection rate of the 4-valent HPV vaccine against HPV types 6/11/16/18 related high-grade vulvar intraepithelial neoplasia (VIN) was 100%. Giuliano et al. [69] confirmed in a sample of 10,147 that the 9-valent vaccine reduced the risk of high-grade VIN associated with HPV by 100%. Due to the rarity of high-grade VIN caused by other HPV types, the protective effect of the 9-valent vaccine was predominantly attributed to high-grade VIN caused by HPV type 16, with no statistically significant protection against lesions caused by other types [69]. Research has evaluated the effectiveness of HPV vaccination in preventing the recurrence of vulvar HSIL; results showed that the recurrence rate after surgical treatment for vulvar HSIL was 19% in vaccinated women and 32% in unvaccinated women [70], although the reduction in recurrence rate was not significant. Among young women who were uninfected with HPV, the effectiveness of vaccination in preventing HPV-related infections exceeded 90%, but such pronounced protective effects were not observed in middle-aged women [71]. The protective role of HPV vaccination against vulvar cancer is well supported by evidence, indicating that vaccination can reduce the risk of vulvar lesions by over 90% for women without prior HPV infection, thus contributing to the prevention of vulvar cancer.

4.4. Anal Cancer

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In recent years, the incidence of anal cancer worldwide has been increasing, particularly among men who have sex with men (MSM), HIV-infected individuals, HPV-infected individuals, and patients with gynecological cancers [6,72,73]. In 2022, the global incidence of anal cancer was 54,194 cases, with 21,960 deaths [3]. Anal cancer is primarily caused by HPV infection (80%), with HPV16 being the most common type [74]. The HPV infection and transformation patterns in anal cancer are similar to those in cervical cancer (CC) [75]. Most anal cancers are SCC, occurring mainly in the anal canal and surrounding areas [76].

A clinical trial conducted in Costa Rica [77] randomly assigned 7,466 female participants aged 18-25 to receive either a quadrivalent HPV vaccine or a hepatitis A vaccine as a control. Anal swabs were taken from the study subjects for HPV DNA testing in the fourth year, and an analysis of the results for 4,210 participants found that the vaccine provided 62.0% protection against anal HPV 16/18 infections [77]. For 1,989 participants who were HPV 16/18-negative at baseline and received the full vaccination, the vaccine's protection rate against anal HPV 16/18 infections was 83.6% [77]. Swedish et al. [78] studied 202 MSM aged 20-72 with postoperative high-grade anal intraepithelial neoplasia (HGAIN) who were vaccinated with the HPV vaccine and followed for two years. Compared to those who did not receive the vaccine, those who completed three doses of the quadrivalent HPV vaccine after surgery had a hazard ratio (HR) of 0.52 for HGAIN recurrence, suggesting that vaccination may prevent HGAIN recurrence. Another randomized controlled study involving 237 MSM aged 16-26 found that the incidence of anal intraepithelial neoplasia (AIN) or anal cancer in those vaccinated with the quadrivalent HPV vaccine was only 2.0 per 100,000 over seven years, compared to 90.6 per 100,000 in the placebo group [79]. Additionally, the effectiveness of at least one dose of the HPV vaccine in preventing anal HPV infections was 59% for males aged ≤18 and 18% for males aged >18 [80], indicating that males should receive the HPV vaccine at an early age.

4.5. Penile Cancer

Penile cancer is extremely rare but has a high disability rate [81]. In 2022, there were 37,699 new cases of penile cancer globally, with 13,729 deaths [3]. HPV infection is considered a significant risk factor for penile cancer, with HPV16 being the most common subtype [82]. In a clinical trial conducted by Giuliano et al. [83], which included 4,068 males aged 16-26 from 18 countries, it was found that among those who received all three doses of the quadrivalent HPV vaccine and had negative HPV 6/11/16/18 DNA in pre-vaccination perianal-genital swabs or biopsy samples, three cases of penile intraepithelial neoplasia (PIN) were observed, all of which were in the control group.

A cross-sectional study of 687 MSM tested for HPV in penile swab specimens compared the HPV infection rates between vaccinated and unvaccinated individuals. The results showed that the HPV infection rate in MSM vaccinated before the age of 18 was significantly lower than that in unvaccinated individuals, with an efficacy of 85% in preventing quadrivalent HPV-related infections [84]. Further clinical trials with longer observation periods or larger sample sizes are needed to assess the protective effect of the vaccine against penile cancer.

4.6. Head and Neck Cancer (HNC)

In HNC, HPV has the highest attributable risk for oropharyngeal cancer, while the association with other cancer types is relatively low [9]. In 2022, there were 946,456 new cases of HNC and 482,001 deaths [3]. Approximately 90% of these cases are head and neck squamous cell carcinoma (HNSCC) [3]. The incidence of HNSCC has been rising primarily due to HPV infection, particularly HPV16 and HPV18 [85]. Additionally, tobacco use, chronic alcohol consumption, mechanical irritants, radiation exposure, and various occupational exposures contribute to the increased incidence of HNC [86]. Epstein-Barr virus and hepatitis B virus are other pathogenic factors for HNC, with Epstein-Barr virus considered a biomarker for nasopharyngeal carcinoma [87,88].

A study by Chaturvedi et al. [89] involving 8,067 participants in the National Health and Nutrition Examination Survey(NHANES) from 2011 to 2014 found that four years after vaccination, the oral HPV 6/11/16/18 infection rate was significantly lower in the HPV vaccine group compared to

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the unvaccinated group, especially among men. Schlecht et al. [90] reported that the oral HPV 6/11/16/18 infection rate was reduced by 83% in adolescent females who received more than one dose of the quadrivalent vaccine. Research on 1,784 high school students aged 14-17 in Colombia [91] found that the oral HPV16 infection rate was reduced by 72% in those who received two doses of the quadrivalent HPV vaccine. Notably, the risk of oral HPV16 infection was higher in males, with the vaccinated group consisting entirely of females and 88.7% of the unvaccinated group being male [91]. Chaturvedi et al. [92] suggested that the HPV vaccine may provide herd immunity, with the decrease in oral HPV infections among males potentially attributed to increased vaccination uptake among females, while the lack of significant herd immunity for females may be due to the low prevalence of oral HPV infections in women.

Modelling studies on HPV vaccination among males in the United States indicated that, at the current vaccination rate, if coverage were to increase to 80%, the incidence of HPV-related oropharyngeal cancer is expected to decline significantly after 2060 [93]. We believe that with the implementation of HPV vaccination, reductions in smoking rates, promotion of safe sexual practices, and early accurate diagnoses, the incidence of HNC will significantly decrease in the future.

5. The Present and Future of HPV Vaccines

5.1. HPV Vaccination Status and Vaccination Recommendations

In 2018, the World Health Organization (WHO) issued a global call to action for the elimination of CC[94]. This initiative aims to achieve the 90-70-70 targets by 2030, which are defined as 90% of girls fully vaccinated against HPV by the age of 15, 70% of women receiving two high-efficiency screenings in their lifetime at the ages of 35 and 45, and 90% of women diagnosed with cervical disease receiving treatment and care[94]. The success of this initiative relies on high vaccination rates, widespread screening, and ensuring timely treatment, thus overlooking many barriers to women's access to healthcare in various regions, including economic hardship, cultural stigma, and inadequate infrastructure[95]. As of now, only 15% of young girls globally have received the preventive HPV vaccine[5]. Although the HPV vaccine has successfully prevented certain types of HPV infections, it is most effective when administered before individuals become sexually active and are exposed to the virus[96].

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) approved the quadrivalent HPV vaccine for the first time in 2006, recommending it for administration at ages 11 to 12, with the earliest possible age being 9[97]. For those who have not been adequately vaccinated before, the age limit can be extended up to 26[98]. In 2015, ACIP recommended the nine-valent vaccine as one of the three HPV vaccines for routine vaccination, advising vaccination for females aged 13 to 26 and males aged 13 to 21 who have not yet been vaccinated[99,100]. The quadrivalent HPV vaccine was approved in Canada in 2006 for use in females aged 9 to 26, and in 2010 it was approved for males aged 9 to 26; in 2011, the vaccination age was further expanded to include females under 45[101,102]. The bivalent HPV vaccine was approved for Canadian women in 2010, and the nine-valent HPV vaccine was approved for both males and females in 2015[103]. Some cities or regions may provide partial government funding, but the primary mode of vaccination remains out-of-pocket payment[104]. Due to the relatively low cost-effectiveness of promoting the HPV vaccine among males, only a few developed countries, such as Australia and the United Kingdom, offer free HPV vaccination for males. Although vaccinating females against HPV can benefit most men who have sex with women (MSW), it does not provide the same protection for men who have sex with men (MSM) [104]. Research indicates that the HPV infection rate among MSM is significantly higher than that among MSW[105,106]. Additionally, the incidence rate of anal cancer among MSM is comparable to that of individuals who have never received the HPV vaccine (80 per 100,000 per year) [107]. Therefore, in promoting HPV vaccination and developing vaccination programmes, consideration should be given to extending this protection to the MSM population.

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5.2. Efficacy and Safety of HPV Vaccine

Efficacy of the HPV Vaccine refers to the ability of the body to prevent HPV infection and related cancers following vaccination. In a multinational, double-blind, placebo-controlled trial, 12,000 women aged 15-26 who received the quadrivalent HPV vaccine showed a 98% protective rate against CIN2 and CIN3+, HPV16 and HPV18 infections, and adenocarcinoma in situ (AIS) [107]. A 2019 study found that antibodies induced by the nonavalent vaccine could cross the placenta, thereby protecting the foetus from HPV6 and HPV11 infections [108]. A recent study in England assessed the national HPV vaccination programme launched in 2008 for girls aged 12-13, showing that vaccinated females had an 83.9% reduction in CC incidence and a 94.3% reduction in CIN3 incidence compared to unvaccinated women [102]. A study of the long-term immunogenicity of the quadrivalent vaccine revealed sustained antibody responses to HPV 6/11/16/18 for up to 14 years post-immunisation [109]. These studies indicate that the current vaccines are effective, with antibodies maintained for an extended period, significantly reducing the risk of HPV-related cancers.

HPV vaccines exhibit good safety profiles, although they come with some post-vaccination adverse reactions, most of which are mild and of short duration. The most common reactions include redness and pain at the injection site. The bivalent vaccine tends to cause headaches, fever, vomiting, dizziness, muscle pain, and diarrhoea [110]. A cohort study of Danish and Swedish girls receiving the quadrivalent HPV vaccine did not find connections to neurological, immune, or thromboembolic side effects [111]. The nonavalent vaccine, using aluminium as an adjuvant and with virus-like particles more than twice the size of the quadrivalent vaccine, showed more systemic and local adverse reactions [112]. Concerns have been raised about a potential link between HPV vaccination and autoimmune diseases [113]. However, a large-scale study involving 3,983,824 women (including 789,082 who received the quadrivalent HPV vaccine) found no significant association between the vaccine and multiple sclerosis or other demyelinating diseases[114]. HPV vaccines are currently regarded as safe, effectively preventing vaccine-type HPV infections and associated cellular abnormalities, including pre-cancerous and benign lesions [115].

5.3. Future Efforts for HPV Vaccines

Expanding the scope of approved HPV vaccines to cover high-risk populations, such as transplant recipients, HIV-infected individuals, and men who have sex with men, is a key focus [116]. Developing more diverse types of HPV vaccines, which are broader spectrum and can protect against more HPV types [116]. Additionally, creating vaccines that can treat existing HPV infections, particularly for patients with early-stage cancers or precancerous lesions, would provide substantial benefits.

Currently, the potential mechanisms of HPV immune evasion in cancers remain unclear. Future research could focus on elucidating the effects of HPV infection on the local tissue microenvironment, exploring the relationships between HPV and other immune checkpoints, assessing the potential of immune checkpoint blockade strategies in HPV-related cancers, delving into the mechanisms of HPV integration into the host genome and its impact on genomic instability and mutation accumulation, and investigating the relationships between HPV and cytokine balance and their effects on immune responses [4].

Long-term follow-up studies are also needed to evaluate the enduring immunological effects and long-term safety of vaccines. Monitoring vaccine efficacy includes assessing the impact of vaccination on the incidence of HPV-related cancers and the resulting population-level immunity. Research into the co-administration of HPV vaccines with other vaccines, such as those for measles, rubella, and influenza, should be conducted to optimise vaccination schedules and enhance coverage and efficiency. Through these efforts, the effectiveness and impact of HPV vaccines will be further enhanced, contributing to the prevention and treatment of HPV-related diseases, particularly cancers.

6. Conclusions

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HPV, owing to its unique molecular virology characteristics and immune evasion mechanisms, boasts a remarkably high infection rate among the population. Vaccination against HPV can effectively block the transmission of the virus and prevent HPV-related cancers. Current studies have confirmed the efficacy and safety of prophylactic HPV vaccination in preventing HPV infections and associated cancers. However, numerous challenges remain. Under the influence of economic conditions, healthcare resources, educational levels, and awareness, the global vaccination rate for preventive vaccines remains low, particularly in low- and middle-income countries. Nonetheless, in the future, we can enhance the accessibility, affordability, and coverage of HPV vaccines by expanding the indications of already licensed vaccines, continuously developing new vaccines, and conducting in-depth research on the mechanisms of HPV immune evasion in cancers.

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