



HPV and radiosensitivity of cervical cancer: a narrative review

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Background and Objective: Cervical cancer (CC), the most common gynecological malignancy, is divided into two categories: human papillomavirus-related [HPV positive (HPV+)] and non-HPV-related [HPV negative (HPV-)]. Compared with HPV- CC, HPV+ CC has better radiosensitivity and prognosis. We conducted a literature search and summarized relevant studies to explore the detailed mechanisms by which HPV+ improves the prognosis of CC compared to HPV-.

Methods: PubMed was used to search the literature on human papillomavirus, cervical cancer, and radiotherapy up to June 2022.

Key Content and Findings: Compared with HPV- CC, HPV+ CC has better radiotherapy outcomes and better prognosis. HPV improves the radiotherapy sensitivity of CC by inhibiting damaged DNA repair, increasing cell cycle arrest, reducing hypoxia, increasing cellular immune response, and other mechanisms. However, the effect of HPV on radiotherapy sensitivity of CC is not consistent and is affected by HPV type, viral load, and many other factors. Partial HPV+ CCs, due to hypoxia and other factors, are resistant to radiotherapy and have a poor prognosis. HPV- CC has poor radiotherapy sensitivity and poor prognosis. With the spread of the vaccine, HPV- CC will gradually increase, which is a cause for concern.

Conclusions: The radiosensitivity was significantly increased in patients with HPV+ CC, compared to HPV- patients. HPV improves the radiotherapy sensitivity of cervical cancer through a number of pathways. Meanwhile, the relationship between HPV and radiotherapy sensitivity is influenced by a number of factors. Some HPV+ CCs showed radiotherapy resistance, and HPV- CCs deserve further attention.

Keywords: Human papillomavirus (HPV); cervical cancer (CC); radiotherapy sensitivity; radiotherapy resistance

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Introduction

In 2020, there were an estimated 604,000 new cases of cervical cancer (CC) worldwide. The incidence rate of new tumors was 6.5%, second only to breast, colorectal, and lung cancers, and in the same year, 342,000 CC patients died. With a mortality rate of 7.7%, CC is the fourth leading cause of cancer death in women (1). Despite the initiation of primary prevention with vaccination and secondary

prevention with cancer screening, CC remains a leading cause of death among women with cancer worldwide.

Persistent infection with high-risk human papillomavirus (HPV) is a risk factor for CC, with types 16 and 18 accounting for about 70% of all HPV-positive (HPV+) CCs (2). HPV is a non-enveloped, double-stranded circular DNA virus that infects epithelial cells and continuously expresses oncoproteins such as E6 and E7, resulting in continued proliferation, immune evasion, and malignant

Table 1 Search strategy summary

Items	Specification
Date of search	2022-06-01
Databases and other sources searched	PubMed database
Search terms used	Human papillomaviruses, cervical cancer, radiotherapy
Timeframe	From December 2000 to June 2022
Inclusion and exclusion criteria	English literature including clinical trials, meta-analyses, and reviews were collected for review
Selection process	Yue Huang and Qian Zheng searched the database independently, and all authors jointly discussed and selected the literature for this review

transformation of infected cells, leading to cervical carcinogenesis (3).

Radiotherapy is an important treatment for cervical cancer. Early cervical cancer is mainly treated by surgery, supplemented by radiotherapy. The standard treatment for locally advanced cervical cancer is concurrent chemoradiotherapy. Part cervical cancers have poor response to radiotherapy, that is, radiotherapy resistance. Causes of insensitivity to radiotherapy include hypoxia, increased DNA repair ability and so on. CC studies have shown a significant survival advantage for HPV+ patients relative to HPV- patients. One study of squamous CC showed that there was a statistically significant difference in disease-free survival (DFS) in HPV- patients (51.9 months, n=8) compared with HPV+ patients (109.9 months, n=128) (P=0.010) (4). Another CC study showed a statistically significant difference between HPV- (n=21) and HPV+ (n=193) groups in terms of progression-free survival (PFS) (59.8 vs. 132.2 months, P=0.010) and overall survival (OS) (77.0 vs. 153.8 months, P=0.010) (5). In a meta-analysis study including 2,838 cases of CC from 17 studies, HPV+ patients had a better prognosis [OS: hazard ratio (HR) =0.610, P=0.001; PFS: HR =0.362, P<0.001] compared with HPV- patients (6). One study of head and neck tumors has shown that HPV+ tumors account for 30% of cases (7). Radiotherapy is also an essential modality in treating head and neck tumors. A more significant survival benefit was found in HPV+ patients by comparing HPV+ and HPV- head and neck tumors [HR =0.46; 95% confidence interval (CI): 0.37–0.57] (3). Similarly, in head and neck tumors, HPV increases the radiotherapy efficacy of tumors mainly by reducing hypoxia and altering DNA repair (3). This study reviewed the detailed mechanisms of HPV infection in CC for increasing

sensitivity to radiotherapy and the factors influencing it. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5930/rc>).

Methods

A literature search was conducted in the PubMed database with the keywords human papillomaviruses, cervical cancer, radiotherapy. The search included studies published up to June 2022. The search strategy details are shown in *Table 1*.

Although HPV improves radiotherapy sensitivity and prognosis, HPV+ tumors are highly heterogeneous and sensitivity to radiotherapy is inconsistent. The type of HPV infection, integration status, and infection titer may affect the efficacy of radiotherapy for tumors. At the same time, some HPV+ CCs have shown radiotherapy resistance.

Mechanisms of HPV increasing radiotherapy sensitivity

Radiotherapy damages cellular deoxyribonucleic acid (DNA) by direct or indirect ionization. Damage types include base-pair damage, base-pair deletions, cross-links, and single or double strand breaks (DSBs). Immediately after radiation damage occurs, cells arrest the cell cycle to examine and repair DNA damage. Repair is mainly performed by two mechanisms: non-homologous end-joining (NHEJ) and homologous recombination (HR). If the damage is too severe to repair, apoptosis or other cell death pathways are initiated, with DSBs most often leading to cell death (8).

Compared with HPV- cells, HPV+ squamous cell carcinoma cells have shown higher radiosensitivity, with a survival fraction after 2 Gy (SF2) of 0.59 for HPV- vs. 0.22

for HPV+ ($P<0.0001$) (9). The main mechanisms through which HPV improves radiosensitivity include damaging DNA repair, increasing G2/M cycle arrest, reducing hypoxia and cancer stem cells (CSCs), and increasing cellular immune response.

Damaged DNA repair

Phosphorylated histone 2AX (γ -H2AX) is a marker of DNA damage. One study found that HPV+ cells still had persistent γ -H2AX aggregates up to 48 hours after irradiation, whereas HPV- cells began to dissolve γ -H2AX aggregates within 4 hours of irradiation. After transfection of HPV- cells with E6/E7, γ -H2AX foci induced by radiotherapy were still present 24 hours later. Compared with HPV- cells, HPV+ cells had a longer duration of DNA damage after radiotherapy, indicating that HPV affected DNA repair and thus improved radiosensitivity (8).

HPV affects DNA repair through E6 and E7. P53 is an important regulator that moderates multiple downstream pathways for a wide range of cellular responses, including the cell cycle, DNA repair, and apoptosis. E6 degrades P53, resulting in cell cycle dysregulation, impaired repair, and increased resistance to apoptosis. E7 degrades *Rb* protein and results in the overexpression of p16. P16 inhibits the binding of DNA repair protein *RAD51* to DSBs and affects the HR repair pathway (3).

Increased G2/M cycle arrest

The cell cycle is divided into G1, S, G2, and M phases, and the radiosensitivity of cells in different phases differs. Cells in S phase are the most resistant to radiation, and cells in M phase are the most sensitive to radiation. One study showed that before radiotherapy, there was no significant difference in the cell cycle between HPV- and HPV+ cells. After radiotherapy, the G2/M cell cycle arrest prolongation rate of HPV- versus HPV+ cells was 0% vs. 85% ($P=0.002$) (9).

The *Rb* protein is a G1 phase checkpoint controller and plays a key role in the negative control of the cell cycle. E7 binds to degrade *Rb* protein, activates the cell cycle transition from G1/S phase, and accumulates in G2/M phase (3). In addition, residual wild-type p53, which has not yet been degraded by E6 after radiotherapy, induces G2/M arrest. HPV+ cells improve radiosensitivity by degrading *Rb*, as well as residual p53, leading to cell cycle arrest and increased apoptosis (10).

Reduced CSCs and hypoxia

CSCs, compared with differentiated tumor cells, can repair DNA damage more effectively and have stronger radioresistance. CSCs are dependent on microenvironment support and are more commonly found in hypoxic microenvironments (11). HPV+ tumors have a lower CSC population than HPV- tumors. The percentage of cells expressing the CSC marker CD98 in HPV+ tumors has been found to be significantly lower than that in HPV- tumors (22.0% vs. 71.5%, $P<0.001$). In HPV+ tumors, the prognosis of patients with high CD98 expression was significantly worse than that of patients with low CD98 expression, with 5-year OS of 36.4% vs. 71.9% ($P<0.001$) and 5-year PFS of 27.3% vs. 70.5% ($P<0.001$) (12).

Oxygen is very important for radiotherapy. Hypoxia leads to reduced DNA damage from radiotherapy (13). Hypoxia is an important cause of radiotherapy resistance. Furthermore, hypoxia can potentially maintain or enhance the stem cell phenotype of cancer cells and contribute to the emergence of metastatic clones (14). E6 reduces antioxidant activity, and E7 inhibits glutathione transferase to reduce free radical scavenging, induces more reactive oxygen species and free radicals, and makes HPV+ tumors less hypoxic (15). It has been shown that radiotherapy combined with the hypoxic sensitizer nimorazole only improved the local control rate of HPV- head and neck squamous cell carcinoma, while HPV+ tumors did not benefit from it (16).

Increased cellular immune response

HPV+ tumors may display a unique inflammatory microenvironment, thereby enhancing radiosensitivity. In the process of malignant transformation, HPV+ tumors take various measures for immune evasion, and there is still strong immune cell tumor infiltration. One study found that after radiotherapy, the surface of HPV+ tumors expressed more immune regulatory proteins and chemokines, with more tumor infiltrating T cells present, compared with HPV- tumors (17). Radiotherapy-induced tumor cell damage and inflammation lead to the release of tumor antigens and HPV virus antigens, which awakens the body's immune response to the tumor and recruits a large number of immune cells and inflammatory factors, thereby triggering a stronger immune response (3).

Factors affecting the radiosensitivity and HPV

Although HPV+ tumors have a better response to

radiotherapy than HPV- tumors, HPV+ tumors are highly heterogeneous. The relationship between HPV and radiotherapy sensitivity is influenced by many factors, including the integration of HPV gene status, types, and loads, among others.

HPV integration

HPV integration is an essential step in cervical carcinogenesis and does not occur in all tumors. HPV integrates into host genes, causing deletion, rearrangement, and amplification of integration sites and neighboring genes. Abnormalities in the genes can lead to dysregulation of their transcription, affecting radiotherapy sensitivity and prognosis. One study showed that in HPV+ CC treated with radiotherapy, the nonintegrated group had better recurrence-free survival (RFS) than the HPV-integrated patient group ($P=0.005$) (18).

Integration sites are randomly located on DNA, and different integration sites have different effects on the sensitivity to radiotherapy. A typical integration site is *RAD51B*, an essential part of DNA double-strand break repair. HPV can integrate into the vicinity of *RAD51B*, resulting in the deletion of this gene, impaired DNA repair, and greater tumor sensitivity to radiotherapy (19). Other integration sites, such as near the *MYC* and *HMG A2* (high mobility group A2) genes, can lead to elevated *MYC* and *HMG A2* expression in tumors and influence radiotherapy sensitivity (20). The *MYC* proto-oncogene inhibits cell cycle checkpoint proteins and blocks DNA double-strand break repair, and increases radiotherapy sensitivity (21). *HMG A2* protein is a transcriptional regulator that moderates the transcription of multiple genes and affects various biological processes. In antitumor therapy, *HMG A2* promotes DNA repair and thus affects the efficacy of radiotherapy (22). Less than 10% of HPV integration sites are associated with known oncogenes (23), and the remaining integration sites have unclear genetic and radiotherapy sensitivity implications. There is still a need for further exploration.

Type of HPV infection

HPV types are divided into two categories: alpha-7 (18, 39, and 45) and alpha-9 (16, 31, 33, 52, and 58). The most common type of HPV is 16 (57%), followed by 18 (16%) (2). A clinical study showed that among 1,010 patients with locally advanced CC treated with radiotherapy, the best

disease-specific survival (DSS) ($P=0.075$) and local control ($P=0.013$) were achieved in patients infected with alpha-9 only, followed by both alpha-7 and alpha-9, and the worst was with alpha-7 only (24). One study has suggested that type 18 has a worse prognosis than type 16 (25). The reasons for this trend may be related to DNA repair, viral integration, and the stage of the disease. HPV type 18 CC may have higher DNA repair activity and viral integration rates (77% vs. 83%) (26), thus affecting radiotherapy sensitivity. In addition, HPV 16 tumors are more likely to have early disease than non-HPV 16 tumors (36% vs. 23%, $P=0.020$) and cause the emergence of prognostic differences (27).

Viral load

HPV load at initial treatment was associated with prognosis. Two studies reported better local control in the high viral load group compared with the low HPV baseline group ($P=0.04$). Low viral load was associated with poorer DFS and local RFS, with HRs of 2.51 and 5.82, respectively (28,29).

It has been suggested that cervical tumors with high and low viral loads represent distinct molecular subsets. HPV oncoproteins play a major role in tumor development in high viral load tumors. After radiotherapy, HPV load was found to decrease significantly in high load tumors, which downregulated the expression of E6 and E7. Tumor suppressor pathways such as p53 and pRb are restored, and DNA repair and apoptosis pathways are reactivated to increase radiosensitivity. In low viral load tumors, HPV acts as a driver of tumor progression and requires additional stimuli to coinduce tumorigenesis. This may lead to multiple complex genetic alterations involving enriched DNA replication, cell cycle control, and extracellular matrix control, making tumors less sensitive to radiotherapy. Tumors with a low viral load, even when the load decreased after radiotherapy, did not restore the p53 and pRb tumor suppressor pathways and were therefore relatively resistant to radiotherapy (28,29).

Infection persistence and clearance

After the end of treatment, HPV clearance or infection persists, correlating with prognosis. One study reported that patients with HPV clearance had better overall and local control rates than those with persistent infection at 9 months ($P=0.024$ and $P=0.02$, respectively) (30). At 24 months after treatment, 62% of HPV-cleared patients had good disease control compared with 30% of those with

persistent infection (30). Persistent HPV infection after radiotherapy significantly increases the risk of recurrence, likely because HPV-carrying tumor cells continue to survive and maintain their proliferative potential after radiotherapy, increasing the risk of recurrence (31).

Radiotherapy-resistant HPV-related cervical tumors

Although HPV improves radiosensitivity, the radiosensitivity of HPV+ tumors is not consistent. The radiosensitivity conveyed by HPV status may depend on multiple factors. HPV function changes, hypoxia, gene mutation, and immune response affect the radiosensitivity. Approximately 30% of cervical treatments are radioresistant and have a poor prognosis, with a 5-year cause-specific survival rate of 10% and a 5-year PFS of 0% (32).

Changes in HPV function

A subset of HPV+ tumors, although retaining part of the HPV molecular signature, have significantly altered HPV function, show poor treatment response, and have clinical manifestations similar to HPV- tumors. The expression of the E1^{E4} splice isoform has been found to be low in these tumors. E1^{E4} is associated with cell metabolism, apoptosis, and autophagy. Cell lines with low E1^{E4} expression had reduced PI3K/AKT activity, activated glutamine metabolism, resistance to autophagy and apoptosis, higher SF2 values (Pearson $r=-0.88$, $P=0.007$), and poorer radiosensitivity (33).

In addition, HPV function is altered, which may lead to p16 negativity. Degradation of Rb by E7 results in overexpression of p16. P16 impairs DNA repair pathways HR and NHEJ and improves radiosensitivity. About 5% of HPV+ CC are p16-negative, and their prognosis is relatively poor, and they tend to be radioresistant. In HPV+ tumors, the 5-year DFS rates of p16 overexpression and p16 negativity were 76.8% vs. 58.2% ($P=0.007$) (27). P16-negative HPV+ tumors have poor prognosis, and thus it has been suggested that p16 overexpression, but not HPV infection, can improve radiosensitivity and prognosis. However, in HPV- tumors, p16 overexpression did not improve radiosensitivity. Clinically, about 7–20% of HPV- tumors show p16 overexpression (11), and of this subset of tumors, 83% have p53 mutations and still show radioresistance with poor prognosis. P16 did not improve the radiosensitivity of HPV- tumors, possibly because

HPV- tumors have more complex gene mutations, stronger invasion and metastasis ability, and radioresistance (5).

Hypoxia

Hypoxia is an important factor leading to radioresistance. It was found that hemoglobin <110 g/L was associated with reduced PFS ($P=0.05$) and OS ($P=0.08$) (34). Currently, photon radiotherapy is routinely used for CC. Photons are low linear energy transfer (LET) rays, which act mainly through indirect ionization and require oxygen to form and fix the damage. Sufficient oxygen is required in the tumor to achieve the maximum cytotoxic effect.

Recent studies have found that hypoxia can induce a quiescent state of HPV tumor cells. Hypoxia mediates the decrease of HPV E6/E7 expression through the *PI3K/mTORC2/AKT* signaling pathway, inducing HPV tumor cells to enter a quiescent state and cell cycle arrest in G1 phase. This contributes to radioresistance, immune evasion, and tumor recurrence. After improvement of hypoxia, tumor cells do not fully regain radiosensitivity immediately, and it takes time to leave the quiescent state and re-enter the cell cycle (35,36).

Gene mutation and immune response

TP53 is an important tumor suppressor gene that affects DNA repair, the cell cycle, cell apoptosis, and so on. *TP53* mutations are associated with radioresistance in CC. *TP53* mutations were present in 5.7% of HPV+ CCs, and *TP53* mutations were significantly associated with worse PFS (HR =3.53, $P=0.042$) (37).

In addition, reduced local immune responses may contribute to radioresistance. CD19 is a marker of B cells. In one study, among patients with head and neck squamous carcinoma, those with high CD19 expression had a better 5-year prognosis than those with low CD19 expression (5.65 vs. 2.70 years, $P<0.001$), regardless of HPV infection (38). Tumor cells lose or down-regulate surface antigens to achieve the purpose of immune escape. Radiation kills tumor cells and attracts inflammatory factors and immune cells, forming an immune response. Radiotherapy can regulate the immune response process, such as enhancing the presentation of tumor cell antigens and increasing the ability of T lymphocytes to kill tumor cells. In this way, tumor immune escape can be reduced and anti-tumor immune response can be performed (3,38). A weaker immune response, less effective in killing tumors, is

associated with radiation resistance.

HPV- tumors

Approximately 5.5–11% of cervical neoplasms are reported to be non-HPV-related (6), including true HPV- tumors and pseudo-HPV- tumors. Pseudo-HPV negativity may be caused by a low viral load, HPV latency, destruction of targeted segments, non-high-risk HPV infection, and detection methods. HPV- CC has a poor prognosis, which may be related to gene mutation, tumor pathological type, and disease stage.

Gene mutation

In HPV- CC, *TP53*, *PTEN*, and β -catenin genes (*CTNNB1*) are significantly mutated (6). *HMG2* and *MEX3A* are significantly elevated in HPV- CC cells (6). The normal functions of the *TP53* gene include cell cycle inhibition and promoting cell apoptosis. *TP53* mutation can promote the formation of tumor stem cells, inhibit cell apoptosis, inhibit autophagy, and lead to radiotherapy resistance (39,40). The *PI3K/Akt* signaling pathway is critically involved in cell growth and metabolism. The *PTEN* gene is a negative regulator of the *PI3K/Akt* signaling pathway. *PTEN* mutation causes hyperactivation of the *PI3K/Akt* signaling pathway. Activated *PI3K/AK* signal reduces radiotherapy sensitivity by enhancing DNA repair, increasing hypoxia and angiogenesis (41,42). *CTNNB1* is a vital activator downstream of the oncogenic Wnt signaling pathway. One of the targets of the Wnt/ β -catenin pathway is the *LIG4* gene, which encodes DNA repair. Overactivation of the Wnt pathway can enhance HR by upregulating the *LIG4* gene, which is closely associated with developing resistance to radiotherapy (43,44). *HMG2* protein is a transcriptional regulator that can affect radiotherapy sensitivity by promoting DNA repair (22). Muscle EXcess 3A (*MEX3A*) is an RNA-binding protein that mediates *MAPK/ERK* pathway activation, promoting tumor proliferation and anti-apoptosis, and affecting radiotherapy sensitivity (45). All of these mutated genes are associated with DNA repair and cellular regulation, thus affecting radiotherapy sensitivity and promoting the development of radiotherapy resistance.

Pathological types

Adenocarcinoma is divided into HPV-related and non-

HPV-related. Non-HPV-related adenocarcinoma includes gastric adenocarcinoma, clear cell adenocarcinoma, mesonephric duct adenocarcinoma, and endometrioid adenocarcinoma (46). One study reported that clear cell carcinoma of the cervix (CCC) had a significantly lower 5-year OS and RFS than HPV+ cervical adenocarcinoma ($P=0.003$ and 0.032 , respectively) (47). For gastric-type mucinous carcinoma (GAS) and usual type endocervical adenocarcinoma (UEA) patients with postoperative recurrence who received radiotherapy, the response rate was 50.0% vs. 81.8% ($P=0.001$) (48). Rare types of CC are radioresistant, which may be related to strong invasion and metastasis ability and immune evasion. Compared with UEA, GAS was significantly associated with ovarian metastasis (5/95 vs. 3/233, $P=0.048$) and positive ascites cytology (10/87 vs. 8/205, $P=0.013$) (48). The expression rate of immune checkpoints in CCC was significantly lower than that in cervical squamous cell carcinoma. The expression ratio of programmed cell death ligand 1 (PD-L1) in CCC and squamous cell carcinoma was 22% vs. 91% ($P<0.001$), and the expression of V-domain Ig suppressor of T cell activation (VISTA) was 74% vs. 34% ($P<0.001$) (49). Lower immune checkpoints, representing fewer immune cells in the tumor microenvironment, result in more effective immune evasion.

In recent years, researches have shown that HPV- tumors are not all rare types. One study reported 21 cases of HPV- CC, including 12 cases of squamous cell carcinoma and 6 cases of adenocarcinoma (5). Another study reported 8 cases of HPV- CC, including 3 cases of squamous cell carcinoma and 5 cases of adenocarcinoma (4). Compared with HPV+ CC, adenocarcinoma is more common than squamous cell carcinoma in HPV- CC, and the radiosensitivity of adenocarcinoma is worse than that of squamous cell carcinoma. The 5-year PFS for patients with locally advanced cervical adenocarcinoma/adenosquamous carcinoma was 30.0% vs. 47.6% for patients with squamous cell carcinoma ($P=0.044$) (50). Another study showed that the prognosis of patients with cervical adenocarcinoma/adenosquamous carcinoma was worse than that of patients with squamous cell carcinoma, with 5-year OS of 26.7% vs. 58.6% ($P=0.004$) (51).

Disease stages

Compared with HPV+ CC patients, HPV- CC patients have been reported to be more likely to have locally advanced disease (91% vs. 57%, $P<0.01$), more lymph node metastasis (67% vs. 36%, $P<0.01$), and patients were older

(58 vs. 51 years, $P=0.04$) (5).

HPV- CC has more complex gene mutations, adenocarcinoma is the more common pathological type, later stage and lymph node metastasis are more common, and the patient is older, leading to worse radiosensitivity and prognosis.

HPV-CC has strong radiotherapy resistance and poor prognosis, suggesting the need for more aggressive treatment. Low-LET radiation is oxygen dependent, and hypoxia can lead to radiation resistance. High LET radiation does not require oxygen and directly damages the DNA of tumor cells, which is more effective in killing tumor cells (52). Compared with HPV+ CC, HPV- CC is relatively more hypoxic. Radiotherapy resistance to HPV- CC may be alleviated with high-LET radiation therapy.

Conclusions

Compared with HPV- CC, HPV improves the radiosensitivity of tumors and the prognosis of patients through a variety of mechanisms. The relationship between HPV and radiosensitivity of cervical cancer is influenced by many factors, including HPV type, viral load, viral integration, and so on. Some HPV-related tumors show radio resistance, which is related to HPV function changes and hypoxia. The mechanism of HPV and radiosensitivity still needs to be further explored. With the widespread application of the HPV vaccine, the incidence of high-risk HPV+ CC will gradually decrease, while the proportion of HPV- CC and low-risk HPV+ CC may gradually increase, which is worthy of further attention.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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