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Review Article

Cervical Cancer Screening and Prevention

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Abstract

Cervical cancer has caused numerous deaths in women worldwide over the past few decades. It is a serious clinical problem that needs to be solved, though its morbidity and mortality have declined in recent years. The current treatments against cervical cancer are hysterectomy, radiotherapy, and chemotherapy, with certain limitations. Meanwhile, progress has been made in the screening and prevention of cervical cancer, focusing on human papillomavirus (HPV) infection, which is considered a necessary but insufficient cause. This review summarizes our current knowledge of screening and prevention of cervical cancer and its relation to HPV.

Introduction

Cervical cancer ranks fourth among malignancies in female patients worldwide. It starts in the lower part of the uterus and occurs on the surface of the cervix. The main causative agents of cervical cancer are human papillomaviruses (HPVs) that invade stratified epithelia.[1] For many cases, the transiently viral infection can be self-cleared by the human immune system within 6–18 months.[1,2] HPV persistent infection usually takes years or even decades after primary infection, resulting in premalignant diseases or cervical malignancy.[3] The cancer development is divided into three stages: normal, cervical squamous intraepithelial lesion (SIL, also called cervical intraepithelial lesion [CIN]), and cervical cancer.[3]

There are no specific effective treatments for cervical cancer except surgical approaches, given that the pathogenesis of cervical cancer and HPV replication is still poorly understood. Some treatments have currently been applied, which can control disease progression or prolong survival time to various extents.[4] Other options to reduce morbidity and mortality include prevention and screening, the two most effective interventions, namely the primary (HPV vaccine) and secondary (screening) approaches.[5] Vaccines have been developed recently to block the infection of different HPV types.[6] On the other side, the implementation of cervical cancer screening is particularly important, allowing women to be aware of their self-status and to be appropriately treated as early as possible to stop the transition to cervical cancer. This mini-review aims to summarize the current knowledge of cervical cancer screening and prevention. Before describing it, we will introduce the concept of cervical cancer and its related HPV replication, followed by the details of the screening and prevention in the next sections.

Keywords: Cervical cancer; hr-HPV; TCT; Vaccine.

Abbreviations: CIN, cervical intraepithelial lesion; FDA, food and drug administration; HC-2, hybrid capture 2; HPV, human papillomavirus; hr-HPV, high-risk HPV; HSIL, high-grade SIL; LCR, long control region; LSIL, low-grade SIL; SIL, cervical squamous intraepithelial lesion; TCT, thin prep cytologic test; WHO, World Health Organization.

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The overview of cervical cancer

The epidemiology of cervical cancer

Cervical cancer ranks fourth, after breast, colorectal, and lung cancers, among malignancies in female patients worldwide. International Agency for Research on Cancer reported 604,000 new cases and 342,000 deaths related to cervical cancer globally in 2020. Its morbidity and mortality rates account for 6.6% and 7.7%, respectively, among all cancers.[7] According to the World Health Organization (WHO), cervical cancer will cause more than 443,000 global deaths annually by 2030.

The mortality rates of cervical cancer vary based on population locations and economic conditions. Approximately 85% of the deaths occur in underdeveloped or developing countries.[8] For instance, the data of Global Cancer Statistics of 2020 showed that cervical cancer has extremely high mortality in some underdeveloped areas such as sub-Saharan Africa, Melanesia, South America, and some parts of Southeast Asia, as well as most parts of Africa. In contrast, 7 to 10 times lower morbidity and mortality are observed in developed areas like North America, Australia, and others.[7,9]

The majority of deaths from cervical cancer occur among the population of older ages. This can be explained by the fact that HPV infection and primary cervical precancerous lesions are often

asymptomatic in patients for the first few years and will progress to cancer much later.[10,11] Globally, the average age for the diagnosis is 53 years, while the average decreased age is 59 years.[12] For example, the mean diagnosis age in Singapore was 68 in 2018, and the average age of death was 76 in Martinique in the same year.[13] 70% of deaths occurred in women older than 50 years in South Africa during 2004–2012, with around 25% of diagnosed patients aged between 40 to 49.[14] The median diagnosis age in the USA was 47 years in 2003.[15] The reason for the age differences among many areas might come from the low economic levels, the poor living conditions, and the insufficient medical service in these undeveloped regions. In addition, those local people lack the awareness of seeking medical attention, even if diagnosed with the disease.

The characteristics of cervical cancer

Compared to other women-susceptible cancers, cervical cancer has unique characteristics. Firstly, progression to cervical cancer can be triggered by many risk factors, including HPV infection, immunodeficiencies,[16] sexual and reproductive factors, long-term oral contraceptive use,[17] smoking, and chlamydia trachomatis infection.[18,19] Among them, the HPV persistent infection is considered the primary causing factor,[20] which is associated with a history of sexually-transmitted infection, HPV-related vulvar or vaginal disorders, and multiple sexual partners.[14,21] Approximately 85% to 90% of HPV infections can be cleared spontaneously over several months by the human immune system, and only 10% to 15% persist.[22] Of these, only 0.3%–1.2% of initial infections will eventually progress from high SIL to invasive cervical cancer.[16] The high-risk HPV (hr-HPV) subtypes are responsible for almost all cases of cervical cancer. The majority of HPV infections display no signs of cervical cancer in patients for the first few years. Once patients present with the symptoms, most of them are diagnosed at the advanced stages of cancer.

Secondly, cervical cancer experiences progressive development from normal epithelium lesions to premalignant squamous intraepithelial lesions (SIL), including low-grade SIL (LSIL) and high-grade SIL (HSIL). LSIL (also referred to as CIN1) is categorized as mild dysplasia, while high SIL (also referred to as CIN2/3) is a dysplastic lesion.[23,24] During this process, HPVs rapidly replicate themselves in either episomal or integrated forms. It remains unknown what determines whether an HPV infection will naturally regress to normalcy or progress to high-grade lesions (HSIL or cervical cancer).[25]

The treatment of cervical cancer

People often show no symptoms in the early stages and will not seek medical attention until they become severe to interfere with their daily activities. Most LSILs eliminate on their own. HSILs require immediate treatments, depending on the location of the lesions. The current treatments include hysterectomy, radiotherapy, chemotherapy, or a combination. Radical hysterectomy is the primary method, and excisional therapy with cervical conization or LEEP is the gold standard for treating HSIL. Chemotherapy and radiotherapy are considered adjunctive approaches.

Chemotherapy is applied as a less damaging treatment for patients independently or in combination with surgical and radiation therapies. Many agents, such as cidofovir (acrylic nucleoside phosphonate derivative), podophyllin (cytotoxin inducing mitotic arrest), vidarabine (DNA polymerase inhibitor) and interferons, impart antiviral and immunomodulatory functions to treat cervical cancer. Other drugs like cisplatin, 5-fluorouracil, carboplatin, paclitaxel, and topotecan are used to treat advanced and recurrent cervical lesions. The exact drug names are listed in Table 1.[26–34] Among them, cisplatin is the most effective, inducing oxidative stress and apoptosis in cancer cells.[35]

Those classical treatments come with various side effects. Firstly, surgeries cause additional damage to nearby tissues and blood vessels. Certain complications, such as post-operative hemorrhage, blood aggregation, and post-operative infection, may arise during and/or after hysterectomy in vivo.[36] Secondly, radiotherapy can not avoid killing a significant number of normal cells. Finally, chemotherapy may cause the human body to develop drug resistance.

Those treatments cannot satisfy all patients with various conditions. For example, conservative treatment is urgently needed for pregnant women to reduce the damage to the fetus and mother. On the other hand, female hormonal variation must be considered during novel treatment development because the variation may promote viral reactivation during pregnancy to accelerate the progression of cervical cancer. Neoadjuvant Chemotherapy[37] has been reported to control the tumor and delay delivery until fetal maturity without serious adverse events on the mother and fetus. It is also usually applied to other cervical cancer patients before radical surgical resections. Brachytherapy[38] has fewer side effects than traditional radiotherapy and shortens the overall treatment time, which may also benefit pregnant patients. In addition, cervical conization is a good choice that does not harm the fetus, the mother, or even the conception process.[39] To develop more effective treatments, it is crucial to better understand the pathogenesis of cervical cancer and the mechanisms of how HPVs infect the host cells and accomplish their replication.

The relationship between HPV and cervical cancer

HPVs are small, non-enveloped double-strand DNA viruses. Over 400 isolates have been reported in the papillomaviridae family, and over 200 have been identified to infect humans.[40] HPVs contain episomal DNA genomes of approximately 8 kb, encased in non-enveloped icosahedral capsids of about 55 nm in diameter. The HPV genome can be divided into three major regions: an early region (E), a late region (L), and a long control region (or upstream regulatory region).[41] The early region encodes at least seven viral proteins with different regulatory functions (E1, E2, E4, E5, E6, E7, and E8), while the late region mainly encodes two viral structural proteins, L1 and L2.[40] In addition, the upstream regulatory region contains the viral *cis*-acting regulatory sequences that regulate viral replication, transcription and post-transcriptional control via the late regulatory element.[41]

HPV subtypes

According to the association with cervical cancer, HPVs are defined as low-risk and high-risk groups. Low-risk HPV types are often associated with anogenital warts, cutaneous lesions, benign mucosal lesions, and recurrent respiratory papillomatosis.[42] High-risk HPV types are responsible for over 99.7 % of cervical cancer cases.[43,44] There are 15 hr-HPVs: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. Among these, HPV16 is the most prevalent subtype globally, followed by HPV18.[45] These two subtypes account for 55% and 15 % of the total cervical cancer cases, respectively.[43]

HPV can also be classified into five evolutionary HPV genotype groups (α, β, γ, μ, and ν),[46] based on the sequencing similarity of the viral genomes. Of these, the α-HPVs, as the largest group, contain 64 subtypes (including 15 hr-HPVs mentioned above) that mainly infect mucosal epithelia. The second group, β-HPVs, main-

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Table 1. Current therapeutic drugs

Current Therapeutic Drugs			
Name	**Mechanism**	**Pros or cons**	**References**
Cisplatin	Bind with genomic DNA (gDNA) or mitochondrial DNA (mtDNA) to create DNA lesions, block the production of DNA, mRNA and proteins, arrest DNA replication, and activate several transduction pathways of necrosis or apoptosis.	Gold standard for treating cancer; drug resistance	Ghosh S. Cisplatin: The first metal-based anticancer drug[26]
Carboplatin		Carboplatin is less nephrotoxic, neurotoxic and ototoxic, and much less emetogenic than cisplatin	Go RS, *et al*. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin[27]
Paclitexel	Paclitexel induces mitotic arrest and apoptosis through stabilization of the mitotic spindle. This inability deconstructs the mitotic spindle during mitosis leads to the cessation of the cell cycle with the arrest at the G2/M phase	Lack of aqueous solubility; as an potent radiosensitizer that causes cell cycle arrested at the G2/M phase	Marupudi NI, *et al*. Paclitaxel: a review of adverse toxicities and novel delivery strategies[28]
5-Fluorouraci	Working as an antimetabolite to prevent cell proliferation, it primarily inhibits the enzyme thymidylate synthase to block the thymidine formation required for DNA synthesis.	Along with a long-term side effect: cognitive impairment	Wigmore PM, *et al*. Effects of 5-Fluorouraci[29]
Topotecan	Topotecan is a semisynthetic analog of camptothecin (topoisomerase I inhibitor), which inhibits the topoisomerase I enzyme, causes double-stranded DNA breaks during replication, and leads to cell death.	Combination with cisplatin and/or radiation therapy, produces high objective response rates and prolongs survival.	Ackermann S, *et al*. Topotecan in cervical cancer[30]
Pembrolizumab (Keytruda)	Working as a PD1 inhibitor. Blockade of PD1 prevents T-cell PD1/tumor cell PDL1 interaction, leading to restoration of T-cell mediated anti-tumor immunity	Greater efficacy for pembrolizumab in patients whose tumors expressed PD-L1, and thus a companion diagnostic for detecting programmed death ligand 1 (PD-L1) expression needed to be developed equally rapidly to confirm that PD-L1 was a predictive biomarker in select indications	Kwok G, *et al*. Pembrolizumab (Keytruda); Emancipator K. Keytruda and PD-L1: a Real-World Example of Co-development of a Drug with a Predictive Biomarker[31]
VGX-3100	VGX-3100 consists of two DNA plasmids encoding optimized synthetic consensus E6 and E7 genes of HPV-16 and HPV-18	Target E6 and E7 in HPV-associated malignancies as immunotherapy, greater than previously reported immune responses to therapeutic HPV vaccines	Trimble CL, *et al*. Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomized, double-blind, placebo-controlled phase 2b trial[32]
Bevacizumab (Avastin)	Bevacizumab is a humanized monoclonal antibody that targets VEGF-A, which can inhibit the process of angiogenesis	Inhibit sustained angiogenesis	Mukherji SK. Bevacizumab (Avastin)[33]
Tisotumab vedotin	Tisotumab vedotin binds to tissue factors on target cells and, upon internalization, releases monomethyl auristatin E (MMAE), a microtubule-disrupting agent, resulting in cell cycle arrest and apoptotic cell death.	Cytotoxicity: bystander cytotoxicity of adjacent tumor cells and multiple immune-related effects, including immunogenic cell death, antibody-dependent cellular toxicity, and antibody-dependent cellular phagocytosis	Coleman RL, *et al*. Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study[34]

ly infect cutaneous epithelia and are associated with non-melanoma squamous cell carcinomas.[47,48] Other three groups often cause only benign diseases.[43]

The function of viral proteins

During the HPV life cycle, the viral proteins play multiple functional roles. The early proteins regulate the host cellular environment and viral genome replication. Viral proteins E1, E2, E6, and E7 are best studied. For example, E1, in tandem with E2, regulates the immediate-early viral transcription. Expression of E2 regulates the viral early promoter activities to direct expression of E6 and E7, ensuring the continued survival of HPV-infected cells. The repression of the p97 promoter activities by E2 leads to the low expression of the viral proteins in infected basal cells to escape the immune surveillance.[43,49,50] The E6 and E7 oncoproteins can act individually or co-operatively to delay terminal differentiation and to prevent cell cycle exit, providing a suitable environment for further genome amplification.[51,52] Capable of modulating the immune response to the viral infection, E6 is required for episomal genome maintenance and inhibition of host cell apoptosis via the degradation of p53. The degradation of pRb by E7 results in unscheduled entry into the S phase of the cell cycle to promote cell transformation eventually.[53]

Capsid proteins L1 and L2 are responsible for viral genome protection and the entry of HPVs to the host epithelial cells. The L1 protein can bind to heparin sulfate proteoglycans on the surface of basal keratinocytes. The minor capsid protein L2 contributes to the interaction of virions with the secondary receptors after the primary attachment of virions.[43,54–57] L2 is also important for the nuclear transport of the viral genome to initiate viral replication.[58]

HPV life cycle

It is well known that HPVs specifically infect the settled parts of the human body. They exclusively replicate in keratinocytes within squamous epithelia of the cutaneous or mucosal surfaces.[59] HPVs enter into the basal layer cells of the epithelium through microabrasions or the single-layered squamous cellular junction to persist their infection.[60,61] Once the persistent infection is established, the genome is thought to be replicated around 50–100 copies per cell, using host replication machinery.[57] As the infected basal cell divides, one daughter cell remains in the basal layer, while the other migrates to the upper suprabasal layers as it undergoes terminal differentiation. Upon differentiation, the genome levels rapidly increase to around thousand copies per cell in a process called amplification. This amplification is strictly associated with epithelial differentiation, followed by virion production. The production requires the expression of the viral L1, L2, and E1□E4 proteins. The new virions are assembled in the nucleus and released in the uppermost layers of the epithelium.

Cervical cancer screening

Because HPV infection and cervical precancerous lesions are often asymptomatic at early stages of cancer formation, it is necessary to develop effective screening and prevention strategies against cervical cancer. The effective HPV vaccine prevention and screening measures allow cervical cancer to be treatable by surgical resection and concurrent chemoradiation. However, public awareness of these measures still needs to be emphasized. We will next introduce the current knowledge of cervical cancer screening.

Screening methods

With the development of screening techniques (Fig. 1), the asymptomatic disease has gradually become foreseeable at its early stages. Currently, the common screening methods include cytological examination, HPV detection, ultrasound examination, magnetic resonance examination, etc. Regarding the appropriate age of screening, the US Preventive Services Task Force suggests that women aged 21 to 29 years should be screened every three years with cytology alone and that women aged 30 to 65 years opt for cytology alone every three years, hr-HPV testing every five years, or both tests (co-testing) every five years. It is unnecessary to screen women older than 65 who have had adequate prior screening and women younger than 21 years who have done at least one-time screening before.[62] Importantly, an HPV-positive screening result requires patients for additional tests such as referral to colposcopy or testing repeats. In contrast, an HPV-negative result allows a safe extension of the screening interval, clearly demonstrated in a 14-year follow-up study of a population-based randomized cohort in the Netherlands.[63] In this study, cervical cancer incidences among HPV-negative women at different intervals are not significantly different.[64] Therefore, the recommended screening interval for HPV-negative women in Europe can be extended up to 10 years depending on age and screening history.

Cytological examination

Cervical cytology is the simplest and most effective examination method for early diagnosis of cervical cancer. Pap smear (also called Pap test) was developed to detect cervical epithelial cell lesions 50 years ago. This technique plays an important role in diagnosing malignant tumors and precancerous lesions. Although its clinical application reduces the mortality of cervical cancer patients, Pap smear has a high false negative rate. In addition, Pap smear samples are usually blurry due to the influence of various factors, leading to unpredictable detection errors.

Thin prep cytologic test (TCT) is a liquid-based thin layer detection system to make cytological classification diagnoses. TCT is an advanced cytologic test with a lower false negative rate for cervical cancer and precancerous lesions than Pap smear. Another advantage of TCT is its' higher detection rate with a clearer background after the removal of blood, mucus, and inflammatory cells in the specimen. The detection rate of cervical cancer cells by TCT is 100%, and TCT can also find some precancerous lesions. This breakthrough identifies those patients with carcinogenesis at much earlier stages and helps the patients get earlier and more effective treatments. The shortcoming of TCT is that the accuracy of the screening is determined by the subjective consciousness of the pathologists. Alternatively, the molecular test of HPV DNA has been gradually appreciated as a more objective and sensitive tool than the cytological test.

hr-HPV detection

In recent years, HPV detection has become the necessary screening method for cervical cancer. As mentioned above, cervical cytology mainly identifies precancerous lesions or cervical cancer. As an adjunct measure to cervical cytology, HPV testing identifies women with cervical diseases and those at risk of developing cervical cancer later.[65] Meanwhile, HPV detection provides detailed information on HPV genotyping, which helps clinicians understand the related pathology and possibly provides more precise treatments.

Various detection kits have been applied to identify hr-HPVs, most of which are based on nucleic acid amplification. Since 2001, five of them have been approved by the US Food and Drug Administration (FDA), including the Hybrid Capture 2 (HC-2) HPV DNA test, Cervista HPV HR test, Cobas 4800 HPV test, Aptima

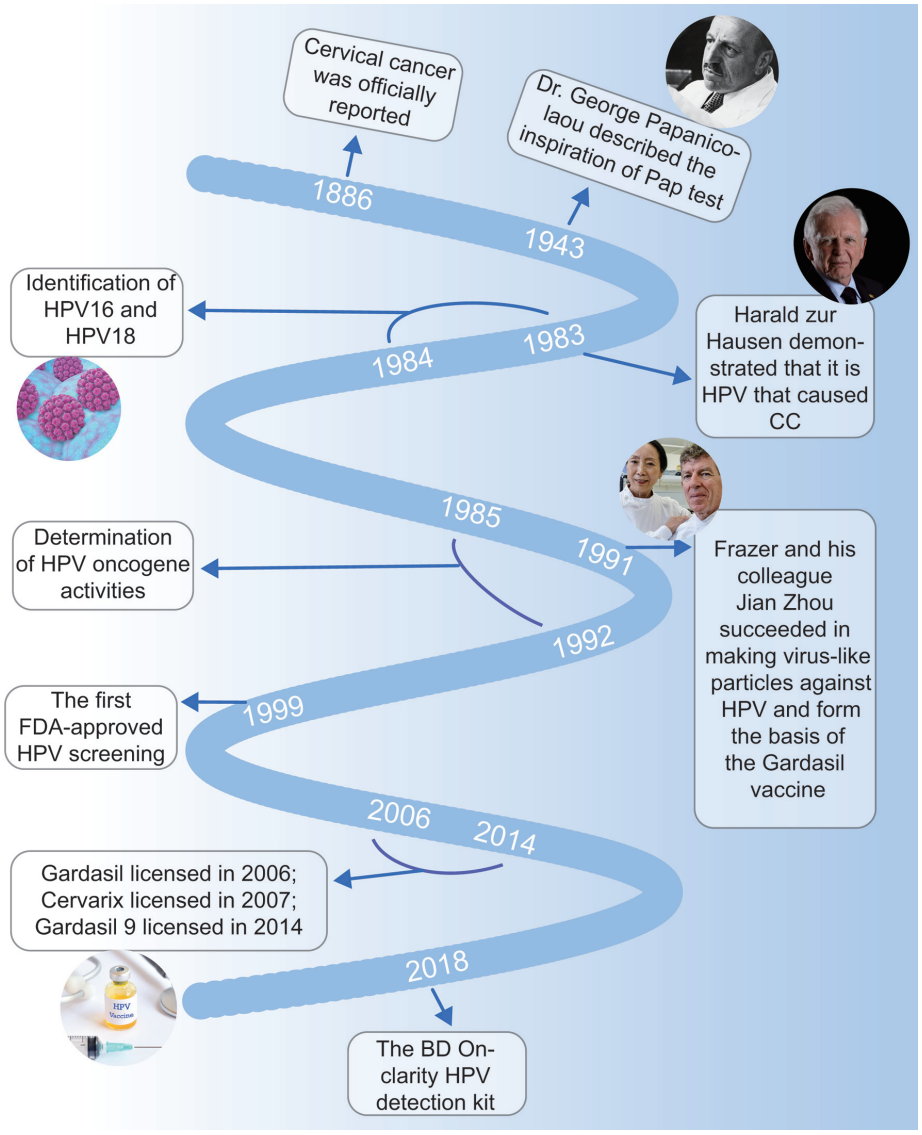

Fig. 1. This figure shows the milestone events in HPV screening and prevention. These events include identifying cervical cancer and its major causing agents and the progressive establishment in the screening and vaccine approaches.

HPV assay, and BD Onclarity HPV assay. Among these, HC-2 technology is a non-radioactive HPV-DNA detection method to determine HPV DNAs at molecular biology levels. Cervista HPV HR test, approved in 2009 by the FDA for combined examination with TCT specimens, targets specific nucleic acid sequences of L1, E6, and E7 genes.[66] The test covers 14 hr-HPV types but cannot distinguish any in between.

To improve operational convenience, the Cobas and Aptima HPV tests were approved in 2011 by FDA for use with thin prep specimens, compared to the two methods described above. The Cobas is a qualitative test that amplifies L1 DNA of 14 hr-HPV types by PCR and nucleic acid hybridization. The test specifically identifies HPV16 and 18 without needing a separate examination. This test stayed on the historical stage shortly,[67] likely because it had not been adequately validated in HPV-vaccinated women. The Aptima HPV test is designed for qualitatively detecting E6/E7 viral mRNAs of 14 hr-HPV types without genotyping test included.[67] The rationale behind this is that the existence of the E6/E7 mRNAs is considered not stable for transient infection but for persistent infection. To distinguish hr-HPV subtypes better, The BD Onclarity HPV Assay was approved by FDA in early 2018. The fully automated assay utilizes real-time PCR and nucleic acid hybridization to detect DNAs of 14 hr-HPV types, with extended genotyping for HPV16,18, 31, 45, 51, and 52.[67]

Additionally, serological and medical imaging examinations have gradually been applied to screen cervical cancer. These techniques, such as ultrasound and magnetic resonance imaging, are designed according to different physical principles to improve the resolution of the diagnosis, which greatly improves the efficiency and accuracy of cervical cancer screening. High-risk HPV tests are more sensitive and reproducible than others.[68] Recently, HPV testing has been an alternative to cytology in some European countries. WHO has also issued recommendations for the gradual introduction of HPV testing technology into low- and middle-income

countries. In 2020, the results of a clinical study of cervical cancer screening based on the large-scale population in China showed[69] that the use of high-risk HPV screening technology had a better screening effect, which provides sufficient scientific evidence for the final elimination of cervical cancer in China.

The prevention of cervical cancer

Hippocrates said, "Prevention is better than cure," which is particularly true for cervical cancer.[70] Three prophylactic HPV vaccines were approved in the 2000s (Fig. 1), capable of preventing infection with multiple HPV types known to cause cervical cancer. These are the bivalent vaccine Cervarix, the quadrivalent vaccine Gardasil, and the 9-valent vaccine Gardasil9. Cervarix targets high-risk HPV16/18 that are responsible for 70% of cervical cancer cases, Gardasil prevents infection of HPV16/18/6/11, and Gardasil9 covers HPV31, 33, 45, 52, and 58 in addition. The guidelines for HPV vaccination are slightly different for eligibility in different countries. The WHO suggests that the most optimal vaccination population is girls aged 9 to 13 without sexual experience. The American Cancer Society recommends that the best age to receive the vaccine is 11 to 12 years. In China, HPV vaccines are available for females aged 9 to 45. While the vaccinated girls reach their screening ages, the current prevention and screening guideline is not fully programmed yet to direct them differently from those who have not been vaccinated. For these vaccinated women, a model-based analysis study suggested that the screening could be later and less frequently combined with primary HPV testing rather than cytology.[71] Another Italian study reported that the screening should start at 30 with an HPV test and have longer intervals of rescreening, which still needed further research to be determined.[72]

The global incidence of cervical lesions is significantly reduced because of the application of these vaccines. The prophylactic HPV vaccines have achieved great success, and approximately 95% of vaccinated individuals are prevented from persistent infections or precancerous lesions. A National HPV Vaccination Programme for preventing HPV infection and associated diseases has been funded and implemented in Australia since 2007, using the quadrivalent HPV vaccine. Initially, this program was only for girls but extended to boys in 2013.[73] Consequently, Australia has the highest vaccine uptake rates worldwide. However, male vaccination is not drawn attention in other countries. For example, HPV vaccination among men was not recommended in the United States until 2011. Every year in the U.S., 15,793 men are diagnosed with HPV-related cancers.[74]

Despite the obvious achievements, the prophylactic vaccines still face challenges in that those licensed vaccines lack the abilities to help those who are already HPV-infected and on the way into the associated tumors.[74,75] Thus, new therapeutic HPV vaccines have been developed and tested at experimental research or clinical trial stages. The new testing vaccine family mainly includes DNA vaccines, RNA replicant vaccines, peptide vaccines, vector vaccines, etc. These vaccines aim to generate cell-mediated immunity against transformed cells rather than neutralizing antibodies. However, no vaccine has yet been licensed for therapeutic use.[76]

Methods

Search strategy

All full-text articles describing the screening and prevention of cervical cancer were searched using Medline or PubMed with English-language restriction and a time restriction within September 2022. The following keywords were used in our searches, such as "cervical cancer," "HPV vaccine," "screening," "prevention," and "therapy." Furthermore, the reference lists of each article were manually searched to prevent the omission of any pertinent study.

Perspective

Each year, more than half a million women are diagnosed with cervical cancer, resulting in over 300,000 deaths worldwide. The screening and prevention of cervical cancer are indispensable to reduce this incidence. This review introduces the characteristics of cervical cancer and summarizes the current knowledge of the screening and prevention of cervical cancer. Though several generations of screening and vaccines have been developed over decades, which greatly decrease the morbidity and mortality of cervical cancer, the desire to improve these measures still exists.

In May 2018, the WHO Director-General called for actions to eliminate cervical cancer by scaling up prevention, screening, and treatment interventions with the help of global citizens. The WHO for the Elimination of Cervical Cancer a Public Health Problem provided a strategy: an increase of population with HPV vaccination to 90%, twice-lifetime cervical screening to 70%, and treatment of pre-invasive lesions and invasive cancer to 90% (also known as the 90-70-90 targets). This elimination goal could be realized with the joint efforts of society, including individuals, families, communities, civil society, and government agencies at all levels.[13]

The current vaccines only cover part of hr-HPVs and low-risk HPVs, while there are more than 200 subtypes. The threat of many of these HPV subtypes is underestimated and not covered by the vaccines due to the lack of knowledge regarding the relationship between other diseases rather than cervical cancer and those viruses. Thus, the next-generation vaccines are expected to cover more subtypes of high-risk and low-risk HPVs. Research on new prophylactic vaccines has never been stopped, and many efforts have been made to explore new expression systems such as *E. coli*, cost reduction of vaccines, and the development of L2 vaccines with broad-spectrum protection for simplicity and efficiency. Those next-generation vaccines are aimed to remove many limitations of the current vaccines, which is a major step in the fight against cervical cancer.

Although the current HPV vaccines are available for females aged 9 to 45, vaccination is not strongly recommended for those older than 26 or younger than 9. This age limitation is still a big issue indicating that the vaccine has certain impacts on our immune system. Thus, a better and safer vaccine should be developed for kids younger than nine without increasing costs. HPV vaccination rates remain low in many low-income countries, mainly because the local people can not afford the cost of the current prophylactic HPV vaccines. How to greatly reduce the economic burden still severely dampen the spread out of the vaccination in those underdeveloped or developing areas.

One disadvantage of the licensed HPV vaccines is that they cannot help those persistently infected people. Therapeutic HPV vaccines are urgently expected for the infected population to terminate the development of cervical cancer. The current therapeutic vaccines in trials lack the capabilities to generate enough anti-tumor activities via boosting T cell response. This restriction mainly comes from the immunosuppressive properties of the tumor microenvironment. To address this question, more ecosystemic studies are needed to investigate the tumor microenvironment of cervical cancer.

Early screening is required to prevent cervical cancer since it takes decades for a viral infection to develop into a lesion or cancer. The cytology approach can only detect the changes until the lesion or cancer occurs. The responsibility then falls on the HPV detection kits that cannot tell us the time. A better understanding of cervical cancer development and its related pathogenesis is required to address this issue. More detailed work and efforts should be followed by the scientists and clinicians of public health to better estimate the screening starting time statistically. The combination of multi-screening methods should be the key to reducing underdiagnosis or misdiagnosis of cervical cancer and its precancerous lesions.

The HPV detection kits can not distinguish the transient infection from the persistent infection, which may yield false positive results for the patients. In addition to L1, most current kits target E6 or E7 oncogenes expressed in transient and persistent infections. It might be feasible to include E1□E4 or E2□E8, which are late genes expressed in differentiated upper epithelial and often seen during the persistent infection.

Historically, recurrent cervical cancer has been treated with platinum-based chemotherapy.[77] Given that chemotherapy often causes drug resistance, patients with locally advanced and metastatic cervical cancer have a poor prognosis. As an upgrade, immunotherapy appears in the history stage. One example is the pembrolizumab (anti-PD1 antibody) treatment. Programmed death ligand 1 (PD-L1) is an essential immune checkpoint protein that binds to programmed cell death 1 (PD-1) on T-lymphocytes,[78] resulting in inhibition of T cells response and tumor immunosuppression. The US FDA approved this treatment for recurrent or metastatic cervical cancer in June 2018.[79] One great advantage of this treatment is its non-toxic properties for cervical cancer patients. Other targets similar to PD-L1 should be further explored. Overall, with the development of novel approaches to prevention, screening, and treatments, we are positive to eliminate cervical cancer within a few decades and apply the knowledge to other HPV-related diseases.

Conclusions

With the development of cervical cancer screening and prevention, the morbidity and mortality of cervical cancer have declined in recent years. Primary HPV detection is becoming more popular, replacing other screening methods in developed and developing countries. In the meantime, applying the prophylactic vaccines greatly reduces cervical cancer occurrence and certain types of HPV infection. However, the prophylactic vaccines do not affect patients infected with HPV. The therapeutic

HPV vaccines are expected to meet the requirement. More efforts should be focused on molecular mechanisms underlying how HPV triggers cervical cancer information. In summary, the combination of next-generation screening and prevention approaches will contribute to the goal of "the global elimination of cervical cancer."

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Contributed to study concept and design (SYH), acquisition of the resources (ML, ZLY, LJ, and ZYC), drafting of the manuscript (ML and ZLY), critical revision of the manuscript (ML and ZLY), and supervision (SYH).

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