Review Article

Cervical cancer: Epidemiology, risk factors and screening

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Abstract

Cervical cancer is one of the leading causes of cancer death among females worldwide and its behavior epidemiologically likes a venereal disease of low infectiousness. Early age at first intercourse and multiple sexual partners have been shown to exert strong effects on risk. The wide differences in the incidence among different countries also influenced by the introduction of screening. Although the general picture remains one of decreasing incidence and mortality, there are signs of an increasing cervical cancer risk probably due to changes in sexual behavior. Smoking and human papillomavirus (HPV) 16/18 are currently important issues in a concept of multifactorial, stepwise carcinogenesis at the cervix uteri. Therefore, society-based preventive and control measures, screening activities and HPV vaccination are recommended. Cervical cancer screening methods have evolved from cell morphology observation to molecular testing. High-risk HPV genotyping and liquid-based cytology are common methods which have been widely recommended and used worldwide. In future, accurate, cheap, fast and easy-to-use methods would be more popular. Artificial intelligence also shows to be promising in cervical cancer screening by integrating image recognition with big data technology. Meanwhile, China has achieved numerous breakthroughs in cervical cancer prevention and control which could be a great demonstration for other developing and resource-limited areas. In conclusion, although cervical cancer threatens female health, it could be the first cancer that would be eliminated by human beings with comprehensive preventive and control strategy.

Keywords: Cervical cancer; epidemiology; risk factors; screening

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Introduction

Cervical cancer is the second common female malignant tumor globally which seriously threatens female's health. Persistent infection of high-risk human papillomavirus (HPV) has been clarified to be the necessary cause of cervical cancer (1,2). The clear etiology accelerated the establishment and implementation of comprehensive prevention and control system of cervical cancer. In May 2018, the World Health Organization (WHO) issued a call for the elimination of cervical cancer globally, and more than 70 countries and international academic societies acted positively immediately (3-6). Thereafter, in November 17, 2020, WHO released the global strategy to accelerate the elimination of cervical cancer as a public health problem to light the road of cervical cancer prevention and control in future which mean that 194 countries promise together to eliminate cervical cancer for the first time (7). At this milestone time point, we reviewed the update progress of cervical cancer prevention and

control in epidemiology, risk factors and screening, in order to pave the way of cervical cancer elimination.

Epidemiology for cervical cancer

Cervical cancer is one of the leading causes of cancer death among women (8). Over the past 30 years, the increasing proportion of young women affected by cervical cancer has ranged from 10% to 40% (9). According to the WHO and International Agency for Research on Cancer (IARC) estimates, the year 2008 saw 529,000 new cases of cervical cancer globally. In developing countries, the number of new cases of cervical cancer was 452,000 and ranked second among malignancies in female patients (10). Conversely, the number of new cases of cervical cancer was 77,000 in developed countries and ranked tenth among female malignancies.

In 2018 worldwide with an estimated 570,000 cases and 311,000 deaths, cervical cancer ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women (11). However, approximately 85% of the worldwide deaths from cervical cancer occur in underdeveloped or developing countries, and the death rate is 18 times higher in low-income and middle-income countries compared with wealthier countries (12). Cervical cancer ranks second in incidence and mortality behind breast cancer in lower Human Development Index (HDI) settings; however, it is the most commonly diagnosed cancer in 28 countries and the leading cause of cancer death in 42 countries, the vast majority of which are in Sub-Saharan Africa and South Eastern Asia (13). The highest regional incidence and mortality rates are seen in Africa (14). In relative terms, the rates are 7–10 times lower in North America, Australia/New Zealand, and Western Asia (Saudi Arabia and Iraq) (15).

In China, cervical cancer is the second largest female malignant tumor (11). According to the data from National Cancer Center in 2015, there were 98,900 new cases and 30,500 deaths of cervical cancer (16). In the past 20 years, the incidence and mortality of cervical cancer have been increasing gradually in China (17).

Between 2004 and 2007, the Chinese scientific research team, cooperated with WHO/IARC and the Cleveland Medical Center in the United States in 8 rural and urban areas (Xiangyuan county of Shanxi Province, Yangcheng county of Shanxi Province, Xinmi county of Henan Province, Hotan Prefecture of Xinjiang Uygur Autonomous Region, Shanghai City, Beijing City, Shenzhen City of Guangdong Province, and Shenyang City of Liaoning Province), carried out a population-based multicenter HPV type distribution study among females aged 15–59 years old, clarifying the dominant HPV types of rural and urban populations in China, as well as female HPV infection status and age distribution (18). Studies have confirmed that persistent infection of high-risk HPV is closely related to the occurrence of cervical cancer. There are 14 types of high-risk HPV, namely HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 73. A multi-center cross-sectional survey study showed that the infection rate of high-risk HPV in China is about 14.3%, and the dominant types are HPV16 (2.9%), HPV52 (1.7%), HPV58 (1.5%), HPV33 (1%) and HPV18 (0.8%), and showed double peaks during adolescence and perimenopause (19). Globally, HPV16 has the highest infection rate, HPV18 is the second most common type, while HPV 33 is common in Asia, and HPV52 and HPV58 have relatively low infection rates. This shows that compared with the global HPV epidemiology, HPV epidemiology in China has both similarities and differences.

Subsequently, the Chinese scientific research team conducted a cross-sectional multi-center cervical cancer and precancerous HPV genotyping study based on 19 hospitals in 7 geographic regions (Northeast China, North China, Northwest China, Central China, East China, Southwest, and South China). Through the pathological laboratory procedures of strict quality control, it was found that the dominant HPV types in cervical cancer tissue were HPV16, 18, 31, 52 and 58, respectively, and that HPV16 and 18 were the most carcinogenic, which could cause more than 84.5% of cervical cancer (20). The above research on HPV dominant types from different perspectives provides solid scientific evidence and support for the future research and application of preventive HPV vaccine and *in vitro* diagnostic technology, epidemiological research and health economics research in the Chinese population.

Risk factors for cervical cancer

A number of risk factors for cervical cancer are linked to exposure to the HPV (21,22). Invasive cancer development process could prolong up to 20 years from the precursor lesion caused by sexually transmitted HPV (23). However, there are also other numerous risk factors (such as reproductive and sexual factors, behavioral factors, etc) for

cervical cancers which include sexual intercourse at a young age (<16 years old), multiple sexual partners, smoking, high parity and low socio-economic level (24,25).

Sexually transmitted infections (STI)

HPV

The primary cause of pre-cancerous and cancerous cervical lesions is infection with a high-risk or oncogenic HPV types. Most cases of cervical cancer occur as a result of infection with HPV16 and 18. High-risk types, especially HPV16, are found to be highly prevalent in human populations (22). The infection is usually transmitted by sexual contact, causing squamous intraepithelial lesions. Most lesions disappear after 6–12 months due to immunological intervention. However, a small percentage of these lesions remain and can cause cancer.

The results of a meta-analysis showed that the highest prevalence of HPV occurs at the age of 25 years, which could be related to changes in sexual behavior (26). In a meta-analysis study, the bimodal distribution of cervical cancer in some regions has been studied. In this distribution, immediately after sexual intercourse, an outbreak of HPV can be observed, which is followed by a plateau at adult age; the second peak again is observed after 45 years old (27). Permanent infection with one of the high-risk types of HPV over time leads to the development of cervical intraepithelial neoplasia (CIN). The major mechanisms through which HPV contributes to carcinogenesis involve the activity of two viral oncoproteins, E6 and E7, which interfere with major tumor suppressor genes, P53 and retinoblastoma. In addition, E6 and E7 are associated with changes in host DNA and virus DNA methylation. Interactions of E6 and E7 with cellular proteins and DNA methylation modifications are associated with changes in key cellular pathways that regulate genetic integrity, cell adhesion, immune response, apoptosis, and cellular control (28).

Human immunodeficiency virus (HIV)

The risk of developing infection from high-risk HPV types is higher in women with HIV (29). The results of the studies on the relationship between HIV and cervical cancer suggested a higher rate of persistent HPV infection with multiple oncogene viruses, more abnormal Papanicolau (Pap) smears, and higher incidence of CIN and invasive cervix carcinoma among people with HIV (23). Women infected with HIV are at increased risk of HPV infection at an early age (13–18 years) and are at high risk of cervical cancer. Compared with non-infected women, HIV positive patients with cervical cancer are diagnosed at an earlier age (15–49 years old) (30).

Reproductive and sexual factors

Sexual partners

Factors relating to sexual behavior have also been linked to cervical cancer. One study found that an increased risk of cervical cancer is observed in people with multiple sexual partners (31). Moreover, many studies have also suggested that women with multiple sexual partners are at high risk for HPV acquisition and cervical cancer (32,33). From the meta-analysis, a significant increased risk of cervical diseases was observed in individuals with multiple sexual partners compared to individuals with few partners, both in non-malignant cervical disease and in cervical cancer (34). The association remained exist even after controlling for the status of HPV infection, which is a major cause of cervical cancer. Also, early age at first intercourse is a risk factor for cervical cancer (35).

Oral contraceptive (OC) pills

OC pills are known to be a risk factor for cervical cancer. In an international collaborative epidemiological study of cervical cancer, the relative risk in current users increased with an increase in the duration of OC use. It has been reported that the use of OC for 5 years or more can double the risk of cancer (36). And in a multi-center case-control study, among women who tested positive for HPV DNA, the risk of cervical cancer increased by 3 times if they have used OC pills for 5 years or more (37). In addition, a recent systematic review & meta-analysis also suggested that OC pills use had a definite associated risk for developing cervical cancer especially for adenocarcinoma. This study concluded that use of OC pills is an independent risk factor in causing cervical cancer (38).

Cervical cancer screening

With the background of cervical cancer elimination worldwide, cervical cancer screening plays an increased role in the comprehensive prevention and control besides HPV vaccination, especially those methods that demonstrated excellent clinical performance.

Overview of cervical cancer screening methods

The screening methods for cervical cancer are mainly as

following: traditional Pap smear, visual inspection with acetic acid & Lugol's iodine (VIA/VILI), liquid-based cytology (LBC) and HPV testing. The disease burden of cervical cancer has been significantly reduced in developed countries by Pap smear, mainly in the United States, since 1950s. However, the accuracy of traditional Pap smear could be easily affected by following factors: the level of cytological room, professional technicians, sampling method, slide quality, dyeing skills, and cytological personnel experience. In developed countries with high standard experimental conditions and technical level, the sensitivity of cytology is as high as 80%–90%, in contrast, in resource-limited regions, it could be as low as 30%–40%. To overcome the limitations of traditional Pap smear in cervical cancer screening, LBC was developed and approved by Food and Drug Administration (FDA) in 1996 for clinical-use purpose. Compared with the traditional Pap smear, the sensitivity of LBC was significantly improved. Meanwhile, organized and practicable LBC screening program has also been established in developed countries which could ensure cervical cancer screening strategy is carried out continuously and effectively.

Cervical cancer screening has been facilitated since the cause clarified. HPV-based testing is a pivotal part for cervical cancer screening besides cytology-based tests.

The detection of high-risk HPV in cervical lesion biopsies and exfoliated cells has evolved from restriction endonuclease cleavage patterns and hybridization techniques to polymerase chain reaction (PCR)-based system (39) and most recently next-generation sequencing (NGS) assays (40). Currently, HPV genotyping is primarily based on the detection of individual types by various methods that utilizing the highly conserved *L1* gene and PCR-based methods. These PCR methods employed consensus primers that could target and amplify different sized fragments such as 455 bp with the MY09/11|PGMY system (41), 150 bp with the GP5+/6+ system (42), or <100 bp with SPF10 (43). And another point that is worth noting is that all these techniques remained the most validated methodology to identify and characterize clinically relevant HPV (44-46).

Additionally, the type-specific probes are always to be used to achieve HPV genotyping, besides DNA sequencing (46,47). Other types of assays may be type-specific with immediate discrimination and quantitation of specific HPV types in an "onetube" assay. These methods employ real-time (RT)-PCR techniques, coupled with beta-globin detection for internal quality control utilizing specialized detection systems (48).

Cervical cancer malignant pathways are tightly correlated to the viral E6 and E7 oncoprotein activities which could also contribute to the accumulation of cellular genomic mutations and viral integration (47). Therefore, identification of HPV E6/E7 mRNA has been shown to be promising in cervical cancer screening. And most of the assays utilized reverse transcriptase PCR or nucleic acid sequence-based amplification to identify E6/E7 genome fragments (49).

Recently, the correlation between increased HPV CpG site methylation levels and high-grade cervical lesions has also been demonstrated in numerous studies and has facilitated the development of quantitative assays targeted CpG methylation (50,51). Studies indicate that NGS assays can provide single-molecule CpG methylation levels to help unravel the mechanism of methylation in cervical cancer development (39,50).

The application of HPV detection has accelerated the transition of cervical cancer screening from morphology to molecular biology. HPV testing was initially used as a triage method for the reflex triage of population with atypical squamous cells of undetermined significance (ASC-US). In 2014, FDA approved HPV detection for the use in cervical screening. Thereafter, HPV detection plays an increasingly important role in the practice of cervical cancer screening. At present, more than 425 HPV testing has been developed worldwide, of which more than 150 is from China. To restrict and standardize HPV testing market, China released guidelines for the clinical performance evaluation for HPV testing against clinical endpoints in 2015. In other countries, it is also necessary to set similar regulations in consideration that 59.7% of HPV tests on the global market without a single peer-reviewed publication (49). To improve the coverage of cervical cancer screening, HPV testing that is rapid, simple, inexpensive could be more popular and can further promote the application in practice. In 2008, *care*HPV was developed in China, which demonstrated excellent performance in screening, although it was easy to use, cheap, fast and friendly to the laboratory requirements (52,53). In 2018, the *care*HPV achieved the pre-qualification certification issued by WHO, which was expected to benefit more people in developing countries and resource-poor areas such as Africa and Southeast Asia (54). In addition, the cost-effective reflex triage, referral of women, and management strategies appropriate to various resource level areas were also in evaluation (55-58).

In recent years, with the rapid development of science and technology, the application of artificial intelligence (AI) based products is booming. In cervical cancer prevention and control, AI also showed to be promising in cytology-based screening and colposcopy examination based on the image pattern recognition (59,60). These AI-based technology or system can intelligently identify lesions and assist medical staff in clinical examination and diagnosis which could alleviate difficulties in diagnosis in primary clinics.

Screening practice in China

In China, cervical cancer screening started since 1990s, although late compared with Western countries, China still achieved great breakthroughs. Common screening methods were introduced into China for the first time after clinical performance evaluation in high-risk areas which included HPV DNA detection (Hybrid Capture II, HC2), LBC and visual inspection with VIA/VILI (61-63). At the same time, these studies also further made it clear that "one or more HPV tests in a lifetime for cervical cancer screening could be feasible in developing countries" which had important impact on the clinical practice of cervical cancer screening in China and even in the world.

In July 2019, the State Council issued the "Healthy China Action (2019–2030)" plan, emphasizing the need to move forward the diagnosis and treatment and optimize the allocation of medical resources, from the treatment-centered to the health-centered, and to improve health level of the whole people. The program also clearly points out that cervical cancer screening coverage rate needs to reach more than 80% by 2030 (64), indicating the importance and severity of cervical cancer prevention and control.

Finally, the achievements of scientific research should be able to be developed into products and applied in practice. Based on the experience and study findings, two "National Demonstration Base for Early Diagnosis and Treatment of Cervical Cancer" were set up in Shenzhen Maternal and Child Health Hospital (City type) and Xiangyuan Maternal and Child Health Hospital (Rural type) in Shanxi Province in February 2005 (65). Thereafter, National Health and Family Planning Commission of China and China Women's Federation launched cervical cancer and breast cancer screening program for women aged 35–64 years old in rural areas in 2009 (66), which was also one of the major public health service projects in China organized by national government. Different screening and management strategies have been set up for various resource-level regions. Up to 2017, the project has offered cervical cancer screening for 73.99 million women. Currently, the project has covered 1,501 counties (67). Meanwhile, China has developed effective cervical cancer prevention and control network which covered screening, diagnosis to treatment, follow-up and rehabilitation step by integrating government support and leadership, multi-sectors' cooperation, professional personnel support and whole society participation. In 2017, Chinese Preventive Medicine Association released the "Guideline for Comprehensive Prevention and Control of Cervical Cancer" to further promote the standardized and development of cervical cancer prevention and control in China (68).

The priority of public health measures for cancer prevention and control reflects the government and society's attention to public's health, especially in resource-limited areas, and also reflects the civilization and progress of a country and society.

A large number of studies around the world have confirmed that cervical cancer could be prevented and controlled well by screening and early treatment. And it has been widely recognized if only considering the effect of cancer screening. However, the screening methods or solutions with the best effect may be not the best one. In the case of limited health resources, it is necessary to analyze and compare the input and output of different programs from the perspective of health economics which included how to scientifically determine the initial age of screening and time interval, select appropriate screening programs according to local health resources, and focus on cancer intervention in order to maximize the use of limited health resources. And then, we could determine the screening solution that not only has a good effect of disease prevention and control, but also is in line with the principle of cost-effectiveness.

Conclusions

The disease burden of cervical cancer has decreased significantly in developed countries and regions in last decades, however it is still serious in less developed countries and regions, and effective preventive measures in these areas still face serious challenges. At present, there are various available prevention and control measures that are cost-effective and scientific evidence-based to meet the

needs of areas with different economic levels. It is gratifying to note that the globe has achieved a strategic consensus on the elimination of cervical cancer and also has developed and released the global strategy to accelerate the elimination of cervical cancer. Although the global elimination of cervical cancer has a long way to go, it is believed that through large-scale continuous promotion and widely use of existing effective prevention and control measures, cervical cancer will become the first cancer eliminated by human beings.

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Footnote

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