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Practice Guidelines

Guidelines for cervical cancer screening in China

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ABSTRACT

In response to the incidence of cervical intraepithelial neoplasia and cervical cancer in China and global screening strategies, a collaborative effort was undertaken by seven Chinese medical associations to develop this guideline for cervical cancer screening. The guideline recommends high-risk human papillomavirus (hr-HPV) testing as the preferred method for primary screening, which should have been approved by authoritative institutions and clinically validated for primary screening. In areas without access to HPV testing, cytology can be used as an alternative. However, it is recommended to replace cytology with HPV-based screening as conditions permit. Cotesting (HPV testing in combination with cytology) is recommended for areas with sufficient medical resources, opportunistic screening populations, and partial special populations. The guideline recommends that individuals with a cervix initiate cervical cancer screening at the age 25 years and undergo HPV testing alone or cotesting every five years, or cytology alone every three years. Women over the age of 65 who have had documented adequate negative prior screening in the past may terminate screening. Corresponding screening programs are proposed for different special populations. The development of these guidelines is an important step in the effort to eliminate cervical cancer in China.

Cervical cancer is a common malignant tumor that poses a serious threat to women's health and has become a major global public health issue. In November 2020, the World Health Organization (WHO) launched the Global Cervical Cancer Elimination Initiative (CCEI) 2020 to accelerate the elimination of cervical cancer. China has subsequently issued several documents to promote the prevention and control of cervical cancer nationwide actively.

In January 2023, the National Health Commission and ten other departments issued the " Accelerate the Elimination of Cervical Cancer (2023–2030)", which calls for further improvement of the cervical cancer

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Table 1
Rating the recommendations.

Recommendation level	Implication
1	Based on high-level clinical studies, there is a high level of consensus among experts
2A	Based on high-level evidence, there is a consensus among experts, or based on low-level clinical research evidence, there is a high level of consensus among experts
2B	Based on low-level clinical research evidence, there is a consensus among experts
3	Regardless of the level of clinical evidence, there is a significant divergence of opinions among experts

prevention system, enhance comprehensive control capacity, and accelerate the elimination of cervical cancer in China.

In the secondary prevention of cervical cancer, there are three key phases: screening, triage/diagnosis, and management. Screening coverage remains low in rural areas as well as central and western regions in China, and large variations exist across provincial-level administrative divisions.[1] To achieve the targets set by WHO to eliminate cervical cancer as a public health problem, based on the existing consensus and practices of cervical cancer screening in China,[2] a collaborative effort was initiated by experts from seven Chinese medical associations, including the Chinese Society for Colposcopy and Cervical Pathology of China Healthy Birth Science Association (CSCCP) and Chinese Society of Gynecologic Oncology, Chinese Medical Association et al., to develop the "Chinese Cervical Cancer Screening Guidelines." These guidelines aim to standardize cervical cancer screening in China and reduce the incidence and mortality rate of invasive cervical cancer.

To provide clearer, more specific, standardized, and actionable recommendations, this guideline is divided into two parts. The first part outlines the primary screening strategies for cervical cancer, while the second part focuses on the management strategies for individuals with abnormal screening results. This guideline represents the first part of the "Chinese Cervical Cancer Screening Guidelines."

1. Overview

It is now well-established that persistent infection with high-risk human papillomavirus (hr-HPV) is the main cause of cervical cancer and cervical dysplasia, which include low-grade squamous intraepithelial lesions (LSIL), also known as cervical intraepithelial neoplasia (CIN 1), and high-grade squamous intraepithelial lesions (HSIL), which include CIN 2 and CIN 3. Adenocarcinoma in situ (AIS), is also referred to as high-grade cervical glandular intraepithelial neoplasia (HG-CGIN). HSIL and AIS are precancerous lesions of cervical cancer.

The principle of " Equal management for equal risk " proposed by the American Society of Colposcopy and Cervical Pathology (ASCCP), recommends using CIN 3+ as the main clinical end point for risk estimates.[3] CIN 3+ was chosen instead of CIN 2+ because it is a more pathologically reproducible diagnosis; and the HPV type distribution in CIN 3+ lesions more closely approximates that of invasive cervical cancers than the larger range of types found in CIN2. In addition, CIN 2 has appreciable regression rates in the absence of treatment.

1.1. HPV infection rate in China

According to the "Global HPV and Related Diseases" data report, there are significant variations in HPV infection rates in different regions.[4] In the general population of women aged 20 and above in China, the overall HPV infection rate is 15.0%. The common HPV types include HPV 52, 58, 53, 16, and 51, and the HPV infection rate is higher in the central and western regions compared to the eastern region.[5] Additionally, HPV infection is closely related to age and has two peak infection periods, occurring at ages 17–24 and 40–44.[6] In Chinese women with normal cervical cytology, LSIL, HSIL, and invasive cancer, the infection rates of high-risk HPV types are 15.6%, 69.8%, 86.0%, and 88.7%, respectively.[7] A nationwide multicenter study based on hospitals revealed that the high-risk HPV infection rates in cervical squamous cell carcinoma and cervical adenocarcinoma are 97.6% and 74.5%, respectively.[8,9]

1.2. The burden of cervical intraepithelial neoplasia and cervical cancer in China

The standardized prevalence rates of histologically confirmed CIN1, CIN2, and CIN3 and above in China are 3.1%, 1.3%, and 1.2%, respectively.[6] The occurrence of AIS is relatively low, and accurate prevalence data were not available. In recent years, the incidence and mortality rates of cervical cancer in China have shown a continuous upward trend. The standardized incidence rate increased from 2.53 per 100,000 in 1999–2000 to 11.34 per 100,000 in 2016.[10,11] The standardized mortality rate rose from 1.42 per 100,000 to 3.36 per 100,000, with average annual increases of 8.5% and 5.4%, respectively.[10] The growth rate in rural areas was significantly higher than in urban areas.[12] Additionally, there has been a trend of younger age at onset, particularly in rural areas, where the standardized average age at onset decreased by 5.18 years between 2000 and 2014.[12] According to the International Agency for Research on Cancer (IARC) in 2020, China had 109,000 new cases of cervical cancer and 59,000 deaths, accounting for 18.2% and 17.3% of global incidence and mortality cases, respectively.[13]

Given the severity of cervical cancer incidence in China, it is necessary to develop management guidelines for cervical cancer screening to guide the standardized implementation of cervical cancer screening and improve screening rates, triage, and disease management in China. The recommendation level and quality of evidence were graded using the system that has been used for previous consensus guidelines in China, as shown in Table 1.

2. Cervical cancer screening methods

Cervical cancer screening (referred to as primary screening in this guideline) targets sexually active women of appropriate age with the aim of early detection, diagnosis, and treatment of cervical precancerous lesions and early-stage cervical cancer. Primary screening methods include: 1). Organized population-based screening: planned and organized screening of women of appropriate age in the general population.2). Opportunistic screening: Screening for cervical cancer among sexually active women of appropriate age who visit healthcare facilities.

The main cervical cancer screening methods currently used in China are as follows.

2.1. Human papillomavirus (HPV) testing

Persistent infection with high-risk HPV is the primary cause of cervical cancer. High-risk HPV DNA tests identify a group of high-risk carcinogenic HPV genotypes, typically including up to 14 types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, which are Group 1 carcinogens, and HPV66 and 68).[14] Currently, HPV testing is classified into two categories based on whether the viral genome is genotyped or not: 1). HPV non-typing test: It can simultaneously detect 14 high-risk types of HPV, but does not specifically distinguish the types; 2). HPV genotyping test: This test allows for partial or complete genotyping of 14 high-risk genotypes. It mainly includes HPV16/18 genotyping and other 12 high-risk HPV genotypes. As for the value of genotyping and extended genotyping methods for various HPV types, these are still under clinical research in China.

It has been reported that the risk of progressing to HSIL and cervical cancer after persistent hr-HPV infection is closely associated with the HPV genotype, especially in the case of HPV16/18, which carries a higher risk of developing cervical cancer or precancerous lesions. Among HSIL cases, the infection rate of HPV16/18 is approximately 52%. In

cervical squamous cell carcinoma, HPV16/18 is the most common, accounting for 84.5%.[8,15] HPV18 can lead to 50% of AIS and invasive cancers.[16] Although further typing of other high-risk genotypes may provide more detailed risk stratification for diagnostic triage and to help monitor persistent HPV infection, the clinical significance of this is still under discussion. A multicenter, open-label, randomized clinical trial and a real-world study in China have shown[17,18] that HPV testing, compared to cytology, can detect more HSILs and above, confirming the effectiveness of HPV testing for cervical cancer screening. Simultaneously, HPV testing exhibits a higher negative predictive value and a lower rate of missed diagnoses. HPV primary screening has a better benefit-risk ratio compared to cotesting (HPV testing combined with cytology).[19] Current consensus/guidelines recommend the use of hr-HPV testing as the primary screening method for cervical cancer.[3,20–24]

The advantages of using hr-HPV testing as a primary screening method for cervical cancer include higher sensitivity in detecting precancerous lesions, better negative predictive value, and the ability to extend screening intervals. Due to machine operation, there are fewer human interference factors, making it easier to control the quality. However, a limitation is that HPV positivity may only indicate an HPV infection status, not necessarily the presence of precancerous lesions, which can lead to psychological stress, overdiagnosis, and overtreatment in those being screened.

Recommendation: High-risk HPV testing is recommended as the preferred method for primary screening, using HPV assays that are approved by domestic and international authoritative institutions and clinically validated for primary screening. (Recommendation Level: 1).

Currently, the collection methods for HPV testing include clinician-collected cervical samples or self-sampling by women. Self-sampling for screening involves women participating in screening using self-collection brushes to collect vaginal cell samples for hr-HPV testing. Using PCR-based HPV testing to examine vaginal self-sampling samples can yield screening sensitivity equivalent to that of samples collected by clinicians.[25] Due to the advantages of convenience, privacy protection, and cost savings, self-sampling screening has been widely implemented worldwide and incorporated into government-led cervical cancer screening programs covering the entire population in multiple countries and regions.[14] Large-scale studies have also been conducted in China.[25,26] Further exploration is needed to determine how to effectively utilize internet-based self-sampling HPV testing models.

2.2. Cytology

Cytology, also referred to as traditional cytological test or Pap smear. In the mid-20th century, the Pap smear was introduced into cervical cancer screening and served as the main method for several decades, leading to a 50%–70% reduction in cervical cancer mortality.[27] In comparison to traditional Pap smears, liquid-based cytology (LBC) offers standardized preparation, clearer cell structures and backgrounds, and more stable quality.

The Bethesda system (TBS) for reporting cervical cytology was established in Bethesda, Maryland, United States, during a conference held at the National Cancer Institute (NCI) in 1988. It was officially adopted in 1991 and underwent revisions in 2001 (second edition) and 2014 (third edition), which is the currently utilized version.[28] The Bethesda system classifies cytological morphological abnormalities as follows: atypical squamous cells (ASC), atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC). It also includes atypical glandular cells (AGC), adenocarcinoma in situ (AIS), and adenocarcinoma for glandular cell abnormalities. Currently, more than 90% of laboratories in China use TBS system reporting terms.[29]

Cytology has a specificity of >90% for detecting CIN2+ but has a lower sensitivity of only 53%–81%,[30] which is lower than HPV testing.[21,31] The accuracy of AIS diagnosis through cytology is only approximately 50%, which can lead to underdiagnosis of AIS.[32] Additionally, cytology results are not only dependent on the skills of cytologists but also influenced by sample collection, slide preparation, patient age, and the nature of the lesions. Although cytology has lower sensitivity for detecting HSIL and above, it provides good specificity and can assess immediate risks.

In rural and resource-limited areas, which have higher incidence and mortality rates of cervical cancer, cytology continues to be more available and less expensive than sending off an HPV test.[33] Therefore, without the widespread application of HPV DNA testing, cytology remains an important screening method.

Recommendation: In areas where high-risk HPV DNA testing is not available, cytology is recommended. When conditions are favorable, screening methods based on hr-HPV testing are recommended (Recommendation level: 2A).

2.3. Cotesting

Cotesting refers to the combination of HPV testing and cervical cytology in screening for cervical cancer. Cervical cytology has higher specificity and positive predictive value but lower sensitivity. On the other hand, HPV testing has higher sensitivity and negative predictive value but lower specificity. The combination of both methods provides complementary advantages. In 2012, the American Cancer Society (ACS) recommended women ages 30–65 years should be screened with cotesting every 5 years (preferred).[34] Subsequently, there has been a shift towards using HPV testing as the primary screening method based on existing guidelines and opinions.[20–22] However, large-scale studies conducted abroad have also indicated that cotesting significantly improves the detection of cervical precancerous lesions and cervical cancer compared to HPV testing alone.[35,36] In spite of this, the cost of cotesting is higher compared to individual HPV testing or cytology.[37] A large-scale comparative study in the general population in China, suggests that primary HPV testing with type 16/18 genotyping has a higher sensitivity and negative predictive value (NPV) to detect CIN2+ by comparing with cotesting, possesses optimal cost/effectiveness in the first round of screening and is a feasible strategy of cervical cancer screening for Chinese women.[38] However, according to data from a hospital in the United States in 2021, cotesting accounted for 93% of all screenings,[39] indicating that cotesting remains the primary method for opportunistic cervical cancer screening in healthcare facilities.

Recommendation: It is recommended to use cotesing for women in regions with sufficient healthcare resources, opportunistic screening populations, and certain special populations. (Recommendation level: 1).

2.4. Visual inspection

Visual inspection refers to the visual examination of the cervix using the acetic acid test (unaided visual inspection using acetic acid, VIA) and the Lugol iodine solution test (unaided visual inspection with Lugol iodine, VILI). These methods involve the application of acetic acid or Lugol iodine solution to the cervix, followed by visual observation of the morphology, borders, extent, contour, and disappearance of abnormal epithelial staining on the cervical surface to make a preliminary diagnosis. VIA/VILI requires training for the operators.[40,41] Due to the low sensitivity and specificity of these methods, they are not widely used in cervical cancer primary screening in China at present.

Recommendation: It is recommended to use VIA/VILI as cervical cancer screening in areas with limited healthcare resources where HPV testing or cytology is not available. (Recommendation level: 2B).

2.5. Other cervical cancer screening methods

Other methods such as methylation,[42] HPV integration,[43] HPV viral load,[44] immunocytochemistry staining,[45,46] and artificial intelligence

(AI) technology[47] et al., show potential applications in screening. However, further large-scale prospective research data need to be accumulated for these methods.

In conclusion, considering the public health needs of China's large population and cost-effectiveness, different primary screening methods can be chosen based on the availability of healthcare resources. High-risk HPV testing is preferred and cotesting or cytology alone is acceptable where access to primary HPV testing is limited or not available. Other screening methods require validation and approval for their scope of application.

3. Cervical cancer screening program

3.1. General population

(1) Age to begin screening: Cervical cancer screening should begin at age 25. This recommendation is mainly based on the higher prevalence of HPV infection among women under 25, rates of persistence and progression are low, and regression of precursor abnormalities is high compared with older age groups.[22] Early intervention may have adverse effects on pregnancy outcomes. With the increasing vaccination rates for young women against HPV, the incidence of HPV-related precancerous lesions and cancer may decline further.
(2) Women aged 25–64: Primary HPV test alone every 5 years (preferred); cotesting every 5 years or cytology alone every 3 years are acceptable options.
(3) Women>65 years: Discontinue screening among individuals with a cervix who are older than age 65 years, who have no history of CIN2+ within the past 25 years, and who have documented adequate negative prior screening in the prior 10 years. Individuals aged >65 years without documentation of prior screening should continue screening until criteria for cessation are met.

3.2. Special populations

(1) **High-risk women under 25 years old**: Females under 25 years old with high-risk factors for cervical cancer, including a history of multiple sexual partners, early sexual activity, immunosuppressed and/or human immunodeficiency virus (HIV), and smoking individuals.[48,49]

Recommendation: For high-risk populations of females under 25 years old, early screening is recommended, and shorten the screening interval appropriately. (Recommendation level: 2B).

(2) **Pregnant women:** The purpose of screening for cervical cancer in pregnant women is to rule out the presence of cervical cancer. Cervical cancer screening during pregnancy is safe and does not pose a threat to the health of the mother and fetus.[50]

Recommendation: For women who have never undergone cervical cancer screening, or women who are due for a cervical cancer screening, it is recommended to perform cervical cancer screening before or during pregnancy. The screening method can be either a cytology alone or a cotesting. (Recommendation level: 2A).

(3) **Women after hysterectomy**:
1) For women who have undergone hysterectomy due to cervical precancerous lesions: The recurrence rate of CIN 2 and above after HSIL treatment is 1.1%–17.7%, and the risk of developing invasive cervical cancer is 2.6–5 times higher than that of the general population.[51,52]

Recommendation: For women who have undergone a total hysterectomy due to cervical abnormalities, it is recommended to undergo cotesting annually. If three consecutive cotesting yield negative results, the screening interval can be extended to every 3 years, and this should be continued for 25 years. (Recommendation level: 2A).

2) For women who have undergone hysterectomy due to benign uterine diseases (non-cervical abnormalities): Due to the low incidence of vaginal cancer, routine screening is not recommended in the absence of suspicious clinical symptoms or signs. For patients with unclear presence of precancerous lesions before surgery, if there are clinically suspicious symptoms or signs, cotesting is recommended. (Recommendation level: 2B).

(4) **Immunocompromised populations:** Immunocompromised individuals include those with HIV, solid organ transplant, and hematopoietic stem cell transplantation (HSCT), as well as those with systemic lupus erythematous, and those with inflammatory bowel disease or rheumatologic disease requiring current immunosuppressive treatments. Although the literature for other immunosuppressed populations remains limited, which suppress cell-mediated immunity, have also been associated with cervical cancer.[53] Therefore, the cervical cancer screening strategy for immunocompromised individuals without HIV uses the guidelines developed for people living with HIV.[54] Blood disorder patients who are sexually active should undergo routine cotesting before HSCT.[55] When conducting screening, factors such as age, previous screening history, expected survival rate, disease status, and risk factors need to be considered. It is recommended that healthcare professionals and patients discuss and determine an appropriate screening plan, providing individualized advice based on the severity of the disease.

Recommendation: It is recommended to screen sexually active immunocompromised females as early as possible, following the screening strategy for HIV-infected populations. (Recommendation level: 2A).

(5) **Women HPV vaccination**: Prophylactic HPV vaccines do not cover all high-risk HPV types and cannot prevent infection by all HPV types. Individuals who have already been sexually active before receiving the HPV vaccine may have already been infected with HPV. Vaccination against HPV does not block the progression of existing HPV infections. Therefore, individuals who have received the HPV vaccine should still undergo regular screening.[56] With the widespread use of HPV vaccines, further research is needed in China to determine the screening intervals, methods, and other aspects for individuals who have received HPV vaccination, based on evidence-based studies.

Recommendation: Follow age-specific screening recommendations (same as unvaccinated individuals). (Recommendation level: 2B).

Guidelines for cervical cancer screening management in China clarifies the purpose of cervical cancer screening in China, formulates appropriate screening methods that suit the national context, and provides guidance on the target population for screening, including special populations (Table 2). Based on evidence-based medicine principles, it presents recommended practices and their corresponding recommendation levels for cervical cancer screening. The aim is to provide guidance and improve the management of cervical cancer screening for healthcare

Table 2
Recommended levels for evidence-based recommendations.

Cervical Cancer Screening Methods		Recommendation level
HPV test	High-risk HPV testing is recommended as the preferred method for primary screening, using HPV assays that are recognized by domestic and international authoritative institutions and clinically validated for primary screening.	1
Cytology	In areas where high-risk HPV testing is not available, cervical cytology is recommended. When conditions are favorable, screening methods based on high-risk HPV testing should be adopted.	2A
Cotesting	It is recommended to use cervical cancer screening for women in regions with sufficient healthcare resources, opportunistic screening populations, and partial special populations	1
Visual inspection	It is recommended to use cervical cancer screening in areas with limited healthcare resources where HPV testing or cytology is not available	2B
Screening recommendations for different populations		
General Population	Screening initiation age: Women aged 25; Women aged 25–64: HPV testing every 5 years, or cotesting, or cytology testing every 3 years; Screening termination age: Women aged > 65, with previous adequate screening history[a]	1
Special Populations		
High-risk females under 25 years old	Early screening is recommended and shortening the screening interval appropriately	2B
Pregnant women[b]	It is recommended to perform cervical cancer screening before or during pregnancy. The screening method can be either cytology alone or a cotesting	2A
Women after hysterectomy		
A. Hysterectomy due to cervical abnormalities	It is recommended to undergo cotesting annually. If three consecutive cotesting yield negative results, the screening interval can be extended to every 3 years, and this should be continued for 25 years	2A
B. Hysterectomy due to benign uterine diseases (non-cervical abnormalities)	If there are no suspicious clinical symptoms or signs, routine screening is not recommended. For patients with unclear preoperative cervical lesions before hysterectomy, if there are clinically suspicious symptoms or signs, it is recommended cotesting.	2B
Immunocompromised women who are sexually active	It is recommended to screen sexually active immunocompromised females as early as possible, following the screening strategy for HIV-infected populations	2A
Preventive HPV vaccination	The screening strategy is the same for individuals who have not received the HPV vaccine.	2B

[a] Adequate screening history: Within the past 10 years, having had three consecutive cytology screenings, or two consecutive HPV screenings or cotestings, with the most recent screening within 5 years, and all screening results being normal. Additionally, there should be no history of CIN (cervical intraepithelial neoplasia), persistent HPV infection, or high-risk factors such as treatment for HPV-related diseases.
[b] Women who have never undergone cervical cancer screening;

professionals involved in cervical cancer prevention and treatment to enhance the overall level of cervical cancer screening management.

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Declaration of competing interest

There is no conflict of interest.

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