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Effect of HPV integration on prognosis of young women with CIN2 in China: protocol for a multicentre prospective cohort study

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ABSTRACT

Introduction Cervical cancer, a major global health concern, is primarily caused by human papillomavirus (HPV) infection. Although cervical intraepithelial neoplasia grade 2 (CIN2), a precancerous lesion, exhibits high spontaneous regression rates (50%–60%), particularly in younger women, current clinical management lacks accurate risk stratification. This study examines HPV integration status as a prognostic biomarker in women aged 18–45 diagnosed with CIN2, with the objective of developing a predictive tool for personalised therapeutic strategies and minimising overtreatment in this high-regression population.

Method and analysis This multicentre cohort study will be implemented across 20 tertiary Grade A hospitals in China, encompassing eastern, western, central and northern regions. It will recruit 240 CIN2 patients, collecting sociodemographic, lifestyle and medical history data via questionnaires. Clinical examinations will be performed at baseline and follow-up. Disease regression ((to cervical intraepithelial neoplasia grade 1 [CIN1] or lower)) and non-regression (persistent CIN2 or progression) will be evaluated. Prognostic factors will be analysed using Cox proportional hazards models, adjusting for confounders such as age, weight and socioeconomic status.

Ethics and dissemination The cohort study protocol and informed consent procedures adhere to the Declaration of Helsinki and pertinent Chinese clinical research regulations. Ethical approval has been obtained from the Clinical Research Review Committee of the Fujian Maternal and Child Health Hospital (2022KYLLR01018) and from the participating hospitals. Written informed consent is secured from all participants prior to enrolment, with detailed information provided regarding study objectives, procedures, potential risks and benefits and participants' rights. Results will be published in peer-reviewed scientific journals, presented at academic meetings and conferences and released to the public through press releases.

Trial registration number ClinicalTrials.gov (NCT05282095); Pre-results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The multicentre, open-label, prospective cohort design of the study enhances both its credibility and generalisability by focusing on a well-defined age group (18–45 years) that exhibits relatively high spontaneous regression rates for cervical intraepithelial neoplasia grade 2 (CIN2).
⇒ Comprehensive data collection methods, including biological samples and questionnaires, ensure a thorough assessment of participants' conditions.
⇒ The research addresses a critical gap in identifying reliable biomarkers for risk stratification in CIN2 patients.
⇒ The exclusion criteria may limit the applicability of findings to broader CIN2 patient populations.
⇒ Potential variability in human papillomavirus integration testing methodologies across different centres could affect consistency in results.

INTRODUCTION

Cervical cancer continues to be a major global public health concern, ranking as the fourth most prevalent cancer among women worldwide.[1] The disease burden has shown a concerning upward trend, with global cases increasing from 530 000 in 2008 to 600 000 in 2020, accompanied by a rise in mortality from 275 000 to 340 000 during the same period.[2 3] In China, the age-standardised incidence rate has reached 10.7 cases per 100 000 women, exceeding the WHO-established threshold.[3] While the overall incidence continues to rise, a notable downward trend has been observed in women under 45 years of age, suggesting potential changes in risk factors or screening effectiveness in this demographic.[4]

Human papillomavirus (HPV) infection, especially with high-risk genotypes, is the primary aetiological factor, accounting for over 90% of cervical cancer cases.[5–8] Among

the 14 known high-risk HPV types, persistent infection can lead to cervical intraepithelial neoplasia grade 2 (CIN2), a recognised precursor to cervical cancer.[9–12] The natural progression and therapeutic options for CIN2 have long posed a clinical challenge. Studies indicate that, without treatment, the progression rate of the disease is approximately 10.28%–13%, with about 5% of untreated patients ultimately developing cervical cancer.[13–15] However, existing evidence suggests that a significant proportion of cases (50%–60%) may naturally regress within 2 years, particularly in young women (under the age of 25), where the regression rate can be as high as 74.7%.[16–19] Consequently, the performance of a conisation procedure on the transformation zone of cervical dysplasia in all CIN2 patients may result in an overuse of therapy.[19] The variability in the course of this disease highlights the necessity for improved risk stratification to guide clinical management.

Developing triage strategies for CIN2 patients to differentiate between high-risk and low-risk populations for disease progression and offering personalised therapeutic interventions can substantially mitigate the risk of overtreatment. To address this issue, Berggrund *et al*[20] proposed HPV viral loads as a predictor of the presence of cervical intraepithelial neoplasia. Dick *et al*[21] used FAM19A4/miR124-2 methylation analysis to triage patients. Currently, there are no biomarkers with good clinical application effects for predicting the progression of CIN2. Therefore, it is of significant importance for the early prevention of cervical cancer to precisely screen and validate disease progression biomarkers in women with CIN2.

Following infection, the virus may persist in its episomal form or integrate into the host genome, with both patterns potentially coexisting (episomal/integrated).[22] The form of HPV presence in the human body is associated with disease progression, and the detection of HPV integration status is a critical parameter for evaluating cervical lesions and prognosis.[23] Current research shows that HPV integration plays a significant role in the progression from CIN2 to cervical cancer, and it can effectively predict the risk of progression in cervical lesions (area under the receiver operating characteristic curve [AUC] = 0.883).[24] However, this association lacks validation from prospective cohorts, particularly concerning young women who have higher rates of regression and residual considerations, thereby limiting its clinical applicability.

This multicentre, open-label, prospective cohort study aims to assess the predictive value of HPV integration testing in women aged 18–45 diagnosed with CIN2. By examining the association between HPV integration status and disease progression, we aim to provide evidence for a more accurate risk stratification tool. This could inform clinical decision-making, potentially minimising unnecessary interventions while ensuring appropriate management of high-risk cases. The study focuses on this specific age group due to their higher spontaneous regression rates and reproductive considerations, where overtreatment may have significant consequences.

METHOD AND ANALYSIS

Study design and setting

This research constitutes a multicentre, open-label, prospective cohort study. The primary objective is to elucidate the relationship between the integration status of various HPV genotypes, the length of integrated fragments, their specific integration sites and the natural outcomes of the disease in young women with CIN2 and CIN2-3 (cervical intraep epithelial neoplasia grade 2-3, referring to the histopathological diagnosis of the biopsy cervix showing an excessive state of CIN2 to CIN3; the term 'subsequent CIN2' encompasses both CIN2 and CIN2-3). It aims to determine the prognostic value of various HPV integration statuses in predicting the clinical course of disease in young women with CIN2 to develop effective triage strategies for this population and evaluate their impact on clinical outcomes. Additionally, we will collect vaginal fornix swabs to assess alterations in the vaginal microbiome and their potential implications for CIN2 prognosis. Building on previous research, we hypothesise that vaginal dysbiosis may obstruct HPV clearance and affect the outcomes of CIN2.[25–28] Therefore, a secondary objective of this study is to elucidate the relationship between cervical HPV integration status and vaginal microbial diversity in young women diagnosed with CIN2, as well as its significance for disease prognosis.

We will enrol women aged 18 to 45 years who have been diagnosed with CIN2 via histopathology for participation in this study. Participants will be categorised into an HPV integration group (exposed group) and a non-HPV integration group (unexposed group) based on their HPV integration status at enrolment. According to the 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines,[29] the follow-up period for all participants will be 12 months, which includes scheduled visits at 3, 6, 9 and 12 months postenrolment, in addition to the baseline questionnaire and examination. During each follow-up visit, biological samples will be collected, and participants will complete questionnaires to ensure a comprehensive assessment and maintain logical continuity throughout the study. To reduce the loss to follow-up rate, we provide explanations and health education during recruitment, and patients are included in the study after giving their consent. Furthermore, each institution designates dedicated follow-up consultation rooms and physicians for the patients. Throughout the follow-up process, dedicated follow-up physicians will notify patients of their appointments 15 days prior.

The reporting of this study protocol will adhere to the STrengthening the Reporting of OBservational studies in Epidemiology guideline (online supplemental file 1).

This study is sponsored by the Fujian Maternal and Child Health Hospital and conducted under the academic supervision of the National Clinical Research Center for

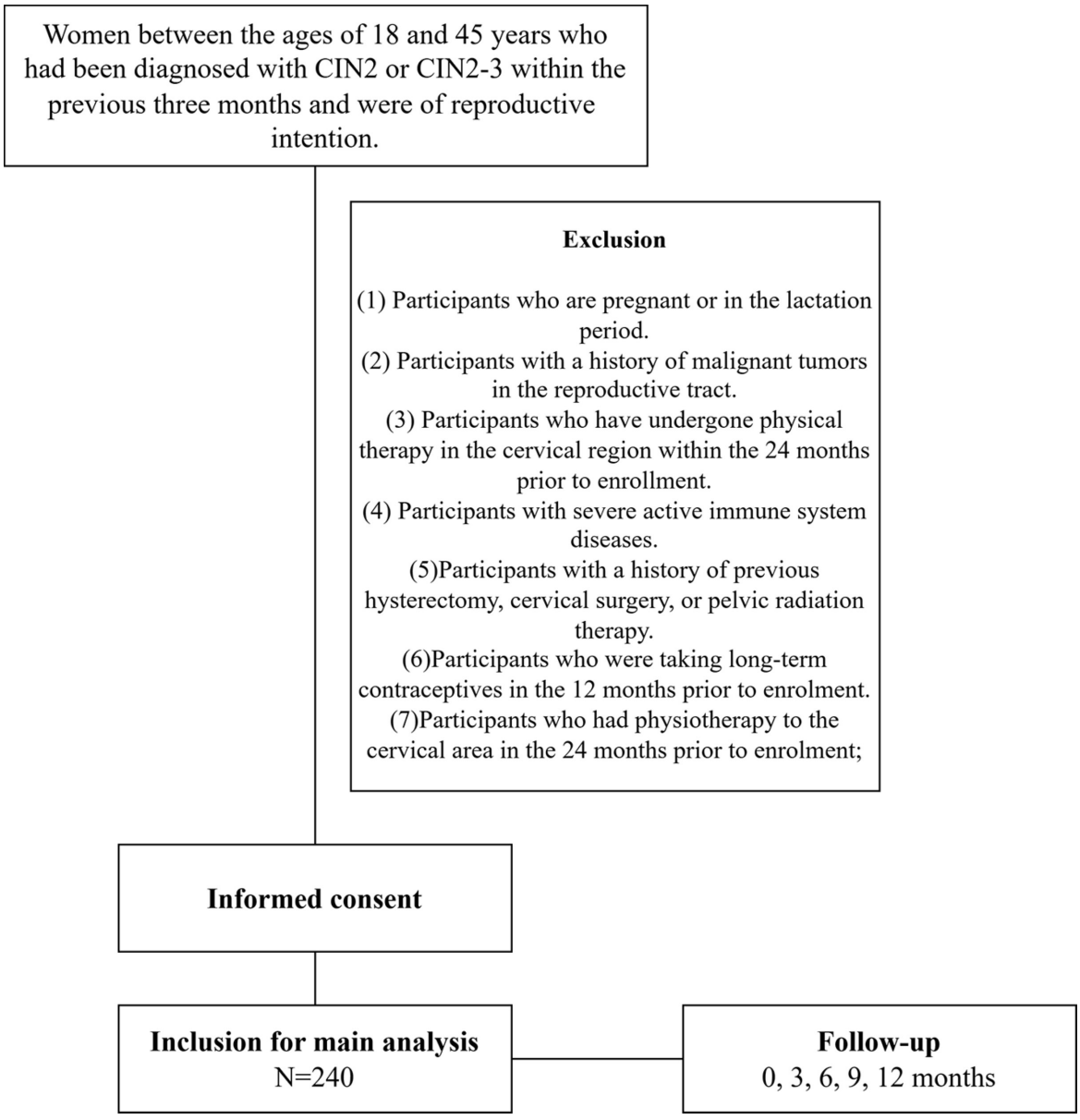

Figure 1 Selection flowchart. CIN2, cervical intraepithelial neoplasia grade 2.

Obstetric and Gynecological Diseases at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Recruitment of participants is scheduled to commence on 1 August 2023, across 20 participating clinical centres. These centres are tertiary Grade A hospitals (the highest level in the Chinese hospital classification system, representing comprehensive medical institutions with advanced facilities and expertise) strategically distributed across eastern, western, central and northern regions of China, ensuring a balanced representation of diverse socioeconomic and geographic populations. The study duration is projected to be 34 months, with completion expected by 31 May 2026.

In its current protocol version (2.0), this cohort study adheres to the Declaration of Helsinki and has received approval from the Clinical Research Review Committee of Fujian Maternal and Child Health Hospital (2022KYLLR01018). Additionally, the study has been registered in ClinicalTrials.gov (NCT05282095).

Selection and eligibility

We will conduct a prospective cohort study. Participants will consist of women diagnosed with CIN2 at the Fujian Maternal and Child Health Hospital or other research centres within the past 3 months. These participants will be consulted for their consent to participate in the study at the time of their diagnosis. They will be enrolled in the study after signing the informed consent form.

The study population comprises women aged between 18 and 45 years who have been diagnosed with CIN2 within the preceding 3 months and have reproductive intentions. At the time of enrolment, patients must not have undergone any surgical, physical or pharmacological treatments, and the area of

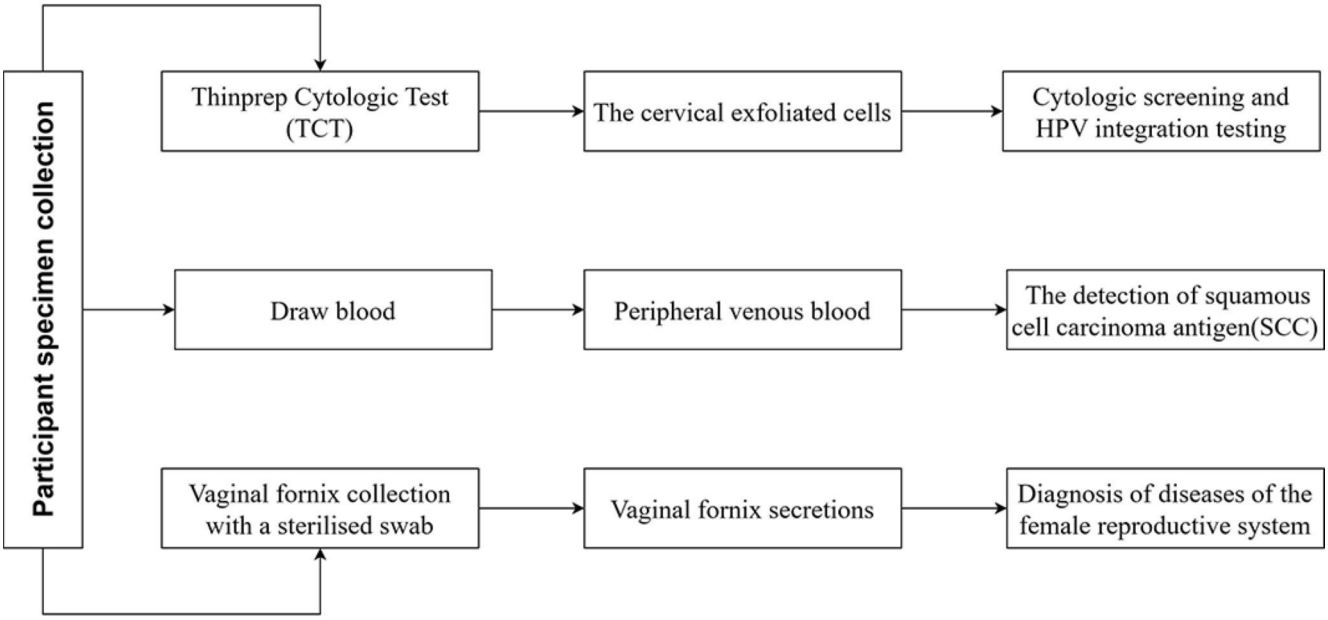

Figure 2 Specimen collection flowchart. HPV, human papillomavirus.

the colposcopic lesion must not exceed 50% of the total cervical area. During the follow-up period, no surgical, physical or pharmacological treatment will be administered in the absence of disease progression. Prior to sampling, participants are required to refrain from vaginal douching for 72 hours and from sexual intercourse for 24 hours prior to the procedure. Furthermore, participants are required to refrain from any treatment related to reproductive tract infections, HPV or other sexually transmitted infections (STIs), as well as from using antibiotics or vaginal microecological products for 1 month before sampling. It is essential that participants comprehend their voluntary involvement in the 12-month follow-up of this study and provide signed informed consent. Additionally, participants should not meet any exclusion criteria listed in figure 1.

Sample size calculation

The sample size was calculated based on findings from a pilot study, which was conducted in Wuhan, China, and involved 24 participants, and an extensive review of relevant literature in the field. In the pilot study, approximately 25% of CIN2 patients tested positive for HPV integration, while around 30% of HPV integration-positive patients demonstrated CIN2 regression after 1 year. Accordingly, the sample size was calculated using a significance level of α=0.05 and a power of β=0.2, with an anticipated 1 year CIN2 regression rate of 50% among integration-negative patients.[16]

Considering a projected loss-to-follow-up rate of 20%, this study aims to recruit 180 HPV integration-negative CIN2 patients and 60 HPV integration-positive patients, totalling 240 participants. Therefore, the study plans to enrol 240 eligible female participants.

Study procedures

This study is initiated by the Fujian Maternal and Child Health Hospital, under the supervision of the National Clinical Research Center for Obstetric and Gynecological Diseases at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Patient recruitment is planned to take place across 20 medical institutions nationwide. The study targets women diagnosed with CIN2 through histopathology within the past 3 months and aged 45 years or younger. All enrolled patients must not have undergone any cervical treatment targeting CIN2 lesions. On enrolment, each patient is assigned a unique identifier to ensure the confidentiality of their personal information. The researchers overseeing patient enrolment will provide a general overview of the study to participants, obtain their informed consent and use a computer to access the study website for entering basic patient information and disease-related clinical data. The specimens will be collected in the following sequence: four swabs of vaginal fornix secretions,[30] one sample of cervical exfoliated cells[31] and two tubes of peripheral venous blood[32] (5 mL of EDTA-anticoagulated whole blood and 5 mL of non-anticoagulated serum each). Cervical exfoliated cells will be used for HPV integration testing and cytology screening. Peripheral venous blood will be analysed for squamous cell carcinoma antigen levels,[30] while vaginal fornix secretions will be evaluated for diagnosing conditions affecting the female reproductive system. Detailed specimen collection and processing protocols are illustrated in figure 2.

The enrolment questionnaire will collect basic information about the participants. During the 3-month, 6-month, 9-month and 12-month follow-up visits,

participants are required to access the study website and complete a follow-up questionnaire to provide clinical information related to their condition. For further details on the enrolment and follow-up questionnaires, please refer to online supplemental file 2. Specimens will be collected from each patient at every follow-up visit, including four sterile swabs of vaginal fornix secretions and one sample of cervical exfoliated cells. Cervical exfoliated cells collected during the 3-month and 9-month follow-up visits will be used for HPV genotyping, whereas those collected at the 6-month and 12-month follow-up visits will serve for HPV integration detection. At the 6-month and 12-month follow-up visits, all patients will undergo a colposcopic examination and a histopathological biopsy to confirm the status of their lesions. At the 3-month and 9-month follow-up visits, the decision to perform colposcopy will be based on cervical cancer guidelines and screening outcomes. Details of each follow-up visit and the use of biological specimens are presented in table 1.

Study endpoints

Two specialised physicians will assess the specimens in accordance with the WHO's Classification of Tumours: Female Genital Tumours.[14] The final diagnosis of the patient is determined by two experts and evaluated based on all biopsy results. In the event of a discrepancy, a third expert is consulted for the final determination. Additionally, in order to minimise the risk of underestimating the severity of the lesion, multiple biopsies are performed on each patient, with samples taken from different areas.

The primary study endpoint is to determine the rate of non-regression of CIN2 at the study's conclusion, as determined by histological findings from cervical outlet biopsies. Non-regression is defined as the persistence of CIN2 status or progression to higher-grade lesions.

Secondary endpoints include the 6- and 12-month regression rates for CIN2. Regression is defined as a reduction in disease severity, resulting in regression to CIN1 or a lower lesion level. Furthermore, the regression trend has been incorporated into the secondary endpoints. A regression trend is characterised by a decrease in the surface area of dysplastic cells within the surface epithelium of the original CIN2 lesion, without achieving CIN1 status. Additionally, the eradication of HPV infection is considered a regression trend for CIN2, as its elimination often precedes the regression of CIN2 lesions.[33]

Treatment indication

According to current guidelines for managing cervical cancer and precancerous lesions, participants exhibiting the following findings at any follow-up visit will be classified into the non-regression group and receive treatment.[29 34 35]

A. Disease progression to histopathologically confirmed cervical intraepithelial neoplasia grade 3 (CIN3) or a more severe classification on cervical biopsy.
B. CIN2 lesions comprising over 50% of the visible cervix surface area at any follow-up examination.

Furthermore, if a participant contracts a STI during the study, immediate treatment will be provided. Following treatment, a decision regarding exclusion from the study will be made, depending on the nature of the STI. In cases where the infection is considered to potentially influence the study's outcomes, detailed documentation will be performed, and the data will be incorporated into the statistical analyses.

Management of lost-to-follow-up data

For participants lost to follow-up, researchers will retain preloss data and categorise these individuals into the appropriate analytic groups. Participants who did not undergo any follow-up visits postenrolment will be excluded from the analysis.

Statistical analysis

Descriptive statistics will be presented as means and SD for continuous variables, while categorical variables will be reported as frequency counts and percentages. Results will be described through tabulations of numbers (N) and proportions (%). The primary statistical analysis will use Cox proportional hazards regression to estimate HRs with corresponding 95% CIs, evaluating the association between the exposed group (HPV integration) and the unexposed group (HPV non-integration). Cox proportional hazards regression will be used to control for potential confounding variables or modifying factors in analysing the association under study. The model will incorporate the following covariates: age, cervical cytology result at the time of the index CIN2 diagnosis, the number of cervical biopsies taken at the index CIN2 diagnosis, the frequency of follow-up visits during the surveillance period and other potential confounding variables. This methodology allows for the adjustment of these factors, thereby producing more robust estimates of hazard ratios.

Missing data will be handled by evaluating the missing data patterns and applying multiple imputation techniques when data are missing at random. All analyses will be performed using the R Project for Statistical Computing (V.4.3.2, Vienna, Austria). All statistical analyses will involve two-tailed tests, with a significance threshold set at $p \leq 0.05$.

Patient and public involvement

Patients will not be involved in the design or methodology of the study. Test results for participants' specimens will be communicated in writing or via text message within seven working days after the completion of each test.

Project status

Recruitment and sample collection for the study commenced on 1 August 2023. Sample collection will continue until 31 December 2025, coinciding with the final visit of the last patient. Concurrently, all tissue blocks will undergo sectioning and evaluation. Tissue sections

Table 1 Definition and schedule of patient information collection

Variable modules	Definition	T0	T1	T2	T3	T4
Basic data	Including age, careers, weight, menstruation, maternity, smoking history, drinking history, education level, household income, HPV vaccination status, etc.	•				
Sexual behaviour	Including age at first intercourse, number of sexual partners in the last 5 years, contraceptive methods, etc	•				
Medical history	Any long-term medications or supplements taken in the last 1 year	•				
Family medical history	Including family history of hypertension, family history of hyperlipidaemia, family history of diabetes, family history of cancer, etc	•				
Clinical symptoms	Including vulvar itching, vulvar burning, vaginal odour, irregular vaginal bleeding, lower abdominal pain, painful urination or lower back pain, pain during sexual intercourse, etc	•				
Recent medication history	Therapies or medications used in the last 6 months	•				
HPV integrated test results	Testing using collected cervical exfoliated cells	•		•		•
HPV genotype test results	Testing using collected cervical exfoliated cells		•		•	
Vaginal vault discharge	For detection of vaginal microecology		•	•	•	•
SCC test results	Use of peripheral blood to detect SCC	•				
Colposcopy and histopathologic biopsy	Clarification of cervical lesions.			•		•

T0, baseline; T1, 3 months; T2, 6 months; T3, 9 months; T4, 12 months.
HPV, human papillomavirus; SCC, squamous cell carcinoma.

from enrolled women will subsequently be evaluated by the expert panel, as previously outlined. The review process for tissue sections will occur throughout the entire sample collection phase of the study. Data management and primary analyses are anticipated to be conducted between 1 December 2025 and 31 May 2026.

As of 15 May 2024, the study has successfully recruited 60 participants. Future recruitment efforts and the study duration may be extended, with an application to the local ethics committee to be submitted at the appropriate time.

ETHICS AND DISSEMINATION

The study, along with its informed consent documentation, adheres to the Declaration of Helsinki and relevant regulatory standards governing clinical research in China. Written informed consent is obtained from all

participants before their enrolment in the study. Participants are thoroughly informed about the study objectives, procedures, potential risks and benefits, their right to withdraw at any time and the measures taken to ensure confidentiality. Ethical approval has been obtained from the Clinical Research Review Committee of the Fujian Maternal and Child Health Hospital, with the ethical review number 2022KYLLR01018. Additional approvals have been granted by the participating hospitals. The study has been registered at ClinicalTrials.gov (NCT05282095). This study is conducted in strict accordance with the principles of ethics, poses minimal to no risks to participants and ensures the health rights of participants. In the event of CIN2 progression and the presence of STIs, immediate treatment will be administered, and exclusion will be determined on a case-by-case basis. All data are anonymised to protect participant confidentiality.

Publication in peer-reviewed scientific journals will achieve dissemination to the medical and scientific community. Additionally, results will be presented at academic meetings and conferences and released to the public through press releases.

DISCUSSION

In this study protocol, we have outlined a multicentre, open-label, prospective cohort study to assess the value of HPV integration in predicting disease progression in young patients with CIN2, thereby addressing the critical need to reduce overtreatment. Cervical cancer continues to be a major global health challenge, ranking as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated 606 000 new cases and 342 000 deaths worldwide in 2020.[1 2 34] The burden of cervical cancer is expected to increase further, placing additional pressure on healthcare systems already strained by limited resources.[36] While surgical interventions can be effective, they often carry significant adverse effects, highlighting the importance of precise risk stratification and prevention strategies to minimise morbidity and mortality.

The integration status of HPV has emerged as a promising biomarker for risk stratification in CIN2, offering a potential tool to reduce overtreatment and facilitate targeted interventions for high-risk patients. However, this study is not without limitations. First, the exclusion criteria, while necessary to ensure a homogeneous study population, may limit the generalisability of findings to broader CIN2 populations, such as older women or those with comorbidities. Second, the multicentre design, though enhancing the study's external validity, introduces potential variability across participating centres, despite standardised protocols. Third, the 12-month follow-up period, while sufficient to capture short-term outcomes, may not fully reflect long-term disease progression or regression patterns. Fourth, the reliance on participant compliance with presampling restrictions (eg, abstaining from sexual intercourse or vaginal douching) may introduce variability in sample quality. Finally, the study's focus on women aged 18–45, while justified by higher spontaneous regression rates and reproductive considerations, limits its applicability to older populations who may also benefit from improved risk stratification.

Despite these limitations, the study addresses a critical gap in cervical cancer prevention by investigating a promising biomarker for CIN2 risk stratification. The comprehensive data collection approach, incorporating biological samples and clinical questionnaires, provides a robust foundation for understanding HPV integration's prognostic value. The findings have the potential to significantly impact clinical practice by informing more precise management strategies, particularly in reducing overtreatment of CIN2 in young women—a prevalent issue in global cervical cancer prevention programmes.

Future research should focus on validating these findings in broader populations, including older women and those with prior treatments, as well as exploring the role of HPV integration in conjunction with other biomarkers, such as vaginal microbiome profiles. The ultimate goal is to develop a comprehensive risk stratification tool that balances the need for cancer prevention with the avoidance of unnecessary interventions, particularly in young women where overtreatment carries significant consequences.

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