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Original Research Article

CITRUS, cervical cancer screening trial by randomization of HPV testing intervention for upcoming screening: Design, methods and baseline data of 18,471 women

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ABSTRACT

Background: To assess the efficacy of screening with concurrent liquid-based cytology and human papillomavirus (HPV) testing for primary cervical cancer screening, we initiated a randomized trial entitled CervIcal cancer screening Trial by Randomization of HPV testing intervention for Upcoming Screening (CITRUS).
Methods: Between June 2013 and March 2015, women aged 30–64 years of age who participated in a regular cervical cancer screening program (every 2 years) were invited to enrollment of our study. After giving their informed consent, 18,402 women were randomly assigned to liquid-based cytology as the control group (n = 9145) or to HPV DNA testing with liquid-based cytology as the intervention group (n = 9257). We subsequently compared the incidence rate of cervical intraepithelial neoplasia (CIN), the rate of false positive tests and the rate of overdiagnosis, as well as assessing the risks and benefits of receiving screening for women in both groups. The primary outcome of our study was the incidence of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) during the study period of around 6 years.
Results: In the control group, 97.9% of women were NILM, and 2.06% ASC-US or worse (ASC-US+). In the intervention group, 87.13% of women were NILM/HPV negative, 0.72% ASC-US/HPV negative, 10.34% NILM/HPV positive, 0.69% ASC-US/HPV positive, 0.90% worse than ASC-US/either HPV. Positive HPV testing was not linearly related to age in our study.
Conclusions: Insights from CITRUS will provide future prospects for cervical cancer screening focused on the use of HPV testing in Japan.
Clinical trial registration number: NCT01895517, UMIN000010843, TRIUC1312.

1. Introduction

From the results of basic research [1], infection with human papillomavirus (HPV) is widely accepted as the major cause of cervical cancer. The period between infection and the onset of cervical cancer, which includes the continuous infection of HPV and conversion to dysplasia or worse and continuation thereof, is known to be more than 10 years [2], with the possibility that dysplasia regresses spontaneously.

Abbreviations: AGC, atypical glandular cells; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells cannot exclude an HSIL; ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; DNA, deoxyribonucleic acid; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; JSCC, Japanese Society of Clinical Cytology; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy; SCC, squamous cell carcinoma; SIL, squamous intraepithelial lesion.

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The purpose of cervical screening is to prevent invasive cervical carcinoma by detecting precancerous lesions such as grade 2 (CIN2) and grade 3(CIN3) cervical intraepithelial neoplasia. Cervical cancer screening by cytology has reduced the incidence of invasive cervical cancer in many countries, as has been reported on numerous occasions in the literature [3]. However, cervical cancer remains the fourth most common cancer in the world among women [4]. Also, in recent years, human papillomavirus (HPV) testing is known to have more sensitivity than cytology for the detection of CIN, whereas it has less specificity [5,6]. However, increased sensitivity in screening modality may increase the false-positive rate due to the presence of regressing lesions.

In western countries, several randomized controlled trials have been performed in which HPV-based screening for cervical cancer was compared with cytology-based cervical screening, and women were followed up for at least two rounds of cervical screening [7–11]. Despite the difference in protocols, these studies have shown a relatively low incidence of CIN3+ after first screening using HPV testing compared with cytology alone. Moreover, pooled analysis of four European trials led to a conclusion that HPV testing based screening may provide 60–70% greater protection against cervical carcinoma in comparison with cytology-based screening [12].

The World Health Organization has recommended that scientific investigation be performed in each specific country to choose strategies for cervical cancer screening, as sensitivity and specificity may be influenced by the diagnostic performance of cytological diagnosis according to how the medical checkup is performed, the degree of skill of cytotechnologist, and by regional or country-specific circumstances such as sexual activity [13,14]. Accordingly, we believe that a specific trial is needed in Japan due to differences from western countries.

A nationwide cervical cancer screening program by Papanicolaou (Pap) smear test has been implemented in Japan since 1983. Since then, the incidence of cervical cancer has declined. However, scientific evidence of the relative efficacy of HPV-based versus cytology-based screening has not yet been elucidated in our country. Therefore, we have been in need of scientific evidence for the implementation of HPV-based cervical screening.

Under such circumstances, this trial, which is a population-based, open-labeled, randomized controlled study, was launched as part of a cervical screening program organized by municipalities. Our goal was to assess whether HPV testing decreases the cumulative incidence of CIN3+ and CIN2+ as precursors of cervical cancer. Further, we explored the appropriate screening interval to decrease overdiagnoses of regressive CIN based on a comparison with other similar trials.

We describe the trial design and cross-sectional baseline data of the 18,471women enrolled in CITRUS, including the age-related prevalence of HPV test status and cytology results at baseline.

2. Patients and methods

2.1. Trial design

CITRUS was initiated in the setting of regular screening programs, as a population-based, open-labeled, randomized (1:1) controlled study of participants undergoing cervical cancer screening. This trial was approved by the institutional review board at Keio University School of Medicine (approval number: 20130042). All participants received information on the purpose and nature of this study as well as potential risks and benefits. Thereafter, written informed consent for participation was obtained from each patient. The study is registered at Clinical Trial.gov (NCT01895517) and UMIN Clinical Trials Registry (UMIN000010843). In addition, this study is being performed in accordance with the Declaration of Helsinki and the Ethical Guideline on Clinical Studies of the Ministry of Health, Labour and Welfare of Japan.

2.2. Participants

Eligibility for this trial is as shown in Table 1. Briefly, women aged 30–64 years who were not pregnant, had never undergone hysterectomy or cervical conization, had never had cytological abnormalities or cervical invasive cancer, and who were not scheduled to receive planned HPV testing in the next six years were eligible for enrollment.

2.3. Study settings

Patients were enrolled for 22 months (from June 2013 to March 2015) from hospitals, medical centers and community-based medical facilities in Yamanashi Prefecture and Kashiwa City, Chiba Prefecture. Initially, the enrollment period was 10 months, but this period was extended to 22 months due to insufficient accrual of participants. The follow-up is ongoing and will end when screening results for all registered participants are obtained or when investigation to collect follow-up data for all registered participants is completed. Also, the steering committee reviews the data at 2 and 4 years to evaluate whether it is appropriate to continue the study. Based on the results of the interim data review, this committee recommended the continuation of the study. Final analysis will be commenced at 6 years after when last participants who enable follow-up are registered.

2.4. Randomization

The patients were divided into two groups according to stratified randomization, and the factor was regions (Yamanashi

Table 1
Clinical eligibility criteria.

Inclusion criteria
1. Women aged 30 to 64 years at the time of informed consent
2. Participants who provided written informed consent

Exclusion criteria
1. Women who will receive planned HPV DNA testing in a local government cervical cancer program within the next six years.
2. Women who have previously had invasive cervical cancer.
3. Women who have undergone cervical conization.
4. Women who have undergone hysterectomy.
5. Women who have had or currently have cytological abnormalities and are under follow-up.
6. Women who are found to be pregnant.
7. Women judged ineligible for this trial by a physician.

HPV, Human Papillomavirus; DNA, DeoxyriboNucleic Acid.