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SPECIAL COMMUNICATION

World Health Organization Guidelines for treatment of cervical intraepithelial neoplasia 2–3 and screen-and-treat strategies to prevent cervical cancer

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ABSTRACT

Background: It is estimated that 1%–2% of women develop cervical intraepithelial neoplasia grade 2–3 (CIN 2–3) annually worldwide. The prevalence among women living with HIV is higher, at 10%. If left untreated, CIN 2–3 can progress to cervical cancer. WHO has previously published guidelines for strategies to screen and treat precancerous cervical lesions and for treatment of histologically confirmed CIN 2–3. *Methods:* Guidelines were developed using the *WHO Handbook for Guideline Development* and the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. A multidisciplinary guideline panel was created. Systematic reviews of randomized controlled trials and observational studies were conducted. Evidence tables and Evidence to Recommendations Tables were prepared and presented to the panel. *Results:* There are nine recommendations for screen-and-treat strategies to prevent cervical cancer, including the HPV test, cytology, and visual inspection with acetic acid. There are seven for treatment of CIN with cryotherapy, loop electrosurgical excision procedure, and cold knife conization. *Conclusion:* Recommendations have been produced on the basis of the best available evidence. However, high-quality evidence was not available. Such evidence is needed, in particular for screen-and-treat strategies that are relevant to low- and middle-income countries.

1. Introduction

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion that is diagnosed by histology and has three stages: CIN1, CIN2, and CIN3. If left untreated, CIN2 or CIN3 (CIN 2–3) can progress to cervical cancer. It is estimated that approximately 1%–2% of women worldwide develop

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CIN 2–3 each year, and the prevalence is reportedly higher in HIV-positive women, at around 10% [1–5]. Standard practice for diagnosis of CIN is to perform a colposcopic visual examination in women who screen positive, take biopsy samples of suspicious lesions, and then treat only when CIN 2–3 has been histologically confirmed. Treatments include cryotherapy, loop electrosurgical excision procedure (LEEP; including large loop excision of the transformation zone or cone biopsy with loop excision), and cold knife conization (CKC).

An alternative approach to diagnose and treat CIN is "screen and treat," in which treatment decisions are based on the results of a screening test instead of histologic confirmation. Treatment is provided soon or, ideally, immediately after a positive screening test. The goals of the screen-and-treat strategy are to reduce cervical cancer and related mortality with few adverse events, while linking screening with treatment to make the process more convenient for women. The strategy includes a screening test or a sequence of tests, links to appropriate treatments for women who screen positive, and referral for treatment of women with invasive cervical cancer. Widely used screening tests include tests for HPV, cytology (cervical smears), and unaided visual inspection with acetic acid (VIA). However, there is some uncertainty across national programs about which tests to provide and what treatment to provide for women who screen positive.

In 2004, WHO published a guide to assist clinicians and program managers in the diagnosis and treatment of CIN to prevent and control cervical cancer entitled *Comprehensive Cervical Cancer Control: a Guide to Essential Practice (C4-GEP)*. Since then, new evidence for the effects of treatments and screening tests for CIN has become available. On the basis of this evidence, WHO published updated recommendations for the use of cryotherapy to treat CIN in 2010 [6,7]. In the present report, guidelines that provide recommendations for the use of cryotherapy, LEEP/large loop excision of the transformation zone, and CKC to treat histologically confirmed CIN 2–3 are described, along with recommendations for screen-and-treat strategies. For countries where a screen-and-treat program or treatment protocol already exists, these recommendations were developed to assist decision makers to determine which screen-and-treat program or treatment should be used. For countries where a screening program or treatment protocol does not currently exist, these recommendations can be used to determine which screen-and-treat program or treatment protocol to implement. The target audiences for these guidelines are primarily low- and middle-income countries. These guidelines have been previously published by WHO, and they are reproduced here by permission of WHO; additional details and background materials are available on the WHO website [8,9].

2. Materials and methods

The methods for developing the present guidelines followed the *WHO Handbook for Guideline Development* [10].

2.1. Guideline Development Group

The Guideline Development Group (GDG) consisted of 18 members who provided expert clinical guidance and support. An External Review Group consisted of 35 professionals including healthcare providers with experience in screening and treating CIN, pathologists, researchers in cervical cancer prevention and treatment, program directors, health educators, epidemiologists, public health officers, nurses, and methodologists. The GDG worked with the Methods Group (MG) from the MacGRADE Centre at McMaster University, a WHO Collaborating Centre, with expertise in evidence synthesis and guideline development processes.

2.2. Formulating questions and determining outcomes

In February 2011, the GDG met and identified screening and treatment questions, and outcomes to consider when making recommendations. Then, by anonymous survey, the GDG prioritized the questions by clinical relevance and ranked outcomes from 1 (not at all important in decision making) to 7 (very important). They agreed on eight questions comparing screen-and-treat strategies, nine questions for treating CIN 2–3 or adenocarcinoma in situ, and outcomes ranked as 4 (important) or higher (Box 1).

2.3. Systematic review of the evidence

The MG conducted systematic reviews of the diagnostic accuracy of tests and the effects of treatment following the methods of the Cochrane Collaboration [11]. The full reviews have been published [12,13]. Briefly, the MG searched Medline and Embase up to February 2012 for randomized and nonrandomized controlled trials, and observational studies of treatments and for screening strategies related to HPV compared with VIA, and VIA compared with cytology; and from January 2010 to November 2011 to update a review being conducted for HPV compared with cytology [14]. The search for adverse events of treatments was updated to July 2012, and the search for colposcopy was updated to September 2012.

To compare benefits and harms of one screen-and-treat strategy with another, the MG developed a mathematical model. The model includes data for CIN 2–3 prevalence, natural progression, the pooled diagnostic test accuracy for screening tests, and pooled effects of treatment for women of unknown and known HIV status. It provides data for downstream consequences of treatment/no treatment after women screen positive or negative, such as cervical cancer, mortality, recurrence of CIN 2–3, adverse events of treatment (and overtreatment), resource use, and feasibility. The predicted benefits and harms from the model, and the quality of evidence assessed using the Grading of Recommendations Assessment, Development and Evaluations (GRADE) approach were summarized in evidence tables [15]. The quality of the evidence is assessed as high ⊕⊕⊕⊕, moderate ⊕⊕⊕⊖, low ⊕⊖⊖⊖, or very low ⊕⊖⊖⊖. The summary and quality of the evidence, patient values and preferences, and resource implications and feasibility were compiled into Evidence to Recommendations Tables to facilitate decision making (available on the WHO website) [8,9].

2.4. Development of recommendations

On April 26–28, 2012, a meeting to review the tables and develop recommendations was convened. It was chaired by a member of the

Box 1

Outcomes for treatment and screen-and-treat strategies identified as important to making recommendations (in order of importance).[a]

Treatment outcomes	Screen-and-treat outcomes
1. Residual/recurrent CIN 2–3 (after 6, 12, and 24 months)	1. Mortality from cervical cancer
2. Damage to other organs/other surgery required (e.g. injury to bladder or urethra)	2. Cervical cancer incidence
3. Major bleeding (requiring hospitalization/blood transfusion)	3. Detected CIN 2–3
4. Maternal death	4. Major infections (requiring hospitalization and antibiotics [e.g. pelvic inflammatory disease])
5. HPV negative (after 6, 12, and 24 months)	5. Maternal bleeding
6. Major infections (requiring hospitalization and antibiotics)	6. Premature delivery
7. Premature delivery	7. Fertility
8. Spontaneous abortions	8. Identification of sexually transmitted infections (benefit)
9. Pelvic inflammatory disease	9. Minor infections (requiring outpatient treatment only)
10. Infertility	
11. Minor bleeding (requiring packing or suturing)	

Abbreviation: CIN, cervical intraepithelial neoplasia.

[a] Partly reproduced from the WHO guidelines [9], by permission of WHO.

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