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Book Review

Book Review: IARC handbooks of cancer prevention, volume 18: Cervical cancer screening

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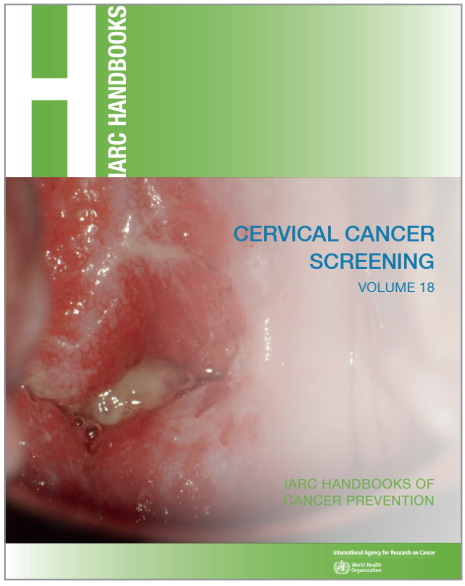
Conflict of Interest
No potential conflicts of interest relevant to this article was reported.



By IARC Working Group on the Evaluation of Cancer-Preventive Interventions
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Can we eliminate cervical cancer?

Cervical cancer is preventable and curable as long as it is detected early and managed effectively. However, cervical cancer is a global burden as it is the fourth most commonly diagnosed female cancer and the fourth most common cause of female cancer deaths worldwide [1]. In 2020, cervical cancer accounted for approximately 604,000 new cases and 342,000 deaths. The burden of cervical cancer varies markedly across the world, with a 10-fold variation between the highest and lowest incidence rates and a more than 15-fold variation between the highest and lowest mortality rates. The highest cervical cancer incidence and mortality rates are observed in countries with the lowest levels of the Human Development Index. The incidence rates are also higher in countries with a high prevalence of human immunodeficiency virus (HIV) infection or lack of sustained cervical cancer screening programs.

Since Dr. Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization (WHO), announced a global call to action toward eliminating cervical cancer in 2018 [2], cervical cancer has become a major public health problem. In 2020, WHO launched a

global initiative to accelerate the elimination of cervical cancer and endorsed an ambitious, historical milestone [3]. All countries should meet the following targets by 2030 to achieve the goal of elimination, defined as a threshold of 4 cases of cervical cancer per 100,000 women per year, by the next century: 1) 90% of girls fully vaccinated with the human papillomavirus (HPV) vaccine by the age of 15 years; 2) 70% of women screened using a high-performance test by the age of 35 years, and again by the age of 45 years; and 3) 90% of women with precancer treated and 90% of women with invasive cancer managed. Indeed, cervical cancer screening and prevention have become more critical than ever.

International Agency for Research on Cancer (IARC) handbooks of cancer prevention, volume 18 represents the view and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met remotely between June and October 2020. The Working Group of 27 independent international experts reviewed the scientific evidence and assessed the cancer-preventive and adverse effects of various screening methods for cervical cancer. This handbook updates the previous IARC handbooks of cancer prevention, volume 10, which was published in 2005.

What is "cancer prevention"? This handbook starts with the definition of cancer prevention, which encompasses primary, secondary, and tertiary prevention. In brief, primary prevention refers to actions that can lower the risk of developing cancer. Secondary prevention entails methods that can find and alleviate precancerous conditions or find cancers in the early stages when they can be treated more successfully. Tertiary prevention aims to reduce the impact of long-term disease and disability caused by cancer or its treatment. The IARC handbooks of cancer prevention provide critical reviews and evaluations of the scientific evidence on the secondary cancer prevention measures, also implemented in volume 18.

The IARC handbooks of cancer prevention, volume 18 highlights that the purpose of cervical cancer screening and treatment is to reduce the incidence of and mortality from cervical cancer by identifying women with precancerous cervical lesions and early invasive cancer and treating them appropriately. The handbook consists of 7 chapters:

Chapter 1 introduces the global burden of cervical cancer with epidemiologic data. Incidence, mortality, and trends in incidence of cervical cancer are presented by WHO regions and countries. The lifetime risk of cervical cancer and the prevalence of HPV infection in women are presented. Chapter 1 also provides a pathologic overview of the cervical tumors [4] and the revised International Federation of Gynecology and Obstetrics (FIGO) staging [5]. Treatment methods of cervical precancerous lesions are also introduced: destructive or ablative techniques, including cryosurgery and thermal coagulation, and excisional techniques, including cold-knife excision, large loop excision of the transformation zone (LLETZ)/loop electrosurgical excision procedure (LEEP), and hysterectomy.

Chapter 2 introduces the cervical cancer screening programs currently available in various WHO regions and countries. The screening tests in existing programs globally include cytology alone, HPV testing alone, HPV and cytology co-testing, and visual inspection. Two main categories of screening, "organized population-based programs" and "opportunistic screening", are explained and compared. In general, organized population-based screening programs are regarded as more effective, cost-effective, and equitable than opportunistic screening. Quality assurance with performance indicators (also known as quality measures) of screening programs are also introduced in this chapter.

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Chapter 3 provides strategies to increase the participation of women in the cervical cancer screening programs. Positive and negative determinants of screening participation are comprehensively analyzed in multidimensional aspects of health frameworks: health policy and structural aspects and at the individual, health system, and health provider levels.

Chapter 4 introduces preventive (benefits) and adverse effects (harms) of cervical cancer screening methods based on the review of randomized screening trials and observational studies: 1) visual screening methods (e.g., visual inspection with acetic acid [VIA] and visual inspection with Lugol's Iodine [VILI]); 2) cytological methods (e.g., conventional cytology and liquid-based cytology); 3) HPV testing; and 4) Colposcopy. Chapter 4 also provides evidence-based evaluations on the comparative effectiveness of screening methods. Examples include HPV DNA testing versus VIA, HPV DNA testing versus cytology, HPV DNA testing alone versus co-testing (combined HPV DNA testing and cytology), etc.

One half of Chapter 5 introduces "screen-and-treat approaches" designed to require fewer resources and decrease the need for repeat visits, compared to "multistep cervical cancer screening programs," which require infrastructure, skilled workforce, quality control efforts, and multiple visits. The other half of Chapter 5 introduces cervical cancer screening methods and surveillance strategies for women at differential risks, such as women living with HIV, those with a personal history of cervical precancerous lesions, older women, and HPV vaccinated populations.

Chapter 6 summarizes Chapters 1 to 5, and Chapter 7 provides conclusive statements on the comparative effectiveness of cervical cancer screening methods and triage based on the study results.

In real world, public health options to prevent cervical cancer vary among the regions and relate to many factors. Therefore, this handbook provides no definite recommendations concerning regulations or legislation, which are the responsibility of individual governments or other international authorities. However, this handbook may help national and international authorities or health agencies devise cervical cancer prevention programs, develop evidence-based interventions or recommendations, estimate the balance of benefits and harms, and consider cost-effectiveness evaluations.

This handbook broadens our viewpoint regarding cervical cancer screening programs and points out the issues we usually overlook during clinical practice. First, the IARC Working Group emphasizes that quality assurance is particularly important in cervical cancer screening, in which vast populations of apparently healthy women are invited to participate in detecting asymptomatic disease. Quality assurance measures the quality of service delivered and enables variability in service to be identified and adjustments to be made so that uniform care is provided to the participants in screening programs. WHO has provided global, core, and optional quality indicators, ready to use in local screening programs.

Second, the IARC Working Group points out that all cervical cancer screening programs have potential physical and psychological harms. Women who felt pain during the cytological examination were less likely to participate in further cervical cancer screening. This handbook introduces scientific evidence that good communication positively affected the screening experience and improved screening adherence. Psychological harms (e.g., anxiety and distress) may occur before, during, or after screening and may relate to receiving the

results or treatment procedures. Some harms might originate from a false-positive test result of the screening test or overscreening. These harms may lead to unnecessary examinations and treatments and waste of medical resources. In the implementation of a population-based screening program, the balance of potential benefits against potential harms should be explicitly weighed at the population level.

Third, the IARC Working Group conducted a comprehensive literature review and considered that the use of self-sampling approaches for HPV DNA detection provided high values of sensitivity and specificity compared with the use of clinician-collected samples. The self-sampling approach has a great potential to reduce social inequalities in screening, especially if offered in person within the primary healthcare system. However, the self-sampling studies had some limitations. The evidence on whether self-collected samples could be used for genotype comparison or for the detection of adenocarcinoma and adenocarcinoma in situ remains limited. To date, diagnostic protocols and workflow have not been well documented. The trade-offs in coverage or participation when self-sampling is implemented at a large scale need to be explored further.

This handbook might not suit those who want to quickly search the updated guidelines for screening and treatment for cervical precancerous lesions and cervical prevention [6]. Instead, this handbook objectively integrates streams of current evidence on cervical cancer prevention, which can be used as the basis of public health decisions. Therefore, we would like to recommend this handbook to researchers studying public health science, health policy-makers, government agencies, and healthcare professionals, especially gynecologic oncologists and general gynecologists, who are on the frontline of cervical cancer screening.

Unfortunately, this handbook does not address the effects of HPV vaccination and HPV vaccination programs, as they are all related to primary prevention. The readers might find out information and recommendations on the bivalent, quadrivalent, or nonavalent HPV vaccines and their recommendations on the websites of WHO [7] and Centers for Disease Control and Prevention [8] and elsewhere [9].

Although HPV vaccination and cervical cancer screening are complementary, they have been managed separately because they apply to different periods in a woman's lifetime. However, both should be viewed in the same continuum in the natural history of cervical cancer. The integration and optimization of HPV vaccination and cervical cancer screening programs will provide a long-term, positive effect on the elimination of cervical cancer. Hope to say 'goodbye' to cervical cancer in the near future.

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