

CERVICAL CANCER SCREENING

VOLUME 18

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met remotely, 12–16 October 2020

LYON, FRANCE - 2022

IARC HANDBOOKS OF
CANCER PREVENTION

GENERAL REMARKS

WHO initiative

In May 2018, Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization (WHO), announced a global call to action towards the elimination of cervical cancer, to support and engage countries to scale up evidence-based, cost-effective interventions. In August 2020, the Seventy-third World Health Assembly endorsed the WHO global strategy to accelerate the elimination of cervical cancer as a public health problem 2020–2030 ([WHO, 2018, 2020](#)).

WHO guidance for cervical cancer prevention is integral to reaching the United Nations Sustainable Development Goals targets for both health (Goal 3) and gender equality (Goal 5). Meeting the following targets by 2030 will put all countries on the path towards the goal of elimination as a public health problem, which is defined as a threshold of 4 cases of cervical cancer per 100 000 women per year, by 2100:

- 90% of girls fully vaccinated with the human papillomavirus (HPV) vaccine by age 15 years;
- 70% of women screened using a high-performance test by age 35 years and again by age 45 years; and
- 90% of women identified with cervical disease receive treatment (90% of women with

precancer treated, and 90% of women with invasive cancer managed).

In this context, countries are updating their protocols for secondary prevention of cervical cancer. The 2030 cervical cancer elimination targets require up-to-date evidence on screening tests and modalities of screening, as well as new and simpler algorithms for screening and treatment of precancerous lesions that can be implemented at scale.

History of cervical cancer screening

Cervical screening was introduced before the etiology and natural history of cervical cancer were understood, i.e. before the discovery that cervical cancer is caused by a persistent infection with a carcinogenic HPV type. Early cytologists recognized that microscopic signs of invasive cancer, as well as some earlier signs suggesting a less definite probability of cancer, could be found in exfoliated cells (not just in fixed tissue).

The technology of cervical screening based on exfoliated cervical cells was proposed in 1928 by Papanicolaou ([Papanicolaou, 1928](#)) and Babeş ([Babeş, 1928](#)) and was formally validated in 1941 ([Papanicolaou & Traut, 1941](#)). However, it was not until the 1950s and 1960s that cervical screening by cytology (commonly known as Pap

testing) gained a prominent position in primary care. Pap tests reported with the five-level classification system for the probability of cancer became the mainstay of cervical cancer prevention, mostly as an opportunistic intervention in women's primary care visits, initially in the USA and Canada.

In the 1960s, Denmark, Finland, and Sweden, and jurisdictions such as British Columbia in Canada, instituted organized screening programmes for all adult women. Norway started a programme in the 1970s, and England implemented a fully organized programme in the late 1980s ([Läärä et al., 1987](#); [Quinn et al., 1999](#); [Safaeian et al., 2007](#)). Throughout the rest of the 20th century, worldwide use of cervical cytology grew, but coverage remained low in resource-limited regions.

Where cytology screening programmes have been established and maintained, they have proven to be successful in reducing the burden of cervical cancer. A successful programme requires high population coverage coupled with technical and programmatic quality assurance. However, because multiple visits and treatments are required in such programmes, they engender high societal cost. This is probably why cervical cytology-based screening programmes have not achieved broad global coverage.

During the 1980s, the central causal role of HPV infection in cervical cancer was established, and the Bethesda system ([Solomon, 1989](#)) introduced the category of atypical squamous cells of undetermined significance (ASC-US) (see Sections 1.2.3c and 4.3.1d).

By the mid-1990s, it had been established that persistent infections with certain subtypes of HPV were the necessary cause of almost all cases of cervical cancer. Accordingly, the HPV research community, in collaboration with the nascent HPV testing industry, proposed that only abnormalities that test positive for carcinogenic HPV types should merit referral for colposcopy. Large-scale clinical studies confirmed the

value of such tests, and HPV testing was adopted in some countries as an adjunct test for women with ASC-US. The concurrent advent of liquid-based cytology, which is based on automated processing and production of thin-layer cervical slides, substantially improved the efficiency of Pap smear reading. Liquid-based cytology also enabled HPV testing of women with ASC-US on the same sample.

Although triage of ASC-US-positive women with HPV testing was quickly adopted in several high-resource settings, the usefulness of HPV testing as a primary screening test was immediately evident. Molecular testing for the DNA or RNA of carcinogenic HPV types was shown to have the high sensitivity and throughput required in mass screening. Trials were launched in Europe and North America to compare cytology with HPV testing; they showed the effectiveness of HPV testing in long-term follow-up of studies using multiple rounds of screening.

Detection of one of the carcinogenic HPV types is now established to be the most sensitive test for identifying women at elevated risk of developing cervical precancer and cancer. However, HPV infection is very common and is typically transient. In well-organized settings, follow-up surveillance of women with an HPV-positive test result is used to determine the persistence of the infection; this is the hallmark of an increased risk of cancer. Alternatively, to determine which HPV-positive women are at sufficiently high risk to recommend treatment, a secondary test (triage test) can be performed. Common options for triage are HPV genotyping, cytology (conventional or liquid-based), or colposcopy, and molecular biomarkers are now marketed for this purpose (see Section 4.4.7).

The above-mentioned developments have taken place mainly in high-resource settings. In resource-limited settings, cervical cancer screening based on direct visualization of the cervix, either unaided or aided by magnification or using visualization enhancements with acetic

acid or Lugol's iodine, has been widely used, although without extensive assessment.

Definition of cervical precancer

Cervical screening aims to identify precursors of cervical cancer, thus enabling ablative or excisional treatment to prevent invasive cancer. Therefore, screening is distinguished from stage shifting, which is the diagnosis and treatment of cancer at an earlier stage, to improve the chance of a cure.

The design and evaluation of cervical screening tests and strategies depend on very careful definition of serious precursors that represent true surrogate end-points for risk of invasive cancer. Unless the screening target of precancer is defined accurately and strictly, error is introduced into screening tests and assessments of programme effectiveness.

In this *Handbook*, the Working Group used stringent definitions of precancer, for example by considering only cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma in situ (AIS) and lesions found in association with carcinogenic HPV types.

Inequalities

The main structural determinant of participation in cervical cancer screening is social inequality in health. Cervical cancer disproportionately affects women of low socioeconomic status who have poor access to screening, diagnosis, and treatment services. Contextual aspects, including education, employment, and social protection policies, act as modifiers or buffers that influence the effects of socioeconomic status on participation ([Goss et al., 2013](#); [Yabroff et al., 2020](#)).

Gender inequality, which refers to the differential access of women to structural resources, power, authority, and control, is also a critical determinant of women's capacity to prevent cervical cancer ([Kangmennaang et al., 2018](#)). How health-care services are organized and respond to women's needs has been correlated with screening participation. Self-collection of samples for HPV testing has been shown to be effective in increasing screening participation among underscreened women ([Arrossi et al., 2015](#)). Therefore, it has great potential to reduce social inequalities in screening, especially if offered in person within the primary health-care system.

Women living with HIV in low-resource settings

Women living with HIV have a higher risk of acquiring HPV, of having persistent HPV infection, and of developing large precancerous lesions, and have a high rate of treatment failure and recurrence of precancer. The natural history of HPV infection in women living with HIV drives the screening and treatment programmes for effective prevention of cervical cancer in women living with HIV in all geographical regions of the world, especially in the regions with the highest prevalence of HIV and incidence of invasive cervical cancer.

Section 5.2.1 of this *Handbook* presents a narrative review of the issues encountered with screening of women living with HIV, mostly in low-resource settings. However, the evaluations are of the effectiveness of the screening methods in the general population, without a particular focus on women living with HIV. For recommendations for screening in this population, the reader is referred to the updated WHO guidelines for screening and treatment of cervical precancer for cervical cancer prevention ([WHO, 2021](#)).

Impact of the COVID-19 pandemic on cervical cancer screening

The start of the COVID-19 pandemic, in early 2020, led to a gradual suspension of cancer control activities in most countries. For cervical cancer, screening services were interrupted or scaled down substantially to enable hospitals, clinics, and laboratories to prioritize the health-care needs of patients affected by COVID-19. In addition, with the closing of primary and secondary schools, school-based HPV vaccination was interrupted. Cancer control leaders worldwide have confirmed that reductions in cervical cancer screening activities were dramatic and that coverage of HPV vaccination will return to pre-pandemic levels over time.

The reduced access to screening and vaccination after the reopening of services, which is probably caused by safety concerns, will eventually disappear. As societies reopen and the public regains confidence in resuming health-seeking behaviours, screening and vaccination coverage will return to pre-pandemic levels. However, it is expected that the health-care disruptions that took place in 2020 and beyond will lead to a worsening in the severity of lesions detected on screening in the next few years, and a measurable increase in the incidence of cervical cancer. The most relevant question is: how long will it take for cervical cancer control activities (i.e. screening and vaccination) to reach the planned heightened levels proposed by WHO for the elimination of the disease?

Integration of screening and vaccination in the elimination of cervical cancer as a public health problem

The ambitious goal of eliminating cervical cancer as a public health problem, as adopted by WHO and sanctioned by several countries, is a pressing opportunity. It requires concerted action by all countries, vaccine manufacturers, donor communities, manufacturers of diagnostic tests, and the global health-care community to reach the global targets by 2030. Properly deploying such an ambitious action plan will require the integration of all processes related to HPV vaccination, cervical cancer screening, and clinical treatment and follow-up of all women with precancerous lesions and cancer.

The first 10 years of HPV vaccination programmes have provided evidence on the impact of vaccination with the bivalent or quadrivalent vaccines, which target HPV16 and HPV18. The nonavalent vaccine has been deployed only in the past few years, and therefore its impact has not been ascertained to the same extent as that of the bivalent and quadrivalent vaccines. The impact of the bivalent and quadrivalent vaccines is clear in terms of the decrease in the prevalence of infections with HPV16 and HPV18 and of cervical lesions associated with these HPV types ([Pollock et al., 2014](#); [Kavanagh et al., 2017](#)). It is plausible to expect that in the near future the prevalence of lesions caused by HPV types 31, 33, 45, 52, and 58 will also decrease comparably in countries that have introduced the nonavalent vaccine in their programmes. Such additional reductions may be observed towards the end of the 2020s, as the first birth cohorts vaccinated with the nonavalent vaccine become old enough to attend cervical cancer screening.

As the prevalence of cervical precancer decreases further in settings with established screening and vaccination programmes, the clinical utility of high-frequency screening will be questioned, because of the deterioration of the balance of benefits and harms that is inherent in any disease-screening activity. An important challenge for future policy-makers will be the decision to stop screening altogether in settings that maintain only a few screening opportunities during a woman's lifetime (e.g. countries in Europe with organized screening programmes) or to decrease to one or two screens over a lifetime in settings that maintain high-frequency screening (e.g. the USA).

In this regard, a possible decision framework is to use benchmarks of risk tolerance based on screening practices for other cancer types that are rare (Tota et al., 2020). For example, vulvar cancer and vaginal cancer are less common than cervical cancer in the USA today but have relatively poor survival. Although screening would be feasible via cytology and HPV testing for these cancer types, it is not practised and there has never been a proposal for screening. Therefore, the burdens of morbidity and mortality caused by vulvar and vaginal cancers are benchmarks of risk tolerance for inaction in prevention that could assist eventual decisions to stop cervical cancer screening altogether or to decrease to one or two screens over a lifetime (Tota et al., 2020).

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