HAUTE AUTORITÉ DE SANTÉ

PUBLIC HEALTH GUIDELINES SUMMARY

Evaluation of human papillomavirus (HPV) tests for primary screening of precancerous and cancerous lesions of the cervix and the role of p16/Ki67 dual immunostaining

July 2019

CONTEXT

Since the Ministerial Order of 4 May 2018, cervical cancer screening in France has been based on an organised national screening programme. The national screening programme is based on current French guidelines for cervical cancer screening, i.e., cytology testing in asymptomatic women aged 25 to 65 years every 3 years, following two consecutive normal tests performed one year apart. In its 2010 guidelines, the HAS considered that switching to the HPV test as a screening test was premature but might ultimately be implemented once organised screening was in place, particularly in terms of coverage and quality assurance measures. Guaranteeing the quality of the cervical cancer screening programme is crucial insofar as this programme is aimed at populations who are not ill and given that it presents associated risks (particularly in terms of unnecessary procedures), is funded collectively and should make it possible to offer treatment of equivalent quality to all participating women, across the whole territory.

In view of the changing context of cervical cancer screening in France and the availability of new scientific data, the Directorate General for Health requested that HAS evaluate the role of the HPV test and the use of p16/Ki67 dual immunostaining in the primary screening strategy for precancerous and cancerous lesions of the cervix.

Epidemiological context

- Approximately 3,000 new cases of invasive cancer in France and over 1,000 deaths each year.
- Three-quarters of cases diagnosed in young women, aged 25 to 64 years.
- An inadequate screening coverage rate (~60%).

HPV INFECTION AND THE NATURAL COURSE OF

Human papillomavirus (HPV) is a highly resistant small DNA virus that infects the cutaneous epithelia and mucous membranes. Around 40 types of HPV infect mucosal epithelia; they are classified on the basis of their oncogenic potential. Infection with low-risk or non-oncogenic types, such as types 6 and 11, can cause genital warts. High-risk types of HPV (HR-HPV) can cause cervical cancer and other anogenital and oropharyngeal cancers. Currently, 12 HPVs are considered to be carcinogens and, among these, HPV 16 and 18 are the most common.

HPV infection is the most common sexually transmitted infection worldwide and is spread by contact with skin or mucous membranes: most sexually active women and men (~80%) will be infected by the virus during their lifetime.

The risk of high-risk HPV infection increases significantly after the mean age of sexual debut and activity and then decreases with age. In the majority of cases, these infections are asymptomatic and quickly become undetectable in the tissues. Approximately 90% of infections are no longer detectable after 2 years.

If HPV infection persists, it can cause cervical cancer. Persistent genital infection with high-risk HPV is a necessary risk factor for cervical cancer but is not in itself sufficient. Other concomitant risk factors (viral factors, endogenous host-related factors and behavioural factors) appear to play a role in the development of cervical cancer.

The development of cervical cancers follows a series of necessary stages that occur at specific ages: infection with a high-risk HPV, persistence of infection, precancerous lesions, invasive cancer. Cervical cancer is characterised by its slow progression and the existence of curable precancerous lesions.

Available tests: cytology and HPV test

Cytology (Pap smears) and HPV tests both require a cervical sample to be taken by a clinician. The HPV test can also be performed on self-collected vaginal samples.

- **Cytology**
  - this consists of morphological analysis of cervical cells for the early detection of abnormal cells and precancerous cells that could evolve into cancerous lesions;
  - in terms of accuracy, this method has a sensitivity for the detection of precancerous lesions of between 51 and 53% and a specificity of between 96 and 98%;
  - interpretation of cytology is subjective and variable depending on the observer, representing a limitation.
- **The HPV test**
  - the HPV test is a molecular detection method that enables detection of the nucleic acids of high-risk HPV genotypes. The objective of this test is to identify HPV infections that are associated with a risk of developing a precancerous or cancerous lesion;
  - the French National Cancer Institute (INCa) guidelines of 2016 recommend the HPV test as a triage test (i.e., as a second-line test following an abnormal cytology test);
  - in comparison with cytology:
    - the HPV test presents greater sensitivity for the detection of precancerous lesions,
    - it is more effective in terms of reducing the incidence of precancerous lesions and invasive cancers in women over the age of 30 years,
    - it offers a longer period of protection against precancerous lesions and invasive cancer following a negative test,
    - the specificity of the HPV test to detect precancerous lesions is lower: triage of women with a positive HPV screening test is therefore important,
    - in women under the age of 30 years: the prevalence of transient HPV infections is high and there is a risk of over-diagnosis and over-treatment, potentially leading to obstetric complications in future pregnancies;
  - the possibility of performing HPV tests on self-collected vaginal samples would make it possible to:
    - facilitate the screening of women who never undergo screening or who are not screened at the recommended frequency,
    - improve screening coverage.

MAIN RECOMMENDATIONS

The present recommendations concern immunocompetent women eligible for cervical cancer screening, aged between 25 and 65, who have not undergone total hysterectomy. Based on current knowledge, the screening recommandation will be the same, irrespective of whether women have been vaccinated against HPV or not.

Key messages

- **Maintenance of cervical cancer screening procedures and triage strategies for women aged 25 to < 30 years**
  - between the ages of 25 and 30, cervical cancer screening continues to be based on the use of two cytology tests one year apart, then after 3 years if the results of the first two are normal;
  - in this context, liquid-based cytology is recommended: collection in a liquid medium makes it possible to perform an HPV test on the same sample (reflex test), and avoids the need to recall women for collection of a second sample in the event of an abnormal result, as would be the case for a conventional Pap smear;
  - the INCa recommendations on the management of women with an abnormal cervical cytology result apply[1].
- **Modification of cervical cancer screening procedures for women aged 30 to 65 years**
  - from the age of 30 years, the HAS recommends that the HPV test replace cytology as the primary cervical screening test;
  - based on current cervical cancer screening guidelines, which recommend three-yearly cytology testing between the ages of 25 and 30 years, HPV tests in women from the age of 30 will be performed 3 years after the last normal cytology test;
  - the interval between two HPV screening tests is 5 years, as long as tests are negative.
- **Self-collected vaginal sampling: an alternative to collection of cervical samples by a health professional for an HPV test for certain women**

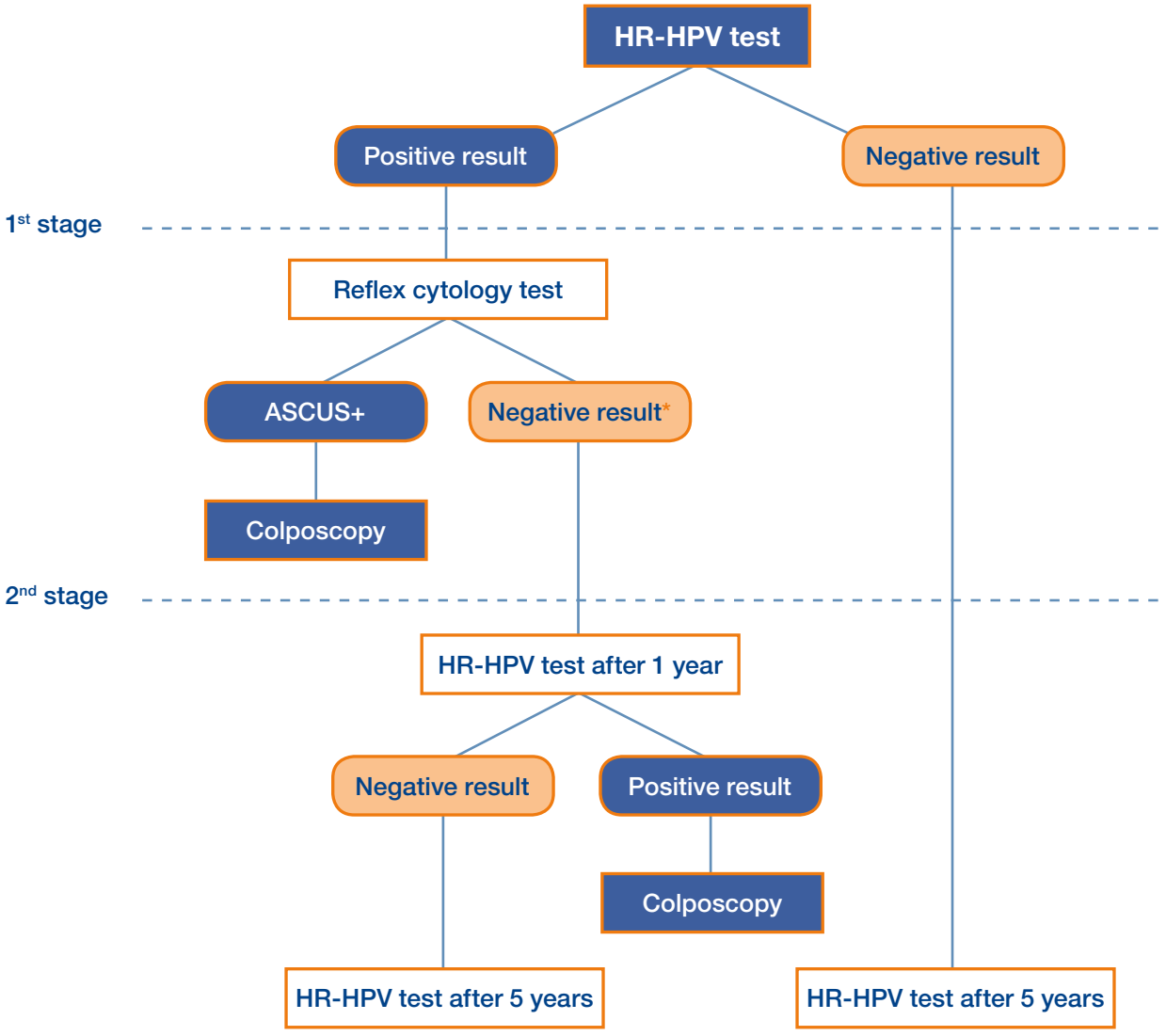
  Self-collected vaginal sampling should be offered, from the age of 30, to women who are not screened or who are inadequately screened: it facilitates the screening of women who never undergo screening or who are underscreened.
- **Triage strategies for women with a positive HPV test**

  For women aged 30 to 65 years, in whom an HPV test has been used for primary cervical screening, a two-stage triage strategy is recommended. After a positive HPV test, a reflex cytology test should be performed:
  - if the cytology result is ASCUS or more severe abnormalities, women should be recalled for a colposcopy;
  - if the cytology result is negative, an HPV test is performed one year later (see algorithm). If this triage HPV test performed one year later is positive a colposcopy should be performed; if this triage HPV test is negative, a new HPV screening test should be done 5 years later.
- **Role of p16/Ki67 dual immunostaining in the cervical cancer screening strategy**

  In view of the available data, the use of p16/Ki67 dual immunostaining for primary screening or as a triage test following a positive HPV test is not recommended.

1. www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Conduite-a-tenir-devant-une-femme-ayant-une-cytologie-cervico-uterine-anormale-Thesaurus

Triage algorithm for women aged 30 to 65 years to whom an HPV test has been proposed for primary cervical cancer screening



* negative result for intraepithelial or malignant lesions

GLOBAL PREVENTIVE STRATEGY

Cervical cancer screening must be part of a global preventive strategy incorporating all the methods of prevention. In particular, this strategy is based on vaccination, the early treatment of precancerous lesions and the appropriate and rapid treatment and management of women with cervical cancer.

HAS

This document presents the main points of the public health guideline for "Evaluation of human papillomavirus (HPV) tests for primary screening of precancerous and cancerous lesions of the cervix and the role of p16/Ki67 dual immunostaining"- July 2019

These recommendations and the scientific rationale can be consulted in full on **www.has-sante.fr**