Updated evidence-based recommendations for cervical cancer screening in France

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Introduction   A national organized cytology-based cervical cancer screening program was launched in 2018 and rollout is ongoing. Concomitantly, the High Authority for Health (HAS) recently assessed new evidence on primary HPV testing to update screening recommendations.

Methods   The HAS commissioned systematic reviews and meta-analyses to evaluate the effectiveness of primary HPV screening; accuracy of HPV testing on self-samples; effectiveness of self-sampling to reach underscreened women; and triage strategies to manage HPV-positive women. Recommendations developed by the HAS were reviewed by a multidisciplinary group.

Results   Compared with cytology screening, HPV screening is more sensitive to detect precancers but less specific. In women aged ≥30, if the test is negative, HPV screening greatly reduces the risk of developing precancer and cancer for at least 5 years. HPV testing, using validated PCR-based assays, is as sensitive and slightly less specific on self-samples than on clinician-taken samples. Self-sampling is more effective to reach underscreened women than sending invitations to have a specimen taken by a clinician. Two-time triage strategies ensure a sufficiently high risk if triage-positive to justify referral and low risk if triage-negative allowing release to routine screening.

Conclusions   The HAS recommends three-yearly cytology screening for women aged 25–29 and HPV screening for those aged 30–65 with an extension of the screening interval to 5 years if the HPV test is negative. Self-sampling should be offered to underscreened women aged ≥30. HPV-positive women should be triaged with cytology. Those with abnormal cytology should be referred for colposcopy and those with normal cytology re-tested for HPV 12 months later. Recommendations for implementation of HPV-based screening in the organized program are provided. *European Journal of Cancer Prevention* 31: 279–286 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Background

In 2018, there were an estimated 2920 new cases of cervical cancer and 1120 deaths from it in mainland France (Defossez *et al.*, 2019). The incidence and mortality of cervical cancer have been declining over the past several decades, as in other high-income countries (Karim-Kos *et al.*, 2008; Arbyn *et al.*, 2009). This has been attributed to the widespread use of cervical cytology screening (IARC, 2005). However, these reductions have slowed since 2005.

Apart from some locally organized programs in a few departments (Hamers *et al.*, 2018), cervical screening in France was mostly opportunistic until quite recently. In 2010, the French National Authority for Health (HAS) recommended the implementation of a population-based organized cervical screening program (HAS, 2010). Three-yearly cervical cytology for women aged 25–65 years was the recommended screening method. At that time, there was insufficient evidence to recommend the human papillomavirus (HPV) test as a primary screening method, and having an organized cervical cancer screening program was deemed necessary before primary HPV screening could be considered. In 2016, the French National Cancer Institute issued guidance for clinical management of abnormal cervical cytology (INCa, 2016). In 2018, a nationwide population-based organized screening program was launched and rollout is currently ongoing. It aims at increasing screening coverage to 80%, reducing inequalities in access to screening and decreasing cervical cancer incidence and mortality by 30% within 10 years (République française, 2014). While the invitation strategy excludes women recently screened opportunistically, the program is designed for the entire target population of asymptomatic women aged 25–65 years and includes all screened women – opportunistically or following invitations. The 3-year coverage for cervical screening with cytology for the period 2015–2017, prior to the launching of the organized program, was 59% (Hamers and Jezeweski-Serra, 2019).

The recognition of the strong causal relationship between persistent cervical infection with high-risk HPV (hrHPV) types and occurrence of cervical cancer (Bosch *et al.*, 2002) has led to the development of a series of HPV tests to detect nucleic acid of the virus. The detection of hrHPV is considered to be potentially useful as a primary screening test (von Karsa *et al.*, 2015) and international criteria for hrHPV tests for primary screening use have been described (Meijer *et al.*, 2009). HAS has recently assessed new evidence on the use of HPV testing in primary cervical cancer screening to update the national recommendations. The objective of this paper is to provide a summary of the literature review and to explain how the recommendations were made on the level of evidence that could be derived from systematic reviews and meta-analyses.

Methods

Scoping and question generation
The main stakeholders were consulted to identify a list of key issues to be addressed (see Box 1). These constituted the starting point for developing research questions.

Neither the test accuracy nor the effectiveness of cytology for cervical cancer screening was reviewed as those had been established previously (Arbyn *et al.*, 2010; HAS, 2010). The evidence review addressed also the age for starting screening with HPV test and the screening interval. Cost-effectiveness of cervical cancer screening in France comparing screening with HPV testing and cytological screening was evaluated previously by the French National Cancer Institute (Barre *et al.*, 2017) and was not reassessed in the current evaluation. The role of co-testing (systematic use of both cytology and HPV test) was not considered as the potential benefit of co-testing versus HPV test alone is extremely small and this strategy has been shown to be inefficient (Arbyn *et al.*, 2012; Schiffman *et al.*, 2018).

Scientific evidence retrieval and synthesis
HAS commissioned the Belgian institute for health, Sciensano, to conduct systematic literature reviews and meta-analyses to investigate the scientific evidence of specific questions related to the key issues (1) to (4) (see Box 1). The detailed methodology for the scientific evidence review is described in an annex of the HAS scientific report (HAS, 2019), which is available from the second author (A.P.) upon request (a.poullie@has-sante.fr). The evaluation of HPV testing on self-samples was published in 2018 (Arbyn *et al.*, 2018). The questions were disentangled into participants, interventions, comparisons, outcomes and study design (PICO) components. Pubmed-Medline, Embase and the Cochrane Library were searched until 15 April 2018. Diagnostic accuracy questions were assessed taking into account the STARD guidelines (Bossuyt *et al.*, 2003) and using the QUADAS checklist (Whiting *et al.*,

2003; Whiting *et al.*, 2011) to evaluate the quality and design of included studies. Efficacy questions were addressed using the CONSORT framework (Moher *et al.*, 2001) and the Cochrane tool for assessing the risk of bias in randomized trials (Higgins *et al.*, 2011). The meta-analyses followed PRISMA guidelines for reporting of meta-analyses, and recommendations established by The Cochrane Collaboration for diagnostic test accuracy and intervention trials (Deeks *et al.*, 2010; Moher *et al.*, 2009). Random-effects models were used for computing pooled estimates.

The higher sensitivity for precancers of hrHPV-based screening compared to cytology screening is associated with a drop in specificity, which may result in a decreased cross-sectional positive predictive value (PPV) and may lead to unnecessary follow-up and overtreatment of screen-positive women, in particular in women younger than 30 years. Hence, the triage of women with a positive hrHPV test is an important clinical issue to address. A risk-based approach was used to evaluate triage algorithms of HPV-screened positive women (Wentzensen *et al.*, 2016; Arbyn *et al.*, 2017). The risk of precancer (cervical intraepithelial neoplasia grade 3 or worse disease [CIN3+]) for women with a positive triage result (=PPV) and for those with a negative triage result (complement of the negative predictive value [cNPV] = 1 − NPV) and the proportion of triage-positive women, that will be referred for colposcopy was computed using three hypothetical background situations: (1) lower risk group where the average risk of CIN3+ prior to triage is 5%; (2) medium group with a CIN3+ risk of 9%; and (3) higher risk group with CIN3+ risk of 15%. Pretest-posttest probability plots were constructed to help evaluate the utility of triage strategies. A strategy was considered acceptable when the posttest risk of CIN3+ in case of a positive triage (PPV) exceeds 10% and when this risk is lower than 1% in case of a negative triage (cNPV).

Contextual evidence
A narrative review of the gray and published literature was done to provide an overview of experiences in countries that recently switched to HPV-based screening or plan to do so. Issues related to the integration of HPV-based within the national organized screening program were mostly based on the opinion of the working group members, described in the HAS evaluation report (HAS, 2019). The question on whether screening strategy should be adapted according to HPV vaccination status was handled by reviewing policies and recommendations in other countries and considering the low vaccination coverage in France (Fonteneau *et al.*, 2019).

Evidence appraisal and formulation of recommendations
A working group of experts in obstetrics and gynecology, pathology, virology, general practice medicine,

public health and health economics was convened by HAS. The working group was asked to appraise and interpret the scientific evidence considering the overall balance of risks and benefits and to provide inputs on feasibility, implementation and other informal evidence. Recommendations were drafted by HAS and reviewed and approved by the working group before submission to review by a larger group of experts and stakeholders.

Box 1. Key issues and related specific research questions to be addressed

(1) What is the role of hrHPV testing in primary screening for cervical cancer?

- What is the diagnostic accuracy of the hrHPV test compared to cytology in primary cervical cancer screening to detect cervical precancer?
- What is the efficacy of HPV-based compared to cytology-based screening to prevent cervical precancer and cancer?

(2) What is the role of self-sampling for HPV-based cervical cancer screening?

- What is the diagnostic accuracy of hrHPV testing on vaginal self-sampled versus on cervical clinician-taken samples?
- What is the efficacy of offering vaginal self-sampling kits to reach underscreened women compared to sending invitation or reminder letters?

(3) What are the optimal triage algorithms to manage women with a positive HPV screening test?

- What is the best test or combination of tests which results in the highest sensitivity for cervical precancer and lowest burden of follow-up?

(4) What is the role of the p16 or p16/Ki67 molecular markers in primary screening?

- What is the diagnostic accuracy of p16 or p16/Ki67 compared to cytology or hrHPV test in primary cervical cancer screening?

(5) Should the cervical cancer screening strategy differ according to HPV vaccination status?

(6) What are the organizational issues for the implementation of HPV-based screening in the national organized cervical cancer screening program?

Results
Evidence summary
What is the diagnostic accuracy of the hrHPV test compared to cytology in primary cervical cancer screening to detect cervical precancer?
Previous diagnostic test accuracy meta-analyses (Arbyn *et al.*, 2012; Koliopoulos *et al.*, 2017), were updated with focus on new RCTs conducted in high-income countries

Table 1 Role of the hrHPV test in primary screening for cervical cancer screening: results of the evidence review to answer research questions related to key issue (1) (see Box 1)

Diagnostic accuracy of the hrHPV test compared to cytology in primary cervical cancer screening to detect cervical precancer

Outcome	No of RCTs	Relative sensitivity (95% CI)
hrHPV test vs. CC		
CIN2+	6	1.39 (1.23–1.57)
CIN3+	5	1.28 (1.09–1.51)
hrHPV test vs. LBC		
CIN2+	3	1.44 (0.87–2.39)
CIN3+	3	1.47 (0.75–2.88)

Efficacy of HPV-based compared to cytology-based screening to prevent cervical precancer and cancer

Outcome	No of RCTs	Detection rate ratio (95% CI)
CIN3+	5	0.39 (0.31–0.50)
Cancer	4	0.21 (0.06–0.74)

CC, conventional cytology; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN2+, CIN grade ≥2; CIN3+, CIN grade ≥3; HPV, human papillomavirus: hrHPV, high-risk HPV; LBC, liquid-based cytology; RCT, randomized controlled trial.

(the Canadian FOCAL (Ogilvie *et al.*, 2018) and the Australian COMPASS (Canfell *et al.*, 2017) trials), demonstrating higher sensitivity of hrHPV testing than cervical cytology to detect cervical precancer (CIN2+ and CIN3+) (Table 1).

However, a higher cross-sectional sensitivity of hrHPV testing for detecting CIN2+ and CIN3+ does not provide sufficient evidence to assume that HPV-based screening will decrease the incidence of cervical cancer more than cytology-based screening. Indeed, CIN2 and even CIN3 lesions can regress without treatment (Ostor, 1993; Tainio *et al.*, 2018) and it cannot be excluded from cross-sectional findings that HPV tests may just pick up a more regressive disease. To prove that more progressive lesions are detected by hrHPV testing, it must be demonstrated that women with a negative screening test have a lower incidence of precancer or cancer by screening with HPV testing compared to screening with cytology. Evaluating the efficacy of screening requires a longitudinal (preferentially randomized) design to assess for the reduction in disease.

What is the efficacy of HPV-based compared to cytology-based screening to prevent cervical precancer and cancer?
The updated systematic review of six RCTs comparing cytology with HPV-based included the Canadian trial FOCAL (Ogilvie *et al.*, 2018) and four European RCT conducted in Sweden (Swedescreen), England (ARTISTIC), Italy (NTTC phase I) and the Netherlands (POBASCAM) (Naucler *et al.*, 2007; Kitchener *et al.*, 2009; Ronco *et al.*, 2010; Rijkaart *et al.*, 2012). The results confirm the compelling evidence that HPV-based screening results in a lower incidence of CIN3+ and of cervical cancer than screening with cytology among women that were baseline screen-negative (Table 1).

A pooled analysis of the individual patient data from the four above-mentioned European RCTs provided more details regarding the protection against invasive cervical cancer by HPV-based compared to cytology-based screening (Ronco *et al.*, 2014). The main results were

- the protective effect became observable 2.5 years after screening (relative protection of 0.45 [95% confidence interval (CI), 0.25–0.81];
- the protective effect was similar for early (stage 1A) or advanced (stages ≥1A) cervical cancer;
- the protective effect was observed both in the total screened group (relative protection of 0.60 [95% CI, 0.40–0.89]) and in women with a negative screening test at baseline (relative protection of 0.30 [95% CI, 0.15–0.60]);
- there was no protective effect observed in the age group of <30 years (relative protection of 0.98 [95% CI, 0.19–5.20]);
- HPV-based screening protects more than cytology against adenocarcinoma (relative protection of 0.31 [95% CI, 0.14–0.69]) when compared to the protection against squamous carcinoma (relative protection of 0.78 [95% CI, 0.49–1.25]).

What is the diagnostic accuracy of hrHPV testing on vaginal self-sampled versus on cervical clinician-taken samples?

The meta-analysis included a total of 56 studies (Arbyn *et al.*, 2014; Arbyn *et al.*, 2018). High-risk HPV tests based on PCR were as sensitive on self-samples as on clinician

samples to detect CIN2+ or CIN3+ (Table 2). However, hrHPV tests based on signal amplification were less sensitive on self-samples. The specificity to exclude CIN2+ was 2 or 4% lower on self-samples than on clinician samples, for hrHPV assays based on PCR or signal amplification, respectively.

What is the efficacy of offering vaginal self-sampling kits to reach underscreened women compared to sending invitation or reminder letters?

The meta-analysis of RCTs included a total of 25 participation trials (Verdoodt *et al.*, 2015; Arbyn *et al.*, 2018). The different trials used very different strategies to offer the self-sampling kits including mailing kits directly to women's home address, opt-in where women had to request a sampling kit; community campaigns and door-to-door interventions. Mailing self-sample kits to the women's home address resulted in a higher participation than invitation or reminder letters (Table 2). Opt-in strategies were generally not significantly more effective than invitation letters. Direct offer of self-sampling kits by health professionals to women in communities that were underscreened generated high participation rates (>75%); these studies were conducted in resource-constrained settings.

The adherence to follow-up was statistically significantly lower in women who tested positive for hrHPV in the self-sampling arm versus women in the control arm in the trials in which follow-up adherence was reported in both arms (relative adherence of 0.91 (95% CI, 0.80–1.04). The rate of CIN 2+ detected per 1000 women was 2.8 times higher (95% CI, 1.44–3.61) in the self-sampling arms than in the control arms.

What is the best test or combination of tests which results in the highest sensitivity for cervical precancer and lowest burden of follow up?

The review aimed at identifying triage testing with biomarkers (HPV16 and 16/18 genotyping, p16, p16/Ki67) and repetition of hrHPV-DNA testing, cytology and/or combinations thereof which results in the highest sensitivity for cervical precancer at the lowest burden of follow-up. Diverse triage strategies were available in 59 identified studies on clinician collected samples, ranging from one-step to two-step triage strategies with diverse methods such as cytology, repeat hrHPV testing, HPV genotyping and/or p16 or p16/Ki67 immunochemistry. A total of 29 strategies (reported in 51 studies) to triage women HPV positive on a clinician-taken sample and 20 strategies (reported in 10 studies) to triage women HPV positive on a self-sample were retrieved. The pooled sensitivity and specificity of the identified triage strategies to identify CIN2+ and CIN3+ precancerous lesions were computed.

The triage strategy that was best documented – in 26 studies – is reflex cytology triage at cut-off atypical squamous cells of undetermined significance (ASC-US),

Table 2   Role of self-sampling in HPV-based cervical cancer screening: results of the evidence review to answer research questions related to key issue (2) (see Box 1)

Diagnostic accuracy of hrHPV testing on vaginal self-samples vs cervical clinician-taken samples

Type of hrHPV test	Outcome	No. of studies	Relative sensitivity (95% CI)	Relative specificity (95% CI)
SA-based hrHPV test				
	CIN2+	23	0.85 (0.80–0.89)	0.96 (0.93–0.98)
	CIN3+	9	0.86 (0.76–0.98)	0.97 (0.95–0.99)
PCR-based hrHPV test				
	CIN2+	17	0.99 (0.97–1.02)	0.98 (0.97–0.99)
	CIN3+	8	0.99 (0.96–1.02)	0.98 (0.97–0.99)

Efficacy of offering vaginal self-sampling kits to reach underscreened women compared to sending invitation or reminder letters

Invitation scenario	Analysis	No of RCTs	Relative participation (95% CI)
Mail to all			
	PP	21	1.87 (1.43–2.44)
	ITT	21	2.33 (1.86–2.91)
Opt-in			
	PP	8	0.73 (0.51–1.04)
	ITT	8	1.22 (0.93–1.61)

CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN2+, CIN grade ≥2; CIN3+, CIN grade ≥3; HPV, human papillomavirus: hrHPV, high-risk HPV; ITT, intention to treat; PCR, polymerase chain reaction; PP, per protocol; RCT, randomized controlled trial; SA, signal amplification

Table 3 Optimal triage algorithms to manage women with a positive HPV screening test: results of the evidence review to answer research questions related to key issue (3) (see Box 1)

Triage strategy		No of studies	Absolute sensitivity (95% CI)	Absolute specificity (95% CI)	PPV of CIN3+[a]	cNPV of CIN3+[a]
Triage 1	Triage 2					
One-step triage[b]						
ASC-US+	–	26	0.76 (0.68–0.84)	0.71 (0.67–0.75)		
Two-step triage[b]						
ASC-US+	hrHPV test	2	0.96 (0.94–.98)	0.67 (0.64–0.69)	0.12	0.001
ASC-US+	ASC-US+	2	0.995 (0.98–1.00)	0.35 (0.32–0.37)	0.20	0.005

[a]PPV and cNPV calculated based on a pretriage risk of CIN3+ of 8% in women screened HPV-positive.
[b]Only selected triage strategies are shown; details of all strategies evaluated are available in the HAS evaluation report (HAS, 2019).
ASC-US+, atypical squamous cells of undetermined significance or more severe lesions; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN3+, CIN grade ≥3; HPV, human papillomavirus: hrHPV, high-risk HPV; NPV, negative predictive value; cNPV, complement of NPV; PCR, polymerase chain reaction; PPV, positive predictive value.

meaning that women with ASC-US or more severe lesions on cytology are referred for colposcopy and further investigations if needed whereas women with negative cytology return to routine HPV screening 5 years later (Table 3). The sensitivity of this strategy is considered to be too low to safely allow negative women to return to routine screening. Adding a second, delayed triage step for women who had a negative cytology triage increased the sensitivity but also decreased the specificity.

In a hrHPV-positive population with a pretriage intermediate underlying background risk of CIN3+, a two-step triage strategy with twice cytology (reflex cytology at the time of screening followed by second cytology 6–12 months later if the first cytology was negative) at cut-off ASC-US offers a good balance between efficiency (four to nine referrals to detect one CIN3+, ~40% of referrals) and safety (risk of CIN3+ in triage-negative women of 0.5–0.9%). If the background risk is higher, the safety becomes borderline (risk of CIN3+ in next 3–5 years of 1.4%). The safety of two-step triage strategy can be increased by adding HPV16 or HPV16/18 genotyping and/or hrHPV testing (=co-testing at triage) or by replacing cytology with a repeat hrHPV test. In these scenarios, safety criteria are obviously fulfilled, even when the background risk is high, but referral rate is high (67 to 71%).

A two-step triage strategy with twice cytology (reflex cytology at the time of screening followed by a second cytology 6–12 months later if the first cytology was negative at cut-off ASC-US yielded acceptable results in low- and medium-risk situations, and borderline safety in a high-risk situation. ASC-US reflex cytology followed by delayed hrHPV testing with or without cytology one year later was also satisfactory in medium- and high-risk situations but was less efficient (PPV <10%), in a low-risk situation.

What is the diagnostic accuracy of p16 or p16/Ki67 compared to cytology or hrHPV test in primary cervical cancer screening?

In total, three studies were included. These studies assessed overexpression of the p16 protein by an anti-p16 ELISA assay, or by a double immunostaining on p16 and Ki67. Testing with p16/Ki67 showed good cross-sectional specificity but lower sensitivity for cervical precancer compared to HPV screening. More data regarding longitudinal safety are needed.

Recommendations

Based on the review of the scientific and contextual evidence, HAS updated its recommendations on cervical cancer screening. The main messages are listed in Box 2. For the full recommendation statement, please see the HAS report (HAS, 2019).

Box 2. Recommendations for cervical cancer screening: main messages

The recommendations concern asymptomatic women who have a cervix (who have not had a hysterectomy with removal of the cervix) and are aged 25–65 years.
In the current state of knowledge, the screening procedure should be the same for HPV-vaccinated and unvaccinated women.

Screening methods, age, interval and management of women screened HPV-positive

- For women aged 25–29 years, screening recommendations remain unchanged. Women should be screened with cytology every 3 years, as previously recommended. Liquid-based cytology should be used. Women with abnormal cervical cytology should be managed according to existing guidelines produced by the French National Cancer Institute.
- Women aged 30–65 years should be screened with hrHPV testing as the primary screening test, at a 5-year screening interval.
- hrHPV testing on vaginal self-sampling is an alternative to hrHPV testing on clinician collected cervical samples for some women. Self-sampling should be offered to underscreened women from the age of 30 years.
- Women who have a hrHPV-positive test on screening should be managed using a two-step triage strategy. The first step is a reflex cytology, thus performed at the time of screening on the specimen collected for screening. If the cytology result is ASC-US or more severe abnormalities, the woman should be referred to colposcopy. If the cytology is negative, the women should be called 12 months later for a repeat HPV test

with colposcopy referral if HPV-positive and return to routine screening 5 years later if HPV-negative.

Implementation of HPV-based screening in the national organized cancer screening program

- Quality control should be set up for HPV testing. Compliance with screening recommendations by clinicians and labs should be monitored. Only assays that are clinically validated for use in cervical cancer screening should be used. Consideration should be given to tender procedures for supplying hrHPV tests across the country.
- Healthcare providers should ensure that screening tests (cytology or HPV test) are offered in accordance with recommendations regarding women's age and screening interval.
- To enable women to make an informed choice about screening, information materials and communication actions on HPV screening for women and for health care professionals should be developed.
- As it is the case for cervical screening with cytology, HPV test should be fully reimbursed every 5 years for women aged 30–65 years.

Discussion

Following other countries in Europe and elsewhere (Lew *et al.*, 2017; CADTH, 2019; American Cancer Society, 2020; Maver and Poljak, 2020), France has also recommended the use of the HPV test as the primary cervical cancer screening method, in July 2019. A year later, in July 2020, these recommendations were officially integrated into the national population-based cervical cancer screening program through a ministerial order (Ministère des Solidarités et de la santé, 2020) and a guidance for program evaluation, including performance indicators, was produced (Santé publique France, 2020).

The transition to complete rollout of HPV primary screening may be long and complex. For instance, in the Netherlands, the first European country that introduced HPV primary screening, in 2017, the new program started only after a preparation phase of more than 4 years. The implementation of HPV primary screening is now being rolled out in France. However, as in most countries, the onset of the COVID-19 pandemic in early 2020 led to a scaling down of cancer screening activities (Richards *et al.*, 2020), which may result in delaying complete HPV screening rollout.

A switch to HPV testing constitutes a major operational and culture shift for clinicians, women, and laboratories (CADTH, 2019). Acceptance of this new screening test (i.e. sexually transmitted infection) may be challenging. Preventing a potential drop in screening and providing easily accessible information and education material to the public and to clinician are important.

A list of clinically validated tests for HPV-based cervical cancer screening, based on the Meier criteria, was produced in 2015 (Arbyn *et al.*, 2015). As evidence accrues, the validation principles and the list of tests need updating.

One major issue is the change in laboratory configuration, workflow and human resources. The cervical cytology workload is expected to decrease substantially, which will likely result in job or revenue losses for cytopathologists. However, cytology as a triage test for HPV-positive samples remains key in the screening process. Staff reconversion while ensuring that expertise is kept and that a sufficient number of staff will embrace a career path that may no longer appear attractive will be a challenge. Because of the lower specificity of primary HPV screening compared to cytology screening, the number of colposcopy referrals is expected to increase.

Nonattendance is a concern with existing cervical cancer screening programs. Besides high efficacy, HPV testing has the additional advantage that it can be performed on self-collected vaginal samples and studies have shown that providing self-sampling kits improves participation of underscreened women. Modalities for offering self-sampling in France still have to be defined.

Most HPV infections clear spontaneously. Only a small proportion of HPV infections persist and, eventually, may develop into CIN3+ (Schiffman *et al.*, 2007). Hence, appropriate triage testing, management and follow-up of HPV-positive women are of critical importance in optimizing the balance of benefits and harms for primary HPV screening. However, there is no consensus on the optimal management of HPV-positive women. Triage strategies were considered acceptable when the PPV (risk of CIN 3+ when the triage was positive) was greater than 10% and the cNPV (risk of CIN 3+ when screening was negative) was lower than 1%. There are no universal thresholds and it is up to each country to define acceptable thresholds (Arbyn *et al.*, 2017).

Compliance of HPV-positive women to triage is a major challenge. Two-step triage strategies are characterized by a certain degree of drop-out of women under follow-up. Triage of women with HPV-positive on a self-collected sample is a further challenge because these women, often hard to reach, must be referred to a clinician for cytological cervical sampling. Emerging molecular markers which may be useful in triage of HPV-positive women are being developed, including extended genotyping, methylation markers, expression of oncoproteins such as E6 and E7, viral mRNA testing, evolution of type-specific viral load. In the future, these may provide alternatives for the currently recommended triage strategy. Ideally one would aim at a one-step triage using tests that could be performed on self-samples.

Conclusion

These recommendations constitute a milestone towards the elimination of cervical cancer in France. Population-based information must be established to monitor and evaluate their implementation. Screening program performance indicators including participation, adherence, quality and impact should be published regularly.

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Conflicts of interest

References

American Cancer Society (2020). Cervical cancer prevention and screening: financial issues. https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/prevention-screening-financial-issues.html. [Accessed 3 August 2020].

Arbyn M, Raifu AO, Weiderpass E, Bray F, Anttila A (2009). Trends of cervical cancer mortality in the member states of the European Union. *Eur J Cancer* **45**:2640–2648.

Arbyn M, Snijders PJ, Meijer CJ, Berkhof J, Cuschieri K, Kocjan BJ, Poljak M (2015). Which high-risk HPV assays fulfil criteria for use in primary cervical cancer screening? *Clin Microbiol Infect* **21**:817–826.

Arbyn M, Smith SB, Temin S, Sultana F, Castle P; Collaboration on Self-Sampling and HPV Testing. (2018). Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. *BMJ* **363**:k4823.

Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, *et al.* (2010). European guidelines for quality assurance in cervical cancer screening. Second edition–summary document. *Ann Oncol* **21**:448–458.

Arbyn M, Xu L, Verdoodt F, Cuzick J, Szarewski A, Belinson JL, *et al.* (2017). Genotyping for human papillomavirus types 16 and 18 in women with minor cervical lesions: a systematic review and meta-analysis. *Ann Intern Med* **166**:118–127.

Arbyn M, Ronco G, Anttila A, Meijer CJ, Poljak M, Ogilvie G, *et al.* (2012). Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. *Vaccine* **30** (Suppl 5):F88–F99.

Arbyn M, Verdoodt F, Snijders PJ, Verhoef VM, Suonio E, Dillner L, *et al.* (2014). Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* **15**:172–183.

Barré S, Massetti M, Leleu H, De Bels F (2017). Organised screening for cervical cancer in France: a cost-effectiveness assessment. *BMJ Open* **7**:e014626.

Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV (2002). The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* **55**:244–265.

Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, *et al.*; Standards for Reporting of Diagnostic Accuracy. (2003). The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med* **138**:W1–12.

CADTH (2010). HPV testing for primary cervical cancer screening: a health technology assessment. CADTH Optimal Use Report; vol **7**, no 1b. Ottawa: CADTH. https://www.cadth.ca/sites/default/files/ou-tr/op0530-hpv-testing-for-pcc-report.pdf. [Accessed 3 December 2020].

Canfell K, Caruana M, Gebski V, Darlington-Brown J, Heley S, Brotherton J, *et al.* (2017). Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: results of the Compass pilot randomised trial. *Plos Med* **14**:e1002388.

Deeks JJ, Bossuyt PM, Gatsonis C (eds) (2010). *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0*. The Cochrane Collaboration. https://srdta.cochrane.org/

Defossez G, Le Guyader-Peyrou S, Uhry Z, Grosclaude P, Colonna M, Dantony E, *et al.* (2019). *Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018 - Volume 1: Tumeurs solides: Étude à partir des registres des cancers du réseau Francim*. Saint-Maurice: Santé publique France. https://www.santepublique-france.fr/content/download/190597/2335082. [Accessed 3 December 2020].

Fonteneau L, Barret A, Levy Bruhl D (2019). Evolution of human papillomavirus vaccination coverage in France - 2008-2018. *Bull Epidémiol Hebd* 424–430.

Hamers FF, Jezeweski-Serra D (2019). Cervical cancer screening coverage in France, 2012-2017. *Bull Epidémiol Hebd* 417–423.

Hamers FF, Duport N, Beltzer N (2018). Population-based organized cervical cancer screening pilot program in France. *Eur J Cancer Prev* **27**:486–492.

HAS (2010). *Recommandations en santé publique. État des lieux et recommandations pour le dépistage du cancer du col de l'utérus en France*. Saint-Denis La Plaine: Haute Autorité de santé. https://www.has-sante.fr/upload/docs/application/pdf/2010-11/synthese_recommandations_depistage_cancer_du_col_de_luterus.pdf. [Accessed 3 December 2020].

HAS (2019). *Recommandations en santé publique. Évaluation de la recherche des papillomavirus humains (HPV) en dépistage des lésions pré-cancéreuses et cancéreuses du col de l'utérus et de la place du double immuno-marquage p16/Ki67: argumentaire*. Saint-Denis La Plaine: Haute Autorité de santé. https://www.has-sante.fr/jcms/p_3102981/fr/rapport-hpv. [Accessed 3 December 2020].

Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al.*; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**:d5928.

IARC (2005). *Handbooks of Cancer Prevention: Volume 10-Cervix Cancer Screening*. Lyon: IARC Press. https://publications.iarc.fr/_publications/media/download/3960/ff5840132ff86533aa8d965afba99a597070e8e8.pdf. [Accessed 3 December 2020].

INCa (2016). *Conduite à tenir devant une femme ayant une cytologie cervico-utérine anormale*. Boulogne-Billancourt: Institut national du cancer. https://www.e-cancer.fr/content/download/178363/2343581/file/Conduite_a_tenir_devant_une_femme_ayant_une_cytologie_cervico-uter-ine_anormale_Thesaurus_mel_20170123.pdf. [Accessed 3 December 2020].

Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh, J. W. (2008). Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* **44**:1345–1389.

Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, *et al.* (2009). HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncol* **10**:672–682.

Koliopoulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PP, Mustafa RA, *et al.* (2017). Cytology versus HPV testing for cervical cancer screening in the general population. *Cochrane Database Syst Rev* **8**:CD008587.

Lew JB, Simms KT, Smith MA, Hall M, Kang YJ, Xu XM, *et al.* (2017). Primary HPV testing versus cytology-based cervical screening in women in Australia vaccinated for HPV and unvaccinated: effectiveness and economic

assessment for the National Cervical Screening Program. *Lancet Public Health* **2**:e96–e107.

Materia E, Rossi L, Spadea T, Cacciani L, Baglio G, Cesaroni G, et al. (2002). Hysterectomy and socioeconomic position in Rome, Italy. *J Epidemiol Community Health* **56**:461–465.

Maver PJ, Poljak M (2020). Primary HPV-based cervical cancer screening in Europe: implementation status, challenges, and future plans. *Clin Microbiol Infect* **26**:579–583.

Meijer CJ, Berkhof J, Castle PE, Hesselink AT, Franco EL, Ronco G, et al. (2009). Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. *Int J Cancer* **124**:516–520.

Ministère des Solidarités et de la Santé (2020).Arrêté du 30 juillet 2020 modifiant l'arrêté du 29 septembre 2006 relatif aux programmes de dépistage organisé des cancers et relatif a` l'organisation du dépistage organisé du cancer du col de l'utérus. Journal officiel de la république française. 15 août 2020. n° 0200. https://www.legifrance.gouv.fr/download/file/wApphLOCTCpq4PIbCpuUReDH88V2_zW0rTU0Ov0dQlU=/JOE_TEXTE. [Accessed 3 December 2020].

Moher D, Schulz KF, Altman D; CONSORT Group (Consolidated Standards of Reporting Trials). (2001). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* **285**:1987–1991.

Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Open Med* **3**:e123–e130.

Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, et al. (2007). Human papillomavirus and Papanicolaou tests to screen for cervical cancer. *N Engl J Med* **357**:1589–1597.

Ogilvie GS, van Niekerk D, Krajden M, Smith LW, Cook D, Gondara L, et al. (2018). Effect of screening with primary cervical HPV testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL randomized clinical trial. *JAMA* **320**:43–52.

Ostör AG (1993). Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* **12**:186–192.

République française (2014). Plan cancer 2014-2019. *Guérir et prévenir les cancers: donnons les mêmes chances à tous, partout en France.* Paris: Ministère des Affaires sociales et de la Santé, Ministère de l'Enseignement supérieur et de la Recherche. https://solidarites-sante.gouv.fr/IMG/pdf/2014-02-03_Plan_cancer-2.pdf. [Accessed 3 December 2020].

Richards M, Anderson M, Carter P, Ebert BL, Mossialos E (2020). The impact of the COVID-19 pandemic on cancer care. *Nat Cancer* 1–3.

Rijkaart DC, Berkhof J, Rozendaal L, van Kemenade FJ, Bulkmans NW, Heideman DA, et al. (2012). Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. *Lancet Oncol* **13**:78–88.

Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al.; International HPV screening working group. (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet* **383**:524–532.

Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al.; New Technologies for Cervical Cancer screening (NTCC) Working Group. (2010). Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol* **11**:249–257.

Santé publique France (2020). *Dépistage organisé du cancer du col de l'utérus: Définition des indicateurs de performance et format des données pour l'évaluation du programme national.* Saint-Maurice: Santé publique France. https://www.santepubliquefrance.fr/content/download/341119/3015876. [Accessed 3 December 2020].

Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S (2007). Human papillomavirus and cervical cancer. *Lancet* **370**:890–907.

Schiffman M, Kinney WK, Cheung LC, Gage JC, Fetterman B, Poitras NE, et al. (2018). Relative performance of HPV and cytology components of cotesting in cervical screening. *J Natl Cancer Inst* **110**:501–508.

Tainio K, Athanasiou A, Tikkinen KAO, Aaltonen R, Cárdenas J, Hernándes, et al. (2018). Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. *BMJ* **360**:k499.

Verdoodt F, Jentschke M, Hillemanns P, Racey CS, Snijders PJ, Arbyn M (2015). Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of randomised trials. *Eur J Cancer* **51**:2375–2385.

von Karsa L, Arbyn M, De Vuyst H, Dillner J, Dillner L, Franceschi S, et al. (2015). European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. *Papillomavirus Res* **1**:22–31.

Wentzensen N, Schiffman M, Palmer T, Arbyn M (2016). Triage of HPV positive women in cervical cancer screening. *J Clin Virol* **76** (Suppl 1):S49–S55.

Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J (2003). The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* **3**:25.

Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al.; QUADAS-2 Group. (2011). QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* **155**:529–536.