

NEW CERVICAL CANCER SCREENING GUIDELINES ON BOTH SIDES OF THE ATLANTIC

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ABSTRACT

Large population-based trials showed that the human papillomavirus (HPV) DNA test can be even more effective than Pap tests in preventing cervical cancer. Nevertheless, there are still many questions on how to implement HPV testing in screening, and particularly how to manage its lower specificity. In this paper, we compare the recommendations concerning the cervical cancer screening tools proposed by the most influential agencies and scientific societies in the last 3 years. We included six documents that evaluated the use of HPV DNA tests and formulated recommendations: the U.S. Preventive Services Task Force (USPSTF) systematic review and recommendations, the multi-societal USA, Canadian Task Force on Preventive Health Care (CTFPHC), the Dutch Health Council recommendations, and the Italian Health Technology Assessment report. The USPSTF review and the Canadian document concluded that there is no sufficient evidence to recommend HPV as a primary screening test, while the others conclude that HPV tests can be used as the primary screening test in patients starting from 30 years of age. The interval after a negative HPV test is 5 years for all the documents except the Dutch (5-10 year interval). The only relevant difference between recommendations is the role of cytology: co-testing in the USA, triage in Europe. The new European and USA guidelines on cervical cancer screening represent a further step towards protocol harmonisation, even if there are still some differences. This harmonisation was achieved through an evidence-based approach to the introduction of HPV as a primary test and through a general reduction of the intensity of screening protocols.

Keywords: Cervical cancer, HPV test, mass screening, guidelines.

INTRODUCTION

Cervical cancer is still a major cause of death among women around the world.¹ The burden of disease is concentrated in low and medium-income countries.² In most of the industrialised countries, incidence and mortality have decreased dramatically over the last few decades thanks to the diffusion of Pap test and screening programmes.^{1,3,4} In fact, Pap tests make it possible to identify cellular abnormalities that are the expression of precancerous lesions. The treatment of precancerous lesions (high-grade cervical intraepithelial neoplasia, CIN2+) through non-invasive surgery is very effective in preventing cancer.¹

The identification of persistent infection with oncogenic types of HPV as the necessary, but not sufficient, cause of cervical cancer⁵ has led to the creation of two new tools for cancer prevention: a HPV test for screening, and a HPV vaccine to prevent infection.⁶

Since the first studies on HPV DNA test accuracy were conducted, it has been clear that the new test is more sensitive but less specific than the Pap test in identifying CIN2+.⁷ Recently, several large population-based trials⁸⁻¹² showed that the HPV DNA test can be more effective than the Pap test in preventing cervical cancer. Nevertheless, there are still many questions on how to implement

the HPV test in screening, and particularly how to manage its lower specificity.^{7,13}

In 2011-13, several new guidelines and recommendations on cervical cancer screening were published, all posing one of the main questions: whether the HPV DNA test should be recommended as primary screening test or not.¹⁴⁻¹⁹ In this paper, we compare the recommendations concerning the cervical cancer screening tools proposed by the most influential agencies and scientific societies in the last 3 years.

METHODS

Sources of Information and Guidelines Selection

Although this is not a systematic review, in order to identify the most recent guidelines (since 2011) on population screening for cervical cancer, a literature search of the major databases was carried out. Specifically, we searched PubMed and general websites on healthcare and some specific sites for guidelines, and we studied the websites of several scientific societies of interest.

The aim was to identify all documents sufficiently updated and assess if they take into consideration the new main results of the European HPV test trials,⁸⁻¹¹ i.e. after 31st December 2010. Only documents with national or international relevance were included.

We included all the documents producing recommendations on screening in the general female population that included the HPV DNA test as primary screening test in their scope. Included documents are systematic reviews producing recommendations, guidelines, and HTA reports. This review is an update and a subset of a larger one that collected guidelines and recommendations for the cervical screening programme. Complete methods of the previous review are described on the 'Osservatorio Nazionale Screening' website (www.osservatorionazionalecreening.it). The search was updated on 31st July 2013.

Data Extraction

Two independent reviewers extracted the main conclusions and recommendations from the selected documents: target age, interval recommended, first level test, management of individuals according to first level test results, and

assessment procedures (Table 1). The extraction forms were defined by a working group and then submitted to external advisors for review and piloting on two sample documents. The working group, the methods, and the list of external advisors are published online at www.osservatorionazionalecreening.it. Furthermore, specifically regarding whether or not to recommend the HPV as the primary screening test, the reviewers extracted the following items: main conclusions, studies included in the efficacy analysis, summary of the evidence and its level, summary of the recommendation and its strength. The extraction tables were then merged in a consensus process by the two reviewers.

RESULTS

We found eight documents that evaluated the use of the HPV DNA test and formulated recommendations, two of which were excluded due to their regional or local relevance.^{20,21} Three documents were from the USA: one systematic review commissioned by the USPSTF,¹⁸ a document reporting the USPSTF recommendations,¹⁷ and the multi-societal recommendations by the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology Screening Guidelines.¹⁶ Two other documents were from Europe: the Dutch Health Council recommendations,¹⁴ i.e. a proposal formulated by the council to the Government, and the Italian health technology assessment (HTA) report,¹⁹ which includes in its second chapter a draft of the unpublished European Guidelines. The sixth document reports the recommendations of the Canadian Task Force on Preventive Health Care.¹⁵

All the documents considered studies on accuracy, in particular one previous systematic review⁷ and one large randomised trial,²² but the use of this information in the production of the recommendations was not uniform. Regarding efficacy data, the trials available are the same for all the reviews: five European trials (NTCC,^{11,23} POBASCAM,^{8,24} ARTISTIC,^{9,25} SWEDESCREEN,¹⁰ Finland^{26,27}) and one trial from rural India.¹² All the reviews considered the study by R. Sankaranarayanan et al.¹² separately because the intervention and the comparator were 'once-in-a-lifetime' screenings, and the results

cannot be used to estimate the effect in industrialised countries.

Some important observational studies were also considered by some reviews, in particular the pooled analysis of European cohort studies,²⁸ used by all of the documents to establish the best screening interval, and the study by Katki et al.,²⁹ as confirmation of the effectiveness in real practice (considered only by USPSTF recommendations and multi-societal guidelines).

Another difference among the reviews regarding the available data was the follow-up data on invasive cancer in the POBASCAM trial,²⁴ which have been included in all of the reviews except the first USPSTF, because it was not published when the authors closed the literature search.

The analyses concentrated on two main points: 1) is the HPV test more sensitive than the Pap test for CIN3+ at baseline screening? 2) If so, is there a decrease in the CIN3+ detection at following rounds in women who underwent HPV screening compared to those screened with the Pap test at baseline, i.e. were the excess lesions found with HPV at baseline persistent? These two points take into account efficacy and safety at the same time, i.e. the sum of the CIN2+ detected at first and subsequent rounds directly measure the relative overdiagnosis³⁰ and the reduction of CIN3, and in particular, cancers at subsequent rounds measure the efficacy. The two points are clearly treated as distinct from each other in the two European documents and in the multi-societal document, while the USPSTF and the Canadian documents do not clearly separate the two points.

The separate analysis of baseline data (providing information on sensitivity), and subsequent rounds (testing the efficacy in reducing incidence), led the European and the multi-societal documents not to consider the Finnish trial in the efficacy analysis, since the second round data have never been published. The USPSTF systematic review and the Canadian document, instead, considered the Finnish trial even for the efficacy endpoint. Given the absence of second round results, the Finnish trial is the only European trial that did not register a reduction in the incidence of CIN3 and cancer during follow-up.

Table 2 reports the general conclusions, evidence syntheses, and recommendations of the six documents on the use of the HPV DNA test as primary screening. Two documents^{15,18} conclude that there is no convincing evidence for the use of HPV, while the others conclude that HPV can be recommended: the Italian, the Dutch, and the multi-societal documents state that HPV is preferable to or more effective than Pap tests, while the USPSTF recommendations consider the two equivalent.

Table 1 summarises the main recommendations given by the six documents on screening. The starting age varies from 21 (USA) to 30 (NL), while the stopping age is 65 for all except for the Netherlands, where it is 60. All the documents recommend shifting the primary screening test from Pap tests to HPV at the age of 30. The interval to be deemed HPV negative is 5 years for the USA and Italy, while for the Netherlands it is 5 years until age 40, then 10 years. Co-testing is recommended in the 2012 USA guidelines, and triage is recommended in Italy and the NL.

Women with cytology and HPV testing positive are referred to colposcopy in all four documents (**Figure 1**). Furthermore, in the USA documents, there is also the option to type the HPV and to refer the women who are infected by HPV16/18 to colposcopy. For women testing positive with HPV and negative for cytology, the recommendations differ slightly:

- In the USA, women are referred to 1-year for a HPV test and cytology; women testing either HPV positive or cytology positive are referred to colposcopy.³¹
- In Italy, women are referred to 1-year for HPV only. If the test is still positive, women are referred to colposcopy; if negative, to 5-year screening.
- In the Netherlands, women are referred to 6-month cytology control; if cytology is positive, they are referred to colposcopy; if cytology is negative, they are referred to 5-year HPV tests.

Finally, all the documents state that the recommendations should be updated in the short-term because new evidence will be produced by trials on stand-alone HPV tests^{16,18} and on triage biomarkers.^{14,16,19} In addition, updates will eventually take into

account the impact of vaccinated cohorts on screening performance.¹⁹

DISCUSSION

Despite the fact that the six documents are based on almost the same body of evidence, four documents^{14,16,17,19} recommend the use of HPV as primary screening and two do not.^{15,18} The level of evidence and the grade of recommendations are essentially the same for the four documents recommending the use of HPV test: the highest level of evidence and the strongest grade of recommendation. The only difference is the comparison with Pap test screening: equivalence for the USPSTF document (a Pap test every 3 years is equal to HPV every 5 years) and superior for the other documents.

To better understand why the conclusion of the first USPSTF document was not to recommend HPV, while the second reached the opposite conclusion, it is worth analysing in detail the process that led to the recommendations. The recommendations are essentially identical to the multi-societal ones, but are clearly in contrast with the conclusions of the systematic review, commissioned by the USPSTF itself, published just 4 months earlier. In the final paragraph of the recommendations, it is explained that the debate³² started after the publication of the systematic review and the publication of new evidence. In particular, the update of POBASCAM follow-up²⁴ and the observational data of the Kaiser Permanente²⁹ led to a different interpretation of the whole evidence body and consequently to different recommendations. Obviously, the synchronicity with the multi-societal work resulted in a larger scientific consensus on the final conclusions.

When analysing the interpretation of the available evidence provided by the two documents not recommending the HPV in detail, two main justifications for their conclusion emerge. Firstly, as the trials adopted different protocols, the authors decided not to pool the results. Thus, there is no statistical power on the reduction of cancer incidence. Secondly, as most of the trials adopted a co-testing strategy, the strongest evidence is for this strategy. However, it produces an enormous increase in unnecessary work-up, adding harm due to HPV false positives to that of the Pap test

false positives. The conclusions in the USPSTF systematic review are also supported by considerations on the scarce applicability of 5-year intervals in the setting of opportunistic screening in the USA.

The interpretation of the evidence by the USA documents recommending HPV differs as: 1) the overall evidence that HPV can further reduce cancer incidence is strong; 2) the strongest evidence is for co-testing, and; 3) the unnecessary work up for false positive can be controlled with longer intervals and the final balance of benefit and harm is in favour of HPV.

The interpretation given by the two European documents is different still as: 1) the CIN3 and cancer reduction in HPV arms versus Pap test arms is consistent in all the studies, and does not depend on the protocol adopted (co-testing or HPV stand-alone or HPV followed by triage); 2) as the most efficient strategy is HPV followed by triage, this the recommended strategy. It must be noted that all the trials used in the systematic reviews to estimate HPV efficacy were conducted in Europe,^{8,11,26} where the co-testing strategy has never been considered a plausible option for a priori cost-effectiveness considerations (it is clearly inefficient). Thus, the trials adopted a co-testing strategy^{8-11,33} only as a precautionary principle or to allow the comparison of multiple strategies. However, once confirmed that the number of lesions found and treated at baseline in HPV negative women was negligible, all the data analyses focused on measuring the effectiveness of a triage strategy or a stand-alone strategy.^{25,34,35}

The interpretation given by the European documents allows a more complete use of the evidence, but also requires more assumptions concerning the natural history of the disease. The validity of the assumptions and the appropriateness of the ancillary evidence use are crucial. In this case, the assumption that main differences in cancer incidence between the two arms were due to the adoption of HPV and not to other characteristics of the protocol adopted was strongly supported by the natural history of the disease,^{1,5} and was consistent with the results of the trials themselves.

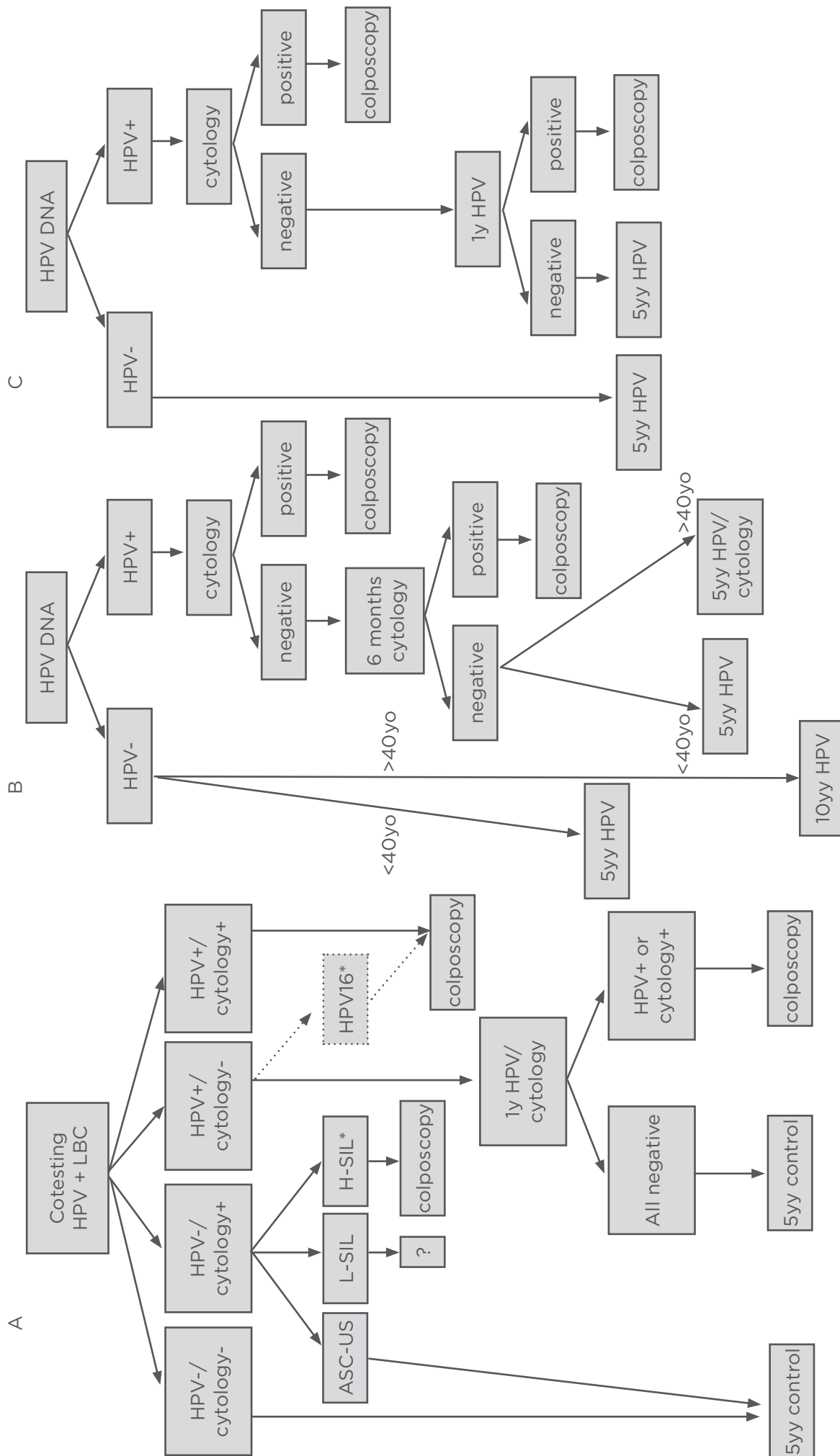


Figure 1. Simplified flowcharts of the HPV screening-based algorithms in the four documents recommending the HPV DNA test as a primary screening test.

A. USPSTF recommendations and multi-societal USA Guidelines^{16,17,29}

B. Recommendations of the Dutch Health Council¹⁴

C. Italian HTA report¹⁹

Table 1. Synthesis of the recommendations of the six documents about cervical cancer screening.

Country	Year	Agency	Screening target population		HPV for primary screening recommended	Target age for HPV primary test		Management of abnormal results		HPV typing recommended
			Start	Stop		Start	Stop	HPV+ cyto-	HPV- cyto+	
USA	2011	USPSTF ¹⁸	21	65	no			-	-	-
USA	2012	USPSTF ¹⁷	21	65	yes	30	65	Cotesting (a)	Colposcopy	1 year HPV + cytology
USA	2012	ACS ASCCP ASCP ¹⁶	21	65	yes	30	65	Cotesting (a)	Colposcopy	1 year HPV + cytology
Canada	2013	Canadian Task Force ¹⁵			no			-	-	-
Italy	2012	Ministry of Health ¹⁹	25	64	yes	30-35	64	Triage (b)	Colposcopy	1 year HPV
Netherlands	2011	Health Council ¹⁴	30	60	yes	30	60	Triage (b)	Colposcopy	1 year HPV + cytology

(a) Both cytology and HPV performed simultaneously as primary screening test.

(b) Cytology performed sequentially only in case of HPV positive results.

(c) Non-management for HPV negative L-SIL was reported in the multi-societal guidelines in 2012, according to the recommendations by the American Society for Colposcopy and Cervical Pathology (ASCCP) published in 2013, these women would be referred to 1-year control with HPV and cytology.

Table 2. Document conclusions, evidence statements with related level of evidence, and recommendations with related grade about HPV-DNA as primary screening test for cervical cancer reported in the six documents.

Document	Conclusion	Included studies for efficacy analysis	Evidence	HPV recommendation
USPTF Moyer (2012) ¹⁷		NTCC ^{11,23} ARTISTIC ^{9,25} POBASCAM (only preliminary data) ⁸ SWEDESCREEN ¹⁰ Finnish ⁴	30-65 years: The benefits of screening with co-testing (cytology/HPV testing) every 5 years outweigh the harms. Evidence level: high	Screen with cytology every 3 years or co-testing (cytology/human papillomavirus testing [HPV]) every 5 years. Grade of recommendation: A (Offer or provide this service)
USPTF Withlock (2011) ¹⁸			<30 years: The potential harms of screening with HPV testing (alone or with cytology) outweigh the potential benefits. Evidence level: adequate	USPTF recommend do not screen with HPV test. Grade of recommendation: D (Discourage the use of this service)
USPTF Withlock (2011) ¹⁸	'... more complete evidence is needed before HPV-enhanced primary screening is widely adopted for women aged 30 years or older.'	NTCC ^{11,23} ARTISTIC ^{9,25} POBASCAM (including follow up) ²⁴ SWEDESCREEN ¹⁰ Finnish ⁴ Kaiser Permanente ²⁹		
HTA Italian Ronco (2012) ¹⁹	'There is clear scientific evidence that a screening based on validated tests for the DNA of oncogenic HPV as primary test and applying an appropriate protocol is more effective than screening based on cytology in preventing invasive cancers of the uterine cervix. In addition, it entails a limited - if any - increase of the undesired effects...'	NTCC ^{11,23} ARTISTIC ^{9,25} POBASCAM (including follow up) ²⁴ SWEDESCREEN ¹⁰		'... the crucial requirement to introduce HPV-based screening programmes is the capacity to guarantee the application of appropriate screening protocols.'

<p>Netherlands Health Council recommendations (2011)⁴</p>	<p>The Committee concludes that there is clear evidence that hrHPV screening is more effective than cytology as a primary screening method. As hrHPV screening detects high-grade CIN and cervical cancer earlier, the present frequency of screening can be reduced.</p>	<p>NTCC^{11,23} ARTISTIC⁹ POBASCAM (including follow up)²⁴ SWEDESCREEN¹⁰</p>	<p>30-65 years: absolute increase in CIN3+ detection in first round (ranging from 17% to 31%). Absolute decrease in cancer detected at second round (ranging from 0.03% to 0.05%).</p> <p>Evidence level: high</p>	<p>The Committee recommends a switch to hrHPV screening. The continued use of cytology as a primary screening test, alongside hrHPV testing, is not efficient.</p>
<p>ACS-ASCCP-ASCP (2012)¹⁶</p>		<p>NTCC^{11,23} ARTISTIC^{9,25} POBASCAM (including follow up)²⁴ SWEDESCREEN¹⁰ Finnish⁴ Kaiser Permanente²⁹</p>	<p><30 years: Because of the high prevalence of HPV in women aged younger than 30 years, HPV testing should not be used to screen women in this age group due to the potential harms</p> <p>Evidence level: insufficient</p>	<p>30-65 years: should be screened with cytology and HPV testing ('cotesting') every 5 years (preferred) or cytology alone every 3 years (acceptable).</p> <p>Grade of recommendation: cotesting preferred</p>
<p>Canadian TFPHC (2013)¹⁵</p>	<p>'These updated recommendations do not address screening with tests for human papillomavirus virus, because there is not yet sufficient data on its effect on mortality and incidence of invasive carcinoma.' 'However, we will revisit this issue as new data become available.'</p>	<p>NTCC^{11,23} ARTISTIC^{9,25} POBASCAM (including follow up)²⁴ SWEDESCREEN¹⁰ Finnish⁴ Kaiser Permanente²⁹</p>	<p>No use of HPV as primary screening test. More research is needed on the effectiveness and optimal use of HPV screening in decreasing the incidence of and mortality due to cervical cancer.</p> <p>Grade of recommendation: ?</p>	<p><30 years: HPV testing should not be used to screen women in this age group</p> <p>Grade of recommendation: PAP test acceptable</p>

Looking at the last 20 years of cervical cancer screening on both sides of the Atlantic, we can see a progressive alignment towards less intensive protocols in order to reduce overdiagnosis and undesired effects,³⁶ and to increase efficiency. Before 2010, the starting age in the USA was 18,³⁷ there was no stopping age, and the interval was 1 year. In the same period, the starting age in Europe was 22-30,³⁸ the stopping age 60-65, and the interval was 3-5 years. In 2010, the USA introduced a stopping age, increased starting age to 21, and increased the interval to 2-3 years.³⁹ In 2012 in the USA and Europe, with the introduction of HPV testing, the starting age was identical (at least for HPV, i.e. 30), as were the interval and the stopping age.^{16,17} The only difference was the role of cytology: co-testing in the USA, triage in Europe.

Public health interventions such as screening programmes involve the whole health system. Recommendations on mass screening, therefore, cannot be based only on the efficacy of the intervention, but must also take into account its acceptability by health operators and population, its feasibility, and whether it is affordable. Organisational and cost barriers are explicitly

mentioned by some of the documents^{14,19} even if in some cases they are not clearly distinguished from the efficacy evaluation.^{18,32} Thus, all of the conclusions drafted by the guidelines must be considered valid within their context (with the exception of the USPSTF systematic review,¹⁸ which was superseded by the recommendations in 2012¹⁷) and applied judiciously.

For those countries with a national health system, such as many European countries, the question is not what guidelines are the best, but which guidelines are in place in that specific country, which programme will be implemented by the health system, and what the role of each health professional is in this programme.

CONCLUSION

The new European and U.S. guidelines on cervical cancer screening represent a further step towards protocol harmonisation, even if there are still some differences. This harmonisation was achieved through an evidence-based approach to the introduction of HPV as a primary test and through a general reduction of the intensity of screening protocols.

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