

Educational Day of National Cervical Cancer Screening Programme ZORA
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Supplements to the European Guidelines for Cervical Cancer Screening (2015)

Implementation of HPV-based Technology

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HPV Supplements - Recently published

- *European guidelines for quality assurance in cervical cancer screening. Second edition, Supplements (2015)* Anttila A, Arbyn A, De Vuyst H, Dillner J, Dillner L, Franceschi S, Patnick J, Ronco G, Segnan N, Suonio E, Törnberg S & von Karsa L (eds.). Office for Official Publications of the European Union, Luxembourg
 - Von Karsa L, Arbyn M, DeVuyst H, Dillner J, Dillner L, Franceschi S, Patnick J, Ronco G, Segnan N, Suonio E, Törnberg S, Anttila A (2015) European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. <http://dx.doi.org/10.1016/j.pvr.2015.06.006i>
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Background

- European Guidelines for Quality Assurance in Cervical Cancer Screening, 2nd Edition, 2008:

“**Piloting** with validated HPV DNA testing can be recommended [for cervical cancer screening] if performed in an organised screening programme with careful monitoring of the quality and systematic evaluation of the aimed outcomes, adverse effects and costs.”

Five European RCTs comparing hrHPV testing to cytology

Study	Publication(s)	Age of women (y) (median)	Screening interval (y)	Follow-up (y) (median)	Number of women	HPV test type
Finland	Anttila 2010	30-60 (>45?)	5	3.3	58 076	HC2
SWEDESCREEN	Elfström 2014	32-38 (mean 35)	3	11	12 527	PCR GP5+/6+
POBASCAM	Rijkaart 2012	29-56 (41)	5	9	44 102	PCR GP5+/6+
ARTISTIC	Kitchener 2014	20 - 64	3	6	24 510	HC2
NTCC	Ronco 2014	25-60 (45, 2 nd round)	3	6.5	94 370	HC2



Key recently published evidence

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

*Guglielmo Ronco, Joakim Dillner, K Miriam Elfström, Sara Tunesi, Peter J F Snijders, Marc Arbyn, Henry Kitchener, Nereo Segnan, Clare Gilham, Paolo Giorgi-Rossi, Johannes Berkhof, Julian Peto, Chris J L M Meijer, and the International HPV screening working group**

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HPV Supplements

Authors, Editors & Literature Group

HPV Primary screening G. Ronco, M. Arbyn, C. Meijer, P. Snijders
(S 1) 36 Recs. J. Cuzick

Organization (S2) A. Anttila, G. Ronco, F. Nicula, P. Nieminen,
17 Recs M. Primic-Žakelj

HPV vaccination (S3) H. de Vuyst, R. Howell-Jones, D. Levy-Bruhl,
9 Recs L. Mosina, P. Giorgi Rossi, S. Franceschi

Literature Group P. Armaroli, R. Banzi, C. Bellisario, S. Minozzi,
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L. Dillner, S. Franceschi, J. Patnick, N. Segnan,
E. Suonio, S Törnberg, L. von Karsa

European Guidelines, 2nd Edition, Supplements, 2015:

- Conventional cervical cytology with Papanicolaou staining (Pap smear) and validated liquid-based cervical cytology (LBC) are evidence-based screening tests that fulfil the requirements of the Council Recommendation on Cancer Screening of 2 Dec. 2003 if performed in accordance with the European guidelines for quality assurance in cervical cancer screening.

The applicable items in the Council Recommendation of 2 December 2003 are 1(a) for conventional cervical cytology with Papanicolaou staining (Pap smear) and 1(a) in combination with 6(e) for validated liquid-based cervical cytology (LBC) (see Annex 2).

European Guidelines, 2nd Edition, Supplements, 2015:

- Primary testing for oncogenic HPV with validated assays also fulfils the requirements of the Council Recommendation of 2 December 2003 for evidence-based screening tests, provided the recommendations in Supplements 1 and 2 to the second edition of the European guidelines for quality assurance in cervical cancer screening are followed.

The applicable items in the Council Recommendation are 6(c) and 6(e) (see Annex 2)..

Screening for cervical cancer with primary testing for human papillomavirus (S1)

- Suitability of HPV primary testing for use in cervical cancer screening programs
 - Avoidance of co-testing (HPV and cytology primary testing) at any given age
 - Age at which to start HPV primary testing in cervical cancer screening programs
 - Age at which to stop HPV primary testing in cervical cancer screening programs
 - Screening interval after a negative HPV primary test
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Screening for cervical cancer with primary testing for human papillomavirus (S1) – cnt'd

- Management of women without an adequate HPV primary test result
 - Management of women after a positive HPV primary test
 - Secondary testing (Cytology triage and referral after triage testing)
 - Management of women at follow-up testing
 - Self-sampling in screening programmes using HPV primary testing
 - Selection of HPV tests suitable for primary cervical cancer screening
 - Implementation of HPV primary testing in cervical cancer screening programs
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Developing the evidence base for quality assurance of cervical screening based on HPV primary testing

CLINICAL QUESTION:

What is the reduction in the burden of CIN3/AIS+ and cervical cancer incidence and mortality among women screened by hrHPV testing, cytology or the combination of both?

PICOS methodology to guide systematic evidence review

- P: patients/population characteristics
 - I: experimental intervention on which the question is focused
 - C: comparison intervention / control /reference group
 - O: outcome measure relevant for the clinical question
 - S: study design on which to base the evidence search
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What is the reduction in the burden of CIN3/AIS+ and cervical cancer incidence and mortality among women by hrHPV testing, cytology or the combination of both?

P: asymptomatic women participating in cervical cancer screening

I1: testing for presence of nucleic acids of hrHPV

I2: testing for presence of nucleic acids of hrHPV in combination with cervical cytology

C1: cytological screening alone (versus I-1) or combination of cervical cytology and testing for hrHPV (versus I-1)

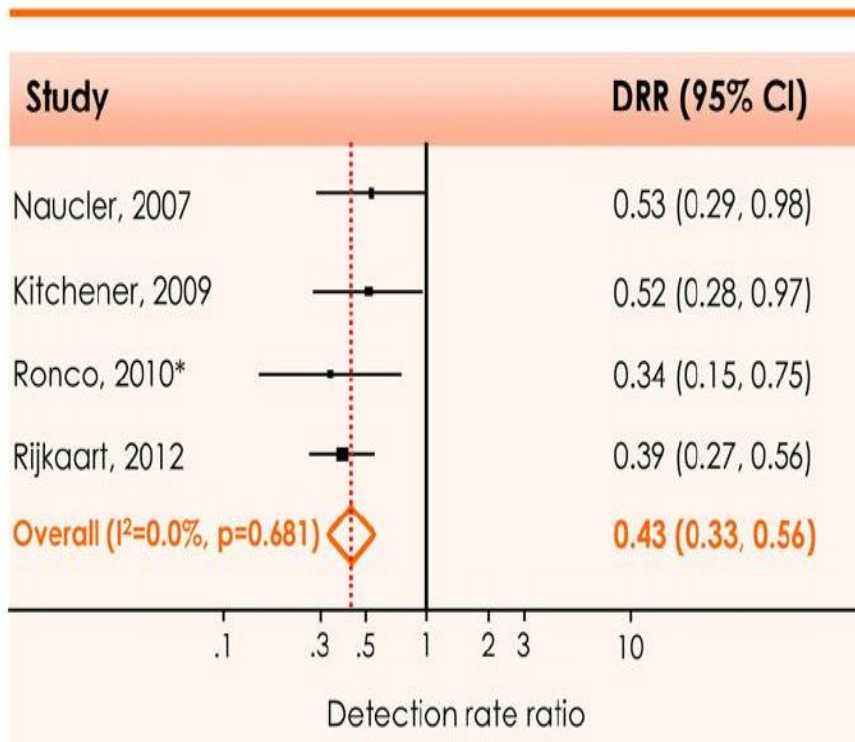
C2: HPV-based screening alone (versus I-2)

O: detection rate of CIN3/AIS, and invasive cervical cancer and mortality from cervical cancer after recruitment, taking information from the subsequent screening rounds into account; ratios of detection rates. Triage/follow-up procedures applied to ascertain outcome should be taken into account.

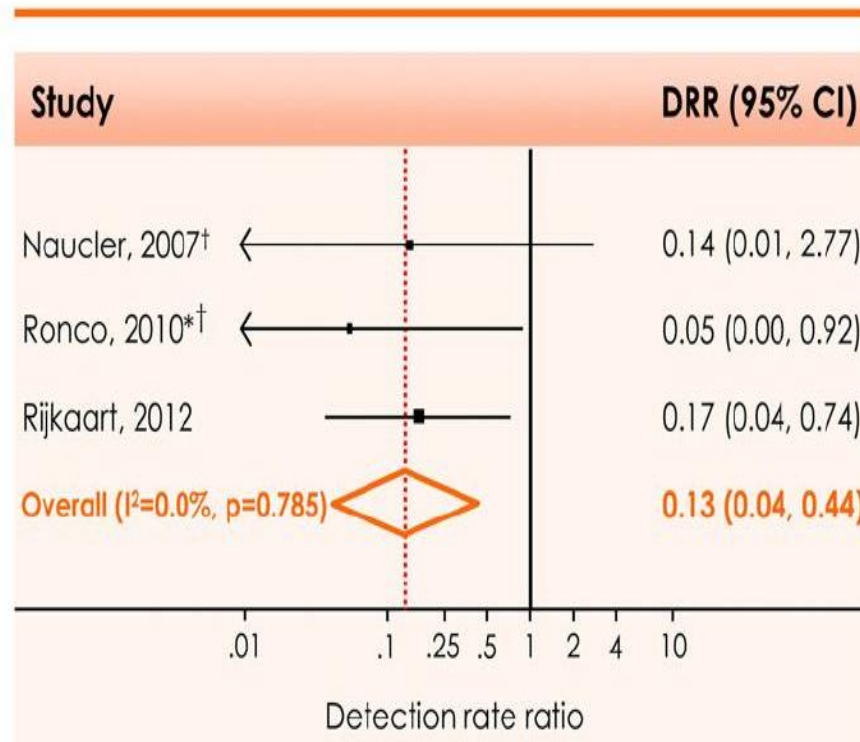
S: RCTs 2nd and further screening rounds; cohort studies with follow-up according to initial screen test results, including studies with registry linkages (screening, follow-up, cancer)

Evidence

CIN3+



CERVICAL CANCER



*Restricted to women older than 35 years.

†continuity correction (+.5 in each cell because of zero cancer cases among HPV-negative women).

Source: Arbyn et al. Vaccine 2012

CONCLUSION

- All 4 RCTs that have published 2nd round results showed a reduction of CIN3+ at the second screening round in the arm that used HPV alone in one trial, or in co-testing for primary screening compared to the arm that used cytology.
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CLINICAL QUESTION

- What is the amount of over-diagnosis (diagnosis of regressive or non-progressive lesions) associated with HPV-based, cytology-based and combined screening (HPV & cytology)?
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Study design



- Overdiagnosis of regressive lesions can be evaluated in randomised trials by comparing the overall detection of precursor lesions in the HPV and in the cytology arm over two or more screening rounds.
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CONCLUSION

- The large ratio (over 3) observed for CIN2 below age 35 in the Italian trial (NTCC) strongly suggests that HPV screening in younger women leads to substantial overdiagnosis of regressive CIN2.
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RECOMMENDATION 1.1

- Primary testing for oncogenic HPV can be used in an organized, population-based programme for cervical cancer screening **(I-A)** provided the other recommendations in this supplement are followed **(VI-A)**. Primary testing for oncogenic HPV outside an organized population-based programme is not recommended (see also Suppl. 2, Rec. 2.1) **(VI-E)**.^{Sect 1.2.1.3; 1.2.3}
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RECOMMENDATION 1.2

- Only one primary test (either cytology or testing for oncogenic HPV) should be used at any given age in cervical cancer screening (see also Rec. 1.3 – 1.7 **(II-A)**).^{Sect 1.3.1}
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RECOMMENDATION 1.3 – 1.5, 1.8

- Routine HPV primary screening can begin at age 35 years or above (see also Rec. 1.1) **(I-A)**.^{Sect 1.3.2.1}
 - Routine HPV primary screening should not begin under age 30 years **(I-E)**.^{Sect 1.3.2.1}
 - The available evidence is insufficient to recommend for or against beginning routine HPV primary screening in the age range 30 - 34 years **(VI)**.^{Sect 1.3.2.1}
 - The screening interval for women with a negative HPV primary test result should be at least 5 years **(I-A)** and may be extended up to 10 years depending on the age and screening history **(III-C)**.^{Sect 1.3.3}
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RECOMMENDATION 1.11

- Cervical screening programmes using HPV primary testing must adopt specific policies on triage, referral and repeat testing of women with positive primary test results, taking into account the guidance in Rec. 1.12 – 1.31). The policies must include guidance on when women with positive HPV test results should be invited to return to routine screening **(VI-A)**. Sect 1.3.5
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RECOMMENDATION 1.14 – 1-16

- Women testing positive for oncogenic HPV at primary screening should be tested without delay for cervical cytology (cytology triage) **(I-A)**.^{Sect 1.4.1.1} The cytology test should preferably use the specimen collected during the HPV screening visit **(VI-A)**.^{Sect 1.4.1.1}
 - Direct referral to colposcopy of all HPV-positive women is not recommended **(I-D)**.^{Sect 1.4.1.1}
 - Depending on the result of cytology triage, HPV-positive women should be referred to repeat testing, or to colposcopy (see Rec. 1.18 - 1.21) **(I-A)**.^{Sect 1.4.1.1}
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RECOMMENDATION 1.21 – 1.22

- Women who have negative cytology (negative for epithelial abnormality) at triage after a positive initial HPV primary test in a screening episode should be followed up by re-testing after an interval shorter than the regular screening interval, but after at least 6 - 12 months (see also Sect. 1.4.1 and Rec 1.23 and 1.24) **(VI-A)**.^{Sect 1.4.1.2}
- Direct referral to colposcopy of women with negative cytology at triage is not recommended **(I-D)**.^{Sect 1.4.1.2}

RECOMMENDATION 1.32 and 1.35

- The clinical accuracy of HPV primary testing on self-collected samples taken for cervical screening is sufficient to conduct organized, population-based pilot programmes for women who have not attended screening despite a personal invitation and a personal reminder (see also Rec. 1.33 and Suppl. 2, Rec. 2.8 - 2.13) **(III)**.^{Sect 1.7}
 - Like cervical cytology testing, HPV testing should be performed only on samples processed and analysed in qualified laboratories, accredited by authorized accreditation bodies and in compliance with international standards. The laboratory should perform a minimum of 10,000 tests per year (see also Rec. 1.34) **(VI-A)**.^{Sect 1.6}
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RECOMMENDATION 2.1

- Irrespective of the method of primary testing (cytology or HPV assay) cervical cancer screening should always be performed in an organized, population-based screening programme with comprehensive quality assurance covering all steps in the screening process (see also Suppl. 1, Rec. 1.34 and Annex 1 and 2) **(VI-A)**.^{Sect 2.3}
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RECOMMENDATION 2.4

- If a decision is made to implement HPV primary testing in an existing population-based cervical screening programme, comprehensive planning, feasibility testing and pilot programmes should be conducted prior to routine implementation to ensure that an appropriate balance between harm and benefit is achieved in the transition to HPV primary screening, including effective and efficient use of resources (see also Annex 1) **(VI-A)**.^{Sect 2.3.1}
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RECOMMENDATION 2.5

- If a decision is made to implement a population-based cervical screening programme in a country or region previously lacking such a programme, special attention must be paid not only to selecting the method of primary testing (cytology or HPV testing), but also to testing and developing the capacity for a population-based approach to programme implementation including building up comprehensive quality assurance (see also Rec. 2.4 and Annex 1 and 2) **(VI-A)**.^{Sect 2.3.2}
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RECOMMENDATION 2.6

- The introduction of new population-based screening programmes should be coordinated by a unit with a comprehensive mandate and sufficient autonomy and resources to ensure that the European quality assurance guidelines are followed and that international experts familiar with the process and determinants of successful programme implementation can be consulted (see also Annex 1) **(VI-A)**.^{Sect 2.3.322}
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RECOMMENDATION 2.14 – 2.15

- Monitoring of population-based cervical screening programmes should include the performance parameters defined in the European guidelines for quality assurance in cervical cancer screening (Suppl. 2, and Chap. 2 and 7 of the second edition) **(VI-A)**.^{Sect 2.6}
- Programmes should achieve an invitation coverage of 95% (acceptable level) **(III-A)**; >95% is desirable **(III-A)**.^{Sect 2.6.1}

RECOMMENDATION 2.16 – 2.17

- Programmes should achieve an examination coverage of 70% (acceptable level) **(III-A)**; >85% is desirable **(VI-A)**.^{Sect 2.6.1}
- Programmes should achieve a participation rate of 70% (acceptable level) **(III-A)**, >85% is desirable **(VI-A)**.^{Sect 2.6.1}

Thank you for your attention!