This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 847845

Guidance document (draft v0.1)

Project acronym	RISCC
Project number	847845
Project Title	RISCC
Call/Topic identifier	H2020-SC1-BHC-2018-2020 / H2020-SC1-2019-Two-Stage-RTD
Project start date	January 1st 2020 (M1)
Project end data	December 31st, 2024 (M60)

Change log			
Version	**Date**	**Author**	**Reason for change**
0.1	27-2-2025	J. Berkhof	Initial draft

This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 847845

Table of Contents

This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 847845

1 Summary of contents

The aim of the guidance document is to provide information on key findings of the RISCC project and how they can be considered when implementing risk-based screening. The guidance document also provides links to repositories with software for estimating precancer (i.e. CIN grade 3 or ACIS) and cancer risks and modelling risk-based strategies by means of simulation. In addition, the document includes links to ICT platform software currently used in the Netherlands and Sweden for running a risk-based screening program by sending invitations and storing screening results. In Section 2, we present the main recommendations from the RISCC project and explain how they can be used to formulate a risk-based screening scenario. In Section 3, we give an overview of publications by RISCC participants that support the recommendations in Section 2. Finally, in Section 4, we provide links to open-source platforms.

2 RISCC recommendations for risk-based screening

1. The traffic light: a metaphor for risk-based screening.

A risk-based program consists of a series of decision points that answer the question of who should be screened (orange/red), who should be referred for colposcopy (red), and who should not be screened (green). If a woman attends screening and is not immediately referred for colposcopy (red) or sent back to routine screening (light turns green), she will be monitored for a short period of time until her risk of cervical cancer is low enough for routine screening (light turns green) or sufficiently high for colposcopy referral (light turns red). This approach, in which the probability of cervical cancer is updated after the results of one or more repeat tests are available, is already used in several European countries.

2. HPV DNA testing should be used as a primary test

Large, randomised trials from the RISCC consortium and from other research groups have documented large differences in (pre)cancer risk in the risk of (pre)cancer in women with a normal cytology result and a negative HPV test. The combination of HPV testing and cytology is inefficient because the risk of women with a negative co-test result is only slightly lower than the risk of women with a negative HPV test while co-testing is substantially more expensive. In regions where screening is still based on cytology, we recommend switching to screening with HPV testing only.

3. The HPV test is a strong predictor of cervical cancer risk

The HPV test will tell you whether you are at risk of cervical cancer, but most HPV infections are transient. But the HPV test gives more information than just a simple positive/negative result. Many HPV tests now provide information about the viral genotype which is a strong predictor of precancer and cancer. RISCC screening studies and other studies indicated that HPV16 and HPV18 are associated with a relatively high risk of cancer and that HPV33 is associated with a high risk of precancer. On the

other hand, HPV35/51/56/59/66/68 are associated with a low risk of precancer. RISCC studies have also shown that HPV infections that have persisted for at least two screening rounds have a much higher risk of precancer and cancer than new HPV infections.

4. HPV-positive women are most often managed by cytology, but their performance should be carefully monitored.

If the risk of precancer and cancer based on HPV genotype and/or previous round HPV test results is not high enough to warrant immediate referral for colposcopy, cytology testing can be used to identify women with a high (pre)cancer risk. The performance of cytology is known to vary between settings and needs to be monitored in the real-world program. The RISCC studies also showed that DNA methylation analysis can be used as an alternative to cytology. The sensitivity and specificity of DNA methylation were comparable to those of cytology, but an advantage of DNA methylation analysis is that it is a molecular PCR test that does not require judgement of a cytotechnician.

5. Conservative management of high-grade lesions is possible when methylation and genotyping negative.

Screening can lead to considerable overtreatment because many high-grade lesions will not progress to cancer but will regress spontaneously when left untreated. The risk of regression of a high-grade lesion can be predicted by methylation analysis and genotyping. In particular lesions that are negative for a methylation test and negative for HPV16/18 have a high risk of regressing if left untreated. The RISCC team also observed that lesions observed in vaccinated women were methylation-negative, indicating that they have a low progression potential.

6. An HPV self-sampling (test) has a similar performance as an HPV test on a sample collected by a healthcare professional.

HPV self-sampling has a similar performance as to HPV testing on a sample collected by a healthcare professional in terms of the sensitivity to detect cervical precancer but also in terms of the specificity of identifying women without cervical lesions, provided that validated PCR-based HPV assays are used. An analysis by RISCC researchers of the performance of HPV self-sampling as a primary screening test in the Dutch screening program highlighted the importance of following standardized procedures for collection, transport, storage, and handling of self-samples in the laboratory. When evaluating the performance of HPV self-sampling locally, it is recommended to use a paired study design, where women receive both a self-collected and a clinician-collected HPV test. Self-sampling helps to increase the proportion of the population screened (also in remote or underserved areas), is less costly, and is more convenient for the women being tested. A limitation of HPV self-sampling is that (triage) cytology cannot be performed on a self-collected sample, but RISCC researchers showed that DNA methylation analysis on a self-collected sample can achieve high sensitivity and specificity for the detection of precancer. Therefore, HPV testing and triage testing by genotyping and methylation analysis can be done without the need to see a health professional for another sample for cytology.

7. The intensity of screening in vaccinated populations should be drastically reduced to maintain a favorable benefit-to-harm ratio.

Vaccination reduces the risk of acquiring an HPV infection and greatly reduces the risk of cervical precancer and cancer. Therefore, in vaccinated populations, it should be possible to reduce screening by delaying the screening start age and extending the screening interval. The number of screens can possibly be reduced to one or two screens lifetime when the vaccine provides broad spectrum protection, i.e. against multiple HPV types in addition to HPV16 and HPV18. To achieve strong herd effects among unvaccinated women, a high vaccination coverage is required and gender-neutral vaccination is recommended. It is also important to consider that it is likely that genotype replacement occurs after vaccination, but its impact on cancer risk remains to be seen. To guide the transition to less frequent screening, the HPV test and the HPV genotype result in the first round of screening provides important information about the residual precancer and cancer risk after vaccination and can give direction on how to de-intensify screening. We recommend linkage studies, in which vaccination status is linked to the HPV prevalence in the first round, to determine whether a uniform screening strategy can be offered to vaccinated women and unvaccinated women who are protected via herd effects, or whether separate screening start ages should be adopted for vaccinated and unvaccinated women.

3 Publications by RISCC participants to support the RISCC recommendations

Recommendation 1 and 3.

Nationwide registry-based trial of risk-stratified cervical screening. Arroyo Mühr LS, Wang J, Hassan SS, Yilmaz E, Elfström MK, Dillner J.Int J Cancer. 2025 Jan 15;156(2):379-388.

Impact of cervical screening by human papillomavirus genotype: Population-based estimations. Wang J, Elfström KM, Lagheden C, Eklund C, Sundström K, Sparén P, Dillner J.PLoS Med. 2023 Oct 27;20(10):e1004304.

Risk of cervical precancer among HPV-negative women in the Netherlands and its association with previous HPV and cytology results: A follow-up analysis of a randomized screening study. Inturrisi F, Rozendaal L, Veldhuijzen NJ, Heideman DAM, Meijer CJLM, Berkhof J.PLoS Med. 2022 Oct 28;19(10):e1004115.

Women with a positive high-risk human papillomavirus (HPV) test remain at increased risk of HPV infection and cervical precancer ≥15 years later. Inturrisi F, Bogaards JA, Siebers AG, Meijer CJLM, Heideman DAM, Berkhof J.Tumour Virus Res. 2022 Dec;14:200240.

Risk of Cervical Intraepithelial Neoplasia Grade 3 or Worse in HPV-Positive Women with Normal Cytology and Five-Year Type Concordance: A Randomized Comparison. Inturrisi F, Bogaards JA, Heideman DAM, Meijer CJLM, Berkhof J.Cancer Epidemiol Biomarkers Prev. 2021 Mar;30(3):485-491.

Recommendation 2.

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, Kitchener

H, Segnan N, Gilham C, Giorgi-Rossi P, Berkhof J, Peto J, Meijer CJ; International HPV screening working group. Lancet. 2014 Feb 8;383(9916):524-32.

Human papillomavirus-based cervical screening and long-term cervical cancer risk: a randomised health-care policy trial in Sweden. Wang J, Elfström KM, Dillner J.Lancet Public Health. 2024 Nov;9(11):e886-e895

Accuracy and effectiveness of HPV mRNA testing in cervical cancer screening: a systematic review and meta-analysis. Arbyn M, Simon M, de Sanjosé S, Clarke MA, Poljak M, Rezhake R, Berkhof J, Nyaga V, Gultekin M, Canfell K, Wentzensen N.Lancet Oncol. 2022 Jul;23(7):950-960.

Clinically validated HPV assays offer comparable long-term safety in primary cervical cancer screening: A 9-year follow-up of a population-based screening cohort. Oštrbenk Valenčak A, Kroon KR, Fabjan D, Mlakar J, Seme K, Berkhof J, Poljak M.Int J Cancer. 2025 Feb 15;156(4):788-801.

Recommendation 4.

Colposcopy Referral and CIN3+ Risk of Human Papillomavirus Genotyping Strategies in Cervical Cancer Screening. Kroon KR, Bogaards JA, Heideman DAM, Meijer CJLM, Berkhof J. Cancer Epidemiol Biomarkers Prev. 2024

Colposcopy referrals and CIN3 detection after triage by host cell DNA methylation and/or HPV genotyping in HPV positive women with low-grade cytology from a population-based Dutch primary HPV screening trial. Verhoef L, Bleeker MCG, Polman N, Kroon KR, Steenbergen RDM, Ebisch RMF, Melchers WJG, Bekkers RLM, Molijn AC, van Kemenade F, Meijer CJLM, Heideman DAM, Berkhof J.Int J Cancer. 2025 Mar 1;156(5):1065-1073.

Verhoef L, Bleeker MCG, Polman N, Steenbergen RDM, Meijer CJLM, Melchers WJG, Bekkers RL, Molijn AC, Quint WG, van Kemenade FJ, Berkhof J, Heideman DAM. Performance of DNA methylation analysis of ASCL1, LHX8, ST6GALNAC5, GHSR, ZIC1 and SST for the triage of HPV-positive women: Results from a Dutch primary HPV-based screening cohort. Int J Cancer. 2022 Feb 1;150(3):440-449.

Recommendation 5.

Low methylation marker levels among human papillomavirus-vaccinated women with cervical high-grade squamous intraepithelial lesions.vLouvanto K, Verhoef L, Pimenoff V, Eriksson T, Leppälä S, Lagheden C, Gray P, Scibior-Bentkowska D, Sumiec E, Nieminen P, Dillner J, Berkhof J, Meijer CJLM, Lehtinen M, Nedjai B, Heideman DAM.Int J Cancer. 2024 Nov 1;155(9):1549-1557

Clinical Regression of High-Grade Cervical Intraepithelial Neoplasia Is Associated With Absence of FAM19A4/miR124-2 DNA Methylation (CONCERVE Study). Kremer WW, Dick S, Heideman DAM, Steenbergen RDM, Bleeker MCG, Verhoeve HR, van Baal WM, van Trommel N, Kenter GG, Meijer CJLM, Berkhof J.J Clin Oncol. 2022 Sep 10;40(26):3037-3046.

Recommendation 6.

Sociodemographic Characteristics and Screening Outcomes of Women Preferring Self-Sampling in the Dutch Cervical Cancer Screening Programme: A Population-Based Study. Aitken CA, Inturrisi F, Kaljouw S, Nieboer D, Siebers AG, Melchers WJG, van den Brule AJC, Molijn A, Hinrichs JWJ, Niesters HGM, van Kemenade FJ, Berkhof J, de Kok IMCM.Cancer Epidemiol Biomarkers Prev. 2023 Feb 6;32(2):183-192.

Clinical performance of high-risk HPV testing on self-samples versus clinician samples in routine primary HPV screening in the Netherlands: An observational study. Inturrisi F, Aitken CA, Melchers WJG, van den Brule AJC, Molijn A, Hinrichs JWJ, Niesters HGM, Siebers AG, Schuurman R, Heideman DAM, de Kok IMCM, Bekkers RLM, van Kemenade FJ, Berkhof J.Lancet Reg Health Eur. 2021 Nov 9;11:100235.

Staged design recommendations for validating relative sensitivity of self-sample human papillomavirus tests for cervical screening. Brentnall AR, Cuschieri K, Sargent A, Berkhof J, Rebolj M.J Clin Epidemiol. 2024 Feb;166:111227

HPV-based Cervical Cancer Screening on Self-samples in the Netherlands: Challenges to Reach Women and Test Performance Questions. Arbyn M, Costa S, Latsuzbaia A, Kellen E, Girogi Rossi P, Cocuzza CE, Basu P, Castle PE.Cancer Epidemiol Biomarkers Prev. 2023

Cervical cancer screening improvements with self-sampling during the COVID-19 pandemic. Elfström M, Gray PG, Dillner J.Elife. 2023 Dec 12;12:e80905.

HPV testing of self-samples: Influence of collection and sample handling procedures on clinical accuracy to detect cervical precancer. Arbyn M, Latsuzbaia A, Castle PE, Sahasrabuddhe VV, Broeck DV.Lancet Reg Health Eur. 2022 Feb 17;14:100332.

Evaluation of DNA methylation biomarkers ASCL1 and LHX8 on HPV-positive self-collected samples from primary HPV-based screening. Verhoef L, Bleeker MCG, Polman N, Steenbergen RDM, Ebisch RMF, Melchers WJG, Bekkers RLM, Molijn AC, Quint WG, van Kemenade F, Meijer CJLM, Berkhof J, Heideman DAM.Br J Cancer. 2023 Jul;129(1):104-111

Recommendation 7.

Scientific approaches toward improving cervical cancer elimination strategies. Lehtinen M, Bruni L, Elfström M, Gray P, Logel M, Mariz FC, Baussano I, Vänskä S, Franco EL, Dillner J.Int J Cancer. 2024 May 1;154(9):1537-1548

The quality of life of frequently vs. infrequently screened HPV vaccinated women. Taavela K, Eriksson T, Huhtala H, Bly A, Harjula K, Heikkilä K, Hokkanen M, Nummela M, Kotaniemi-Talonen L, Lehtinen M, Louvanto K.Qual Life Res. 2024 Apr;33(4):941-949

Ecological diversity profiles of non-vaccine-targeted HPVs after gender-based community vaccination efforts. Pimenoff VN, Gray P, Louvanto K, Eriksson T, Lagheden C, Söderlund-Strand A, Dillner J, Lehtinen M.Cell Host Microbe. 2023 Nov 8;31(11):1921-1929.

Baseline findings and safety of infrequent vs. frequent screening of human papillomavirus vaccinated women. Louvanto K, Eriksson T, Gray P, Apter D, Baussano I, Bly A, Harjula K, Heikkilä K, Hokkanen M,

Huhtinen L, Ikonen M, Karttunen H, Nummela M, Söderlund-Strand A, Veivo U, Dillner J, Elfstöm M, Nieminen P, Lehtinen M.Int J Cancer. 2020 Jul 15;147(2):440-447.

Estimating the direct effect of human papillomavirus vaccination on the lifetime risk of screen-detected cervical precancer. Inturrisi F, Lissenberg-Witte BI, Veldhuijzen NJ, Bogaards JA, Ronco G, Meijer CJLM, Berkhof J.Int J Cancer. 2021 Jan 15;148(2):320-328.

4 Online tools

4.1 Estimating disease progression risks

In order to implement a risk-based screening program, it is important to know the CIN3+ and cancer risks by age, HPV genotype, cytology, previous screening attendance, and previous HPV results. Risks can be estimated from data stored in screening registries or risk estimates can be taken from the available literature. To estimate risks in women with an HPV-positive result, we developed a flexible statistical model framework. This model provides easy-to-interpret parameters and can produce accurate estimates for HPV screening cohort data, also when the data set is only of moderate size. In RISCC, this prevalence-incidence-clearance model has been applied to the data stored in the RISCC screening trial database and provides accurate estimates of the probability of CIN3+ at baseline and the probability of CIN3+ during follow-up. The software and detailed information can be found at the following Github account:

GitHub - kelsikroon/PICmodel: Code and examples for R package to accompany paper "A prevalence-incidence-clearance model for interval-censored screening data in a population with a temporarily elevated disease risk" (unpublished)

4.2 Modeling risk-based screening scenarios

The RISCC partners have also developed a simulation model that can be used to compare the effectiveness and cost-effectiveness of different risk-based screening strategies. The model simulates the individual health trajectories of women throughout their lives. The model has a natural history module for cervical cancer, as well as flexible components that characterise different women's risk profiles and cervical cancer screening interventions. The model is also designed to account for temporal variation in HPV prevalence and demographics in the simulated population. The model code and Guided User Interface, together with supporting documentation, has been made publicly available as open-source material at the end of the RISCC project. The link to the Gitlab account is

https://iarc-ice.gitlab.io/miarc/shiny.prometheos/index.html.

This is a R Shiny package that comes with a getting started tutorial. The link should open an app home page and provides detailed information about how to set up the model and how to compare strategies.

4.3 ICT platform software for running a risk-based screening programme

Risk-based screening programmes have been implemented in the Netherlands and Sweden. In the Netherlands, the characteristics of the risk-based screening programme are:

1) The screening interval depends on age and the HPV result. Women aged 45 and 55 are only invited when they did not attend five years earlier or did not have an HPV negative screening result five years earlier. Women aged 65 are only invited when they were HPV positive five years earlier and were not referred to the gynaecologist.
2) Women with a positive HPV test will receive HPV16/18 genotyping and cytology. Women with HSIL or HPV16/18 & ASCUS/LSIL are referred to the gynaecologist immediately, while other women are invited back for cytology after one year.

The ICT platform software is available at the following Github account: GitHub - BVO-NL/rivm-screenit

In Sweden, a more advanced risk-based screening program is offered, where women at high risk of cancer are invited to participate in HPV self-sampling through mHealth/eHealth tools (Arroyo-Muhr, Int J Cancer 2024). Beta versions of the source code are stored in private repositories on GitHub. The repositories will be public once version 1.0 is ready. The developer of the ICT platform software is dr. Roxana Martinez (roxana.martinez@ki.se).