Prevalent vs incident high risk HPV infection – PECO 2

Systematic review report

PECO 2

This systematic review addresses the following PECO which is summarised in detailed in Table 1

For individuals undergoing cervical HPV screening is the risk of CIN3+ with an incident HPV16/18 infection and negative, pLSIL or LSIL cytology lower than or equivalent to the risk with a prevalent high risk HPV infection other than 16/18 and LSIL cytology?

Table 1. PECO components

Population	***Exposure***	***Comparator ****	***Outcome***	***Study design***
Individuals undergoing cervical HPV screening	Incident HPV 16/18 infection and negative, pLSIL or LSIL cytology	Prevalent hr-HPV other infection and LSIL cytology	CIN3+ (primary outcome) or cancer (secondary outcome) on follow-up of positive screen	Cohort Cross-sectional

CIN3+ = cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ or cancer; HPV = human papillomavirus; hr-HPV other = high risk HPV other than 16 or 18, LSIL = low-grade squamous intraepithelial lesion; pLSIL = low-grade squamous intraepithelial lesion
** Rationale for choosing this group as the comparator is that screening participants with this set of test results at their initial screen are referred for a 12-month repeat test, rather than colposcopy. If those with incident HPV16/18 infection and negative, pLSIL or LSIL cytology have similar or lower risk than this group, this would potentially lend support to deferring colposcopy until after a 12-month repeat test.*

1. METHODS

1.1 Selection Criteria

Table 2. Selection criteria.

	Inclusion criteria	***Exclusion criteria***
Study type	Observational	
Study design	Cohort studies Cross-sectional studies	Case-control studies Modelling
Population	Women undergoing cervical screening using HPV test	Restricted to women with cancer, CIN3+ or CIN2+
Exposure	HPV16/18, HPV16 or HPV 18 positive on second/subsequent HPV test and HPV negative or negative for that HPV type on initial HPV test – incident infection AND Negative, pLSIL or LSIL cytology	
Comparator	High risk HPV other than 16 or 18 positive on first HPV test – prevalent infection (ie prior HPV status unknown) AND LSIL cytology	
Outcome	CIN3+ (primary outcome) or cervical cancer • Immediate risk following positive test • Risk on follow-up By genotype and cytology if available	CIN2+
Publication date	2015 onwards	
Publication type	Peer-reviewed journal article or letter or comment that reports original data	Conference abstract Editorial

		Letter or article that does not report original data
Language	English	

CIN = cervical intraepithelial neoplasm; CIN3+ = cervical intraepithelial neoplasia grade 3 (HSIL), adenocarcinoma in situ or cancer; HPV = human papillomavirus; LSIL = low-grade squamous intraepithelial lesion; pLSIL = low-grade squamous intraepithelial lesion

1.2 Definitions and terminology

For the purposes of this review:

Prevalent infection *refers to an infection detected on first HPV test;*

Incident infection *refers to an infection detected on a second or subsequent HPV test where all previous HPV tests were negative or negative for that HPV type.*

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described in section 1.4 below) and by searches of the following websites and databases in February and March:

- International Health Technology Assessment (HTA) database
- Guidelines International Network (GIN) database
- National Institute for Health and Care Excellence (NICE) Guidelines website
- Scottish Intercollegiate Guidelines Network (SIGN) website
- NHS England website
- Public Health Wales website
- World Health Organisation website
- The American Cancer Society website
- The American college of Obstetricians and Gynecologists website
- U.S. Preventive Services Task Force website
- University of Michigan Rogel Cancer Centre website
- The American Society of Clinical Oncology website
- NCCN Clinical Practice Guidelines in Oncology website
- British Columbia Medical Association website
- Health Canada
    - Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines (2016) website
- Toward Optimized Practice (TOP Alberta doctors) website
- Cancer Care Ontario website
- European Society of Medical Oncologists (ESMO) website
- The Danish Health and Medicines Authority website
- Haute Autorite de Sante website

To be considered for adoption by the Working Party, guidelines had to be evidence-based and meet the pre-specified criteria of scores of greater or equal to 70% for the following domains: rigour of development, clarity of

presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/). Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence or did not assess the risk of bias or where this is not possible, appraise the quality of the evidence.

1.4 Literature searches

Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations) and Embase databases were searched on 23rd May 2023 combining text terms and database-specific subject headings for cervical lesions or cancer, screening and human papillomavirus. Searches were limited to articles published in English from 1st January 2015 onwards and were designed to identify potentially relevant studies in populations that included Aboriginal and Torres Strait Islander peoples. A complete list of the terms used is included as Appendix A. On 3rd March 2023 the Cochrane Database of Systematic Reviews was searched from inception using the search terms “human papilloma virus” and “colposcopy” and the INAHTA database was searched from 2005 onwards using the search terms “HPV” and “human papilloma virus”. Reference lists of collected articles, recent relevant guidelines and reviews were checked for potential additional articles.

Titles and abstracts and full texts were screened for eligibility by one reviewer. Reasons for exclusion were recorded for studies excluded at the full text screening stage.

1.5 Data extraction and analyses

One review author extracted data from the studies which was checked by a second reviewer. Any discrepancies were resolved through discussion or by consulting a third reviewer, if required. We extracted following data from the included studies:

- *Study characteristics*: Author, publication year, country, and study design.
- *Participants*: Participant description, number of participants, age of participants
- *Screening program details:* screening frequency and test
- *Exposure*: Description of exposure, levels of exposures reported, number of exposed participants.
- *Comparator*: Description of comparator/reference group, number of unexposed/comparator group participants.
- *Follow-up:* Follow-up protocols for different screen results
- *Outcomes*: Outcomes reported

The risk estimates along with the 95% confidence interval were extracted (where reported). We could not conduct meta-analysis due to very limited and heterogeneous data.

1.6 Risk of bias assessments and quality appraisals

The risk of bias for the primary outcome, cervical intraepithelial neoplasia grade 3 or worse (CIN3+) was assessed using a modified version of the Newcastle-Ottawa Scale designed specifically to assess biases in

observational cohort studies (Kirk 2018). Prior to the assessments, potential sources of bias were identified and discussed by the reviewers with content experts to develop rulings to guide with the assessment of the risk of bias by a single reviewer. The sources of bias assessed were selection of exposed and unexposed cohorts, measurement of exposure, measurement of outcome, reverse causation, length of follow-up, participation, completeness of follow-up, accuracy of outcome and censoring dates, differences in follow-up, differences in missing exposure data, adjustment for important confounders and over-adjustment. A study was considered at low risk of bias overall if all sources of bias were rated as low risk, at moderate risk of bias overall if at least one source of bias was rated as moderate risk and at high risk of bias overall if at least one source of bias was rated as high risk.

1.7 GRADE assessment of the certainty of the evidence

A GRADE (grading of recommendation, assessment, development and evaluation) approach was used to assess the certainty of the body of evidence for the 5-year risk of CIN3+. This was considered the most relevant outcome and was less dependent on how the different groups were assessed for CIN3+ (https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence).

The certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness of the results, imprecision, inconsistency of the results, and publication bias based on guidance for assessing narrative syntheses provided by Murad 2017 and prognostic studies provided by Foroutan 2020 with additional guidance for the assessment of imprecision provided by Guyatt 2011. For the assessment of imprecision, the upper limit of the 95% confidence interval for the risk associated with a prevalent high risk HPV infection other than 16/18 and LSIL cytology was applied as the recommendation threshold ie if the upper limit of the 95% confidence interval for the risk associated with incident HPV16/18 infections was greater than the recommendation threshold the certainty of the evidence was rated down for imprecision (Guyatt 2011). Where there was only one study inconsistency could not be rated. As per GRADE guidance for prognostic studies (Foroutan 2020), studies started with a high level of certainty in the evidence and were downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were serious concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias.

2. RESULTS

2.1 Guidelines searches

Twenty-eight potentially relevant guidelines were identified. At least some recommendations in six of these were based on systematic reviews published in English. Of these, none included recommendations that addressed the question of interest (Appendix B).

2.2 Literature searches

Figure 1 outlines the process of identifying relevant articles for this systematic review update. The combined Medline and Embase search identified 2455 citations and the search of the Cochrane Database of Systematic

Reviews and INHATA database identified 125 citations, resulting in a total of 2580 citations. Titles and abstracts were examined by one reviewer, and 64 articles were retrieved for a more detailed evaluation. Another three potentially relevant articles were identified from reference lists of collected articles, recent relevant guidelines and reviews. Three articles reporting on two cohort studies met the eligibility criteria. No relevant studies that included Aboriginal or Torres Strait Islander peoples were identified.

The reasons for exclusion of studies after full text screening are provided in Appendix C. The main reasons for exclusion were no exposure of interest (n = 39), no comparator of interest (n = 9) and no outcome of interest (n = 9).

Characteristics of the included studies are summarised in Table 3.

Two studies reported both the risk of CIN3+ following incident HPV16/18-positive cytologies that currently require immediate colposcopy and following prevalent high-risk HPV other-positive LSIL that currently does not require immediate colposcopy.

No studies were found comparing incident HPV16/18-positive cytologies and any prevalent LSIL (regardless of HPV status) that did not require immediate colposcopy in the previous cytology-based screening program.

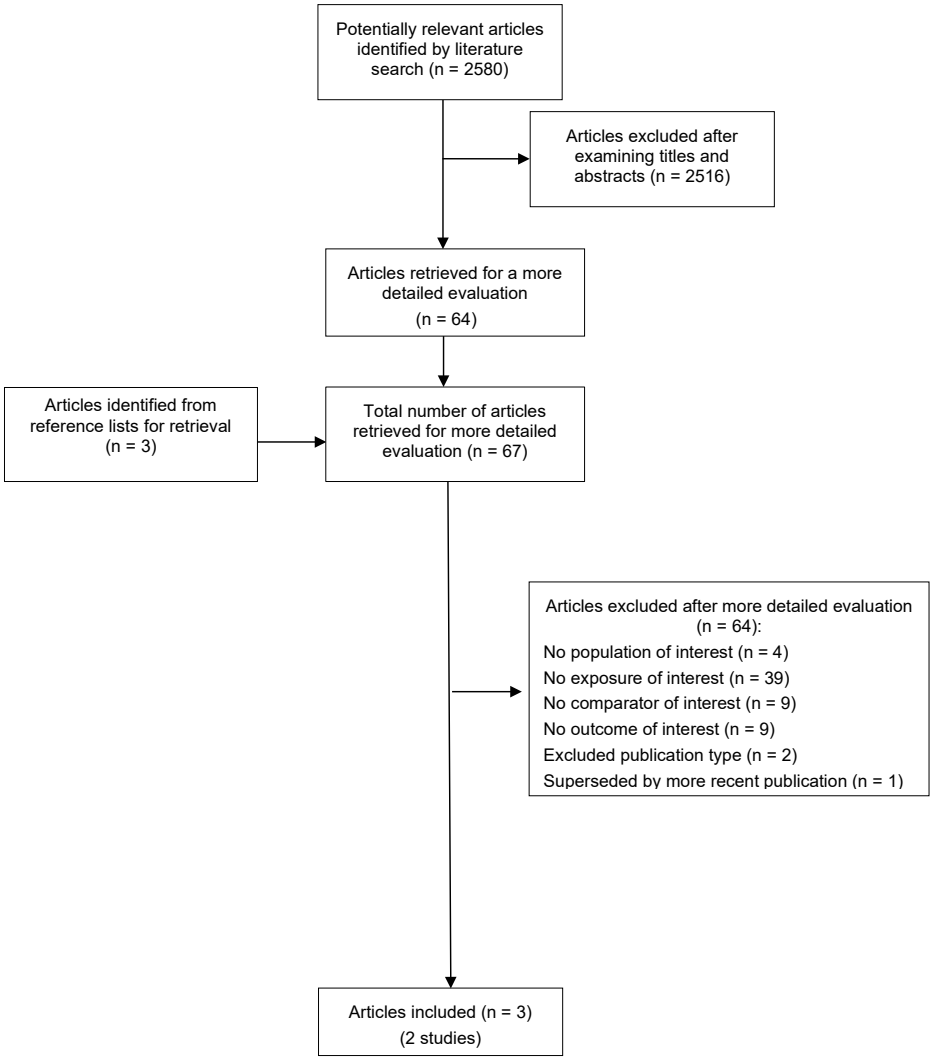

Figure 1. Process of inclusion and exclusion of studies for the systematic review update.

2.3 Study characteristics

Table 3. Characteristics of studies reporting both the risk of CIN3+ following incident HPV16/18-positive cytologies that currently require immediate colposcopy, and following prevalent high-risk HPV other-positive LSIL that currently does not require immediate colposcopy.

Study	***Study design***	***Population***	***Screening program***	***Exposure***	***Comparator***	***Follow-up***	***Outcomes***
Demarco 2020 Cheung 2020 (USA)	Cohort	Individuals aged 25-65 years who underwent routine cervical screening between 2003 and 2017 at Kaiser Permanente Northern California (KPNC) who were members of the KPNC/National Cancer Institute guidelines cohort with an HPV and a cytology test result at initial screen N = 1,546,462 Subgroup: participants in the KPNC Persistence and Progression study who underwent cervical screening between 2007 and 2011 N = 11,759	3-yearly HPV (HC2 with HPV typing of HPV-positive samples) and cytology **co-test**	HPV-positive and **previous HPV test was negative** NILM *HPV16-positive* n = 275 *HPV18-positive* n = 109 ASC-US HPV16-positive n = 155 *HPV18-positive* n = 52 LSIL *HPV16-positive* n = 120 *HPV18-positive* n = 27	HPV-positive on **first known HPV test** ASC-US *hrHPV other-positive* n = 1024 LSIL *hrHPV other-positive* n = 669	immediate colposcopy if HPV-positive ASC-US, LSIL, or more severe cytological abnormalities, and annual co-testing if HPV-positive NILM or HPV-negative ASC-US. If undergoing annual co-test for HPV-positive NILM or HPV-negative ASC-US referral to colposcopy if cytological abnormalities (from 2003) or a second HPV-positive NILM (from 2006) on next follow-up co-test.	**CIN3+** Immediate risk 5-year risk Incidence rates **Cancer *^** Immediate risk 5-year risk Incidence rates
Gilham 2020 (UK)	Cohort	Individuals undergoing population-based screening who underwent first HPV test either as co-test or hidden between 2001 and 2003 as participants in the ARTISTIC screening trial aged 20-64 years N = 24,496	3-yearly HPV (HC2 with HPV typing of HC2 positive samples) and cytology with management determined by **co-test** results in intervention arm (75% of participants) and by cytology only in control arm (~25% participants)	HPV-positive (HC2 and HPV typing assay) on second **actionable or hidden** screen following HPV-negative first screen N = 387 Normal cytology n = 269 *16/18 HPV-positive* n = 75 Borderline or low-grade cytology n = 110 *16/18 HPV-positive* n = 49	HPV-positive (HC2 and HPV typing assay) on first **actionable or hidden** (baseline) HPV screen N = 2780 Borderline or low-grade cytology *hrHPV other-positive* n = 568	*Baseline and second screens* Immediate colposcopy if moderate or severe cytology (Kitchener 2009) Repeat cytology at 6 months if borderline or low grade cytology HPV retest at 12 and 24 months if actionable HPV-positive and normal cytology (intervention arm only) *Third screen* All participants underwent screening as per national guidelines	**CIN3+** 5-year cumulative risk 10-year cumulative risk

ASC-US = atypical squamous cells of undetermined significance; CIN3+ = cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ or cancer; HC2 = Hybrid Capture 2 test; hrHPV other = high risk HPV infection other than 16 or 18 HPV infections; LSIL= low-grade squamous intraepithelial lesion; NILM = negative for intraepithelial lesions or malignancy
*^ obtained from https://lhncbc.nlm.nih.gov/LHC-research/LHC-projects/image-processing/cervixca.html accessed 190623

2.4 Results by outcomes of interest

1. CIN3+ (primary outcome) – Table 4
2. Cervical cancer (secondary outcome) – Table 5

2.4.1 Risk of CIN3+

Table 4. Risk of CIN3+ following incident HPV16/18- positive cytologies that currently require immediate colposcopy and prevalent high-risk HPV other-positive LSIL that currently does not require immediate colposcopy

Study	***Exposure – HPV negative test followed by 16/18HPV-positive cytology ≤ LSIL***					***Comparator (Benchmark - hrHPV other positive LSIL on first HPV test***				
	Cytology (HPV positive test)	***hrHPV genotype***	***No. CIN3+***	***N***	***Risk of CIN3+***	***Cytology***	***hrHPV genotype***	***No. CIN3+***	***N***	***Risk of CIN3+***
Immediate risk of CIN3+										
Demarco 2020 *^	NILM	HPV16	<39	275	2.96% (95%CI = 0.88 – 5.03)	LSIL	hrHPV other	<76	669	3.66% (95%CI = 2.72 – 4.60)
	ASC-US	HPV16	<28	155	5.34% (95%CI = 2.66 – 8.03)					
	LSIL	HPV16	<23	120	6.70% (95%CI = 3.28 – 10.13)					
	NILM	HPV18 (16 negative)	<9	109	2.49% (95%CI = 0.39 – 4.59)					
	ASC-US	HPV18 (16 negative)	<5	52	2.45% (95%CI = -0.35 – 5.24)					
	LSIL	HPV18 (16 negative)	<2	27	3.48% (95%CI = -1.40 – 8.36)					
5-year risk of CIN3+										
Demarco 2020** *^	NILM	HPV16	39	275	7.11% (95%CI = 4.81 – 9.42)	LSIL	hrHPV other	76	669	4.70% (95%CI = 3.60 – 5.80)
	ASC-US	HPV16	28	155	10.16% (95%CI = 6.22 – 14.11)					
	LSIL	HPV16	23	120	11.29% (95%CI = 6.51 – 16.07)					
	NILM	HPV18 (16 negative)	9	109	3.77% (95%CI = 1.12 – 6.42)					
	ASC-US	HPV18 (16 negative)	5	52	4.22% (95%CI = 0.63 – 7.81)					
	LSIL	HPV18 (16 negative)	2	27	3.48% (95%CI = -1.4 – 8.36)					
Gilham 2020^	Normal	HPV16/18	2	75	2.7% (95%CI = 0.7-10.2)	Borderline or low-grade	hrHPV other	38	568	6.7 (95%CI = 4.9-9.1)
	Borderline or low-grade	HPV16/18	4	49	8.2% (95%CI = 3.1-20.3)					
10-year risk of CIN3+										

Gilham 2020^	Normal	HPV16/18	2	75	2.7% (95%CI = 0.7-10.2)~	Borderline or low-grade	hrHPV other	41	568	7.3 (95%CI = 5.4-9.7)
	Borderline or low-grade	HPV16/18	4	49	8.2% (95%CI = 3.1-20.3)~					

** used prevalence-incidence mixture models to calculate 5-year risk
*^ confidence intervals obtained from https://lhncbc.nlm.nih.gov/LHC-research/LHC-projects/image-processing/cervixca.html accessed 190623
^ used Kaplan Meier method to calculate cumulative risk
~ 10-year risk the same as 5-year risk
ASC-US = atypical squamous cells of undetermined significance; CI = confidence interval; CIN3+ = cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ or cancer; hrHPV other = high risk HPV infection other than 16 or 18 HPV infections; LSIL= low-grade squamous intraepithelial lesion; NILM = negative for intraepithelial lesions or malignancy

2.4.2 Risk of cervical cancer

Table 5. Risk of cervical cancer following incident HPV16/18- positive cytologies that currently require immediate colposcopy and prevalent high-risk HPV other-positive LSIL that currently does not require immediate colposcopy

Study	***Exposure – HPV negative test followed by 16/18HPV-positive cytology ≤ LSIL***					***Comparator (Benchmark - hrHPV other positive LSIL on first HPV test***				
	Cytology (HPV positive test)	***hrHPV genotype***	***No. cancer***	***N***	***Risk of cancer***	***Cytology***	***hrHPV genotype***	***No. cancer***	***N***	***Risk of cancer***
5-year risk of CIN3+										
Demarco 2020** *^	NILM	HPV16	5	275	0.96% (95%CI = 0.10 – 1.83)	LSIL	hrHPV other	1	669	0.06% 95%CI: Not available
	ASC-US	HPV16	3	155	1.18% (95%CI = -0.16 – 2.52)					
	LSIL	HPV16	2	120	0.89% (95%CI = -0.35 – 2.41)					
	NILM	HPV18 (16 negative)	1	109	0.44% (95%CI = -0.43 – 1.31)					
	ASC-US	HPV18 (16 negative)	3	52	2.51% (95%CI = -0.34 – 5.36)					
	LSIL	HPV18 (16 negative)	0	27	0					

** used prevalence-incidence mixture models to calculate 5-year risk
*^ data obtained from https://lhncbc.nlm.nih.gov/LHC-research/LHC-projects/image-processing/cervixca.html accessed 190623
ASC-US = atypical squamous cells of undetermined significance; CI = confidence interval; CIN3+ = cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ or cancer; hrHPV other = high risk HPV infection other than 16 or 18 HPV infections; LSIL= low-grade squamous intraepithelial lesion; NILM = negative for intraepithelial lesions or malignancy

2.5 Risk of bias assessments for CIN3+ outcomes

Risk of bias assessments

The results of the risk of bias assessments for the included studies are shown in **Table 6**.

Table 6: Risk of bias for the included cohort studies for the outcome of CIN3+

Risk of Bias Domains	Studies		
	Demarco 2020 *Immediate risk*	**Demarco 2020** *5-year risk*	**Gilham 2020** *5-year and 10-year risk*
Selection of exposed and non-exposed cohorts	Moderate	Moderate	Low
Measurement of exposure	Low	Low	Low
Measurement of outcome	Moderate	Moderate	Moderate
Outcome of interest absent at the start of the study?	Low	Low	Low
Follow-up long enough for outcome to occur?	Low	Low	Low
Participation rate	Low	Low	Low
Completeness of follow-up	Low	Moderate	Low
Difference in follow-up between exposed and non-exposed incident *HPV 16/18 negative cytology vs hrHPV other LSIL/ borderline or low-grade cytology*	High	Moderate	Moderate
Difference in follow-up between exposed and non-exposed *HPV 16/18 pLSIL or LSIL/ borderline or low-grade vs hrHPV other LSIL/ borderline or low-grade cytology*	Low	Low	Low
Accuracy of dates of outcome or censoring	Low	Low	Low
Difference in missing data for exposure between those with or without the outcome	Low	Low	Low
Comparability of exposed and unexposed cohorts (confounding)[1]	Moderate	Moderate	Moderate
Covariates are appropriately included in statistical analysis models	NA	NA	NA
Overall Risk of Bias *for incident vs prevalent HPV positive low grade cytology*	Moderate	Moderate	Moderate
Overall Risk of Bias *for incident HPV positive negative cytology vs prevalent HPV positive low grade cytology*	High	Moderate	Moderate

[1] *Important confounders:* ***Age****, race, hormonal contraceptives use, smoking, and income – age most important*
NA = not applicable as analyses did not control for confounding

Key to overall rating
High risk of bias – high risk of bias in any domain
Moderate risk of bias – moderate or low risk of bias in all domains
Low risk of bias – all domains low risk of bias

2.6 GRADE assessment of the certainty of the evidence for the risk of 5-year CIN3+

Table 7. GRADE assessment of the certainty of the evidence from cohort studies for the outcome of 5-year risk of CIN3+ for incident HPV16/18-positive negative or low-grade cytology and for prevalent high-risk HPV other than types 16 or 18 and LSIL cytology (for whom immediate colposcopy is currently not recommended).

GRADE domain	***Rating***	***Reason for downgrading or upgrading***	***Certainty of evidence***
*Incident HPV16/18 positive **negative cytology** vs prevalent hr-HPV other LSIL cytology*			
Risk of bias	Serious concerns	The risk of bias for both of the two included studies was assessed as moderate. In both studies the follow-up of the exposed and the comparator differed. It was assumed that CIN3+ not detected at baseline due to less intense baseline investigations for one of the groups will be detected with ensuing follow-up.	**Very low certainty** as to whether risk for incident HPV16 or HPV18-positive normal cytology is unacceptably greater than benchmark risk
Indirectness	No serious concerns	The populations, interventions, comparators and outcomes of both studies were considered relevant. The results of the USA study were directly relevant as the risks for LSIL were reported separately. The result of the UK study may be of less relevance as the results were for borderline or low-grade cytology ie pLSIL and LSIL equivalents were not distinguished	
Imprecision	Serious concerns (HPV16-positive) Very serious concerns (HPV16/18- or HPV18-positive)	*Contextualised – Is the risk greater than the recommendation threshold* *If threshold for recommendation is **upper limit** of CI for prevalent hr-HPV other-positive LSIL* (highest acceptable risk of CIN3+ not requiring immediate colposcopy) In both studies the CI for incident HPV16-, HPV18- and HPV16/18-positive negative cytology crosses the threshold – risk may be greater or lower than threshold Point estimate for incident HPV16-positive negative cytology is greater than the point estimate for prevalent hr-HPV other-positive LSIL – risk may be greater than threshold (small numbers of events so likely inadequately powered to show differences let alone non-inferiority)	
Inconsistency	Serious concerns	In the USA study the point estimate for the risk for incident HPV16-positive negative cytology (n = 275) is 7.11% which is higher than the point estimate of 4.70% for the risk for prevalent hr-HPV other-positive LSIL (n= 669) whereas the point estimate for the risk for incident HPV18-positive negative cytology (n = 109) was lower at 3.77%. In the UK study the point estimate for the risk for incident HPV16/18-positive negative cytology (n = 75) is 2.7% which is lower than the point estimate of 6.7% for the risk for prevalent hr-HPV other-positive borderline of low-grade cytology (n= 568). These differences are not readily explained by differing screening programs or proportions of p16 and p18 infections	
Publication bias	Undetected	Neither of two studies were designed to specifically assess the comparison of interest so publication bias unlikely. No formal statistical test could be used to detect publication bias due to < 10 studies (the minimum number of studies needed for a funnel plot) reporting this outcome.	
*Incident HPV16/18 positive **low-grade cytology** vs prevalent hr-HPV other LSIL cytology*			
Risk of bias	No serious concerns	The risk of bias for both of the two included studies was assessed as moderate. Neither study adjusted for age and the assessment of this source of bias based was on the assumption that the age of the two groups did not differ markedly. Both exposed and non-exposed were followed up in the same manner in both studies.	**Moderate** **F***or incident HPV16-positive LSIL or ASC-US cytology or HPV16/18-positive borderline or low-grade cytology* Moderate certainty that the risk is not low
Indirectness	No serious concerns	The populations, interventions, comparators and outcomes of both studies were considered relevant. The results of the USA study were directly relevant as the risks for LSIL were reported separately. The results of the UK study may be of less relevance as the results were for borderline or low-grade cytology ie pLSIL and LSIL equivalents were not distinguished	
Imprecision	Serious concerns	*Contextualised – Is the risk greater than the recommendation threshold?*	

Commented [SH1]: Threshold for recommendation does this sound reasonable? OK with Working group? -

	(HPV16- or HPV16/18-positive) Very serious concerns (HPV18- positive)	*If threshold for recommendation is **upper limit** of CI for prevalent hr-HPV other LSIL*- (highest acceptable risk of CIN3+ not requiring immediate colposcopy) CIs for incident HPV16- and HPV18-positive ASC-US, LSIL and for HPV16/18-positive borderline or low-grade cytology crossed the threshold in both studies- Point estimates and 95%CIs for incident HPV16-positive ASC-US (10.1, 6.22-14.115) and LSIL (11.29, 6.51-16.07%) cytology are greater than the point estimate and 95% CI for prevalent hr-HPV other-positive LSIL (4.70, 3.60-5.80%) however the number of events were less than 300 – risk probably greater than threshold . The point estimate for incident 16/18-positive borderline or low-grade cytology (8.2%) is greater than the point estimate for prevalent hr-HPV other-positive borderline or low-grade cytology (6.7%) – risk may be greater than threshold Point estimates for incident HPV18-positive ASC-US and LSIL cytology are lower than the point estimate for prevalent hr-HPV other-positive LSIL – risk may be greater or lower than threshold (small numbers of events so likely inadequately powered to show differences let alone non-inferiority)	enough to support recommending tests rather than immediate colposcopy for incident HPV16-positive ASC-US or LSIL **Low** *For incident HPV18-positive LSIL or ASC-US* Low certainty that the risk is not low enough to support recommending tests rather than immediate colposcopy for incident HPV18-positive ASC-US or LSIL
Inconsistency	No serious concerns	In the USA study the point estimate for the risk for incident HPV16-positive ASC-US and for incident HPV16-positive LSIL was greater than the point estimate for the benchmark and in the UK study the point estimate for incident HPV16/18-positive borderline or low-grade cytology was greater than the point estimate for the benchmark. In the USA study the point estimates for the risk for incident HPV18-positive ASC-US and for incident HPV18-positive LSIL were lower than the point estimate for the benchmark however the CI for their confidence intervals crossed the upper limit of the CI or the benchmark.	
Publication bias	Undetected	Neither of the two studies were designed to specifically assess the comparison of interest so publication bias unlkely. No formal statistical test could be used to detect publication bias due to < 10 studies (the minimum number of studies needed for a funnel plot) reporting this outcome.	

ASC-US = atypical squamous cells of undetermined significance; CI = confidence interval; hr-HPV = high-risk HPV; LSIL = low-grade squamous intraepithelial lesion; pLSIL = possible LSIL

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2.7 Summary of findings

Outcome: 5-year CIN3+

Benchmark	***Prognostic factor***	***Absolute effect estimates***		***Certainty in evidence***	***Plain text summary***
		Benchmark	***Prognostic factor***		
Prevalent hr-HPV other-positive LSIL (1 study, N = 669)	Incident HPV16-**positive normal cytology** (N = 275)	47/1000	71/1000		*For incident HPV16, HPV18-or HPV16/-positive normal cytology* 5-
		Difference: 24 **more** per 1000			

	Incident HPV18-positive normal cytology (N = 109)	38/1000 Difference: 9 **less** per 1000	Very low due to serious risk of bias, imprecision and inconsistency	year CIN3+ risk may or may not be unacceptably greater than benchmark Very low certainty that the risk is low enough to support recommending offering tests rather than immediate colposcopy for individuals with HPV16- or 18-positive negative cytology
Prevalent hr-HPV other-positive borderline or low-grade cytology (1 study, N = 568)	Incident HPV16/18-**positive normal cytology** (N = 75)	67/1000 | 27/1000 Difference: 40 **less** per 1000		
Prevalent hr-HPV other-positive LSIL (1 study, N = 669)	Incident HPV**16-positive ASC-US cytology** (N = 155)	47/1000 | 102/1000 Difference: 55 **more** per 1000	Moderate due to serious imprecision	**F***or incident HPV16-positive LSIL or ASC-US cytology* 5-year CIN3+ risk is probably not low enough /unacceptably greater than the benchmark for follow-up tests rather than immediate colposcopy Moderate certainty that the risk is not low enough for incident HPV16-positive ASC-US or LSIL to support recommending offering tests rather than immediate colposcopy for incident HPV16-positive ASC-US or LSIL
	Incident HPV**16-positive LSIL cytology** (N = 120)	113/1000 Difference: 66 **more** per 1000		
Prevalent hr-HPV other-positive borderline or low-grade cytology (1 study, N = 568)	Incident HPV16/18-**positive borderline or low-grade cytology** (N = 49)	67/1000 | 82/1000 Difference: 15 **more** per 1000		
Prevalent hr-HPV other-positive LSIL (1 study, N = 669)	Incident HPV18-**positive ASC-US cytology** (N = 52)	47/1000 | 42/1000 Difference: 5 less per 1000	**Low** due to very serious imprecision	**F***or incident HPV18-positive LSIL or ASC-US* 5-year CIN3+ risk may not be low enough /may be unacceptably greater than the benchmark for follow-up tests rather than immediate colposcopy Low certainty that the risk is low enough for incident HPV18-positive ASC-US or LSIL to support recommending offering tests rather than immediate colposcopy incident HPV18-positive ASC-US or LSIL
	Incident HPV18-**positive LSIL cytology** (N = 27)	35/1000 Difference: 12 less per 1000		

ASC-US = atypical squamous cells of undetermined significance; CI = confidence interval; hr-HPV = high-risk HPV; LSIL = low-grade squamous intraepithelial lesion

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APPENDICES

Appendix A: Medline and Embase database (via Ovid platform) search strategy

Database(s): **Embase Classic+Embase** 1947 to 2023 May 19**, Ovid MEDLINE(R) ALL** 1946 to May 18, 2023

#	Searches
1	Uterine Cervical Neoplasms/
2	CIN*.tw.
3	CIN 2*.tw.
4	CIN 3*.tw.
5	Cervical Intraepithelial Neoplasia/
6	(cervi* adj5 (cancer* or tumor* or tumour* or malignan* or neoplas* or carcinoma* or adenocarcinoma* or precancer* or pre-cancer*)).tw.
7	AIS.tw.
8	(adenocarcinoma* adj5 endocervi*).tw.
9	Adenocarcinoma in Situ/
10	HSIL.tw.
11	squamous intraepithelial lesion*.tw.
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	(screen* or testing or surveillance).tw.
14	(Hpv* adj5 (first or prevalen* or inciden* or persist* or subsequent)).tw.
15	(Human papillomavir* adj5 (first or prevalen* or inciden* or persist* or subsequent)).tw.
16	(hrHpv adj5 (first or prevalen* or inciden* or persist* or subsequent)).tw.
17	(hr Hpv* adj5 (first or prevalen* or inciden* or persist* or subsequent)).tw.
18	14 or 15 or 16 or 17

19	12 and 13 and 18
20	(current or past).tw.
21	(hr HPV or hrHPV or HPV* or human papillomavir*).tw.
22	20 and 21
23	13 and 20 and 21
24	19 or 23
25	limit 24 to yr="2015 -Current"
26	limit 25 to conference abstracts [Limit not valid in Ovid MEDLINE(R); records were retained]
27	limit 26 to medline
28	26 not 27
29	25 not 28
30	remove duplicates from 29
31	limit 30 to english language

Appendix B: Potentially relevant guidelines reportedly based on systematic reviews

Developer	*Publication or link*	*Title*	*Year*	*Reasons for not adopting*
U.S. Preventive Services Task Force	https://jamanetwork.com/journals/jama/fullarticle/2697704 https://www.ncbi.nlm.nih.gov/books/NBK526306/	Screening for cervical cancer	2018	No relevant recommendations
WHO	https://www.who.int/publications/i/item/9789240030824	WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition	2021	No relevant recommendations
WHO	Santesso N, Mustafa RA, Schunemann HJ et al. (2016) Int J Gynaecol Obstet: 132(3):252-8	World Health Organization Guidelines for treatment of cervical intraepithelial neoplasia 2-3 and screen-and-treat strategies to prevent cervical cancer	2016	No relevant recommendations

NICE	https://www.nice.org.uk/guidance/dg32	Adjunctive colposcopy technologies for assessing suspected cervical abnormalities	2018	No relevant recommendations
Saudi Arabia Ministry of Health	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6074318/	Clinical Practice Guidelines on the Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention in Saudi Arabia	2016	No relevant recommendations
Italian Group on Cervical Screening	https://www.imrpress.com/journal/EJGO/42/5/10.31083/j.ejgo4205157	Evidence-based guidelines for follow up of women treated for cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) in Italian screening programmes	2021	No relevant recommendations

Appendix C: Excluded studies

Article	***DOI/ PMC/ PMID***	***Reason for exclusion***
Caeiro 2021	http://doi.org/10.31557/APJCP.2021.22.6.1907	No intervention of interest
Castle 2019	https://doi.org/10.1093/jnci/djy192	No comparator of interest
Chiappetta 2015	PMC4730099	No intervention of interest
Comes 2016	https://doi.org/10.1016/j.patol.2016.06.002	No intervention of interest
Coser 2016	https://doi.org/10.1016/j.bjid.2015.10.008	No outcome of interest
Cusick 2016	http://dx.doi.org/10.1016/j.pvr.2016.05.004	Excluded publication type
Del Mistro 2019	https://doi.org/10.1111/1471-0528.15893	No intervention of interest
Depuydt 2015	https://doi.org/10.1002/cam4.473	No intervention of interest
Dijkstra 2016	https://doi.org/10.1136/bmj.i4924	No intervention of interest
Ebisch 2018	https://doi.org/10.1371/journal.pone.0206219	No intervention of interest
Egemen 2020	https://doi.org/10.1097/LGT.0000000000000529	No comparator of interest
Elfgren 2017	https://doi.org/10.1016/j.ajog.2016.10.042	No intervention of interest
Finnish Cancer Registry 2023	https://cancerregistry.fi/statistics/screening-statistics/	No intervention of interest
Fu 2015	https://doi.org/10.1002/ijc.29602.	No outcome of interest
Fujiwara 2019	https://doi.org/10.31557/APJCP.2019.20.1.81	No intervention of interest
Gage 2015	https://doi.org/10.1002/ijc.29143	No comparator of interest
Gage 2016	https://doi.org/10.1158/1055-9965.EPI-15-0669	No intervention of interest
Ge 2019	https://doi.org/10.1016/j.jasc.2019.01.001	No population of interest
Ge 2019b	https://doi.org/10.1002/cncy.22192	No intervention of interest

Gilham 2019 HTA	https://doi.org/10.3310/hta23280	Superseded by peer-reviewed Gilham 2020 with results for genotyping rather than HC2 test
Gui 2021	https://doi.org/10.1371/journal.pone.0253493	No intervention of interest
Gultekin 2018	https://doi.org/10.1002/ijc.31212	No intervention of interest
Gultekin 2020	https://doi.org/10.1016/j.ygyno.2020.04.698	No intervention of interest
Guo 2017	https://doi.org/10.1002/cncy.21877	No intervention of interest
Hammer 2020	https://doi.org/10.1002/ijc.32950	No comparator of interest
Huijsmans 2016	https://doi.org/10.1186/s12885-016-2961-2	No outcome of interest
Inturrisi 2021	https://doi.org/10.1158/1055-9965.EPI-20-1336	No intervention of interest
Inturrisi 2022	https://doi.org/10.1371/journal.pmed.1004115	No intervention of interest
Kares 2019	https://doi.org/10.1111/apm.12990	No intervention of interest
Li 2022	https://doi.org/10.6004/jnccn.2022.7032	No intervention of interest
Lian 2016	https://doi.org/10.1016/j.jasc.2015.06.001	No population of interest
Maggino 2016	https://doi.org/10.1038/bjc.2016.216	No intervention of interest
Malagon 2023	https://doi.org/10.1093/infdis/jiad043	No outcome of interest
Massad 2018	https://doi.org/10.1001/jama.2018.7911	Excluded publication type
Mchome 2021	https://doi.org/10.1016/j.ijid.2021.07.011	No outcome of interest
Monsonego 2015	https://doi.org/10.1016/j.ygyno.2015.01.551	No intervention of interest
Ogilvie 2018b	https://doi.org/10.1001/jama.2018.7464	No intervention of interest
Park 2015	https://doi.org/10.1371/journal.pone.0118938	No intervention of interest
Park 2019	https://doi.org/10.3802/jgo.2019.30.e50	No intervention of interest
Partanen 2022	https://syoparekisteri.fi/assets/files/2023/01/Cervical_Cancer_Screening_in_Finland_2022.pdf	No intervention of interest
Pasquale 2015	https://doi.org/10.1177/0969141314561707	No comparator of interest
Pasquale 2020	https://doi.org/10.1177/0969141320905325	No comparator of interest
Passamonti 2017	https://doi.org/10.1177/0969141316663580	No outcome of interest
Persson 2015	https://doi.org/10.1371/journal.pone.0127444	No intervention of interest
Phianpiset 2020	https://doi.org/10.1097/AOG.0000000000003982	No intervention of interest
Polman 2019	https://doi.org/10.1002/ijc.32004	No comparator of interest
Rebolj 2022	https://doi.org/10.1136/bmj-2021-068776	No outcome of interest

Ronco 2015	PMID: 26405779	No outcome of interest
Ryu 2016	https://doi.org/10.1002/dc.23533	No intervention of interest
Schiffman 2016	https://doi.org/10.1002/ijc.30375	No intervention of interest
Smelov 2015	https://doi.org/10.1002/ijc.29085	No intervention of interest
Song 2020	https://doi.org/10.7150/jca.48357	No intervention of interest
Stoler 2023	https://doi.org/10.1016/j.ygyno.2023.01.004	No intervention of interest
Strang 2021	https://doi.org/10.1016/j.ajog.2021.05.038	No intervention of interest
Sultana 2022	https://doi.org/10.1177/09691413221080635	No intervention of interest
Veijalainen 2016	https://doi.org/10.1111/aogs.13013	No intervention of interest
Veijalainen 2021	https://doi.org/10.1111/aogs.14021	No intervention of interest
Veldhuijzen 2015	https://doi.org/10.1158/1055-9965.EPI-14-0628	No outcome of interest
Veldhuijzen 2017	https://doi.org/10.1002/ijc.30865	No comparator of interest
Wright 2015	https://doi.org/10.1016/j.ygyno.2014.11.076	No intervention of interest
Xu 2021	https://doi.org/10.1158/1940-6207.CAPR-20-0456	No comparator of interest
Yang 2018	https://doi.org/10.1002/dc.23843	No intervention of interest
Zhao 2015	https://doi.org/10.5858/arpa.2014-0028-OA	No population of interest
Zheng 2015	https://doi.org/10.1002/cncy.21557	No population of interest