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CADTH Reference List

HPV Testing for Primary Cervical Cancer Screening

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Summary of Abstracts

CADTH

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Key Messages

- Four randomized controlled trials and 19 non-randomized studies were identified regarding the clinical utility of primary high-risk HPV testing for asymptomatic cervical cancer screening.
- Seven economic evaluations were identified regarding the cost-effectiveness of primary high-risk HPV testing for asymptomatic cervical cancer screening.
- One evidence-based guideline regarding primary high-risk HPV testing for asymptomatic cervical cancer screening was identified.

Research Questions

1. What is the clinical utility of primary high-risk HPV testing for asymptomatic cervical cancer screening?
2. What is the cost-effectiveness of primary high-risk HPV testing for asymptomatic cervical cancer screening?
3. What are the evidence-based guidelines regarding primary high-risk HPV testing for asymptomatic cervical cancer screening?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were HPV testing and cervical cancer screening. No filters were applied to limit retrieval by publication type. Comments, newspaper articles, editorials, and letters were excluded. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2019 and July 28, 2021. Internet links were provided, where available.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. The Overall Summary of Findings was based on information available in the abstracts of selected publications. Open access, full-text versions of evidence-based guidelines were reviewed when abstracts were not available and relevant recommendations were summarized.

Results

Four randomized controlled trials (RCTs)[1-4] and 19 non-randomized studies[5-23] were identified regarding the clinical utility of primary high-risk HPV testing for asymptomatic cervical cancer screening. Seven economic evaluations[24-30] were identified regarding the cost-effectiveness of primary high-risk HPV testing for asymptomatic cervical cancer screening. One evidence-

Table 1: Selection Criteria

Criteria	Description
Population	Q1, Q2, Q3: Asymptomatic adults eligible for cervical cancer screening
Intervention	Q1, Q2, Q3: Primary high-risk HPV testing (with or without cytology triage; i.e., co-testing)
Comparator	Q1, Q2: Cytology-based testing (e.g., Pap smear, liquid-based cytology) Q3: Not applicable
Outcomes	Q1: Clinical utility (e.g., time to treatment, incidence of cervical cancer, detection rate, quality of life, mortality) Q2: Cost-effectiveness (e.g., ICER, cost per QALY gained, cost per patient adverse event avoided) Q3: Recommendations regarding best practices (e.g., which test in which situation, contraindications for testing)
Study designs	HTAs, systematic reviews, RCTs, non-randomized studies, economic evaluations, evidence-based guidelines

HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; Pap = Papanicolaou test; QALY = quality-adjusted life-year; Q = question; RCT = randomized controlled trial.

based guideline[31] regarding primary high-risk HPV testing for asymptomatic cervical cancer screening was identified. No relevant health technology assessments or systematic reviews were identified.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

Overall Summary of Findings

Four RCTs[1-4] and 19 non-randomized studies[5-23] were identified regarding the clinical utility of primary high-risk HPV testing for asymptomatic cervical cancer screening. A detailed summary of the identified studies can be found in Table 2.

Two RCTs[1,2] and 9 non-randomized studies[5-13] assessed co-testing strategies (HPV testing with cytology) compared to cytology alone. Both RCTs found HPV co-testing led to the higher detection of cervical intraepithelial neoplasia grade 2 or above (CIN2+) lesions and increased colposcopy referrals compared to cytology alone.[1,2] Most non-randomized studies also found co-testing, compared to cytology alone, to be associated with a greater detection of lesions or cervical cancer.[6-11] One study found the detection of atypical squamous cells of undetermined significance (ASC-US) to be higher in the cytology group, with no difference in detection of CIN2+.[13] Four studies found co-testing was associated with an increase in colposcopy referrals,[5,8,10,11] while 1 study found lower colposcopy referrals with co-testing.[6] One study found no difference between groups in referral for intensified follow-up.[12]

Two RCTs[3,4] and 11 non-randomized studies[11,14-23] compared HPV testing alone to cytology testing. One RCT found HPV testing led to reduced colposcopy referrals.[3] The other RCT found screening with HPV testing every 4 years was as safe as cytology every 2 years when detecting CIN2+.[4] Five non-randomized studies found HPV testing had a higher detection rate for CIN2+/CIN3+ than cytology,[10,14,16,19,20] and 1 reported HPV testing detected a significant number of lesions that were missed by cytology.[22] One study found CIN2+ detection was higher with clinician-collected HPV tests than cytology and self-collected tests.[21] Two studies found cytological abnormalities or CIN2+ to be similar between self-collected HPV tests

and cytology.[15,21] One study reported HPV testing had similar detection of ASC-US+ cytology as conventional cytology.[23] Three studies found HPV testing was associated with more colposcopies than cytology.[10,16,23] One study found HPV testing to be associated with a lower misdiagnosis rate,[10] while 2 studies found HPV testing to be associated with higher overdiagnosis or more clinically irrelevant findings.[14,20] One study reported HPV and cytology testing were similar in the number of overlooked cervical cancers, while HPV testing overlooked some non-cervical gynecological cancers.[17] One study reported the prevalence of cancers missed by HPV testing, compared to cytology, was higher among patients over 50.[18]

Seven economic evaluations were identified regarding the cost-effectiveness of HPV testing for cervical cancer screening.[24-30] All studies found HPV testing to be more cost-effective than cytology testing.[24-30] A detailed summary of the identified studies can be found in Table 2.

One evidence-based guideline from the American Cancer Society recommends HPV primary testing for cervical cancer screening, if available.[31] A detailed summary of the included guideline and recommendation can be found in Table 3.

Table 2: Summary of Included Studies

First author, year	Study characteristics and population	Intervention and comparator(s) of interest	Relevant outcome(s)	Authors' conclusions
Randomized controlled trials — co-testing				
Chan et al. (2020)[1]	**Study design:** RCT **Population:** Women aged 30 to 60 **N** = 15,955	**Intervention:** HPV testing with LBC **Comparator(s):** LBC only	Detection of CIN2+ lesions, number of colposcopies	Detection of CIN2+ lesions was higher in the intervention group than the control group. At the second screening 36 months later, CIN2+ detection was lower in the intervention group. In total, CIN2+ detection was higher in the intervention group, with a fourfold increase in colposcopies.
Han et al. (2020)[2]	**Study design:** RCT **Population:** Women aged 35 to 64 **N** = 182,119	**Intervention:** Co-testing with HR-HPV and cytology **Comparator(s):** HPV or cytology alone	Positivity rate for CIN2+, colposcopy referral rate, biopsy referral rate	Co-testing group had higher CIN2+ positivity rate, colposcopy referral rate, and biopsy referral rate.
Randomized controlled trials — HPV testing compared to cytology-based testing				
Zhang et al. (2021)[3]	**Study design:** RCT **Population:** Women aged 35 to 64 **N** = 60,732	**Intervention:** HR-HPV **Comparator(s):** Cytology	Colposcopy referral rate, risk ratio for disease (CIN2+, CIN3+)	HR-HPV testing led to reduced colposcopy referral rates. HR-HPV testing also had higher risk ratio for disease.
Coldman et al. (2020)[4]	**Study design:** RCT **Population:** Women aged 25 to 65 **N** = 19,009 assigned, 15,729 completed the protocol	**Intervention:** HPV testing **Comparator(s):** LBC	CIN2+	Screening with HPV using a 4-year interval is as safe as LBC with a 2-year interval.
Non-randomized studies — co-testing				
Kono et al. (2021)[5]	**Study design:** Cohort study **Population:** Women aged 30 to 49 **N** = 25,074	**Intervention:** Co-testing with HPV and cytology **Comparator(s):** Cytology alone	Colposcopy referral rate	Adding HPV led to an increase in colposcopy referrals.
Zhao et al. (2021)[6]	**Study design:** Cohort study **Population:** Women aged 35 to 64 **N** = 1,160,981	**Intervention:** HR-HPV testing with cytology or genotyping triage **Comparator:** Cytology alone	Screening positive rates, colposcopy referral rate, detection of CIN2+	HPV testing had a higher screening positive rate, lower colposcopy referral (due to lower referral threshold), and higher detection rate of CIN2+.

First author, year	Study characteristics and population	Intervention and comparator(s) of interest	Relevant outcome(s)	Authors' conclusions
Kaufman et al. (2020)[7]	**Study design:** Cohort study **Population:** Women aged 30+ **N** = 13,633,071	**Intervention:** Co-testing with HPV and LBC **Comparator(s):** HPV or cytology alone	Diagnosis of cervical cancer	Co-testing with HPV and LBC enhances screening for detection for cervical cancer compared to HPV or LBC alone.
Thomsen et al. (2020)[8]	**Study design:** Cohort study **Population:** Women aged 30 to 59 **N** = 28,352	**Intervention:** Co-testing (HPV, with cytology triage) **Comparator(s):** Cytology, with HPV triage	Referral to colposcopy, detection of CIN3+	HPV-based screening detected more cases of CIN3+ and led to more colposcopies.
Hashiguchi et al. (2019)[9]	**Study design:** Cohort study **Population:** Women **N** = 17,284	**Intervention:** Co-testing with HPV and cytology **Comparator(s):** Cytology alone	Detection of CIN3+	The number of women diagnosed with CIN3 + increased with co-testing.
Kang et al. (2019)[10]	**Study design:** Cohort study **Population:** Women **N** = 21,568	**Intervention:** Co-testing with HR-HPV and cytology **Comparator(s):** HR-HPV or cytology alone	Detection of CIN2+/ CIN3+, misdiagnosis rate, number of colposcopies	Co-testing detected the same number of CIN2+/ CIN3+ cases as HR-HPV alone; both detected more than cytology. HR-HPV screening also had lower misdiagnosis rate than cytology and higher number of colposcopies.
Rebolj et al. (2019)[11]	**Study design:** Cohort study **Population:** Women **N** = 578,547	**Intervention:** Co-testing with HR-HPV (with cytology triage) **Comparator(s):** LBC alone	Referral for colposcopy; detection of CIN2+, detection of cervical cancer	HR-HPV was associated with increased colposcopies, higher detection of CIN2+, and higher detection of cervical cancer.
Veijalainen et al. (2019)[12]	**Study design:** Cohort study **Population:** Women aged 35 to 60 **N** = 17,770	**Intervention:** Co-testing with HR-HPV (with cytology triage) **Comparator:** Conventional Pap cytology	Referral to intensified follow-up	Referral for intensified follow-up was similar between groups.
Zhang et al. (2019)[13]	**Study design:** Cohort study **Population:** Women aged 35 to 64 **N** = 7,138	**Intervention:** Co-testing with HPV (with cytology triage) **Comparator:** Conventional cytology	Detection of ASC-US, detection of CIN2+	Detection of ASC-US was higher in the cytology group. There was no significant difference in detection of CIN2+ between groups.

First author, year	Study characteristics and population	Intervention and comparator(s) of interest	Relevant outcome(s)	Authors' conclusions
Non-randomized studies — HPV testing compared to cytology-based testing				
Loopik et al. (2021)[14]	**Study design:** Retrospective cohort study **Population:** Women **N** = 45,280	**Intervention:** HR-HPV testing **Comparator:** Cytology-based testing	Referral rate, detection of CIN2+/ CIN3+, detection of cervical cancer, overdiagnosis	HR-HPV testing was associated with increased referral rates, higher detection of CIN2+ and CIN3+, higher detection of cervical cancer, and higher overdiagnosis.
Reques et al. (2021)[15]	**Study design:** Non-randomized interventional study **Population:** Women aged 25 to 65 **N** = 687	**Intervention:** Self-collected HPV **Comparator:** Pap smear	Cytological abnormalities, screening completion	Proportion of cytological abnormalities was similar between groups. Provision of a self-collected HPV test increased participation in cervical cancer screening.
Thomsen et al. (2021)[16]	**Study design:** Cohort study **Population:** Women aged 30 to 59 **N** = 40,048	**Intervention:** Primary HPV testing **Comparator:** Primary cytology testing	Referral for colposcopy, detection of CIN3+	HPV-based screening led to increased CIN3+ detection and increased colposcopy referrals.
Andersen et al. (2020)[17]	**Study design:** Cohort study **Population:** Women aged 50+ **N** = 4,043	**Intervention:** Primary HPV testing **Comparator:** Primary LBC testing	Overlooked cancers (cervical, non-cervical gynecological)	At baseline, HPV testing overlooked 5 cases of gynecological (non-cervical) cancer. LBC and HPV both overlooked 2 cases of cervical cancer.
Kurokawa et al. (2020)[18]	**Study design:** Cohort study **Population:** Women who underwent co-testing with HPV and cytology **N** = 115,273	**Intervention:** HPV testing **Comparator:** Cytology testing	Prevalence of CIN2, CIN3, SCC, or cervical adenocarcinomas	Prevalence of CIN2, CIN3, SCC, and cervical adenocarcinomas was low. The prevalence of cancers missed by HPV was higher among patients older than 50 years of age.
Ma et al. (2020)[19]	**Study design:** Cohort study **Population:** Women who received cervical cancer screening services **N** = 9,972	**Intervention:** HPV testing **Comparator:** LBC	Detection rate of CIN2+	HPV group had the highest detection rate of CIN2+.

First author, year	Study characteristics and population	Intervention and comparator(s) of interest	Relevant outcome(s)	Authors' conclusions
Aitken et al. (2019)[20]	**Study design:** Cohort study with historical control **Population:** Women eligible for screening **N** = 937,719	**Intervention:** HR-HPV testing **Comparator:** Cytology testing	CIN2+ detection, number of clinical irrelevant findings	HR-HPV was associated with increased CIN2+ detection and more clinically irrelevant findings (mostly because of national policy change recommending colposcopy).
Arrossi et al. (2019)[21]	**Study design:** Retrospective cohort study with historical control **Population:** Women aged 30+ **N** = 79,196	**Intervention:** HPV testing **Comparator:** Cytology testing	Detection of CIN2+	Compared to cytology-based screening, CIN2+ detection was higher with clinician-collected HPV tests; CIN2+ detection with self-collected tests was comparable to cytology-based screening.
Levi et al. (2019)[22]	**Study design:** Cohort study **Population:** Women aged 24+ **N** = 16.102	**Intervention:** HR-HPV testing **Comparator:** LBC	CIN2+/CIN3+ cases	HR-HPV testing detected a significant number of patients with premalignant lesions missed by cytology. All CIN3+ cases were detected with HR-HPV.
Lindroth et al. (2019)[23]	**Study design:** Cohort study **Population:** Women aged 30 to 65 **N** = 40,048	**Intervention:** HPV testing **Comparator:** Cytology testing	ASC-US or worse, colposcopy referral	HPV screening showed similar detection of ASC-US+ cytology as conventional cytology screening and increased colposcopy referral rates.
Economic evaluations				
Jansen et al. (2021)[24]	**Study design:** Model-based CEA **Population:** 30-year-old unvaccinated females with lifelong follow-up	**Intervention:** HR-HPV testing **Comparator:** Cytology testing	Mortality, colposcopy referral, QALYs	HR-HPV testing was found to be more effective and more cost-effective.
Vale et al. (2021)[25]	**Study design:** Model-based CEA **Population:** Women aged 25 to 64 or 30 to 64	**Intervention:** HR-HPV testing every 5 years for women 25 to 64, or hybrid (cytology for women 25 to 29 every 3 years, and HR-HPV for women 30 to 64 every 5 years) **Comparator:** Cytology testing every 3 years	QALY, ICER	HR-HPV testing and hybrid testing were dominant over the cytology testing.

First author, year	Study characteristics and population	Intervention and comparator(s) of interest	Relevant outcome(s)	Authors' conclusions
Fogelberg et al. (2020)[26]	**Study design:** Model-based CEA **Population:** Unvaccinated women aged 23 to 64	**Intervention:** HPV and cytology co-testing **Comparator:** HPV testing not preceded by cytology	Cost-effectiveness	The optimal strategy is HPV-based screening every 5 years for women 23 to 50 and every 10 years for women older than age 50 years.
Zhao et al. (2020)[27]	**Study design:** Model-based CEA **Population:** NR	**Intervention:** HPV testing **Comparator:** Cytology testing	Cost-effectiveness	HPV testing every 5 years was a dominant strategy.
Campos et al. (2019)[28]	**Study design:** Model-based CEA **Population:** Women aged 30 to 65 (HPV) or 20 to 65 (Pap)	**Intervention:** HPV testing every 5 years with referral to colposcopy or cryotherapy **Comparator:** Pap testing every 2 years with referral to colposcopy	Cost per year of life saved	HPV testing followed by cryotherapy for eligible HPV-positive women was the least costly and most effective strategy at US$490 per year of life saved.
Termrungruanglert et al. (2019)[29]	**Study design:** Model-based CEA **Population:** Women aged 30 to 65	**Intervention:** HPV testing with cytology triage **Comparator:** Pap smear testing	ICER per QALY	The ICER per QALY gained with the HPV primary screening triage was US$1,395. The authors stated this was cost-effective.
Vassilakos et al. (2019)[30]	**Study design:** Model-based CEA **Population:** Non-attendees to cervical cancer screening	**Intervention:** Self-collected HPV with colposcopy or Pap triage **Comparator:** Cytology screening with HPV triage	ICER per QALY	When compared to the absence of screening, self-collected HPV strategies are more cost-effective, with lower ICER per QALY than cytology-based screening.

ASC-US = atypical squamous cells of undetermined significance; CEA = cost-effectiveness analysis; CIN1 = cervical intraepithelial neoplasia grade 1; CIN2 = cervical intraepithelial neoplasia grade 2; CIN2+ = cervical intraepithelial neoplasia grade 2 or above; CIN3 = cervical intraepithelial neoplasia grade 3; CIN3+ = cervical intraepithelial neoplasia grade 3 or above; HR-HPV = high-risk HPV; ICER = incremental cost-effectiveness ratio; LBC = liquid-based cytology; Pap = Papanicolaou test; QALY = quality-adjusted life-year; RCT = randomized controlled trial; SCC = squamous cell carcinoma.

Table 3: Summary of Included Guidelines

Recommendation	Strength of recommendation
American Cancer Society (2020)[31]	
• Individuals with a cervix should undergo primary HPV testing every 5 years from age 25 to 65 (preferred). • If primary HPV testing is not available, co-testing (HPV with cytology) every 5 years, or cytology alone every 3 years, is acceptable.	• Strong

References

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

Co-testing (Human Papillomavirus Testing With Cytology-Based Testing) Compared to Cytology-Based Testing

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Human Papillomavirus Testing Compared to Cytology-Based Testing

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Non-Randomized Studies

Co-testing (Human Papillomavirus Testing With Cytology-Based Testing) Compared to Cytology-Based Testing

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Human Papillomavirus Testing Compared to Cytology-Based Testing

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Guidelines and Recommendations

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Appendix 1: References of Potential Interest

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Unclear or No Comparator

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Randomized Controlled Trials

Alternative Outcome — Cumulative Risk

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Non-Randomized Studies

Diagnostic Accuracy

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