

Systematic review report for question 6

PICO Question 6: For women with biopsy confirmed CIN2 what is the safety and effectiveness of p16 immunohistochemistry and treating only p16 positive CIN2 while conservatively managing p16 negative CIN2 when compared with treating all CIN2 cases?

Population	Study design	Intervention	Control	Outcome
Women with biopsy confirmed CIN2*	Randomized or pseudo-randomized controlled trial	Using p16 immunohistochemistry to stratify management: p16 positive cases treated with excision and p16 negative cases conservatively managed	Treat all CIN2 with excision of transformation zone.	Cervical cancer mortality Cervical cancer diagnosis CIN3+ detection

*Sub group analysis of women under 30 where possible

1. METHODS

1.1. Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (<http://guideline.gov/>) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to be directly relevant, based on systematic reviews of the evidence and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (<http://www.agreetrust.org/resource-centre/agree-ii/>).

1.2. Literature Search

Medline, Premedline, Embase, CENTRAL, Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) databases, were searched for articles published from 2004 until 31st August 2015, using text terms and, where available, database-specific subject headings. In these databases searches for CIN2 were combined with searches for p16, and where possible, database-specific filters for identifying randomized controlled trials and systematic reviews/meta-analyses of randomized controlled trials. To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for search strategies are included as Appendix A. Abstracts for the 2015 EUROGIN conference were searched using the terms CIN2 and p16. Reference lists of relevant articles and guidelines were checked for additional potentially relevant articles.

1.3. Inclusion Criteria

Selection criteria	Inclusion criteria
Study type	Intervention
Study design	Randomised controlled trial (RCT) or pseudo-randomised controlled trial or Systematic reviews or meta-analyses of RCTs or pseudo-randomised controlled trials
Population	Women with biopsy confirmed CIN2*
Intervention	p16 positive cases treated with excision and p16 negative cases conservatively managed
Comparator	All CIN2 treated with excision of transformation zone.
Outcomes	Cervical cancer mortality or Cervical cancer diagnosis or CIN3+ detection
Language	English
Publication period	After 31 st December 2003 and before 1 st September 2015

Conference proceedings other than those from the EUROGIN 2015 were not included.

2. RESULTS

2.1. Guidelines

One set of guidelines was identified (The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology.

Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ, Wilbur DC, Members of LAST Project Work Groups. (2012) The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 136 (10):1266-97) that contained potentially relevant recommendations. These recommendations were based on indirect evidence from diagnostic accuracy studies rather than direct evidence from clinical trials and thus did not specifically address the PICO question.

2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The searches identified a total of 76 citations. Titles and abstracts were examined however none of the articles identified were potentially relevant to the systematic review. Thus no studies were found that directly answered the clinical question and met the inclusion criteria for this systematic review. As such there were no studies of Aboriginal and/or Torres Strait Islander women that met the inclusion criteria.

Database or Source	Number of Citations	Number of Articles Collected	Number of Articles Included	ATSI filter results
Medline + CENTRAL + Embase	76	0		0

HTA + DARE	0			
EUROGIN 2015 abstracts	0			
Snowballing	N/A			

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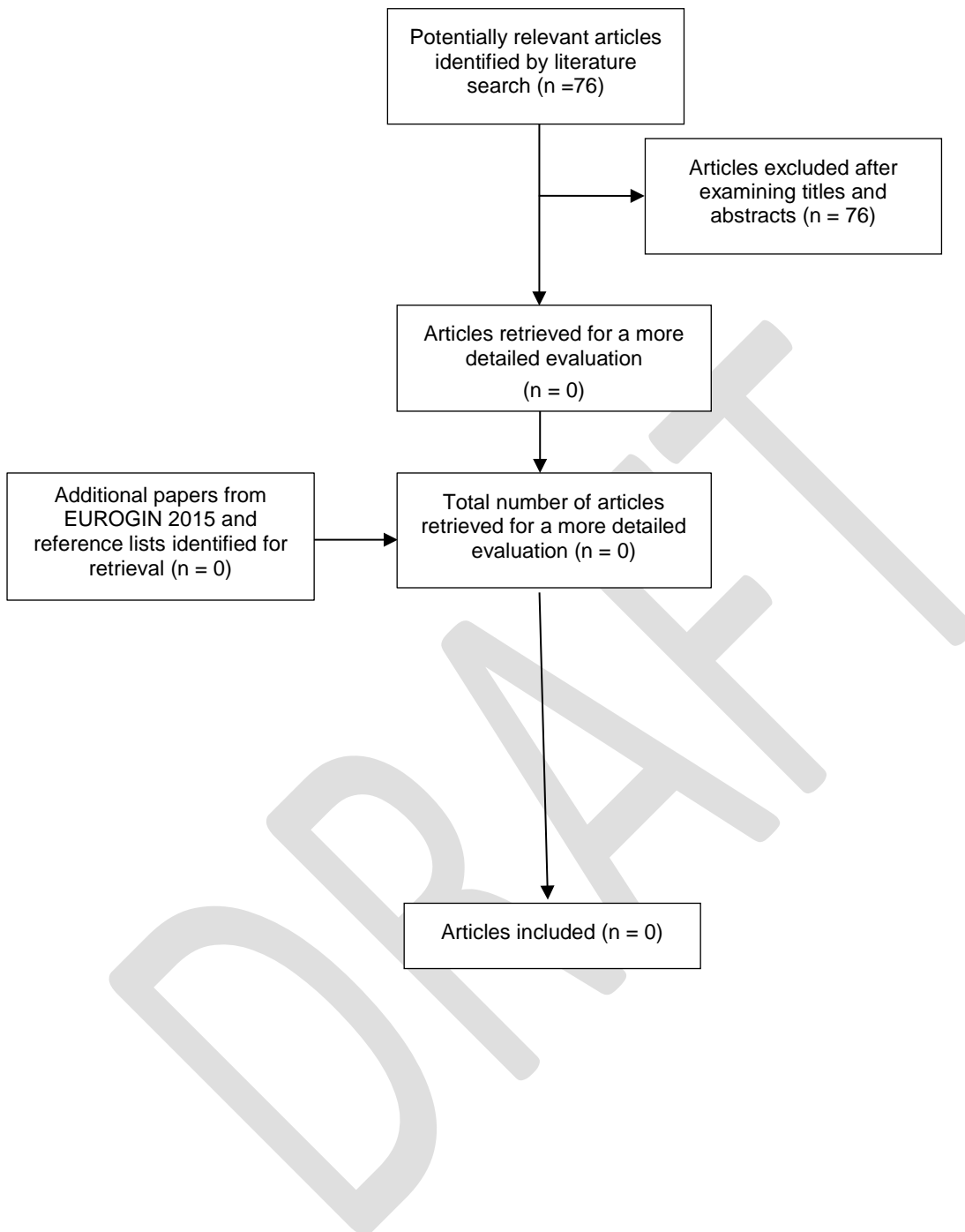


Figure 1. Process of inclusion and exclusion of studies

APPENDICES

Appendix A: Search strategies used

For Medline, Premedline, Embase and CENTRAL databases (via OvidSP):

#	Searches
1	Uterine cervical neoplasms/
2	Cervical Intraepithelial Neoplasia/
3	cervi*.mp.
4	CIN*.mp.
5	high-grade neoplas*.mp.
6	high grade neoplas*.mp.
7	HG neoplas*.mp.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	p16.mp.
10	p16*.mp.
11	genes, p16/
12	cyclin-dependent kinase.mp.
13	cyclin-dependent kinase inhibitor p16/
14	CDK.mp.
15	CDKI.mp.
16	9 or 10 or 11 or 12 or 13 or 14 or 15
17	excision*.mp.
18	cone biops*.mp.
19	(cone adj3 biops*).mp.
20	coni?ation.mp.
21	CKC.mp.
22	LEEP.mp.
23	LLETZ.mp.
24	loop electro-excisional procedure.mp.
25	SWETZ.mp.
26	NETZ.mp.
27	laser con*.mp.
28	laser excis*.mp.
29	Fischer con*.mp.
30	treatment.mp.
31	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

32	8 and 16 and 31
33	randomized controlled trial.pt.
34	controlled clinical trial.pt.
35	placebo.ab.
36	randomi?ed.ab.
37	randomly.ab.
38	trial.ab.
39	groups.ab.
40	33 or 34 or 35 or 36 or 37 or 38 or 39
41	32 and 40
42	limit 41 to english language
43	limit 42 to yr="2004 -Current"
44	remove duplicates from 43

Used the Cochrane sensitivity maximizing filter for identifying randomized controlled trials (<http://handbook.cochrane.org>, accessed 12/09/2015)

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia\$.ti,ab) AND (Oceanic ancestry group/ OR aborigin\$.ti,ab. OR indigenous.mp.)) OR torres strait\$ islander\$.ti,ab

From the Lowitja Institute at <http://www.lowitja.org.au/litsearch-background-information> accessed 30/09/2013)

For Database of Abstracts of Reviews of Effects and Health Technology Assessment (DARE) and Health Technology Assessments (HTA) databases:

#	Searches
1	Uterine cervical neoplasms/
2	Cervical Intraepithelial Neoplasia/
3	cervi*.mp.
4	CIN*.mp.
5	high-grade neoplas*.mp.
6	high grade neoplas*.mp.
7	HG neoplas*.mp.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	p16.mp.
10	p16*.mp.
11	genes, p16/
12	cyclin-dependent kinase.mp.

13	cyclin-dependent kinase inhibitor p16/
14	CDK.mp.
15	CDKI.mp.
16	9 or 10 or 11 or 12 or 13 or 14 or 15
17	excision*.mp.
18	cone biops*.mp.
19	(cone adj3 biops*).mp.
20	coni?ation.mp.
21	CKC.mp.
22	LEEP.mp.
23	LLETZ.mp.
24	loop electro-excisional procedure.mp.
25	SWETZ.mp.
26	NETZ.mp.
27	laser con*.mp.
28	laser excis*.mp.
29	Fischer con*.mp.
30	treatment.mp.
31	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	8 and 16 and 31

Appendix B:

NHMRC Evidence Hierarchy for Intervention studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: <ul style="list-style-type: none">- Phase II clinical trial- Non-randomised, experimental trial⁹- Controlled pre-test/post-test study- Adjusted indirect comparisons- Interrupted time series with a control group- Cohort study- Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none">- Phase I clinical trial- Historical control study- Two or more single arm study¹⁰- Unadjusted indirect comparisons- Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

According to the standards of the National Health and Medical Research Council

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title	Reason why not adopted
2014	College of American Pathologists and American Society for Colposcopy and Cervical Pathology	The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology.	Did not directly address PICO as to whether p16 triage improved patient outcomes

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