Recurrence After Biopsy-Confirmed Cervical High-Grade Intraepithelial Lesion Followed by Negative Conization: A Systematic Review and Meta-analysis

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Abstract: The aim of the study is to assess the recurrence rate (as cervical intraepithelial neoplasia 2+ [CIN2+]) in patients who had a confirmed high-grade squamous intraepithelial lesion (CIN2–3) in a cervical biopsy specimen followed by a negative conization specimen.

Materials and Methods: A systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Ovid/MEDLINE, Ovid/Embase, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched from inception until January 2023. The study protocol was registered in PROSPERO (ID number CRD42023393951). The search identified 3,089 articles; 1,530 were removed as duplicates, and 1,559 titles and abstracts were assessed for inclusion. The full text of 26 studies was assessed for eligibility, and finally, 12 studies with 1,036 patients were included. All included studies were retrospective cohort studies. A proportion meta-analysis was performed.

Results: For patients with negative conization specimens, the recurrence rate as CIN2+ during follow-up was 6% (95% CI, 1.8%–12.1%; $I^2 = 49.2$; $p < .0001$, 215 patients and 4 studies) in the proportion meta-analysis, ranging from 0.3% to 13.0% for the individual studies. For patients with ≤CIN1 conization specimens, the recurrence rate as CIN2+ during follow-up was 3.6% (95% CI, 1.2%–7%; $I^2 = 75.1$; $p < .0001$, 991 patients and 10 studies) in the proportion meta-analysis and ranged from 0.6% to 13.0% for the individual studies.

Conclusions: The recurrence rate as CIN2+ for patients with a confirmed high-grade intraepithelial lesion on a cervical biopsy followed by a negative conization specimen is 6%. In patients with negative and CIN1 conization specimens, the recurrence rate is 3.6%.

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Ethical approval was not required, as only data from previously published studies were retrieved and analyzed. No new data were extracted or presented.

All the authors confirm that have adhered to all editorial policies for submission as described in the Information for Authors for the Journal and attest to having met all authorship criteria.

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Cervical intraepithelial neoplasia (CIN) is a squamous lesion of the uterine cervix diagnosed by cervical biopsy and histologic examination.[1] Cervical intraepithelial neoplasia has 3 degrees of severity, CIN1, CIN2, and CIN3, which are based on the severity of atypical cellular changes and the proportion of the thickness of the epithelium affected.[2] In 2012, the Lower Anogenital Squamous Terminology project published changes in the grading terminology for human papillomavirus (HPV)–associated squamous lesions of the anogenital tract. The system now has only 2 tiers: low-grade (CIN1) and high-grade intraepithelial lesions (CIN2–3).[3]

The goal of management in patients diagnosed with CIN2–3 on cervical biopsy is to prevent possible progression to cancer, the risk of which is approximately 0.3%–2%.[2] Prompt treatment is recommended, except in pregnant patients and patients younger than 25 years.[4] Treatment typically involves excision with a loop electrosurgical excision procedure (LEEP) or cold knife cone (CKC), both of which allow subsequent histopathological evaluation of the lesion.[4,5] If a CIN2–3 lesion is confirmed in the conization specimen, several known prognostic factors predict the risk of recurrence after treatment, including positive margin status,[6] positive posttreatment HPV test (especially the HPV16 subtype),[7,8] and large lesion size (greater than two thirds of the surface of the cervix),[9] among others. However, few data are available regarding the recurrence risk in patients with biopsy-confirmed CIN2–3 and a negative pathology report for the conization specimen (≤CIN1).

The objective of this systematic review and meta-analysis was to assess the rate of recurrence as a high-grade (CIN2+) lesion in patients with a cervical biopsy specimen showing a CIN2–3 lesion, followed by a negative conization specimen.

METHODS

Eligibility Criteria, Information Sources, and Search Strategy

Our findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.[10] The study protocol was registered in PROSPERO (ID number CRD42023393951). A comprehensive search strategy developed by a medical research librarian specializing in systematic reviews, in consultation with the authors, was used to search the Ovid MEDLINE, Ovid Embase, Cochrane Central, and ClinicalTrials.gov databases. Databases were searched from inception to January 21, 2023. Searches were restricted to articles reporting human studies and published in English. We excluded case reports, protocols, comments, editorials, and abstracts. Deduplication was performed manually in EndNote. The full

search strings for all databases can be found in Supplemental Digital Content 1, http://links.lww.com/LGT/A323.

Study Selection and Data Extraction

After the initial search, Covidence software (Melbourne, Australia) was used to screen the citations. Two authors (N.M.S., D.V.C.). independently screened the titles and abstracts of the articles to identify potentially relevant studies. Disagreements were resolved by consensus and by seeking the opinion of a third author (R.P.). Two authors (N.M.S., D.V.C.) then independently screened the full text of the selected articles for inclusion. Disagreements were resolved by consensus and by seeking the opinion of a third author (R.P.). Finally, 2 authors independently extracted data using a data extraction form created with Covidence, and we resolved disagreements by discussion or consulted a third author (R.P.). All types of studies published in the English-language literature were considered for inclusion.

We included only studies reporting patients with cervical biopsy showing pathology-confirmed high-grade CIN (CIN2–3) followed by a negative conization specimen (≤CIN1). We considered specimens classified as CIN1 as "negative" on the basis of their low risk of progression to cancer or even to CIN3 (less than 3% at 5 years for CIN3).[11] We excluded studies with patients younger than 18 years, patients with microinvasive or invasive lesions, and patients whose diagnosis was based on cytologic or colposcopic evaluation without pathology-confirmed biopsy. When 2 or more articles were published by the same authors or using the same data source, only the most recent article was included. Studies in which specimens were obtained by LEEP, CKC, or laser conization were included. The primary outcome was the rate of recurrence as high-grade intraepithelial lesions (CIN2+), as defined by study authors, during follow-up.

The risk of bias was assessed independently by 2 authors (N.M.S., D.V.C.) using the Newcastle-Ottawa Quality Assessment Scale, with a maximum of 7 points instead of 9 points for each study, as the comparability category was not evaluated given that all included studies were single-arm retrospective studies. Any discordance in scoring was resolved through discussion or involvement of a third author (R.P.) if necessary.

The data were presented as medians or means (according to whether they were normally distributed) for quantitative variables and raw counts with percentages for qualitative variables, respectively. The descriptive statistics were calculated using SPSS 20, and a proportion meta-analysis was performed, with the help of a statistician, using JBI Sumari software (the University of Adelaide, Australia) with Freeman-Tukey transformation. The I^2 statistic was used to assess for statistical heterogeneity, and we used a random effects model if heterogeneity was judged to be high ($I^2 > 40$) or a fixed effects model if heterogeneity was judged to be low ($I^2 < 40$). According to local regulations, no institutional review board approval was required for this type of study. Ethical approval was not required, as only data from previously published studies were retrieved and analyzed. No new data were extracted or presented.

RESULTS

In total, 3,089 articles were identified, 1,530 were removed as duplicates, and 1,559 abstracts and titles were assessed for inclusion. The full text of 26 studies was assessed. Thirteen studies[12–24] were excluded because they did not report the recurrence rate or did not report it for the specific group of interest, and one study[25] was excluded because it included patients without biopsy-confirmed CIN2–3 lesions. Thus, 12 studies with 1,036 patients were included in the systematic review (see Figure 1).

All included studies were retrospective cohort studies. The study periods ranged from 1991 to 2019. Five studies were carried out in the United States,[26–30] 2 in Korea,[31,32] and 1 each in Australia,[33] Turkey,[34] Italy,[35] China,[36] and Spain.[37] Regarding inclusion criteria, 9 studies[26,28,30–32,34–37] considered patients with CIN2–3 lesions, 2 studies[27,29] included patients with high-grade squamous intraepithelial lesions (HSILs), and 1 study[33] included only patients with CIN2 lesions. Eight studies[26,27,29–32,35,37] included patients who underwent LEEP, 3 studies[28,33,36] included patients who had LEEP or CKC, and 1 study[34] included only patients who underwent CKC.

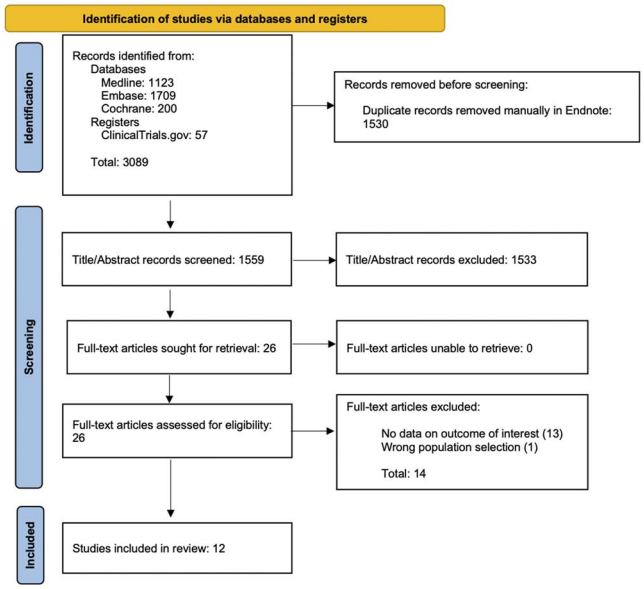

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

TABLE 1. Main Characteristics of Included Studies

Author and year	Inclusion period	High-grade intraepithelial lesion definition	Surgical procedure	Negative conization definition	*n*	Age, y	Follow-up
Livasy[26] (2004)	1991–2001	CIN2–3	LEEP	Negative	75	Median 29; range 19–62	Pap test, no more details
Ryu[31] (2010)	2003–2005	CIN2–3	LEEP	Negative	28	Mean 39.3; SEM ± 8.4; range 24–70 (whole cohort)	Cervical cytology and HPV tests were obtained at each visit, every 3–6 mo for 2 y and annually thereafter.
Ding[33] (2011)	2000–2007	CIN2	LEEP, CKC	CIN1 + negative	37	Median 28; range 18–59 (whole cohort)	High-risk HPV testing was performed at the 2-or 12-mo posttreatment visit.
Witt[27] (2012)	2003–2010	HSIL	LEEP	CIN1 + negative	73	Mean 33.2; range 16–69 (whole cohort)	Not specified.
Baser34 (2014)	2008–2012	CIN2–3	CKC	Negative	22	Mean 39.4; SEM ± 10.8; range 23–59	Pap tests were performed every 3 mo. An HPV-DNA test was performed at the fourth visit (1 y after conization).
Giannella[35] (2015)	2006–2011	CIN2–3	LEEP	CIN1 + negative	67	Mean 37.5; SEM ± 8.1 (whole cohort)	Colposcopy and Pap test every 6 mo for 2 y.
Nam[32] (2015)	2001–2010	CIN2–3	LEEP	CIN1 + negative	110	Mean 38.7; SEM ± 8.8; range 21–69	Cervical cytological and HPV testing were obtained at each visit, every 3–6 mo during the first 2 y and annually thereafter.
Walavalkar[28] (2016)	2009–2012	CIN2–3	LEEP, CKC	CIN1 + negative	100	Mean 36; range 17–62	Cervical cytology was obtained at 6-mo intervals after the conization.
Kuroki[29] (2016)	2007–2014	HSIL	LEEP	CIN1 + negative	14	Mean 38; SEM ± 12.3	Not specified.
Aly[30] (2021)	2018	CIN2–3	LEEP	CIN1 + negative	8	Median 34; range 25–54 (whole cohort)	Cytology and HPV testing. No more details.
Bradbury[37] (2022)	2014–2019	CIN2–3	LEEP	CIN1 + negative	175	Median 38; IQR 31–45 (whole cohort)	Cytology and HPV testing at 6 and 24 mo. Median follow-up time of 25 mo.
Guo[36] (2022)	2010–2019	CIN2–3	LEEP, CKC	CIN1 + negative	327	Mean 38.8; SEM ± 9.8 (whole cohort)	Cervical cytology and HPV tests at each visit, every 3 mo for 2 y and annually thereafter.
Total					1,036		

IQR indicates interquartile range.

TABLE 2. Recurrence as CIN2+ After Negative Conization Specimen

	Preconization biopsy result				Conization specimen pathology result				
Author and year	**CIN2**	**CIN3**	**CIN2–3**	**HSIL**	**CIN1**	**Negative**	**CIN1 and negative**	***N* total**	**No. patients with CIN2+ recurrence**
Livasy[26] (2004)	—	—	75	—	—	75	—	75	10
Ryu[31] (2010)	—	—	28	—	—	28	—	28	1
Ding[33] (2011)	37	—	—	—	17	20	—	37	0
Witt[27] (2012)	—	—	—	73	—	—	73	73	7
Baser[34] (2014)	—	—	22	—	—	22	—	22	1
Giannella[35] (2015)	—	—	67	—	—	—	67	67	5
Nam[32] (2015)	—	—	110	—	20	90	—	110	3
Walavalkar[28] (2016)	—	—	100	—	—	—	100	100	1
Kuroki[29] (2016)	—	—	—	14	—	—	14	14	1
Aly[30] (2021)	6	2	—	—	—	—	8	8	0
Bradbury[37] (2022)	—	—	175	—	104	71	—	175	1
Guo[36] (2022)	—	—	327	—	—	—	327	327	4
Total									34

The mean age was reported in 8 studies[27–29,31,32,34–36] and ranged from 33.2 to 39.3 years; the other 4 studies[26,30,33,37] reported median age, which ranged from 29 to 38 years. Regarding the definition of a negative conization specimen, 9 studies[27–30,32,33,35–37] considered negative and CIN1 results (≤CIN1) as a "negative specimen," and 3 studies[26,31,34] considered only negative results in this category. None of the studies that included CIN1 specimens as negative reported margin status. Follow-up schemas varied among studies and included the use of cytology, HPV detection, or both at different intervals. Only 2 studies did not report details regarding follow-up.[27,29] Details of the patient populations and recurrence rates of the included studies are provided in Tables 1 and 2.

Nine studies received 6 out of a possible 7 points on the modified Newcastle-Ottawa Scale. The other 3 studies[27–29] received 5 out of 7 points. Details of the quality assessment are provided in Supplemental Digital Content 2, http://links.lww.com/LGT/A324.

Ten of the 12 studies, which included 991 patients with negative and CIN1 conization specimens considered as negative, contributed to the proportion meta-analysis. The recurrence rate as CIN2+ during the follow-up was 3.6% (95% CI, 1.2%–7.0%; $I^2 = 75.1$; $p < .0001$) and ranged from 0.6% to 13.0% in the individual studies. The other 2 studies[30,33] did not contribute to the proportion meta-analysis as they reported zero events. Details are provided in the forest plot for the proportion meta-analysis in Figure 2 and in Table 2.

Four of the 5 studies, which included 215 patients with only negative specimens, contributed to the proportion meta-analysis. The recurrence rate as CIN2+ among these patients during follow-up was 6.0% (95% CI, 1.8%–12.1%; $I^2 = 49.2$; $p < .0001$) and ranged from 0.3% to 13.0% in the individual studies. The other study[33] did not contribute to the proportion meta-analysis as it reported zero events. Details are provided in the forest plot for the proportion meta-analysis in Figure 3.

DISCUSSION

Based on a proportion meta-analysis of retrospective evidence, the recurrence rates as CIN2+ for patients who had a confirmed high-grade cervical intraepithelial lesion on a cervical biopsy, followed by a negative conization specimen or ≤ CIN1 specimen are 6% and 3.6%, respectively.

When patients with high-grade CIN (CIN2–3) are treated with a surgical conization procedure,[4] residual disease and margin status are assessed routinely. The recurrence rate in patients with CIN2–3 conization specimens and negative margins has been reported to range from 1% to 7%,[38–40] which is similar to the rate found in our review of patients without residual disease in the conization specimen.

Even when cervical biopsy showed CIN2–3, the reported rates of negative conization specimens ranged from 8.2% to 26.9% of patients, depending on the preoperative biopsy findings (CIN2 vs. CIN3), the patients' age, the criteria used to define a negative specimen (≤CIN1 vs. negative), and other factors.[12,14,18,25] The reasons for obtaining a negative conization specimen after a biopsy-confirmed

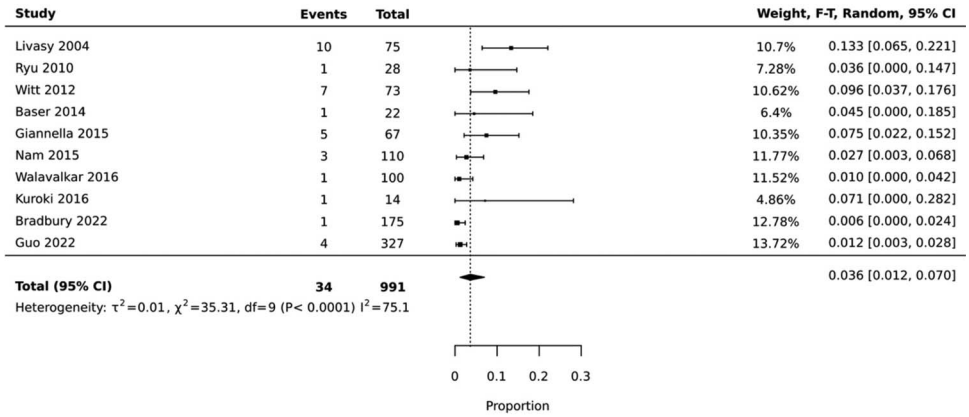

FIGURE 2. Proportion meta-analysis of recurrence rate in patients with negative and CIN1 conization specimens.

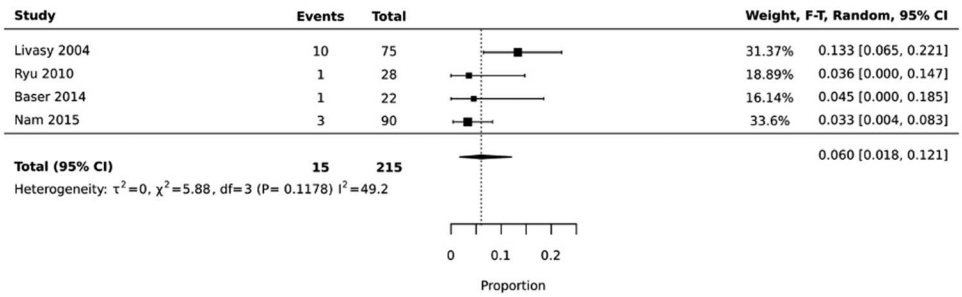

FIGURE 3. Proportion meta-analysis of recurrence rate in patients with only negative conization specimens.

diagnosis of a high-grade CIN vary but could include dysplasia that was missed at the initial evaluation of the conization specimen, presurgical biopsy overcalled as a high-grade CIN, an inadequate conization specimen well because of incorrect identification of the lesion location, inadequate specimen size, or endocervical curettage absence,[25] the complete removal of a lesion with the initial biopsy, or an immune response triggered by the biopsy resulting in clearance of HPV and the lesion.[22]

Until now, the recurrence rate in patients with a negative conization specimen after a biopsy-confirmed high-grade CIN (CIN2–3) had not been thoroughly evaluated. The recurrence rate of 6% in these patients is like that of patients with CIN2–3 and negative-margin conization specimens. However, the recurrence rate in the studies included in our review varied (0.3%–13%), and the rate was higher when only negative conization specimens were considered than when both negative and CIN1 (≤CIN1) specimens were considered. In addition, the reasons for these differences in recurrence rates remain unclear, but possible reasons for the higher recurrence rate in patients with negative conization specimens could include missed high-grade lesions in the conization specimen, HPV reinfection, or immune compromise. In addition, we identified a high degree of clinical and statistical heterogeneity among the included studies, including differences in screening for abnormalities, definitions of negative conization specimens (≤CIN1 vs. negative), the proportion of CIN2 versus CIN3 lesions in the study populations, and follow-up schemas. Nonetheless, patients should be followed and advised regarding the results.

Strengths and Limitations

Our review's main strength is its rigorous data collection and analysis methodology. We implemented a preregistered protocol with a comprehensive search strategy, specified selection criteria, and a rigorous predefined process for data analysis and meta-analysis performance. However, the review also has some limitations. The included studies were all retrospective cohort studies, which may have selection and publication bias. In addition, the clinical and statistical heterogeneity of the studies must be highlighted. They included different populations regarding age, the initial abnormalities identified on screening tests, different conization techniques, and different follow-up schemas. A related limitation is the uncertainty about the validity or quality of the pathology results; there was no central pathology review of the slides or predefined protocol for conization specimen processing, for example, regarding the number of slides or the use of immunohistochemistry. Finally, because we limited the search to studies published in English, we could have missed some relevant references published in other languages, and because the studies were conducted over a long period, there could be performance bias.

CONCLUSIONS

The specific population of patients with a biopsy-confirmed CIN followed by a negative conization specimen may have a high risk of CIN2+ recurrence, but the quality of the evidence is low. The recurrence rates as CIN2+ for patients with a biopsy-confirmed high-grade CIN followed by a negative conization specimen are 6% if only negative specimens are considered and 3.6% if ≤CIN1 specimens are considered. Multi-institutional efforts to obtain prospective evidence could be constructed to better define the risk and prognosis of these patients, as there are still many gaps regarding the reasons for a negative specimen, the true risk of recurrence, and required follow-up schemas. Patients should be counseled regarding this finding and followed up, probably with the same schemas used for patients with conization specimen-confirmed high-grade CIN with negative margins.

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