Original Article

# Relationship between positive margin and residual/recurrence after excision of cervical intraepithelial neoplasia: a systematic review and meta-analysis

**Hailing Feng[1#], Hai Chen[2#], Dan Huang[3#], Shengke He[1], Zhiqian Xue[1], Zhongjun Pan[1], Huajun Yu[1], Yongqun Huang[4]**

[1]Department of Pathology, Danzhou People's Hospital Affiliated to Hainan Medical University, Danzhou, China; [2]Department of Pharmacy, Hainan West Central Hospital, Danzhou, China; [3]Department of Obstetrics and Gynecology, Danzhou People's Hospital Affiliated to Hainan Medical University, Danzhou, China; [4]Department of Obstetrics and Gynecology, The Fifth People's Hospital of Hainan Province, Haikou, China

*Contributions:* (I) Conception and design: H Feng, H Chen, D Huang, Y Huang; (II) Administrative support: S He; (III) Provision of study materials or patients: H Feng, D Huang, Y Huang; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: H Feng, H Chen, D Huang, Y Huang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

*Correspondence to:* Yongqun Huang. Department of Obstetrics and Gynecology, The Fifth People's Hospital of Hainan Province, Haikou, 571127, China. Email: a364305196@163.com.

**Background:** The relationship between endocervical and ectocervical margin status and residual or recurrence after cervical intraepithelial neoplasia (CIN) resection has been controversial. We investigated the relationship between the excision margins and residual/recurrence to assess indicators for the scope of resection and the risk of treatment failure by using meta-analysis.

**Methods:** Literature searches were performed in PubMed, Medline, Embase, Central, Wangfang and CNKI databases. Patients after CIN resection were grouped according to whether there was residual or recurrence, and the differences in exposure factors between the two groups were compared. Or they were grouped by exposure factor, and compare the differences in residual and recurrence rates under different grouping conditions. The observed outcome was postoperative residual or recurrence. The risk of bias in the literature was assessed using the Newcastle-Ottawa Scale (NOS). The chi-square test were used for heterogeneity. Subgroup explored the sources of heterogeneity. Publication bias was assessed using funnel plots and Egger's test.

**Results:** A total of 11 studies were included in this study, 8 studies were at low risk of bias and 3 studies were at high risk of bias. The 11 studies included 3065 patients, 774 patients with positive margins and 2,291 patients with negative margins. The rate of residual/recurrence after excision of CIN in patients with positive margins was significantly higher than in patients with negative margins [odds ratio (OR) =3.99, P<0.00001]. There was no heterogeneity among the studies (P=0.16), with publication bias (P<0.05). The residual/recurrence rate was significantly higher in patients with positive endocervical margins than in patients with negative endocervical margins (OR =2.59, P<0.00001). There was no heterogeneity among studies (P=0.78) and no publication bias (P<0.05). There was no significant difference in residual/recurrence rate between positive and negative ectocervical margins (OR =1.14, P=0.36). There was no heterogeneity among studies (P=0.32) and no publication bias (P<0.05).

**Conclusions:** Positive endocervical margins, but not external cervical margins, are risk factors for residual/recurrence of CIN after resection. Close attention to the status of the endocervical margins is recommended. More aggressive treatment and frequent follow-up are needed for patients with positive endocervical margins.

**Keywords:** Cervical intraepithelial neoplasia (CIN); ectocervical margins; endocervical margins; positive excision margins

 

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## Introduction

Cervical cancer is the most common malignant tumor of the female reproductive system, with new incidence accounting for 5% of all new cancer cases globally every year, most of which are in developing countries (1-3), and the mortality rate has increased in recent years (4). Cervical intraepithelial neoplasia (CIN) is a cervical precancerous lesion that is closely related to cervical cancer and its incidence has been increasing in recent years (5,6). According to the depth of the lesion, it is classified as CINI, CINII, and CINIII, and the risk of developing invasive cervical cancer increases with each level (7). The WHO basic practice guide for comprehensive prevention and treatment of cervical cancer emphasizes treatment of CINIII to inhibit the occurrence and development of cervical cancer (8). Cervical cancer can be avoided by screening cervical lesions and treating CIN.

Excision biopsy is a standard method of CIN treatment, but there is a risk of treatment failure. A study showed that 4–18% of patients had residue or recurrence detected within 2 years after the initial resection (9). The extent of resection has to be balanced with the side effects of the treatment. The extent of prior cervical resection has been associated with preterm birth and other adverse pregnancy events (10,11). The relationship between the status of endocervical and ectocervical cervical margins and residual/recurrence after CIN resection is controversial. Park *et al.* pointed out that a positive incisional margin will increase the residual or recurrence rate after CIN resection (12). Alder *et al.* (13) pointed out that the margin status cannot accurately predict postoperative residual or recurrence. A positive external cervical margin does not increase the associated risk. Differences in results between these studies may be related to subject bias, choice of surgical approach, and quality of follow-up. Most of the studies were independent retrospective analyses with small sizes and have not provided convincing evidence. Therefore, we conducted a meta-analysis to explore the relationship between the margin status, including the endocervical and ectocervical margin, and the residual or recurrence after CIN resection. We present the following article in accordance with the MOOSE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1466/rc).

## Methods

### *Literature retrieval*

A literature search was conducted in the PubMed, Medline, Embase, Central, Wangfang and CNKI databases, using the search terms ("CIN" OR "cervical intraepithelial neoplasia" OR "cervical dysplasia" OR "Cervical precancerous lesion") AND ("margin" OR "recurrence"). Document language was not limited. The search deadline is April 18, 2022.

### *Literature screening*

Inclusion criteria: (I) CIN patients undergoing resection; (II) subjects divided into groups according to whether there was residual or recurrence, and the differences in exposure factors between groups were compared, or the differences in residual and recurrence rates under different grouping conditions were compared according to exposure factors; (III) exposure factors include margin status; (IV) clear diagnosis of postoperative residual or recurrence after CIN in patients; (V) case-control study or cohort study.

Exclusion criteria: (I) duplicate report; (II) unclear diagnosis of CIN or unclear status of the margin; (III) lost to follow-up rate >20%; (IV) incomplete study data and unable to be provided by correspondence author.

### *Data extraction*

Two researchers (Feng and Huang) jointly extracted the author, title, publication time, sample size, margin status, number of residual or recurrent cases and other information in the study. Any missing data was obtained by contacting the author. If there was disagreement about the data, consensus was achieved through discussion.

### *Evaluation of the risk of bias in the literature*

Two researchers used the Newcastle-Ottawa scale (NOS) to evaluate the risk of bias of the literature included in the study, including the selection of subjects (4 points), comparability between groups (2 points) and exposure

 

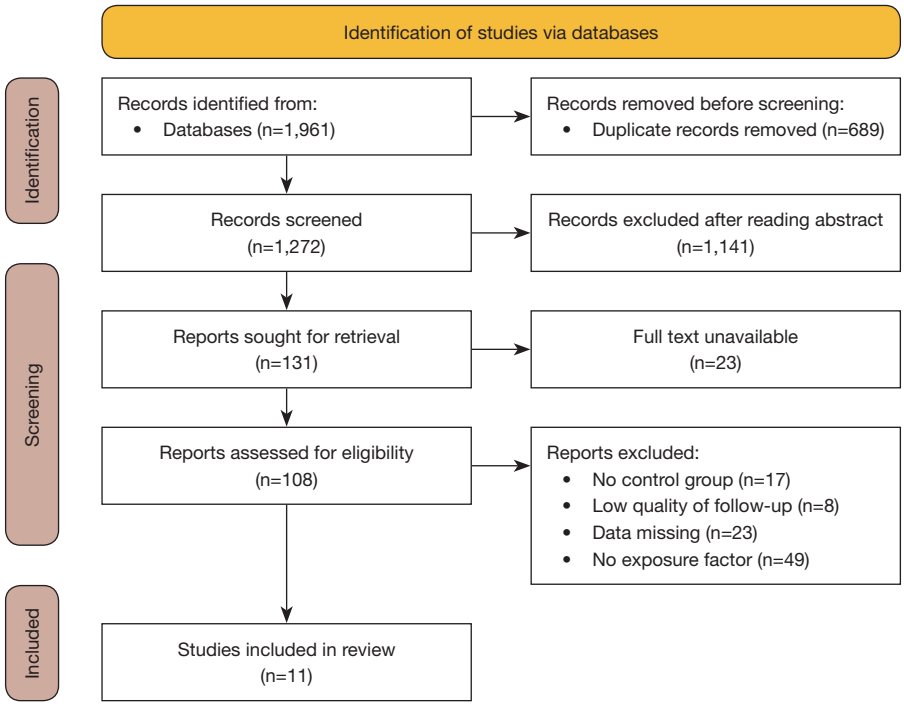


**Figure 1** Flow chart of literature retrieval.

factor measurement (3 points), for a total of 9 points. A score ≥5 points was considered low risk of bias, otherwise high risk of bias (14). The two researchers jointly completed the literature risk of bias evaluation and disagreements were resolved by consensus.

### *Heterogeneity and publication bias tests*

#### Statistical analysis

We used Cochrane software RevMan5.3 for statistical analysis of the data. The odds ratio (OR) value and 95% confidence interval (CI) of cohort studies and case-control studies were calculated for pooled analysis. OR values were not adjusted for other factors. The Chi-square test was used as the heterogeneity test. When $I^2$ corrected by degrees of freedom was >50% or P<0.1, it was considered that there was heterogeneity among the studies, and a random-effects model was used. Subgroup was used to explore the causes of heterogeneity. When $I^2$ corrected by degrees of freedom was ≤50% and P≥0.1, it was considered that there was no heterogeneity, and a fixed-effects model was used. Funnel plots and Egger test were used for the publication bias test. Two-way P<0.05 indicated statistical significance.

## Results

### *Study data*

A total of 1,961 studies were retrieved, 1,950 were excluded, and a final 11 (12,13,15-23) were included in the meta-analysis. Eight studies were at low risk of bias, and 3 studies were at high risk of bias. The 11 studies included 3,065 patients, 774 patients with positive margins and 2,291 patients with negative margins. *Figure 1* is a flow chart of literature screening and *Table 1* shows the baseline study information and NOS score.

### *Margin status and residual/recurrence*

The 11 studies reported the correlation between the resection margin status and the residual or recurrence rate after CIN resection. There was no heterogeneity among the 11 studies ($Chi^2$=14.27, P=0.16, $I^2$=30%), and the fixed-effects model was selected for combined analysis as shown in *Figure 2*. The residual or recurrence rate of patients with a positive margin was significantly higher than for patients with a negative margin. The funnel plot and Egger test in *Figure 3* showed the points biased to the left, indicating publication bias (P<0.05).

**Table 1** Study characteristics and NOS scores

| Author | Year | Study type | No. of patients | | NOS |
|---|---|---|---|---|---|
| | | | Margins positive | Margins negative | |
| Alder *et al.* (13) | 2020 | Cohort | 283 | 641 | 7 |
| Alonso *et al.* (15) | 2006 | Cohort | 66 | 135 | 6 |
| Cejtin *et al.* (16) | 2017 | Case-control | 19 | 96 | 6 |
| Lu *et al.* (17) | 2006 | Case-control | 44 | 134 | 4 |
| Chikazawa *et al.* (18) | 2016 | Case-control | 61 | 140 | 7 |
| Demarquet *et al.* (19) | 2019 | Cohort | 48 | 261 | 5 |
| Leguevaque *et al.* (20) | 2010 | Cohort | 105 | 344 | 6 |
| Park *et al.* (21) | 2007 | Case-control | 54 | 23 | 4 |
| Park *et al.* (12) | 2008 | Cohort | 28 | 208 | 4 |
| Park *et al.* (22) | 2009 | Case-control | 36 | 207 | 5 |
| Torné *et al.* (23) | 2013 | Cohort | 30 | 102 | 6 |

NOS, Newcastle-Ottawa Scale.

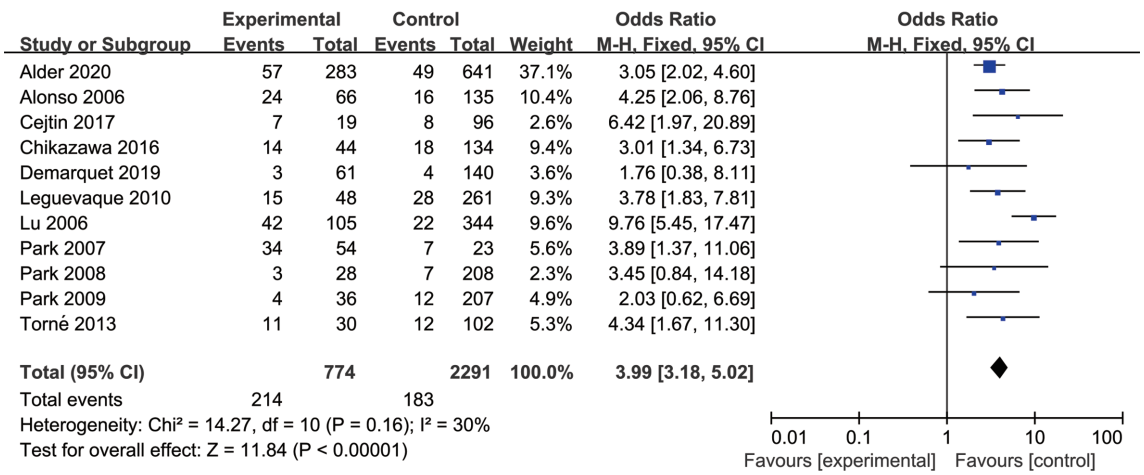


**Figure 2** Comparison of residual or recurrence rate after resection between positive and negative margin groups. CI, confidence interval.

### *Status of the endocervical margin and residual or recurrence*

A total of 7 studies reported the correlation between the status of the endocervical margin and the residual or recurrence rate after CIN resection. There was no heterogeneity among the studies ($Chi^2$=3.26, P=0.78, $I^2$=0%), so the fixed-effects model was selected for combined analysis as shown in *Figure 4*. The residual or recurrence rate of patients with positive endocervical margins was significantly higher than for patients with negative margins. The funnel plot and Egger test in *Figure 5* showed the roughly symmetrical distribution of the points within the confidence interval, indicating no publication bias (P>0.05).

### *Status of the ectocervical margin and residual or recurrence*

A total of 5 studies reported the correlation between the status of the ectocervical margin and the residual

 

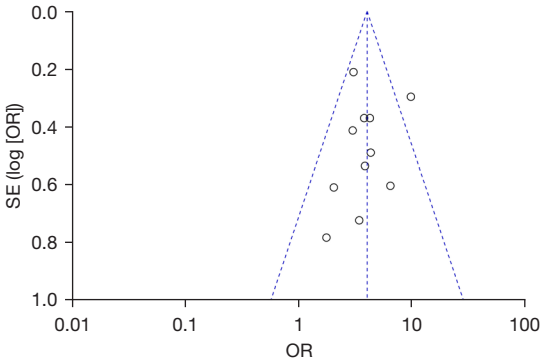


**Figure 3** Funnel plot of residual or recurrence rate after resection in the positive and negative margin groups. OR, odds ratio; SE, standard error.

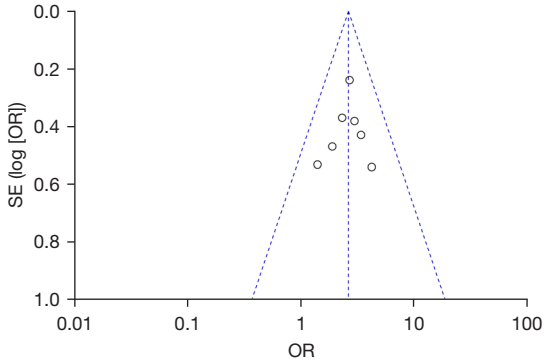


**Figure 5** Funnel plot of the residual or recurrence rate after resection between the positive endocervical margin group and the negative margin group. OR, odd ratio; SE, standard error.

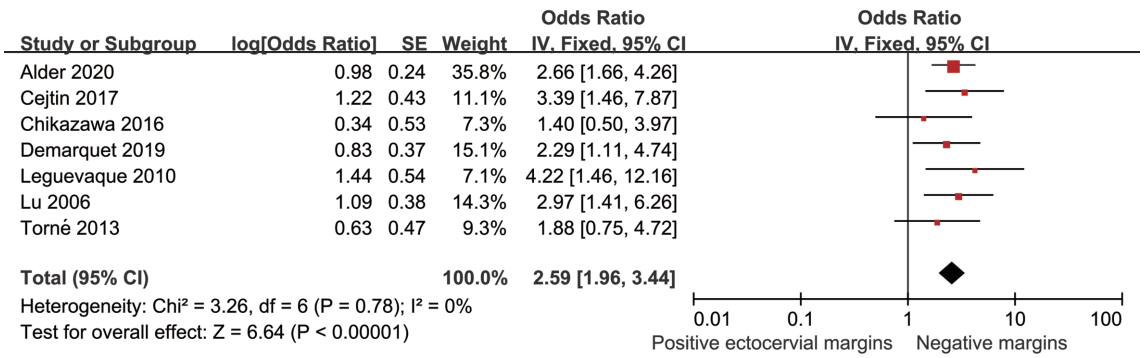


**Figure 4** Comparison of residual or recurrence rate after resection between the positive endocervical margin group and the negative margin group. CI, confidence interval.

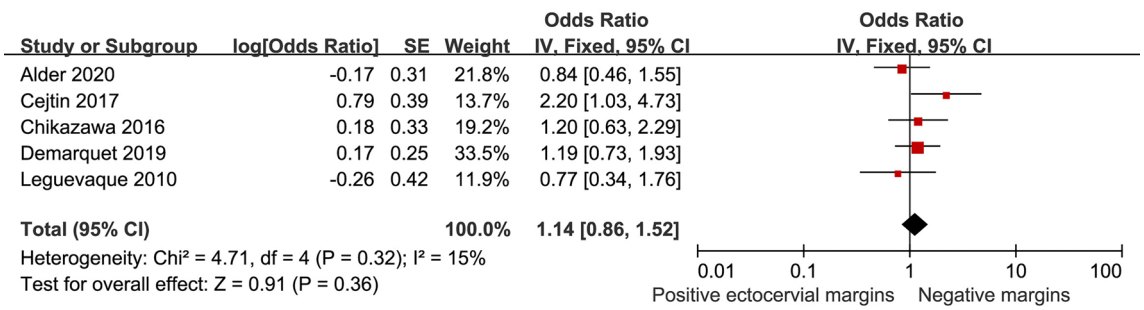


**Figure 6** Comparison of residual or recurrence rate after resection between the positive ectocervical margin group and the negative margin group. CI, confidence interval.

or recurrence rate after CIN resection. There was no heterogeneity among the studies ($Chi^2$=4.71, P=0.32, $I^2$=15%), so the fixed-effects model was selected for combined analysis as shown in *Figure 6*. There was no significant difference in the residual or recurrence rate between positive and negative margins after resection. The funnel plot and Egger test showed in *Figure 7* shows the roughly symmetrical distribution of the points within the

 

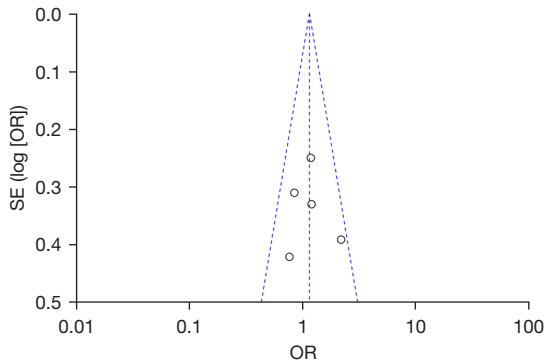


**Figure 7** Funnel plot of the residual or recurrence rate after resection between the positive ectocervical margin group and the negative margin group. OR, odds ratio; SE, standard error.

confidence interval, indicating no publication bias (P>0.05).

## Discussion

We analyzed 11 studies including 3,065 patients after CIN resection that reported the correlation between resection margin status and the residual or recurrence rate. There were 774 patients with a positive margin, accounting for 25.25% of the total patients and similar to the 23.1% of patients with positive margins after resection reported previously (24). In our analysis, the postoperative residual or recurrence rate of patients with a positive margin was ≈27.65%, and that of patients with a negative margin was ≈7.99%, similar to the results of the previous meta-analysis (24). Our results showed that patients with positive margins had a 3.99 (95% CI: 3.18, 5.02) increased risk of postoperative residue or recurrence compared with patients with negative margins. A positive margin is a risk factor for residual or recurrence after resection, which is consistent with all the results of our analysis. However, one study has pointed out that the status of the margin could not accurately predict postoperative residual or recurrence (13). Some comorbidities, including human papillomavirus (HPV) persistent infection, HIV infection, viral hepatitis, malignant tumor and diabetes mellitus, are also risk factors for residual or recurrence after resection. Arbyn *et al.* believe that a positive margin increases the risk of postoperative residue or recurrence (11). Nevertheless, the accuracy of high-risk HPV test results in predicting cervical resection failure was higher than for the margin status. Alder *et al.* showed that when positivity for high-risk HPV and margins exists simultaneously, the increase in the risk of residual or recurrence was more significant, and much higher than for patients with positive high-risk HPV and negative margins (13). The combination of margin status and HPV test results could improve the accuracy of predicting residual or recurrence after resection. Cejtin *et al.* suggested that the predictive efficacy of endocervical curettage for residual or recurrence after CIN resection was better than margin status (16).

We analyzed the relationship between endocervical and ectocervical margin status and residual or recurrence after resection. A positive endocervical margin was a risk factor for postoperative residual or recurrence, but a positive ectocervical margin did not increase the risk of postoperative residue or recurrence. The results of Alder *et al.* (13), Demarquet *et al.* (19), and Leguevaque *et al.* (20) are consistent with our results. Those studies clearly pointed out that a positive cervical intimal margin was a risk factor for postoperative residue or recurrence, whereas a positive cervical outer margin did not increase the risk. Cejtin *et al.* believe that positive endocervical and ectocervical margins in HIV-positive patients will increase the risk of postoperative residue or recurrence (16). Chikazawa *et al.* suggested the risk of residue or recurrence increased when the ectocervical margin was positive or both the endocervical and ectocervical margins were positive (18). Our analysis suggested that the status of the endocervical margin might more accurately predict the postoperative residual or recurrence rate, but this needs to be confirmed by further research.

The status of the margin is affected by some factors, one being the surgical method (24). The proportion of positive margins after electrosurgical resection might be higher than after cold knife resection, but our analysis showed no clinical significance. Electrosurgery may lead to fragmentation of the resected specimens, so false-positive margins might be more common. Another study (25) pointed out that positive margins might be related to surgical experience; that is, operative skill was directly related to the proportion of positive margins. Lesion size and conical resection size correlated with margin status (24). Demarquet *et al.* pointed out that the size of the resection affected the occurrence of postoperative residue or recurrence, and the extent of pyramidal resection should be carefully controlled (19). At present, there is no consensus on further treatment of positive margins after resection of CIN.

In conclusion, a positive endocervical margin but not positive ectocervical margins increases the risk. Some studies included in the analysis were at significant risk of bias, which may have affected the results to some extent.

 

Prospective studies with large samples are still needed to confirm our results. For patients with a positive endocervical margin, more active treatment measures are recommended.

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## Footnote

*Reporting Checklist:* The authors have completed the MOOSE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1466/rc

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1466/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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