

## INPLASY

## Global incidence and risk factors for cervical cancer after cervical intraepithelial neoplasia: A systematic review and meta-analysis

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**Review question / Objective** To estimate the global incidence of cervical cancer following CIN treatment and to explore risk factors associated with progression to cervical cancer.

**Condition being studied** Cervical intraepithelial neoplasia (CIN) is a precursor lesion of cervical cancer. Although local treatment effectively eradicates the lesion, women remain at an elevated risk of developing cervical cancer after treatment.

**METHODS****Search strategy** PubMed:

((("Cervical Intraepithelial Neoplasia"[Mesh] OR "Uterine Cervical Dysplasia"[Mesh] OR "Carcinoma in Situ"[Mesh:noexp]) OR (CIN[tiab] OR CIN1[tiab] OR CIN2[tiab] OR CIN3[tiab] OR "cervical intraepithelial neoplasia"[tiab] OR "cervical

dysplasia"[tiab] OR "cervical intraepithelial dysplasia"[tiab] OR "cervical carcinoma in situ"[tiab] OR "cervix carcinoma in situ"[tiab] OR "cervical squamous intraepithelial lesion"[tiab] OR SIL[tiab] OR HSIL[tiab] OR LSIL[tiab])) AND (("therapy"[Subheading] OR "Therapeutics"[Mesh] OR "Surgical Procedures, Operative"[Mesh] OR "Conization"[Mesh] OR "Electrosurgery"[Mesh] OR "Cryotherapy"[Mesh] OR "Laser Therapy"[Mesh]) OR (treated[tiab] OR treatment[tiab] OR therapy[tiab] OR therapeutic[tiab] OR excision[tiab] OR excisional[tiab] OR conisation[tiab] OR conization[tiab] OR cone[tiab] OR LLETZ[tiab] OR LEEP[tiab] OR "large loop excision"[tiab] OR "loop electrosurgical excision"[tiab] OR "cold knife"[tiab] OR laser[tiab] OR ablation[tiab] OR ablative[tiab] OR cryotherapy[tiab] OR NETZ[tiab])) AND (("Uterine Cervical Neoplasms"[Mesh] OR "Cervical Cancer"[tiab] OR "cervical carcinoma"[tiab] OR "cervix cancer"[tiab] OR "cervix carcinoma"[tiab] OR "invasive cervical cancer"[tiab] OR "cervical malignancy"[tiab] OR "cervical tumor"[tiab])) AND (("Risk Factors"[Mesh] OR "Incidence"[Mesh] OR

"Disease Progression"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh] OR "Neoplasm Residual"[Mesh] OR "HPV persistence"[tiab] OR "recurrence"[tiab] OR "progression"[tiab] OR "residual disease"[tiab] OR "risk factor"[tiab] OR "risk factors"[tiab] OR "predictor"[tiab] OR "predictors"[tiab] OR "determinants"[tiab] OR "associated factors"[tiab] OR "contributing factors"[tiab] OR "incidence"[tiab] OR "mortality"[tiab] OR "survival"[tiab] OR prognosis[tiab])

#### EmBase:

1. exp cervical intraepithelial neoplasia/ OR exp uterine cervix dysplasia/ OR exp carcinoma in situ/
2. (CIN or CIN1 or CIN2 or CIN3 or "cervical intraepithelial neoplasia" or "cervical dysplasia" or "cervical intraepithelial dysplasia" or "cervical carcinoma in situ" or "cervix carcinoma in situ" or "cervical squamous intraepithelial lesion" or SIL or HSIL or LSIL).ti,ab,kw.
3. 1 OR 2
4. exp therapy/ OR exp surgery/ OR exp conization/ OR exp electrosurgery/ OR exp cryotherapy/ OR exp laser therapy/
5. (treated or treatment or therapy or therapeutic or excision or excisional or conisation or conization or cone or LLETZ or LEEP or "large loop excision" or "loop electrosurgical excision" or "cold knife" or laser or ablation or ablative or cryotherapy or NETZ).ti,ab,kw.
6. 4 OR 5
7. exp uterine cervix tumor/ OR exp cervix cancer/ OR exp invasive cervical carcinoma/
8. ("cervical cancer" or "cervical carcinoma" or "cervix cancer" or "cervix carcinoma" or "invasive cervical cancer" or "cervical malignancy" or "cervical tumor").ti,ab,kw.
9. 7 OR 8
10. exp risk factor/ OR exp disease course/ OR exp neoplasm recurrence/ OR exp cancer recurrence/ OR exp cancer incidence/ OR exp cancer mortality/
11. ("risk factor" or "risk factors" or predictor or predictors or determinants or "associated factors" or "contributing factors" or incidence or recurrence or progression or "residual disease" or "HPV persistence" or mortality or survival or prognosis).ti,ab,kw.
12. 10 OR 11
13. 3 AND 6 AND 9 AND 12

#### Cochrane library:

- #1 MeSH descriptor: [Cervical Intraepithelial Neoplasia] explode all trees
- #2 MeSH descriptor: [Uterine Cervical Dysplasia] explode all trees

#3 MeSH descriptor: [Carcinoma in Situ] this term only

#4 (CIN OR CIN1 OR CIN2 OR CIN3 OR "cervical intraepithelial neoplasia" OR "cervical dysplasia" OR "cervical intraepithelial dysplasia" OR "cervical carcinoma in situ" OR "cervix carcinoma in situ" OR "cervical squamous intraepithelial lesion" OR SIL OR HSIL OR LSIL):ti,ab,kw

#5 #1 OR #2 OR #3 OR #4

#6 MeSH descriptor: [Therapeutics] explode all trees

#7 MeSH descriptor: [Surgical Procedures, Operative] explode all trees

#8 MeSH descriptor: [Conization] explode all trees

#9 MeSH descriptor: [Electrosurgery] explode all trees

#10 MeSH descriptor: [Cryotherapy] explode all trees

#11 (treated OR treatment OR therapy OR therapeutic OR excision OR excisional OR conisation OR conization OR cone OR LLETZ OR LEEP OR "large loop excision" OR "loop electrosurgical excision" OR "cold knife" OR laser OR ablation OR ablative OR cryotherapy OR NETZ):ti,ab,kw

#12 #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13 MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees

#14 ("cervical cancer" OR "cervical carcinoma" OR "cervix cancer" OR "cervix carcinoma" OR "invasive cervical cancer" OR "cervical malignancy"):ti,ab,kw

#15 #13 OR #14

#16 MeSH descriptor: [Risk Factors] explode all trees

#17 MeSH descriptor: [Incidence] explode all trees

#18 MeSH descriptor: [Disease Progression] explode all trees

#19 MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees

#20 ("risk factor" OR "risk factors" OR predictor OR predictors OR determinants OR "associated factors" OR "contributing factors" OR incidence OR recurrence OR progression OR "residual disease" OR "HPV persistence" OR mortality OR survival OR prognosis):ti,ab,kw

#21 #16 OR #17 OR #18 OR #19 OR #20

#22 #5 AND #12 AND #15 AND #21

#### Web of Science:

TS=(("Cervical Intraepithelial Neoplasia" OR "cervical dysplasia" OR "cervical intraepithelial dysplasia" OR "cervical carcinoma in situ" OR "cervix carcinoma in situ" OR "cervical squamous intraepithelial lesion" OR CIN OR CIN1 OR CIN2 OR CIN3 OR SIL OR HSIL OR LSIL) AND (treated OR treatment OR therapy OR therapeutic OR excision OR excisional OR conisation OR

conization OR cone OR LLETZ OR LEEP OR "large loop excision" OR "loop electrosurgical excision" OR "cold knife" OR laser OR ablation OR ablative OR cryotherapy OR NETZ) AND ("cervical cancer" OR "cervical carcinoma" OR "cervix cancer" OR "cervix carcinoma" OR "invasive cervical cancer" OR "cervical malignancy") AND ("risk factor" OR "risk factors" OR predictor OR predictors OR determinants OR "associated factors" OR "contributing factors" OR incidence OR recurrence OR progression OR "residual disease" OR "HPV persistence" OR mortality OR survival OR prognosis)).

**Participant or population** Women with histologically or cytologically confirmed cervical intraepithelial neoplasia who underwent local treatment.

**Intervention** Risk factor studies reporting associations between at least one of the following factors and cervical cancer outcomes: CIN grade, margin status, post-treatment HPV status, age, immunosuppression, smoking history, oral contraceptive use, parity, and age at first intercourse.

**Comparator** The general female population, women without a history of CIN, or age-/region-matched non-CIN control cohorts.

**Study designs to be included** Prospective or retrospective cohort studies.

**Eligibility criteria** Studies were included if they met the following PICOS criteria: (1) Population: women with histologically or cytologically confirmed cervical intraepithelial neoplasia who underwent local treatment; (2) Exposure: risk factor studies reporting associations between at least one of the following factors and cervical cancer outcomes: CIN grade, margin status, post-treatment HPV status, age, immunosuppression, smoking history, oral contraceptive use, parity, and age at first intercourse; (3) Comparator: the general female population, women without a history of CIN, or age-/region-matched non-CIN control cohorts; (4) Outcomes: the primary outcome was the incidence of cervical cancer; secondary outcomes included risk factors for cervical cancer development after CIN treatment; (5) Study design: prospective or retrospective cohort studies.

**Information sources** PubMed, Embase, Cochrane Library, and Web of Science.

**Main outcome(s)** The primary outcome was the incidence of cervical cancer; secondary outcomes

included risk factors for cervical cancer development after CIN treatment.

**Quality assessment / Risk of bias analysis** Newcastle-Ottawa Scale.

**Strategy of data synthesis** A generalised linear mixed model was applied to pool the raw incidence rates after logarithmic transformation, with results subsequently back-transformed to the original scale for interpretability. For risk factors, odds ratios (ORs) with their 95% confidence intervals (CIs) were used as the effect measure. All pooled estimates were derived using random-effects models.

**Subgroup analysis** Pre-specified subgroup analyses were conducted according to study design, geographic region, CIN grade, follow-up duration, and study quality; subgroup differences were evaluated using interaction tests.

**Sensitivity analysis** To test the robustness of the pooled results, a leave-one-out sensitivity analysis was performed by sequentially omitting each study and recalculating the summary estimates.

**Country(ies) involved** China.

**Keywords** Cervical intraepithelial neoplasia; cervical cancer; incidence; risk factors; systematic review; meta-analysis.

#### Contributions of each author

Author 1 - Tong Tong.

Author 2 - Qi Si.

Author 3 - Xinyao Duan.

Author 4 - Ziyang Li.

Author 5 - Wenxi Yan.

Author 6 - Pingping Jia.

Author 7 - Huanhuan Zhao.

Author 8 - Jing Ma.

Author 9 - Na Wang.