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Full length article

# Risk of cervical stenosis after cervical excision in postmenopausal patients

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ABSTRACT

*Objective:* Cervical excision may cause cervical stenosis, leading to suboptimal follow-up of dysplasia and delayed diagnosis of cervical and endometrial pathology. This study aimed to quantify the risk of stenosis development after electrosurgical cervical excision in postmenopausal patients.
*Methods:* Retrospective cohort study based on data collection from electronic medical records and the Danish National Pathology Data Bank. Patients aged ≥45 years who underwent electrosurgical cervical excision in the Gynecological Department, at Randers Regional Hospital from1st of January 2012 to 31st December 2019 were included. Primary outcome was risk of cervical stenosis following cervical excision.
*Results:* Of the 567 cervical excisions conducted within the study period, 300 patients (52.9 %) met the inclusion criteria. Among these, 79 postmenopausal patients (26.3 %) developed cervical stenosis after cervical excision. Patients with stenosis were significantly older (median 64 years) compared to those without stenosis (median 61 years) (p = 0.004). Patients aged >60 years at the time of cervical excision exhibited an increased risk of cervical stenosis (relative risk 1.51 (95 % confidence interval 1.08–2.18)) compared to those ≤60 years.
*Conclusion:* More than one in four postmenopausal patients experienced the development of cervical stenosis following cervical excision. Patients should be adequately informed of the possible risk of cervical stenosis development prior to undergoing diagnostic or therapeutic cervical excision procedure.

## Introduction

Cervical cancer is a highly preventable malignancy through efficient screening for precancerous lesions and detection of high-risk human papilloma virus (HPV). However, it remains the fourth most prevalent cancer in the female population globally [1]. In countries with comprehensive screening strategies, postmenopausal patients are over-represented among cervical cancer cases, and are also more likely to be diagnosed with advanced-stage disease [2–4].

Diagnostic examination for screen-positive individuals includes colposcopic examination of the cervix and histopathological analysis of biopsies from area indicative of dysplasia. In postmenopausal patients, the transformation zone (TZ) is often partly or completely (TZ3) retracted into the cervical canal [5], compromising colposcopy efficacy and increasing the risk of overlooked pathology. Thus, a recent study revealed that more than half of cervical intraepithelial neoplasia grade two or worse (CIN2+) were missed by biopsies when compared to cervical excision in postmenopausal patients with TZ3 [6]. Several international guidelines suggests that diagnostic cervical excision should be considered in patients with a TZ3 and/or age >50 years [7–10].

Cervical stenosis constitutes a notable post-excision complication, that can impair sufficient follow-up. The incidence in premenopausal patients is minimal and seldom necessitates intervention [11–15]. However, existing research regarding postmenopausal patients are

*Abbreviations:* AGC, Atypical Glandular Cells; AIS, Adenocarcinoma in situ; ASCUS, Atypical squamous cells of undetermined significance; ASCH, Atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion; CIN, Cervical intraepithelial neoplasia; CIN1, Cervical intraepithelial neoplasia grade 1; CIN2, Cervical intraepithelial neoplasia grade 2; CIN3, Cervical intraepithelial neoplasia grade 3; CIN2+, Cervical intraepithelial neoplasia grade two or worse; CI, Confidence interval; HPV, Human papilloma virus; HSIL, High-grade squamous intraepithelial lesion; IQR, Interqurtile ranges; LSIL, Low-grade squamous intraepithelial lesion; RCT, Randomised controlled trial; TZ, Transformation zone; TZ3, Transformation zone retracted into the cervical canal.

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limited by small cohorts and diverse excision methodologies, in which the risk varies substantial from 10.6 to 59 % [11,13–16].

Adequate and timely follow-up after cervical dysplasia is essential to detect residual or recurrent disease. Postmenopausal patients exhibit an increased risk of persistent HPV infection after cervical excision and dysplasia recurrence compared to premenopausal patients [15,17]. The presence of cervical stenosis may pose a challenge to sufficient follow-up after cervical excision, also potentially delaying the diagnosis of endometrial pathologies [18,19].

This study aimed to quantify the risk of cervical stenosis development after electrosurgical cervical excision in postmenopausal patients.

## Methods

### *Setting*

The Danish national cervical cancer screening programme is offered to individuals aged 23–64 years. Procedures related to screening, diagnosis, follow-up, and treatment is free of charge. During the study period, the age group 23–49 years was invited for cytology-based screening every third year, and the age group 50–59 years every fifth year. In 2012, HPV-based screening was introduced in the screening program for women aged 60–64 year. From April 2019 an intervention study was conducted, offering an extra HPV screening test to the 65–69 year olds [20,21]. All patients included in this study, were referred for colposcopy after an abnormal screening result according to national guidelines [22].

### *Study design and population*

This retrospective cohort study was conducted in the colposcopy clinic, at Department of Obstetrics and Gynecology, Randers Regional Hospital, Denmark. Postmenopausal patients aged ≥45 years who underwent cervical excision between 1st January 2012 and 31st December 2019 were included. Patients were excluded if they were premenopausal, had previous cervical excision, or were diagnosed with cervical cancer in the cervical excision specimen. Patients were considered postmenopausal when they had experienced 12 consecutive months without menstruation.

Excision procedure was conducted under local anesthesia within the colposcopy clinic or in the day surgery unit with local or general anesthesia. All cervical excisions were performed as electrosurgical excision procedures, either with loop electrode or linear electrode, based on the extent of the lesion and the preference of the surgeons.

In accordance with the national guideline, patients underwent follow-up with a test-of-cure (cytology and HPV-test) six months after cervical excision. Patients with negative surgical margins underwent follow-up by general practitioners and returned to the standard screening program upon negative HPV and cytology results. Patients with positive margins received follow-up at the colposcopy clinic at six and 12 months. The phrase 'uncertain margins' referred to cases where dysplastic changes extended into burned areas in the resection margin. In case of uncertain margins, patients were offered the same follow-up as with positive margins.

### *Data sources and endpoints*

Data were collected from the electronic medical records (Systematic®) and the Danish National Pathology Data Bank from March to July 2021. The Danish National Pathology Data Bank provided cytology, HPV-testing, and histopathology results for colposcopic-guided punch biopsies, and cervical excision specimens. Medical records contributed demographic and clinical data, including age, menopausal status, hormone therapy, smoking habits, and HPV vaccination status.

Both cytology and histology were analyzed at the Department of Pathology. Cytology slides were interpreted and classified by cytotechnicians using computer-assisted microscopy (BD, Focal-Point GS Imaging System) and categorized per the Bethesda 2014 grading system [23]. HPV DNA testing was performed using Cobas 4800 (Roche Diagnostic) providing individual detection of HPV 16 and 18 and pooled detection of 12 other oncogenic HPV types [24].

Histology was evaluated according to the cervical intraepithelial neoplasia (CIN) classification [25] into normal, CIN1, and CIN2+ (CIN2, CIN3, Unclassifiable CIN, and adenocarcinoma in situ (AIS)). The term unclassifiable CIN was used when the full height of the epithelium was not distinguishable. Clinically it was managed as CIN2.

Cervical stenosis was defined as narrowing that prevented endocervical brush-sampling (Rovers Cervex-Brush®) at any time after cervical excision during the study period. Stenosis management was classified into'no intervention', 'dilatation in colposcopy clinic', or 'dilatation in day surgery unit'. In case of recurrence of dysplasia that required repeat cervical excision or hysterectomy, data collection termineded at the intervention date.

### *Statistics*

Data was entered and stored within REDCap (Vanderbilt University, Nashville, Tennesse, United States). Statistical analyses were conducted utilizing GraphPad Prism 10 (GraphPad Software, 2023, Boston, Massachusetts, United States). Continuous variables were reported as medians and interqurtile ranges (IQR), while categorial variables were presented as numbers and percentages. For binary outcomes, relative risk with corresponding 95 % confidence intervals was calculated. The Mann-Whitney *U* test was employed for continuous variables, and the $chi^2$-test for categorical variables. P-value less than 0.05 were considered statistically significant.

## Results

During the study period 567 patients aged ≥45 years underwent cervical excision (Fig. 1). Following the study exclusions of 267 patients (47 %), 300 postmenopausal patients with median age of 62 years (IQR: 55–68 years) were included for analysis (Table 1).

The majority of patients (61.7 %) exhibited high-grade squamous intraepithelial lesion (HSIL) or atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion (ASCH) in the referral cytology test preceding cervical excision, while 19.3 % of patients exhibited low-grade squamous intraepithelial lesion (LSIL) or atypical squamous cells of undetermined significance (ASCUS). Another 15.3 % exhibited either a positive HPV-test only or a positive HPV-test in conjunction with normal cytology. Prior to cervical excision, CIN2+ was detected in 143 patients (47.7 %), while 44.7 % had either no biopsies or non-representative biopsies. Examination of cervical excision specimens revealed 209 patients (69.7 %) had negative margins, while 91 patients (30.3 %) had positive or uncertain margins (Table 1).

Subsequent to cervical excision, 79 patients (26.3 %) developed either complete or partial stenosis (Table 2). This proportion increased to 40.1 % (n = 79/197) when the analysis was confined to patients monitored only within our department. (Data not tabulated). Cervical canal dilatation was performed in 67.1 % (n = 53/79) of patients with cervical stenosis, with 30 patients (38.0 %) receiving the procedure under local anesthesia in the outpatient clinic, and 23 patients (29.1 %) undergoing cervix dilatation in the day surgery unit under general or local anesthesia with sedation.

Patients who developed stenosis were significantly older than patients without stenosis (median age: 64 vs 61 years, p = 0.004) (Table 2). Among patients > 60 years at the time of cervical excision, there was an increased risk of stenosis (RR 1.51 (95 % CI: 1.08–2.18)) compared to those ≤60 years. A smaller proportion of patients who developed stenosis were smokers (15.2 % vs. 24.4 %, $p < 0.001$).

During the follow-up period, patients with stenosis were less likely to exhibit a normal cytology result (64.6 %) compared to those without

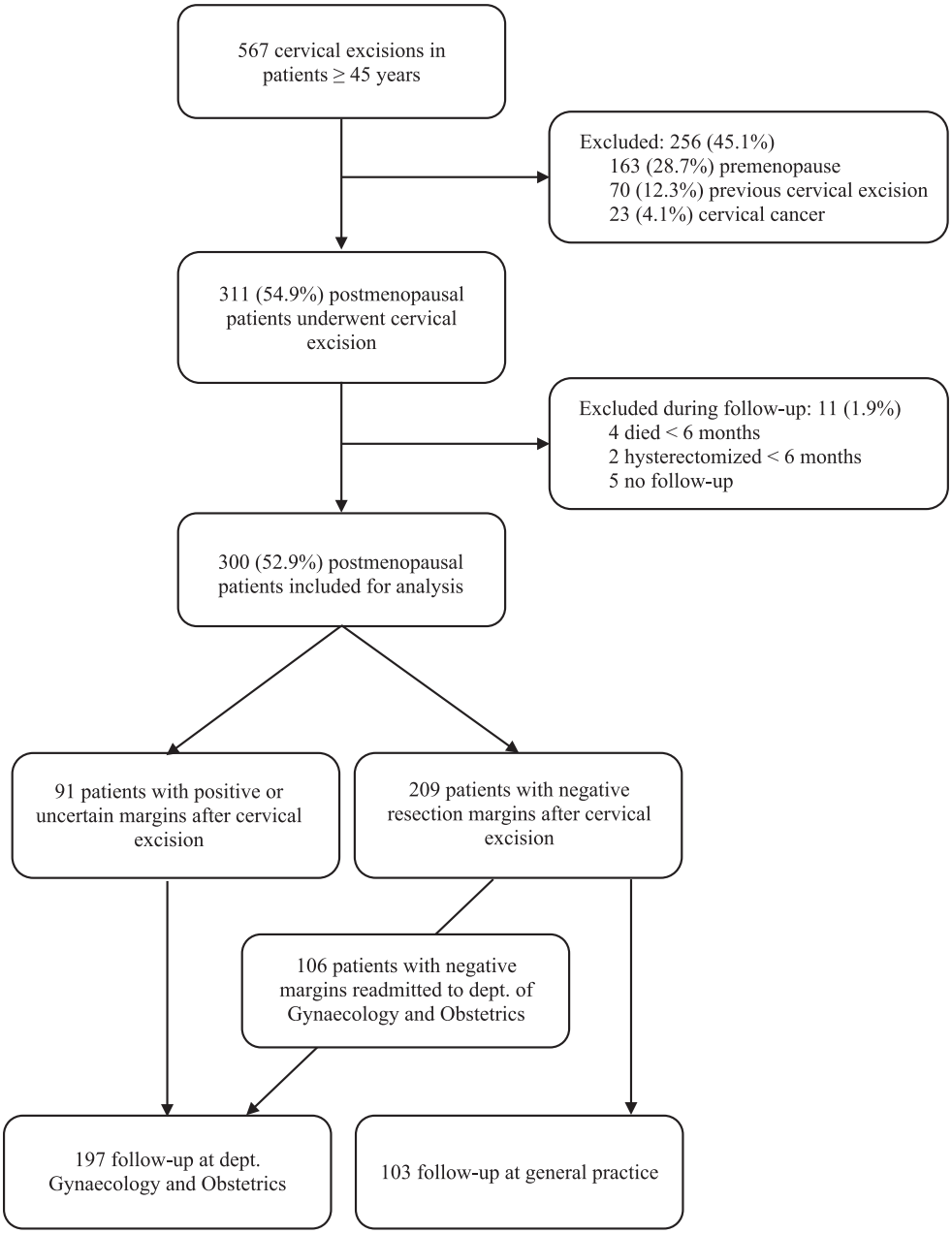


**Fig. 1.** Flow chart of patients included in the study.

stenosis (79.2 %, $p = 0.03$) Additionally, there was a higher incidence of unsatisfactory cytology tests (ie. Too few squamous or columnar epithelial cells) among patients with stenosis (11.4 %) versus those without (1.8 %) (Table 2).

Notably, 91 patients (30.3 %, n = 91/300) who underwent cervical excision presented with normal histopatholgy results. Within this group, 40 patients (44.0 %, n = 40/91) had previously shown HSIL in cervix cytology (Table 3). Analysis of cervical excision specimens from these patients indicated full representation of the TZ in 33 cases and partial representation in five. In two instances, the depth of excision was insufficient to adequately represent the TZ (data not tabulated).

## Discussion

### *Main findings*

Our study demonstrated that cervical stenosis was considerable common, as more than every fourth postmenopausal patient (26.3 %) who underwent cervical excision developed cervical stenosis. This percentage raised to 40.1 % when the analyses was limited to patients receiving follow-up only at the Gynaecological Department. Advanced age emerged as the primary risk factor for cervical stenosis development, while the risk was independent of the histological outcome of the cervical excision specimen. Remarkably, 40.6 % of postmenopausal patients were subject to overtreatment with cervical excision, as evidenced by normal histology or CIN1 in their excision specimens.

### *Strengths and limitations*

The study's principal strength lies in the access to national registries, ensuring comprehensive test results encompassing cytology, HPV-testing, and histology. However, there are some limitations that should be addressed. Data retrieval from medical records after cervical excision was feasible for only two-thirds of patients (65.7 %), with the

**Table 1**
Basic characteristics for the study population (n = 300).

| | |
|---|---|
| **Median age in years (IQR)** | 62.0 (55.0–68.0) |
| **Menopausal status** | |
| Postmenopausal | 286 (95.3) |
| Menopausal status unknown | 14 (4.7) |
| **Smoking,** *n* (%) | |
| Yes | 66 (22.0) |
| No | 153 (51.0) |
| Unknown | 81 (27.0) |
| **HPV-vaccination,** *n* (%) | |
| Yes | 22 (7.3) |
| No | 127 (42.3) |
| Unknown | 151 (50.3) |
| **Local hormone used at the time of cervical excision,** *n* (%) | |
| Yes | 54 (18.0) |
| No | 175 (58.3) |
| Unknown | 721 (23.7) |
| **Referral test**, *n* (%) | |
| Abnormal cytology | |
| *ASCUS* | 38 (12.7) |
| *LSIL* | 20 (6.7) |
| *ASCH or HSIL* | 185 (61.7) |
| *AGC or AIS* | 4 (1.3) |
| HPV-test only or positive HPV-test and normal cytology | |
| *HPV 16/18* | 28 (9.3) |
| *HPV 16/18 and HPV other* | 9 (3.0) |
| *HPV other* | 9 (3.0) |
| Other indication for cervical excision | 7 (2.3) |
| **Histopathology, punch biopsies,** *n* (%) | |
| Normal/CIN1 | 23 (7.7) |
| CIN2 | 22 (7.3) |
| AIS/CIN3 | 69 (23.0) |
| CIS | 3 (1.0) |
| Unclassifiable CIN | 49 (16.3) |
| Non-representative | 82 (27.3) |
| Biopsies not performed | 52 (17.3) |
| **Excision method,** *n* (%) | |
| Loop electrode | 231 (77.0) |
| Linear electrode | 69 (23.0) |
| **Resection margins,** *n* (%) | |
| Negative margins | 209 (69.7) |
| Positive margins/margins cannot be evaluated | 91 (30.3) |
| **Median height of the cervical excision (mm)** *missing data 11 cervical excisions* | 12.67 (11.26–14.08) |

Abbreviations: *AGC* Atypical Glandular Cells, *ASCH* Atypical Squamous Cells, cannot exclude High-grade, *ASCUS* Atypical Squamous Cells of Undetermined Significance, *CIN* Cervical Intraepithelial lesions, *HPV* Human Papilloma Virus, *HSIL* High-grade Squamous Intraepithelial Lesion, *IQR* Inter quartile range, *LSIL* Low-grade Squamous Intraepithelial Lesion.

remainder undergoing follow-up at their general practitioner, potentially leading to an underestimation of the true prevalence of cervical stenosis. The retrospective design of the study resulted in missing data for smoking, vaccination status, and hormone usage. Furthermore, a large proportion of patients (n = 28.7 %) aged ≥45 years who underwent cervical excision were excluded due to premenopausal status. In most cases the medical journal held information on menopausal status or time of last menstrual period, with only a few missing values (n = 14/567, 2.5 %).

**Table 2**
Risk factors for cervical stenosis.

| No stenosis, n = 221 | | Stenosis, n = 79 | RR (95 % CI) | P-value |
|---|---|---|---|---|
| **Median age in years (IQR)** | 61.0 (54.5–67.0) | 64.0 (58.0–71.0) | | *P = 0.004* |
| **Age groups,** *n* (%) | | | | |
| >60 years | 115 (52.0) | 54 (68.4) | 1.51 (1.08–2.18) | |
| ≤60 years | 106 (48.0) | 25 (31.6) | | |
| **Smoking,** *n* (%) | | | | |
| Yes | 54 (24.4) | 12 (15.2) | | *P < 0.001* |
| No | 96 (43.4) | 57 (72.2) | | |
| Missing | 71 (32.1) | 10 (12.7) | | |
| **HPV-vaccination,** *n* (%) | | | | |
| Yes | 17 (7.7) | 5 (6.3) | | *P = 0.03* |
| No | 84 (38.0) | 43 (54.4) | | |
| Missing | 120 (54.3) | 31 (39.2) | | |
| **Local hormone,** *n* (%) | | | | |
| Yes | 40 (18.1) | 14 (17.7) | | *P = 0.77* |
| No | 131 (59.3) | 44 (55.7) | | |
| Missing | 50 (22.6) | 21 (26.6) | | |
| **Excision method,** *n* (%) | | | | |
| Loop electrode | 175 (79.2) | 56 (70.9) | | *P = 0.16* |
| Linear electrode | 46 (20.8) | 23 (29.1) | | |
| **Resection margins,** *n* (%) | | | | |
| Negative margins | 164 (74.2) | 45 (57.0) | 0.5 (0.40–0.83) | *P = 0.006* |
| Positive margins/not evaluated | 57 (25.8) | 34 (43.0) | | |
| **Median height of the cervical excision (mm)** *Missing data 11, no cervical stenosis n = 217, cervical stenosis n = 73* | 12.63 (8.22–17.04) | 12.81 (7.70–17.92) | | *P = 0.77* |
| **Histopathological results in cervical excisions,** *n* (%) | | | | |
| Normal | 67 (30.3) | 24 (30.4) | | *P = 0.99* |
| Abnormal | 154 (69.7) | 55 (69.6) | | |
| CIN1 | 22 (10.0) | 9 (11.4) | | |
| CIN2+[a] | 132 (59.7) | 46 (58.2) | | |
| **Cytology and HPV-test at 6 months follow-up** | | | | |
| HPV-test | | | | |
| Negative | 126 (57.0) | 36 (45.6) | | *P = 0.09* |
| Positive | 73 (33.1) | 37 (46.9) | | |
| *HPV 16/18* | 20 (9.1) | 16 (20.3) | | |
| *HPV other* | 53 (24.0) | 21 (26.6) | | |
| *Missing* | 22 (10.0) | 6 (7.6) | | |
| Cytology | | | | |
| Normal | 174 (78.7) | 51 (64.6) | | *P = 0.03* |
| Abnormal | 22 (10.0) | 15 (19.0) | | |

(*continued on next page*)

**Table 2** (*continued*)

| No stenosis, n = 221 | | Stenosis, n = 79 | RR (95 % CI) | P-value |
|---|---|---|---|---|
| *ASCUS/LSIL* | 15 (6.8) | 10 (12.7) | | |
| *HSIL/ASCH* | 7 (3.2) | 5 (6.3) | | |
| Missing | 21 (9.6) | 4 (5.1) | | |
| Unsatisfactory cytology | 4 (1.8) | 9 (11.4) | | |

Abbreviations: *ASCH* Atypical Squamous Cells, cannot exclude High-grade, *ASCUS* Atypical Squamous Cells of Undetermined Significance, *CIN* Cervical intraepithelial lesions, *HSIL* High-grade Squamous Intraepithelial Lesion, *HPV* Human Papilloma Virus, *IQR* Inter quartile range, *LSIL* Low-grade Squamous Intraepithelial Lesion.

[a] *CIN2+* is defined as unclassifiable CIN, CIN grades 2 and 3, and Adenocarcinoma in situ.

**Table 3**
Histopathological results detected in cervical excisions compared with referral test.

| Histology | Referral test | | | | |
|---|---|---|---|---|---|
| | Abnormal cervical cytology, n = 247 | | HPV-test only or positive HPV-test and normal cytology, n = 46 | | Other indication[a], n = 7 |
| | ASCUS/ LSIL | HSIL+[b] | HPV 16/ 18 | HPV other | |
| Normal | 19 | 40 | 26 | 4 | 2 |
| CIN1 | 10 | 16 | 2 | 1 | 2 |
| CIN2+ [c] | 29 | 133 | 9 | 4 | 3 |

Abbreviations: *ASCUS* Atypical Squamous Cells of Undetermined Significance, *CIN* Cervical Intraepithelial lesions, *HPV* Human Papilloma Virus, *HSIL* High-grade Squamous Intraepithelial Lesion, *LSIL* Low-grade Squamous Intraepithelial Lesion.

[a] Broad cervical polyp, postcoital bleeding.

[b] HSIL+ is defined as High-grade squamous intraepithelial lesions, Atypical Squamous Cells, cannot exclude High-grade, atypical glandular lesions or adenocarcinoma in situ.

[c] CIN2+ is defined as unclassifiable CIN, CIN grades 2 and 3, and Adenocarcinoma in situ.

### *Interpretation*

We found that the risk of cervical stenosis in postmenopausal patients after their first cervical excision was 26.3 %. This is roughly in the mid-range of what previous studies have shown. A retrospective study reported a stenosis development rate of 10.6 % after straight wire cervical excision in patients ≥46 years (n = 141) [15]. This study did not differentiate between pre- and postmenopausal subjects, which likely accounts for the lower stenosis frequency relative to our findings. Conversely, a randomised controlled trial (RCT), which investigated cervical stenosis prevention after loop cervical excision in postmenopausal patients, identified a stenosis incidence of 39.3 % (n = 117) [26]. It is somewhat higher than our results, possibly due to inclusion of patients with multiple cervical excisions.

Both our study and other research have found that increasing age is a risk factor for stenosis development after cervical excision [11–15]. In postmenopausal patients, a significant decrease in estrogen level leads to atrophy and shrinkage of the epithelial cells. Furthermore, postmenopausal patients lack the natural dilation of the cervical canal by menstrual blood which contributes to the risk of cervical stenosis [15]. Hormone replacement therapy has been associated with a reduced incidence of cervical stenosis [14,16]. The potential beneficial effect of locally administered estrogen in stenosis prevention remains speculative, as current studies lacks sufficient data regarding this matter. However, an ongoing RCT (EU Clinical Trials Register. EudraCT Number: 2022-000269-42) will hopefully provide answer to this question.

Some studies indicate that deep excisions with cone heights exceeding 16.5–20 mm increases the risk of stenosis development [11,12,26]. Our analysis revealed no apparent difference in cone height between patients with and without cervical stenosis, with an average excision depth of 12.7 mm, slightly below the measurements in the above-mentioned studies.

Our finding suggests a correlation between stenosis development and positive resection margins along with abnormal cytology at 6 month follow-up. Postive margins and persistent HPV infection are recognized predictors of recurrent disease [4]. Nonetheless, our observations may indicate that patients with negative margins and no HPV infection at follow-up were predominantly evaluated in general practice. Surprisingly, it is relatively common to obtain a representative test-of-cure sample from the exocervix in cases of partial or even complete stenosis. If cytology is normal and HPV-test is negative, general praticioner may not refer the patient for stenosis intervention, given its often asymptomatic nature. In our clinic, a group of patients with stenosis did not undergo cervical dilatation, primarily due to negative HPV-tests from the exocervix (85 %), highlighting a clinical challenge, as lesions within the cervical canal or uterine cavity may be missed due to stenosis.

Histological examination of cervical excision specimens surprisingly showed that 30.3 % were normal. Additionally, 10.3 % of patients were diagnosed with CIN1 within the cervical specimen. Indeed, our study suggests that 40.6 % of patients were subjected to unnecessary cervical excision. Furthermore, 40 patients (21.6 %, n = 40/185) exhibited no dysplasia in their excision specimen even though their cytology test showed HSIL. The TZ was fully represented in the majority of these cases. This emphasizes the diagnostic challenge in differentiating dysplasia from atrophy in cytology tests among postmenopausal patients, as both conditions exhibit immature cellular characteristics and an increased nuclear to cytoplasmic ratio, thereby complicating accurate diagnosis [27].

Clinical management of screen-positive postmenopausal patients is complex. On one hand, there exists a potential risk of undiagnosed dysplasia during colposcopy, which increases the risk of subsequently cervical cancer development. On the other hand, there is the risk of overtreatment when diagnostic cervical excision is performed, and the risk of subsequent stenosis development, which complicates future follow-up. Hence, a retrospective case series of postmenopausal patients who underwent hysterectomy for postsurgical cervical stenosis found histopathological abnormalities in 47.2 % (17) [18]. Preoperatively, none of these patients had high-grade cytological abnormalities in ectocervical obtained cytology test or abnormal ultrasound findings. Notably, we demonstrated that patients with cervical stenosis present significant challenges in obtaining reliable cytology results during follow-up, as the incidence of unsatisfactory cytology test was considerably higher (11.4 % vs. 1.8 %).

The HPV prevalence among older Danish women is 4.3 % [28], and implementation of the current HPV screening has precipitated a substantial rise in colposcopies and cervical excisions within this age group. A see-and-treat study suggests that HPV positive patients with normal cytology might be suitable for follow-up, whereas those with additional ASCUS/LSIL/HSIL in their cytology should undergo cervical excision [6]. To guide the clinical management, P16/Ki67 dual-stain cytology has been proposed as a useful risk marker, with suggestions that dual-stain negative patients with a TZ3 could safely be monitored with repeated cervical sampling rather than diagnostic cervical excision [29]. In the future improved risk stratification is essential to determine patients who are better candidates for follow-up with repeated cervical sampling as opposed to diagnostic cervical excision.

## Conclusion

More than every fourth postmenopausal patient who underwent cervical excision developed cervical stenosis and the risk increased significantly with age. Therefore, postmenopausal patients should be

adequately informed about the potential risk of cervical stenosis development prior to cervical excision and particularly when counselling on the choice between diagnostic cervical excision or continued conservative follow-up. Biomarkers may prove valuable in customised follow-up programmes, yet a deeper understanding of their clinical utility in postmenopausal patients is needed.

## CRediT authorship contribution statement

**Eva Hauge:** Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization. **Line Winther Gustafson:** Writing – review & editing, Visualization, Formal analysis. **Mette Tranberg:** Writing – review & editing, Visualization, Formal analysis. **Pinar Bor:** Writing – review & editing, Visualization, Supervision, Formal analysis, Conceptualization.

## Ethics approval

This study received approval by the Regional Ethics Committee in Central Denmark Region on the 8th of marts 2021, reference number 723,811 and journal number 1-16-02-147-2.

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## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Line Winther Gustafson reports a relationship with Roche that includes: funding grants. Mette Tranberg reports a relationship with Roche that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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