Long-term incidence of endometrial cancer after endometrial resection and ablation: A population based Swedish gynecologic cancer group (SweGCG) study

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Abbreviations: EA, endometrial ablation; EC, endometrial cancer; GynOp, National Quality Register of Gynecological Surgery; ICD, International Statistical Classification of Diseases and Related Health Problems; NCR, National Cancer Registry; NPR, National Patient Registry; SIR, standardized incidence ratio; TCRE, transcervical resection of the endometrium.

Abstract

Introduction: Minimally invasive methods to reduce menorrhagia were introduced in the 1980s and 1990s. Transcervical endometrial resection (TCRE) and endometrial ablation (EA) are two of the most frequently used methods. As none of them can guarantee a complete removal of the endometrium, there are concerns that the remaining endometrium may develop to endometrial cancer (EC) later in life. The primary aim was to analyze the long-term incidence of EC after TCRE and EA in a nationwide population. The secondary aim was to assess the two treatment modalities separately.

Material and Methods: The Swedish National Patient Registry and National Quality Registry for Gynecological Surgery were used for identification of women who had...
TCRE or EA performed between 1997–2017. The cohort was followed from the first TCRE or EA until hysterectomy, diagnosis of EC, or death. Follow-up data were retrieved from the National Cancer Registry and the National Death Registry. Expected incidence for EC in Swedish women was calculated using Swedish data retrieved from the NORDCAN project after having taken into account differences of age and follow-up time. Cumulative incidence of EC after TCRE and EA, was calculated. A standardized incidence ratio was calculated based on the expected and observed incidence, stratified by age and year of diagnosis.

**Results:** In total, 17,296 women (mean age 45.1 years) underwent TCRE (n = 8,626) or EA (n = 8,670). Excluded were 3,121 who had a hysterectomy for benign causes during follow up. During a median follow-up time of 7.1 years (interquartile range 3.1–13.3 years) the numbers of EC were 25 (0.3%) after TCRE and 2 (0.02%) after EA, respectively. The observed incidence was significantly lower than expected (population-based estimate) after EA but not after TCRE, giving a standardized incidence ratio of 0.13 (95% confidence interval [CI] 0.03–0.53) after EA and 1.27 (95% CI 0.86–1.88) after TCRE. Median times to EC were 3.0 and 8.3 years after TCRE and EA, respectively.

**Conclusions:** There was a significant reduction of EC after EA, suggesting a protective effect, whereas endometrial resection showed an incidence within the expected rate.

**Key words**
endometrial ablation, endometrial cancer incidence, endometrial cancer risk, menorrhagia, transcervical endometrial resection

## 1 | INTRODUCTION

Transcervical hysteroscopic resection of the endometrium (TCRE) was introduced in the 1980s and was initially offered as an alternative to hysterectomy and to women with anesthesiological or surgical contraindications for hysterectomy.\(^1\)\(^-\)\(^3\) TCRE is a procedure that removes the endometrium with an electrosurgical wire loop under direct visual control.

During the 1990s, non-hysteroscopic ablative techniques of endometrial destruction (endometrial ablation; EA) were developed, which were less dependent on the availability of experienced hysteroscopy surgeons, faster, and considered safer. EA is a procedure that destroys the lining of the endometrium. The method may include cold or heated fluids, microwave energy, or high-energy radiofrequencies. The indications for the procedure expanded to include women who experienced heavy menstrual bleeding without objective signs and symptoms, such as anemia and measured blood loss greater than 80 mL per menstrual period.\(^4\)

Despite endometrial resection or ablation, some patients (10%–15%) end up with a hysterectomy within a few years because of abdominal pain and/or a benign diagnosis (fibroids or abnormal uterine bleeding).\(^5\)\(^,\)\(^6\)

As neither TCRE nor EA guarantees a complete removal of the endometrium, there are concerns that the remaining endometrium may develop to endometrial cancer (EC) later in life. The diagnosis of EC may be delayed because of adhesions masking the symptoms of bleeding/discharge.\(^7\)\(^-\)\(^9\) Some of the medical conditions where TCRE or EA are chosen instead of hysterectomy are obesity and diabetes mellitus,\(^10\) conditions which also have the potential to influence the risk of developing EC.\(^11\)\(^,\)\(^12\)

EC is the most common gynecological cancer in the industrialized world, with approximately 400,000 women diagnosed annually worldwide.\(^13\)\(^,\)\(^14\) In Sweden, EC accounts for 4.5% of all cancer in women with 1325 new cases in 2019.\(^13\)

Some studies have addressed the risk of EC after TCRE and EA and found no increased risk.\(^5\)\(^,\)\(^16\)\(^-\)\(^18\) nor was there any delay in diagnosis when comparing EA and medical management in a retrospective cohort study.\(^19\)
The primary aim of the present study was to analyze the incidence of EC after TCRE and EA in a nationwide population and the secondary aim was to assess the long-term risk of EC after each of the two treatment modalities.

2 | MATERIAL AND METHODS

2.1 | Study cohort

The present register-based retrospective observational cohort study analyzed follow-up data from women who underwent TCRE or EA in Sweden between January 1, 1997 and December 31, 2017. The follow up was from the date of the first TCRE or EA to hysterectomy, EC, death, or the end of the study December 31, 2017.

The study population was identified from two national data sources: The National Patient Registry (NPR), representing the main source, and National Quality Register of Gynecological Surgery (GynOp), with TCRE or EA performed between 1997 and 2017.

2.2 | Data sources

In Sweden, all citizens, since 1947, are allocated a unique personal identification number at birth or immigration enabling official registers and research. Data were collected from four Swedish national registers; the NPR, the GynOp, the National Cancer Registry (NCR), and the National Death Registry.

The NPR is a comprehensive national register at the National Board of Health and Welfare, established in 1964. Registration is mandatory for every healthcare provider of inpatient care and for those of outpatient specialized care clinics. From 1987, the register of inpatient care has been comprehensive. Visits to doctors in specialized outpatient care have been reported since 1997. The NPR contains information about hospital admission and discharge diagnoses according to the WHO International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) and surgical codes according to the Swedish Classification of Operations and major procedures. Women who underwent TCRE (surgical codes LCB28) and EA (LCA16, LCB32) between January 1, 1997 and December 31, 2017 were identified. Women who had a surgical operation after TCRE or EA that could affect the risk of developing EC such as subtotal hysterectomy (LCC10, LCC11, LCC20, MCA30) and total hysterectomy (LCDO00, LCDO1, LCD10, LCD11, LCD96, LCD97, LCD04, LCD30, LCD31, LCD40, LEF 13) were excluded.

The NCR was established in 1958. Reporting to the register is mandatory. The register has over 95% coverage of all malignant tumors and 99% are morphologically verified. Tumors are classified according to the WHO version ICD-7 to the International Classification of Diseases for Oncology (ICD-O/3.2). Linkage to the National Cause of Death Registry ensures lifelong follow up and provides date of death. By using the personal identity numbers, all women diagnosed with EC (version ICD-O/2 to ICD-O/3.2; C54.0–9) between January 1, 1997 and December 31, 2017 from the NCR were identified and included in the study. To ensure that women did not have undiagnosed EC before TCRE and EA, women diagnosed with EC within a maximum of 3 months after the intervention were excluded in the analysis to exclude those with an EC diagnosis at surgery. The women were followed up to hysterectomy, EC, death, or end of study December 31, 2017, whichever came first, via the NCR and NPR.

The GynOp Register collects preoperative, intraoperative, and postoperative information on women undergoing gynecological surgery. The registration in GynOp concerning the studied surgical interventions was implemented in 2012 and in 2017, 59% of the performed TCRE and EA in NPR were also registered in GynOp. Registered TCRE and EA were retrieved between 2012 and 2017. In 2015–2017, 38 out of 50 clinics (not complete coverage of private clinics) reported EA and TCRE to the GynOp register. The data in the GynOp were matched with the NR and used in the additional subgroup analyses. Data in the GynOp are collected by medical doctors, on paper or on-line and patient questionnaires are administered as part of the routine medical care. From the GynOp we retrieved descriptive data regarding age, body mass index (BMI), uterine size (probe measurement), and physical status according to the American Society of Anesthesiologists (ASA) scoring system.

2.3 | Statistical analyses

Descriptive data are presented as medians with interquartile ranges (IQR) or numbers and percentages. Differences of medians were tested using the Wilcoxon rank-sum test. Follow-up time was calculated from the date of the first TCRE or EA performed to the first of the following events: hysterectomy, EC, death, or end of study December 31, 2017.

The standardized incidence ratio (SIR) was defined as the observed number of EC during the observation time divided by the expected number of cases, using incidence rates from the Swedish population stratified for 5-year age groups (0–4, 5–9,... 80–84, 85+), gender and calendar year. Incidence rates for EC in Sweden were calculated by use of competing risk analysis. EC or death were competing events and the end of the study was a censoring event. The Stata macro “strate”, originally written by David Clayton and Michael Hills, was used for calculation of SIR. The observed and expected numbers of EC were plotted as cumulative incidence by follow-up time up to 20 years.

Cumulative incidence of hysterectomy after TCRE or EA was calculated by use of competing risk analysis. EC or death were competing events and the end of the study was a censoring event. The Stata program macro “stcrprep” written by Paul Lambert was used to prepare data for estimating cumulative incidence and performing a log rank test.

In a subgroup analysis, univariate and multivariate Poisson regressions were performed to analyze explanatory factors for the choice of endometrial ablative procedure, TCRE or EA.
All statistical tests were two-sided, and a p value less than 0.05 was considered statistically significant. Statistical analyses were carried out with Stata/MP 16.1 for Mac (Intel 64-bit, StataCorp LLC).

2.4 | Ethical approval

The study was approved on November 20, 2015 by the ethical review board at Gothenburg University, Sweden (D.no 814–15) with an amendment (T1108-18) approved on December 10, 2018.

3 | RESULTS

The NPR and GynOp identified 17 488 women with codes for TCRE and EA operations. Out of them, 31 were excluded because of misclassification where 12 women had a date for hysterectomy before the date of endometrial operation and 19 had a date of EC before the date of TCRE or EA. In addition, 161 were excluded because of a date of EC diagnosis within 90 days after TCRE/EA, leaving 17 296 for follow up. There were no women with EC in the histopathological report within 90 days after hysterectomy. The median follow up for the cohort was 7.1 years (IQR 3.1–13.3 years).

In total, 17 296 women underwent minimally invasive endometrial surgery during the study period encompassing TCRE (n = 8626) and EA (n = 8670) (Table 1). In our total cohort of 17 296 women from the NPR, 15% of performed surgeries were reported to the GynOp between 2007 and 2017. In the GynOp 2531 women were identified with ICD codes for TCRE (1692; 66.8%) and EA (839; 33.2%). The median age at surgery for the total cohort was 45.1 years, with a statistically significant difference between TCRE and EA (p < 0.001). EA was more often used than TCRE in the age groups 30–39 and 40–49 years, whereas TCRE was used more often than EA in the age groups 50–59 and 60–69 years (Table 1).

3.1 | Follow up

During the 20-year study period, the total follow-up time covered 126 376 woman-years (61 510 woman-years for TCRE and 64 867 woman-years for EA). During follow up, 3121 (18%) of the women had a hysterectomy for indications other than EC, whereof

| Age at MIS (years) | Total cohort n = 17 296 | TCRE n = 8626 | EA n = 8670 |
|-------------------|------------------------|--------------|------------|
| Median (IQR)      | 45.1 (41.0–49.2)       | 46.2 (42.0–51.3) | 44.2 (40.5–47.8) |
| <30               | 258 (1.5%)             | 139 (1.6%)   | 119 (1.4%) |
| 30–39             | 3123 (18.1%)           | 1321 (15.3%) | 1812 (20.9%) |
| 40–49             | 10 140 (58.6%)         | 4557 (52.8%) | 5583 (64.4%) |
| 50–59             | 2753 (15.9%)           | 1693 (19.6%) | 1060 (12.2%) |
| 60–69             | 589 (3.4%)             | 529 (6.1%)   | 60 (0.7%) |
| 70–79             | 314 (1.8%)             | 287 (3.3%)   | 27 (0.3%) |
| 80–89             | 109 (0.6%)             | 100 (1.2%)   | 9 (0.1%) |

Status at end of follow up

|                     | Total cohort n = 17 296 | TCRE n = 8626 | EA n = 8670 |
|---------------------|------------------------|--------------|------------|
| Hysterectomy        | 3121 (18.0%)           | 1565 (18.1%) | 1556 (18.0%) |
| Endometrial cancer  | 27 (0.2%)              | 25 (0.3%)    | 2 (0.02%) |
| Death               | 441 (2.6%)             | 278 (3.2%)   | 163 (1.9%) |
| Alive December 31, 2017 | 13 707 (79.2%) | 6 758 (78.3%) | 6 949 (80.2%) |

Time to hysterectomy (years)

|                     | Median, IQR            |            |
|---------------------|------------------------|------------|
|                     | 1.3, 0.5–3.2           | 1.1, 0.5–2.8 | 1.5, 0.7–3.6 |

Time to endometrial cancer (years)

|                     | Median, IQR            |            |
|---------------------|------------------------|------------|
|                     | 3.5, 1.1–9.8           | 3.0, 1.1–6.9 | 8.3, 5.2–11.4 |

Time to death (years)

|                     | Median, IQR            |            |
|---------------------|------------------------|------------|
|                     | 7.8, 3.8–12.2          | 7.5, 3.6–11.8 | 8.6, 4.1–12.8 |

Time to alive at end of follow up (years)

|                     | Median, IQR            |            |
|---------------------|------------------------|------------|
|                     | 7.1, 3.1–13.3          | 6.9, 3.1–11.8 | 7.3, 3.1–13.8 |

Abbreviations: EA, endometrial ablation; IQR, interquartile range; MIS, minimally invasive surgery; TCRE, transcervical resection of the endometrium.

Age significantly lower in the EA group compared with TCRE p < 0.001 (two-sided Wilcoxon rank-sum test).
1565 were performed after TCRE and 1556 after EA. The median time to hysterectomy was for the total cohort 1.3 years (IQR 0.5–3.2), for TCRE 1.1 years (IQR 0.5–2.8 years), and for EA 1.5 years (IQR 0.7–3.6 years) (Table 1 and Figure 1).

By the end of the follow-up period a total of 441 (2.6%) women had died, 278 (3.2%) in the TCRE group and 163 (1.9%) in the EA group. The median time to death in the total cohort was 7.8 years (IQR 3.8–12.2 years), 7.5 years (IQR 3.6–11.8 years) after TCRE and 8.6 years (IQR 4.1–12.8 years) after EA. By the end of the study, December 31, 2017, 13 707 (79.2%) women were alive; 6758 (78.3%) after TCRE and 6949 (80.2%) after EA (Table 1).

3.2 | Endometrial cancer incidence

During the follow up, 27 (0.2%) women developed EC, 25 (0.3%) after TCRE and 2 (0.02%) after EA. The median time to EC diagnosis was 3.5 years (IQR 1.1–9.8 years) in the total cohort, 3.0 years (IQR 1.1–6.9 years) after TCRE, and 8.3 years (IQR 5.2–11.4 years) after EA. The median age at diagnosis of EC was 63.8 years (IQR 56.9–71.4 years) (Table 2). The age-standardized SIR (95% CI) based on expected incidence and observed incidence of EC was 0.78 (95% CI 0.53–1.13) after total follow up in TCRE/EA methods combined. After TCRE the total SIR was 1.27 (95% CI 0.86–1.88) and after EA it was 0.13 (95% CI 0.03–0.53) (Table 2 and Figure 2). During the first 5 years after TCRE there was a significantly increased risk of EC with an SIR of 2.87 (95% CI 1.79–4.62) (Table S1).

All EC except one (serous) were of endometrioid histology. Nineteen out of 27 were diagnosed as International Federation of Gynecology and Obstetrics (FIGO) Stage I, one as Stage II, and two each as Stage III and IV, respectively. Data regarding FIGO stage was missing in three patients. For further information regarding the individual characteristics of women with EC after TCRE/EA see Table S2.

3.3 | Factors associated with choice of surgical method

Data on preoperative variables (BMI, ASA score, intruterine probe measurement) were found in 767 women in the GyNo register. These variables and age were entered in a univariable Poisson regression model and showed that TCRE (n = 476) was used more often than EA (n = 291) in women aged 50 years or older (p < 0.001) and EA was used more often in women with a larger uterus (probe measurement ≥10 cm) (p = 0.007) (Table S3). In the multivariable Poisson regression model, age was the strongest independent factor for the choice of method. Further, there was a tendency, although not significant, for ASA score 3–4 and uterine size to be of importance for the choice of surgical method, when adjusted for age (p = 0.08) (Table S3).

4 | DISCUSSION

To our knowledge, this is the largest study exploring the long-term incidence of EC after TCRE and EA. We found that the age SIR of EC was significantly lower than expected after EA methods. TCRE showed neither a reduction nor an increase in risk of EC.

Endometrial ablation appears to be protective against EC, which has also been reported by Soini et al.5 who performed a nationwide long-term follow up after EA in Finland in 1997–2014. However, their study, as well as our study, lacked data on the specific devices used. In addition, TCRE in our study showed the same risk of EC as in the general population. This is consistent with Neuwirth et al.16 who followed 509 women after TCRE. Our data raise several questions about what differentiates the TCRE method from EA methods in terms of patient selection and effects on the uterus and the endometrium.

Considering the indications for using TCRE or EA there may be a doctors’ bias in the choice of method based on the woman’s age or the size of the uterus and the surgeon’s preferences. In our study, more women over the age of 50 years received treatment with TCRE compared with EA. Further, we acknowledge that our cohort has not reached the highest incidence age for EC.14 Age is a known risk factor for EC and it may be reasonable to believe that an extended time to follow up would include an older study population with an increased risk of EC in both cohorts. However, we would like to emphasize that when we calculated the expected number of EC for both surgical methods and compared this with the observed number of EC, we did consider differences in age and follow-up time. According to our analysis, the expected number of EC after EA was estimated to be 15 cases but only two women developed EC during follow up. In addition, variables of interest like BMI and ASA-score at surgery, which to some but not full extent were coded in the registers, did not appear to deviate significantly between the cohorts (Table S3).

With reference to the idea that TCRE is a method depending on the skill and experience of the surgeon and most likely is used on fewer selective indications than EA it would be reasonable to
assume that TCRE is also less complete and reaches less deep into the myometrium and so leaves more endometrium in situ than EA methods. Further, one can hypothesize that a larger part of the endometrium located intramurally (for example adenomyosis) is left behind by TCRE, which potentially could lead to a poorer protection against EC. 29,30

We did not have complete control of known risk factors for EC in our cohort because of missing information in the registers. Probably women with obesity are more likely to be offered TCRE or EA than more invasive surgery. Further, as women undergoing EA or TCRE for heavy menstrual bleedings are likely to have increased BMI and other risk factors for EC in comparison with the general population this strengthens our results of a reduction in EC after EA. Different EA devices and time affecting the uterine wall may induce various thermal effects on the endometrium/myometrium, which may have an impact on the risk of developing EC later in life. However, as only two EC were found in the EA group, we have no reason to believe that those factors would have affected our results in a decisive way.

In our study approach, we neither had valid information concerning the quality of preoperative and postoperative investigations, nor the occurrence of simple, complex, or atypical endometrial hyperplasia. However, there are reasons to believe that a histopathological analysis of the resected endometrium was performed after TCRE whereas endometrial samples before EA are consistent with the recommendations according to clinical guidelines. The initial increase of EC incidence after TCRE registered during the first 5 years was unexpected. One can speculate whether precancerous changes could have been overlooked by the pathologist when the resected endometrium was analyzed after the TCRE.

The incidence of EC was not increased after TCRE and EA combined, which is consistent with other studies.16–18 Dood et al19 did not find any difference in EC incidence when comparing first- and second-generation EA methods with medical management. However, Dood et al19 and other investigators equate TCRE with various EA devices. In contrast to our study, none of the other investigators report results on TCRE and EA separately. Instead, data are presented only for TCRE,16 combining TCRE and EA17,18 or EA alone.5 We argue that TCRE and EA are different surgical methods with a common goal to achieve amenorrhea and should therefore be analyzed and reported separately.

Our results suggest that EA could be recommended as a primary non-medical and minimally invasive procedure for treatment of menorrhagia. An additional factor in favor of this recommendation is the
lower complication rate with EA procedures. The main strengths in our study are the large cohort followed for a sufficiently long time, the valid EC diagnosis due to complete coverage in the NCR, and most importantly the reporting of TCRE and EA separately. Not having a life-long follow up could be considered a limitation. However, we plan to extract new data at a later time-point. We do not have complete coverage on registered endometrial operations performed at private clinics. However, a majority of clinics do report to the NPR because there is a case-cost system in Sweden.

5 | CONCLUSION

Our results need to be confirmed by further studies with even longer follow up. If there is an indication and the woman consents to choose a non-hormonal minimally invasive surgical method to treat heavy menstrual bleeding, we suggest using EA to achieve a positive additive effect to the reduced menstrual bleeding. EA showed a significantly reduced EC incidence, suggesting a protective effect.

AUTHOR CONTRIBUTIONS

All authors designed the study and analyzed the results. EH extracted data and performed the statistical analyses. AFR, PDK, CB, and EH wrote the manuscript. All authors critically revised the manuscript, approved the final version and are accountable for all aspects of the work.

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CONFLICT OF INTEREST

Elisabeth Åvall-Lundqvist has received honoraria from Roche; and served on advisory boards for Astra Zeneca and Clovis Oncology. The other authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION
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