Long-term Follow-up after Endometrial Ablation in Finland: Cancer Risks and Later Hysterectomies

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Short Title: Cancer Risk After Endometrial Ablation

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Précis

Endometrial ablation is not associated with elevated endometrial cancer or breast cancer risk and most women treated with endometrial ablation do not need later hysterectomy in Finland.

Abstract

Objective: To study the risk for endometrial cancer and breast cancer, and hysterectomy rate after endometrial ablation in Finland.

Methods: In this retrospective cohort study, all women with endometrial ablation at ages 30-49 in Finland (1997-2014) were extracted from the Hospital Discharge Register and linked to Cancer Registry and Finnish Central Population Register. The primary outcome was cancer incidences in the endometrial ablation cohort compared with those in the background population of same age. Secondarily, postablation hysterectomy rate was compared with that of a control cohort of similar-aged women extracted from the Finnish Central Population Register. Multivariate regression models with adjustment for age, parity, number of cesarean deliveries, history of sterilization, and the duration of follow-up were evaluated as risk factors for postablation hysterectomy.

Results: In total, 154 cancers (the standardized incidence ratio [observed-to-expected ratio] 0.96, 95% confidence interval [CI] 0.82-1.13) were diagnosed among 5,484 women treated with endometrial ablation during the follow-up of 39,892 women-years. The standardized incidence ratio for endometrial cancer was 0.56 (95% CI 0.12-1.64), and for breast cancer 0.86 (95% CI 0.67-1.09). A total of 1,086 (19.8%) women had postablation hysterectomy. Risk for hysterectomy was almost fourfold in the endometrial ablation cohort compared with 26,938 controls (adjusted hazard ratio [aHR]) 3.63, 95% CI 3.32-3.96). Factors predisposing to postablation hysterectomy were leiomyomas (aHR 1.78, 95% CI 1.03-3.10), age under 35 years (aHR 1.44, 95% CI 1.15-1.81), at least two prior cesarean deliveries (aHR 1.27, 95% CI 1.04-1.55), and history of sterilization (aHR 1.15, 95% CI 1.01-1.32).

Conclusion: Endometrial ablation was not associated with an elevated endometrial cancer or breast cancer risk in Finland. Leiomyomas, young age, and history of prior cesarean deliveries or sterilization were associated with an increased risk for postablation hysterectomy.

Introduction

Heavy menstrual bleeding is the most common form of abnormal uterine bleeding. It decreases the quality of life of up to 25% of women (1) and causes a significant economic burden due to substantial amount of outpatient visits and surgical interventions (1,2). Most patients with heavy menstrual bleeding can be treated with medical therapy or endometrial ablation without hysterectomy (3,4). During the last decades, new non-hysteroscopic endometrial ablation techniques, safe and easy to perform in outpatient office setting, have replaced the older hysteroscopic endometrial ablation methods (5,6).

The effect of endometrial ablation on later risk for cancer, endometrial cancer in particular, is not well known (7,8) and population-based studies reporting solely the impact of the new non-hysteroscopic endometrial ablations on endometrial cancer do not exist. In addition, it is unknown if heavy menstrual bleeding is associated with increased risk for breast cancer. Women using levonorgestrel-releasing intrauterine system for heavy menstrual bleeding have decreased risk for endometrial cancer, but increased risk for breast cancer (9, 10).

Optimally, endometrial ablation relieves heavy menstrual bleeding permanently, but in some cases later hysterectomy is needed (5,11). If the factors predisposing to hysterectomy could be clarified, more individualized risk-benefit estimations could be made before treatment decisions.

Thus, our primary aim of this nationwide study was to assess the risk for endometrial cancer and breast cancer among women treated with endometrial ablation in Finland. Our secondary aim was to identify risk factors for postablation hysterectomy.

Materials and Methods

This study was approved by the Institutional Review Board of Hyvinkää Hospital. The Finnish National Institute for Health and Welfare, after consulting the data protection authority, approved the use of the confidential health register data in this research. Finnish Central Population Register gave their permission to get the requested data on the cases and to select the control women.

In this observational nationwide cohort study, we collected information on all women in Finland who in 1997-2014 were between the ages of 30-49 years and had undergone endometrial ablation according to the Hospital Discharge Register. Five control women of the same age (+/- six months), living in the same area, and alive at the index date were randomly selected for each endometrial ablation case from the Finnish Central Population Register to assess the risk for later hysterectomy in the endometrial ablation treated women and in the general population. The index date was the date of endometrial ablation of the case. Endometrial ablation cases with cancer diagnosis before the beginning of the follow-up and their controls, as well as other controls with a cancer diagnosis before the index date were excluded.

All study data were obtained from administrative registers in Finland. The data linkages were done using the unique personal identity code issued by the Finnish Population Register Centre since 1967 to all citizens and permanent residents of Finland and used as the identification key in all national registers.

Data on the endometrial ablations and other surgical procedures were obtained from the registers of the National Institute for Health and Welfare. The information on surgical

procedures since 1986 was obtained from the Hospital Discharge Register which has summary information on patients discharged from public and private hospitals since 1969, with almost 100% coverage (12), and the data accuracy and completeness have been reported to be good (13). The codes of surgical procedures in this register are according to NOMESCO Classification of Surgical Procedures since 1997. The code LCA 16 (destruction of the endometrium) was used to extract the endometrial ablation patients from the register. The data about sterilization procedures were obtained from the Sterilization Register, kept by the National Institute for Health and Welfare. This register has information in electronic form on all sterilizations performed in Finland since 1987.

The information on all liveborn deliveries was extracted from The Finnish Central Population Register which has data on all live births in Finland in electronic form since 1969. Information on the mode of deliveries was collected from the Medical Birth Register of the National Institute of Health and Welfare which contains information on all deliveries of live births and stillbirths with a gestational age of at least 22 weeks or birth weight of at least 500 g since 1987.

The data on cancer cases were extracted from the Finnish Cancer Registry, which receives notifications of all cancer cases from hospitals and pathology laboratories, covering virtually 100% of diagnosed cancers in Finland since 1953 (14). Since 1961, reporting of new cancer cases is mandatory by law in Finland. Cancer notifications submitted to the Finnish Cancer Registry are stored in a database, and regular quality checks and cross-linkages with the data of the Finnish Central Population Register and cause-of-death data of the Statistics Finland are done to ensure the correctness of data.

Our primary outcomes were all cancer diagnoses after endometrial ablation, especially endometrial cancer and breast cancer. The expected number of cancers was calculated by multiplying the number of women-years in each 5-year age group and calendar period by the corresponding cancer incidence among all Finnish women for each primary cancer site. The women-years at risk were calculated, starting from the date of endometrial ablation and ending on December 31, 2014, or on emigration, or death, whichever occurred first. In addition, censoring at the date of hysterectomy in the analyses for endometrial cancer risk was done. We calculated standardized incidence ratios by dividing the number of observed cancer cases by the expected cancer cases to assess the cancer risks among endometrial ablation treated women. Ninety-five percent confidence intervals (CIs) for the standardized incidence ratios were based on the assumption that the number of observed cases represents a Poisson distribution (15).

The secondary outcome was hysterectomy after endometrial ablation. The independent variables for the secondary outcome were the age at the endometrial ablation, parity, number of prior cesarean deliveries, history of prior tubal sterilization, indication of endometrial ablation, and the follow-up time from endometrial ablation. Adjusted hazard ratios (aHR) with 95% CIs for hysterectomy were calculated with a multivariate Poisson regression model using women-years as a model offset. The adjusted multivariate model included the following variables: age at endometrial ablation, parity, number of cesarean deliveries, sterilization, and the follow-up time. When comparing the risk for hysterectomy between endometrial ablation cohort and controls (i.e. women without endometrial ablation), the follow-up for the controls started from the index date of the corresponding endometrial ablation case. When estimating the cumulative risk of hysterectomy, we defined death as a

competing event that would prevent hysterectomy, and estimated cumulative incidence by using a cause-specific hazard method proposed by Putter et al. (16).

Statistical significance was set at $p<.05$. Statistical analyses were conducted in statistical program R (version 3.3.2) using popEpi package (version 0.4.1)

Results

During the study period 1997-2014, a total of 5,591 women were treated with endometrial ablation in Finland. After excluding women with history of cancer before the follow-up and their controls (105 women in the endometrial ablation group and 494 matched controls), women with prior cancer in the control group (n=485), and two women with discrepancies in hysterectomy codes in the endometrial ablation group and their ten controls, the final study cohort included 5,484 endometrial ablation treated women and 26,938 controls. The mean age (± standard deviation, SD), at endometrial ablation was 42.4 ± 4.4 years (Table 1). The median number of endometrial ablations performed yearly in Finland during the study period was 329 (range 143-511). Over the study period, the number of endometrial ablations increased; during 2010-2014 the growth was approximately 40%. Charasteristics of the study cohorts are shown in Table 1. The mean follow-up time was 7.3 years (maximum 18 years).

In total, 154 new cancer cases were diagnosed among the endometrial ablation treated women during 39,892 women-years at risk (Table 2). The standardized incidence ratio for all cancers was 0.96 (95% confidence interval [CI] 0.82-1.13; 154 observed compared with 160 expected cases). The standardized incidence ratio for all cancers in the first year of follow-up was 0.94 (95% CI 0.50-1.61), in one to five years 1.00 (95% CI 0.75-1.31), and after five years 0.94 (95% CI 0.76-1.16).

During the study period 1997-2014, the age-standardized incidence rate of endometrial cancer in the Finnish population was 14.2/100,000 women-years, adjusted for age according to the World Standard Population. After endometrial ablation, the standardized incidence ratio for endometrial cancer was 0.56 (95% CI 0.12-1.64; three observed compared with five

expected cases). Of the three endometrial cancer cases diagnosed after endometrial ablation, two cases were diagnosed at early stage and one at unknown stage.

The standardized incidence ratio for breast cancer among endometrial ablation treated women was 0.86 (95% CI 0.67-1.09; 67 observed compared with 78 expected cases). The standardized incidence ratios for other cancers types were similarly not increased (data not shown).

A total of 1,086 (19.8%) of women treated with endometrial ablation had hysterectomy during the follow-up. Six women (0.1%) had a repeat endometrial ablation during the follow-up. In the control cohort, 2,521 (9.4%) women had hysterectomy during the follow-up. The mean age (± SD) at hysterectomy was 44.7 ± 5.2 years in endometrial ablation cohort, and 44.4 ± 5.7 years in the control cohort. The main indications for hysterectomy after endometrial ablation were heavy menstrual bleeding (47.8%), leiomyomas (18.9%), other unspecified indications (14.0%), dysmenorrhea (9.1%), and endometriosis or adenomyosis (8.0%). In 20 cases (1.8%), the main indication for hysterectomy was endometrial hyperplasia.

The aHR for hysterectomy in endometrial ablation treated women compared with controls was 3.63 (95% CI 3.32-3.96, $p<.001$). Compared to the control cohort, the risk for hysterectomy in the endometrial ablation cohort was highest during the first five years but at ten years after endometrial ablation, the risk was still slightly increased (aHR 1.69, 95% CI 1.13-2.51) (Figure 1). Post-ablation hysterectomy risk was highest among women with a prior history of leiomyoma diagnosis (aHR 1.78, 95% CI 1.03-3.10, $p=.016$), age younger than 35 years at endometrial ablation (aHR 1.44, 95% CI 1.15-1.81, $p=.002$), or those with two or more prior cesarean deliveries (aHR 1.27, 95% CI 1.04-1.55, $p=.020$) or with history

of sterilization (aHR 1.15, 95% CI 1.01-1.32, p=.040) (Table 3). The median time from endometrial ablation to hysterectomy was 4.9 years (range 0.0-18.0 years). The risk of hysterectomy was highest during the first year after endometrial ablation (aHR 4.44, 95% CI 3.67-5.36, p<.001), and decreased during the follow-up (Table 3).

Discussion

We found that endometrial ablation was not associated with an increased risk for endometrial cancer or breast cancer in Finland. Later hysterectomy was needed only in 19.8% of cases. Young age, leiomyomas, and history of cesarean deliveries or sterilization predicted subsequent hysterectomy. Little is known about the impact of the new non-hysteroscopic endometrial ablation techniques on later cancer risk. In our study, the risk for endometrial cancer was not altered after endometrial ablation.

Only 0.05% of women treated with endometrial ablation were diagnosed with endometrial cancer in our study. This is in line with a Scottish study which included also first-generation endometrial ablations (7). Singh et al. (17) found no cases of endometrial cancer among 1,521 women with endometrial ablation with a median follow-up of 10 years but they did not report whether the follow-up was censored at hysterectomy, after which risk for endometrial cancer disappears. The risk for endometrial cancer among premenopausal women with irregular uterine bleeding has been reported to be increased (18) but association with heavy menstrual bleeding remains unknown. Our finding of postablation endometrial cancer risk comparable to that of general population is based on a small number of cases but suggests that no increased risk exists.

Our finding of no effect of endometrial ablation on breast cancer risk is in line with the only previous study (7). In that study, 1.15% of the women with endometrial ablation had subsequent diagnosis of breast cancer and this was 1.22% in our study. Treatment of heavy menstrual bleeding with levonorgestrel-releasing intrauterine system was associated with an increased risk for breast cancer (9,10) which could relate to altered intrinsic hormonal factors

(i.e., hyperestrogenism, chronic anovulation). Our findings, however, imply that heavy menstrual bleeding per se is not a risk factor for breast cancer.

Post-ablation hysterectomy rate of 19.8% is comparable to previous studies with women of similar age and follow-up (13-20%) (7,8,19,20). The need for postablation hysterectomy usually emerges in the first years (7,20) which was also noticed in our study; 75% of hysterectomies were performed during four years after endometrial ablation. The risk for hysterectomy was almost four times higher compared with other women of the same age. In several studies, young age at endometrial ablation is a significant risk factor for hysterectomy (19-22). Leiomyomas were a significant risk factor for hysterectomy in our study as well as in a large study from England (22) and in a smaller US study (23). We also found that women with postablation hysterectomy were more likely to have prior cesarean deliveries, a finding already reported (20,23). In our study, majority of women with endometrial ablation were sterilized, which reflects the contraception policy; in Finland sterilization is strongly recommended before endometrial ablation.

The strengths of this study are large cohort size, long follow-up time, and population-based data from national administrative and health registers with high level of coverage enabling this type of research (24). We had virtually complete data on all endometrial ablations and other gynecological operations, cancer diagnoses, and the deaths during the follow-up minimizing the risk of selection bias. Also, our study represents solely the effects of the new endometrial ablation techniques which are exclusively used currently with no difference in efficacy compared with the first generation endometrial ablations (6,25). A limitation was the lack of data on the specific endometrial ablation devices used but differences in effectiveness between various non-hysteroscopic endometrial ablation devices do not exist (25). In Finland,

data on the ethnic background cannot be recorded in the register studies according to current data protection legislation. However, almost all Finns are Caucasians. Hence we can conclude that the results of our study are generalizable to the Caucasian population of the developed countries.

This study supports the role of endometrial ablation as an effective alternative to hysterectomy in selected women with heavy menstrual bleeding. In most cases a subsequent hysterectomy can be avoided, although there are factors that predict increased postablation hysterectomy risk. Most importantly, endometrial cancer or breast cancer risk seems to be unaffected by endometrial ablation which is reassuring when choosing treatment alternatives for heavy menstrual bleeding.

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Table 1. Baseline characteristics of all Finnish women treated with endometrial ablation in 1997-2014 at ages 30-49 years and their control group at the beginning of the follow-up.

Patient charasteristic	Endometrial ablation	Controls	*p**
Number of women	5,484	26,938	
Age at the beginning of follow-up (y)			
30-34	329 (6.0%)	1,624 (6.0%)	.955
35-39	1,286 (23.5%)	6,364 (23.6%)	.789
40-44	2,152 (39.2%)	10,569 (39.2%)	1.000
45-49	1,718 (31.3%)	8,381 (31.1%)	.772
Parity			
0	282 (5.1%)	4,370 (16.2%)	<.0001
1	575 (10.5%)	4,373 (16.2%)	<.0001
2	2,082 (38.0%)	9,951 (36.9%)	.160
3	1,629 (29.7%)	5,557 (20.6%)	<.0001
≥4	917 (16.7%)	2,687 (10.0%)	<.0001
History of tubal sterilization, n (%)	3,698 (67.4%)	5,114 (19.0%)	<.0001
Indication of endometrial ablation			
Heavy menstrual bleeding	4,488 (81.8%)	NA	NA
Leiomyomas	44 (0.8%)	NA	NA
Endometriosis/Adenomyosis	23 (0.4%)	NA	NA
Endometrial hyperplasia	23 (0.4%)	NA	NA
Other abnormal uterine bleeding	42 (0.8%)	NA	NA
Dysmenorrhea	30 (0.5%)	NA	NA
Other	834 (15.2%)	NA	NA
* Chi-square test for equal proportions			
NA, not appicable			

NA, not applicable

Table 2. Cohort of Finnish Women Treated with Endometrial Ablation at Ages 30 to 49: Follow-up 1997-2014.

Age	n	Women-Years	Cancer Diagnoses
30-34	329	558	0
35-39	1,286	3,389	2
40-44	2,151	9,408	27
45-49	1,718	13,613	53
50-54	0	9,086	42
> 55	0	3,839	30
total	5,484	39,892	154

Number of all women classified according to the age at endometrial ablation, women-years classified according to age at follow-up, and cancers classified according to age at diagnosis. Follow-up started from the date of endometrial ablation and ended on 31 December 2014, or on emigration, or death, whichever occurred first.

Table 3. Poisson Multivariable Regression Model Analysis of Predictors for hysterectomy after endometrial ablation.

Variable	Number of Hysterectomies	HR (95% CI)	*p*	aHR (95% CI)*	*p*
Age at index date (y)					
30-34	92	1.46 (1.17-1.83)	.001	1.44 (1.15-1.81)	.002
35-39	292	1.16 (1.00-1.34)	.055	1.15 (0.99-1.34)	.069
40-44†	416	1		1	
45-49	286	0.91 (0.78-1.05)	.196	0.90 (0.77-1.05)	.171
Number of deliveries before index date					
0†	56	1		1	
1	122	1.13 (0.82-1.55)	.459	1.06 (0.77-1.46)	.729
2	387	0.89 (0.67-1.17)	.398	0.82 (0.62-1.10)	.186
≥3	521	1.02 (0.78-1.35)	.873	0.91 (0.68-1.20)	.495
Number of cesarean delivieres before index date					
0†	838	1		1	
1	135	1.23 (1.02-1.47)	0,028	1.09 (0.91-1.32)	.336
≥2	113	1.44 (1.18-1.75)	<.001	1.27 (1.04-1.55)	.020
History of tubal sterilization before index date					
no†	312	1		1	
yes	774	1.17 (1.02-1.33)	.023	1.15 (1.01-1.32)	.040
Indication of endometrial ablation					
Heavy menstrual bleeding†	873	1		1	
Leiomyomas	13	1.76 (1.02-3.05)	.042	1.78 (1.03-3.10)	.041
Endometriosis/Adenomyosis	6	1.47 (0.66-3.27)	.350	1.44 (0.64-3.24)	.380
Endometrial hyperplasia	7	1.02 (0.49-2.15)	.959	1.35 (0.64-2.85)	.428
Other abnormal uterine bleeding	6	0.63 (0.28-1.40)	.254	0.66 (0.30-1.47)	.311
Dysmenorrhea	6	1.07 (0.48-2.38)	.872	1.06 (0.47-2.37)	.888
Other	175	0.76 (0.65-0.89)	.001	0.83 (0.71-0.98)	.029
Follow-up time, years since index date					
0-0.99	351	4.47 (3.70-5.40)	<.001	4.44 (3.67-5.36)	<.001
1-4.99	535	2.44 (2.04-2.92)	<.001	2.43 (2.03-2.91)	<.001
5-9.99†	154	1		1	
10-14.99	37	0.69 (0.48-0.99)	.042	0.68 (0.48-0.98)	.038
≥15	9	1.17 (0.60-2.29)	.647	1.14 (0.58-2.23)	.702

HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio

Index date, the date of endometrial ablation and the beginning of the follow-up.

* Adjusted for age at endometrial ablation, parity, number of cesarean deliveries, sterilization, and follow-up time.

† Reference level

Figure 1. Cumulative Risk for Hysterectomy after Endometrial Ablation in Finland. Follow-up 1997-2014.