Vaginal estrogen therapy utilization and associated outcomes in younger survivors of endometrial cancer

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Abstract

Objectives: To evaluate the utilization of vaginal estrogen therapy (ET) and outcomes associated with its use among younger endometrial cancer survivors, using a propensity score-matched cohort.

Methods: We conducted a cohort study using data from the TriNetX database's US Collaborative Network, which includes electronic health records and insurance claims data from 68 health care organizations. Women 18-51 years old diagnosed with endometrial cancer between November 1, 2005, and December 31, 2023, were included. We used 1:1 propensity score matching to create cohorts with and without vaginal ET in the year after their endometrial cancer diagnosis. We estimated hazard ratios (HRs) with 95% CIs for the primary outcome of endometrial cancer recurrence and assessed the risks of negative control outcomes.

Results: We identified 1,412 endometrial cancer survivors with vaginal ET and 23,859 without vaginal ET. After propensity score matching, the vaginal ET and non-ET groups included 1,412 individuals each. The mean ET treatment duration was 1.88 years (SD, 0.36 y). Endometrial cancer recurrence risk was not increased among those with vaginal ET use (HR, 0.87; 95% CI, 0.60-1.27).

Conclusions: Endometrial cancer survivors with short-term exposure to vaginal ET did not have an elevated risk of endometrial cancer recurrence compared with those without vaginal ET.

Key Words: Cancer survivorship, Endometrial cancer, Vaginal estrogen.

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The incidence of early-onset endometrial cancer in US women 50 years and younger has increased steadily from 2.2 to 3.3 per 100,000 women between 2000 and 2019.[1] Though fertility-sparing treatment options are available for younger women diagnosed with early-stage endometrial cancer, the standard treatment involves hysterectomy and bilateral salpingo-oophorectomy.[2] Younger endometrial cancer survivors who enter early menopause as a result of their cancer treatment often experience worse vasomotor symptoms (hot flashes, night sweats) and genitourinary symptoms of menopause (vaginal dryness, urinary symptoms, dyspareunia) than those entering menopause naturally.[3-5] Menopause symptoms can negatively affect women's sleep, work, social functioning, sexual health, mood, and more, significantly impairing women's quality of life.[6,7]

Systemic estrogen therapy (ET) delivers higher doses of estrogen and is indicated for the treatment of vasomotor symptoms of menopause, whereas vaginal ET delivers lower doses of estrogen with minimal systemic absorption and is used to relieve genitourinary symptoms of menopause. Evidence on the safety of vaginal ET after endometrial cancer remains limited,[4,8] and both patients and providers may be hesitant with its use due to concerns about cancer recurrence, particularly given that endometrial cancer is often estrogen-dependent.[9-11] Also, despite its localized effect, low-dose vaginal estrogen used to share the same black boxed warning as systemic ET, which likely further deters women from utilizing vaginal ET for fear of adverse effects.[12] Gynecologic cancer survivors are therefore commonly prescribed non-hormone treatments for menopausal symptoms.[3]

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In the past two decades, endometrial cancer incidence has increased in the United States among younger, premenopausal women.[13-15] There is an urgent need to understand the utilization patterns of vaginal ET in this population and to examine outcomes associated with vaginal ET use. The objectives of this study were to characterize the use of vaginal ET in endometrial cancer survivors and to assess outcomes of vaginal ET use versus nonuse, using a propensity-matched cohort and nationwide data.

METHODS

Data

This retrospective cohort study was conducted using deidentified electronic health records from the TriNetX US Collaborative Network. TriNetX is a global research platform that collects electronic medical data from participating health care organizations. Updated every 2-4 weeks, the the database includes electronic medical record data, including diagnosis codes, procedural codes, laboratory results, prescription medications, and more. As the TriNetX platform only provides aggregated counts and deidentified data, the institutional review board at our institution has determined the use of TriNetX data to be exempt from review.

Cohort

We identified women who had a first endometrial cancer diagnosis between November 1, 2005, and December 31, 2023. Women 18-51 years old at the time of their endometrial cancer diagnosis were included, as these women are likely premenopausal or perimenopausal at the time of the cancer diagnosis. We excluded individuals treated with an intrauterine device (CPT 58300, ICD-10-CM Z30.430) or with a fertility preservation procedure (Z31.84) within 3 months after the endometrial cancer diagnosis, as these individuals would not be eligible for ET. Women who had used medroxyprogesterone acetate (Provera) or megestrol acetate (Megace) within 3 months after the endometrial cancer diagnosis were also excluded, since these progestins are often used for fertility preservation in younger women with endometrial cancer. An age cutoff of 51 years was used, as this is the median age of menopause in the United States.[16] For confounding control, we excluded individuals with any history of conditions that are contraindications for ET: cerebral infarction, venous embolism or thrombosis, pulmonary embolism, myocardial infarction, or breast cancer.

The index date was defined as the date of the first endometrial cancer diagnosis. To better identify persistent vaginal ET users, those in the vaginal ET group were required to have two vaginal ET prescriptions in the year after the index date. The exposure of interest was prevalent vaginal ET use after endometrial cancer diagnosis, and women with prior vaginal ET use were not excluded. To reduce confounding, we excluded those with any systemic ET in the year after the index date. The comparator group included those without a vaginal or systemic ET prescription in the year after their initial endometrial cancer diagnosis. A graphical depiction of the study design is provided in Figure 1, and a flowchart of the cohort and the inclusion and exclusion criteria is depicted in Figure 2. International Classification of Diseases, Tenth Revision (ICD-10) and International Classification of Diseases for Oncology (ICD-O) codes were used to identify women with endometrial cancer. VA National formulary codes were used to identify those with

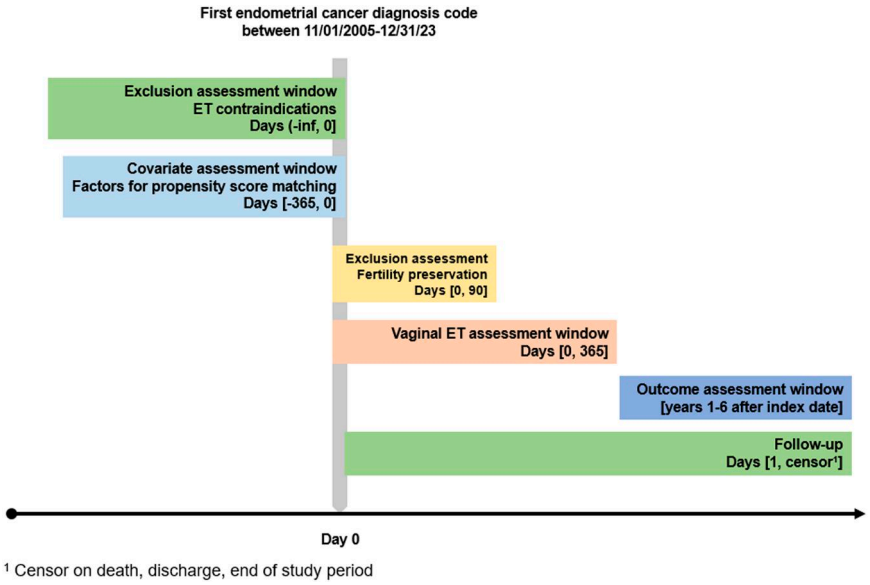

FIG. 1. Graphical depiction of the study design.[17,18] [1]Censor on death, discharge, and end of study period.

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a vaginal ET prescription (GU500). Specific codes are listed in Supplementary Tables 1 and 2, Supplemental Digital Content 1, http://links.lww.com/MENO/B483.

Outcomes

The primary outcome of interest was endometrial cancer recurrence, defined as the presence of a debulking procedure, radiation therapy, chemotherapy, immunotherapy, or other relevant medication occurring one or more years after the index date (Supplementary Table 3, Supplemental Digital Content 1, http://links.lww.com/MENO/B483). Endometrial cancer recurrence was assessed in years 1-6 after the index date, to provide a fixed time window for assessing vaginal ET exposure and to provide a lag time after initiation of vaginal ET. Prior studies suggest a median time to recurrence of ~16-22 months after the initial endometrial cancer diagnosis.[19-21]

In addition, we included negative control outcomes to assess for potential biases.[22] For choosing a negative control outcome, it is important to identify an outcome that would not plausibly be affected by the treatment of interest (ie, vaginal ET) but would be influenced by similar confounding factors as the exposure and outcome of interest (eg, health care utilization). We used influenza vaccination as a negative control, along with a composite negative control outcome, which included codes that are not expected to be associated with either the treatment or outcome but may suggest greater health care utilization (ie, dog bite, viral warts, ingrown nail, sebaceous cyst). A detailed list of the composite negative control outcome variable is included in Supplementary Table 3, Supplemental Digital Content 1, http://links.lww.com/MENO/B483.

Analyses

TriNetX was used to perform 1:1 propensity score matching with logistic regression. Propensity score matching was employed to balance covariates between the vaginal ET group and the comparator group and to reduce bias.[23] Greedy nearest neighbor matching with a caliper of 0.1 of the pooled SDs was applied. The variables selected for matching were determined a priori based on the literature. Standardized mean differences were used to examine covariate balance and to compare the distribution of covariates between the two groups. A standardized mean difference < 0.1 was considered indicative of good balance in covariate distribution between the two groups.

The two groups were matched using baseline characteristics in the year before the index date. These variables included age at the index date, race (White, Unknown Race, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other Race [multiracial or race not listed in the available options]), ethnicity (Hispanic or Latina, Not Hispanic or Latina, Unknown Ethnicity), overweight and obesity, body mass index (BMI) category, nicotine dependence, alcohol related disorders, depressive episode, anxiety, nonpsychotic mental disorders, menopausal and female climacteric states, hypertensive disorders, type 2 diabetes mellitus, hyperlipidemia, diseases of the liver, and disorders of the gallbladder, biliary tract, and pancreas. Sociodemographic variables (problems related to education and literacy, problems related to employment and unemployment, problems related to housing and economic circumstances) and health care utilization variables (office or other outpatient services and preventive medicine services) in the year before the index date were also included as variables in propensity score matching.

We described ET utilization patterns and types of therapies prescribed to endometrial cancer survivors. We presented the absolute risk of the primary outcome, reporting the 5-year recurrence risk in each group (ie, 1- to 6-years postdiagnosis). We also used a conditional Cox proportional hazard regression model to estimate the 5-year hazard ratios (HRs) and 95% CIs for the primary outcome of cancer recurrence, comparing the vaginal ET versus the comparator group after matching, using the same timeframe between 1- to 6-years postdiagnosis. Kaplan-Meier curves are displayed as well. Proportionality was tested using the Schoenfeld approach. Sensitivity analyses were conducted with negative control outcomes as described above. Only incident cases of these negative control outcomes were assessed. For all outcomes, women were censored at the time of death, disenrollment, or the end of the study period, whichever occurred first.

The data used in this study were collected on October 6, 2025, from the TriNetX US Collaborative Network, which provided access to electronic medical records (diagnoses, procedures, medications, laboratory values, and genomic information) from ~61 million individuals from 68 health care organizations across the United States. This retrospective study is exempt from informed consent. The data reviewed is a secondary analysis of existing data, does not involve intervention or interaction with human subjects, and is deidentified per the deidentification standard defined in Section §164.514 (a) of the HIPAA Privacy Rule. The process by which the data is deidentified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule.

RESULTS

We identified 25,408 endometrial cancer survivors 18-51 years old at the time of their cancer diagnosis between November 1, 2005, and December 31, 2023, meeting the inclusion and exclusion criteria (Fig. 1). Most of the endometrial cancer survivors resided in the West South Central (20%), South Atlantic (17%), and Middle Atlantic (16%) regions.

Among the final cohort, 1,412 women had at least two prescriptions for vaginal ET within 1 year of the index date. The comparator group included 23,859 women without vaginal ET within 1 year of the endometrial cancer diagnosis. Before matching, 71.8% of the vaginal ET group were White, compared with

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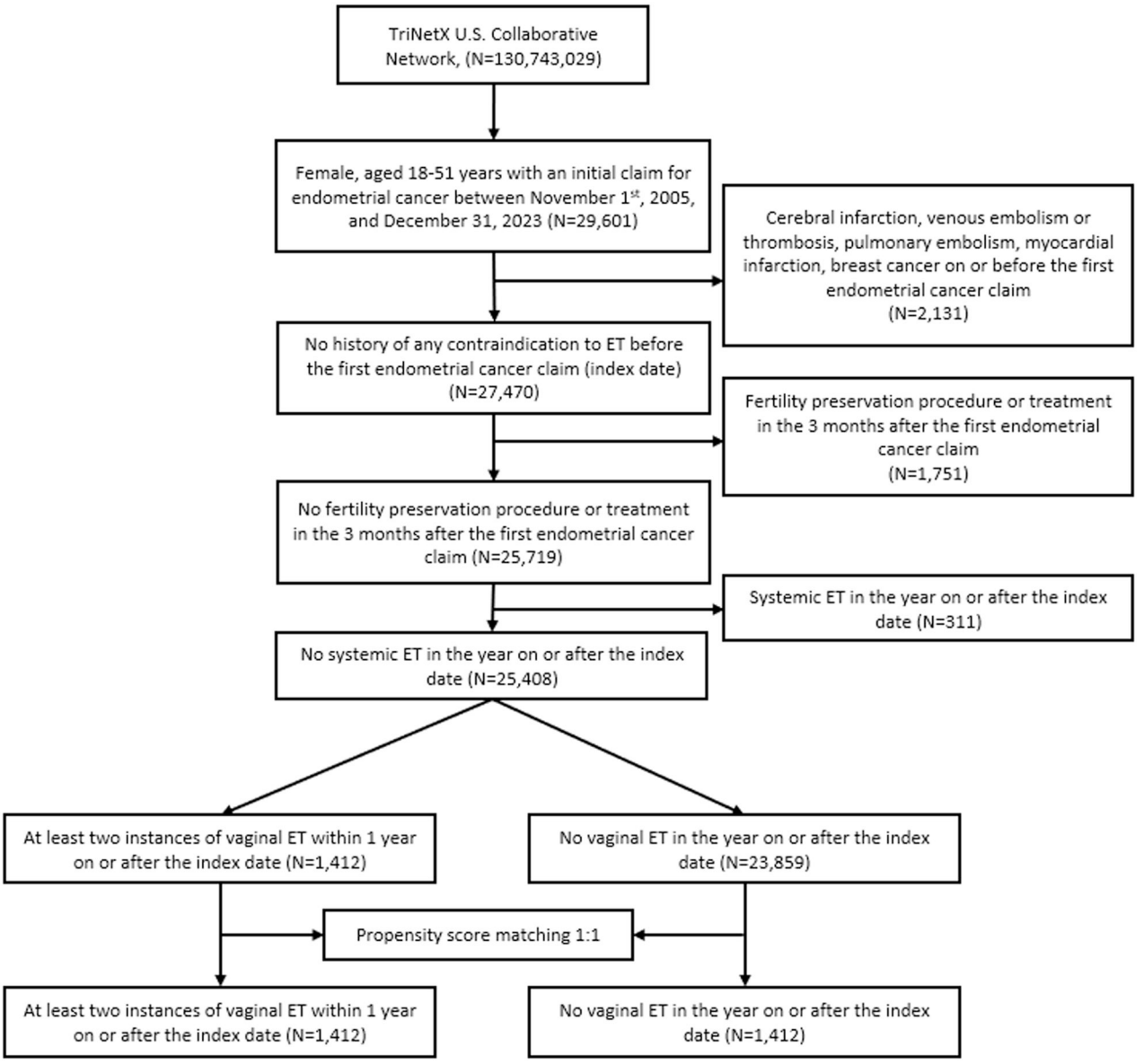

FIG. 2. Cohort inclusion and exclusion criteria. *Note*: The number of patients with at least two instances of vaginal ET within 1 year on or after the index date (1,412) and the number without vaginal ET during that period (23,859) do not sum to the total number without systemic ET. This discrepancy reflects the fact that some patients initiated vaginal ET more than 1 year after the index date. ET, estrogen therapy.

66.5% who were White in the comparator group; in addition, 71.2% of the vaginal ET group identified as non-Hispanic, compared with 66% in the no vaginal ET group. These differences were mitigated after matching.

After matching on baseline characteristics, there were 1,412 women in both groups. The absolute standardized mean differences were all < 0.1 for variables included in the propensity score model, suggesting a good balance of covariate distribution (Table 1). In the vaginal ET group, the mean treatment duration was 1.88 years (SD, 0.36 y). The mean follow-up times for the ET and non-ET groups after matching were 4.54 years (SD, 1.81 y) and 4.07 years (SD, 2.21 y), respectively.

In the matched cohorts, 53 women in the vaginal ET group and 54 women in the comparator group had codes suggesting endometrial cancer recurrence. The vaginal ET group did not have an increased risk of endometrial cancer recurrence (RD: −0.001 [95% CI, −0.015 to 0.013]; RR, 0.98 [95% CI, 0.68-1.42]; HR, 0.87 [95% CI, 0.60-1.27]). The risk difference for flu shot uptake for those with vaginal ET versus no vaginal ET was 1.57 (95% CI, −0.52 to 3.66), indicating greater uptake of the flu shot in

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TABLE 1. Baseline characteristics of endometrial cancer survivors in the TriNetX US data (N,%)[a]

	Before matching			After matching		
	Vaginal ET	**No vaginal ET**	**SMD**	**Vaginal ET**	**No vaginal ET**	**SMD**
Total	1,412	23,859		1,412	1,412	
Age at diagnosis (mean, SD)	42.2 (6.5)	43.3 (6.7)	0.163	42.2 (6.5)	42.0 (7.0)	0.033
Race						
White	1,014 (71.8)	15,870 (66.5)	0.115	1,014 (71.8)	1,037 (73.4)	0.037
Black or African American	113 (8)	2,588 (10.8)	0.097	113 (8)	105 (7.4)	0.021
Asian	82 (5.8)	1,437 (6)	0.009	82 (5.8)	76 (5.4)	0.018
American Indian or Alaska Native	< 10	170 (0.7)	0.001	< 10	< 10	0
Native Hawaiian or Other Pacific Islander	< 10	564 (2.4)	0.135	< 10	< 10	0
Other race (multiracial or race not listed in the available options)	70 (5)	993 (4.2)	0.038	70 (5)	73 (5.2)	0.01
Unknown Race	118 (8.4)	2,237 (9.4)	0.036	118 (8.4)	110 (7.8)	0.021
Ethnicity						
Hispanic or Latino	191 (13.5)	3,888 (16.3)	0.078	191 (13.5)	198 (14)	0.014
Not Hispanic or Latino	1,006 (71.2)	15,745 (66)	0.113	1,006 (71.2)	1,015 (71.9)	0.014
Unknown Ethnicity	215 (15.2)	4,226 (17.7)	0.067	215 (15.2)	199 (14.1)	0.032
Other covariates						
Overweight and obesity	249 (17.6)	4,359 (18.3)	0.017	249 (17.6)	238 (16.9)	0.021
Hypertensive diseases	207 (14.7)	3,903 (16.4)	0.047	207 (14.7)	202 (14.3)	0.01
Type 2 diabetes mellitus	131 (9.3)	2,504 (10.5)	0.041	131 (9.3)	128 (9.1)	0.007
Hyperlipidemia, unspecified	108 (7.6)	2,029 (8.5)	0.031	108 (7.6)	109 (7.7)	0.003
Diseases of the liver	250 (17.7)	4,565 (19.1)	0.037	250 (17.7)	271 (19.2)	0.038
Disorders of the gallbladder, biliary tract, and pancreas	60 (4.2)	1,097 (4.6)	0.017	60 (4.2)	49 (3.5)	0.04
Depressive episode	44 (3.1)	947 (4)	0.046	44 (3.1)	36 (2.6)	0.034
Anxiety disorders	146 (10.3)	1,912 (8)	0.081	146 (10.3)	147 (10.4)	0.002
Menopausal and female climacteric states	200 (14.2)	2,606 (10.9)	0.098	200 (14.2)	190 (13.5)	0.021
Nicotine dependence	46 (3.3)	455 (1.9)	0.085	46 (3.3)	35 (2.5)	0.047
BMI						
< 18.5 kg/m^2	20 (1.4)	283 (0.9)	0.02	20 (1.4)	14 (1)	0.039
18.5-25 kg/m^2	140 (9.9)	1,872 (5.7)	0.073	140 (9.9)	141 (10)	0.002
25-30 kg/m^2	172 (12.2)	2,359 (7.2)	0.073	172 (12.2)	178 (12.6)	0.013
> 30 kg/m^2	437 (30.9)	6,418 (19.5)	0.089	437 (30.9)	407 (28.8)	0.046
Missing	643 (45.5)	12,927 (39.3)	—	643 (45.5)	672 (47.6)	—
Health care utilization						
Office or other outpatient services	473 (33.5)	7,545 (31.6)	0.04	473 (33.5)	450 (31.9)	0.035
Preventive medicine services	224 (15.9)	2,496 (10.5)	0.16	224 (15.9)	204 (14.4)	0.04

BMI, body mass index; ET, estrogen therapy; SMD, standardized mean difference.
Propensity score matching included all covariates listed.
[a]Counts < 10 were suppressed for data privacy.

the vaginal ET group. However, the risk ratio (1.21, 95% CI, 0.94-1.56) and hazard ratio (1.07, 95% CI, 0.82-1.39) were not statistically significant, though all three measures were consistent in the same direction. Similarly, for the negative control outcomes, the risk difference was 1.04 (95% CI, −1.26 to 3.34) while the risk ratio (1.12, 95% CI, 0.87-1.45) and hazard ratio (0.97, 95% CI, 0.74-1.27) were not statistically significant.

DISCUSSION

In this propensity score–matched cohort study using nationwide data, we found that vaginal ET initiation is minimal among younger endometrial cancer survivors, with only 1,412 (5.6%) in the vaginal ET group before matching. The risk of endometrial cancer recurrence was not elevated in the vaginal ET cohort compared with the cohort without vaginal ET use. This finding is consistent with findings from the study of a large cohort of endometrial cancer survivors in Korea which showed no significant increase in the endometrial cancer recurrence rate among individuals utilizing ET.[24] The study had a follow-up time of ~4 years, similar to that in our study.[24] Similarly, in another study with 127 endometrial cancer survivors receiving vaginal estrogen, recurrence was rare: 2.4% for those with stage I/II and 4.7% with stage III/IV.[25]

This study has several strengths. First, using a large, national database lends to the generalizability of the study, and we were able to capture a diverse cohort spanning the United States and reflecting diverse racial/ethnic groups. This is the largest study, to our knowledge, conducted in the United States assessing endometrial cancer recurrence with vaginal ET use in endometrial cancer survivors, using recent years of data. Using natural language processing techniques, the TriNetX database also includes data from the electronic health records not found in traditional claims databases. We were therefore able to match the vaginal ET and non-vaginal ET cohorts by overweight/obesity and BMI, important risk factors for endometrial cancer and endometrial cancer recurrence.

Another strength of the study is the use of negative controls. We found statistically significant risk differences for the flu vaccine uptake and the composite negative outcome variables, suggesting potential bias and unmeasured confounding by health care utilization practices.

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Though we included outpatient services and preventive medicine services in the propensity score model to control for health-seeking behavior, those in the vaginal ET group may exhibit greater health-seeking behavior than those without vaginal ET. In addition, the follow-up time of 4.54 years in the ET group and 4.07 years in the non-ET group provided an extended period to assess the primary outcome. In a prior study examining adjuvant and first-line chemotherapy use in women with endometrial cancer, Knisely et al[26] found that 8.1% of women with endometrial cancer experienced cancer recurrence, with a median time of 13.3 months from hysterectomy to treatment for recurrence. With our long follow-up duration, we were likely able to capture most individuals with endometrial cancer recurrence after their initial diagnosis.

Despite these strengths, certain limitations should be taken into consideration. First, although the database includes oncology information, the large number of missingness for the tumor stage variable made it difficult to stratify by stage without introducing selection bias. However, most women likely had early-stage endometrial cancer, as ~70% of uterine cancers are diagnosed at an early stage.[27] We therefore sought to limit confounding by excluding individuals with indications for ovarian preservation. Another limitation is that the primary outcome of endometrial cancer recurrence was assessed with a proxy, using new surgery and treatment for recurrent cancer in years 1-6 after the initial cancer diagnosis, since there is no specific ICD code for endometrial cancer recurrence. This may lead to misclassification of cancer recurrence, perhaps inflating the number of recurrence incidences. However, most individuals with endometrial cancer recurrence would undergo one of these procedures or treatments, and a similar method was used in a prior study examining endometrial cancer recurrence.[26]

Another limitation is that vaginal ET claims reflect a prescription for vaginal ET, but we are unable to confirm whether women used the medication or picked it up from the pharmacy. However, by requiring women to have two or more vaginal ET claims in the year after the index date, it is likely that those in the vaginal ET cohort were, in fact, vaginal ET users. We also did not have information on the daily estrogen dose, so we were unable to assess for a dose response. In addition, the average duration of vaginal estrogen use was 1.88 years, limiting our ability to evaluate outcomes associated with long-term vaginal ET. Future studies should incorporate longer-term follow-up and assess the effects of extended vaginal ET use. Future studies should also be conducted to identify factors contributing to treatment discontinuation, including barriers to care, treatment costs, and potential adverse effects. Lastly, some women in the comparator group may have initiated vaginal ET in the year after the index date, which may mitigate the observed effects.

CONCLUSIONS

As the rates of endometrial cancer have been increasing in younger women, this study addresses a timely topic that has major implications for endometrial cancer survivors' quality of life. Findings from this study add to a limited body of evidence on vaginal ET use and its associated outcomes in younger endometrial cancer survivors. In considering our findings, it is important to note that menopausal symptoms are unique to each woman, and patients and providers need to engage in shared decision-making when considering the use of vaginal ET for genitourinary symptoms of menopause after endometrial cancer treatment.

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