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Original Article

Effects of hormone therapy on recurrence in endometrial cancer survivors: a nationwide study using the Korean Health Insurance Review and Assessment Service database

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Conflicts of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Objective: The aim of this study was to verify the effects of hormone therapy (HT) on recurrence in endometrial cancer (EC) survivors using the Korean Health Insurance Review and Assessment Service (HIRA) database.
Methods: Using the HIRA claims database, we identified all Korean women who were newly diagnosed with EC and underwent surgical staging between 2010 and 2013. Patient characteristics such as age, HT exposure, lymphadenectomy, and adjuvant therapy were evaluated. Cox proportional hazards models were used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the recurrence of EC.
Results: The mean follow-up time of all 5,667 eligible patients was 47.5 months. Of these, 847 (14.9%) received HT. Recurrence was seen in 446 (7.8%) patients. Univariate analysis revealed an increased recurrence rate in patients older than 50 years (HR=2.05; 95% CI=1.62–2.63), patients with high-risk EC (HR=24.51; 95% CI=18.63–32.35), and patients who underwent lymphadenectomy (HR=1.52; 95% CI=1.21–2.03), and a reduced recurrence rate in patients who received HT (HR=0.62; 95% CI=0.46–0.83). Multivariate analysis confirmed the significant increase in recurrence in patients older than 50 years (HR=1.47; 95% CI=1.14–1.89) and in patients with high-risk EC (HR=23.90; 95% CI=18.12–31.51). HT did not increase the recurrence rate of EC (HR=0.81; 95% CI=0.31–2.10).
Conclusion: This study demonstrates that HT does not increase disease recurrence in EC survivors, despite lack of data that could affect the outcome.

Keywords: Hormone Replacement Therapy; Endometrial Cancer; Recurrence

INTRODUCTION

Endometrial cancer (EC) is the most common cancer of the female genital tract throughout the world. More than 500,000 women are diagnosed with EC annually. In Korea, the incidence of EC increased by 6.9% between 1999 and 2010, and about 2,900 patients were diagnosed with uterine cancer (loosely referred to as EC) in 2018 [1,2].

Author Contributions
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The standard therapy for EC is staging surgery including a total hysterectomy and bilateral salpingo-oophorectomy (BSO). Although EC primarily affects postmenopausal women, 25% of cases occur in premenopausal women, and 5% occur in women under the age of 40 years [3]. Radical surgery, chemotherapy, and/or radiation result in loss of ovarian function and menopausal symptoms such as hot flashes, mood lability, vaginal dryness, and pelvic soft tissue atrophy. In addition, menopausal women are more likely to develop osteoporosis and cardiovascular disease. The most effective treatment for menopausal symptoms is hormone therapy (HT) [4].

Although HT is highly effective in improving menopausal symptoms, women with a history of EC are usually denied this therapy because EC is considered an estrogen-dependent neoplasm [5,6]. Although several studies have been performed in this field, the effect of HT in EC survivors remains controversial [7-9]. Most of them have been retrospective studies with small sample sizes, and one randomized clinical trial (RCT) was prematurely closed [8,10-13]. In addition, most of the studies were performed in patients with stage I and II EC only. In Korea, there has been survey study and retrospective case-controlled study about HT prescription practices for EC survivors [14,15].

Our aim in this study was to determine the effects of HT on recurrence in Korean EC survivors for the first time, using data from the Korean Health Insurance Review and Assessment Service (HIRA) database.

MATERIALS AND METHODS

1. Healthcare system in Korea

In 2000, the health insurance systems in Korea were merged into a single system run by the National Health Insurance Service (NHIS). Consequently, most people living in Korea are insured by the NHIS. Study data were collected from the Korean National Health Insurance (KNHI) claims database from 2007–2015. In Korea, 97% of the population is obligated to enroll in the KNHI program; the remaining 3% are under the Medical Aid Program [16]. HIRA is a government-affiliated organization that performs claims review and quality assessment for the KNHI. Data for the remaining 3% of the population covered by the Medical Aid Program are also reported to the HIRA. Therefore, the HIRA claims database contains information on all claims for approximately 50 million Koreans. Nearly all the information about the volume of a disease can be obtained from this centralized database, with the exception of procedures not covered by insurance, such as cosmetic surgery. The claims data of HIRA include patient diagnosis, treatment, procedures, surgical history, and prescription drugs, which are a valuable resource for clinical research. However, HIRA data are not complete and do not include medical records such as laboratory results and cancer stage.

2. Study population

A flowchart of patient enrollment is shown in **Fig. 1**. Using the HIRA claims database, we identified all Korean women who were newly diagnosed with EC (C54.1) and underwent surgical staging (hysterectomy+BSO±pelvic/paraaortic lymphadenectomy) between January 1, 2010 and December 31, 2015. Exclusion criteria were women who received HT prior to diagnosis, women who had not undergone surgical staging, and women who underwent robotic surgery. The reason for excluding robotic surgery is lack of information because robotic surgery is not covered by national insurance. Patients diagnosed with EC in 2014 and

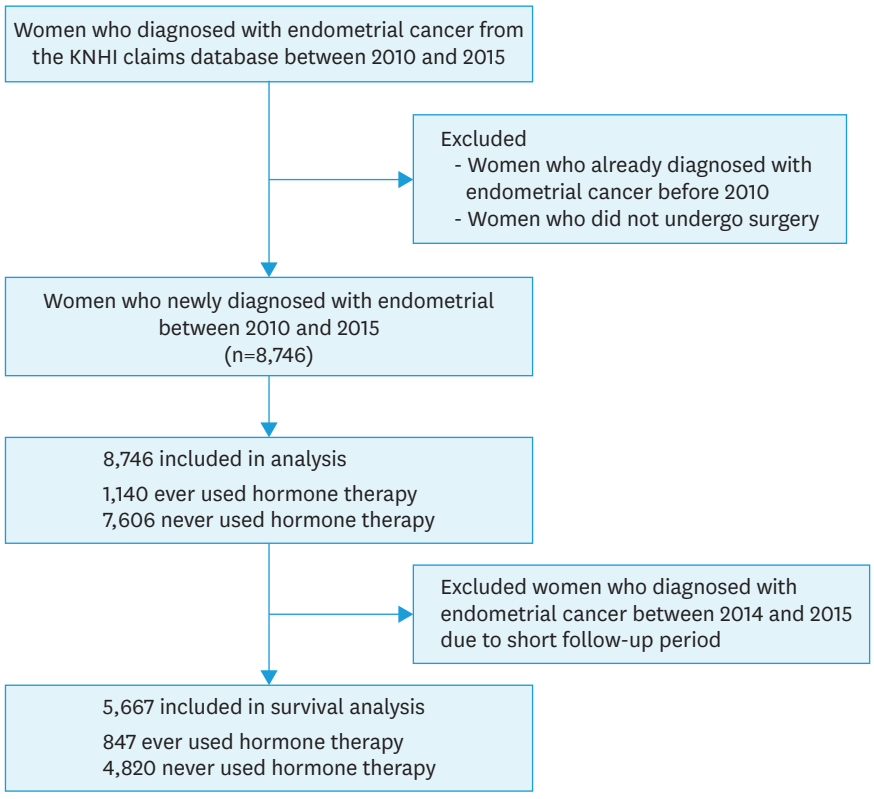

Fig. 1. A flowchart of the study design.
EC, endometrial cancer; HT, hormone therapy; KNHI, Korean National Health Insurance.

2015 were excluded from the analysis of recurrence due to the short follow-up period. This study was approved by the Institutional Review Board of Korea University Medical Center (KUGH16334-001).

3. Outcomes

Using HIRA data, it is not known whether the patient has recurred, but it can be verified whether the patient has received additional treatment. Therefore, recurrence was assessed based on the time of radiation or chemotherapy after surgical staging in this study. The definition of recurrence was based on a three-month follow-up period, because recurrence was assessed every three months in patients with EC [17]. First, we assessed whether the patient had undergone an adjuvant treatment. If no radiation or chemotherapy was given within 3 months after surgery, the patients were classified into the no adjuvant treatment group. Patients who underwent radiation or chemotherapy within 3 months after surgery were classified into the adjuvant treatment group. Recurrence was defined as having received radiation or chemotherapy 3 months after completion of first-line treatment; first-line treatment means surgery in cases of the no adjuvant treatment group but surgery and radiation and/or chemotherapy in cases of the adjuvant treatment group.

4. Measurement of patients' characteristics

Characteristics such as age, postoperative HT exposure, lymph node assessment at surgery, and adjuvant therapy (chemotherapy and radiotherapy [RT]) were obtained from the HIRA claims database. The disease stage was not available in the HIRA claims database.

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In accordance with the National Comprehensive Cancer Network (NCCN) Guidelines for 2018, adjuvant therapy was selected based on a combination of characteristics, including surgical stage, grade, and risk factors (advanced age, lymphovascular space invasion, tumor size, depth of invasion, etc.). Radiation therapy was recommended for all patients, except those with International Federation of Gynecology and Obstetrics (FIGO) stage IA grade 1 or 2 lesions and those with stage IB grade 1 lesions without risk factors [17]. Chemotherapy has been used primarily as an adjuvant treatment for patients with advanced endometrial carcinoma [18]. Therefore, patients who did not receive adjuvant treatment or who underwent adjuvant radiation therapy were considered to have non-high-risk EC, and patients who received chemotherapy were considered to have high-risk EC.

5. Statistical analysis

Continuous and categorical variables were expressed as means±SDs and percentages, respectively. Clinical characteristics were compared by the t-test for continuous variables and the χ^2 test for categorical variables. Cox proportional hazards models were used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the recurrence of EC. All tests were two-sided, and p-values <0.05 were considered statistically significant. Statistical analysis was performed with SAS Enterprise Guide version 6.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

From 2010 to 2015, 8,746 Korean patients were diagnosed with EC and underwent surgery. As shown in **Table 1**, the number of patients with EC increased from 1,241 in 2010 to 1,573 in 2015. Overall, 13% of the patients received HT. From 2010 to 2015, the number of patients who were newly diagnosed with EC and underwent surgery exhibited an increasing trend. This trend was particularly evident in patients over 50 years of age. The number of patients with EC was 26.8% greater in 2015 than in 2010. In 2015, about 28% of these patients were under the age of 50.

Table 2 displays the clinical characteristics of patients with EC. The patients who received HT were younger (age <50: 48% vs. 26%, p<0.001), underwent fewer lymphadenectomies (76% vs. 79%, p=0.051), and received less adjuvant therapy (23% vs. 31%, p<0.001) than patients who did not receive HT. This can be attributed to the more frequent administration of HT in patients with early-stage EC. The most frequently used type of HT was tibolone (32%), followed by progesterone only (30%), estrogen only (22%), and estrogen plus progesterone (16%).

Table 1. Annual number of patients who newly diagnosed with endometrial cancer between 2010 and 2015 in Korea

Characteristics	2010 (n=1,241)	2011 (n=1,412)	2012 (n=1,391)	2013 (n=1,623)	2014 (n=1,506)	2015 (n=1,573)
Age (yr)						
<30	13 (1)	7 (<1)	10 (1)	7 (1)	12 (1)	13 (1)
31–40	90 (7)	92 (7)	85 (6)	87 (5)	103 (7)	98 (6)
41–50	295 (24)	302 (21)	297 (21)	307 (19)	327 (22)	309 (20)
51–60	497 (40)	627 (44)	594 (43)	703 (43)	639 (42)	641 (41)
61–70	250 (20)	281 (20)	294 (21)	354 (22)	290 (19)	356 (23)
>70	96 (8)	103 (7)	111 (8)	165 (10)	135 (9)	156 (10)
Postoperative HT						
No	1,021 (82)	1,193 (84)	1,184 (85)	1,422 (88)	1,340 (89)	1,446 (92)
Yes	220 (18)	219 (16)	207 (16)	201 (12)	166 (11)	127 (8)

Values are presented as number of patients (%).
HT, hormone therapy.

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Table 2. Clinical characteristics of patients by use of HT (2010–2015)

Characteristics	HT (n=1,140)	Control (n=7,606)	p-value
Age (yr)			<0.001
<30	18 (2)	44 (1)	
31–40	134 (12)	421 (6)	
41–50	389 (34)	1,448 (19)	
51–60	477 (42)	3,224 (42)	
61–70	90 (8)	1,735 (23)	
>70	32 (3)	734 (10)	
Lymphadenectomy			0.051
No	274 (24)	1,633 (21)	
Yes	866 (76)	5,973 (79)	
Adjuvant therapy			<0.001
No	874 (77)	5,219 (69)	
Brachytherapy	27 (2)	378 (5)	
Radiotherapy	58 (5)	497 (7)	
Chemotherapy	181 (16)	1,512 (20)	
Type of HT			-
Estrogen only	253 (22)	-	
Estrogen plus progesterone	178 (16)	-	
Tibolone	363 (32)	-	
Progesterone only	346 (30)	-	

Values are presented as number of patients (%).
HT, hormone therapy.

HIRA claims data were analyzed for 5,667 patients who were diagnosed with EC and underwent surgery from 2010 to 2013, while the data for patients diagnosed in 2014 and 2015 were excluded. The mean follow-up period of this study was 47.5±14.0 months, and the mean interval from surgery to HT was 11.0±10.8 months. The mean duration of HT was 15.7±15.5 months in patients with recurrent disease and 23.7±18.7 months in patients without recurrence. Of the patients included in this analysis, 847 (14.9%) received HT, while 4,820 did not receive HT. Recurrence was observed in 446 patients (7.8%), including 50 patients (5.9%) who received HT and 396 patients (8.2%) who did not receive HT.

As shown in **Table 3**, univariate analysis revealed an increased recurrence rate in patients older than 50 years (HR=2.05; 95% CI=1.62–2.63; p<0.001), patients with advanced-stage EC (HR=24.51; 95% CI=18.63–32.35; p<0.001), and patients who underwent lymphadenectomy (HR=1.52; 95% CI=1.21–2.03; p=0.002) and a reduced recurrence rate in patients who received HT. Among the types of HT, estrogen only (HR=0.39; 95% CI=0.23–0.71; p=0.002), estrogen plus progesterone (HR=0.45; 95% CI=–0.29–0.98; p=0.034), and tibolone only (HR=0.50; 95% CI=0.35–0.84; p=0.008) significantly reduced recurrence, while progesterone only (HR=0.89; 95% CI=0.62–1.43; p=0.588) did not.

Multivariate analysis confirmed the significant increase in recurrence in patients older than 50 years (HR=1.47; 95% CI=1.14–1.89; p=0.003) and in patients with high-risk EC (HR=23.90; 95% CI=18.12–31.51; p<0.001). HT did not increase the recurrence rate of EC (HR=0.81; 95% CI=0.31–2.10; p=0.662), and the recurrence rate did not differ according to type of HT (**Table 4**).

DISCUSSION

This was the first large-scale population study in Korea to examine the effects of HT in EC survivors. To our knowledge, this is the largest study including patients in early stages as well as those with advanced disease. There was no significant increase in the disease recurrence

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Table 3. Univariate Cox regression model for associations between clinical factors and recurrence (2010–2013)

Characteristics	Recurrence* (n=446)	HR	95% CI	p-value
Age (yr)				<0.001
<50	75 (4.7)	1.00		
≥50	371 (9.1)	2.05	1.62–2.63	
Lymphadenectomy				0.002
No	75 (5.5)	1.00		
Yes	379 (8.5)	1.52	1.21–2.03	
Adjuvant therapy				<0.001
No adjuvant therapy+brachytherapy+EBRT (low-intermediate risk EC)	59 (1.3)	1.00		
Chemotherapy (high-risk EC)	387 (31.7)	24.51	18.63–32.35	
Postoperative HT				0.001
No	396 (8.2)	1.00		
Yes	50 (5.9)	0.62	0.46–0.83	
Type of HT				
No	396 (8.2)	1.00		
Estrogen	10 (3.9)	0.39	0.23–0.71	0.002
Estrogen plus progesterone	6 (5.4)	0.45	0.29–0.98	0.034
Tibolone	14 (5.3)	0.50	0.35–0.84	0.008
Progesterone	20 (9.5)	0.89	0.62–1.43	0.588

CI, confidence interval; EBRT, external beam radiation therapy; EC, endometrial cancer; HR, hazard ratio; HT, hormone therapy.
*Recurrence presented as number of patients (%).

Table 4. Multivariate Cox regression model for recurrence risk of EC according to each prognostic factor

Characteristics	HR	95% CI	p-value
Age ≥50 yr	1.47	1.14–1.89	0.003
Assessment of lymph node	1.07	0.82–1.39	0.365
Adjuvant therapy*	23.90	18.12–31.51	<0.001
Postoperative HT	0.81	0.31–2.10	0.662
Type of HT			
Estrogen	0.78	0.31–1.96	0.602
Estrogen plus progesterone	0.57	0.21–1.57	0.278
Tibolone	0.88	0.34–2.29	0.795
Progesterone	1.02	0.39–2.67	0.977

CI, confidence interval; EC, endometrial cancer; HR, hazard ratio; HT, hormone therapy.
*Adjuvant therapy is chemotherapy (high-risk EC).

rate in EC survivors who received HT. This pattern was also observed in the subgroup analysis stratified according to the type of HT and the severity of the disease.

The results of this study are consistent with previous literature. Several retrospective studies comparing HT use vs. non-use have been published, and none has demonstrated an increase in recurrence or mortality with HT prescription [19-24]. The only RCT of HT vs. placebo treatment in women with early-stage EC reported no statistically significant difference between the two groups [13]. However, this study had several limitations. The study was closed prematurely after the publication of the Women's Health Initiative study [25]. The majority of the enrolled patients had well-differentiated endometrioid adenocarcinomas, 95% of the patients had stage I lesions, and the absolute recurrence rate was low (overall 2.1%; 1.9% in the placebo group and 2.3% in the estrogen replacement therapy group). A meta-analysis based on one RCT and five observational studies suggested that HT does not increase the risk of recurrence in women with FIGO stage I/II EC (risk of recurrence in the HT group: odds ratio=0.53; 95% CI=0.30–0.96) [26]. In addition, recent Korean retrospective case-controlled study has reported that postoperative HT with drospirenone/estradiol did not increase recurrence or mortality in stage I/II EC survivors [15].

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In the present study, the recurrence rate was 7.8%, which was slightly lower than the previously reported recurrence rates of 10%–15% [27,28]. The reasons for this result include the relatively short period of follow-up (47.5±14.0 months) and the exclusion of advanced-stage patients who did not undergo surgery. Another possible reason is that patients who did not meet the definition of recurrence in this study were excluded from the analysis.

Due to the nature of the HIRA database, the disease stage, which is the most important factor for survival and recurrence analysis, was unknown. To overcome this issue, we stratified patients according to the type of adjuvant treatment in order to assign them to a particular FIGO stage. Thus, those with no adjuvant treatment or receiving radiation therapy were classified as non-high-risk EC, and those receiving chemotherapy were classified as high-risk EC.

It is crucial to know whether stratification of patients according to adjuvant therapy accurately reflects the FIGO stage of disease. Among patients with non-high-risk EC who either did not undergo adjuvant therapy or underwent RT in this study, 11.1% received RT such as brachytherapy and external beam radiation therapy, and the recurrence rate was 1.3% (median follow-up time 47.5 months). These results were very similar to the results of Gynecologic Oncology Group (GOG) 137 for stage I/II EC patients. In GOG 137, 8.1%–11.2% of patients underwent RT, and the recurrence rate was 2.1% (median follow-up time 35.7 months) [13]. In patients with high-risk EC who underwent adjuvant chemotherapy in the present study, the recurrence rate was 31.7%. In previous studies, the recurrence rates of advanced EC were similar to that of the present study, although there were differences in the follow-up periods and recurrence rates among the previous studies. Three RCTs comparing adjuvant chemotherapy vs. pelvic external beam RT in women with high-risk EC reported 5-year progression-free survival rates of 37% (FIGO stage IC grade 3 to stage III) and 20%–28% (FIGO stage I–III) [29,30]. Recently, the PORTEC-3 study reported a 5-year recurrence rate of 25%–31% in high-risk EC patients (stage I grade 3 to stage III) [31].

According to the 2017 HT position statement from the North American Menopause Society (NAMS), current data suggest that the recurrence and death rates of women who received HT among women with early-stage, low-risk EC (grade 1/2 endometrioid subtypes with negative estrogen and progesterone receptors) were similar to those who did not receive HT [32]. However, ET is not recommended for those with more advanced disease stages or higher-risk EC. In this study, the proportion of patients receiving adjuvant chemotherapy was 19.3%, of whom 10.6% underwent HT. HT including ET did not increase the recurrence of EC in patients with advanced disease. However, the stage distribution (especially for stages II, III and IV) and the sub-optimality of the surgery were not evaluated in this study. Therefore, the results should be interpreted with caution.

In the present study, the most common type of HT was tibolone (32%), followed by progesterone only (30%), estrogen only (22%), and estrogen plus progesterone (16%). These results are consistent with the results of a previous study. According to Lee et al. [14], tibolone was the most commonly prescribed drug (61.7%), while estrogen-only prescriptions comprised just 18.5% of the total prescriptions. There were minor differences in the distribution of HT prescription types between the two studies, which may be due to the fact that the study of Lee et al. included only gynecologic oncologists. Although there was no difference in the recurrence of EC according to the HT type in this study, estrogen-only prescriptions should be avoided in patients with advanced EC, according to the NAMS guidelines.

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In this study, the mean interval from surgery to HT was 11 months. The reason for the delay in HT after surgery may be adjuvant treatment or follow-up for recurrence. Previous studies have shown that mean disease-free interval varied between 1 and 15 months before HT [26]. The mean duration of HT in this study was 15 months, which was relatively short compared to the previous reports of 23–64 months [26]. This may be due to the way the duration of HT was measured in this study. In this study, the duration of HT was the period between the first and last prescriptions. Therefore, the duration of HT may be erroneously short, because the HT at the time of the last prescription was not included in the duration. For this reason, analysis of a dose-effect relationship was not performed according to duration of HT (1 year or 2 years).

This study had several limitations. First, there was a lack of clinical information such as stage, histologic type and grade, BMI, parity, oral contraceptive use, smoking history, physical activity, and procedures not covered by insurance such as robotic surgery. Second, because recurrence is not contained in the HIRA data, recurrence was defined as additional treatment after surgery. Therefore, recurrent or progressive patients who did not meet the definition of recurrence may have been excluded from this study. Although this indirect definition may cause bias, several previous studies using HIRA data also used this definition of recurrence. For example, recurrence was defined as additional surgery or chemotherapy after transurethral resection of a bladder tumor in a study of bladder cancer treatment patterns [33]. In addition, recurrence was defined as admission during follow-up after completion of initial treatment in a study of risk factors for schizophrenia recurrence [34]. Finally, since the information on HT duration from HIRA data was inaccurate, the dose dependent effect was not evaluated in the study. Moreover, although the mean duration of HT was almost two years in this study, it was not enough to assess the long-term effect of HT on recurrence in EC survivors.

Relatively short follow-up period, lack of data about medication adherence, and retrospective design are another limitations of this study. However, this is the first nationwide study evaluating the impact of HT on EC survivors with early- and advanced-stage EC in Korea.

In conclusion, postoperative HT did not increase disease recurrence in EC survivors. There was no significant difference in EC recurrence according to the type of HT. This study may support pre-existing evidence for HT in EC survivors suffering from menopausal symptoms.

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REFERENCES

1. Lim MC, Moon EK, Shin A, Jung KW, Won YJ, Seo SS, et al. Incidence of cervical, endometrial, and ovarian cancer in Korea, 1999–2010. J Gynecol Oncol 2013;24:298-302.
PUBMED | CROSSREF
2. Jung KW, Won YJ, Kong HJ, Lee ES. Prediction of cancer incidence and mortality in Korea, 2018. Cancer Res Treat 2018;50:317-23.
PUBMED | CROSSREF
3. Daraï E, Gompel A, Deval B, Laplace C, Lemoine A, Labeyrie E, et al. Hormone replacement therapy after endometrial or ovarian cancer. Gynecol Obstet Fertil 2000;28:198-204.
PUBMED

4. North American Menopause Society. The 2012 hormone therapy position statement of: The North American Menopause Society. Menopause 2012;19:257-71.
PUBMED | CROSSREF
5. Smith DC, Prentice R, Thompson DJ, Herrmann WL. Association of exogenous estrogen and endometrial carcinoma. N Engl J Med 1975;293:1164-7.
PUBMED | CROSSREF
6. Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 1975;293:1167-70.
PUBMED | CROSSREF
7. Singh P, Oehler MK. Hormone replacement after gynaecological cancer. Maturitas 2010;65:190-7.
PUBMED | CROSSREF
8. O'Donnell RL, Clement KM, Edmondson RJ. Hormone replacement therapy after treatment for a gynaecological malignancy. Curr Opin Obstet Gynecol 2016;28:32-41.
PUBMED | CROSSREF
9. Sjögren LL, Mørch LS, Løkkegaard E. Hormone replacement therapy and the risk of endometrial cancer: a systematic review. Maturitas 2016;91:25-35.
PUBMED | CROSSREF
10. Ayhan A, Taskiran C, Simsek S, Sever A. Does immediate hormone replacement therapy affect the oncologic outcome in endometrial cancer survivors? Int J Gynecol Cancer 2006;16:805-8.
PUBMED | CROSSREF
11. Guidozzi F. Estrogen therapy in gynecological cancer survivors. Climacteric 2013;16:611-7.
PUBMED | CROSSREF
12. Mørch LS, Kjaer SK, Keiding N, Løkkegaard E, Lidegaard Ø. The influence of hormone therapies on type I and II endometrial cancer: a nationwide cohort study. Int J Cancer 2016;138:1506-15.
PUBMED | CROSSREF
13. Barakat RR, Bundy BN, Spirtos NM, Bell J, Mannel RS; Gynecologic Oncology Group Study. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2006;24:587-92.
PUBMED | CROSSREF
14. Lee SJ, Yeo SG, Kang SB, Park DC. Attitudes and practices of Korean gynecologists towards hormone replacement therapy in endometrial cancer survivors. Eur J Gynaecol Oncol 2013;34:513-7.
PUBMED
15. Lim S, Kim YH, Lee KB, Lee JM. The influence of hormone therapy with drospirenone-estradiol on endometrioid type endometrial cancer patients. J Gynecol Oncol 2018;29:e72.
PUBMED | CROSSREF
16. Kim HA, Kim S, Seo YI, Choi HJ, Seong SC, Song YW, et al. The epidemiology of total knee replacement in South Korea: national registry data. Rheumatology (Oxford) 2008;47:88-91.
PUBMED | CROSSREF
17. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2018;16:170-99.
PUBMED | CROSSREF
18. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 2006;24:36-44.
PUBMED | CROSSREF
19. Creasman WT, Henderson D, Hinshaw W, Clarke-Pearson DL. Estrogen replacement therapy in the patient treated for endometrial cancer. Obstet Gynecol 1986;67:326-30.
PUBMED
20. Lee RB, Burke TW, Park RC. Estrogen replacement therapy following treatment for stage I endometrial carcinoma. Gynecol Oncol 1990;36:189-91.
PUBMED | CROSSREF
21. Baker DP. Estrogen-replacement therapy in patients with previous endometrial carcinoma. Compr Ther 1990;16:28-35.
PUBMED
22. Bryant GW. Administration of estrogens to patients with a previous diagnosis of endometrial adenocarcinoma. South Med J 1990;83:725-6.
PUBMED | CROSSREF
23. Chapman JA, DiSaia PJ, Osann K, Roth PD, Gillotte DL, Berman ML. Estrogen replacement in surgical stage I and II endometrial cancer survivors. Am J Obstet Gynecol 1996;175:1195-200.
PUBMED | CROSSREF

24. Suriano KA, McHale M, McLaren CE, Li KT, Re A, DiSaia PJ. Estrogen replacement therapy in endometrial cancer patients: a matched control study. Obstet Gynecol 2001;97:555-60.
PUBMED
25. Chlebowski RT, Anderson GL, Sarto GE, Haque R, Runowicz CD, Aragaki AK, et al. Continuous combined estrogen plus progestin and endometrial cancer: The Women's Health Initiative Randomized Trial. J Natl Cancer Inst 2015;108:djv350.
PUBMED
26. Shim SH, Lee SJ, Kim SN. Effects of hormone replacement therapy on the rate of recurrence in endometrial cancer survivors: a meta-analysis. Eur J Cancer 2014;50:1628-37.
PUBMED | CROSSREF
27. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355:1404-11.
PUBMED | CROSSREF
28. Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 1991;40:55-65.
PUBMED | CROSSREF
29. Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. Br J Cancer 2006;95:266-71.
PUBMED | CROSSREF
30. Hogberg T, Signorelli M, de Oliveira CF, Fossati R, Lissoni AA, Sorbe B, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer 2010;46:2422-31.
PUBMED | CROSSREF
31. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:295-309.
PUBMED | CROSSREF
32. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause 2017;24:728-53.
PUBMED | CROSSREF
33. Seo GH, Kim JH, Ku JH. Clinical practice pattern of immediate intravesical chemotherapy following transurethral resection of a bladder tumor in Korea: National Health Insurance Database Study. Sci Rep 2016;6:22716.
PUBMED | CROSSREF
34. Lee SU, Soh M, Ryu V, Kim CE, Park S, Roh S, et al. Analysis of the Health Insurance Review and Assessment Service data from 2011 to 2015. Int J Ment Health Syst 2018;12:9.
PUBMED | CROSSREF