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Thesis for the Degree of Doctor of Philosophy

Hormone Replacement Therapy and Risks of Breast and Gynecologic Cancer

– A Nationwide Cohort Study of Postmenopausal Women in South Korea –

호르몬 대체 요법과 유방암 및 부인암의 위험: 대한민국 폐경 후 여성 대상 전국 코호트 연구

February 2025

Graduate School of
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Hormone Replacement Therapy and Risks of Breast and Gynecologic Cancer

– A Nationwide Cohort Study of Postmenopausal Women in South Korea –

Advisor Jae Yong Han

December 2024

Graduate School of
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Abstract

This study investigates the relationship between hormone replacement therapy (HRT) and the occurrence of breast and gynecologic cancers in postmenopausal women using a nationwide cohort in South Korea.

HRT is widely used to relieve menopausal symptoms and mitigate age-related health conditions. However, its potential link to cancer risks remains controversial. This study investigates the occurrence of breast and gynecologic cancers in postmenopausal women in South Korea, comparing outcomes between HRT users and non-users within a nationwide cohort. Using the Korean National Health Insurance Service (NHIS) data, we conducted a retrospective cohort analysis of 2,003,757 postmenopausal women aged 40 years and older from 2009 to 2021. Participants were categorized by HRT usage into four groups: no use, estrogen-only therapy, estrogen-progestin combination therapy, or tibolone. The incidence of breast, cervical, endometrial, and ovarian cancers was assessed using Cox proportional hazards regression models, providing hazard ratios (HRs) and 95% confidence intervals (CIs). HRT use was linked to an increased risk of breast cancer (HR 1.37, 95% CI 1.33-1.42), with combined estrogen-progestin therapy exhibiting the highest risk (HR 2.16, 95% CI 2.03-2.30). In contrast, cervical cancer risk decreased with HRT use (HR 0.84, 95% CI 0.76-0.92), particularly with longer therapy duration. No significant association was found for ovarian cancer (HR 1.02, 95% CI 0.94-1.12), while tibolone-only therapy was slightly associated with an increased risk of endometrial cancer (HR 1.26, 95% CI 1.01-1.56). The impact of HRT on cancer risk in postmenopausal women varies according to cancer type, therapy duration, and hormone formulation. While HRT is associated with an increased risk of breast cancer, it may reduce the risk of cervical cancer. These findings underscore the importance of adopting personalized HRT approaches tailored to individual risk profiles, enabling informed

clinical decision-making and guiding public health policies.

Keyword : Hormone replacement therapy, breast cancer, gynecologic cancers, postmenopausal women, cancer risk
Student Number : 2019-23487

Table of Contents

List of Tables and Figures

List of Abbreviations

ANOVA; Analysis of variance

BMI; Body mass index

CIs; Confidence intervals

ER; Estrogen receptor

HR; Hazard ratio

HRT; Hormone replacement therapy

ICD-10; International Classification of Diseases, 10th revision

NHIS; National Health Insurance Service

SHBG; Sex hormone-binding globulin

WHI; Women's Health Initiative

WHO; World Health Organization

1. Hormone Replacement Therapy and Risks of Breast and Gynecologic Cancer: A Nationwide Cohort Study of Postmenopausal Women in South Korea

1.1. Introduction

Start your Dissertation. Menopause, as defined by the World Health Organization (WHO), occurs when ovarian function ceases, leading to the cessation of female hormone production. It is typically diagnosed after 12 consecutive months without menstruation. Globally, the average age of menopause ranges from 46 to 52 years, while Korean women experience menopause at an average age of 49.7 years, with a typical range from the early 40s to 58 years [1]. Common symptoms of menopause include vasomotor symptoms such as hot flashes, headaches, sweating, as well as vaginal dryness, anxiety, insomnia, and depression. Additional symptoms, including muscle and joint pain and urogenital syndrome, may significantly reduce quality of life if they are untreated. Moreover, long-term hormonal imbalances after menopause increase the risk of age-related diseases, including osteoporosis, cardiovascular diseases, and dementia [2].

Hormone replacement therapy (HRT) is often used to alleviate menopausal symptoms and enhance postmenopausal quality of life. Effective HRT requires careful selection of the hormone formulation, dosage, administration method, and treatment duration tailored to the individual. The therapy primarily utilizes three types of hormones: estrogen, progestogen, and tibolone. Estrogen-only therapy effectively addresses many menopausal symptoms and helps prevent conditions like osteoporosis caused by estrogen deficiency. However, prolonged use of estrogen alone may increase the risk of endometrial hyperplasia and endometrial cancer, which

can be mitigated by adding progestogen to protect the endometrium [3]. Tibolone, with estrogenic, progestogenic, and androgenic properties, is also effective in relieving menopausal symptoms and preventing osteoporosis and fractures, comparable to other hormone formulations [4].

The use of HRT initially began with estrogen-only therapy in the 1970s in many countries. However, concerns over the risk of endometrial cancer prompted a shift toward combined estrogen-progestogen therapy, which became widely recommended for postmenopausal women by the 1990s. Despite its benefits, studies have shown that HRT is not without risks, particularly concerning cancer [5-9]. In 2002, the Women's Health Initiative (WHI) raised concerns about the safety of HRT, which led to a sharp decline in its use [2] (Figure 1).

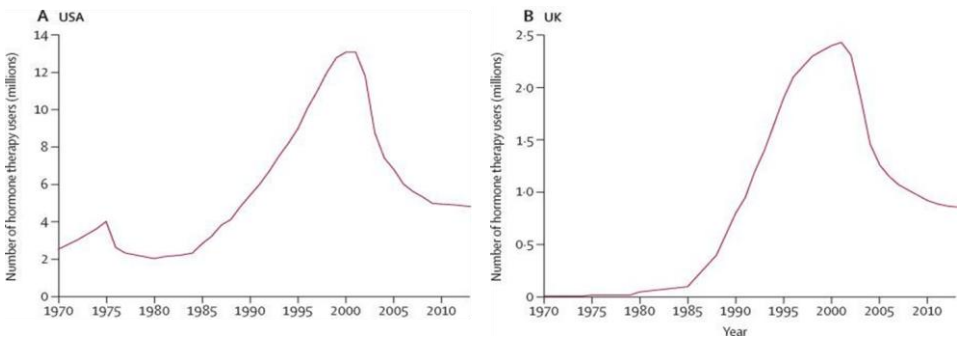
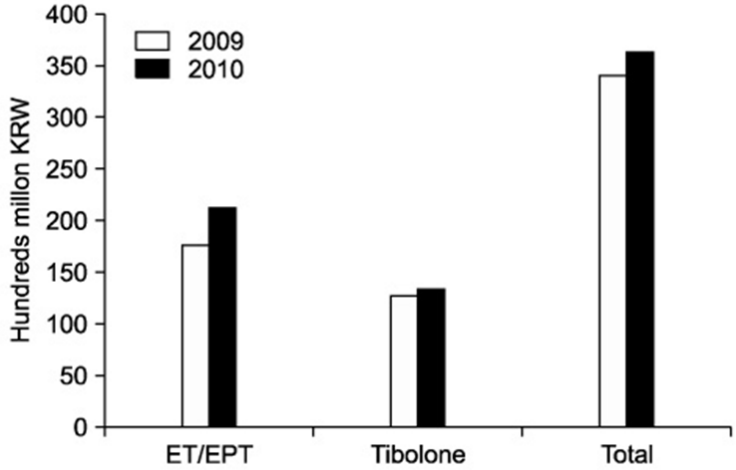


Figure 1. Trends in hormone therapy use in the USA and the UK
(COLLABORATIVE GROUP ON EPIDEMIOLOGICAL STUDIES OF OVARIAN CANCER, et al. The Lancet, 2015)

In Korea, early studies from the United States linking HRT to an increased risk of breast cancer caused many Korean women to avoid it. This trend persisted from 2002 to 2007 until reevaluations by WHI suggested no elevated risk of cardiovascular disease or mortality in younger postmenopausal women using HRT. Following these findings, HRT use in Korea has steadily increased since 2007. According to a 2010 study, 4.5% of Korean women over the age of 50 used HRT, with 60% opting for estrogen or estrogen-progestogen combinations and 40% choosing tibolone [10] (Figure 2).



Medicine	Total consumption cost (KRW)	%
EPT	20,200,000,000	53
ET	2,700,000,000	7
Tibolone	15,200,000,000	40
Total	38,100,000,000	100

Figure 2. Trends in hormone therapy use in South Korea [10]

HRT has been shown to effectively manage menopausal symptoms and mitigate the side effects of cancer treatments, including estrogen depletion experienced by breast cancer survivors, thereby enhancing their quality of life. Additionally, HRT has been associated with a reduced risk of developing certain types of cancers. Previous studies have shown that HRT use is linked to a lower incidence and mortality rate of colorectal cancer [11], as well as a 20% reduction in lung cancer risk among women undergoing therapy [12] (Figure 3).

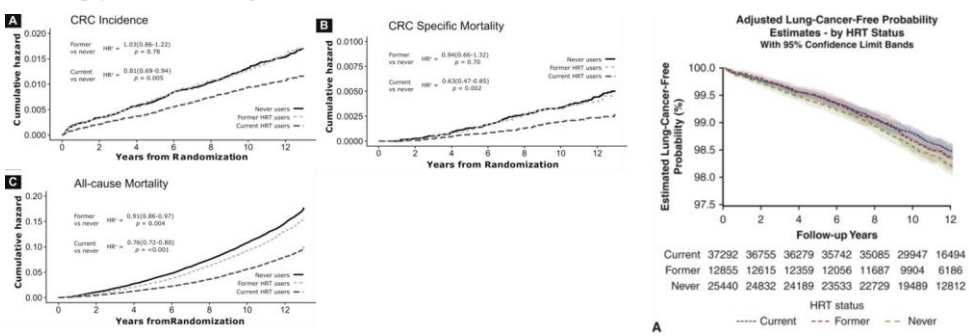


Figure 3. Benefits of HRT in colorectal and lung cancer risk [11, 12]

However, some studies suggest that HRT does not provide exclusively beneficial effects concerning cancer risk in menopausal women. International research on the risk of breast cancer associated with HRT formulations and usage duration indicates significant variability depending on the type of therapy. Combined therapy and long-term use are linked to a higher risk of breast cancer compared to estrogen-only therapy. Specifically, estrogen only and combined estrogen-progestogen therapies are associated with a 17% and 60% increased risk of breast cancer, respectively, with prolonged use (over five years) further amplifying the risk [9]. These findings underscore the complexities of prescribing and managing HRT, given the heightened risk of breast cancer development and recurrence associated with specific HRT types and durations (Figure 4).

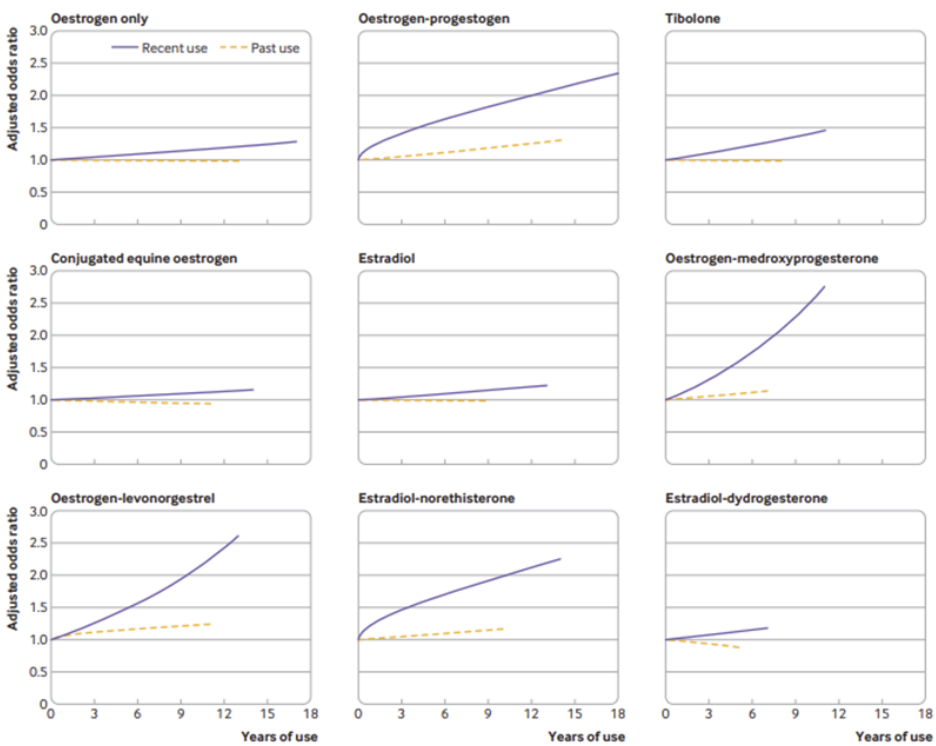


Figure 4. The variability in breast cancer risk by HRT type or duration [9]

A large-scale study conducted in the United Kingdom reported that women who received estrogen-based HRT had an increased

risk of both breast and endometrial cancers compared to non-users. To mitigate this risk, the combined use of estrogen and progestogen is often recommended over estrogen monotherapy. However, combined estrogen-progestogen therapy has also been associated with significant rates of breast and endometrial cancers [13, 14] (Figure 5).

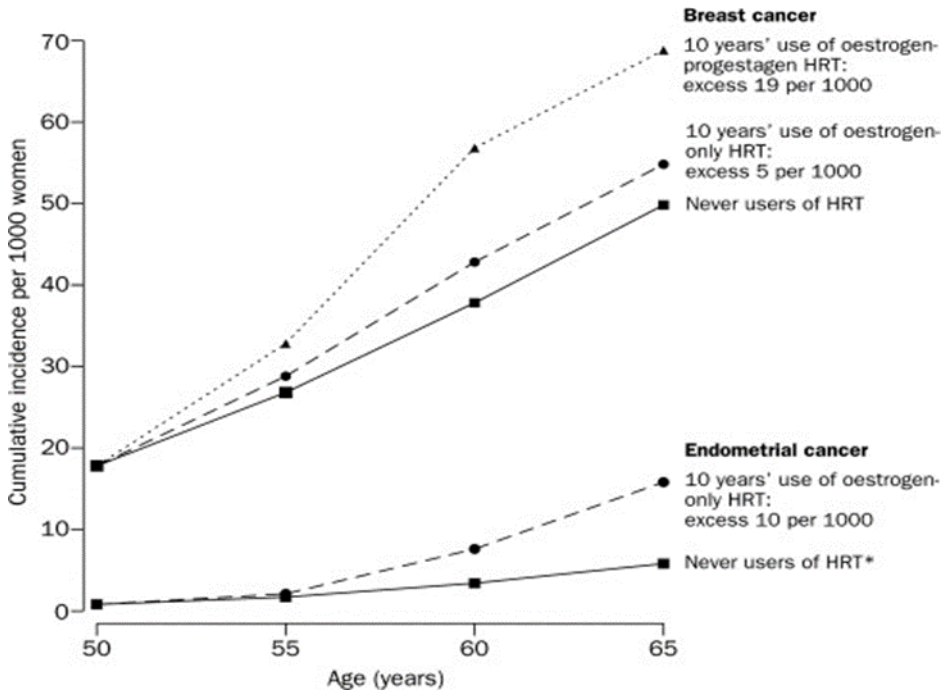


Figure 5. HRT usage increases risk of breast and endometrial cancer [13]

Another study involving approximately 900,000 postmenopausal women in the UK reported a 20% higher incidence of ovarian cancer among HRT users compared to non-users [5]. For every 2,500 HRT users, at least one case of ovarian cancer was observed, and for every 3,300 HRT users, at least one death from ovarian cancer was reported. Furthermore, ovarian, breast, and endometrial cancers collectively accounted for 40% of all female cancers in the UK, with the incidence rates of these three cancers being approximately 63% higher in women undergoing HRT [7].

Thus far, studies exploring the relationship between menopause and the risk of gynecologic cancers have yielded inconsistent results due to variations in research design, participant selection

criteria, hormone types, and exposure definitions, making it difficult to draw definitive conclusions. Moreover, differences in gynecologic cancer rates between Korean women and those in other countries underscore the limitations of generalizing findings from predominantly Western studies [15–17]. Comprehensive research still remains scarce on the risks of ovarian, breast, and endometrial cancers among postmenopausal women using HRT. Research focusing on HRT use, hormone type, and duration in Korean women are crucial for evaluating its effectiveness and safety in this population. Therefore, using data from the National Health Insurance Service (NHIS), this large-scale study tailored to Korean women aims to identify the appropriate target population for HRT, ultimately improving the quality of life for postmenopausal women through its safe and effective application.

1.2. Materials and Methods

1. 2. 1. Data sources

This study utilized data from Korea's NHIS database [18]. As Korea's sole public health insurance system, NHIS provides mandatory universal health coverage for approximately 97% of the Korean population, and has collected comprehensive healthcare utilization data since 2000 [18, 19]. The NHIS database includes information on eligibility, demographics, medical treatments, surgical history, prescription records, and periodic nationwide health screenings [18]. Medical institutions submit claims data to the NHIS for reimbursement, which is then systematically stored in the database [19, 20]. Additionally, the database is linked to mortality data from Statistics Korea, enabling longitudinal follow-up of health outcomes [18, 19]. The NHIS encrypts personal identifiers to protect individual privacy while retaining the ability to track patients over time [19].

1. 2. 2. Study population and data collection

We conducted a retrospective cohort study using data from the NHIS database (NHIS-2023-1-009), covering women aged 40 years or older between 2009 and 2021. The study population included postmenopausal women aged years or older who had undergone both general health examinations and cancer screenings. Postmenopausal status was determined either by self-reported menopause in the cancer screening questionnaire or by the presence of a diagnostic code of N97 based on the International Classification of Diseases, 10th revision (ICD-10). Exclusion criteria included a follow-up period less than one year, a diagnosis of any malignancy within one year of enrollment, and incomplete records with missing variables of interest. Women's age at health examination was calculated as the time interval between their birth date and the date of health examination.

Data collected from the general health examination and cancer

screening questionnaires included age, body mass index (BMI), smoking status, alcohol consumption, parity, age at menarche, and history of hormone therapy use. HRT medications were identified through prescription records in the NHIS database. Participants were categorized into three groups based on their prescriptions: those receiving estrogen, estrogen plus progesterone and those receiving tibolone.

Of the 3,041,191 postmenopausal women initially identified, 2,003,757 were included in the analysis, comprising 1,669,566 non-HRT users and 304,191 HRT users. Prescription records for HRT were collected within one year of the health examination date for participants who reported HRT use, with 100,854 records included in the analysis.

1. 2. 3. Classification and outcomes

Female-specific cancers were identified through the NHIS claims database using both an ICD-10 diagnostic code and a special copayment reduction code (V193). The NHIS operates a copayment reduction program to ease the financial burden on patients with severe illnesses requiring long-term, costly treatments. Under this program, cancer patients registered with code V193 are required to pay only 5% of the total medical expenses for both outpatient and inpatient care, excluding non-covered services. The registration is valid for up to 5 years and can be renewed if continued treatment is needed. The female-specific cancers examined in this study included breast cancer (C50), cervical cancer (C53), endometrial cancer (C54), and ovarian cancer (C56). The onset of female-specific cancers was defined as cases where the primary diagnosis code in the NHIS claims data included the ICD-10 codes of interest for female cancers, along with the special co-payment reduction code V193. The duration until cancer development was defined as the period from the baseline date, marked by the first health screening of postmenopausal women, to the date of diagnosis.

All independent variables were stratified before analysis. Age was divided into 5-year intervals from 40 years to ≥65 years.

BMI was classified according to the Korean Society for the Study of Obesity criteria: normal weight (<25 kg/m²), overweight to class I obesity (25–29.9 kg/m²), and class II obesity (≥30 kg/m²). Lifestyle variables included smoking status, categorized as never or ever/current smoker, and alcohol consumption, classified as none or ≥1 time per week. Sex-specific variables included parity, dichotomized into nulliparous and parous, and age at menarche, categorized according to early menarche criteria [21]. Hormone replacement therapy was stratified into four categories based on duration of use: never used, <2 years, <5 years, and ≥5 years.

1. 2. 4. Statistical analysis

Baseline characteristics were analyzed using Student's t-test for continuous variables, and ANOVA for comparisons among multiple groups. For categorical variables, Chi-square test was performed to assess independence between groups. The main analytical objectives were to examine the associations between: 1) HRT use versus non-use and female cancer incidence, 2) the duration of HRT use and female cancer incidence, and 3) the types of HRT medications and female cancer incidence.

Survival analysis was conducted, with survival defined as the period from the health examination date to the diagnosis of female cancer, while all other cases were treated as censored. Cox proportional hazards regression analysis was used as the primary statistical method. This method models both the influence of multiple variables on survival time and the time to the occurrence of events of interest. Cox regression offers several advantages: it can simultaneously analyze the effects of multiple variables, accommodate censored data, and incorporate both continuous and categorical variables. Also, multiple regression analysis was employed to control for confounding variables. In this study, age was identified as a key confounding variable. To address this, multivariate Cox regression analysis was performed, incorporating age as a covariate in the survival analysis. Results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs), where an

HR greater than 1 indicates increased risk and an HR less than 1 indicates decreased risk. This analysis aimed to systematically evaluate the independent effects of each variable on the outcomes. All statistical analyses and survival analyses were performed using the R statistical software platform, with statistical significance set at $p < 0.05$.

1.3. Results

1. 3. 1. Study Population Characteristics

Figure 6 illustrates the study inclusion criteria and identification process. The analysis included postmenopausal women with data from general medical examination and cancer screenings, sourced from the NHIS database covering the Korean population between 2009 and 2017 (Table 1). The Table 2 categorizes the demographic data of postmenopausal women who used estrogens only, combined estrogen plus progesterone and tibolone. The analysis consisted of 42 participants under the age of 45, 223 participants aged 45 to 49, 1,154 participants aged 50 to 54, 673 participants aged 55 to 59, 445 participants aged 60 to 64, and 188 participants aged 65 and older. Additionally, the analysis included 166 participants in the nulliparous group and 2,557 participants in the parous group (Table 2). A total of 2,003,757 women were included in the final study population, comprising 1,699,566 non-HRT users and 3,041,191 HRT users (Fig. 6).

Table 1. Demographic data of post-menopausal included in analysis

	Breast cancer	**Cervical cancer**	**Endometrial cancer**	**Ovarian cancer**	**Normal**	**P-value**
	(N=24143)	(N=3890)	(N=3539)	(N=4021)	(N=1968164)	
AGE						0
- <45 years	207 (0.9%)	22 (0.6%)	22 (0.6%)	30 (0.7%)	13148 (0.7%)	
- <50 years	1452 (6.0%)	152 (3.9%)	210 (5.9%)	203 (5.0%)	120275 (6.1%)	
- <55 years	8722 (36.1%)	934 (24.0%)	1345 (38.0%)	1114 (27.7%)	619945 (31.5%)	
- <60 years	4945 (20.5%)	699 (18.0%)	796 (22.5%)	672 (16.7%)	340521 (17.3%)	
- <65 years	4431 (18.4%)	742 (19.1%)	623 (17.6%)	741 (18.4%)	327751 (16.7%)	
- >=65 years	4386 (18.2%)	1341 (34.5%)	543 (15.3%)	1261 (31.4%)	546524 (27.8%)	
BMI						0
- <25kg/m^2	14470 (60.0%)	2365 (60.8%)	1980 (56.0%)	2537 (63.1%)	1267852 (64.4%)	
- 25-29kg/m^2	8367 (34.7%)	1332 (34.3%)	1296 (36.6%)	1289 (32.1%)	616668 (31.3%)	
- 30+kg/m^2	1298 (5.4%)	192 (4.9%)	262 (7.4%)	195 (4.8%)	83235 (4.2%)	
Smoking						0
- Never	23030 (95.7%)	3685 (95.1%)	3409 (96.9%)	3846 (96.1%)	1885242 (96.2%)	
- Ever & Now	1030 (4.3%)	190 (4.9%)	108 (3.1%)	156 (3.9%)	75433 (3.8%)	
Drinking						0.006
- Never	19962 (83.3%)	3217 (83.4%)	2941 (83.8%)	3413 (85.6%)	1638450 (83.9%)	
- 1>=Week	3988 (16.7%)	639 (16.6%)	567 (16.2%)	574 (14.4%)	314694 (16.1%)	
Parity						0
- Nulliparous	1027 (4.3%)	88 (2.3%)	162 (4.6%)	169 (4.2%)	56050 (2.9%)	
- Parous	23076 (95.7%)	3797 (97.7%)	3372 (95.4%)	3849 (95.8%)	1909638 (97.1%)	
Age at menarche						0
- <13 years	431 (1.8%)	44 (1.2%)	50 (1.4%)	49 (1.2%)	28577 (1.5%)	
- +13 years	23255 (98.2%)	3776 (98.8%)	3427 (98.6%)	3891 (98.8%)	1904596 (98.5%)	
HRT_DURATION						0
- No	19247 (79.7%)	3368 (86.6%)	2977 (84.1%)	3382 (84.1%)	1670592 (84.9%)	
- <2 years	2685 (11.1%)	335 (8.6%)	310 (8.8%)	373 (9.3%)	184830 (9.4%)	

- 2-4 years	1132 (4.7%)	103 (2.6%)	158 (4.5%)	146 (3.6%)	64608 (3.3%)	
- >=5 years	1079 (4.5%)	84 (2.2%)	94 (2.7%)	120 (3.0%)	48134 (2.4%)	
HRT_YN						0
- No	19247 (79.7%)	3368 (86.6%)	2977 (84.1%)	3382 (84.1%)	1670592 (84.9%)	
- Yes	4896 (20.3%)	522 (13.4%)	562 (15.9%)	639 (15.9%)	297572 (15.1%)	

Table 2. Demographic data in estrogens only, combined estrogen plus progesterone, tibolone users. Abbreviations: BMI, body mass index;

	Breast cancer	**Cervical cancer**	**Endometrial cancer**	**Ovarian cancer**	**Normal**	**P-value**
	(N=2163)	(N=167)	(N=192)	(N=203)	(N=98129)	
AGE						0
- <45 years	32 (1.5%)	5 (3.0%)	3 (1.6%)	2 (1.0%)	1851 (1.9%)	
- <50 years	171 (7.9%)	17 (10.2%)	16 (8.3%)	19 (9.4%)	10972 (11.2%)	
- <55 years	911 (42.1%)	62 (37.1%)	88 (45.8%)	93 (45.8%)	43511 (44.3%)	
- <60 years	540 (25.0%)	46 (27.5%)	51 (26.6%)	36 (17.7%)	21885 (22.3%)	
- <65 years	367 (17.0%)	26 (15.6%)	25 (13.0%)	27 (13.3%)	13830 (14.1%)	
- >=65 years	142 (6.6%)	11 (6.6%)	9 (4.7%)	26 (12.8%)	6080 (6.2%)	
BMI						0.541
- <25kg/m^2	1574 (72.8%)	117 (70.1%)	144 (75.0%)	159 (78.3%)	72806 (74.2%)	
- 25-29kg/m^2	545 (25.2%)	48 (28.7%)	45 (23.4%)	41 (20.2%)	23359 (23.8%)	
- 30+kg/m^2	43 (2.0%)	2 (1.2%)	3 (1.6%)	3 (1.5%)	1949 (2.0%)	
Smoking						0.026
- Never	1986 (92.2%)	156 (94.0%)	184 (96.8%)	186 (92.5%)	91506 (93.6%)	
- Ever & Now	168 (7.8%)	10 (6.0%)	6 (3.2%)	15 (7.5%)	6217 (6.4%)	
Drinking						0.383
- Never	1598 (74.5%)	123 (74.5%)	149 (78.4%)	159 (79.1%)	72319 (74.3%)	
- 1>=Week	548 (25.5%)	42 (25.5%)	41 (21.6%)	42 (20.9%)	25041 (25.7%)	
Parity						0
- Nulliparous	131 (6.1%)	6 (3.6%)	14 (7.3%)	15 (7.4%)	4277 (4.4%)	
- Parous	2030 (93.9%)	161 (96.4%)	178 (92.7%)	188 (92.6%)	93762 (95.6%)	
Age at menarche						0.763
- <13 years	47 (2.2%)	5 (3.0%)	4 (2.2%)	6 (3.0%)	1998 (2.1%)	
- +13 years	2082 (97.8%)	159 (97.0%)	182 (97.8%)	194 (97.0%)	94825 (97.9%)	
HRT_DURATION						0
- <2 years	904 (41.8%)	90 (53.9%)	81 (42.2%)	88 (43.3%)	50471 (51.4%)	
- 2-4 years	552 (25.5%)	32 (19.2%)	56 (29.2%)	47 (23.2%)	23464 (23.9%)	
- >=5 years	707 (32.7%)	45 (26.9%)	55 (28.6%)	68 (33.5%)	24194 (24.7%)	
Estrogen only						0.113
- NO	1995 (92.2%)	155 (92.8%)	180 (93.8%)	184 (90.6%)	89160 (90.9%)	

- YES	168 (7.8%)	12 (7.2%)	12 (6.2%)	19 (9.4%)	8969 (9.1%)	
Estrogen & progesterone						0
- NO	891 (41.2%)	71 (42.5%)	101 (52.6%)	87 (42.9%)	47446 (48.4%)	
- YES	1272 (58.8%)	96 (57.5%)	91 (47.4%)	116 (57.1%)	50683 (51.6%)	
Tibolone						0
- NO	1275 (58.9%)	90 (53.9%)	90 (46.9%)	117 (57.6%)	52182 (53.2%)	
- YES	888 (41.1%)	77 (46.1%)	102 (53.1%)	86 (42.4%)	45947 (46.8%)	
Progesterone only						0.629
- NO	2100 (97.1%)	161 (96.4%)	183 (95.3%)	198 (97.5%)	94911 (96.7%)	
- YES	63 (2.9%)	6 (3.6%)	9 (4.7%)	5 (2.5%)	3218 (3.3%)	

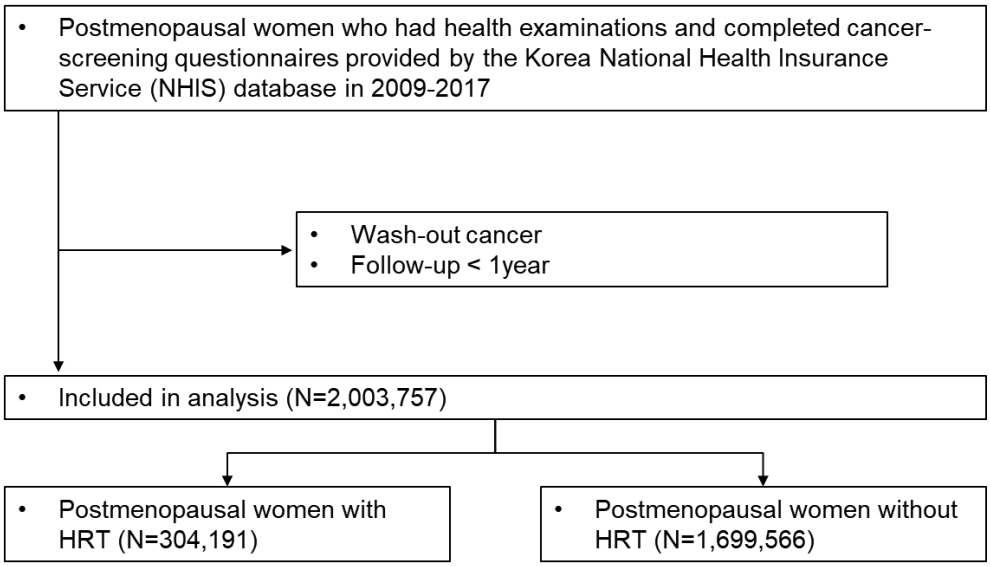


Figure 6. Flow chart for extracting eligible patients.

1. 3. 2. HRT Use and Risk of Female Cancers

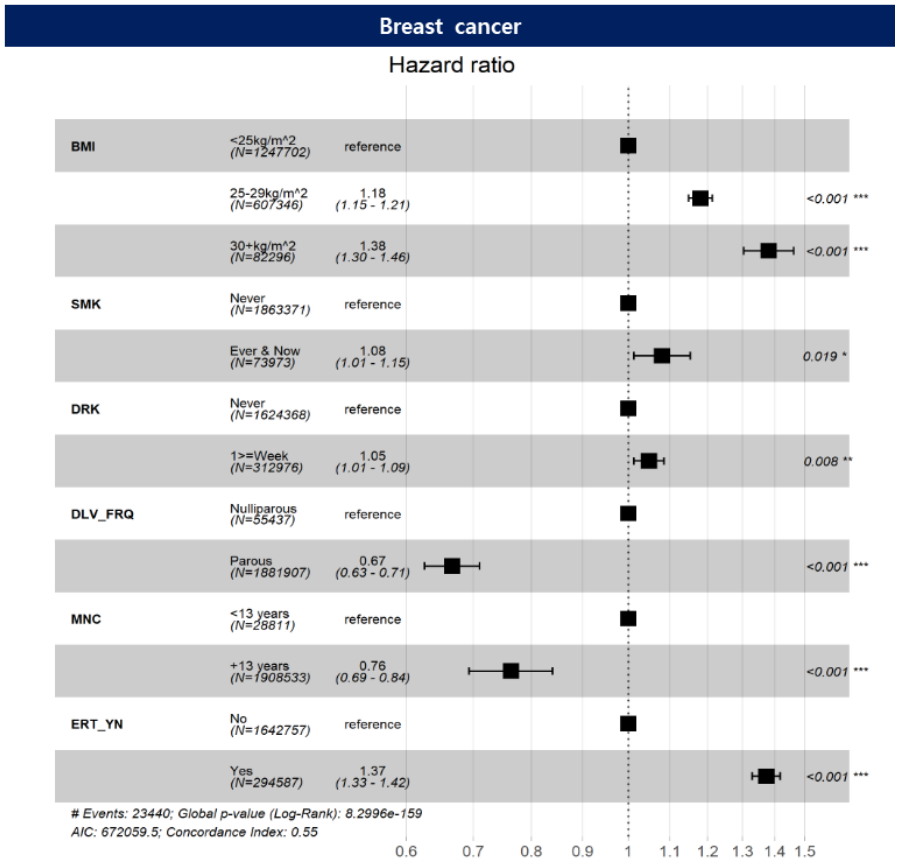
The analysis of female cancer incidence among postmenopausal women revealed an increased risk of breast cancer in HRT users compared to non-users (HR 1.37; 95% CI 1.33–1.42) (Fig. 7A, Table 3). In contrast, HRT use was associated with a decreased risk of cervical cancer (HR 0.84; 95% CI 0.76–0.92) (Fig. 7B, Table 3). No significant association was found between HRT use and the risk of endometrial cancer (HR 1.03; 95% CI 0.94–1.13) (Fig. 7C), or ovarian cancer (HR 1.02; 95% CI 0.94–1.12) (Fig. 7D).

Table 3. Association of HRT use status and incidence of female cancers among post-menopausal women: (A) breast cancer, (B) cervical cancer. In post-menopausal women, BMI, smoking, drinking, age at menarche, and HRT were adjusted

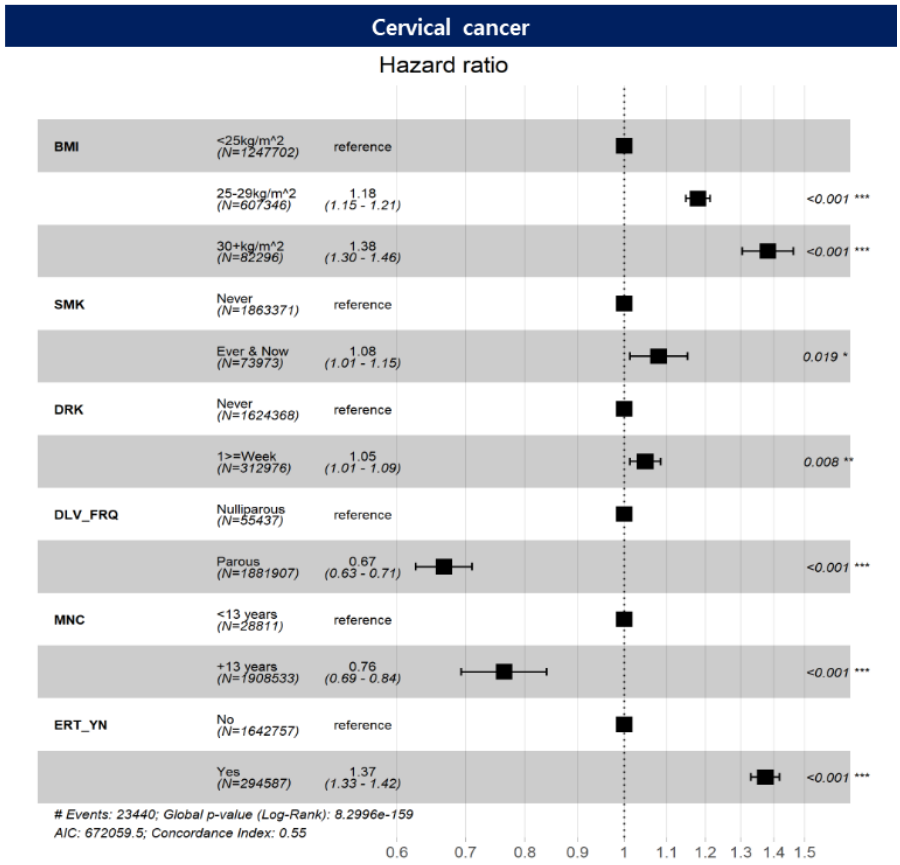
		Breast cancer		Cervical cancer	
Features		**Hazard ratio**	**P-value**	**Hazard ratio**	**P-value**
BMI	<25kg/m^2	1 (Ref.)		1 (Ref.)	
	25-29kg/m^2	1.18 (1.15 - 1.21)	<0.001***	1.12 (1.04 - 1.20)	0.001**
	30+kg/m^2	1.38 (1.30 - 1.46)	<0.001***	1.22 (1.05 - 1.41)	0.01**
Smoking	Never	1 (Ref.)		1 (Ref.)	
	Ever & Now	1.08 (1.01 - 1.15)	0.019*	1.33 (1.15 - 1.55)	<0.001***
Drinking	Never	1 (Ref.)		1 (Ref.)	
	1≥Week	1.05 (1.01 - 1.09)	0.008**	1.09 (1.00 - 1.19)	0.041*
Parity	Nulliparous	1 (Ref.)		1 (Ref.)	
	Parous	0.67 (0.63 - 0.71)	<0.001***	1.25 (1.01 – 1.55)	0.042*
Age at menarche	Age < 13	1 (Ref.)		1 (Ref.)	
	Age ≥ 13	0.76 (0.69 - 0.84)	<0.001***	1.14 (0.84 – 1.54)	0.394
HRT	No	1 (Ref.)		1 (Ref.)	
	Yes	1.37 (1.33 - 1.42)	<0.001***	0.84 (0.76 – 0.92)	<0.001***

*P-value <0.05, **P-value < 0.01, ***P-value < 0.001

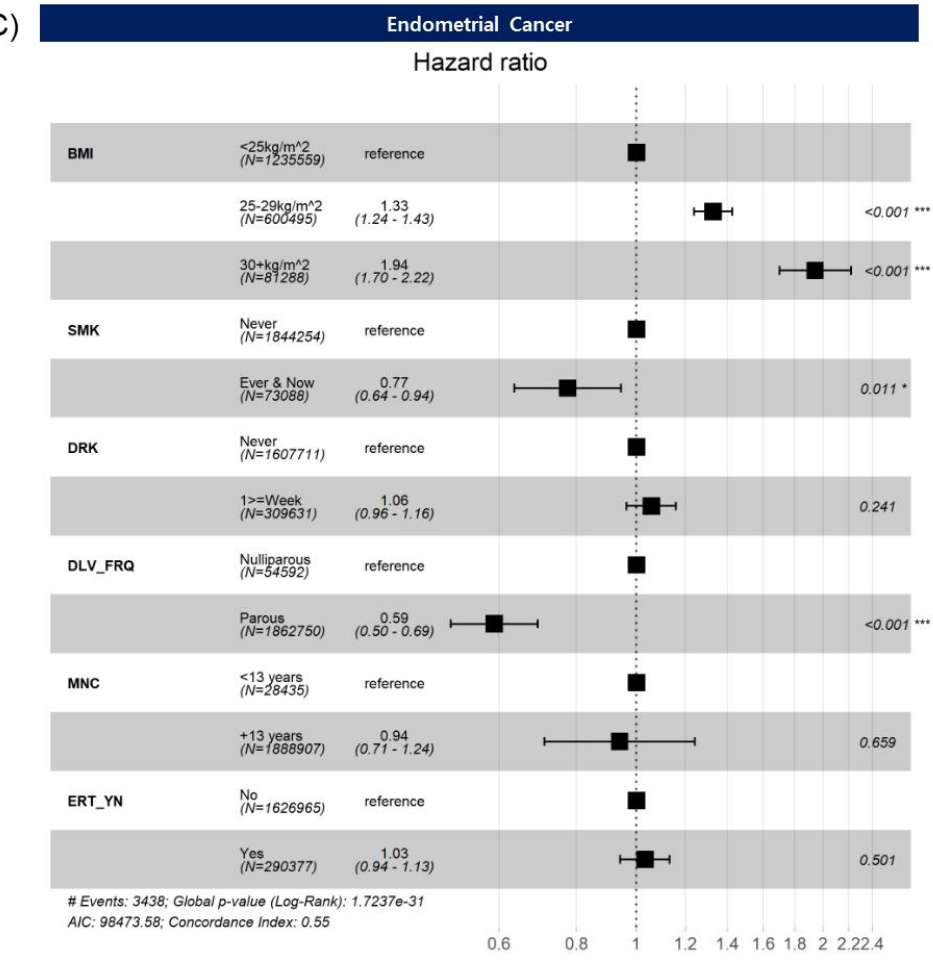
A)


Breast cancer
Hazard ratio
BMI
<25kg/m^2 (N=1247702)
reference
25-29kg/m^2 (N=607346)
1.18 (1.15 - 1.21)
<0.001 ***
30+kg/m^2 (N=82296)
1.38 (1.30 - 1.46)
<0.001 ***
SMK
Never (N=1863371)
reference
Ever & Now (N=73973)
1.08 (1.01 - 1.15)
0.019 *
DRK
Never (N=1624368)
reference
1>=Week (N=312976)
1.05 (1.01 - 1.09)
0.008 **
DLV_FRQ
Nulliparous (N=55437)
reference
Parous (N=1881907)
0.67 (0.63 - 0.71)
<0.001 ***
MNC
<13 years (N=28811)
reference
+13 years (N=1908533)
0.76 (0.69 - 0.84)
<0.001 ***
ERT_YN
No (N=1642757)
reference
Yes (N=294587)
1.37 (1.33 - 1.42)
<0.001 ***
Events: 23440; Global p-value (Log-Rank): 8.2996e-159
AIC: 672059.5; Concordance Index: 0.55
0.6 0.7 0.8 0.9 1 1.1 1.2 1.3 1.4 1.5

B)


Cervical cancer
Hazard ratio
BMI
<25kg/m^2 (N=1247702)
reference
25-29kg/m^2 (N=607346)
1.18 (1.15 - 1.21)
<0.001 ***
30+kg/m^2 (N=82296)
1.38 (1.30 - 1.46)
<0.001 ***
SMK
Never (N=1863371)
reference
Ever & Now (N=73973)
1.08 (1.01 - 1.15)
0.019 *
DRK
Never (N=1624368)
reference
1>=Week (N=312976)
1.05 (1.01 - 1.09)
0.008 **
DLV_FRQ
Nulliparous (N=55437)
reference
Parous (N=1881907)
0.67 (0.63 - 0.71)
<0.001 ***
MNC
<13 years (N=28811)
reference
+13 years (N=1908533)
0.76 (0.69 - 0.84)
<0.001 ***
ERT_YN
No (N=1642757)
reference
Yes (N=294587)
1.37 (1.33 - 1.42)
<0.001 ***
Events: 23440; Global p-value (Log-Rank): 8.2996e-159
AIC: 672059.5; Concordance Index: 0.55
0.6
0.7
0.8
0.9
1
1.1
1.2
1.3
1.4
1.5

C)


Endometrial Cancer
Hazard ratio
BMI
<25kg/m^2 (N=1235559)
reference
25-29kg/m^2 (N=600495)
1.33 (1.24 - 1.43)
<0.001 ***
30+kg/m^2 (N=81288)
1.94 (1.70 - 2.22)
<0.001 ***
SMK
Never (N=1844254)
reference
Ever & Now (N=73088)
0.77 (0.64 - 0.94)
0.011 *
DRK
Never (N=1607711)
reference
1>=Week (N=309631)
1.06 (0.96 - 1.16)
0.241
DLV_FRQ
Nulliparous (N=54592)
reference
Parous (N=1862750)
0.59 (0.50 - 0.69)
<0.001 ***
MNC
<13 years (N=28435)
reference
+13 years (N=1888907)
0.94 (0.71 - 1.24)
0.659
ERT_YN
No (N=1626965)
reference
Yes (N=290377)
1.03 (0.94 - 1.13)
0.501
Events: 3438; Global p-value (Log-Rank): 1.7237e-31
AIC: 98473.58; Concordance Index: 0.55
0.6
0.8
1
1.2
1.4
1.6
1.8
2
2.22.4

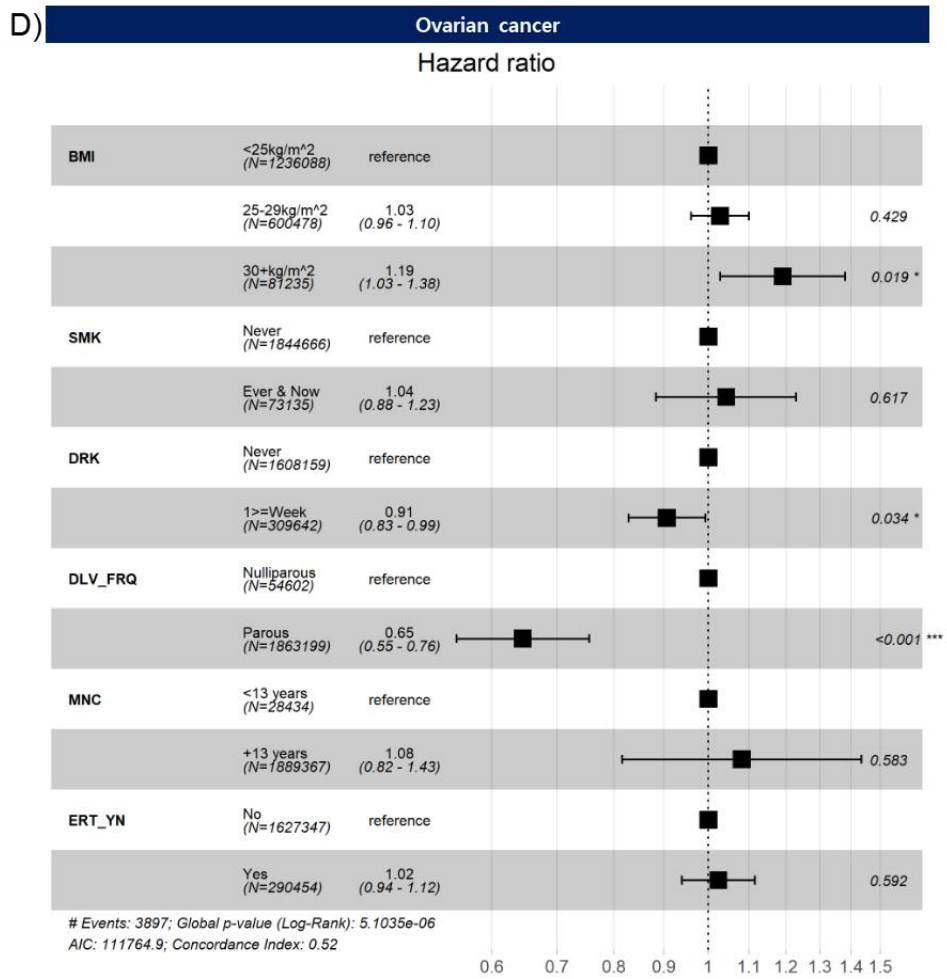


Figure 7. Association of HRT use status and incidence of female cancers among post-menopausal women: (A) breast cancer, (B) cervical cancer, (C) endometrial cancer, (D) ovarian cancer. In post-menopausal women, BMI, smoking, drinking, age at menarche, and HRT were adjusted. Abbreviations: BMI, body mass index; SMK, smoking; DRK, drinking; DLV_FRQ, parity; MNC, age at menarche; ERT_YN, HRT use status.

1. 3. 3. HRT Duration and Risk of Female Cancers

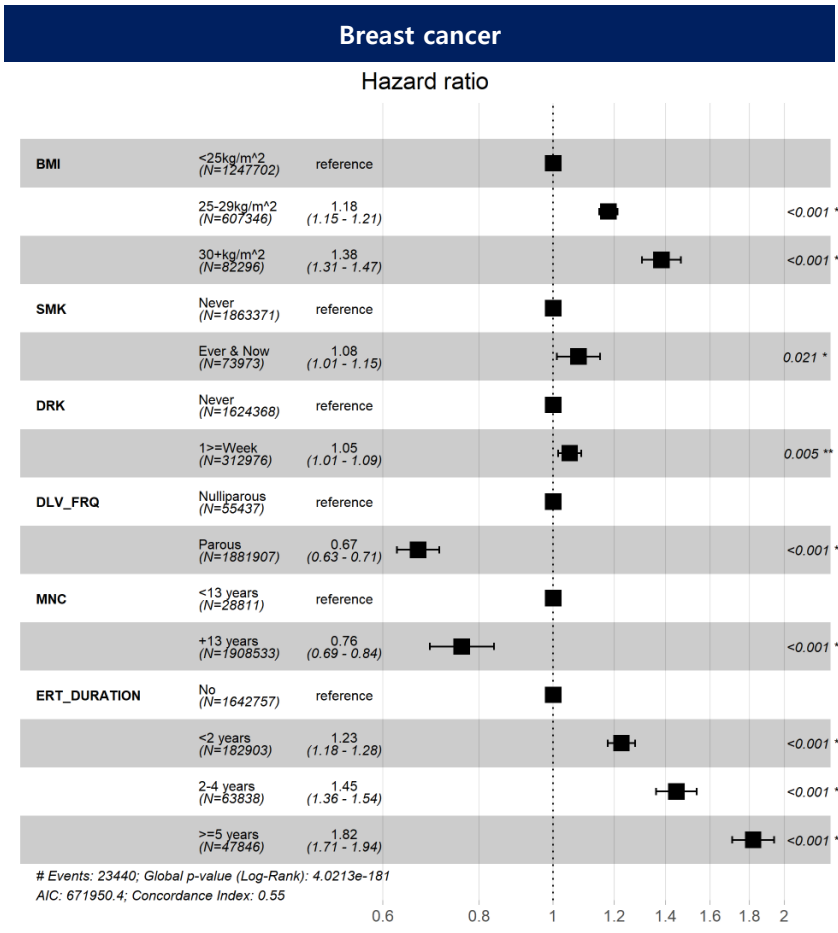
The study further analyzed the risk of female cancers based on the duration of HRT use. The HR for breast cancer gradually increased with longer durations of HRT use compared to non-users. The HR was 1.23 for women who used HRT for less than 2 years (95% CI 1.18–1.28); 1.45 (95% CI 1.36–1.54) for those who used it for 2 to 4 years, and 1.82 (95% CI 1.71–1.94) for those who used it for more than 5 years (Fig. 8A, Table 4). In contrast, the risk of cervical cancer decreased with extended HRT use (Fig. 8B, Table 4). Women who used HRT for less than 2 years had a cervical cancer HR of 0.87 (95% CI 0.78–0.98), while those who used HRT for 2–4 years had an HR of 0.75 (95% CI 0.62–0.92). For endometrial cancer, women who used HRT for 2–4 years had an HR of 1.31 (95% CI 1.11–1.55) compared to non-users (Fig. 8C, Table 4). We found no significant association between HRT duration and ovarian cancer risk (Fig. 8D).

Table 4. Association of HRT duration and incidence of female cancers among post-menopausal women: (A) breast cancer, (B) cervical cancer, (C) endometrial cancer. In post-menopausal women, BMI, smoking, drinking, parity, age at menarche, HRT duration were adjusted

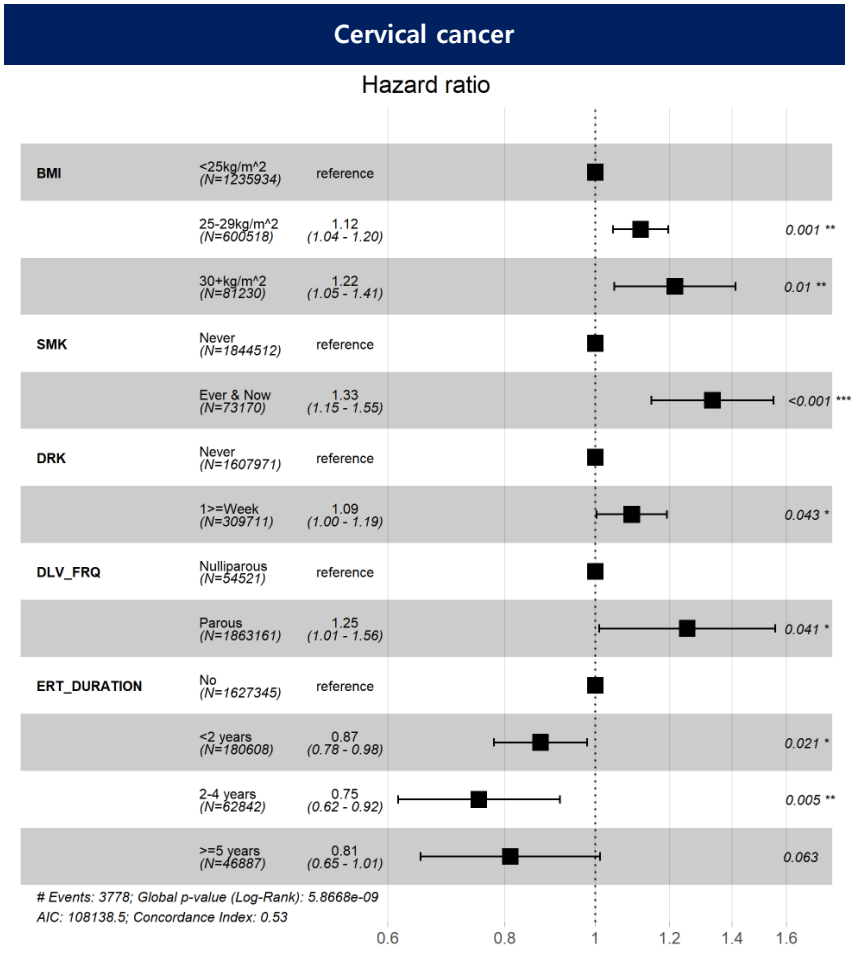
		Breast cancer		Cervical cancer		Endometrial cancer	
Features		**Hazard ratio**	**P-value**	**Hazard ratio**	**P-value**	**Hazard ratio**	**P-value**
BMI	<25kg/m^2	1 (Ref.)		1 (Ref.)		1 (Ref.)	
	25-29kg/m^2	1.18 (1.15 – 1.21)	<0.001***	1.12 (1.04 – 1.20)	0.001**	1.33 (1.24 – 1.43)	<0.001***
	30+kg/m^2	1.38 (1.31 - 1.47)	<0.001***	1.22 (1.05 – 1.41)	0.01**	1.94 (1.70 – 2.22)	<0.001***
Smoking	Never	1 (Ref.)		1 (Ref.)		1 (Ref.)	
	Ever & Now	1.08 (1.01 - 1.15)	0.021*	1.33 (1.15 – 1.55)	<0.001***	0.77 (0.64 – 0.94)	0.011*
Drinking	Never	1 (Ref.)		1 (Ref.)		1 (Ref.)	
	1≥Week	1.05 (1.01 - 1.09)	0.005**	1.09 (1.00 – 1.19)	0.041*	1.06 (0.96 – 1.16)	0.238
Parity	Nulliparous	1 (Ref.)		1 (Ref.)		1 (Ref.)	
	Parous	0.67 (0.63 – 0.71)	<0.001***	1.25 (1.01 – 1.56)	0.042*	0.59 (0.50 – 0.69)	<0.001***
Age at menarche	Age < 13	1 (Ref.)		1 (Ref.)		1 (Ref.)	
	Age ≥ 13	0.76 (0.69 – 0.84)	<0.001***	1.14 (0.84 – 1.54)	0.391	0.94 (0.71 – 1.24)	0.65
HRT duration	No	1 (Ref.)		1 (Ref.)		1 (Ref.)	
	<2 years	1.23 (1.18 – 1.28)	<0.001***	0.87 (0.78 – 0.98)	0.022*	0.93 (0.82 – 1.05)	0.219
	2-4 years	1.45 (1.36 – 1.54)	<0.001***	0.75 (0.62 – 0.92)	0.005**	1.31 (1.11 – 1.55)	0.001**
	≥5 years	1.82 (1.71 – 1.94)	<0.001***	0.81 (0.65 – 1.01)	0.063	1.05 (0.85 – 1.29)	0.653

*P-value <0.05, **P-value < 0.01, ***P-value < 0.001

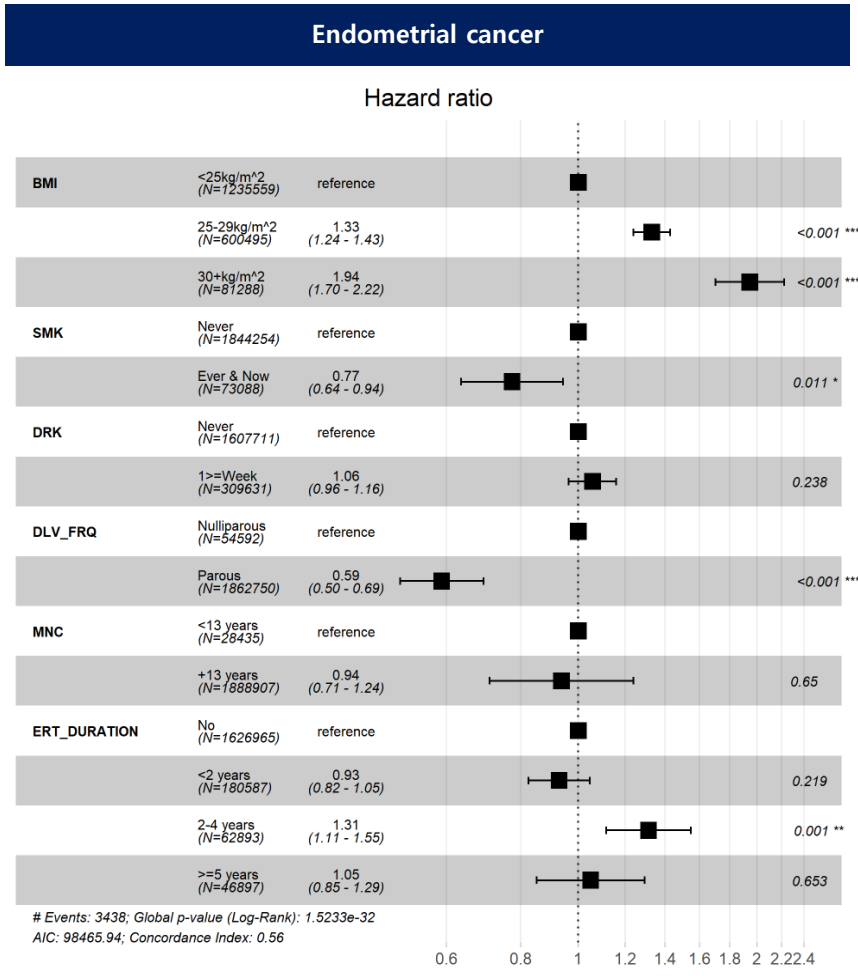
A)


Breast cancer
Hazard ratio
BMI
<25kg/m^2 (N=1247702)
reference
25-29kg/m^2 (N=607346)
1.18 (1.15 - 1.21)
<0.001 ***
30+kg/m^2 (N=82296)
1.38 (1.31 - 1.47)
<0.001 ***
SMK
Never (N=1863371)
reference
Ever & Now (N=73973)
1.08 (1.01 - 1.15)
0.021 *
DRK
Never (N=1624368)
reference
1>=Week (N=312976)
1.05 (1.01 - 1.09)
0.005 **
DLV_FRQ
Nulliparous (N=55437)
reference
Parous (N=1881907)
0.67 (0.63 - 0.71)
<0.001 ***
MNC
<13 years (N=28811)
reference
+13 years (N=1908533)
0.76 (0.69 - 0.84)
<0.001 ***
ERT_DURATION
No (N=1642757)
reference
<2 years (N=182903)
1.23 (1.18 - 1.28)
<0.001 ***
2-4 years (N=63838)
1.45 (1.36 - 1.54)
<0.001 ***
>=5 years (N=47846)
1.82 (1.71 - 1.94)
<0.001 ***
Events: 23440; Global p-value (Log-Rank): 4.0213e-181
AIC: 671950.4; Concordance Index: 0.55
0.6
0.8
1
1.2
1.4
1.6
1.8
2

B)


Cervical cancer
Hazard ratio
BMI
<25kg/m^2 (N=1235934)
reference
25-29kg/m^2 (N=600518)
1.12 (1.04 - 1.20)
0.001 **
30+kg/m^2 (N=81230)
1.22 (1.05 - 1.41)
0.01 **
SMK
Never (N=1844512)
reference
Ever & Now (N=73170)
1.33 (1.15 - 1.55)
<0.001 ***
DRK
Never (N=1607971)
reference
1>=Week (N=309711)
1.09 (1.00 - 1.19)
0.043 *
DLV_FRQ
Nulliparous (N=54521)
reference
Parous (N=1863161)
1.25 (1.01 - 1.56)
0.041 *
ERT_DURATION
No (N=1627345)
reference
<2 years (N=180608)
0.87 (0.78 - 0.98)
0.021 *
2-4 years (N=62842)
0.75 (0.62 - 0.92)
0.005 **
>=5 years (N=46887)
0.81 (0.65 - 1.01)
0.063
Events: 3778; Global p-value (Log-Rank): 5.8668e-09
AIC: 108138.5; Concordance Index: 0.53
0.6
0.8
1
1.2
1.4
1.6

C)


Endometrial cancer
Hazard ratio
BMI
<25kg/m^2 (N=1235559)
reference
25-29kg/m^2 (N=600495)
1.33 (1.24 - 1.43)
<0.001 ***
30+kg/m^2 (N=81288)
1.94 (1.70 - 2.22)
<0.001 ***
SMK
Never (N=1844254)
reference
Ever & Now (N=73088)
0.77 (0.64 - 0.94)
0.011 *
DRK
Never (N=1607711)
reference
1>=Week (N=309631)
1.06 (0.96 - 1.16)
0.238
DLV_FRQ
Nulliparous (N=54592)
reference
Parous (N=1862750)
0.59 (0.50 - 0.69)
<0.001 ***
MNC
<13 years (N=28435)
reference
+13 years (N=1888907)
0.94 (0.71 - 1.24)
0.65
ERT_DURATION
No (N=1626965)
reference
<2 years (N=180587)
0.93 (0.82 - 1.05)
0.219
2-4 years (N=62893)
1.31 (1.11 - 1.55)
0.001 **
>=5 years (N=46897)
1.05 (0.85 - 1.29)
0.653
Events: 3438; Global p-value (Log-Rank): 1.5233e-32
AIC: 98465.94; Concordance Index: 0.56
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0.8
1
1.2
1.4
1.6
1.8
2
2.22.4

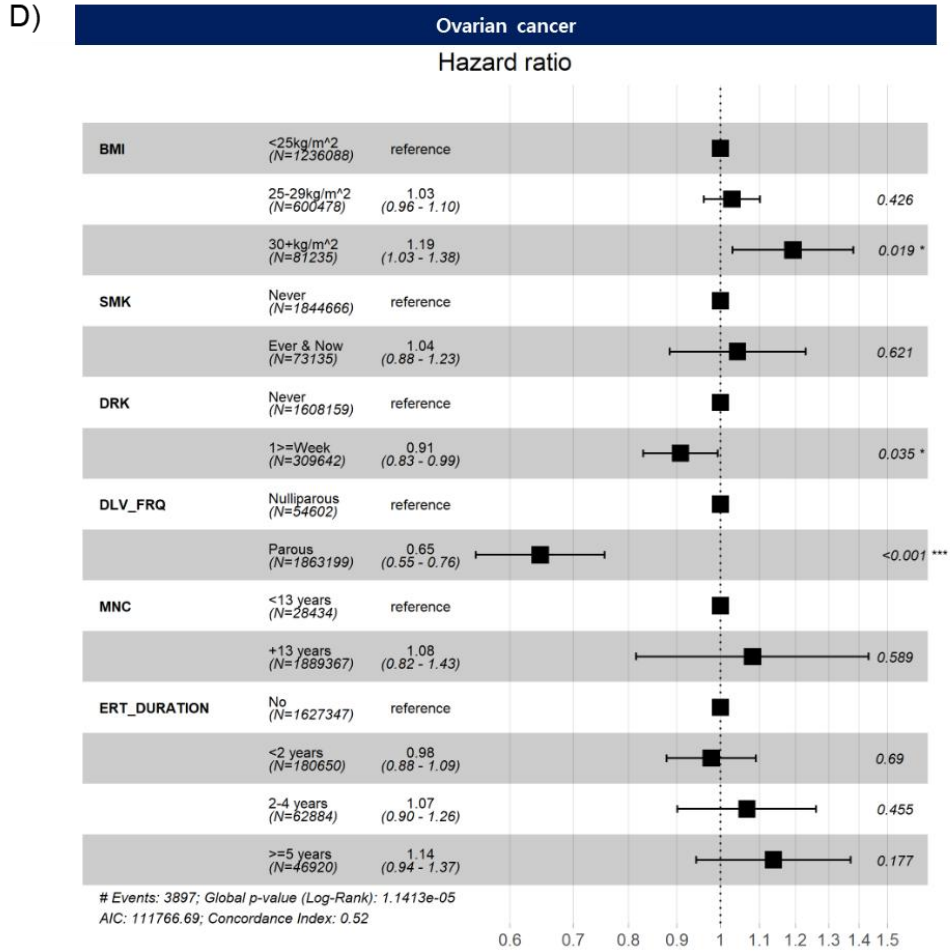


Figure 8. Association of HRT duration and incidence of female cancers among post-menopausal women: (A) breast cancer, (B) cervical cancer, (C) endometrial cancer, D) ovarian cancer. In post-menopausal women, BMI, smoking, drinking, parity, age at menarche, and HRT duration were adjusted. Abbreviations: BMI, body mass index; SMK, smoking; DRK, drinking; DLV_FRQ, parity; MNC, age at menarche; ERT_DURATION, HRT duration.

1. 3. 4. HRT Type and Risk of Female Cancers

This study also analyzed the incidence of female cancers based on the type of HRT used, as shown in Table 5. Estrogen users had a significantly higher risk of breast cancer compared to non-users (HR 1.73; 95% CI 1.44–2.08) (Fig. 9A, Table 5). Similarly, users of combined estrogen and progesterone therapy had an even greater risk of breast cancer (HR 2.16; 95% CI 2.03–2.30) (Fig. 9B, Table 5). However, no significant associations were found for cervical cancer, endometrial cancer, or ovarian cancer among users of combined estrogen and progesterone combined therapy, with HRs [95% CIs] of 0.88 [0.71–1.1], 1.04 [0.83–1.30], and 1.11 [0.91–1.36], respectively (Fig. 9C-E).

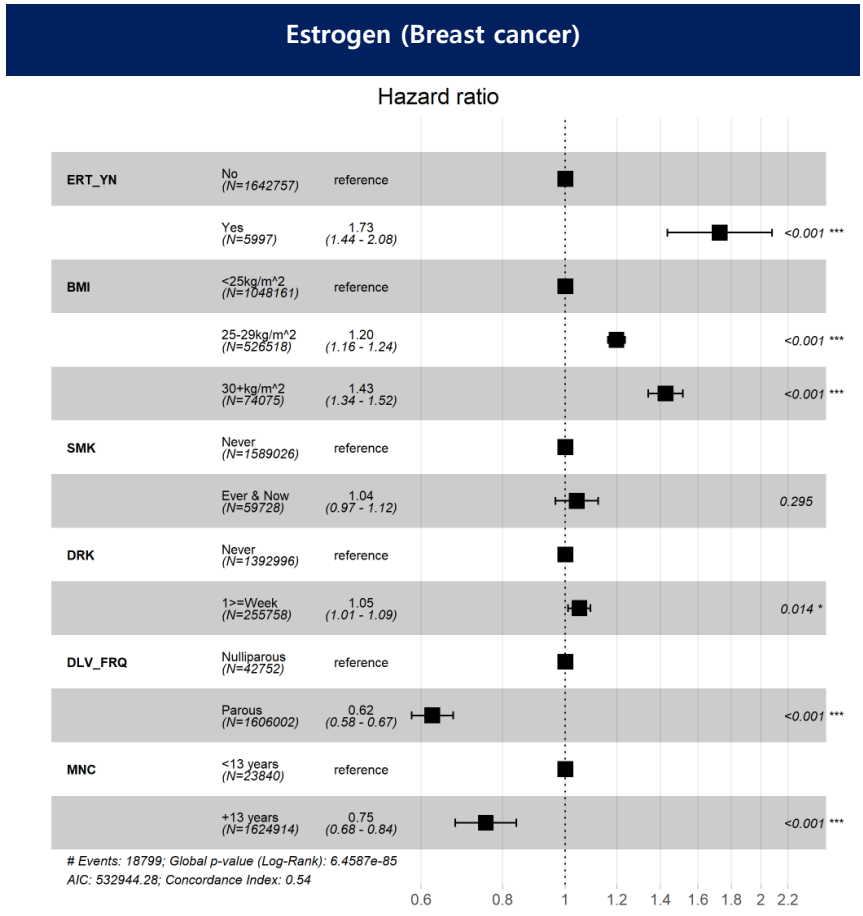
The risk of female cancers associated with tibolone use was also investigated. Tibolone users had a higher risk of breast cancer compared to non-users (HR 1.60; 95% CI 1.49–1.73) (Fig. 10A, Table 5). Additionally, tibolone users showed a significantly higher risk of endometrial cancer (HR 1.26; 95% CI 1.01–1.56) (Fig. 10B, Table 5), but a lower risk of cervical cancer (HR 0.75; 95% CI 0.58–0.97) compared to non-users (Fig. 10C, Table 5). No significant association was found between tibolone use and ovarian cancer risk (HR 0.84; 95% CI 0.66–1.07) (Fig. 10D).

Table 5. Association of HRT type and incidence of female cancers among post-menopausal women: (A) estrogen with breast cancer, (B) estrogens and progesterone with breast cancer, tibolone with (C) breast cancer, (D) endometrial cancer, (E) cervical cancer. In post-menopausal women, type of HRT, BMI, smoking, drinking, parity, and age at menarche were adjusted

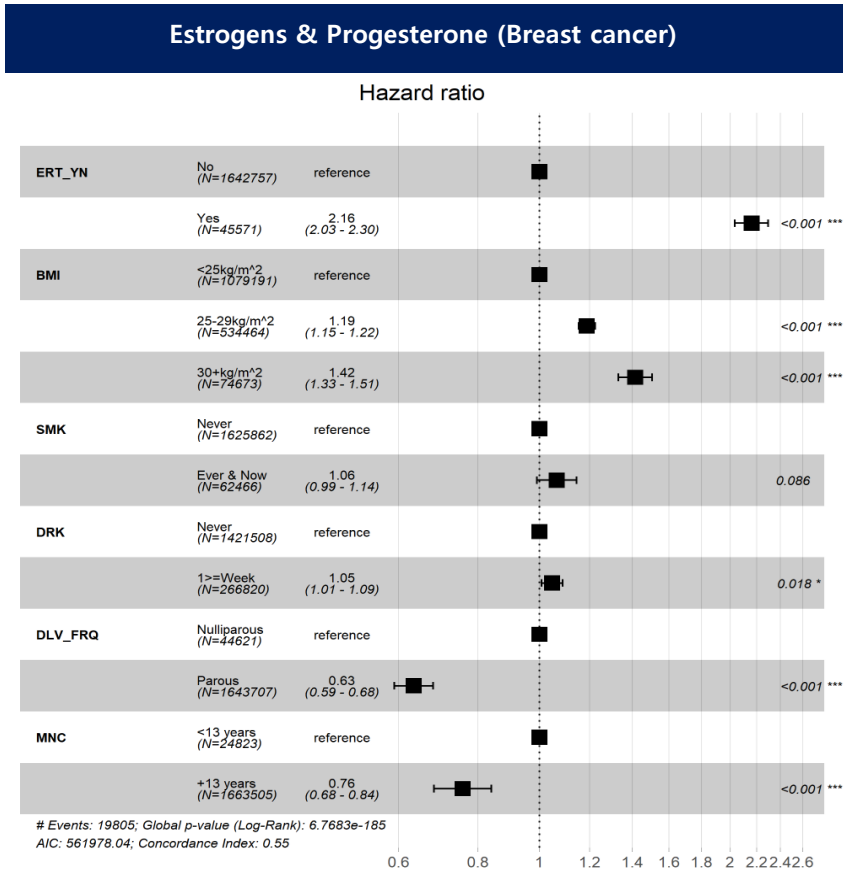
		Estrogen (Breast cancer)		Estrogens & Progesterone (Breast cancer)		Tibolone (Breast cancer)		Tibolone (Endometrial cancer)		Tibolone (Cervical cancer)	
Features		**Hazard ratio**	**P-value**	**Hazard ratio**	**P-value**	**Hazard ratio**	**P-value**	**Hazard ratio**	**P-value**	**Hazard ratio**	**P-value**
HRT type	No	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
	Yes	1.73 (1.44 – 2.08)	<0.001***	2.16 (2.03 – 2.30)	<0.001***	1.60 (1.49 – 1.73)	<0.001***	1.26 (1.01 – 1.56)	0.038*	0.75 (0.58 – 0.97)	<0.3*
BMI	<25kg/m^2	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
	25-29kg/m^2	1.20 (1.16 – 1.24)	<0.001***	1.19 (1.15 – 1.22)	<0.001***	1.20 (1.16 – 1.23)	<0.001***	1.35 (1.25 – 1.45)	<0.001***	1.09 (1.01 – 1.17)	<0.021*
	30+kg/m^2	1.43 (1.34 – 1.52)	<0.001***	1.42 (1.33 – 1.51)	<0.001***	1.42 (1.34 – 1.51)	<0.001***	2.00 (1.74 – 2.30)	<0.001***	1.19 (1.02 – 1.39)	<0.028*
Smoking	Never	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
	Ever & Now	1.04 (0.97 – 1.12)	0.295	1.06 (0.99 – 1.14)	0.086	1.06 (0.98 – 1.14)	0.121	0.76 (0.61 – 0.94)	0.013*	1.34 (1.14 – 1.58)	<0.001***
Drinking	Never	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
	1≥Week	1.05 (1.01 – 1.09)	0.014*	1.05 (1.01 – 1.09)	0.018*	1.05(1.01 – 1.09)	0.017*	1.06(0.96 – 1.17)	0.258	1.09(1.00 – 1.20)	0.057
Parity	Nulliparous	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
	Parous	0.62 (0.58 – 0.67)	<0.001***	0.63 (0.59 – 0.68)	<0.001***	0.64 (0.59 – 0.68)	<0.001***	0.57 (0.48 – 0.69)	<0.001***	1.32 (1.03 – 1.68)	<0.029*
Age at menarche	Age < 13	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
	Age ≥ 13	0.75 (0.68 – 0.84)	<0.001***	0.76 (0.68 – 0.84)	<0.001***	0.77 (0.70 – 0.86)	<0.001***	0.94 (0.69 – 1.27)	0.687	1.23 (0.88 – 1.73)	<0.228

*P-value <0.05, **P-value < 0.01, ***P-value < 0.001

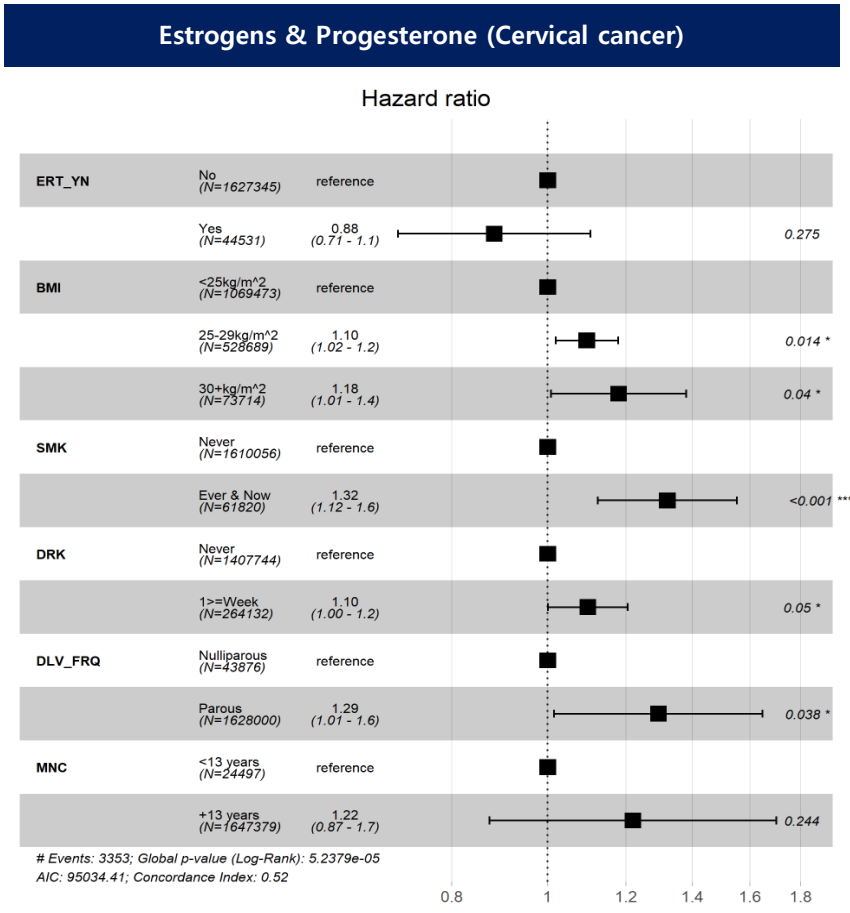
A)


Estrogen (Breast cancer)
Hazard ratio
ERT_YN
No (N=1642757) reference
Yes (N=5997) 1.73 (1.44 - 2.08) <0.001 ***
BMI
<25kg/m^2 (N=1048161) reference
25-29kg/m^2 (N=526518) 1.20 (1.16 - 1.24) <0.001 ***
30+kg/m^2 (N=74075) 1.43 (1.34 - 1.52) <0.001 ***
SMK
Never (N=1589026) reference
Ever & Now (N=59728) 1.04 (0.97 - 1.12) 0.295
DRK
Never (N=1392996) reference
1>=Week (N=255758) 1.05 (1.01 - 1.09) 0.014 *
DLV_FRQ
Nulliparous (N=42752) reference
Parous (N=1606002) 0.62 (0.58 - 0.67) <0.001 ***
MNC
<13 years (N=23840) reference
+13 years (N=1624914) 0.75 (0.68 - 0.84) <0.001 ***
Events: 18799; Global p-value (Log-Rank): 6.4587e-85
AIC: 532944.28; Concordance Index: 0.54
0.6
0.8
1
1.2
1.4
1.6
1.8
2
2.2

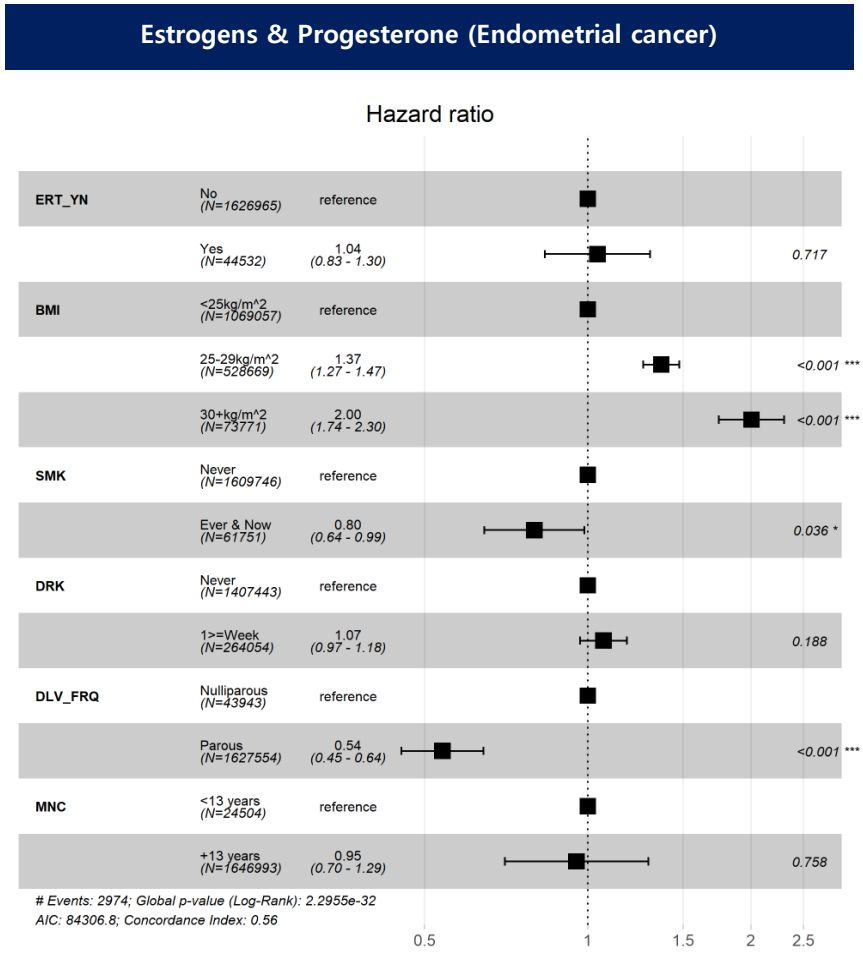
B)


Estrogens & Progesterone (Breast cancer)
Hazard ratio
ERT_YN
No (N=1642757) reference
Yes (N=45571) 2.16 (2.03 - 2.30) <0.001 ***
BMI
<25kg/m^2 (N=1079191) reference
25-29kg/m^2 (N=534464) 1.19 (1.15 - 1.22) <0.001 ***
30+kg/m^2 (N=74673) 1.42 (1.33 - 1.51) <0.001 ***
SMK
Never (N=1625862) reference
Ever & Now (N=62466) 1.06 (0.99 - 1.14) 0.086
DRK
Never (N=1421508) reference
1>=Week (N=266820) 1.05 (1.01 - 1.09) 0.018 *
DLV_FRQ
Nulliparous (N=44621) reference
Parous (N=1643707) 0.63 (0.59 - 0.68) <0.001 ***
MNC
<13 years (N=24823) reference
+13 years (N=1663505) 0.76 (0.68 - 0.84) <0.001 ***
Events: 19805; Global p-value (Log-Rank): 6.7683e-185
AIC: 561978.04; Concordance Index: 0.55
0.6 0.8 1 1.2 1.4 1.6 1.8 2 2.22.42.6

C)


Estrogens & Progesterone (Cervical cancer)
Hazard ratio
ERT_YN
No (N=1627345) reference
Yes (N=44531) 0.88 (0.71 - 1.1) 0.275
BMI
<25kg/m^2 (N=1069473) reference
25-29kg/m^2 (N=528689) 1.10 (1.02 - 1.2) 0.014 *
30+kg/m^2 (N=73714) 1.18 (1.01 - 1.4) 0.04 *
SMK
Never (N=1610056) reference
Ever & Now (N=61820) 1.32 (1.12 - 1.6) <0.001 ***
DRK
Never (N=1407744) reference
1>=Week (N=264132) 1.10 (1.00 - 1.2) 0.05 *
DLV_FRQ
Nulliparous (N=43876) reference
Parous (N=1628000) 1.29 (1.01 - 1.6) 0.038 *
MNC
<13 years (N=24497) reference
+13 years (N=1647379) 1.22 (0.87 - 1.7) 0.244
Events: 3353; Global p-value (Log-Rank): 5.2379e-05
AIC: 95034.41; Concordance Index: 0.52
0.8
1
1.2
1.4
1.6
1.8

D)


Estrogens & Progesterone (Endometrial cancer)
Hazard ratio
ERT_YN
No (N=1626965) reference
Yes (N=44532) 1.04 (0.83 - 1.30) 0.717
BMI
<25kg/m^2 (N=1069057) reference
25-29kg/m^2 (N=528669) 1.37 (1.27 - 1.47) <0.001 ***
30+kg/m^2 (N=73771) 2.00 (1.74 - 2.30) <0.001 ***
SMK
Never (N=1609746) reference
Ever & Now (N=61751) 0.80 (0.64 - 0.99) 0.036 *
DRK
Never (N=1407443) reference
1>=Week (N=264054) 1.07 (0.97 - 1.18) 0.188
DLV_FRQ
Nulliparous (N=43943) reference
Parous (N=1627554) 0.54 (0.45 - 0.64) <0.001 ***
MNC
<13 years (N=24504) reference
+13 years (N=1646993) 0.95 (0.70 - 1.29) 0.758
Events: 2974; Global p-value (Log-Rank): 2.2955e-32
AIC: 84306.8; Concordance Index: 0.56
0.5
1
1.5
2
2.5

E)

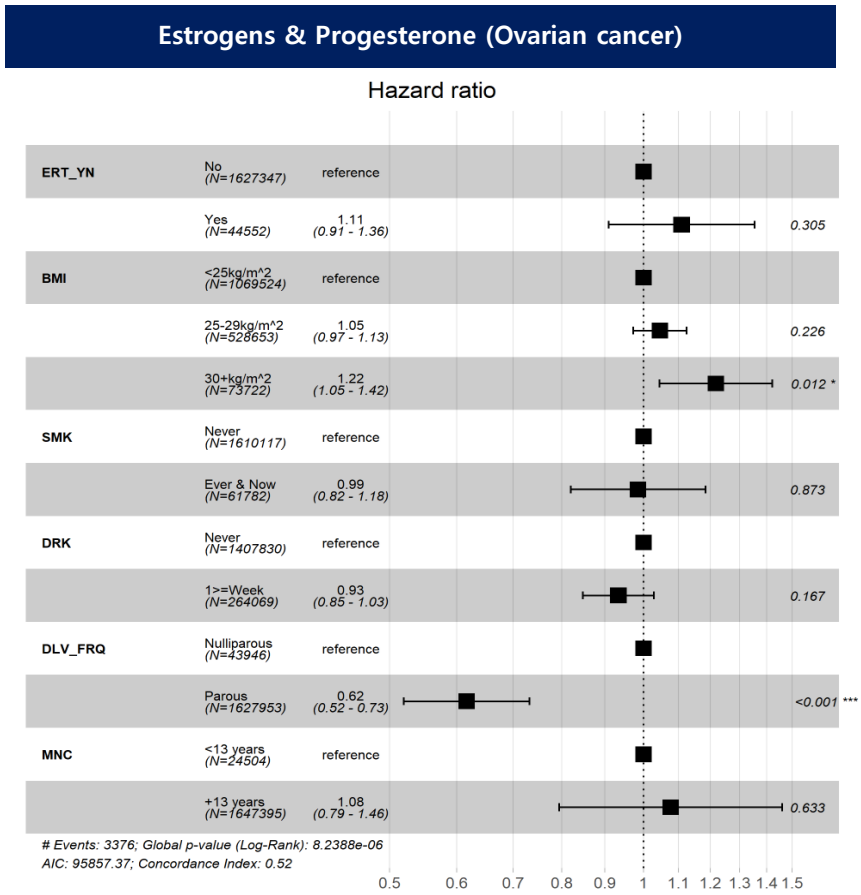
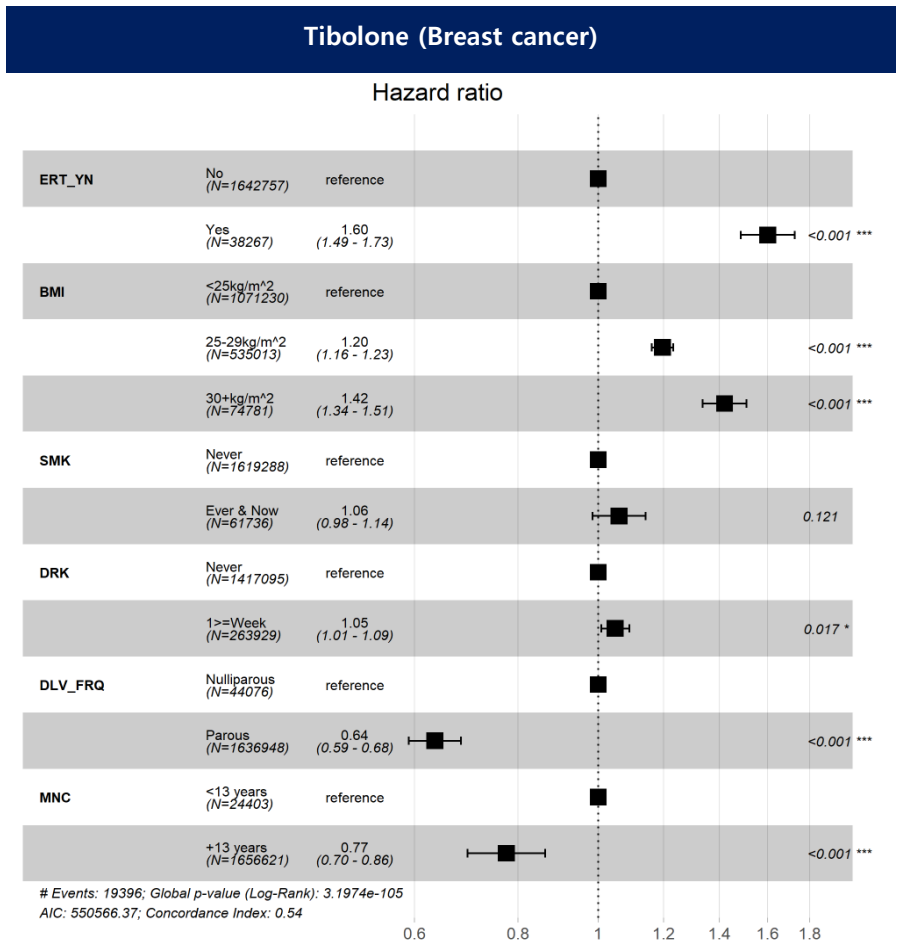
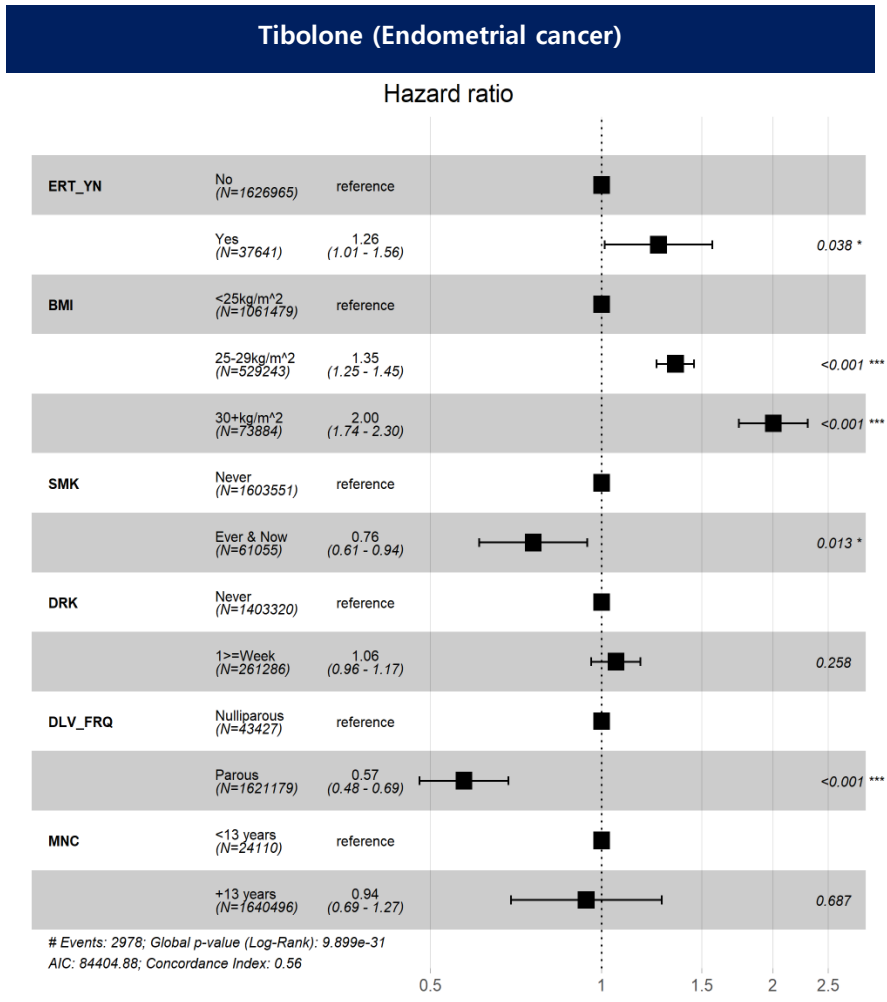


Figure 9. Association of HRT type(estrogen or progesterone) and incidence of female cancers among post-menopausal women: (A) estrogen with breast cancer, (B) estrogens and progesterone with breast cancer, (C) estrogens and progesterone with cervical cancer, (D) estrogens and progesterone with endometrial cancer, (E) estrogens and progesterone with ovarian cancer. In post-menopausal women, type of HRT, BMI, smoking, drinking, parity, and age at menarche were adjusted. Abbreviations: BMI, body mass index; SMK, smoking; DRK, drinking; DLV_FRQ, parity; MNC, age at menarche; ERT_YN, depending on HRT type.

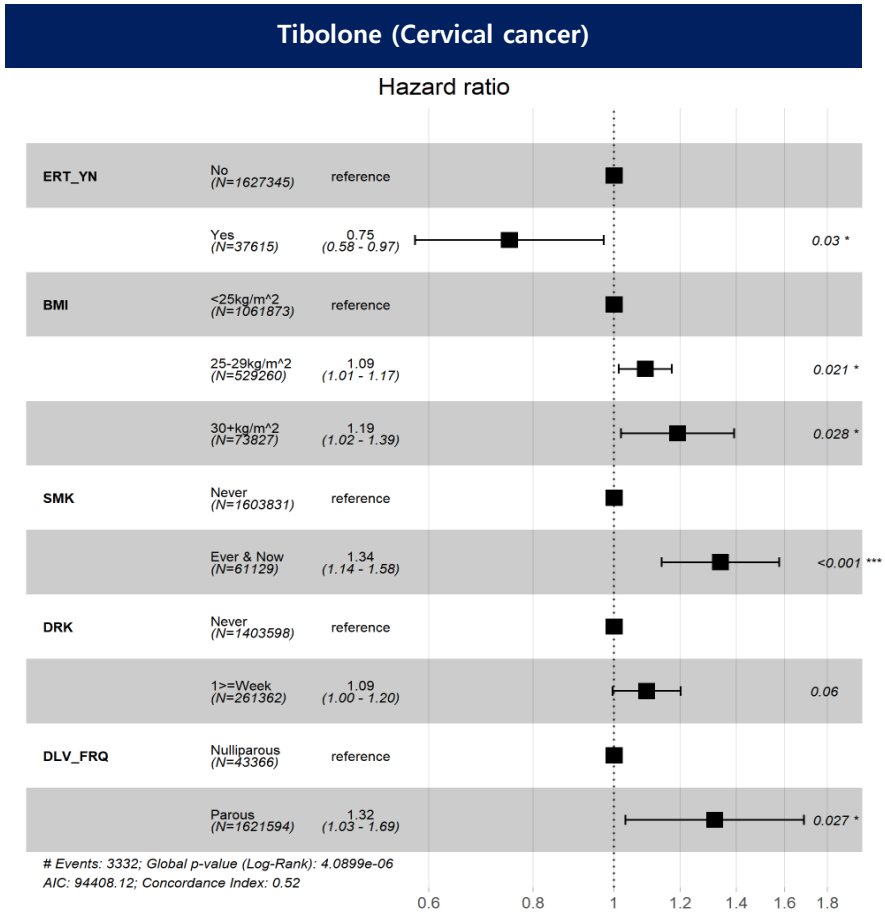
A)


Tibolone (Breast cancer)
Hazard ratio
ERT_YN
No (N=1642757) reference
Yes (N=38267) 1.60 (1.49 - 1.73) <0.001 ***
BMI
<25kg/m^2 (N=1071230) reference
25-29kg/m^2 (N=535013) 1.20 (1.16 - 1.23) <0.001 ***
30+kg/m^2 (N=74781) 1.42 (1.34 - 1.51) <0.001 ***
SMK
Never (N=1619288) reference
Ever & Now (N=61736) 1.06 (0.98 - 1.14) 0.121
DRK
Never (N=1417095) reference
1>=Week (N=263929) 1.05 (1.01 - 1.09) 0.017 *
DLV_FRQ
Nulliparous (N=44076) reference
Parous (N=1636948) 0.64 (0.59 - 0.68) <0.001 ***
MNC
<13 years (N=24403) reference
+13 years (N=1656621) 0.77 (0.70 - 0.86) <0.001 ***
Events: 19396; Global p-value (Log-Rank): 3.1974e-105
AIC: 550566.37; Concordance Index: 0.54
0.6
0.8
1
1.2
1.4
1.6
1.8

B)


Tibolone (Endometrial cancer)
Hazard ratio
ERT_YN
No (N=1626965) reference
Yes (N=37641) 1.26 (1.01 - 1.56) 0.038 *
BMI
<25kg/m^2 (N=1061479) reference
25-29kg/m^2 (N=529243) 1.35 (1.25 - 1.45) <0.001 ***
30+kg/m^2 (N=73884) 2.00 (1.74 - 2.30) <0.001 ***
SMK
Never (N=1603551) reference
Ever & Now (N=61055) 0.76 (0.61 - 0.94) 0.013 *
DRK
Never (N=1403320) reference
1>=Week (N=261286) 1.06 (0.96 - 1.17) 0.258
DLV_FRQ
Nulliparous (N=43427) reference
Parous (N=1621179) 0.57 (0.48 - 0.69) <0.001 ***
MNC
<13 years (N=24110) reference
+13 years (N=1640496) 0.94 (0.69 - 1.27) 0.687
Events: 2978; Global p-value (Log-Rank): 9.899e-31
AIC: 84404.88; Concordance Index: 0.56
0.5
1
1.5
2
2.5

C)


Tibolone (Cervical cancer)
Hazard ratio
ERT_YN
No (N=1627345) reference
Yes (N=37615) 0.75 (0.58 - 0.97) 0.03 *
BMI
<25kg/m^2 (N=1061873) reference
25-29kg/m^2 (N=529260) 1.09 (1.01 - 1.17) 0.021 *
30+kg/m^2 (N=73827) 1.19 (1.02 - 1.39) 0.028 *
SMK
Never (N=1603831) reference
Ever & Now (N=61129) 1.34 (1.14 - 1.58) <0.001 ***
DRK
Never (N=1403598) reference
1>=Week (N=261362) 1.09 (1.00 - 1.20) 0.06
DLV_FRQ
Nulliparous (N=43366) reference
Parous (N=1621594) 1.32 (1.03 - 1.69) 0.027 *
Events: 3332; Global p-value (Log-Rank): 4.0899e-06
AIC: 94408.12; Concordance Index: 0.52
0.6
0.8
1
1.2
1.4
1.6
1.8

D)

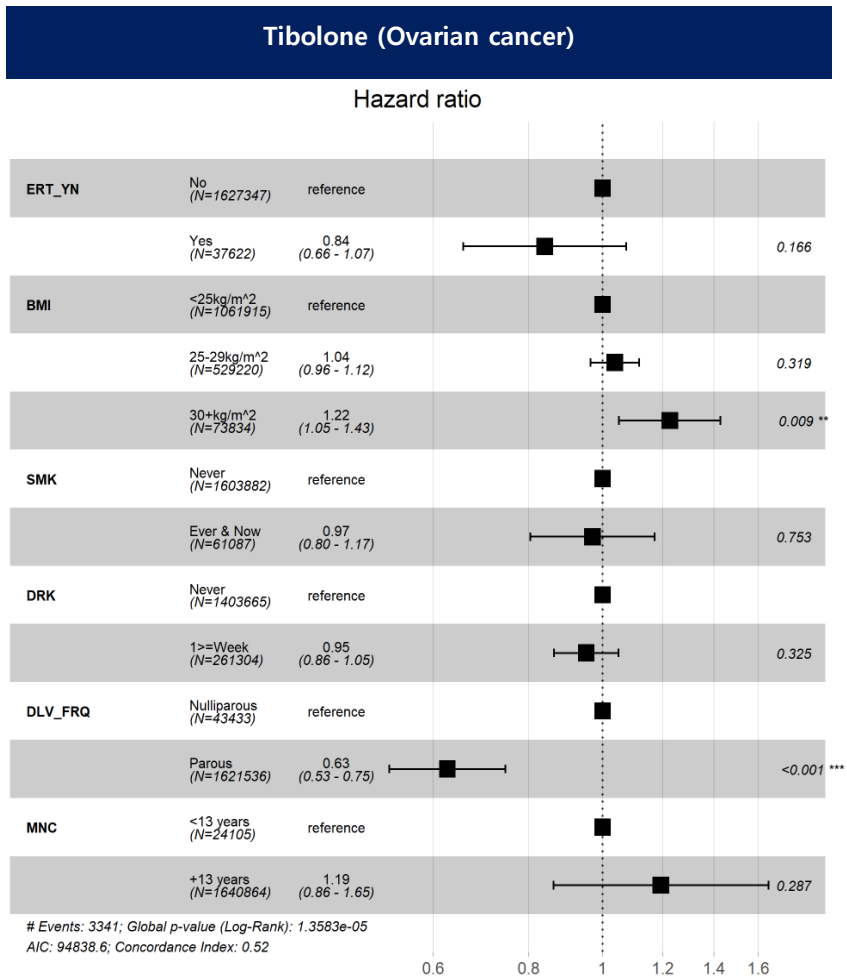


Figure 10. Association of HRT type(tibolone) and incidence of female cancers among post-menopausal women: (A) estrogen with breast cancer, (B) estrogens and progesterone with breast cancer, tibolone with (C) breast cancer, (D) ovarian cancer. In post-menopausal women, type of HRT, BMI, smoking, drinking, parity, and age at menarche were adjusted. Abbreviations: BMI, body mass index; SMK, smoking; DRK, drinking; DLV_FRQ, parity; MNC, age at menarche; ERT_YN, depending on HRT type.

1.4. Discussion

This study investigated the relationship between HRT and the risk of breast and gynecologic cancers in a nationwide cohort of postmenopausal women in South Korea. The findings reveal a complex association between HRT use and cancer risk, influenced by cancer type, duration of HRT use, and specific hormone formulations. Notably, HRT use was associated with a significantly elevated risk of breast cancer compared to non-users, with the risk increasing alongside prolonged duration of HRT. Specifically, women using combined estrogen-progestin therapy had a higher HRs for breast cancer than those using estrogen only. This finding aligns with findings from large-scale Western studies (e.g., WHI and Million Women Study) that have similarly linked combined HRT to higher breast cancer risk. Additionally, women using HRT for longer periods (more than 5 years) exhibited the greatest risk of breast cancer. In contrast, HRT use was associated with a reduced risk of cervical cancer, suggesting a potential protective effect that warrants further investigation [22]. This inverse association with cervical cancer appeared the same for long-term HRT use. However, no significant association was observed between HRT use and ovarian cancer risk, indicating a limited impact of HRT on this type of cancer in the studied population. In the case of endometrial cancer in Korean menopausal women, an increased risk was observed according to the duration of HRT use and the formulation.

The relationship between HRT and cancer risk in postmenopausal women has been extensively studied, particularly in Western populations. While numerous studies have documented an increased risk of breast cancer among HRT users, the findings vary depending on the composition and duration of the therapy. The findings from the WHI highlighted an increased risk of breast cancer among women using combined estrogen-progestin HRT, whereas estrogen-only treatment appeared neutral or even slightly protective in certain groups, such as women with prior

hysterectomy [23, 24]. Evidence also underscores the critical role of therapy duration, with prolonged use linked to a progressively increased risk of breast cancer, while shorter durations are associated with a lower risk [25]. These results align with our findings, where combined HRT was associated with a greater risk of breast cancer, particularly with extended use. Further supporting these results, the Million Women Study, another large-scale cohort from the UK, reported an elevated risk of breast cancer with both the type and duration of HRT, particularly with estrogen-progestin combinations [26]. Additionally, research has shown that HRT increases breast cancer risk by approximately 22% overall (HR 1.22) [27], with specific combinations, such as estradiol hemihydrate with drospirenone, presenting even higher risks (HR 1.51) [27]. Interestingly, therapies such as tibolone and oral estrogen did not show a significant increase in breast cancer risk [15]. Following the Women's Health Initiative study, there was a notable decline in HRT prescriptions, particularly estrogen-progesterone therapies, which correlated with an increase in breast cancer incidence [28]. Despite this decline, tibolone prescriptions have risen significantly, indicating a shift in treatment preferences [28]. While HRT can pose certain risks, particularly for breast cancer with specific regimens, it may also offer protective benefits under certain conditions. This duality underscores the importance of personalized treatment approaches to effectively manage menopausal symptoms while minimizing associated risks.

An intriguing finding from our study is the reduced risk of cervical cancer among HRT users, which is similar with the results [29], who reported that long-term HRT users had a decreased risk of certain gynecologic cancers. While the exact mechanisms underlying this protective effect are not yet fully understood, it may be attributed to HRT's influence on hormonal regulation and local immune responses within the cervix. Further research is needed to elucidate these potential mechanisms and their implications for clinical practice.

The relationship between HRT and the risk of endometrial or

ovarian cancers remain less clear. Previous studies, such as those by Anderson et al. (2003) [30] and Trabert et al. (2018) [31] reported an elevated risk of endometrial cancer associated with estrogen–only HRT, particularly in women with a uterus. These findings are consistent with our observation of a higher risk of endometrial cancer with prolonged HRT use. Regarding endometrial cancer, while estrogen–only HRT users had a moderately elevated risk, the risk was not significant for users of combined HRT [32]. These findings differ from our findings but, as previous studies suggest that the addition of progestin to estrogen may mitigate the endometrial cancer risk associated with estrogen–only therapy, as supported by previous studies [33] . However, we found no significant association between HRT use and ovarian cancer risk in our cohort, which is consistent with studies suggesting minimal or no increased risk of ovarian cancer linked to HRT use [31, 34].

Our study adds valuable insights by examining a South Korean cohort, demonstrating trends that align with the elevated risks associated with HRT in Western populations. These findings are particularly significant given the potential genetic, environmental, and lifestyle differences between Asian and Western cohorts [27]. In comparing our study's findings with Western data, notable differences emerge regarding the association between HRT and cancer incidence. For instance, a study found that the risk of breast cancer due to HRT is lower in Korean women than in their Western counterparts [35]. These disparities can be attributed to various factors. First, genetic variations between Asian and Western populations may influence cancer susceptibility. A study analyzing HRT use and breast cancer risk in Asian women found that the risk increase was modest and comparable to that observed in Western populations. However, the unique genetic makeup of different populations can lead to varying responses to HRT [36]. Second, differences in lifestyle, such as diet, physical activity, and reproductive behaviors, contribute to varying cancer incidences. For instance, dietary patterns prevalent in Asian countries, which are often lower in fat and higher in fiber, may offer protective

effects against certain cancers. Additionally, higher rates of breastfeeding and lower alcohol consumption in some Asian populations can influence cancer risk profiles [37]. Third, lower average BMI in Asian populations might result in different hormonal environments, affecting cancer risk. Research indicates that higher BMI is associated with increased breast cancer risk in postmenopausal women, a trend observed in both Asian and Western populations. However, the overall lower BMI in Asian women may contribute to a reduced baseline risk [38]. Fourth, breast density is a significant risk factor for breast cancer. Studies have shown that HRT use can increase breast density, thereby elevating cancer risk. The distribution of breast density varies among populations, potentially leading to differences in cancer incidence related to HRT use [36].

Studies have linked HRT to varying cancer risks among postmenopausal women, with the risks differing based on cancer type, duration of use, and the composition of hormones [39]. The primary components of HRT, estrogen and progestin, interact differently with tissues in the breast, endometrium, and ovaries, resulting in distinct carcinogenic effects driven by hormonal signaling and cellular responses.

Estrogen promotes cell proliferation and survival by binding to estrogen receptors (ER) in breast tissue. While progestin is designed to mitigate estrogen's proliferative effects in the endometrium, it may enhance estrogenic activity in breast tissue. This interaction encourages mammary cell proliferation and may elevate DNA damage over time, particularly in ER−positive breast cancer subtypes [40]. Estrogen−only HRT is strongly linked to endometrial hyperplasia and an elevated risk of endometrial cancer, particularly in women with an intact uterus. Estrogen stimulates endometrial growth without the regulatory effect of progesterone, increasing the likelihood of malignant transformations. In combined HRT, progesterone counteracts these effects by inducing secretory changes and reducing endometrial proliferation. However, prolonged or improperly managed combined HRT may fail to provide adequate

protective effects, particularly in women with additional risk factors like obesity, which independently increases estrogen levels through peripheral aromatization in adipose tissue [41, 42]. The relationship between HRT and ovarian cancer is less clearly defined, though some studies suggest a modestly elevated risk with long-term use, particularly with estrogen-only HRT. Estrogen may induce proliferative effects in ovarian surface epithelium and promote the progression of early-stage lesions. Additionally, circulating estrogens can expose ovarian tissue to sustained hormonal stimulation, which, without the opposing effect of progesterone, may increase likelihood of malignancy [43-45].

The duration of HRT use is a critical factor in determining cancer risk. Extended use of both estrogen-only and combined therapies have been associated with elevated risks of breast and endometrial cancers [9, 32]. Mechanistically, prolonged estrogen exposure without interruption creates a continuous stimulatory effect on ER-positive cells in the breast and endometrium, fostering conditions conducive to tumor development. Research suggests that even short-term use of combined HRT may increase breast cancer risk, whereas long-term estrogen-only therapy significantly increases the risk of endometrial cancer [9].

The influence of HRT on cancer risk is also modulated by metabolic and inflammatory pathways. Obesity, for example, increases estrogen levels through heightened aromatase activity in adipose tissue, intensifying HRT's effects on estrogen-sensitive tissues. Additionally, the inflammatory environment of adipose tissue further enhances estrogen bioavailability by reducing levels of sex hormone-binding globulin (SHBG), thereby amplifying estrogenic signaling in tissues such as the endometrium and breast [46, 47]. These mechanistic insights underscore the need for careful consideration of HRT duration, formulation, and patient-specific factors when prescribing HRT, as each of these elements uniquely influences the risk of developing cancer in hormone-sensitive tissues.

Despite nuanced findings, this study has several limitations that

should be considered when interpreting the results. First, as an observational study, it is inherently limited in establishing causal relationships between HRT use and cancer risks. Though we used statistical adjustments to control for potential confounders, residual confounding from unmeasured or unknown factors may still exist, restricting our ability to draw definitive causal inferences. Second, this study relies on health insurance claims data, which, while comprehensive, may lack detailed information on lifestyle factors (e.g., dietary habits, family medical history, and physical activity) and other relevant medical details not captured by insurance claims. This limitation could introduce potential biases that affect the accuracy and completeness of our findings on cancer risks associated with HRT. Third, data on HRT are based on self-reported information or insurance claims for prescription refills, which may not accurately reflect adherence to prescribed therapies. This reliance on self-report and claims data may introduce recall bias and misclassification, particularly if patients discontinue therapy or fail to follow prescribed regimens, potentially resulting in underestimation or overestimation of associated cancer risks. Fourth, the exclusive focus on a South Korean cohort limits the generalizability of the findings to other populations or ethnic groups. Genetic, lifestyle, and environmental factors vary across populations, which may influence cancer risk and HRT effects differently. Therefore, further studies in diverse ethnic and geographic populations are needed to confirm the broader applicability of our findings. Finally, although the follow-up period in our study was considerable, it may still be insufficient to fully assess the long-term risks of certain cancers associated with prolonged HRT use, particularly those with longer latency periods. Future studies with extended follow-up will be invaluable in providing a more complete picture of the potential long-term effects of HRT on cancer risks and benefits over time.

Nevertheless, this study has important implications for clinical practice and public health. It underscores the need for careful consideration of HRT use in postmenopausal women, emphasizing

the importance of personalized risk assessments f to guide cancer screening and prevention strategies. The findings may also inform HRT prescription guidelines, particularly regarding the appropriate duration and type of treatment therapy, to optimize benefits while minimizing risks.

In conclusion, this study investigated the relationship between HRT and cancer risks in postmenopausal women using a nationwide cohort in South Korea. Our findings revealed that HRT use is associated with varying cancer risks depending on the type of cancer, duration of therapy, and hormone formulation. Combined estrogen–progestin therapy was linked to an increased risk of breast cancer, particularly with prolonged use. In addition, tibolone–only therapy or duration of certain HRT use elevated the risk of endometrial cancer in women with intact uterus. Conversely, HRT use was associated with a reduced risk of cervical cancer, and no significant relationship was observed for ovarian cancer risk.

These results highlight the critical need for personalized approaches to HRT that take individual risk profiles into account to optimize therapeutic benefits while minimizing potential harms. By incorporating these findings into clinical practice and public health policies, healthcare providers can enhance decision–making and improve outcomes for postmenopausal women. Future research is expected to refine HRT strategies that balance efficacy and safety, addressing the nuanced risks identified in this study.

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국문초록

호르몬 대체 요법(Hormone Replacement Therapy, HRT)은 폐경기 증상을 완화하고 연령 관련 건강 상태를 개선하기 위해 널리 사용되고 있습니다. 그러나 암 위험과의 잠재적 연관성에 대해서는 여전히 논란의 여지가 있습니다. 본 연구는 한국의 폐경 후 여성에서 HRT 사용 여부에 따른 유방암 및 부인암 발생을 조사하기 위해 전국적인 코호트를 활용하여 결과를 비교하였습니다.

2009년부터 2021년까지 한국 국민건강보험공단(NHIS) 데이터를 사용하여 40세 이상 폐경 후 여성 2,003,757명을 대상으로 후향적 코호트 분석을 수행하였습니다. 연구 참여자는 HRT 사용에 따라 미사용 그룹, 에스트로겐 단독 요법 그룹, 에스트로겐-프로게스틴 병합 요법 그룹, 티볼론 사용 그룹의 네 그룹으로 분류되었습니다. 유방암, 자궁경부암, 자궁내막암, 난소암의 발생률은 Cox 비례위험회귀모형을 사용하여 위험비(HR)와 95% 신뢰구간(CI)을 산출하여 평가하였습니다.

분석 결과, HRT 사용은 유방암 위험 증가와 관련이 있었으며(HR 1.37, 95% CI 1.33-1.42), 특히 에스트로겐-프로게스틴 병합 요법이 가장 높은 위험을 보였습니다(HR 2.16, 95% CI 2.03-2.30). 반면, HRT 사용은 자궁경부암 위험 감소와 관련이 있었으며(HR 0.84, 95% CI 0.76-0.92), 특히 치료 기간이 길수록 더 큰 효과를 보였습니다. 난소암에 대해서는 유의미한 연관성을 발견하지 못하였으며(HR 1.02, 95% CI 0.94-1.12), 티볼론 단독 요법은 자궁내막암 위험 증가와 약간의 연관성을 보였습니다(HR 1.26, 95% CI 1.01-1.56).

HRT가 폐경 후 여성의 암 위험에 미치는 영향은 암의 종류, 치료 기간, 호르몬 조성에 따라 달라질 수 있음을 확인하였습니다. HRT는 유방암 위험을 증가시키는 반면, 자궁경부암 위험은 감소시키는 것으로 나타났습니다. 이러한 연구 결과는 폐경 후 여성에게 적합한 HRT 접근법을 통해 위험을 최소화하고 이점을 극대화할 필요성을 강조합니다.