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Original Research

Breast cancer risk association with postmenopausal hormone therapy: Health Insurance Database in South Korea–based cohort study

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Abstract

Context: Although many physicians have been concerned that the menopausal hormones used currently in clinical practice may affect the risk of breast cancer, there are currently few informative updated studies about the associations between menopausal hormone therapy (MHT) and the risk of breast cancer.

Objective: This study aims to evaluate the association between the risk of breast cancer and MHT using the National Health Insurance Database in South Korea (HISK) cohort between 2002 and 2019 retrospectively.

Methods: Postmenopausal women over 40 years of age from 2003 to 2011 were selected as the subject population, and their follow-up data were collected until 2019. We analyzed the risk and mortality of breast cancer according to the type of MHT received, namely, tibolone, combined estrogen plus progestin by manufacturer (CEPM), oral estrogen, combined estrogen plus progestin by physician (CEPP), or topical estrogen.

Results: The risk of breast cancer increased in the CEPM group [hazard ratio (HR) 1.439, 95% CI 1.374-1.507, *P*-value < .001] in comparison with the non-MHT group. However, no significant associations were found between the use of tibolone, oral estrogen, CEPP, or topical estrogen and breast cancer risk in comparison with the non-MHT group (HR 0.968, 95% CI 0.925-1.012; HR 1.002, 95% CI 0.929-1.081; HR 0.929, 95% CI 0.75-1.15; HR 1.139, 95% CI 0.809-1.603). The mortality rate from breast cancer is lower in the MHT group in comparison with the non-MHT group, indicating that significant associations were found for tibolone, CEPM, and oral estrogen (HR 0.504, 95% CI 0.432-0.588; HR 0.429, 95% CI 0.352-0.522; HR 0.453 95% CI 0.349-0.588, *P*-value < .001).

Conclusions: This study suggests that the risk of breast cancer is increased by drugs in the CEPM group but not by tibolone, oral estrogen, CEPP, or topical estrogen. The mortality rate from breast cancer is lower with MHT (tibolone, CEPM, oral estrogen) than without MHT.

Keywords: breast cancer, menopause, estrogen, progestogen, tibolone

Significance

Since large clinical trials of menopausal hormone therapy (MHT) in the early 2000s reported that the combination of conjugated equine estrogens and medroxyprogesterone acetate (MPA) significantly increased the risk of invasive breast cancer, the progestin MPA is no longer used. Previous clinical trials did not include newer drugs that are currently prescribed, and there is insufficient evidence for tibolone, which has androgenic effects. They also included very few young, early menopausal women and many with a high body mass index (BMI). Investigating the effects of MHT, including newer agents, on breast cancer risk in Asian women who are relatively young and have a low BMI is essential for the safe use of MHT.

Introduction

Menopausal hormone therapy (MHT) is considered primarily to reduce various bothersome menopausal symptoms and to prevent osteoporosis caused by postmenopausal estrogen deficiency.[1] Menopausal hormone therapy was first used in the 1940s and became more widely used in the 1960s, which is when it began to have a profound impact on the quality of life of postmenopausal women.[2] A large study on MHT users, known as the Women's Health Initiative (WHI) study in the United States, a placebo-controlled randomized clinical trial (RCT), was conducted in the 1990s.[3] The WHI study provided a comprehensive overview of findings showing that combined equine estrogen (CEE) plus progestin medroxyprogesterone acetate (MPA) significantly increased the risk of invasive breast cancer in postmenopausal women with a uterus, affecting both the intervention and postintervention phases[3-6] but that CEE alone significantly reduced the risk of invasive breast cancer in postmenopausal women with prior hysterectomy

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over extended follow-up.[5] These studies suggested that MPA may lead to the increased risk of breast cancer.

Tibolone is a synthetic steroid with weak estrogenic, progestogenic, and androgenic activity that was developed in the 1960s and has been approved for use in many countries around the world but not in the United States.[7] The Long-Term Intervention on Fractures with Tibolone (LIFT) study found that 1.25 mg of tibolone reduced the risks of fracture and breast cancer in older women with osteoporosis.[8] A meta-analysis of RCTs on tibolone, including the LIFT study, showed that tibolone did not increase the risk of breast cancer; however, many non-RCT studies including Million Women Study (MWS) reported that tibolone did increase the risk of breast cancer although the strongest association described by MWS was actually between estrogen plus progestin MHT and the risk of breast cancer.[9-13]

Many of the previous clinical studies have several limitations. First, a relevant consequence of the WHI study evaluated the use of CEE + MPA, which is no longer prescribed in the current practice. Second, the WHI study included an older cohort (mean age of 63) which had been postmenopausal for over 10 years and therefore not the population that is usually prescribed MHT for the first time. Furthermore, the prevalence of obesity, a well-known risk factor for breast cancer, was reported in 34% of the study population of the WHI.[3] Fourth, the higher dose of tibolone, 2.5 mg, was commonly used at the time, but studies have shown that the lower dose of tibolone, 1.25 mg, is just as effective as the higher dose, 2.5 mg, so the LIFT trial used tibolone 1.25 mg and showed no increased risk of breast cancer.[8,14] The key limitation of the tibolone study is the relatively low level of evidence from non-RCT studies. Earlier tibolone studies did not have enough subjects to prove the safety of tibolone because tibolone is not a mainstream MHT in Europe, with tibolone prescriptions being as low as 2.5% among all MHT prescriptions.[13] Finally, many drugs for MHT based on estrogen and progesterone compositions have emerged recently, and the medical environment of each country and the prescription behavior of each physician have changed substantially over time. Moreover, estradiol hemihydrate 1.03 mg and drospirenone 2 mg (E2/DRSP) are some of the most common drugs among MHTs used in many countries, including the United States, with 3 million prescriptions; however, there are few studies on the effects of E2/DRSP on the occurrence of breast cancer.[15]

Our study aimed to investigate whether various MHTs used in current clinical practice increase the risk of breast cancer in postmenopausal women. Our secondary aim was to analyze the mortality rate from breast cancer in both the MHT and non-MHT groups.

Methods

Database

South Korea provides the National Health Insurance Service (NHIS) for almost all Koreans (~51 million) by law.[16] The NHIS system has been collecting the health and personal information of people who were registered at NHIS beginning in 2000, such as code of diagnosis, code of surgery, prescription drug name, types of medical insurance, income quintile, region of residence, body mass index (BMI), parity, ages at menarche and menopause, smoking, alcohol consumption, and physical exercise.[17] This retrospective cohort study was conducted using the national health checkup and insurance data provided by NHIS from January 1, 2002, to December 31, 2019.

To calculate the sample size, we used the existing research data on Korean breast cancer to find the difference between the two proportions with a power of 0.8, which was found to be 494 086.[18]

Selection of participants

The International Classification of Diseases, 10th Revision (ICD-10), and Korea Health Insurance Medical Care Expenses (2012, 2016, 2019 version) were used to select all the study subjects and results.[19] The study subjects were women over 40 years old who selectively recorded "menopause" in the medical examination records between 2002 and 2011.

We defined the MHT group as women who had received MHT for 6 months or more. The definition of the start date of MHT was the date of the first prescription of MHT. If more than the two kinds of hormones were administered during the cohort period, the last hormone that was used for 6 months or more was defined as the main hormone. We defined the non-MHT group as women who never used MHT from 2002 to 2019. The definition of the start date of the non-MHT group was the first recorded date of menopause in the medical examination record. If there was no examination date in the records, June 30th of the examination year was defined as the examination date.

The following cases were excluded from the MHT group and non-MHT group: (1) cases of menopause first confirmed in 2002 as the washout period. To ensure that only women were selected as new MHT users, we excluded women who were taking medication in 2002 with a menopause code; (2) cases in which the cancer-related diagnostic codes (any C code) were ever given within 180 days after inclusion for study. To reduce the impact of cancer history on outcomes as much as possible, we excluded women who were diagnosed with any cancer within 180 days of being included in the study; and (3) cases in which the diagnostic codes for benign breast disease and in situ carcinoma of the breast were ever given within 180 days after inclusion in the study. To minimize the impact of pre-existing benign breast disease or carcinoma in situ on the risk of breast cancer, we excluded women who were diagnosed with benign breast disease or carcinoma in situ within 180 days of inclusion in the study. The diagnostic codes for benign breast disease include N60 (benign mammary dysplasia), N61 (inflammatory disorders of breast), N62 (hypertrophy of breast), N63 (unspecified lump in breast), N64 (other disorders of breast), D24 (benign neoplasm of breast), and D05 (carcinoma in situ of the breast) (Figure 1).

Outcome

Diagnosis of breast cancer was defined as a case in which the patient visited a medical institution more than three times with diagnostic code of breast cancer "C50" as the main diagnosis or supplementary diagnosis.

In Korea, screening tests are usually performed when a patient comes in for their first outpatient visit, and the results are confirmed at the second outpatient visit. Depending on the test results, additional confirmatory tests can be performed, so in most cases, a definitive diagnosis is given on the third outpatient visit. Therefore, considering this pattern

of outpatient care in Korea, the researchers defined breast cancer as confirmed if there were three or more visits with a diagnosis code of breast cancer. Estimands to define the interventions are shown in Table S1.[20]

Variables

Menopausal hormone therapy was classified into five groups according to the regimen: combined estrogen plus progestin by the manufacturer (CEPM), combined estrogen plus progestogen by physician (CEPP), oral estrogen, tibolone, and transdermal estrogen. The CEPM is defined as a case where a physician prescribes a drug made by a pharmaceutical company in a single form of the estrogen/progestin combination and includes various kinds of drugs, such as E2/DRSP, estradiol valerate/cyproterone acetate (E2/CPA), estradiol hemihydrate/norethisterone acetate (E2/NETA), estradiol hemihydrate/dydrogesterone (E2/DYD), estradiol valerate/MPA (E2/MPA), and estradiol valerate/norethisterone acetate (E2/NETA) (Table S2).[20] The CEPP is defined as a case where a physician selects and prescribes various progestogen to be added to estrogen. The independent variables evaluated based on the inclusion date included age, BMI, socioeconomic status (SES), residential area, Charlson comorbidity index (CCI),[21] parity, age at menarche, age at menopause, smoking, alcohol consumption, physical exercise, and time from menopause to inclusion, among others.

The age group was categorized at 10-year-old intervals and followed the criteria of the Asia–Pacific perspective on BMI.[22] Medical insurance was defined as low SES when medical aid was used, and the residential area was defined as a rural region if the location of the medical institution was not metropolitan. The CCI was calculated by using the diagnostic code when visiting medical institutions from a year before enrollment to the enrollment date for this research.[23] Parity was classified as "0 or no response", "1", "2", or "more than 3". A history of smoking was classified as "never", "past", or "current", and drinking was classified according to the number of drinks per week. Physical exercise was classified as <3 times, 3-4 times, 5-6 times, or every day of the week according to the number of exercise sessions that exceeded 30 min per week. The time from menopause to study inclusion was classified as <5 years, 5-9 years, or 10 years or more.

Statistics

All statistical analyses were conducted using SAS Enterprise Guide 6.1 (SAS Institute Inc. Cary, NC, United States). A statistically significant value was defined as having a P value $< .05$. All statistics were 2-sided. Continuous variables are expressed as the median value (25th percentile, 75th percentile), and categorical variables are expressed as the number (percentage). The Cox proportional hazard model was used for the adjustment of various confounding factors including age, BMI, SES, CCI, parity, age at menarche, age at menopause, smoking, alcohol consumption, physical exercise, and time from menopause to inclusion. The last day of follow-up was set as the date of death or December 31, 2019. As a sensitivity test, analysis of selected subgroups prescribed by gynecologists among the MHT group by the Cox proportional hazard model was carried out to confirm the robustness of the results. The missing values were processed with a listwise deletion method.

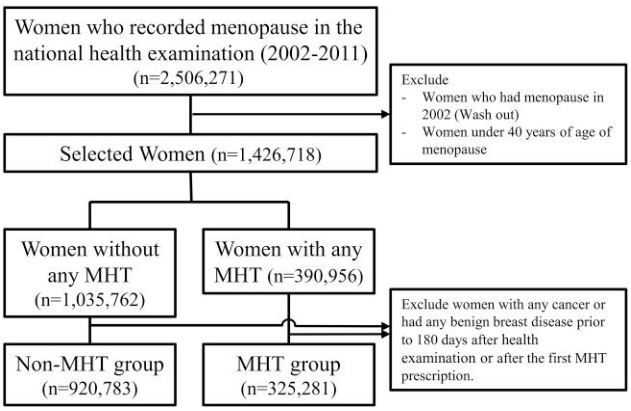

Figure 1. Flowchart to select case-controls according to MHT from the National Health Insurance Database in South Korea, 2002-2019. MHT, menopausal hormone therapy. The MHT and control groups had 325 281 and 920 783 subjects, respectively. The MHT subjects consisted of 165 222 in the tibolone group, 107 088 in the CEPM group, 45 609 in the oral estrogen group, 5633 in the CEPP group, and 1729 in the transdermal estrogen group.

Ethics

This study was approved by Sanggye Paik Hospital IRB (Approval Number: SGPAIK-2020-08-002). The NHIS provided the data to the investigators after removing the variables that can identify individuals. Therefore, the individual included in the data cannot be specified, so it does not cause any damage to the individual included in the data. In addition, this study does not require the provision of informed content to patients included in the data by the Bioethics and Safety Act of South Korea. Data extraction for this study can be done only with NHIS servers according to NHIS's information protection policy, and other than the result value, raw data cannot be taken out.

Results

The MHT and control groups had 325 281 and 920 783 subjects, respectively (Figure 1). The MHT subjects consisted of 165 222 in the tibolone group, 107 088 in the CEPM group, 45 609 in the oral estrogen group, 5633 in the CEPP group, and 1729 in the transdermal estrogen group. The detailed characteristics of women according to menopausal hormone exposure status at the time of recruitment are shown in Table 1. The duration of hormone use was 24 (range: 11-58) months in the tibolone, 25 (range: 11-57) months in the CEPM, 15 (range: 8-35) months in the oral estrogen, 15 (range: 9-35) months in the CEPP, and 13 (range: 8-25) months in the transdermal estrogen. The MHT characteristics according to median duration, duration of taking drugs, duration of previous other MHTs, last dosage of tibolone, and prescribed specialty in each hormone group are shown in Table 2.

Detailed case/person-year values according to each group are shown in Table S2.[20] The results of the chi-square test of breast cancer incidence in the non-MHT group and each MHT group are shown in Table S3.[20] The incidence of breast cancer patients in the non-MHT group was 11 992 (1.3%), and the incidences of breast cancer in the tibolone, CEPM, oral estrogen, CEPP, and transdermal estrogen groups were 2569 (1.6%), 2432 (2.3%), 788 (1.7%), 91 (1.6%), and 36 (2.1%), respectively (Table S4).[20]

Table 1. Characteristics of women according to menopausal hormone exposure status at recruitment, the National Health Insurance Data in South Korea, 2002-2019.

	Non-MHT	Tibolone	CEPM	Oral estrogen	CEPP	Transdermal estrogen	Total
Number of women	920 783	165 222	107 088	45 609	5633	1729	1 246 064
Median age (years)	58 (53-66)	54 (51-58)	52 (50-56)	53 (49-58)	55 (51-59)	53 (50-58)	56 (52-64)
Age at inclusion (years)							
40-49	73 209 (8)	28 299 (17.1)	24 233 (22.6)	11 565 (25.4)	12 524 (24.4)	374 (21.6)	150 204 (11.6)
50-59	423 564 (46)	106 898 (64.7)	70 831 (66.1)	25 026 (54.9)	28 302 (55.2)	1032 (59.7)	655 653 (50.8)
60-69	288 944 (36.8)	26 365 (16.3)	11 026 (10.4)	7309 (16.6)	8512 (17.3)	289 (17.1)	342 445 (29.8)
70-	135 066 (14.7)	3660 (2.2)	998 (0.9)	1709 (3.7)	1904 (3.7)	34 (2)	143 371 (11.1)
Median BMI (kg/m^2)	24 (22.1-26.1)	23.5 (21.8-25.5)	23.2 (21.5-25.1)	23.8 (22.1-25.8)	23.4 (21.7-25.3)	23.7 (22-25.7)	23.9 (22-26)
BMI (kg/m^2)							
<18.5	17 398 (1.9)	2780 (1.7)	2098 (2)	672 (1.5)	119 (2.1)	34 (2)	23 101 (1.9)
18.5-22.9	301 480 (33.5)	64 615 (39.5)	47 191 (44.4)	16 245 (36)	2263 (40.5)	634 (37)	432 428 (35.4)
23-24.9	237 829 (26.4)	45 449 (27.8)	28 583 (26.9)	12 684 (28.1)	1593 (28.5)	460 (26.8)	326 598 (26.7)
25-29.9	303 610 (33.7)	46 190 (28.3)	26 145 (24.6)	13 964 (30.9)	1490 (26.7)	537 (31.3)	391 936 (32.1)
≥30	40 320 (4.5)	4394 (2.7)	2245 (2.1)	1618 (3.6)	119 (2.1)	49 (2.9)	48 745 (4)
SES							
Mid~high SES	878 318 (95.4)	158 760 (96.1)	104 155 (97.3)	44 236 (97)	5481 (97.3)	1672 (96.7)	1 192 622 (95.7)
Low SES	42 465 (4.6)	6462 (3.9)	2933 (2.7)	1373 (3)	152 (2.7)	57 (3.3)	53 442 (4.3)
Region							
Urban area	263 091 (28.6)	50 520 (30.6)	35 431 (33.1)	13 990 (30.7)	2811 (49.9)	778 (45)	366 621 (29.4)
Rural area	657 692 (71.4)	114 702 (69.4)	71 657 (66.9)	31 619 (69.3)	2822 (50.1)	951 (55)	879 443 (70.6)
CCI							
0	597 450 (64.9)	112 197 (67.9)	75 965 (70.9)	31 684 (69.5)	3878 (68.8)	1119 (64.7)	822 293 (66)
1	184 007 (20)	32 201 (19.5)	19 344 (18.1)	8384 (18.4)	1069 (19)	321 (18.6)	245 326 (19.7)
≥2	139 326 (15.1)	20 824 (12.6)	11 779 (11)	5541 (12.1)	686 (12.2)	289 (16.7)	178 445 (14.3)
Parity							
0 or not respond	154 338 (16.8)	26 181 (15.8)	13 949 (13)	9692 (21.3)	1131 (20.1)	377 (21.8)	205 668 (16.5)
1	51 214 (5.6)	13 916 (8.4)	10 856 (10.1)	3336 (7.3)	394 (7)	131 (7.6)	79 847 (6.4)
2	600 845 (74.5)	109 698 (73.2)	74 243 (75)	27 883 (68.2)	3518 (69.8)	1051 (67.4)	817 238 (74.1)
≥3	114 386 (12.4)	15 427 (9.3)	8040 (7.5)	4698 (10.3)	590 (10.5)	170 (9.8)	143 311 (11.5)
Age at menarche (years)							
<13	142 740 (15.6)	23 983 (14.6)	15 288 (14.4)	8251 (18.3)	1054 (18.9)	321 (18.8)	191 637 (15.5)
≥13	773 445 (84.4)	139 904 (85.4)	91 164 (85.6)	36 766 (81.7)	4525 (81.1)	1386 (81.2)	1 047 190 (84.5)
Age at menopause (years)							
40-44	111 204 (12.1)	19 643 (11.9)	12 124 (11.3)	9612 (21.1)	718 (12.7)	335 (19.4)	153 636 (12.3)
45-49	266 849 (29)	53 682 (32.5)	35 865 (33.5)	16 079 (35.3)	1819 (32.3)	626 (36.2)	374 920 (30.1)
50-54	460 919 (54.9)	79 044 (51.9)	51 863 (51.9)	17 590 (40.6)	2642 (51)	655 (40.5)	612 713 (53.7)
55-	81 811 (8.9)	12 853 (7.8)	7236 (6.8)	2328 (5.1)	454 (8.1)	113 (6.5)	104 795 (8.4)
Smoking							
Never	836 143 (96.3)	148 533 (93.6)	96 703 (93.4)	41 592 (95)	5176 (95.5)	1579 (95.8)	1 129 726 (95.7)
Past	8774 (1)	2694 (1.7)	1867 (1.8)	594 (1.4)	73 (1.3)	29 (1.8)	14 031 (1.2)
Current	23 080 (2.7)	7456 (4.7)	4971 (4.8)	1607 (3.7)	173 (3.2)	40 (2.4)	37 327 (3.2)
Alcohol consumption (days)							
None	746 316 (85.7)	124 197 (77.7)	79 140 (76)	35 379 (80.1)	4527 (82.9)	1375 (82.5)	990 934 (83.5)
~2/week	106 761 (12.3)	30 120 (18.8)	21 306 (20.5)	7614 (17.2)	825 (15.1)	258 (15.5)	166 884 (14.1)
3-6/week	13 246 (1.5)	4163 (2.6)	2931 (2.8)	818 (1.9)	74 (1.4)	28 (1.7)	21 260 (1.8)
Daily	4969 (0.6)	1311 (0.8)	782 (0.8)	330 (0.7)	36 (0.7)	6 (0.4)	7434 (0.6)

(*continued*)

Table 1. Continued

	Non-MHT	Tibolone	CEPM	Oral estrogen	CEPP	Transdermal estrogen	Total
Physical exercise (per week)							
None	578 039 (66.2)	95 783 (60)	62 909 (60.4)	26 559 (60.2)	3140 (57.5)	863 (51.9)	767 293 (64.6)
1-2	140 078 (16.1)	30 112 (18.9)	20 075 (19.3)	8394 (19)	1063 (19.5)	365 (21.9)	200 087 (16.8)
3-4	76 693 (8.8)	17 765 (11.1)	11 838 (11.4)	4707 (10.7)	689 (12.6)	252 (15.2)	111 944 (9.4)
5-6	25 590 (2.9)	5847 (3.7)	3892 (3.7)	1473 (3.3)	204 (3.7)	68 (4.1)	37 074 (3.1)
Daily	52 314 (6)	10 183 (6.4)	5471 (5.3)	2968 (6.7)	365 (6.7)	115 (6.9)	71 416 (6)
Period from menopause to inclusion (years)							
<5	333 508 (36.2)	94 219 (57)	71 918 (67.2)	23 295 (51.1)	2803 (49.8)	869 (50.3)	526 612 (42.3)
5-9	191 111 (20.8)	38 028 (23)	21 586 (20.2)	11 230 (24.6)	1359 (24.1)	453 (26.2)	263 767 (21.2)
10-	396 164 (43)	32 975 (20)	13 584 (12.7)	11 084 (24.3)	1471 (26.1)	407 (23.5)	455 685 (36.6)

Data are expressed as the number (%) or median (25 percentile, 75 percentile).
Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CEPM, combined estrogen plus progestin by manufacturer; CEPP, combined estrogen plus progestogen by physician; MHT, menopausal hormone therapy; SES, socioeconomic status.

In the multivariate Cox proportional hazard analysis, the risk of breast cancer increased in the CEPM group [hazard ratio (HR) 1.439, 95% CI 1.374-1.507] comparatively with that of non-MHT group. However, no significant associations were found between the use of tibolone, oral estrogen, CEPP, or topical estrogen and breast cancer risk in comparison with non-MHT users (HR 0.968, 95% CI 0.925-1.012; HR 1.002, 95% CI 0.929-1.081; HR 0.929, 95% CI 0.75-1.15; HR 1.139, 95% CI 0.809-1.603) (Figure 2; Table S5).[20]

The risk of breast cancer decreased with increasing age when patients in their 40s were the comparator. The risk of breast cancer increased with increasing BMI (≥30 kg/m^2: HR 1.356, 95% CI 1.258-1.462) and was increased with a menarche age of <13 years (HR 1.157, 95% CI 1.102-1.214). The risk of breast cancer was reduced when menopause occurred at ~60 years of age compared with the group of patients whose menopause occurred in their early 40s (HR 0.846, 95% CI 0.776-0.922). In addition, the risk of breast cancer decreased over time from the time of menopause (≥10 years: HR 0.846, 95% CI 0.791-0.904). The risk of breast cancer increased in women who had a history of smoking (HR 1.254, 95% CI 1.109-1.419) but not in women with a history of drinking. However, the risk of breast cancer was lowest in the group of women who did not exercise physically at all (Table S5).[20]

In the Cox proportional hazard analysis according to age group, the risk of breast cancer in the CEPM group was increased when the patients were in their 50s and 60s (HR 1.457, 95% CI 1.378-1.542; HR 1.819, 95% CI 1.588-2.084), but that in the tibolone group was increased only when they were in their 60s comparatively with that in the non-MHT group. However, when women were in their 70s, none of the MHT regimens was associated with an increased the risk of breast cancer (Table S5).[20] Moreover, there was no difference in the risk of breast cancer in the subgroup analysis of women using tibolone according to the dosage of tibolone (over 5 mg: HR 1.306, 95% CI 0.326-5.226) (Table 3).

The mortality rate from breast cancer is lower in the MHT group in comparison with the non-MHT group, indicating that significant associations were found for tibolone, CEPM, and oral estrogen (HR 0.504, 95% CI 0.432-0.588; HR 0.429, 95% CI 0.352-0.522; HR 0.453 95% CI 0.349-0.588, *P*-value < .001, respectively) (Table 4; Table S6).[20] To confirm the robustness of this study, we performed a selective analysis according to whether the doctor who prescribed the MHT was a gynecologist or not. The risk of breast cancer was also increased only in the CEPM group (HR 1.407, 95% CI 1.318-1.501) of women who received MHT prescriptions from not only the gynecologist but also non-gynecological specialists (Table S7).[20]

Discussion

Our study presented that MHT (estradiol, tibolone, CEPP, and transdermal estrogen) is not associated with an increased risk with the exception of CEPM and MHT (all types) is associated with a reduced mortality risk. Multiple pharmaceutical companies have been producing many combined estrogen and progestin drugs as a substitute for CEE plus MPA, the prescriptions of which have been drastically reduced due to the reported increased risk of breast cancer over two decades from the RCT by the WHI.[3,6,23,24] However, despite frequent prescriptions of various combined estrogen and progestogen

Table 2. Characteristics of women with MHT, the National Health Insurance Data in South Korea, 2002-2019.

MHT groups	Tibolone	CEPM	Oral estrogen	CEPP	Transdermal estrogen	Total MHT
Median duration (months)	24 (11-58)	25 (11-57)	15 (8-38)	15 (9-35)	13 (8-25)	23 (10-54)
Duration (years)						
<5	125 299 (75.8)	81 362 (76)	38 041 (83.4)	4917 (87.3)	1640 (94.9)	251 259 (77.2)
5-9.9	29 170 (17.7)	19 554 (18.3)	5186 (11.4)	554 (9.8)	84 (4.9)	54 548 (16.8)
≥10	10 753 (6.5)	6172 (5.8)	2382 (5.2)	162 (2.9)	5 (0.3)	19 474 (6)
Duration of previous other MHT (years)			0			
<5	160 995 (97.4)	105 449 (98.5)	44 997 (98.7)	4721 (83.8)	1711 (99)	317 873 (97.7)
5-9.9	3767 (2.3)	1496 (1.4)	554 (1.2)	679 (12.1)	17 (1)	6513 (2)
≥10	460 (0.3)	143 (0.1)	58 (0.1)	233 (4.1)	1 (0.1)	895 (0.3)
Last dosage of tibolone (per day)						
1.25 mg	1540 (0.9)					
2.5 mg	163 528 (99)					
Over 5 mg	136 (0.1)					
Prescribed specialty						
Gynecology	55 088 (33.3)	49 472 (46.2)	19 086 (41.8)	1373 (24.4)	439 (25.4)	125 458 (38.6)
Non-gynecology	110 134 (66.7)	57 616 (53.8)	26 523 (58.2)	4260 (75.6)	1290 (74.6)	199 823 (61.4)

Data are expressed as the number (%) or median (25 percentile, 75 percentile).
Abbreviations: CEPM, combined estrogen plus progestin by manufacturer; CEPP, combined estrogen plus progestogen by physician; MHT, menopausal hormone therapy.

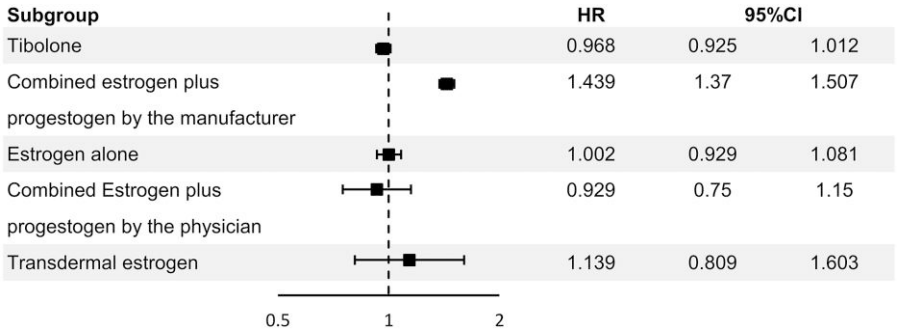

Figure 2. Hazard ratios (HRs) of breast cancer in each MHT subgroup compared with non-MHT group. In the Cox proportional hazard analysis with adjusted for variables, the HR of breast cancer in the CEPM group increased comparatively with that of non-MHT group (HR1.439, 95% CI 1.374-1.507). However, the HRs of breast cancer in the tibolone, oral estrogen, CEPP, and transdermal estrogen group did not increase in comparison with that of non-MHT group (HR 0.968, 95% CI 0.925-1.012; HR 1.002, 95% CI 0.929-1.081; HR 0.929, 95% CI 0.75-1.15; HR 1.139, 95% CI 0.809-1.603).

Table 3. Subgroup analysis for risk of breast cancer according to major variables in tibolone, the National Health Insurance Data in South Korea, 2002-2019.

Tibolone use	HR (95% CI)[a]	*P*-value
Tibolone only (without non-MHT)		
Period from menopause to inclusion (years)		
5-9	1.031 (0.892-1.192)	.68
10-	0.999 (0.772-1.293)	.993
Total period of use (months)	0.998 (0.996-0.999)	<.001
Dosage		
1.25 mg	0.989 (0.65-1.506)	.96
Over 5 mg	1.306 (0.326-5.226)	.706
Prescribed specialty		
Non-gynecology	1.073 (0.985-1.169)	.106
Dosage of tibolone		
Tibolone 1.25 mg vs non-MHT	0.973 (0.64-1.479)	.898
Tibolone 2.5 mg vs non-MHT	0.968 (0.925-1.013)	.162
Tibolone 5 mg vs non-MHT	1.364 (0.341-5.456)	.661

Abbreviations: CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy.
[a]HRs were adjusted for age group, body mass index, socioeconomic status, region, Charlson comorbidity index, parity, age at menarche, age at menopause, smoking, alcohol consumption, physical exercise, and period from menopause to inclusion.

drugs for MHT, study results showing clear outcomes of CEPM with various progestin components, including E2/DRSP, are insufficient. Our cohort study has shown that MHT is not associated with an increase in the risk of breast cancer, with the exception of CEPM.

The drugs used in previous clinical studies were CEE + MPA and CEE, which are classified as CEPP or oral estrogen in this study.[23-25] The details of the drugs in the CEPM group, including estradiol hemihydrate + drospirenone (DRSP), estradiol hemihydrate + norethisterone (NETA), or estradiol valerate + cyproterone acetate (CPA), are described in Table S1. In the WHI study, the risk of breast cancer did not increase when CEE alone was used, and in this study, the risk of breast cancer did not increase with the use of various estrogens (CEE, estradiol valerate, estradiol hemihydrate) alone.[3,23,24] Therefore, the increase in the risk of breast cancer in the CEMP is more likely to be caused by progestin preparations than by estrogen preparation group.[26]

The biological characteristics of estrogens and progestins are determined based on how closely they mimic natural hormones in terms of their compositions and functions. In particular, progestins can be classified according to various properties, including androgenic, antiandrogenic, glucocorticoid, or antimineralocorticoid activity.[2,27-29] There is little research on the

Table 4. Hazard ratios for risk of breast cancer according to MHT drug type, the National Health Insurance Data in South Korea, 2002-2019.

MHT group (reference = non-MHT group)	Formula 1[a]		Formula 2[b]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Total				
Tibolone	0.97 (0.929-1.014)	.182	0.968 (0.925-1.012)	.153
CEPM	1.451 (1.386-1.518)	<.001	1.439 (1.374-1.507)	<.001
Estrogen	1.004 (0.932-1.081)	.915	1.002 (0.929-1.081)	.953
CEPP	0.933 (0.756-1.151)	.518	0.929 (0.75-1.15)	.5
Transdermal estrogen	1.164 (0.835-1.622)	.37	1.139 (0.809-1.603)	.456

Abbreviations: CEPM, combined estrogen plus progestin by manufacturer; CEPP, combined estrogen plus progestogen by physician; CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy.
[a]HRs were adjusted for age group, body mass index, socioeconomic status, region, Charlson comorbidity index, parity, age at menarche, and age at menopause.
[b]HRs were adjusted for age group, body mass index, socioeconomic status, region, Charlson comorbidity index, parity, age at menarche, age at menopause, smoking, alcohol consumption, physical exercise, and period from menopause to inclusion.

direct association of synthetic progestins, such as DRSP, NETA, CPA, or DYD, with the risk of breast cancer. Several clinical studies have reported that combined estrogen and progestin drugs such as E2/DRSP and E2/NETA increase breast density on mammography.[30,31] Mammographic breast density is a strong and independent risk factor for breast cancer development.[32] These combined estrogen and progestin drugs, which increase breast density, may result in a proliferation of the mammary tissue and a growth signal to hidden cancer cells in the breast.[33,34] An increase in mammographic breast density should be regarded as an undesirable adverse event of MHT. Progestins with improved receptor selectivity profiles were introduced into clinical practice years ago.[27,35,36] In an experimental study on the effect of various progestins alone, including MPA, DSRP, and nestorone, or in combination with E2, on breast cancer cells, most progestins improved the ability of breast cancer cells to move in the surrounding environment with different potencies and distinct intracellular intermediates to drive myosin activation and actin remodeling. These findings suggest that each progestin works differently on breast cancer cells, which may have relevant clinical implications.[37]

According to the policy from the NHIS regarding information protection for drug manufacturers, detailed component analysis of the drugs classified in the CEPM group was not possible, and further studies on this would require tracking of the components that increased the risk of breast cancer. In addition, the exact prescription rate of CEPM is unknown, but there are indirect data for estimations. According to a 2007 article, the market share of MHT was in the order of tibolone (38%), E2/CPA (14.4%), and E2/NETA (7.2%) in Korea. The trend since the E2/DRSP launch in 2007 was in the order of E2/CPA, E2/DRSP, E2/DYD, and E2/NETA, according to trend analysis of portal search sites since 2016.

In contrast to combined estrogen and progestogen drugs, tibolone seems to cause little stimulation of breast tissue according to some clinical studies.[8,9] However, as mentioned above, there were contradictory results between the RCT study and the non-RCT studies on tibolone. RCT results showed that tibolone did not increase the risk of breast cancer, but most non-RCTs reported that tibolone increased the risk of breast cancer.[8-11] There are some potential explanations for these conflicting results. First, the differences in study design and the dose of tibolone used were the reason for the inconsistent results of the LIFT study and the non-RCT study.[8,10-13] Second, in the non-RCT studies, women who did not receive tibolone might have undergone fewer breast cancer screening tests than those who did receive tibolone (lead-time bias). Unlike many earlier non-RCT studies, our study showed that tibolone did not increase the risk of breast cancer, but statistically, the risk of breast cancer did not increase with dose. This finding that tibolone does not affect the risk of breast cancer is consistent with previous RCTs. Unlike many other non-RCTs mentioned in our study, all of the subjects in our study were subjects with regular national health screening. Therefore, regular breast cancer screening in the control group may have reduced the bias.

In addition, there have also been positive studies on the androgenic effects of tibolone. Donovitz and Cotten[38] have reported that testosterone (T) and/or testosterone in combination with estradiol (TE) pellet implants significantly reduced the incidence of breast cancer in pre- and postmenopausal women. These findings suggest that the androgenic properties of tibolone do not increase the risk of breast cancer but actually decrease it. Furthermore, level 1 evidence suggests that testosterone may help improve the sexual function of postmenopausal women with sexual problem, with a grade A recommendation. Therefore, postmenopausal women considering MHT need to be given accurate information about the beneficial effects of the androgenic properties of tibolone on the sexual health of postmenopausal women.[39]

In the WHI study, CEE alone did not increase the risk of breast cancer during CEE treatment, but the risk of breast cancer decreased during the follow-up period after discontinuation of CEE.[23] In addition to CEE, which was included in previous studies, our study included various E2s, such as estradiol valerate and estradiol hemihydrate, in the oral estrogen group. We can cautiously suggest that estradiol valerate and estradiol hemihydrate also do not increase the risk of breast cancer.

The CEPP group in our study comprised patients receiving micronized progesterone, DYD, and MPA. In this study, there was no increase in the risk of breast cancer in the CEPP group. Medroxyprogesterone acetate is known to be related to an increased risk of breast cancer in past studies and was classified into the CEPP group in our study.[3,6,23,24] A limitation of this study is that we have the information on the type of progestogen prescribed in the CEMP and CEPP groups, but we don't have any information on the proportion of each progestogen prescribed out of the total progestogen in the CEMP and CEPP groups due to NHIS policy. Therefore, it is difficult to analyze the reasons why the CEPP group was not associated with an increased risk of breast cancer according to each progestogen. However, because it is well known that the potential effects of each progestogens on breast tissue vary widely, we could presume that physicians may have shifted away from MPAs in their choice of progestogen after previous studies found that the most commonly prescribed MPAs were associated with an increased

risk of breast cancer.[26,40,41] However, we could not know the exact proportions of each progestogen in the CEPP group due to NHIS regulations. Further research is needed to grasp the effects of each progestogen on breast cancer.

Transdermal estrogen has usually been considered to improve menopausal symptoms.[42] Transdermal estrogen delivery reduces the first-pass effect of oral delivery and is not subject to gastrointestinal conversion of estradiol to the less active compound estrone.[40,41] Although many investigators have reported the absence of systemic side effects after transdermal estrogen application, there are conflicting results.[43] In this study, the risk of breast cancer among women with transdermal estrogen did not increase compared with that among women in the non-MHT group. The WHI study found that oral CEE alone was not associated with breast cancer risk. In our study, transdermal estrogen was not associated with increased risk of breast cancer. Therefore, the route of administration does not seem to affect breast cancer risk.[3,6,23,24]

Interestingly, although the risk of breast cancer increased in the CEPM group of MHT, the mortality rate from breast cancer was lower in the MHT group than in the non-MHT group. One possible explanation for this discrepancy between the incidence and mortality rate of breast cancer is that the biologic subtype and the stage at diagnosis of breast cancer may affect the mortality rate of breast cancer patients in the MHT group. In other words, since many doctors recommend regular breast screening for women using MHT, earlier breast cancer detection may be possible for the MHT group than for the control group. Therefore, it should be carefully explained to clinicians that they should not overestimate the risk of and mortality from breast cancer when prescribing CEPM to symptomatic women. According to a study conducted based on SEER data from 1987 to 1999, when the use of postmenopausal MHT increased in the United States, the incidence rates of ductal carcinoma remained essentially constant from 1987-1999, while that of lobular carcinoma increased steadily from 9.5% in 1987 to 15.6% in 1999. These results showed that MHT use was more strongly associated with lobular carcinoma than ductal carcinoma.[44,45] Most lobular carcinomas are hormone-dependent breast cancers with good prognosis.[46]

The HR of 1.45 in the CEMP group in this study may deem to be quite risky to both physicians prescribing and women considering MHT. However, as shown in Table S2, with 184 breast cancers per 100 000 person-years in the CEPM group and 111 breast cancers per 100 000 person-years in the non-MHT group, we could confirm that an additional 7 breast cancers per 10 000 person-years were diagnosed in the CEMP arm, which is a clinically very low probability. The earlier WHI trials still provide the best estimate of absolute risk for breast cancer associated with the use of MHT. The HR was 1.21 (95% CI, 0.81-1.80) in women aged 50-59 years at randomization with CEE plus MPA versus placebo, accounting for 6 additional cases of invasive breast cancer per 10 000 person-years.[6] In fact, as the number of subjects in a clinical study increases, even small differences may result statistically significant differences. Therefore, a statistically significant difference does not necessarily mean a clinically significant difference, and physicians need to consider the clinical significance for each of the many women with different clinical factors. In terms of the relative risk factors associated with breast cancer, obesity has a higher relative risk than MHT.[47]

Supplementary data showed that previous smoking and BMI also had a significant association with breast cancer. In the secondary analysis after extended follow-up in the WHI RCT, women who were overweight and obese had an increased risk of invasive breast cancer versus women of normal weight, which is higher HR than CEMP of MHT users. Therefore, it is important to be aware of the increased risk of breast cancer for women with a history of smoking and current obesity.[47] Furthermore, our study showed that physical activity is associated with breast cancer risk. According to a meta-analysis of prospective studies of the association between physical activity, HRT, and breast cancer risk, it has been presented that increasing physical activity is associated with a significant reduction in breast cancer risk, but in women who have ever used HRT, the preventive effect of physical activity appears to be canceled out.[48]

This study has some notable strengths. First, this study included more than one million Asian women, comparable with previous large-scale studies.[3,10,49] Second, the obesity rate among women included in this study was relatively low compared with those in previous studies. Obesity is a confounding factor that is known to be a risk factor for the incidence, recurrence, and prognosis of breast cancer.[50-53] The proportion of obese women included in this study was ~30%, but the ratio of women with obesity with a BMI of 30 or more was <4%, in contrast to 34% in the WHI. Furthermore, the proportion of obese women was ~30%, but the proportion of obese women with a BMI over 30 was <4% in this study, which was also in contrast to the 34% in the WHI study. Third, this study included many CEPM drugs, such as E2/DRSP (Angeliq®), E2/CYP (Climen®), E2/NETA (Cliane®, Esdilo-half), E2/MPA (Femoston®), E2/DYD (Divina, Indivina®), and E2/NETA (Cliovelle®). The majority of drugs in the CEPM group have had no large clinical studies to support their safety in terms of the risk of breast cancer until recently. Admirably, even though tibolone and CEPM currently account for a large portion of all MHT prescriptions, there are not enough large-scale studies in which tibolone or CEPM accounted for the main drugs used for MHT. In this regard, the notable characteristic of this study is its inclusion of relatively large numbers of women prescribed tibolone and CEPM, unlike other studies. Fourth, this study had a relatively high proportion of young women compared with previous studies, especially the WHI study. The majority of women with MHT in this study were in their 40s (17%-25%) and 50s (50%-66%). As mentioned above, the WHI has shown adverse events with MHT in older postmenopausal women over the age of 60 years or who are more than 10 years since menopause. However, this is not the age group at which menopausal symptoms are newly developed. Almost all women who visit hospitals due to menopause symptoms are in their late 40s or 50s. When a clinician counsels a woman with menopausal symptoms regarding MHT, it is desirable to provide appropriate information on the potential risks and benefits that may arise from 5 years of MHT use based on data from women around their 50s. This study can be a crucial basis for showing how MHT affects women in their 40s and 50s who have just begun to develop menopausal symptoms. Finally, we analyzed the effect of MHT by adjusting reproductive and sociocultural variables such as age, BMI, SES, CCI, parity, age at menarche, age at menopause, smoking, alcohol consumption, physical exercise, and the time from menopause to inclusion. Through these adjustments, we tried to determine the actual impact of MHT on breast cancer.

This study has several limitations. First, although adjustments were made for the numerous factors related to the

occurrence of breast cancer, we must be careful in our interpretation of the results because they are not randomized nor blinded into treatment regimens. Second, we were not able to analyze the specific risks of each progestin in the CEMP group associated with the increased breast cancer risk, although this study included various types of estrogen plus progestin. Third, the exact doses and durations of the treatment regimens included in the study are unknown and are a rough estimate. So, we cannot find out the associations between the risk of breast cancer and doses and duration of treatment regimens. Forth, there is a bias that originates from incorrect diagnostic coding. However, national medical expense discounts and private medical insurance coverage are decided depending on the diagnosis of cancer. Therefore, the accuracy of the diagnostic code for cancer in Korea is very high.

In conclusion, our study found that the risk of breast cancer was significantly increased in MHT users CEPM in the group but not in the tibolone, CEPP, oral estrogen, or transdermal estrogen groups, relative to non-MHT. However, the mortality rate from breast cancer in the tibolone group, CEPM group, and oral estrogen groups among the MHT groups was lower than that in the non-MHT group.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

Jin-Sung Yuk [Conceptualization (lead), Data curation (lead), Formal analysis (lead), Methodology (lead), Project administration (lead), Resources (supporting), Supervision (supporting), Writing—review & editing (supporting)], Taeran Kim [Resources (supporting), Writing—review & editing (supporting)], Hyunjin Cho [Resources (supporting), Software (supporting), Supervision (equal), Visualization (supporting), Writing—review & editing (supporting)], and Geumhee Gwak (Conceptualization (equal), Data curation (supporting), Formal analysis (supporting), Resources (lead), Software (lead), Supervision (lead), Validation (lead), Visualization (lead), Writing—original draft (lead), Writing—review & editing (lead)].

Ethics approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and this study was approved by Sanggye Paik Hospital IRB (approval number: SGPAIK-2020-08-002).

Data availability

The availability of the data set generated or analyzed in this study is restricted to protect patient confidentiality. The data set for this study is only available on the NHIS servers and was destroyed in November 2022 due to internal NHIS regulations that allow 1 year for data analysis after the data set is generated. Therefore, the ROW data are not available for sharing by bona fide researchers or for further statistical analysis in the future. The supplementary data underlying this article are available in Harvard Dataverse, DRAFT VERSION at https://doi.org/10.7910/DVN/XLPC5J.

References

1. Grady D, Rubin SM, Petitti DB, *et al.* Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med*. 1992;117(12):1016-1037. https://doi.org/10.7326/0003-4819-117-12-1016
2. Stefanick ML. Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. *Am J Med*. 2005;118(12):64-73. https://doi.org/10.1016/j.amjmed.2005.09.059
3. Rossouw JE, Anderson GL, Prentice RL, *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333. https://doi.org/10.1001/jama.288.3.321
4. Chlebowski RT, Hendrix SL, Langer RD, *et al.* Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003;289(24):3243-3253. https://doi.org/10.1001/jama.289.24.3243
5. Chlebowski RT, Anderson GL, Gass M, *et al.* Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA*. 2010;304(15):1684-1692. https://doi.org/10.1001/jama.2010.1500
6. Manson JE, Chlebowski RT, Stefanick ML, *et al.* Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310(13):1353-1368. https://doi.org/10.1001/jama.2013.278040
7. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric*. 2005;8(Suppl 1):3-63. https://doi.org/10.1080/13697130500148875
8. Cummings SR, Ettinger B, Delmas PD, *et al.* The effects of tibolone in older postmenopausal women. *N Engl J Med*. 2008;359(7):697-708. https://doi.org/10.1056/NEJMoa0800743
9. Formoso G, Perrone E, Maltoni S, *et al.* Short and long term effects of tibolone in postmenopausal women. *Cochrane Database Syst Rev*. 2012;10(10):CD008536. https://doi.org/10.1002/14651858.CD008536.pub2
10. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2003;362(9392):419-427. https://doi.org/10.1016/S0140-6736(03)14596-5
11. Suhrke P, Zahl P-H. Breast cancer incidence and menopausal hormone therapy in Norway from 2004 to 2009: a register-based cohort study. *Cancer Med*. 2015;4(8):1303-1308. https://doi.org/10.1002/cam4.474
12. Roman M, Sakshaug S, Graff-Iversen S, *et al.* Postmenopausal hormone therapy and the risk of breast cancer in Norway. *Int J Cancer*. 2016;138(3):584-593. https://doi.org/10.1002/ijc.29810
13. Bakken K, Fournier A, Lund E, *et al.* Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*. 2011;128(1):144-156. https://doi.org/10.1002/ijc.25314

14. Gallagher JC, Baylink DJ, Freeman R, McClung M. Prevention of bone loss with tibolone in postmenopausal women: results of two randomized, double-blind, placebo-controlled, dose-finding studies. *J Clin Endocrinol Metab*. 2001;86(10):4717-4726. https://doi.org/10.1210/jcem.86.10.7937
15. Mehta J, Kling JM, Manson JE. Risks, benefits, and treatment modalities of menopausal hormone therapy: current concepts. *Front Endocrinol (Lausanne)*. 2021;12:564781. https://doi.org/10.3389/fendo.2021.564781
16. Kim L, Kim JA, Kim S. A guide for the utilization of health insurance review and assessment service national patient samples. *Epidemiol Health*. 2014;36:e2014008. https://doi.org/10.4178/epih/e2014008
17. Sohn M, Jung M. Effects of public and private health insurance on medical service utilization in the National Health Insurance System: national panel study in the Republic of Korea. *BMC Health Serv Res*. 2016;16(1):503. https://doi.org/10.1186/s12913-016-1746-2
18. Park SB, Shin HR, Lee SY. A population-based cohort study of HRT use and breast cancer in Korea. *Asia Pac J Public Health*. 2012;24(2):415-422. https://doi.org/10.1177/1010539510379392
19. Janisch W. The 10th revision of the International Classification of Diseases. *Zentralbl Allg Pathol*. 1990;136:723-727.
20. Gwak G, Yuk J-S, Kim T, Cho H. Replication data for: Breast cancer risk association with postmenopausal hormone therapy: Health Insurance Database in South Korea (HISK)-based cohort study. https://doi.org/10.7910/DVN/XLPC5J, Harvard Dataverse, V1.
21. Quan H, Li B, Couris CM, *et al*. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682. https://doi.org/10.1093/aje/kwq433
22. Gill T. Epidemiology and health impact of obesity: an Asia Pacific perspective. *Asia Pac J Clin Nutr*. 2006;15(Suppl):3-14.
23. Chlebowski RT, Anderson GL, Aragaki AK, *et al*. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized clinical trials. *JAMA*. 2020;324(4):369-380. https://doi.org/10.1001/jama.2020.9482
24. Chlebowski RT, Rohan TE, Manson JE, *et al*. Breast cancer after use of estrogen plus progestin and estrogen alone: analyses of data from 2 Women's Health Initiative randomized clinical trials. *JAMA Oncol*. 2015;1(3):296-305. https://doi.org/10.1001/jamaoncol.2015.0494
25. Saxena T, Lee E, Henderson KD, *et al*. Menopausal hormone therapy and subsequent risk of specific invasive breast cancer subtypes in the California Teachers Study. *Cancer Epidemiol Biomarkers Prev*. 2010;19(9):2366-2378. https://doi.org/10.1158/1055-9965.EPI-10-0162
26. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat*. 2008;107(1):103-111. https://doi.org/10.1007/s10549-007-9523-x
27. Fuhrmann U, Krattenmacher R, Slater EP, Fritzemeier KH. The novel progestin drospirenone and its natural counterpart progesterone: biochemical profile and antiandrogenic potential. *Contraception*. 1996;54(4):243-251. https://doi.org/10.1016/S0010-7824(96)00195-3
28. Kumar N, Koide SS, Tsong Y, Sundaram K. Nestorone: a progestin with a unique pharmacological profile. *Steroids*. 2000;65(10-11):629-636. https://doi.org/10.1016/S0039-128X(00)00119-7
29. Lippert C, Seeger H, Wallwiener D, Mueck AO. The effect of medroxyprogesterone acetate and norethisterone on the estradiol stimulated proliferation in MCF-7 cells: comparison of continuous combined versus sequential combined estradiol/progestin treatment. *Eur J Gynaecol Oncol*. 2001;22(5):331-335.
30. Kiran H, Tok A, Yuksel M, Arikan DC, Ekerbicer HC. Estradiol plus drospirenone therapy increases mammographic breast density in perimenopausal women. *Eur J Obstet Gynecol Reprod Biol*. 2011;159(2):384-387. https://doi.org/10.1016/j.ejogrb.2011.09.023
31. Hirschberg AL, Tani E, Brismar K, Lundstrom E. Effects of drospirenone and norethisterone acetate combined with estradiol on mammographic density and proliferation of breast epithelial cells-a prospective randomized trial. *Maturitas*. 2019;126:18-24. https://doi.org/10.1016/j.maturitas.2019.04.205
32. Bodewes FTH, van Asselt AA, Dorrius MD, Greuter MJW, de Bock GH. Mammographic breast density and the risk of breast cancer: a systematic review and meta-analysis. *Breast*. 2022;66:62-68. https://doi.org/10.1016/j.breast.2022.09.007
33. Greendale GA, Reboussin BA, Sie A, *et al*. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) investigators. *Ann Intern Med*. 1999;130(4 Pt 1):262-269. https://doi.org/10.7326/0003-4819-130-4_Part_1-199902160-00003
34. Warner E, Lockwood G, Tritchler D, Boyd NF. The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of the published literature to examine the effect of method of classification. *Cancer Detect Prev*. 1992;16(1):67-72.
35. Muhn P, Fuhrmann U, Fritzemeier KH, Krattenmacher R, Schillinger E. Drospirenone: a novel progestogen with antimineralocorticoid and antiandrogenic activity. *Ann N Y Acad Sci*. 1995;761(1):311-335. https://doi.org/10.1111/j.1749-6632.1995.tb31386.x
36. Sitruk-Ware R. Pharmacology of different progestogens: the special case of drospirenone. *Climacteric*. 2005;8(Suppl 3):4-12. https://doi.org/10.1080/13697130500330382
37. Fu X-D, Giretti MS, Goglia L, *et al*. Comparative actions of progesterone, medroxyprogesterone acetate, drospirenone and nestorone on breast cancer cell migration and invasion. *BMC Cancer*. 2008;8(1):166. https://doi.org/10.1186/1471-2407-8-166
38. Donovitz G, Cotten M. Breast cancer incidence reduction in women treated with subcutaneous testosterone: testosterone therapy and breast cancer incidence study. *Eur J Breast Health*. 2021;17(2):150-156. https://doi.org/10.4274/ejbh.galenos.2021.6213
39. Davis SR, Baber R, Panay N, *et al*. Global consensus position statement on the use of testosterone therapy for women. *J Clin Endocrinol Metab*. 2019;104(10):4660-4666. https://doi.org/10.1210/jc.2019-01603
40. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer*. 2005;114(3):448-454. https://doi.org/10.1002/ijc.20710
41. Chaumeil JC. Micronization: a method of improving the bioavailability of poorly soluble drugs. *Methods Find Exp Clin Pharmacol*. 1998;20(3):211-215. https://doi.org/10.1358/mf.1998.20.3.485666
42. Wilkinson HN, Hardman MJ. The role of estrogen in cutaneous ageing and repair. *Maturitas*. 2017;103:60-64. https://doi.org/10.1016/j.maturitas.2017.06.026
43. Silva LA, Ferraz Carbonel AA, de Moraes ARB, *et al*. Collagen concentration on the facial skin of postmenopausal women after topical treatment with estradiol and genistein: a randomized double-blind controlled trial. *Gynecol Endocrinol*. 2017;33(11):845-848. https://doi.org/10.1080/09513590.2017.1320708
44. Li CI, Anderson BO, Daling JR, Moe RE. Trends in incidence rates of invasive lobular and ductal breast carcinoma. *JAMA*. 2003;289(11):1421-1424. https://doi.org/10.1001/jama.289.11.1421
45. Li CI, Anderson BO, Porter P, Holt SK, Daling JR, Moe RE. Changing incidence rate of invasive lobular breast carcinoma among older women. *Cancer*. 2000;88(11):2561-2569. https://doi.org/10.1002/1097-0142(20000601)88:11<2561::AID-CNCR19>3.0.CO;2-X
46. Zhao H. The prognosis of invasive ductal carcinoma, lobular carcinoma and mixed ductal and lobular carcinoma according to molecular subtypes of the breast. *Breast Cancer*. 2021;28(1):187-195. https://doi.org/10.1007/s12282-020-01146-4

47. Neuhouser ML, Aragaki AK, Prentice RL, *et al.* Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the Women's Health Initiative randomized clinical trials. *JAMA Oncol*. 2015;1(5):611-621. https://doi.org/10.1001/jamaoncol.2015.1546
48. Pizot C, Boniol M, Mullie P, *et al.* Physical activity, hormone replacement therapy and breast cancer risk: a meta-analysis of prospective studies. *Eur J Cancer*. 2016;52:138-154. https://doi.org/10.1016/j.ejca.2015.10.063
49. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. *BMJ*. 2020;371:m3873. https://doi.org/10.1136/bmj.m3873
50. Park JW, Han K, Shin DW, *et al.* Obesity and breast cancer risk for pre- and postmenopausal women among over 6 million Korean women. *Breast Cancer Res Treat*. 2021;185(2):495-506. https://doi.org/10.1007/s10549-020-05952-4
51. Ecker BL, Lee JY, Sterner CJ, *et al.* Impact of obesity on breast cancer recurrence and minimal residual disease. *Breast Cancer Res*. 2019;21(1):41. https://doi.org/10.1186/s13058-018-1087-7
52. Ayoub NM, Yaghan RJ, Abdo NM, Matalka II, Akhu-Zaheya LM, Al-Mohtaseb AH. Impact of obesity on clinicopathologic characteristics and disease prognosis in pre- and postmenopausal breast cancer patients: a retrospective institutional study. *J Obes*. 2019;2019:3820759. https://doi.org/10.1155/2019/3820759
53. McNee RK, Mason BH, Neave LM, Kay RG. Influence of height, weight, and obesity on breast cancer incidence and recurrence in Auckland, New Zealand. *Breast Cancer Res Treat*. 1987;9(2):145-150. https://doi.org/10.1007/BF01807367