Supplementary table 1. Estimands to define the interventions.

Intervention	Definition
Treatment	Menopausal hormone therapy (MHT)
Population	Menopausal women (≥40 aged)
Variable/Endpoint	Time to onset of breast cancer
Population summary level	Hazard ratio (HR)

Supplementary Table 2. Menopausal hormones by group

MHT (generic name)	Brand name
Tibolone	
Tibolone 2.5mg	Livial, Rabilone, Libolone, Libron, Live on, Liviem, Tiborisi, Tibolan, Tibiol, Pharmbio Korea Tibolone, Hyundai Tibolone
CEPM	
Estradiol Hemihydrate 1.03mg, Drospirenone 2mg	Angelic
Estradiol Valerate 2mg, Medroxyprogesterone Acetate 10mg	Divina
Estradiol Valerate 1mg, Medroxyprogesterone Acetate 2.5mg	Indivina Tab 1mg/2.5mg
Estradiol Valerate 1mg, Medroxyprogesterone Acetate 5mg	Indivina Tab 1mg/5mg
Estradiol Valerate 2mg, Medroxyprogesterone Acetate 2.5mg	Indivina Tab 2mg/2.5mg
Estradiol Hemihydrate 2mg, Norethisterone Acetate 1mg	Cliane
Estradiol Hemihydrate 2.06mg, Dydrogesterone 10mg	Femoston 2/10
Estradiol Hemihydrate 1.03mg, Dydrogesterone 10mg	Femoston 1/10
Estradiol Hemihydrate 1.03mg, Dydrogesterone 5mg	Femoston Coti
Cyproterone Acetate 1mg, Estradiol Valerate 2mg	Climen
Estradiol Hemihydrate 1.03mg, Norethisterone Acetate 0.5mg	Esdiol-half
Estradiol Valerate 1.31mg, Norethisterone Acetate 0.5mg	Cliovelle
Estrogen	
Conjugated Estrogens 0.3mg	Premina 0.3mg
Conjugated Estrogens 0.625mg	Premina 0.625mg
Estradiol Valerate 1mg	Progynova 1mg
Estradiol Valerate 2mg	Progynova 2mg
Estradiol Hemihydrate 1mg	Preda 1mg
CEPP [a]	
Progesterone Micronized 100mg	Utrogestan 100mg
Medroxyprogesterone Acetate 5mg	Provera 5mg
Medroxyprogesterone Acetate 10mg	Provera 10mg
Dydrogesterone 10mg	Duphaston
Transdermal estrogen	
Estradiol Hemihydrate	Estreva Gel, Climara patch, Divigel Gel

MHT, menopausal hormone therapy; CEPM, Combined estrogen plus progestin by manufacturer; CEPP, Combined Estrogen plus progestogen by physician

[a] This group used the progestin below and the estrogen group above simultaneously.

Supplementary Table 3. Case/person-years of breast cancer according to non-MHT and each MHT group, the National Health Insurance Data in South Korea, 2002-2019.

	Non-MHT	Tibolone	CEPM	Oral Estrogen	CEPP	Transdermal estrogen
Total	11,992/10,807,542 (111)	2,569/2,132,480 (120)	2,432/1,320,035 (184)	788/622,523 (127)	91/76,711 (119)	36/23,917 (151)
Age at inclusion (years)						
40~49	1,603/963,159 (166)	417/372,358 (112)	540/302,525 (178)	205/163,022 (126)	22/13,356 (165)	11/5,289 (208)
50~59	6,265/5,000,831 (125)	1,733/1,373,281 (126)	1,627/864,691 (188)	468/339,263 (138)	52/44,647 (116)	19/14,315 (133)
60~69	3,304/3,442,432 (96)	389/344,327 (113)	254/140,968 (180)	106/99,758 (106)	14/16,385 (85)	5/3,907 (128)
70~	820/1,401,119 (59)	30/42,513 (71)	11/11,851 (93)	9/20,481 (44)	3/2,324 (129)	1/407 (245)
BMI (kg/m2)						
<18.5	160/194,004 (82)	45/34,834 (129)	47/25,033 (188)	6/8,941 (67)	/1,616 (0)	1/434 (230)
18.5-22.9	3,710/3,534,024 (105)	983/823,321 (119)	1,139/572,866 (199)	262/220,297 (119)	40/30,490 (131)	10/8,773 (114)
23-24.9	3,063/2,823,278 (108)	692/591,427 (117)	616/356,091 (173)	223/173,941 (128)	22/21,960 (100)	7/6,429 (109)
25-29.9	4,197/3,592,349 (117)	744/605,608 (123)	553/328,788 (168)	262/192,172 (136)	24/20,474 (117)	16/7,438 (215)
≥30	677/465,598 (145)	67/56,335 (119)	53/27,840 (190)	27/22,215 (122)	3/1,613 (186)	2/670 (299)
SES						
Mid~high	11,560/10,358,256 (112)	2,459/2,055,720 (120)	2,364/1,286,312 (184)	765/605,913 (126)	87/74,932 (116)	35/23,217 (151)
Low	432/449,285 (96)	110/76,760 (143)	68/33,723 (202)	23/16,610 (138)	4/1,778 (225)	1/700 (143)
Region						
Urban area	3,971/3,091,313 (128)	816/660,669 (124)	903/441,591 (204)	282/193,143 (146)	51/38,593 (132)	18/10,762 (167)
Rural area	8,021/7,716,229 (104)	1,753/1,471,811 (119)	1,529/878,443 (174)	506/429,380 (118)	40/38,118 (105)	18/13,155 (137)
CCI						
0	7,992/7,081,375 (113)	1,764/1,455,402 (121)	1,697/941,395 (180)	543/435,579 (125)	55/53,208 (103)	19/15,691 (121)
1	2,223/2,125,053 (105)	520/412,420 (126)	478/236,089 (202)	144/112,667 (128)	16/14,502 (110)	14/4,333 (323)
≥2	1,777/1,601,113 (111)	285/264,658 (108)	257/142,551 (180)	101/74,278 (136)	20/9,001 (222)	3/3,892 (77)
Parity (years)						
0 or not respond	2,788/2,222,208 (125)	459/380,826 (121)	372/200,558 (185)	167/142,050 (118)	19/16,873 (113)	6/5,481 (109)
1	916/555,896 (165)	248/169,559 (146)	313/125,518 (249)	76/43,710 (174)	13/5,047 (258)	3/1,702 (176)
2	6,839/6,449,056 (106)	1,612/1,366,603 (118)	1,568/886,347 (177)	476/368,966 (129)	54/46,278 (117)	26/14,239 (183)
≥3	1,449/1,580,382 (92)	250/215,493 (116)	179/107,612 (166)	69/67,797 (102)	5/8,513 (59)	1/2,495 (40)
Age at menarche (years)						
<13	2,749/1,984,249 (139)	413/326,080 (127)	402/197,780 (203)	151/116,324 (130)	14/14,938 (94)	7/4,499 (156)
≥13	9,187/8,752,651 (105)	2,139/1,786,874 (120)	2,017/1,113,082 (181)	622/497,662 (125)	76/60,971 (125)	28/19,107 (147)
Age at menopause (years)						
40-44	2,093/1,485,219 (141)	301/269,303 (112)	294/160,985 (183)	166/134,664 (123)	10/10,245 (98)	4/4,771 (84)

45-49	3,229/3,174,240 (102)	821/702,632 (117)	824/445,822 (185)	291/220,619 (132)	33/25,274 (131)	14/8,717 (161)
50-54	5,576/5,236,949 (106)	1,249/996,010 (125)	1,124/622,925 (180)	290/235,853 (123)	37/35,075 (105)	16/8,852 (181)
55-	1,094/911,134 (120)	198/164,536 (120)	190/90,304 (210)	41/31,387 (131)	11/6,117 (180)	2/1,577 (127)
Smoking						
Never	10,958/9,857,801 (111)	2,283/1,920,381 (119)	2,169/1,191,995 (182)	722/568,458 (127)	84/70,661 (119)	33/21,843 (151)
Past	134/98,666 (136)	60/33,715 (178)	59/22,214 (266)	11/7,887 (139)	1/968 (103)	1/389 (257)
Current	334/257,145 (130)	121/93,159 (130)	118/60,082 (196)	24/21,614 (111)	2/2,210 (91)	1/555 (180)
Alcohol consumption (days)						
None	9,684/8,779,650 (110)	1,903/1,609,712 (118)	1,729/980,049 (176)	596/484,859 (123)	70/61,847 (113)	28/19,040 (147)
~2/week	1,570/1,275,226 (123)	501/386,292 (130)	533/259,802 (205)	153/103,097 (148)	16/11,132 (144)	7/3,579 (196)
3~6/week	169/144,851 (117)	62/50,075 (124)	83/33,707 (246)	13/10,623 (122)	2/952 (210)	/377 (0)
Daily	53/59,818 (89)	20/16,900 (118)	24/9,521 (252)	3/4,472 (67)	/492 (0)	/78 (0)
Physical exercise (per week)						
None	6,961/6,659,464 (105)	1,419/1,217,184 (117)	1,363/762,047 (179)	431/358,866 (120)	54/42,155 (128)	25/11,769 (212)
1~2	2,096/1,702,858 (123)	498/393,868 (126)	475/250,361 (190)	150/115,775 (130)	14/14,623 (96)	2/5,150 (39)
3~4	1,291/937,604 (138)	281/233,854 (120)	306/148,548 (206)	105/65,124 (161)	14/9,562 (146)	4/3,475 (115)
5~6	383/305,678 (125)	110/76,191 (144)	100/48,630 (206)	22/20,147 (109)	/2,859 (0)	1/958 (104)
Daily	766/669,581 (114)	174/140,048 (124)	122/73,365 (166)	56/42,539 (132)	5/5,222 (96)	2/1,678 (119)
Period from menopause to inclusion (years)						
<5	5,388/3,913,643 (138)	1,490/1,196,867 (124)	1,630/868,405 (188)	425/319,725 (133)	49/37,874 (129)	22/12,109 (182)
5~9	2,774/2,352,262 (118)	618/504,317 (123)	473/276,291 (171)	223/153,840 (145)	24/18,874 (127)	5/6,322 (79)
10~	3,830/4,541,637 (84)	461/431,296 (107)	329/175,339 (188)	140/148,959 (94)	18/19,963 (90)	9/5,486 (164)

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

Data are expressed as the case/person-years (case/ 100,000 person-years).

Supplementary Table 4. Breast cancer incidence according to menopausal hormone therapy groups.

		Non-MHT (%)	Tibolone (%)	*p*-value	CEPM (%)	*p*-value	Oral estrogen (%)	*p*-value	CEPP (%)	*p*-value	Transdermal estrogen (%)	*p*-value
Breast cancer	Absent	908,791 (98.7)	162,653 (98.4)	<0.001	104,656 (97.7)	<0.001	44,821 (98.3)	<0.001	5,542 (98.4)	0.045	1,693 (97.9)	0.006
	Present	11,992 (1.3)	2,569 (1.6)		2,432 (2.3)		788 (1.7)		91 (1.6)		36 (2.1)	

MHT, menopausal hormone therapy; CEPM, combined estrogen plus progestin by the manufacturer; CEPP, combined estrogen plus progestogen by the physician

Supplementary table 5. Hazard ratios for risk of breast cancer according to major variables, the National Health Insurance Data in South Korea, 2002-2019.

Variables (reference = non-MHT)	Formula 1[a]		Formula 2[b]	
	HR (95% CI) [a]	P-value	HR (95% CI) [a]	P-value
MHT				
Tibolone	0.97 (0.929-1.014)	0.182	0.968 (0.925-1.012)	0.153
CEPM	1.451 (1.386-1.518)	<0.001	1.439 (1.374-1.507)	<0.001
Oral Estrogen	1.004 (0.932-1.081)	0.915	1.002 (0.929-1.081)	0.953
CEPP	0.933 (0.756-1.151)	0.518	0.929 (0.75-1.15)	0.5
Transdermal estrogen	1.164 (0.835-1.622)	0.37	1.139 (0.809-1.603)	0.456
Age at inclusion (years)				
50~59	0.898 (0.856-0.941)	<0.001	0.956 (0.906-1.008)	0.098
60~69	0.706 (0.667-0.746)	<0.001	0.846 (0.776-0.922)	<0.001
70~	0.422 (0.388-0.46)	<0.001	0.518 (0.462-0.581)	<0.001
BMI (kg/m^2)				
<18.5	0.872 (0.77-0.987)	)31	0.893 (0.787-1.012)	0.077
23-24.9	1.022 (0.983-1.062)	0.271	1.029 (0.989-1.07)	0.155
25-29.9	1.118 (1.078-1.159)	<0.001	1.126 (1.085-1.169)	<0.001
≥30	1.35 (1.254-1.452)	<0.001	1.356 (1.258-1.462)	<0.001
SES				
Low	0.993 (0.902-1.093)	0.886	0.999 (0.905-1.103)	0.98
Region				
Rural area	0.859 (0.832-0.886)	<0.001	0.861 (0.834-0.889)	<0.001
CCI				
1	1.02 (0.982-1.061)	0.304	1.023 (0.983-1.064)	0.26
≥2	1.009 (0.965-1.055)	0.686	1.007 (0.962-1.053)	0.771
Parity				
0	0.715 (0.668-0.766)	<0.001	0.721 (0.672-0.773)	<0.001
2	0.729 (0.691-0.77)	<0.001	0.736 (0.696-0.778)	<0.001
≥3	0.644 (0.601-0.69)	<0.001	0.645 (0.601-0.692)	<0.001
Age at menarche (years)				
≥13	0.862 (0.822-0.904)	<0.001	1.157 (1.102-1.214)	<0.001
Age at menopause (years)				
45-49	0.889 (0.845-0.934)	<0.001	0.853 (0.809-0.9)	<0.001
50-54	0.952 (0.903-1.003)	0.064	0.879 (0.827-0.934)	<0.001
55-	1.115 (1.038-1.197)	0.003	0.999 (0.918-1.087)	0.974

Smoking		
Past	1.254 (1.109-1.419)	<0.001
Current	1.076 (0.99-1.17)	0.086
Alcohol consumption (days)		
~2/week	1.013 (0.972-1.057)	0.535
3~6/week	1.008 (0.902-1.127)	0.888
Daily	0.885 (0.727-1.079)	0.227
Physical exercise (per week)		
1~2	1.079 (1.036-1.123)	<0.001
3~4	1.172 (1.116-1.231)	<0.001
5~6	1.124 (1.035-1.221)	0.006
Daily	1.085 (1.02-1.155)	0.01
Period from menopause to inclusion (years)		
5~9	0.918 (0.879-0.959)	<0.001
10~	0.846 (0.791-0.904)	<0.001

BMI, Body mass index; CCI, Charlson comorbidity index; CEPM, Combined estrogen plus progestin by manufacturer; CEPP, Combined Estrogen plus progestogen by physician; CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy; SES, socioeconomic status

[a] HRs were adjusted for age group, body mass index, socioeconomic status, region, Charlson comorbidity index, parity, age at menarche, 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, period from menopause to inclusion.

Supplementary Table 6. Hazard ratios of mortality in breast cancer patients, the National Health Insurance Data in South Korea, 2002-2019.

MHT group (reference = non-MHT group)	Formula 1 [a] HR (95% CI)	P-value
Breast cancer		
Tibolone	0.504 (0.432-0.588)	<0.001
CEPM	0.429 (0.352-0.522)	<0.001
Oral estrogen	0.453 (0.349-0.588)	<0.001
CEPP	0.474 (0.224-1.005)	0.052
Transdermal estrogen	0.965 (0.399-2.337)	0.938

CI, confidence interval; HR, hazard ratio; CEPM, Combined estrogen plus progestin by manufacturer; CEPP, Combined Estrogen plus progestogen by physician;

[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, period from menopause to inclusion.

Supplementary table 7. Hazard ratios for risk of breast cancer according to physician specialty, the National Health Insurance Data in South Korea, 2002-2019 (Sensitivity test).

MHT	HR (95% CI) [a]	P-value
Tibolone		
Gynecologist		
Tibolone	0.93 (0.864-1.001)	0.052
CEPM	1.407 (1.318-1.501)	<0.001
Estrogen	0.95 (0.844-1.069)	0.391
CEPP	1.073 (0.719-1.602)	0.73
Transdermal estrogen	0.709 (0.295-1.704)	0.442
Non-Gynecologist		
Tibolone	0.988 (0.937-1.041)	0.643
CEPM	1.457 (1.373-1.546)	<0.001
Estrogen	1.03 (0.936-1.133)	0.544
CEPP	0.882 (0.686-1.135)	0.331
Transdermal estrogen	1.271 (0.877-1.842)	0.205

CI, confidence interval; HR, hazard ratio; CEPM, Combined estrogen plus progestin by manufacturer; CEPP, Combined Estrogen plus progestogen by physician

[a] HRs were adjusted for body mass index, socioeconomic status, region, Charlson comorbidity index, parity, age at menarche, age at menopause, smoking, alcohol consumption, physical exercise, period from menopause to inclusion.