

Skin cancer risk from postmenopausal hormone therapy: Health Insurance Database in South Korea (HISK)-based retrospective cohort study

Jin-Sung Yuk¹, Soo-Kyung Lee², Ji An Uh², Yong-Soo Seo¹, Myounghwan Kim¹,
Myoung Shin Kim^{2*}

¹Department of Obstetrics and Gynaecology, Sanggye Paik Hospital, School of Medicine, Inje University, Seoul, Republic of Korea

²Department of Dermatology, Sanggye Paik Hospital, School of Medicine, Inje University, Seoul, Republic of Korea

Background

- **There are conflicting studies on the association between menopausal hormone therapy (MHT) and skin cancers, such as melanoma and non-melanoma skin cancer (NMSC).**
- Estrogens and progestins have been reported to induce photosensitivity and are hypothesised to play a role in skin cancer
- Menopausal hormone therapy (MHT) is known to increase the risk of certain cancers, such as breast cancer

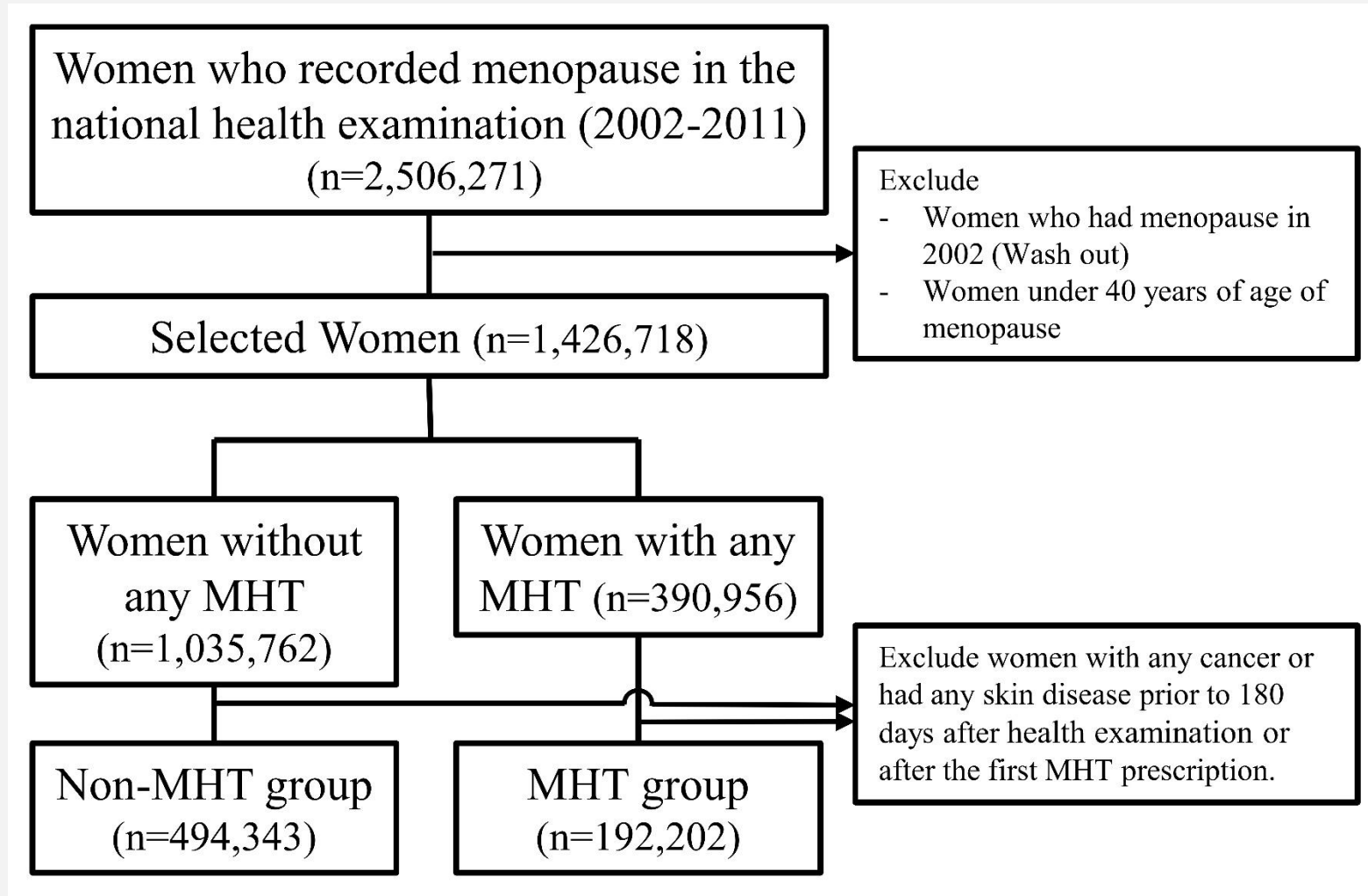
Objective

- This study aimed to evaluate the **risk of skin cancer** from Menopausal hormone therapy (MHT)

Methods_Study subjects

- Data from the National Health Insurance Service in South Korea was used.
 - Patients in the exposure group had at least one MHT for at least 6 months.
 - Patients in the non-exposure group had never been prescribed MHT agents.

Methods_Study subjects



Methods_Variables

- MHT agents investigated in this study
 - Tibolone
 - Combined estrogen and progestin by the manufacturer (CEPM)
 - Estrogen
 - Topical estrogen
 - Combined estrogen and progestin by the physician (CEPP)
- Collected data
 - Age, body mass index (BMI), socioeconomic status (SES), region, Charlson Comorbidity Index (CCI), parity, age at menarche, age at menopause, smoking, alcohol consumption, physical exercise, and the period from menopause to inclusion

Results _ Characteristics of study population

	Non-MHT	Tibolone	CEPM	Oral Estrogen	CEPP	Topical estrogen	Total
Number of women	494,343	97,074	60,776	29,478	3,686	1,188	686,545
Median age (years)	58 [52-64]	54 [50-58]	52 [50-56]	52 [49-57]	54 [51-59]	53 [50-57]	56 [52-62]
Age at inclusion (years)							
40-49	48,869 (9.9)	17,283 (17.8)	14,132 (23.3)	7,882 (26.7)	665 (18)	265 (22.3)	89,096 (13)
50-59	236,883 (47.9)	62,392 (64.3)	39,636 (65.2)	16,151 (54.8)	2,156 (58.5)	715 (60.2)	357,933 (52.1)
60-69	150,340 (34.5)	15,583 (16.4)	6,457 (10.7)	4,524 (15.8)	756 (21.1)	186 (16)	177,846 (28.5)
≥70	58,251 (11.8)	1,816 (1.9)	551 (0.9)	921 (3.1)	109 (3)	22 (1.9)	61,670 (9)
Median BMI (kg/m ²)	23.9 [22.1-26]	23.5 [21.8-25.4]	23.2 [21.5-25.1]	23.8 [22-25.8]	23.4 [21.6-25.2]	23.8 [22.1-25.7]	23.8 [21.9-25.8]
BMI (kg/m ²)							
<18.5	9,560 (2)	1,726 (1.8)	1,229 (2)	451 (1.5)	74 (2)	22 (1.9)	13,062 (1.9)
18.5-22.9	167,506 (34.7)	38,181 (39.8)	26,883 (44.6)	10,628 (36.4)	1,528 (41.9)	436 (37)	245,162 (36.4)
23-24.9	127,678 (26.4)	26,754 (27.9)	16,224 (26.9)	8,148 (27.9)	1,011 (27.7)	315 (26.8)	180,130 (26.7)
25-29.9	158,267 (32.7)	26,853 (28)	14,731 (24.4)	8,939 (30.6)	953 (26.1)	372 (31.6)	210,115 (31.2)
≥30	20,303 (4.2)	2,435 (2.5)	1,204 (2)	1,017 (3.5)	83 (2.3)	32 (2.7)	25,074 (3.7)
SES							
Mid-high SES	472,042 (95.5)	93,364 (96.2)	59,144 (97.3)	28,599 (97)	3,600 (97.7)	1,152 (97)	657,901 (95.8)
Low SES	22,301 (4.5)	3,710 (3.8)	1,632 (2.7)	879 (3)	86 (2.3)	36 (3)	28,644 (4.2)
Region							
Urban area	153,296 (31)	31,814 (32.8)	21,960 (36.1)	9,751 (33.1)	1,937 (52.6)	562 (47.3)	219,320 (31.9)
Rural area	341,047 (69)	65,260 (67.2)	38,816 (63.9)	19,727 (66.9)	1,749 (47.4)	626 (52.7)	467,225 (68.1)
CCI							
0	331,584 (67.1)	68,555 (70.6)	44,727 (73.6)	21,214 (72)	2,619 (71.1)	807 (67.9)	469,506 (68.4)
1	88,339 (17.9)	17,511 (18)	10,040 (16.5)	4,925 (16.7)	632 (17.1)	184 (15.5)	121,631 (17.7)
≥2	74,420 (15.1)	11,008 (11.3)	6,009 (9.9)	3,339 (11.3)	435 (11.8)	197 (16.6)	95,408 (13.9)
Smoking							
Never	450,318 (96.6)	87,386 (94)	54,842 (93.7)	26,805 (94.9)	3,395 (95.8)	1,090 (96.2)	623,836 (95.9)
Past	4,497 (1)	1,494 (1.6)	1,036 (1.8)	379 (1.3)	46 (1.3)	13 (1.1)	7,465 (1.1)
Current	11,531 (2.5)	4,092 (4.4)	2,664 (4.6)	1,056 (3.7)	104 (2.9)	30 (2.6)	19,477 (3)
Alcohol (per week)							
None	401,256 (85.6)	73,285 (78.2)	45,263 (76.8)	22,953 (80.6)	2,984 (83.6)	943 (82.1)	546,684 (83.5)
≤2/week	58,354 (12.5)	17,536 (18.7)	11,787 (20)	4,847 (17)	514 (14.4)	187 (16.3)	93,225 (14.2)
3-6/week	6,429 (1.4)	2,143 (2.3)	1,507 (2.6)	485 (1.7)	53 (1.5)	15 (1.3)	10,632 (1.6)
Daily	2,593 (0.6)	730 (0.8)	395 (0.7)	208 (0.7)	17 (0.5)	3 (0.3)	3,946 (0.6)
Physical exercise (per week)							
None	301,412 (64.2)	54,951 (58.7)	34,883 (59.2)	16,854 (59.2)	2,031 (56.9)	601 (52.7)	410,732 (62.7)
1-2	80,022 (17.1)	18,166 (19.4)	11,710 (19.9)	5,509 (19.4)	715 (20)	246 (21.6)	116,368 (17.8)
3-4	43,862 (9.3)	10,766 (11.5)	6,851 (11.6)	3,127 (11)	442 (12.4)	166 (14.5)	65,214 (10)
5-6	14,004 (3)	3,514 (3.8)	2,208 (3.7)	970 (3.4)	143 (4)	49 (4.3)	20,888 (3.2)
Daily	29,993 (6.4)	6,243 (6.7)	3,308 (5.6)	2,008 (7.1)	239 (6.7)	79 (6.9)	41,870 (6.4)

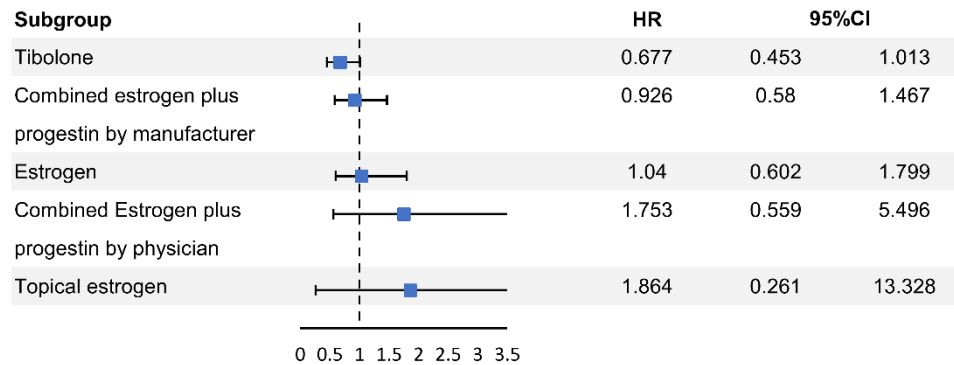
Results _ Risk of Melanoma and NMSC

Melanoma developed in 249 (0.05%) patients in the non-MHT group and in 70 (0.03%) patients in the MHT group. The incidence of NMSC was 1,680 cases (0.34%) in the non-MHT group and 417 cases (0.22%) in the MHT group.

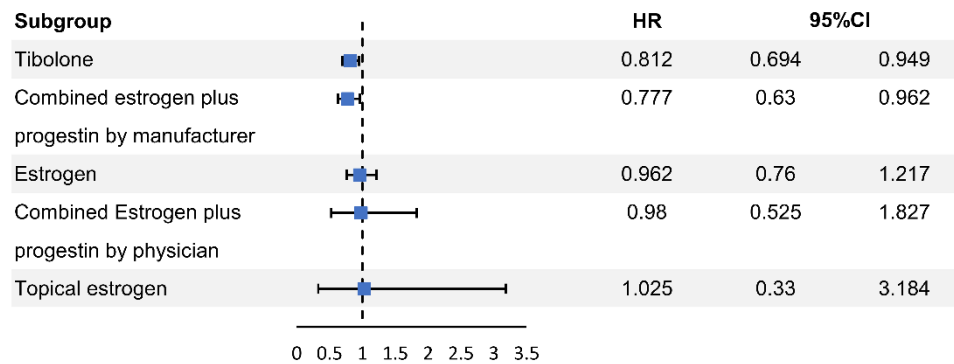
	Non-MHT	Tibolone	Combined Estrogen plus progestin by manufacturer	Oral estrogen	Combined Estrogen plus progestin by physician	Topical estrogen	Total
Median period from menopause to inclusion (yrs)	7 [2-14]	4 [1-8.5]	2.5 [0-6.5]	4.5 [1-9]	4.5 [1-9.5]	4.5 [1-9]	6 [2-12.5]
Melanoma							
Not present	494,094 (99.95)	97,043 (99.97)	60,755 (99.97)	29,464 (99.95)	3,683 (99.92)	1,187 (99.92)	686,226 (99.95)
Present	249 (0.05)	31 (0.03)	21 (0.03)	14 (0.05)	3 (0.08)	1 (0.08)	319 (0.05)
Non-melanoma skin cancer							
Not present	492,663 (99.66)	96,863 (99.78)	60,667 (99.82)	29,394 (99.72)	3,676 (99.73)	1,185 (99.75)	684,448 (99.69)
Present	1,680 (0.34)	211 (0.22)	109 (0.18)	84 (0.28)	10 (0.27)	3 (0.25)	2,097 (0.31)
Total skin cancer							
Not present	492,452 (99.62)	96,835 (99.75)	60,652 (99.8)	29,383 (99.68)	3,673 (99.65)	1,184 (99.66)	684,179 (99.66)
Present	1,891 (0.38)	239 (0.25)	124 (0.2)	95 (0.32)	13 (0.35)	4 (0.34)	2,366 (0.34)

Results _ Risk of Melanoma and NMSC

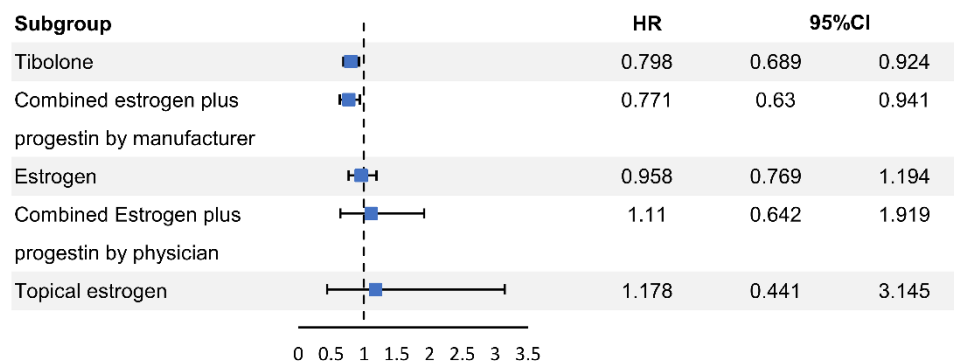
A. Melanoma



B. Non-melanoma



C. Total skin cancer



MHT did not affect the incidence of melanoma in the Cox proportional regression analysis after adjusting for multiple variables.

Tibolone (HR 0.798, 95% CI 0.689-0.924) and **CEPM** (HR 0.771, 95% CI 0.63-0.941) lowered the risk of total skin cancer, while other hormone groups did not change the risk.

Results _ Risk of Melanoma and NMSC

In a subgroup analysis of tibolone only, the risk of total skin cancer did not change at 1.25 mg (half dose) of tibolone (HR 1.499, 95% CI 0.561-4.001)

Tibolone use	HR (95% CI) ^a	P-value
Tibolone only (without non-MHT)		
Period from menopause to inclusion (years)		
5-9	0.87 (0.558-1.358)	0.54
≥10	0.604 (0.284-1.285)	0.19
Total period of use (months)	1 (0.997-1.003)	0.91
Dosage		
1.25 mg	1.761 (0.653-4.748)	0.26
Over 5 mg	0 (0-.)	>0.99
Prescribed specialty		
Non-gynecology	1.314 (0.967-1.785)	0.08
Dosage of tibolone		
Tibolone 1.25 mg vs Non-MHT	1.499 (0.561-4.001)	0.42
Tibolone 2.5 mg vs Non-MHT	0.812 (0.7-0.942)	0.006
Tibolone 5 mg vs Non-MHT	0.001 (0-4.78E+60)	0.93

Results _ Risk of Melanoma and NMSC

- In the Cox proportional regression analysis, older age and obesity increased the risk of melanoma.
- Older age (≥ 70 years: HR 5.202, 95% CI 3.767-7.183), rural areas (HR 1.272, 95% CI 1.144-1.415), age at menopause (≥ 55 years: HR 1.346, 95% CI 1.062-1.707), and long period from menopause to inclusion (≥ 10 years: HR 1.655, 95% CI 1.353-2.025) increased the risk of NMSC.
- Obesity (BMI ≥ 30 : HR 0.766, 95% CI 0.597-0.984), past smoking (HR 0.467, 95% CI 0.233-0.936), alcohol consumption (≤ 2 /week) (HR 0.831, 95% CI 0.706-0.979), and physical exercise (1-2/week) (HR 0.805, 95% CI 0.702–0.922) lowered the risk of NMSC.

Conclusion_Strength of study

- A **large sample size** gives this study statistical power compared to other observational studies,
- It's based on nationwide registry data, it was possible to **increase the accuracy of cancer incidence and minimize selection bias.**
- To the best of our knowledge, there have been no previous studies on NMSC and tibolone. **Considering that tibolone is the most commonly prescribed MTH drug in South Korea,** our results have an implication in real practice

Conclusion_Limitation

- Data did not contain well-known risk factors for skin cancer, such as ultraviolet exposure, family history, and immune status.
 - we presume that ultraviolet exposure was not remarkably different between the MHT groups because the Korean population showed relatively homogeneous ethnicity and low sunburn potential based on their Fitzpatrick skin phototypes.
- The subtypes of NMSC, such as BCC and SCC, could not be obtained.
- We could not obtain a detailed drug list constituting the CEPM group due to the NHIS policy.

Conclusion

MHT is not associated with melanoma in postmenopausal women and that tibolone and CEPM may contribute to lowering the incidence of NMSC in the Korean population

References

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