JMM Journal of Menopausal Medicine
pISSN: 2288-6478, eISSN: 2288-6761
https://doi.org/10.6118/jmm.24014
J Menopausal Med 2024;30:78-87
ORIGINAL ARTICLE

Menopausal Hormone Therapy and Osteoarthritis Risk: Retrospective Population-Based Study in South Korea

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Objectives: This study aimed to investigate the risk of osteoarthritis associated with menopausal hormone therapy (MHT).

Methods: This population-based retrospective cohort study used a database of Korean health insurance claims (2007–2020). Females aged ≥ 40 who initiated menopause-related healthcare visits between 2011 and 2014 were identified. The MHT group comprised females aged ≥ 40 who initiated MHT for ≥ 6 months during this period. The non-MHT group comprised females aged ≥ 40 who attended menopause-related healthcare visits but did not receive MHT. To account for potential confounding factors, the two groups were matched at a 1:1 ratio using propensity score matching.

Results: A cohort of 453,040 postmenopausal females aged ≥ 40 years was identified, with 26,354 assigned to either the MHT or non-MHT group after propensity matching. The median age was 49 years, and the median follow-up was 8.2 years. The Cox proportional hazards model demonstrated an elevated risk of osteoarthritis with MHT (hazard ratio [HR], 1.154; 95% confidence interval [CI], 1.117–1.193) for knee (HR, 1.148; 95% CI, 1.102–1.195) and other arthritis (HR, 1.205; 95% CI, 1.151–1.261), although not statistically significant for hip arthritis. Tibolone (HR, 1.211; 95% CI, 1.161–1.263), estrogen–progestogen therapy (EPT) (HR, 1.092; 95% CI, 1.048–1.137), and estrogen therapy (ET) (HR, 1.235; 95% CI, 1.148–1.329) were associated with a higher risk of osteoarthritis compared to non-MHT users.

Conclusions: MHT was associated with an increased risk of osteoarthritis, consistently observed across tibolone, EPT, and ET, particularly affecting joints other than the hip, with a trend toward an elevated risk of hip osteoarthritis.

Key Words: Estrogens, Hormone replacement therapy, Osteoarthritis, Progesterone, Tibolone

INTRODUCTION

Menopausal hormone therapy (MHT) offers a multifaceted approach to managing postmenopausal health. It is well-established in alleviating common symptoms like night sweats, hot flashes, and vaginal dryness [1]. Furthermore, MHT demonstrably reduces bone loss and fracture risk in postmenopausal females [1].

Osteoarthritis is a prevalent joint disease characterized by inflammation and structural changes in the joints, leading to symptoms such as pain, stiffness, and loss of function [2]. It is estimated to affect 18% of females over the age of 60 globally [3]. A recent study, utilizing data from the Korean National Health and Nutrition Examination Survey, discovered that the prevalence of radiographic osteoarthritis was as high as 44.3% in females aged 50 years and older [4].

The development of osteoarthritis can be categorized into systemic and mechanical factors. Systemic risk factors encompass age, ethnic differences, body mass index (BMI), smoking, balanced diet, and high bone mineral density, all of which are associated with the risk and severity of developing osteoarthritis. Mechanical factors include structural abnormalities, alignment of cartilage, trauma, physical activity, and occupation [2].

Numerous studies have explored the relationship be-

Received: April 25, 2024 **Revised:** June 26, 2024 **Accepted:** July 16, 2024
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tween estrogen and osteoarthritis. In a monkey model, estrogen treatment has been shown to reduce osteoarthritis [5]. Similarly, a large cross-sectional study involving over 4,000 females suggests that estrogen use is associated with a lower prevalence of hip osteoarthritis and may offer protection against its severity [6,7]. However, in a prospective analysis of the Framingham cohort, estrogen tended to reduce knee osteoarthritis, but the difference was not statistically significant [8].

Unlike previous studies, the Women's Health Initiative (WHI) study used joint replacement surgery (arthroplasty) as a marker for symptomatic osteoarthritis. They found a weak association between conjugated equine estrogen (CEE) monotherapy and total arthroplasty, but no significant reduction in hip or knee arthroplasty specifically. Further supporting this, the CEE/medroxyprogesterone acetate (MPA) trial, which included both estrogen and progestin, also found no link between hormone use and arthroplasty risk [9]. These inconsistent results led the North American Menopause Society (NAMS) to conclude that there is no clear observed association between MHT and osteoarthritis [10]. However, most of the hormonal agents used in these studies were specific to CEE. Various menopausal hormones such as tibolone and estradiol hemihydrate/drospirenone are prescribed in Korea rather than CEE [11]. Therefore, a large-scale study on the osteoarthritis risk of various menopausal hormones currently used is needed.

In this retrospective cohort study, we aimed to investigate the risk of osteoarthritis with MHT using Korean health insurance data.

MATERIALS AND METHODS

Data source

The South Korean government has established the National Health Insurance Service (NHIS) as a compulsory national health insurance program, operating under the framework of a single-payer healthcare system [12]. Ensuring the appropriateness of medical expenses billed to NHIS, by healthcare providers in South Korea, falls within the purview of the Health Insurance Review and Assessment Agency (HIRA), a national institution. HIRA diligently curates an extensive database encompassing comprehensive national health insurance utilization data in South Korea [12]. This database serves as a valuable repository containing extensive information related to the entire population of South Korea. It comprises essential patient demographic details, including age, sex, and residential area, as well as precise diagnosis codes, surgical codes, prescription medications, and insurance types. This population-based retrospective cohort study used a database of Korean health insurance claims from 2007 to 2020 provided by the HIRA.

Study population

The patient selection and outcome verification were based on the Tenth Revision of the International Classification of Diseases (ICD-10) and the Korea Health Insurance Medical Care Exposures (2012, 2020 edition).

In our investigation, we initially identified females aged 40 years and older who initiated healthcare visits for menopause-related concerns (N95.1: Menopause and female menopausal status) during the period spanning from January 1, 2011 to December 31, 2014. The criteria for inclusion in the MHT group necessitated that participants were females aged 40 years or above who initiated MHT as a new treatment regimen during the period spanning January 1, 2011 to December 31, 2014. To enhance the specificity of our analysis, we excluded individuals who had employed MHT for less than 6 months. Conversely, for the non-MHT group, we included females who sought medical care for menopause-related issues during this period and excluded those who were prescribed MHT at any time during the whole cohort period.

Subsequently, the study cohort was further refined by excluding individuals with a history of cancer or joint-related conditions (such as joint pain, osteoarthritis, rheumatoid arthritis, gout, or joint deformities) before the study start or within 365 days after the study start, those who received more than one MHT, and those who started MHT before 2011. We then performed 1:1 propensity score matching for the following factors. A flowchart of the patient selection process is shown in Figure 1.

Outcome

Arthritis classification was based on both the number of medical visits and specific diagnosis codes. Hip arthritis was defined as three or more medical visits with diagnosis codes of M16, while knee arthritis was similarly defined with diagnosis codes of M17. For other forms of arthritis, characterized by diagnoses M15, M18, or M19, excluding hip and knee, three or more medical visits were required. Total arthritis, as a composite measure, encompassed individuals with at

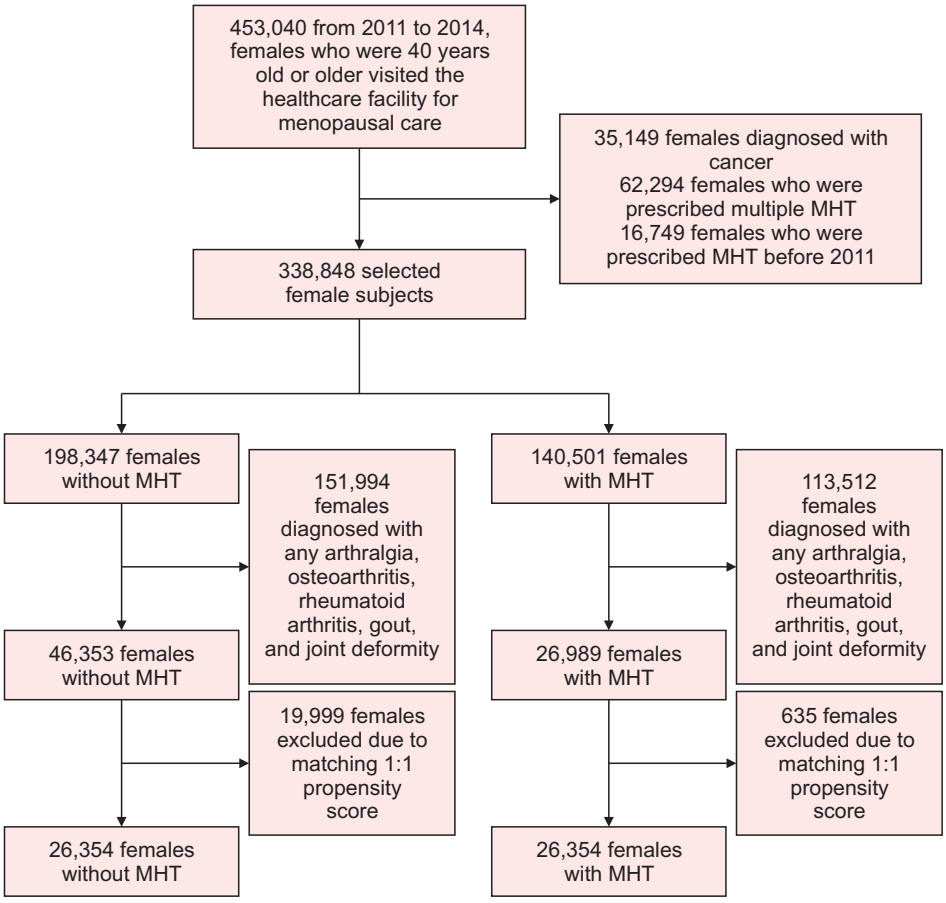


Fig. 1. Schematic representation of the process for categorizing subjects into MHT and Non-MHT groups. MHT: menopausal hormone therapy.

least one arthritis diagnosis identified by the criteria described above.

Exposure

In this study, MHT included tibolone, estrogen–progestogen therapy (EPT), estrogen therapy (ET), and transdermal estrogen. A detailed breakdown of the agents comprising MHT is provided in Supplementary Table 1 (available online).

Variablese

The Charlson comorbidity index (CCI) was calculated utilizing ICD-10 diagnostic codes documented in the medical records during the one year preceding the index date until the study enrollment date [13]. Furthermore, we retrieved data on prior hysterectomy and adnexal surgical procedures by examining the relevant operative codes in the database. We defined the prevalence of endometriosis, uterine fibroids, diabetes mellitus (DM), dyslipidemia, and hypertension as present if the corresponding ICD-10 code was recorded three or more times. Socioeconomic status (SES) was classified as low (medical assistance) or moderate to high (no medical assistance).

Statistics

In this investigation, we conducted a comprehensive statistical analysis employing R version 3.5.1 developed by the R Foundation for Statistical Computing. Significance was established at a level of $P < 0.05$ (two-sided) to denote statistical significance. Categorical variables were represented as numerical counts (percentages), while continuous variables were described by their median values (interquartile range).

To adjust for potential confounding variables, propensity score matching was utilized. This method accounted for several covariates, encompassing age categorized within 10-year intervals, CCI, SES, geographical region of residence, presence of DM, dyslipidemia, hypertension, history of hysterectomy, adnexal surgery, uterine fibroids, and endometriosis. Matching was performed using the nearest neighbor technique with a caliper

size set at 1. Before executing propensity score matching, categorical data were subjected to chi-square testing, and continuous variables were evaluated utilizing parametric *t* tests or non-parametric Mann–Whitney *U* tests, as appropriate. Following the completion of propensity score matching, the analysis of categorical variables was conducted using the Cochran–Mantel–aenszel test. Concurrently, continuous variables underwent scrutiny through the application of either parametric paired *t* tests or non-parametric Wilcoxon signed-rank tests, by their distributional characteristics. To determine the incidence rate of osteoarthritis, the number of osteoarthritis cases was divided by 100,000 person-years.

We applied extended Cox proportional hazards regression models, incorporating time-dependent covariates, to explore the association between the use of MHT and the risk of osteoarthritis. The study's temporal framework was initiated from the date when the first menopause diagnosis code (N95.1) was confirmed. To address the potential for immortal time bias, we quantified the duration between the initial menopausal diagnosis and the initiation of MHT among females in the MHT-exposed group. This time interval was then applied to the non-MHT group by imputing an equivalent period from the date of their menopausal diagnosis. The event of interest was defined as the first documented diagnosis of osteoarthritis, while the censoring date was determined as either the date of death or the most recent healthcare encounter recorded in the insurance claims database, whichever occurred later. Observations on the study participants were tracked through the end of 2020.

Ethics

This investigation received approval from the Institutional Review Board of Sanggye Paik Hospital under the reference number SGPAIK-2023-06-003. Informed consent was deemed unnecessary for this research endeavor due to the absence of personally identifiable information within the datasets employed. The data analysis for this research was performed only on the HIRA server, following the HIRA's information protection policy. The raw data, except for the actual numerical results, were not exportable. The HIRA supplied the research data but had no involvement in the conduct of this research.

RESULTS

Between 2011 and 2014, a comprehensive study was conducted, identifying a cohort of 453,040 postmenopausal females, all aged 40 years or older. The selection process, as depicted in Figure 1, culminated in the assignment of 26,354 subjects to either the MHT or non-MHT groups. The overall age of the subjects assigned to either the MHT or non-MHT groups averaged 49 years (interquartile range: 47–52 years), with a median follow-up period lasting 8.2 years (interquartile range: 6.5–9.5 years).

Following propensity score matching, meticulous analysis revealed that none of the included variables exhibited a standardized mean difference exceeding 0.2. Supplementary Table 2 (available online) provides a detailed overview of the subjects' characteristics before propensity score matching, while Table 1 presents an array of characteristics for the entire study population.

Within the MHT group, among individuals who reported a period of menopausal hormone use, the median duration amounted to 23 months (interquartile range: 11–53 months). Notably, 63.4% of the individuals within the MHT group who reported a period of use, totaling 16,720 subjects, reported a duration of less than 3 years, as outlined in Table 2.

In the context of Cox proportional hazards analysis with time-dependent covariates, our investigation revealed an elevated risk of osteoarthritis associated with MHT usage, as indicated by a hazard ratio (HR) of 1.154 (95% confidence interval [CI], 1.117–1.193), a finding summarized in Table 3. Supplementary Figure 1 (available online) further illustrates the association between MHT usage and the risk of osteoarthritis. The elevated risk associated with MHT usage was observed in both knee arthritis (HR, 1.148; 95% CI, 1.102–1.195) and other arthritis (HR, 1.205; 95% CI, 1.151–1.261) (Table 3 and Fig. 1). Hip arthritis (HR, 1.254; 95% CI, 0.994–1.582) also tended to be associated with an increased risk of osteoarthritis, although this was not statistically significant.

In subgroup analyses by MHT, tibolone (HR, 1.211; 95% CI, 1.161–1.263), EPT (HR, 1.092; 95% CI, 1.048–1.137), and ET (HR, 1.235; 95% CI, 1.148–1.329) were all associated with an increased risk of osteoarthritis (Table 3 and Fig. 2). Supplementary Table 3 (available online) provides a comprehensive depiction of the osteoarthritis risk associated with each specific menopausal hormone, offering valuable insights into the as-

Table 1. Characteristics of subjects in the MHT and non-MHT groups after propensity score matching

	Non-MHT	MHT	Total	*P* value	Standardized mean difference	Missing (%)
Number of subjects	26,354	26,354	52,708			
Median age (y)	49 (47–52)	49 (47–52)	49 (47–52)	0.011	0.043	
Follow-up period (y)	8.1 (6.5–9.4)	8.2 (6.6–9.5)	8.2 (6.5–9.5)	< 0.001	0.041	
Calendar year at inclusion				0.045	0.002	0
2011	7,260 (27.5)	7,240 (27.5)	14,500 (27.5)			
2012	7,307 (27.7)	7,311 (27.7)	14,618 (27.7)			
2013	6,264 (23.8)	6,275 (23.8)	12,539 (23.8)			
2014	5,523 (21.0)	5,528 (21.0)	11,051 (21.0)			
Age at inclusion (y)				0.999	0.001	0
40–49	13,426 (50.9)	13,421 (50.9)	26,847 (50.9)			
50–59	12,369 (46.9)	12,378 (47.0)	24,747 (47.0)			
60–69	548 (2.1)	544 (2.1)	1,092 (2.1)			
70~	11 (0)	11 (0)	22 (0)			
SES				0.881	0.002	0
Mid–high SES	25,989 (98.6)	25,994 (98.6)	51,983 (98.6)			
Low SES	365 (1.4)	360 (1.4)	725 (1.4)			
Region				0.692	0.003	0
Urban area	13,017 (49.4)	13,063 (49.6)	26,080 (49.5)			
Rural area	13,337 (50.6)	13,291 (50.4)	26,628 (50.5)			
CCI				0.015	0.025	0
0	21,348 (81.0)	21,141 (80.2)	42,489 (80.6)			
1	3,013 (11.4)	3,227 (12.2)	6,240 (11.8)			
≥ 2	1,993 (7.6)	1,986 (7.5)	3,979 (7.5)			
Hypertension	3,931 (14.9)	3,964 (15.0)	7,895 (15.0)	< 0.001	0.004	0
DM	1,670 (6.3)	1,649 (6.3)	3,319 (6.3)	0.001	0.003	0
Dyslipidemia	4,737 (18.0)	4,821 (18.3)	9,558 (18.1)	0.326	0.008	0
Uterine fibroids	4,415 (16.8)	4,237 (16.1)	8,652 (16.4)	0.016	0.018	0
Endometriosis	1,297 (4.9)	1,314 (5.0)	2,611 (5.0)	0.726	0.003	0
Previous hysterectomy	1,522 (5.8)	1,533 (5.8)	3,055 (5.8)	0.136	0.002	0
Previous adnexal surgery	749 (2.8)	730 (2.8)	1,479 (2.8)	0.013	0.004	0

The continuous variables are expressed as the median value and the range between the 25th and 75th percentiles. The number and percentage of subjects in each category are shown for the categorical variables.
CCI: Charlson comorbidity index, DM: diabetes mellitus, MHT: menopausal hormone therapy, SES: socioeconomic status.

sociation between each specific menopausal hormone and osteoarthritis risk, a critical aspect of our investigation. The osteoarthritis risk associated with each estrogen and progestogen agent is detailed in Figure 2. In a subanalysis of the duration of MHT use, MHT use was associated with an increased risk of osteoarthritis, regardless of duration (Table 4).

Supplementary Table 4 (available online) furnishes a comprehensive breakdown of osteoarthritis risk occurrence based on specific variables, thereby enhancing our understanding of the multifactorial nature of osteoarthritis risk within our study. In females in their 40s (HR, 1.164; 95% CI, 1.108–1.222) and 50s (HR, 1.137; 95% CI, 1.087–1.189), MHT was associated with a higher risk of osteoarthritis, but MHT was not associated with a higher risk of osteoarthritis in those aged 60

Table 2. Demographic characteristics of females undergoing menopausal hormone therapy

	Median duration (mo)	Duration (y)			Total
		< 3	3–5.9	Over 6	
Total	23 (11.0–53.0)	16,720 (63.4)	5,383 (20.4)	4,251 (16.1)	26,354 (100)
Category 1					
Tibolone	26 (12.0–60.0)	6,536 (59.5)	2,330 (21.2)	2,114 (19.3)	10,980 (100)
E + P	21 (10.0–47.8)	8,462 (66.5)	2,575 (20.2)	1,697 (13.3)	12,734 (100)
Estrogen alone	21 (9.0–52.0)	1,722 (65.2)	478 (18.1)	440 (16.7)	2,640 (100)

The continuous variables are expressed as the median value and the range between the 25th and 75th percentiles. The number and percentage of subjects in each category are shown for the categorical variables.
E: estrogen, P: progesterone.

Table 3. Osteoarthritis risk and incidence per 10,000 person/year on MHT

MHT	No OA cases (%)	OA cases (%)	OA cases/10,000 person-years	Crude
				HR (95% CI)
Non-MHT	19,344 (73.4)	7,010 (26.6)	336 (7,010/208,721)	1
Total OA	18,936 (71.9)	7,418 (28.1)	393 (7,418/188,922)	1.154 (1.117–1.193)
Hip	26,201 (99.4)	153 (0.6)	8 (153/188,922)	1.254 (0.994–1.582)
Knee	21,509 (81.6)	4,845 (18.4)	256 (4,845/188,922)	1.148 (1.102–1.195)
Other	22,464 (85.2)	3,890 (14.8)	206 (3,890/188,922)	1.205 (1.151–1.261)
Total OA by MHT				
Tibolone	7,819 (71.2)	3,161 (28.8)	167 (3,161/188,922)	1.211 (1.161–1.263)
E + P	9,272 (72.8)	3,462 (27.2)	183 (3,462/188,922)	1.092 (1.048–1.137)
Estrogen alone	1,845 (69.9)	795 (30.1)	42 (795/188,922)	1.235 (1.148–1.329)

CI: confidence interval, E: estrogen, HR: hazard ratio, MHT: menopausal hormone therapy, OA: osteoarthritis, P: progesterone.

and older (Supplementary Table 5, available online).

In a sensitivity analysis specifically focusing on postmenopausal females exhibiting a CCI score of 0, we found that MHT use was associated with a higher risk of osteoarthritis, which was in line with the main findings (HR, 1.161; 95% CI, 1.119–1.205).

DISCUSSION

In this study, MHT was associated with a higher risk of osteoarthritis. This trend was observed for both knee osteoarthritis and other forms of arthritis. While hip arthritis also showed a tendency toward increased risk, this association was not statistically significant.

Estrogen and cartilage

Several studies have shown positive effects of estrogen on articular cartilage. In female rats, ovariectomy accelerated cartilage degradation and increased interleukin-1 production. However, treating these rats with estradiol reversed these negative effects [14]. Estradiol was also found to directly reduce cartilage degradation in vitro [14]. Similar results were observed in sheep. Resistance to compression of articular cartilage, a sign of healthy cartilage, decreased after ovariectomy but was restored with estrogen replacement therapy [15]. Supporting these findings from animal studies, a study using magnetic resonance imaging to measure knee cartilage volume found that females who used MHT for more than five years had larger knee cartilage volumes compared to those who did not use MHT [16].

Menopausal hormone therapy and osteoarthritis

Despite the positive association between estrogen and articular cartilage, previous epidemiologic studies examining the relationship between MHT and osteoarthritis have yielded inconsistent results. In one study, monkeys receiving CEE monotherapy had less severe cartilage damage compared to a control group, even after accounting for age and weight [5]. Additionally, the

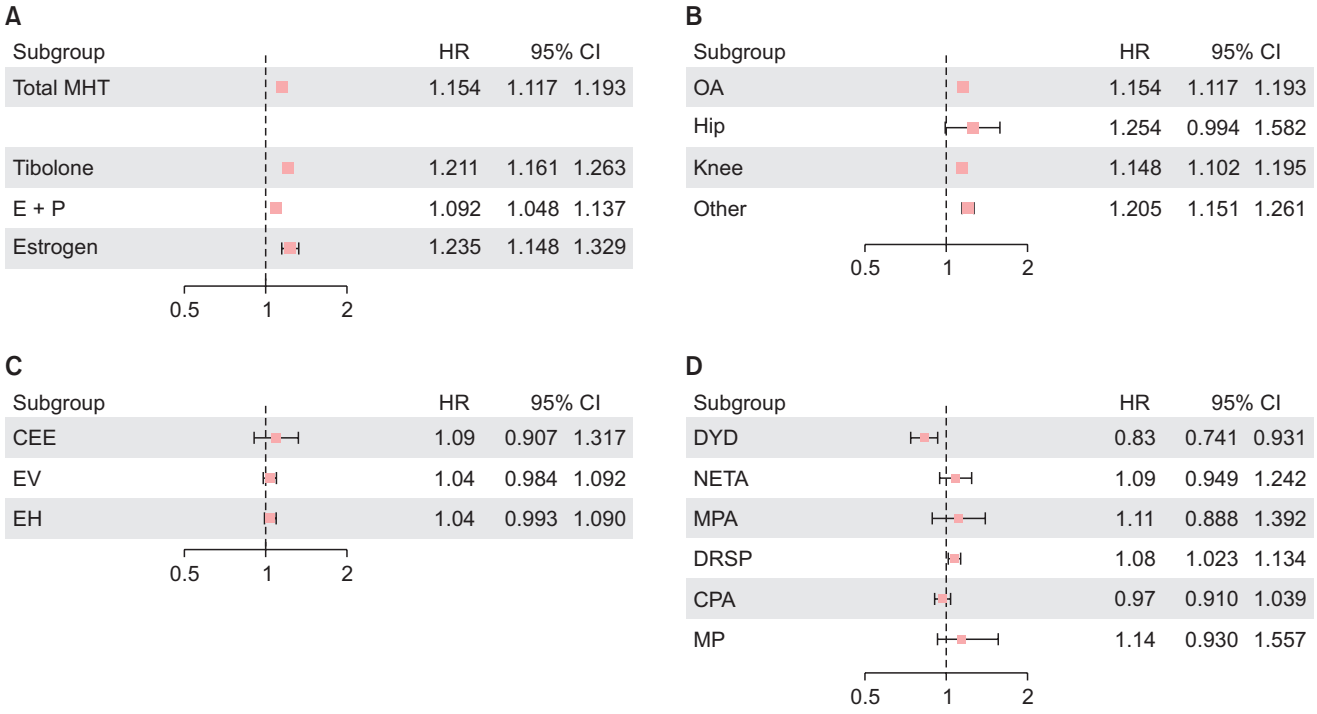


Fig. 2. Risk of osteoarthritis according to MHT type. (A) Categorization of subjects based on MHT type. (B) Site-specific osteoarthritis risk based on MHT. (C) Categorization of subjects based on oral estrogen. (D) Categorization of subjects based on oral progestogen. CEE: conjugated equine estrogen, CI: confidence interval, CPA: cyproterone acetate, DRSP: drospirenone, DYD: dydrogesterone, E: estrogen, EH: estradiol hemihydrate, EV: estradiol valerate, HR: hazard ratio, MHT: menopausal hormone therapy, MP: micronized progesterone, MPA: medroxyprogesterone acetate, NETA: norethisterone acetate, OA: osteoarthritis, P: progesterone.

Table 4. Osteoarthritis risk according to duration of MHT use

MHT	Duration (y)					
	< 3		3–5.9[a]		Over 6[a]	
	HR (95% CI)	*P* value	HR (95% CI)[a]	*P* value	HR (95% CI)[a]	*P* value
Non-MHT	1		1		1	
Total MHT	1.181 (1.138–1.225)	< 0.001	1.188 (1.112–1.269)	0.005	1.149 (1.031–1.280)	0.012
Category 1						
Tibolone	1.232 (1.171–1.297)	< 0.001	1.143 (1.034–1.262)	0.009	1.667 (0.587–4.732)	0.337
E + P	1.125 (1.073–1.179)	< 0.001	1.239 (1.135–1.353)	< 0.001	-	
Estrogen alone	1.270 (1.162–1.389)	< 0.001	1.113 (0.901–1.374)	0.322	1.779 (0.243–13.045)	0.571

CI: confidence interval, E: estrogen, HR: hazard ratio, MHT: menopausal hormone therapy, P: progesterone.
[a]This analysis was tailored to the minimum duration of MHT use and compared only females who were event-free for the same duration as non-MHT users. For example, MHT users with 3–5.9 years of use were compared to non-MHT users who were event-free for at least 3 years.

CEE monotherapy group exhibited significantly higher subchondral bone markers compared to the control group, while also demonstrating a lower prevalence of osteophytes [5]. Further supporting the potential benefits of MHT, a large cross-sectional study involving over 4,000 females aged 65 and over found that MHT users had a lower prevalence of hip osteoarthritis and some protection against moderate osteoarthritis in general [6]. Notably, long-term MHT use exceeding 10 years was associated with a 40% reduced risk of hip osteoarthritis compared to non-users [6]. Also, a cross-sectional study in the United Kingdom (UK) with postmenopausal females aged 45–65 showed a significant protective effect of current MHT use specifically for

knee osteoarthritis, but no benefit for hand osteoarthritis [17].

However, some studies do not support an association between MHT and a reduced risk of osteoarthritis progression. A United States (US) prospective cohort study of over 500 postmenopausal females found no significant protective effect from current MHT on radiographic knee osteoarthritis progression (odds ratio, 0.5; 95% CI, 0.1–2.9) [8]. Similarly, the WHI study observed a borderline significant association between CEE monotherapy and any arthroplasty (HR, 0.84; 95% CI, 0.70–1.00). However, CEE alone did not significantly reduce the risk of specifically hip or knee replacements. Additionally, no link was found between CEE/MPA use and arthroplasty risk [9].

Conversely, other studies suggest that females who use MHT have an increased risk of osteoarthritis, which is consistent with this finding. In the Million Women Study in the UK, MHT was linked to a higher incidence of knee arthroplasty (relative risk [RR], 1.38; 95% CI, 1.30–1.46) and hip arthroplasty (RR, 1.58; 95% CI, 1.48–1.69) [18]. Similarly, an Australian case-control study reported a link between MHT use and an increased risk of total knee arthroplasty (HR, 1.37; 95% CI, 1.14–1.64) [19]. Further supporting these findings, a Korean case-control observed that MHT use exceeding five years was associated with an elevated risk of both knee arthroplasty (HR, 1.23; 95% CI, 1.17–1.29) and hip arthroplasty (HR, 1.46; 95% CI, 1.12–1.89) [20]. Also, a recent meta-analysis indicated an association between MHT and an increased risk of knee osteoarthritis (HR, 1.24; 95% CI, 1.07–1.45) [21].

While the results were inconsistent, studies with larger sample sizes or larger populations generally reported a higher risk of osteoarthritis or arthroplasty. This suggests the need for further investigation into the potential association between MHT use and joint health.

Hypothesis

Studies asserting an association between MHT and increased osteoarthritis risk have faced challenges in interpreting their results, given prior positive findings related to estrogen and cartilage [18-20]. Some studies have suggested a non-biological interpretation, proposing that females prescribed MHT may undergo more arthroplasty due to greater access to healthcare [18,19]. However, in the UK and Australia, where these studies were conducted, there are national health insurance systems with relatively easy access to healthcare. Another study interprets this as an indication bias that females prescribed MHT are more likely to be estrogen-deficient [20]. However, in that study, the observation that arthroplasty risk rises with longer MHT duration cannot be solely attributed to indication bias. This study also cannot provide an exact rationale for the higher rate of osteoarthritis in females using MHT.

One hypothesis to explain our findings is that estrogen's influence on pain sensitivity may have altered joint utilization patterns. Supporting this hypothesis, a study investigating the effects of estrogen levels on brain opioid receptor activity found that a hyperestrogenic state was associated with increased baseline opioid receptor availability and greater activation of pain-relieving opioid neurotransmission during pain stimuli [22]. These findings suggest that estrogen plays a key role in modulating the body's natural pain response in humans [22]. Similarly, studies in rats have shown that estrogen activates inhibitory pain pathways in the spinal cord, leading to pain reduction. In contrast, progestins have been found to have the opposite effect, suggesting a potential mechanism for estrogen's influence on pain sensitivity [23]. Additionally, another rat study demonstrated that ET can decrease neurofilamentous neurotrophins in the synovial membrane of a rat osteoarthritis model, suggesting estrogen's influence on pain-related neuropeptide expression in the joint [24].

In essence, the pain relief experienced with estrogen use might lead to increased joint activity, potentially contributing to joint damage. This concept aligns with previous findings [25]. Combination therapy with an anti-nerve growth factor (NGF) agent and non-steroidal anti-inflammatory agents (NSAIDs) for knee and hip pain proved to be more effective for pain control than NSAIDs alone [25]. However, the risk of rapidly progressive osteoarthritis was increased in the anti-NGF group, possibly because of increased joint loading caused by the analgesic effects of both drugs [25]. Further research is warranted to explore this potential mechanism.

Strengths and limitations

This study has several strengths. First, we tried to reduce bias by excluding females with multiple risk factors such as joint pain and rheumatoid arthritis, or by using propensity score matching. Second, we performed a time-dependent Cox regression analysis to reduce immortal bias. Third, we made a detailed categorization of MHT, which involved a detailed cat-

egorization of MHT types, a method not often used in previous studies.

However, this study has the following limitations. First, we were unable to correct confounding factors such as joint trauma, menarche age, reproductive period, BMI, and occupational overuse of the joint due to the limitations of the HIRA data we used. Second, we defined the diagnosis of osteoarthritis using diagnosis codes, which are subject to coding errors. However, to reduce this coding error, we limited the cases to those with three or more visits to medical institutions. Defining osteoarthritis solely based on arthroplasty may introduce a bias towards older ages, as arthroplasty is more common in older individuals due to advanced disease progression (mean age: 65.4 ± 6.1 years) [20]. Therefore, this study employed the diagnosis code method for defining osteoarthritis.

Conclusion

MHT was associated with a higher risk of osteoarthritis, which remained consistent across tibolone, EPT, and ET. Additionally, MHT use was linked to an increased risk of osteoarthritis in joints other than the hip. However, although not statistically significant, there was an elevated risk of hip osteoarthritis in females using MHT.

FUNDING

This research was supported by the Korean Society of Menopause grant (No: KSM23A002).

CONFLICT OF INTEREST

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

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