European Journal of Obstetrics and Gynecology 310 (2025) 113983



Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology



Full length article



The effect of menopausal hormone therapy on thyroid cancer survivors from the National Health Insurance Database in South Korea cohort

Jin-Sung Yuk [a], Jin Li Lee [a], Yeonjin Shin [a], Gwan Hee Han [a], Sang-Hee Yoon [a], Myoung Hwan Kim [a], Ji Hyun Noh [a], Yujin Lee [b], Jungbin Kim [b], Sam-Youl Yoon [b], Hyunjin Cho [b], Keunho Yang [b], Byung Noe Bae [b], Ki Whan Kim [b], Geumhee Gwak [b,*]

[a] Department of Obstetrics and Gynaecology, Sanggye Paik Hospital, School of Medicine, Inje University, Seoul, Republic of Korea
[b] Department of Surgery, Sanggye Paik Hospital, School of Medicine, Inje University, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Menopausal hormone therapy
Mortality
Survivor
Thyroid cancer

ABSTRACT

Objective: There is a lack of research on how menopausal hormone therapy (MHT) affects the prognosis of postmenopausal thyroid cancer (TC) survivors. This study aimed to evaluate the association between MHT and the risk of death in postmenopausal TC survivors.

Methods: This retrospective cohort study used the data of women with the diagnostic code for TC from the Korean National Health Insurance Database between 2007 and 2021. The postmenopausal women with TC who received radical treatment such as surgery or/and radioactive iodine therapy were divided into two groups – MHT group and non-MHT group – according to whether or not they received MHT after TC treatment. The risk of death in TC survivors was analysed according to the type and duration of the MHT regimen.

Results: Among postmenopausal TC survivors, the risk of death did not differ between the women with MHT duration > 5 years and the non-MHT group, with a hazard ratio (HR) of 0.964 [95 % confidence interval (CI) 0.697–1.334] ($p = 0.826$). However, MHT duration < 5 years was associated with increased risk of death, with the MHT group having an HR of 1.744 (95 % CI 1.105–2.753) ($p = 0.017$) compared with the non-MHT group. A trend was observed towards increased risk of death in women with MHT duration ≤ 6 months, with an HR of 1.703 (95 % CI 0.98–2.962) ($p = 0.059$). The risk of death did not differ between women with MHT duration > 6 months and women in the non-MHT group (HR 1.205, 95 % CI 0.79–1.839) ($p = 0.064$). In analyses by MHT regimen, no increase in the risk of death was observed for any MHT regimen for any duration.

Conclusion: The risk of death in postmenopausal TC survivors who used MHT for > 5 years did not differ from that of their counterparts who did not use MHT. However, postmenopausal TC survivors who used MHT for < 5 years, particularly those who used MHT for < 6 months, had a higher risk of death than their counterparts who did not use MHT.

Introduction

Thyroid cancer (TC) is one of the fastest growing cancer diagnoses worldwide [1]. The age-standardized incidence rates of TC were 10.1 per 100,000 women and 3.1 per 100,000 men in 2020 globally [2]. According to a statistical analysis in Korean women, breast cancer and TC are the most common cancers, followed by colorectal cancer and lung cancer [3]. In general, men have higher incidence and mortality compared with women for many cancer types, such as colon, lung, liver and gastric cancer [4]. However, TC is approximately three times more common in women than men for several reasons, although the exact mechanisms behind the difference are not fully understood [2]. Jackson et al. reported the results of a large prospective cohort study from the National Institutes of Health (NIH)–American Association of Retired Persons (AARP) Diet and Health Study, which found that women had higher rates than men for thyroid and gallbladder cancers alone, and men had higher cancer rates than women for most other common anatomical sites. The researchers emphasized that this male predominance in the incidence of cancer cannot be explained simply by risk factors, and that the role of as-yet-unknown sex-related biological

* Corresponding author at: Department of General Surgery, Sanggye Paik Hospital, School of Medicine, Inje University, 1342 Dongil-ro, Nowon-gu, Seoul, Republic of Korea.
E-mail address: s2606@paik.ac.kr (G. Gwak).

https://doi.org/10.1016/j.ejogrb.2025.113983
Received 20 January 2025; Received in revised form 4 March 2025; Accepted 17 April 2025
Available online 19 April 2025
0301-2115/© 2025 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

factors must be considered [5].

Premenopausal cancer survivors may experience premature menopause due to cancer treatments, such as cytotoxic chemotherapy or therapeutic oophorectomy, and may experience more severe menopausal symptoms than women who menopause naturally [6]. As a result, female cancer survivors face a range of health problems caused by the deficiency or replacement of sex hormones such as oestrogen, progesterone and androgens [7]. The Endocrine Society's definition of the clinical spectrum of menopause includes menopause in women with an intact uterus, menopause in women who have had a hysterectomy but not a bilateral oophorectomy, and menopause associated with radiotherapy or chemotherapy [8]. The reduced production of female hormones by the ovaries can lead to vasomotor symptoms (hot flushes, night sweats), insomnia, arthralgia, increased risk of mood disorders (e.g. depression, anxiety), cognitive decline, sexual dysfunction, lower bone mineral density (BMD), and increased risk of fractures [9]. Physiologic oestrogen/progestin therapy ameliorates many of these health risks, and is considered standard care for women with premature ovarian insufficiency or early menopause [8].

Menopausal hormone therapy (MHT) is one option to treat intolerable physical and psychological symptoms of menopause. The 2022 position statement of the North American Menopause Society (NAMS) stated that the benefit–risk ratio of MHT is favourable to treat bothersome vasomotor symptoms and prevent bone loss for women aged < 60 years or who are within 10 years of menopause onset and have no contraindications [9]. The intervention and extended postintervention follow-up phases of the Women's Health Initiative trials did not indicate that MHT supports the prevention of chronic disease, although it is appropriate for symptom management in some women [10]. Nonetheless, it might be expected that TC survivors may be more reluctant to consider MHT because they are more concerned about recurrence of their cancer. Many studies have shown that certain types of MHT increase the risk of breast cancer, so MHT is contraindicated in breast cancer survivors [11]. Women who are considering MHT should discuss the potential risks and benefits of MHT with their healthcare provider, and make an informed decision based on their individual needs and health history. However, there is a lack of research on the effect of MHT in TC survivors.

The primary aim of this large-scale retrospective cohort study was to evaluate the potential impact of the type and duration of MHT on the survival of TC survivors using big data from the Health Insurance Review and Assessment Service (HIRA).

Methods

Database

The Government of the Republic of Korea offers universal medical insurance coverage for essential medical treatments to all citizens, as mandated by law [12]. HIRA is a national organization responsible for assessing the reasonableness of healthcare institutions' medical insurance claims [12]. Consequently, HIRA maintains a database of the national health insurance data. This database contains extensive patient information, including demographic data (gender, age, residence), diagnostic codes, prescription medications, surgical procedures, and medical insurance type [12]. Diagnoses are classified based on the International Classification of Diseases and Injuries 10th Revision (ICD-10) codes. Cancer patients receive specialized discounts on medical expenses as per the ICD-10 (Cxx) codes ('Health Security System', n.d.). Therefore, cancer diagnoses are recorded with a high degree of precision. This population-based retrospective cohort study used health insurance data from HIRA for the time period between 1 January 2007 and 31 August 2021.

Selection of participants

In this study, the selection of participants and verification of results and various variables were conducted using ICD-10 and Korea Health Insurance Medical Expenses (2012, 2019 editions). Data on female cancer patients aged ≥ 20 years were extracted from 1 January 2007 to 31 August 2021. However, it should be noted that it was not possible to identify women who had been diagnosed with cancer before 2007. As such, in order to extract only those women who were newly diagnosed with cancer, those with a cancer diagnostic code in 2007 were excluded. Furthermore, for calculation of the indicator of suspicion of death (ISD), which will be discussed in the Outcome section below, women newly diagnosed with cancer after 31 December 2019 were also excluded.

To eliminate bias associated with the use of MHT before cancer diagnosis, women whose menopause was not confirmed prior to cancer diagnosis were excluded. Women who were prescribed MHT for > 1 month before cancer diagnosis were also excluded from this study. Among the women thus identified, only patients diagnosed with TC (C73.x) were selected. TC patients were limited to those who had visited a medical institution at least three times with a TC diagnostic code. Among TC patients, women who were prescribed MHT for > 1 month were assigned to the MHT group, and those who were not prescribed MHT for > 1 month were assigned to the non-MHT group. In order to reduce bias by various variables, 1:1 propensity matching was performed based on year of cancer diagnosis, age at diagnosis, socioeconomic status (SES), area of residence, Charlson Comorbidity Index (CCI) score, hypertension, diabetes mellitus, hyperlipidaemia, previous hysterectomy, previous adnexal surgery, uterine fibroids, endometriosis, polycystic ovary syndrome (PCOS), total thyroidectomy for TC (after inclusion), and radiotherapy for TC (after inclusion).

Outcomes

ISD was used to determine the definition of death in TC patients. In South Korea, which has a single-payer medical insurance system, ISD is a useful indicator to estimate death when an individual's actual date of death is unknown. As a result of analysing the claim data, HIRA consider that the probability of death is high if the insured has not attended a medical institution within the last 365 days [13]. As a minimum observation period of 365 days is required for ISD confirmation, study subjects who were first diagnosed with cancer after 31 December 2019 were excluded from the analysis.

Variables

The criteria for all variables used in the study were confirmed based on the day of the first TC diagnosis. Patients were classified into 10-year age groups based on age at first diagnosis, and into three unit groups according to year of diagnosis. Patients who received government subsidies for medical expenses were classified as low SES, and residential areas that did not fall under the classification of large cities in terms of administrative districts were classified as rural areas. CCI scores were calculated using the method of Quan et al. based on insurance data from 365 days before the first cancer diagnosis to the first cancer diagnosis [14]. Hypertension (I10–I15), diabetes mellitus (E10–E14), hyperlipidaemia (E78), uterine fibroids (D25), endometriosis (N80) and PCOS (E28.2) were determined to be present if the individual had visited a medical institution at least three times for the respective condition. Information on hysterectomy, adnexal surgery, radical thyroidectomy for TC, and radioactive iodine (RAI) therapy for TC were identified in the operation code. There are five surgical codes for TC that can be submitted to HIRA: total thyroidectomy, unilateral or bilateral lobectomy, and unilateral or bilateral subtotal lobectomy. Of these, total thyroidectomy and bilateral lobectomy are considered radical surgery, and unilateral lobectomy and unilateral subtotal thyroidectomy are considered lobectomy.

Menopause was defined as at least three visits to medical institutions with menopause-related diagnostic codes (N95, E28.3, M80.0, M80.1, M81.0, M81.1). MHT was classified into five groups according to the regimen: oestrogen plus progestin combined by the manufacturer (COPM), oestrogen plus progestogen combined by the physician (COPP), oral oestrogen, tibolone and transdermal oestrogen. COPM is defined as a case where a physician prescribes a drug made by a pharmaceutical company in a single form of the oestrogen/progestin combination and includes various types of drugs, such as ostradiol/drospirenone, oestradiol valerate/cyproterone acetate, oestradiol hemihydrate/norethisterone acetate, oestradiol hemihydrate/dydrogesterone, oestradiol valerate/medroxyprogesterone acetate, and oestradiol valerate/norethisterone acetate, etc. COPP is defined as a case where a physician selects and prescribes various progestogens to be added to oestrogen. In cases where two or more MHTs were prescribed serially, the last drug prescribed for >1 month was used as the basis.

Statistics

In this study, all statistical analyses were conducted using R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), and SAS Enterprise Guide 7.15 (SAS Institute Inc, Cary, NC, USA) was utilized as a supplementary tool. Two-tailed tests were conducted for all statistical analyses, and $p \leq 0.05$ was considered to indicate significance.

Before propensity score matching, categorical variables were analysed using Pearson's Chi-squared test and Fisher's exact test, and continuous variables were analysed using Student's *t*-test and Wilcoxon rank sum test. After propensity score matching, categorical variables were analysed using the Cochran–Mantel–Haenszel test, and continuous variables were analysed using paired *t*-test and Wilcoxon signed rank test. The balance scale of individual covariates for which matching was performed was evaluated using standardized differences. The Anderson–Darling normality test was utilized to confirm the normality of continuous variables.

Stratified Cox regression analysis after propensity score matching was used to conduct survival analysis on paired study subjects. Furthermore, to address the potential for immortal bias in the drug research, time-dependent Cox regression analysis was adopted. The period from the date of cancer diagnosis to the date of first use of MHT in the MHT group was calculated assuming that the non-MHT group was used.

The Schoenfeld residuals test was used to assess the proportional hazards assumption in Cox regression. If this assumption was violated, an extended Cox regression analysis was performed by dividing the observation period based on the Schoenfeld residuals plot.

The date of initiation for the study's observation in the non-MHT group was established as the date of diagnosis of TC, while the initial date for prescription of MHT was established for the MHT group. The date of censorship was determined as the earliest occurrence of either the date of death or the final day of utilization of a medical facility for any ailment, as recorded in the health insurance data. This study was followed-up until 31 December 2020, considering the calculation of ISD.

All users of MHT, including short-term users of MHT ($\leq$1 month) were included in this study in order to reflect real-life clinical practice, in which the duration of MHT varies considerably. However, as short-term use may be a confounding factor, the MHT group was stratified according to MHT duration: <6 months, 7–18 months and $\geq$ 19 months. As there may be clinical circumstances in which short-term MHT use affects mortality (e.g. terminal illness, severe comorbidities), an immortal time bias mitigation was performed as a key design safeguard to reduce potential confounders of short-term users, and women who had used MHT for >1 month before TC diagnosis were excluded in order to minimize the impact of comorbidities.

To ensure fairness when performing subgroup analyses according to the duration of MHT use, the MHT group and the non-MHT group were compared, with the requirement that all individuals in both groups had survived for a period exceeding the minimum duration of MHT usage. In other words, individuals in the MHT group who had used MHT for ≥ 6 months and individuals in the non-MHT group who had survived for at least 6 months were compared.

In this study, the listwise deletion method was employed to handle missing values in all statistical analyses. To further ensure the robustness of the results, a stratified Cox regression analysis was carried out exclusively on female participants who had undergone both radical thyroidectomy for TC and RAI treatment for TC, as these patients were considered to have the most advanced disease.

Results

A sample of 677,234 individuals aged $\geq$ 20 years diagnosed with any cancer between 1 January 2007 and 31 August 2021 was selected. Women with a cancer-related diagnostic code on 1 January 2007 and women diagnosed with cancer for the first time after 31 December 2019 were excluded when calculating ISD, resulting in a sample of 472,445. From this group, postmenopausal women who had not received MHT for >1 month prior to their cancer diagnosis were identified, resulting in a sample of 80,264. Next, patients diagnosed with TC were selected, resulting in a sample of 47,110. Finally, 7999 women who had received MHT were matched for factors such as patient age, calendar year of cancer diagnosis, SES, residential area, CCI score, hypertension, diabetes mellitus, dyslipidaemia, previous hysterectomy, previous adnexal surgery, uterine fibroids and endometriosis, resulting in a final sample of 15,998 women (Fig. 1).

The median age of the non-MHT group was 52 (range 49–56) years and the median age of the MHT group was 52 (range 49–55) years. The median follow-up period was approximately 9.2 (range 7–11.2) years for the non-MHT group and 9.2 (range 7–11.1) years for the MHT group. The age distribution of the study participants in the MHT group was as follows: 50–59 years (40.5 %), 40–49 years (28.1 %) and 60–69 years (10.5 %). Radical surgery and RAI therapy were performed in 66.9 % and 41.8 % of all TC patients, respectively. Table 1 provides a detailed summary of the characteristics of these patients, including any missing values, after propensity score matching. Supplementary Table 1 provides the same information before the matching process was conducted.

There were 193 (2.4 %) deaths in the non-MHT group and 120 (1.5 %) deaths in the MHT group ($p < 0.001$). Deaths per 1000 person-years for each group were 2 per 1000 person-years for the non-MHT group and 3 per 1000 person-years for the MHT group. The characteristics of MHT usage in postmenopausal women with TC are shown in Table 2. The MHT group was prescribed with tibolone (52.2 %), COPM (30.5 %), oral oestrogen (14 %), COPP (1.5 %) and transdermal oestrogen (1.8 %). The mean MHT duration was 4 (range 1–17) months, with 58.5 % of participants receiving MHT for $\leq$ 6 months, 17.5 % for 7–18 months, and 23.9 % for $\geq$ 19 months. Two-thirds (66.7 %) of all physicians who prescribed MHT were gynaecologists (Table 2).

When comparing the risk of death among postmenopausal TC survivors in the non-MHT and MHT groups, the results varied according to the duration of follow-up and the type of MHT therapy used (Table 3). Within 5 years of starting MHT, the risk of death was higher in the MHT group compared with the non-MHT group [hazard ratio (HR) 1.744, 95 % confidence interval (CI) 1.105–2.753] ($p = 0.017$). However, >5 years after starting MHT, the risk of death was not higher in the MHT group compared with the non-MHT group (HR 0.964, 95 % CI 0.697–1.334) ($p = 0.826$). When the risk of death was examined by MHT regimen, no MHT regimens were associated with increased risk of death for any time period (Table 3).

When the risk of death was analysed by duration of MHT use in the MHT group in comparison with the non-MHT group, there was a trend towards increased risk of death in the subgroup who took MHT for $\leq$ 6 months, but this difference was not significant (HR 1.703, 95 % CI 0.98–2.962) ($p = 0.059$). Among those patients who took MHT for >6 months, there was no significant difference in the risk of death between

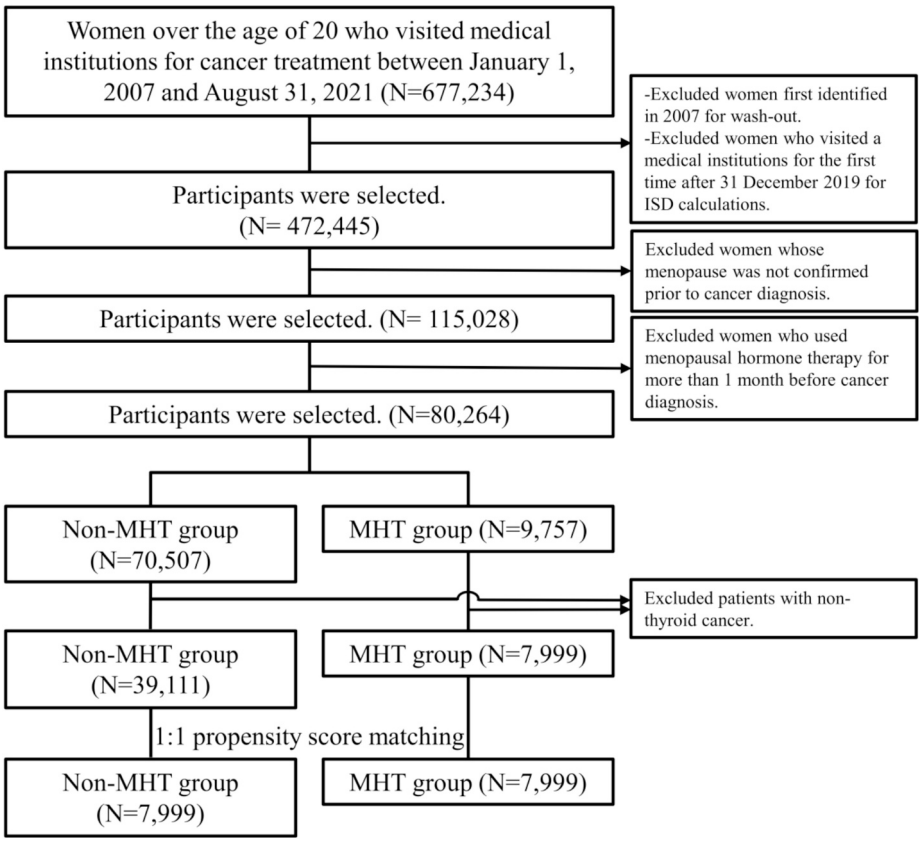


Fig. 1. Flowchart of patient selection for use of menopausal hormone therapy (MHT) among thyroid cancer survivors using Korea Health Insurance Review and Assessment Service data (2007–2021).

those who took MHT for < 18 months and those who took MHT for > 18 months. There was also no significant difference in the risk of death within 5 years of the start of MHT and the risk of death 5 years after the start of MHT in the MHT group in comparison with the non-MHT group (HR 1.205, 95 % CI 0.79–1.839) ($p = 0.064$) (Table 4).

In a sensitivity test that focused solely on those women who had both radical thyroidectomy and RAI therapy (i.e. who could be classified as having more advanced TC), the risk of death was higher in the MHT group compared with the non-MHT group, supporting the main results (HR 2.316, 95 % CI 1.287–4.168). However, in the subanalyses of tibolone (HR 2.133, 95 % CI 0.898–5.069), COPM (HR 1.744, 95 % CI 0.632–4.817), and oestrogen alone (HR 3.149, 95 % CI 0.8–12.387), there was no difference in the risk of death.

Discussion

This study showed that the risk of death in postmenopausal TC survivors who used MHT for > 5 years did not differ from that of their counterparts who did not use MHT. However, postmenopausal TC survivors who used MHT for < 5 years, particularly those who used MHT for < 6 months, had a higher risk of death than their non-MHT counterparts. Related to the association between the change in endogenous oestrogen and risk of TC, some studies have suggested that the incidence of TC rises sharply from the onset of menarche and then declines with the onset of menopause over the lifetime of a woman [15,16]. Other studies have reported that pregnancy, abortion and lactation may result in a transient fluctuation in the risk of papillary TC [17,18].

A recent pooled prospective cohort analysis reported that factors associated with higher risk of differentiated TC included younger age at menarche, younger (<40 years) and older (≥55 years) age at menopause (compared with 40–44 years), ever used MTH, and previous hysterectomy or bilateral oophorectomy. This analysis also found that long-term use of oral contraceptives (≥5 years) and postmenopausal status at baseline were associated with lower risk of TC, and parity, MHT duration, and lifetime number of reproductive years or ovulatory cycles were not associated with lower risk of TC [19]. Evidence on whether the use of exogenous oestrogen, such as oral contraceptives, lactation suppressants and MHT, increases the risk of TC is generally weak and the results of trials are inconsistent [20,21]. It is not clear whether the use of exogenous oestrogen or progesterone for any purpose increases the incidence of TC, although it is clear that oestrogen plays a role in the pathophysiology of TC.

Deli et al. found that trials of MHT in postmenopausal TC survivors are lacking, and it is not possible to draw conclusions about the effects of MHT in postmenopausal TC survivors. However, they suggested that MHT may be warranted in postmenopausal TC survivors because there is no evidence that it has an effect on the development of new TC [22].

The present retrospective study used big data from the National Health Insurance Service to analyse whether the risk of death of postmenopausal TC survivors who were taking MHT differed from that of their counterparts who were not taking MHT. This study showed that the risk of death in postmenopausal TC survivors who used MHT for > 5 years did not differ from that of their counterparts who did not use MHT. However, an important limitation of this study is that data on the causes of death and relapse in TC survivors were not included, so it was not possible to predict how MHT affects TC death and relapse.

A number of menopause-related societies around the world recommend that MHT should be prescribed at the correct dose and for the correct length of time with the aim of eliminating bothersome symptoms of menopause [9,23]. Prescribing MHT to these women may have increased the risk of thrombo-embolism, which could have led to life-threatening complications such as stroke and pulmonary embolism, and contributed to increased risk of death while using MHT [24,25]. In the present study, the risk of death was higher among those who used

Table 1
Comparison of clinical characteristics of non-menopausal hormone therapy (MHT) group and MHT group in postmenopausal women with thyroid cancer after propensity score matching.

Clinical characteristics (%)	Non-MHT	MHT	Total	*p*-value	SD	Missing, %
Number of participants	7999	7999	15,998			
Years of follow-up (years)	9.2 (7–11.1)	9.2 (7–11.2)	9.2 (7–11.1)	0.276	0.013	0
Age (years)	52 (49–56)	52 (49–55)	52 (49–56)	0.39	0.022	0
Age in year of participation (years)				<0.001	0.096	0
20–29	16 (0.2)	7 (0.1)	23 (0.1)			
30–39	167 (2.1)	82 (1)	249 (1.6)			
40–49	2204 (27.6)	2283 (28.6)	4487 (28.1)			
50–59	4672 (40.3)	4723 (40.6)	9395 (40.5)			
60–69	848 (10.6)	796 (10)	1644 (10.3)			
≥70	92 (1.2)	108 (1.4)	200 (1.3)			
Years of participation				0.121	0.017	0
2008–2011	3773 (47.2)	3711 (46.4)	7484 (46.8)			
2012–2015	2961 (37)	2985 (37.3)	5946 (37.2)			
2016–2019	1265 (15.8)	1303 (16.3)	2568 (16.1)			
Socio-economic status				<0.001	0.066	0
Mid–high	7857 (98.2)	7779 (97.2)	15,636 (97.7)			
Low	142 (1.8)	220 (2.8)	362 (2.3)			
Residential area				0.001	0.029	0
Urban area	5568 (69.6)	5462 (68.3)	11,030 (68.9)			
Rural area	2431 (30.4)	2537 (31.7)	4968 (31.1)			
Charlson Comorbidity Index score				0.262	0.017	8
≤2	4757 (59.5)	4738 (59.2)	9495 (59.4)			
3–4	2650 (33.1)	2633 (32.9)	5283 (33)			
≥5	592 (7.4)	628 (7.9)	1220 (7.6)			
Hypertension				0.7	0.075	0
Absent	5699 (71.2)	5686 (71.1)	11,385 (71.2)			
Present	2300 (28.8)	2313 (28.9)	4613 (28.8)			
Diabetes mellitus				0.575	0.009	0
Absent	6741 (84.3)	6715 (83.9)	13,456 (84.1)			
Present	1258 (15.7)	1284 (16.1)	2542 (15.9)			
Dyslipidaemia				0.234	0.01	0
Absent	4992 (62.4)	4954 (61.9)	9946 (62.2)			
Present	3007 (37.6)	3045 (38.1)	6052 (37.8)			
Hysterectomy				<0.001	0.075	0
Absent	7596 (95)	7455 (93.2)	15,051 (94.1)			
Present	403 (5)	544 (6.8)	947 (5.9)			
Adnexal surgery				0.01	0.041	0
Absent	7822 (97.8)	7771 (97.1)	15,593 (97.5)			
Present	177 (2.2)	228 (2.9)	405 (2.5)			
Uterine fibroids				<0.001	0.066	0
Absent	6508 (81.4)	6298 (78.7)	12,806 (80)			
Present	1491 (18.6)	1701 (21.3)	3192 (20)			
Endometriosis				<0.001	0.078	0
Absent	7656 (95.7)	7518 (94)	15,174 (94.8)			
Present	343 (4.3)	481 (6)	824 (5.2)			
PCOS				0.671	0.078	0
Absent	7976 (99.7)	7972 (99.7)	15,948 (99.7)			
Present	23 (0.3)	27 (0.3)	50 (0.3)			
Radical surgery				0.045	0.021	0
Absent	2586 (32.3)	2703 (33.8)	5289 (33.1)			
Present	5413 (67.7)	5296 (66.2)	10,709 (66.9)			
Radioactive iodine therapy				0.182	0.021	0
Absent	4616 (57.7)	4699 (58.7)	9315 (58.2)			
Present	3383 (42.3)	3300 (41.3)	6683 (41.8)			

Data are presented as *n* (%) or median (interquartile range).
PCOS, polycystic ovary syndrome; SD, standardized difference.

Table 2
Characteristics of menopausal hormone therapy (MHT) usage in postmenopausal women with thyroid cancer who underwent MHT.

MHT characteristics	Tibolone	COPM	Oral oestrogen	COPP	Transdermal oestrogen	Total MHT
Number of participants	4172 (52.2)	2441 (30.5)	1123 (14)	120 (1.5)	143 (1.8)	7999 (100)
Median duration (months)	4 (1–19)	4 (1–15)	6 (3–20)	3 (2–11.25)	1 (1–2)	4 (1–17)
Duration (months)						
≤6	2393 (57.4)	1488 (61)	591 (52.6)	74 (61.7)	137 (95.8)	4683 (58.5)
7–18	726 (17.4)	407 (16.7)	233 (20.7)	30 (25)	5 (3.5)	1401 (17.5)
≥19	1053 (25.2)	546 (22.4)	299 (26.6)	16 (13.3)	1 (0.7)	1915 (23.9)
Prescribing specialty						
Gynaecology	2504 (60)	1729 (70.8)	893 (79.5)	96 (80)	112 (78.3)	5334 (66.7)
Non-gynaecology	1668 (40)	712 (29.2)	230 (20.5)	24 (20)	31 (21.7)	2665 (33.3)

Data are presented as *n* (%) or median (interquartile range).
COPM, oestrogen plus progestin combined by the manufacturer; COPP, oestrogen plus progestin combined by the physician.

Table 3
Survival analysis of menopausal hormone therapy (MHT) group in postmenopausal thyroid cancer survivors compared with non-MHT group according to type of regimen of MHT and observation period.

	Unadjusted		Schoenfeld residuals test
Reference (non-MHT)	HR (95 % CI)	*p*-value	*p*-value
MHT			<0.001
<5 years	1.744 (1.105–2.753)	0.017	
>5 years	0.964 (0.697–1.334)	0.826	
MHT group			
Tibolone	1.119 (0.7738–1.619)	0.55	0.136
COPM			0.005
<5 years	1.507 (0.7–3.242)	0.295	
>5 years	1 (0.563–1.775)	1	
Oestrogen alone			0.044
<5 years	1.862 (0.517–6.703)	0.342	
>5 years	1.573 (0.5578–4.438)	0.392	
COPP	(−)		
TO	4.372 (0.4436–43.098)	0.206	0.916

COPM, oestrogen plus progestin combined by the manufacturer; COPP, oestrogen plus progestin combined by the physician; TO, transdermal oestrogen; HR, hazard ratio; CI, confidence interval.

Table 4
Comparison of survival analysis between non-menopausal hormone therapy (MHT) group and MHT group according to the duration of MHT use in postmenopausal women with thyroid cancer.

MHT duration	Unadjusted		Schoenfeld residuals test
	HR (95 % CI)	*p*-value	*p*-value
Intermediate- to long-term use (>6 months)[a]	1.205 (0.79–1.839)	0.387	0.064
Short-term use (≤6 months)[b]			<0.001
Survival < 5 years	1.703 (0.98–2.962)	0.059	
>5 years	0.977 (0.643–1.486)	0.915	
Intermediate-term use (7–18 months)[c]	1.557 (0.874–2.772)	0.133	0.641
Long-term use (≥19 months)[d]			0.008
<5 years	1.295 (0.318–5.279)	0.719	
>5 years	0.612 (0.299–1.253)	0.179	

HR, hazard ratio; CI, confidence interval.
[a] This analysis compared the total non-MHT group surviving for > 6 months and the MHT group using MHT for > 6 months.
[b] This analysis compared the total non-MHT group and the MHT group using MHT for ≤ 6 months.
[c] The separated extended Cox analysis was performed for the non-MHT group surviving for > 7 months and the MHT group using MHT for 7–18 months.
[d] The separated extended Cox analysis was performed for the non-MHT group surviving for > 18 months and the MHT group using MHT for > 18 months.

MHT for < 5 years, especially those who used MHT for < 6 months, compared with those who did not use MHT, for several reasons. First, the increased risk of cardiovascular disease in the early years of MHT use may have contributed to deaths from stroke or thromboembolic events. Cardiovascular disease is more likely to occur in women aged > 60 years who are almost 10 years postmenopausal compared with younger women who are in the menopausal transition or < 10 years postmenopausal. Second, women with a very short life expectancy, such as elderly women with poor nutritional status and a high risk of fracture due to osteoporosis, or those with advanced cancer, may have been prescribed MHT in the short term to improve their general condition or to make them feel more comfortable, which may have contributed to the increased risk of death in the group who used MHT for < 5 years. However, the data used in this analysis were limited, and more research with additional data in these clinical settings is required.

This study also found that no particular MHT regimen was associated with increased risk of death in postmenopausal TC survivors. With regard to the conclusion that tibolone, COPM and oestrogen alone do not increase the risk of death in postmenopausal TC survivors, the authors were unable to find any previous studies that were consistent with or similar to the present findings. Therefore, although the conclusions of this study are of low-level evidence because it was not a well-planned prospective study, they may serve as a compass to help guide future research on MHT in postmenopausal TC survivors.

This is the first study to use Korean HIRA big data to investigate the impact of MHT on postmenopausal TC survivors, although the data are fairly limited to what the government really needs. To date, no large-scale clinical trials have examined the effects of MHT in postmenopausal women with TC. Therefore, clinicians have had to rely on weak evidence from reviews of various observational trials or *meta*-analyses that MHT does not increase the risk of new TC or recurrent TC to suggest that MHT likely does not harm postmenopausal women with TC [20–22]. It is well known that primary treatment for TC includes surgery, RAI therapy, and thyroxine hormone replacement with thyroid-stimulating hormone (TSH) suppression [26]. Many studies have suggested associations between chronic TSH suppression therapy and lower BMD in postmenopausal women with TC [27,28]. Recently, Ku et al. reported evidence from observational studies suggesting that postmenopausal women treated with TSH suppression therapy are at risk for lower BMD [29].

In this study, 66.9 % and 41.8 % of TC patients underwent radical surgery and RAI therapy, respectively (Table 1). These results are in line with previous studies showing that the trend towards surgery and RAI therapy in TC patients is increasing over time [30]. This suggests that approximately 40–60 % of postmenopausal women with TC may have lower BMD than postmenopausal women without TC. Therefore, if MHT does not have an adverse effect on the prognosis of TC, it may be considered as a way to mitigate poor bone health in TC patients at risk of osteoporosis or osteoporotic fractures.

This study has some limitations. First, there was a lack of detailed information to reflect a number of prognostic factors and clinical outcomes, as the big data used in this study were collected mainly for the practical needs of Korean National Health Insurance data. In particular, detailed codes that can accurately provide histological and staging information for TC are not available in the big data used in this study. However, by looking at the extent of surgery and RAI therapy, researchers can compensate, in part, for this limitation by estimating indirectly whether TC is early or advanced. Another limitation of this study was the lack of data regarding cause of death. Without precise information on the cause of death, it is difficult to analyse how MHT may have affected the risk of death in TC survivors because patients with TC have a very low mortality rate compared with patients with other cancers. However, some researchers thought that if any clues could be gleaned to confirm the initial hypothesis that MHT does not affect the risk of death in TC survivors, it would be meaningful, although this limitation could not be overcome due to the inherent limitations of health insurance big data.

This study found that the risk of death when MHT was given to postmenopausal TC survivors varied according to the time point of observation: compared with postmenopausal TC survivors who did not receive MHT, postmenopausal TC survivors who received MHT for > 5 years had increased risk of death, and those who received MHT for < 5 years did not have increased risk of death. However, when the risk of death was examined by MHT regimen, tibolone, oestrogen alone and COMP were not associated with increased risk of death for any time period. Although no association was found between increased risk of death in TC survivors and any MHT regimen, further bias-corrected studies are needed to explain the increased risk of death within 5

years in the overall MHT group. The risk of death in TC survivors should also be assessed and individualized in relation to each of the MHT regimens. Further well-designed studies are needed to evaluate the combined multifactorial effects of MHT on postmenopausal TC survivors, and to gain insight into the real impact of MHT on postmenopausal TC survivors. In this way, appropriate medical decisions can be made to improve the quality of life and survival of postmenopausal women with TC.

Conclusion

This study found that the risk of death in postmenopausal TC survivors who used MHT for > 5 years did not differ from that of their counterparts who did not use MHT. However, postmenopausal TC survivors who used MHT for < 5 years, particularly those who used MHT for < 6 months, had a higher risk of death than their non-MHT counterparts.

Ethics

Sanggye Paik Hospital Institutional Review Board granted ethical approval for this study (Ref. SGPAIK 2022–03-014). HIRA provided the researchers with the raw data after deleting any characteristics that might be used to identify specific participants. Only the research results (in the form of tables, figures and statistics) were permitted to be exported from HIRA's closed server when the entire study analysis was completed. In compliance with the Bioethics and Safety Act of South Korea, informed consent was declared unnecessary because the anonymity of the participants was protected. It should be highlighted that, under HIRA's privacy policy, readers are unable to access the raw data, and HIRA has no interest in the outcome of this study, for which it provided the data.

CRediT authorship contribution statement

Jin-Sung Yuk: Writing – review & editing, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jin Li Lee:** Writing – review & editing. **Yeonjin Shin:** Writing – review & editing. **Gwan Hee Han:** Writing – review & editing. **Sang-Hee Yoon:** Writing – review & editing. **Myoung Hwan Kim:** Writing – review & editing. **Ji Hyun Noh:** Writing – review & editing. **Yujin Lee:** Writing – review & editing. **Jungbin Kim:** Writing – review & editing. **Sam-Youl Yoon:** Writing – review & editing. **Hyunjin Cho:** Writing – review & editing. **Keunho Yang:** Writing – review & editing. **Byung Noe Bae:** Writing – review & editing. **Ki Whan Kim:** Writing – review & editing. **Geumhee Gwak:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2025.113983.

References

[1] Zhai M, Zhang D, Long J, et al. The global burden of thyroid cancer and its attributable risk factor in 195 countries and territories: a systematic analysis for the Global Burden of Disease Study. Cancer Med 2021;10:4542–54.
[2] Pizzato M, Li M, Vignat J, et al. The epidemiological landscape of thyroid cancer worldwide: GLOBOCAN estimates for incidence and mortality rates in 2020. Lancet Diabetes Endocrinol 2022;10:264–72.
[3] Jung KW, Won YJ, Kang MJ, Kong HJ, Im JS, Seo HG. Prediction of cancer incidence and mortality in Korea, 2022. Cancer Res Treat 2022;54:345–51.
[4] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–33.
[5] Jackson SS, Marks MA, Katki HA, et al. Sex disparities in the incidence of 21 cancer types: quantification of the contribution of risk factors. Cancer 2022;128:3531–40.
[6] Marino JL, Saunders CM, Emery LI, Green H, Doherty DA, Hickey M. Nature and severity of menopausal symptoms and their impact on quality of life and sexual function in cancer survivors compared with women without a cancer history. Menopause 2014;21:267–74.
[7] Yeo W, Pang E, Liem GS, et al. Menopausal symptoms in relationship to breast cancer-specific quality of life after adjuvant cytotoxic treatment in young breast cancer survivors. Health Qual Life Outcomes 2020;18:24.
[8] Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015; 100:3975–4011.
[9] NAMS Position Statement. The 2022 hormone therapy position statement of the North American Menopause Society. Menopause 2022;29:767–94.
[10] 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;310:1353–68.
[11] Yuk JS, Kim T, Cho H, Gwak G. Breast cancer risk association with postmenopausal hormone therapy: Health Insurance Database in South Korea-based cohort study. Eur J Endocrinol 2024;190:1–11.
[12] 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.
[13] Yuk JS, Ji HY, Shin JY, Kim LY, Kim SH, Lee JH. Comparison of survival outcomes in women with unsuspected uterine malignancy diagnosed after laparotomic versus laparoscopic myomectomy: a national, population-based study. Ann Surg Oncol 2016;23:1287–93.
[14] 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;173:676–82.
[15] Li N, Du XL, Reitzel LR, Xu L, Sturgis EM. Impact of enhanced detection on the increase in thyroid cancer incidence in the United States: review of incidence trends by socioeconomic status within the Surveillance, Epidemiology, and End Results registry, 1980–2008. Thyroid 2013;23:103–10.
[16] He JL, Zhang C, Hu MJ, et al. Reproductive and menstrual factors for papillary thyroid cancer risk: a case–control study in Chinese women. Cancer Epidemiol 2021;73:101964.
[17] Horn-Ross PL, Canchola AJ, Ma H, Reynolds P, Bernstein L. Hormonal factors and the risk of papillary thyroid cancer in the California Teachers Study cohort. Cancer Epidemiol Biomarkers Prev 2011;20:1751–9.
[18] Rossing MA, Voigt LF, Wicklund KG, Daling JR. Reproductive factors and risk of papillary thyroid cancer in women. Am J Epidemiol 2000;151:765–72.
[19] O'Grady TJ, Rinaldi S, Michels KA, et al. Association of hormonal and reproductive factors with differentiated thyroid cancer risk in women: a pooled prospective cohort analysis. Int J Epidemiol 2024;53:dyad172.
[20] Bae JM. Hormonal replacement therapy and risk of thyroid cancer in women: a meta-epidemiological analysis of prospective cohort studies. J Menopausal Med 2021;27:141–5.
[21] Apostolou K, Zivaljevic V, Tausanovic K, et al. Prevalence and risk factors for thyroid cancer in patients with multinodular goitre. BJS Open 2021;5:zraa014.
[22] Deli T, Orosz M, Jakab A. Hormone replacement therapy in cancer survivors – review of the literature. Pathol Oncol Res 2020;26:63–78.
[23] de Villiers TJ, Gass ML, Haines CJ, et al. Global consensus statement on menopausal hormone therapy. Climacteric 2013;16:203–4.
[24] Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case–control studies using the QResearch and CPRD databases. BMJ 2019;364:k4810.
[25] Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ 2008;336:1227–31.
[26] Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1–133.
[27] Yoon BH, Lee Y, Oh HJ, Kim SH, Lee YK. Influence of thyroid-stimulating hormone suppression therapy on bone mineral density in patients with differentiated thyroid cancer: a meta-analysis. J Bone Metab 2019;26:51–60.

[28] Lee Y, Yoon BH, Lee S, Chung YK, Lee YK. Risk of osteoporotic fractures after thyroid-stimulating hormone suppression therapy in patients with thyroid cancer. J Bone Metab 2019;26:45–50.
[29] Ku EJ, Yoo WS, Lee EK, et al. Effect of TSH suppression therapy on bone mineral density in differentiated thyroid cancer: a systematic review and meta-analysis. J Clin Endocrinol Metab 2021;106:3655–67.
[30] Cho BY, Choi HS, Park YJ, et al. Changes in the clinicopathological characteristics and outcomes of thyroid cancer in Korea over the past four decades. Thyroid 2013; 23:797–804.