



# Hormonal Replacement Therapy and Risk of Thyroid Cancer in Women: A Meta-Epidemiological Analysis of Prospective Cohort Studies

Jong-Myon Bae

Department of Preventive Medicine, Jeju National University School of Medicine, Jeju, Korea

**Objectives:** Many experimental studies have reported that female sex hormones involve thyroid cancer development because the incidence rate of thyroid cancer in women (TCW) is 3 times higher than in men. Three previous systematic reviews reporting no association between hormone replacement therapy (HRT) and TCW risk had the same search year of 2014. The aim was to reevaluate the association between HRT use and TCW risk using a meta-epidemiological study of prospective cohort studies.

**Methods:** The study preferentially used all studies selected by the existing systematic reviews and then secured an additional cohort from the list citing the studies. The selection criterion was defined as the prospective cohort study assessing the association between HRT and TCW risk by adjusted relative risk and its 95% confidence intervals (CI) from multivariate analysis. A random-effects model meta-analysis was applied to estimate summary relative risk (sRR) and its 95% CI. A publication bias was evaluated by Egger's test; moreover, the statistical significance level was set at 5%.

**Results:** Nine cohort studies were finally selected. The random-effect model was applied because of heterogeneity ( $I^2 = 64.3\%$ ). The sRR and its 95% CI from a random-effects model meta-analysis had no statistical significance in the association between HRT and TCW risk (sRR = 1.11; 95% CI, 0.98–1.26). Additionally, Egger's test revealed no statistical significance ( $P = 0.91$ ).

**Conclusions:** HRT is not associated with TCW risk based on the random-effects model meta-analysis of prospective cohort studies published until now.

**Key Words:** Hormone replacement therapy, Meta-analysis, Risk factor, Thyroid neoplasms

## INTRODUCTION

Thyroid cancer is the most common malignancy involving the endocrine system [1], and its incidence shows a rising trend [2,3]. Based on the epidemiological fact that women have 3 times higher incidence rates than men [2], many experimental studies have reported that female sex hormones involve developing thyroid cancer [4,5].

Three systematic reviews evaluating the association between hormone replacement therapy (HRT) and risk of thyroid cancer in women (TCW) did not show

statistical significance [6-8] (Table 1). All of them performed the fixed-effects model meta-analysis under the low heterogeneity, and the summary relative risk (sRR) was the same for all of them at 1.05. This could be attributed to the same search year as 2014. Thus it needs to extend the searching year till 2021 as this year and then conduct an updated meta-analysis.

In addition, Williams et al. [9] pointed that most cases had been excluded in a previous meta-analysis due to extracting adjusted RR in the longest versus shortest duration of drug intake. This means that the highest versus lowest method (HLM) in extraction was applied

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Address for Correspondence: Jong-Myon Bae, Department of Preventive Medicine, Jeju National University School of Medicine, 102 Jejudaehak-ro, Jeju 63243, Korea

Tel: 82-64-755-5567, E-mail: jmbae@jejunu.ac.kr, ORCID: <https://orcid.org/0000-0003-3080-7852>

**Table 1.** Summary of previous systematic reviews for evaluating the association between hormonal replacement therapy and risk of thyroid cancer in women

| Study                   | Searching      | Selected cohort studies | sRR (95% CI)     | $I^2$ (%) |
|-------------------------|----------------|-------------------------|------------------|-----------|
| Caini et al. [6] (2015) | July 2014      | 8                       | 1.05 (0.89–1.24) | 14        |
| Cao et al. [7] (2015)   | September 2014 | 8                       | 1.05 (0.91–1.20) | 0.0       |
| Wang et al. [8] (2015)  | November 2014  | 5                       | 1.05 (0.89–1.25) | 17.8      |

sRR: summary relative risk, CI: confidence intervals.

when a selected study has no information about the ever group. Accordingly, only a portion of the information reported by the selected cohort study was used for meta-analysis. To overcome the limitations of HLM, the interval collapse method (ICM) is applied to the study that did not provide the HRT ever group risk [10]. The aim was to re-evaluate the association between HRT use and TCW risk using a meta-epidemiological study [11] of prospective cohort studies.

## MATERIALS AND METHODS

According to the purpose, this meta-epidemiological study maximized to use of 8 prospective cohort studies [12–19] selected by the existing systematic reviews that applied extensive and comprehensive search strategies. The author made a list of articles that cited previously selected studies till June 30, 2021 was made using the ‘cited by’ option by PubMed (<https://pubmed.ncbi.nlm.nih.gov>). This searching strategy assumes that studies conducted with the same research hypothesis have a high likelihood of citing the articles included in the previous systematic reviews [20]. Any study satisfying a selection criterion on the list was secured. The selection criterion was defined as the same as the 3 systematic reviews in Table 1 such that a prospective cohort study assessing the association between HRT history and TCW risk by adjusted relative risk (RR) and its 95% confidence intervals (CI) from multivariate analysis.

Adjusted RRs and their 95% CI of the HRT ever group in TCW and papillary thyroid cancer in women (PTCW) were extracted from each selected study. If a study did not provide the risk information of the ever group, the ICM was applied [10]. For RRs and their 95% CIs values in the categories with the never group as a reference, a fixed-effects model meta-analysis was applied to estimate the RR and its 95% CI of the ever group in the study. Additionally, risk information about 2 kinds of HRT history as past and current group, and 3 kinds of HRT drugs as estrogen only, estrogen plus

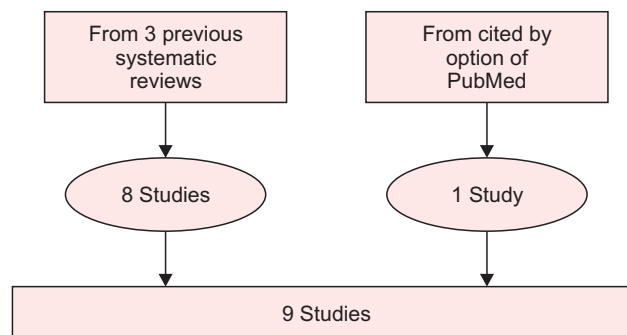


Fig. 1. Flow chart of the final selection of prospective cohort studies.

progesterone, and others were extracted to conduct subgroup analyses.

The level of heterogeneity was evaluated by the  $I^2$  value (%) [21]. A random-effects model meta-analysis was applied to estimate sRR and its 95% CI [22] because selected cohort studies were performed for multiple participants with various protocols [23]. And then subgroup analyses by HRT history and HRT drugs were performed. A publication bias was evaluated by the symmetry of a funnel plot [24] and Egger’s test [25]. StataSE 14 statistical program (StataCorp, College Station, TX, USA) was used, and the statistical significance level was set at 5%.

## RESULTS

From a list of articles that cited 8 selected studies till June 30, 2021, Schubart et al. [26] published in 2021 was secured (Fig. 1). Of the 9 cohort studies selected finally, 4 studies [15,16,18,26] did not report the adjusted RR for the HRT ever group, so the RRs and their 95% CI applying ICM were estimated (Fig. 2).

The sRR and its 95% CI from the random-effects model meta-analysis did not have a statistical significance in the association between HRT history and TCW risk (sRR = 1.11; 95% CI, 0.98–1.26) (Fig. 2). There was also no statistical significance in the PTCW

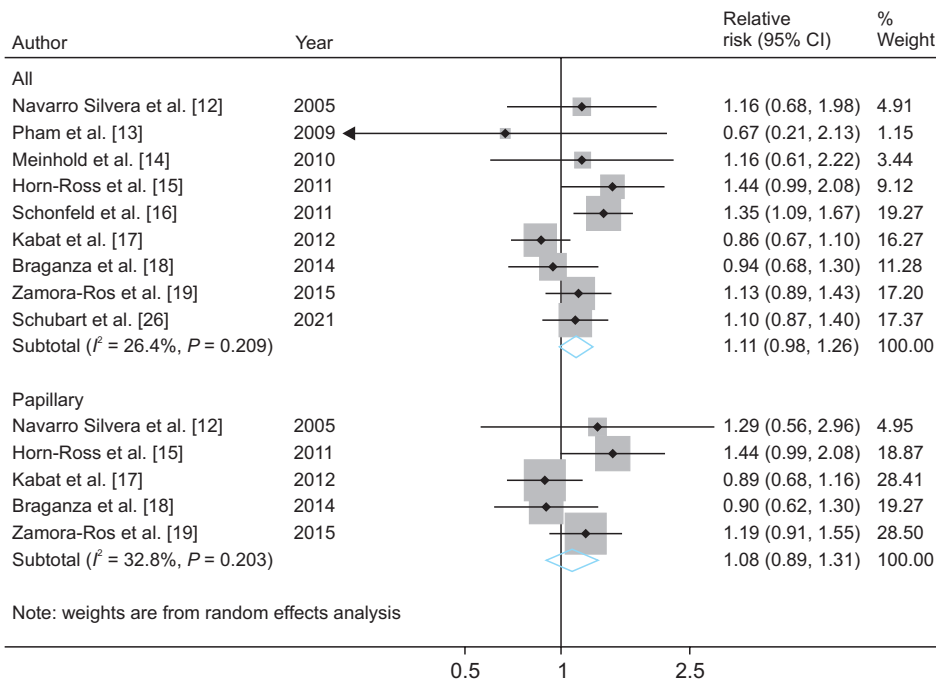


Fig. 2. Funnel plot of summary relative risk and 95% confidence intervals for the association between hormone replacement therapy and thyroid cancer risk.

Table 2. Subgroup analyses by history and drugs of hormonal replacement therapy (HRT)

| Variable    | Category               | Thyroid cancer in women |            | Papillary thyroid cancer in women |               |
|-------------|------------------------|-------------------------|------------|-----------------------------------|---------------|
|             |                        | sRR (95% CI)            | Reference  | sRR (95% CI)                      | Reference     |
| HRT history | Ever                   | 1.11 (0.98–1.26)        | [12-19,26] | 1.08 (0.89–1.31)                  | [12,15,17-19] |
|             | Past                   | 1.07 (0.88–1.29)        | [16-18,26] | 0.86 (0.62–1.21)                  | [17,18]       |
|             | Current                | 1.05 (0.83–1.33)        | [16-18,26] | 0.90 (0.71–1.16)                  | [17,18]       |
| HRT drugs   | Estrogen only          | 0.90 (0.71–1.15)        | [17,26]    | 1.13 (0.57–2.24)                  | [15,17]       |
|             | Estrogen + progestogen | 0.93 (0.72–1.21)        | [17,26]    | 1.04 (0.77–1.40)                  | [15,17]       |
|             | Others                 | 0.88 (0.38–2.04)        | [17,26]    | 1.06 (0.42–2.65)                  | [15,17]       |

sRR: summary relative risk, CI: confidence intervals.

risk (sRR = 1.08; 95% CI, 0.89–1.31).

Table 2 summarizes the results of subgroup analyses conducted by HRT history and HRT drugs. All categories in TCW and PTCW showed no statistical significance. The funnel plot showed no asymmetry (Fig. 3), and Egger’s test was no statistical significance ( $P = 0.91$ ).

## DISCUSSION

The results can be summarized that the HRT ever history did not increase or reduce TCW and PTCW risk. Subgroups by HRT history and HRT drugs also had the same results.

When comparing the results of this study applying a random-effects model meta-analysis with the system-

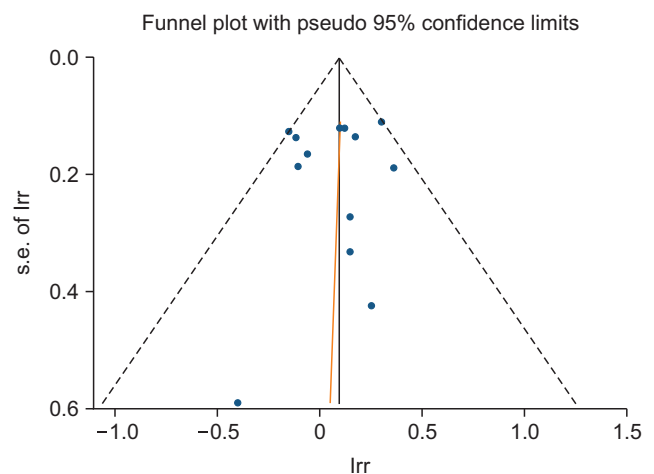


Fig. 3. Funnel plot ( $P$  value of Egger’s test = 0.91). lrr: logarithm of relative risk, s.e.: standard error.

atic reviews in [Table 1](#), the sRR value shifted from 1.05 to 1.11 under no statistical significance. On the other hand, the sRRs in [Table 1](#) were estimated from a fixed-effects model meta-analysis based on the low level of heterogeneity. For comparison, a fixed-effects model meta-analysis was performed on 9 cohorts in [Figure 1](#), and the sRR showed a statistical significance (sRR = 1.12; 95% CI, 1.01–1.23;  $I^2 = 26.4\%$ ). However, it would be more valid to take the results estimated from the random-effects model meta-analysis because selected cohort studies had been performed for multiple participants with various protocols [\[23\]](#).

The main advantages of this meta-epidemiological study are as follows. Firstly, this study applied different searching strategies from the existing systematic reviews. As shown in [Table 1](#), previous systematic reviews performed extensive and comprehensive searches for databases, but the number of selected studies was different. On the other hand, this study preferentially used all of the studies selected by the existing systematic reviews and then secured an additional cohort from the list citing the studies [\[20\]](#). This method could maximize the results of existing systematic reviews. And it could be expected to provide an opportunity to utilize the studies selected in this study when performing an updated meta-analysis in the future. Lastly, this study maximally utilized the information reported from the selected studies by applying the ICM rather than the HLM in the extraction process. Jin and Lang [\[27\]](#) reported statistical significance in the association between HRT history and risk of lung cancer in women by applying the ICM method to the HRT ever group. This example showed increasing statistical power by applying the ICM method that uses most of the information reported.

On the other hand, the main limitation of this study is that only the risks according to HRT history and drugs were investigated. The sRR in the past and the current group were 1.07 and 1.05, respectively, so that additional inferences could not. It is necessary to perform a dose-response meta-analysis by HRT periods [\[28\]](#). However, only Kabat et al. [\[17\]](#) reported the relevant information, so that it is impossible to perform a dose-response meta-analysis. In addition, only one cohort study could be added for the updated meta-analysis, although the author extended the search date to June 2021. However, Schubart et al. [\[26\]](#) followed 113,137 women for 25 years, and the weight of the meta-analysis was 17.37% ([Fig. 2](#)). It was the second-highest

weight on the estimated meta-analysis result.

In conclusion, HRT is not associated with the TCW risk based on the random-effects model meta-analysis of prospective cohort studies published till now. However, an updated meta-analysis reflecting cohort studies to be published in the future is needed because the risk from the fixed-effect model meta-analysis showed statistical significance and some experimental studies have suggested the estrogen and estrogen receptor-mediated pathway in thyroid cancer cells [\[4,5\]](#). Through this, it would be expected that more accurate and valid conclusions can be drawn about the direction of risk and whether its risk is statistically significant.

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## CONFLICT OF INTEREST

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

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