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Evaluation of the risk of thyroid cancer following hysterectomy through meta-analysis

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ABSTRACT

Objectives: Thyroid cancer is observed more frequently in women than men, possibly due to the influence of hormonal factors. This study aims to conduct a meta-analysis encompassing both prospective and retrospective observational studies to examine the risk of thyroid cancer in women who have undergone hysterectomy surgery.

Material and methods: The literature search identified 356 articles by May 2022, and eight reported hazard ratios for thyroid cancer in women who underwent hysterectomy surgery. After the eliminations, we performed three different meta-analyses with studies that included patients who underwent only total abdominal hysterectomy (TAH), total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO), and underwent hysterectomy with or without BSO. The reporting of this study has been conducted in accordance with the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews).

Results: Our study showcases a comprehensive meta-analysis that includes eight observational studies, both retrospective and prospective, exploring the link between hysterectomy and the likelihood of developing thyroid cancer. This analysis is based on data from more than 12 million individuals, encompassing over 24,000 cases. Women who had undergone TAH (HR = 1.586, 95% CI: 1.382–1.819, $p < 0.001$), women who had undergone TAH and BSO (HR = 1.420, 95% CI: 1.205–1.675, $p < 0.001$), and women who had undergone hysterectomy with or without BSO had an increased risk (HR = 1.623, 95% CI: 1.387–1.899, $p < 0.001$) of developing thyroid cancer later in life.

Conclusions: We found that hysterectomy had a statistically significant risk effect on the development of thyroid cancer. The limited number of previous studies, the low amount of information, the lack of homogeneous distribution of the patients in the studies, and the unknown characteristics of thyroid cancer developing after hysterectomy were the limitations of this study. Nevertheless, our findings can positively affect public health because of the potential to enlighten the etiological mechanisms leading to thyroid cancer. Future researches should first aim to explain the underlying mechanisms of developing thyroid cancer after hysterectomy.

Keywords: thyroid cancer; hysterectomy; oophorectomy; artificial menopause; surgical menopause; meta-analysis

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INTRODUCTION

Among the malignancies affecting the endocrine system, thyroid cancer is the most prevalent [1–2]. Over the decades, there has been a global increase in the incidence of thyroid cancer [3–4]. Ionizing radiation, benign diseases of the thyroid, a genetic inclination, and elevated body mass index are among the recognized risk factors for thyroid cancer [3, 5, 6]. Based on epidemiological studies, it is possible to say that hormonal factors can create or regulate the risk of thyroid cancer. Indeed, the occurrence of thyroid cancer is three times higher in women compared to men [7–9]. This rate against women is at its highest point in reproductive age, and it gradually decreases as the age progresses [9]. Therefore, this suggests that reproductive factors and sex hormones may cause a higher incidence in women. It has been proposed that estrogen plays a role in the etiology of thyroid cancer by directly affecting proliferative and neoplastic pathways through receptors [10]. In addition, the fact that women use health services more in reproductive age than men [11] increases the likelihood of incidental and

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may constitute a gender difference in incidence. Although several studies have investigated the relationship between reproductive exposures and thyroid cancer risk (e.g., pregnancy, breastfeeding, menarche/menopausal age, and oral contraceptive use), no clear association has been shown for most [12–14].

Both *in vitro* and *in vivo* research have demonstrated the ability of estrogen to promote the growth and modulate the metastatic characteristics of human thyroid tumor cells [15–18]. The estrogen receptor (ER) provides the estrogen effect primarily [10]. As evidenced by increased proliferation and ERs expression, estrogen increases cell adhesion, migration, and invasion, which means that both benign and malignant thyroid cells respond to estrogen [16]. Moreover, there is evidence that estrogen acts by inducing the growth of human thyroid tumor cells through the mitogen-activated protein kinase pathway [15]. Different epidemiological research exploring the link between the predominance of females and reproductive and hormonal factors in thyroid cancer have not been able to identify robust or consistent correlations [19–20].

Hysterectomy, whether performed with or without bilateral salpingo-oophorectomy (BSO), is one of the most common gynecological surgeries among women [21]. The BSO procedure leads to surgical menopause in women who have not yet experienced natural menopause [22]. This surgical menopause results in a sudden decrease in estrogen levels [22]. Moreover, hysterectomy without BSO can also impair ovarian function by disrupting the blood flow to the ovaries or causing damage to ovarian tissue [23–24]. Therefore, premenopausal women experience menopause earlier after hysterectomy than those who do not have hysterectomy [25]. In this regard, various epidemiological studies have been conducted, assuming the development of thyroid cancer after hysterectomy, after hysterectomy and BSO, and after hysterectomy with or without BSO. Various cohort-type studies have examined the relationship between hysterectomy and the subsequent risk of developing thyroid cancer. However, studies on this subject are limited in number. In some of the studies conducted, an association was found between hysterectomy and the risk of thyroid cancer. However, this association has not been shown in some of them. The relationship between external estrogen exposure as a potential risk factor for thyroid cancer, and the early depletion of natural estrogen as a possible protective factor against it, remains intricate and yet to be fully understood. All this suggests that higher evidentiary scientific data are needed to clarify its success in predicting the risk of thyroid cancer after hysterectomy. Consequently, the primary goal of this meta-analysis was to elucidate the correlation between undergoing a hysterectomy and the associated risk of developing thyroid cancer.

MATERIAL AND METHODS

Search strategy

Using a systematic electronic search approach as of May 2022, we conducted a search for published literature in various databases including PubMed, Medline, Google Scholar, Scopus, Web of Science, and Science Direct. The data of our study were deciphered from all the studies conducted. The following keywords and combinations were used: thyroid cancer, hysterectomy, oophorectomy, artificial menopause, surgical menopause, and meta-analysis. The search was limited to being published in English and conducted on people. The search strategy schematically presents the decode flow diagram (Fig. 1). Our research adheres to the standards set by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) guidelines, as outlined in reference [26–27].

Inclusion criteria

The inclusion criteria were as follows:

1. Estimating the association between types of hysterectomy and thyroid cancer risk in women.
2. Cohort or case-control design.
3. Showing hazard ratios (HRs) with 95 % confidence intervals [95 % confidence intervals (CIs)].

Case-only studies and studies not about the relationship of types of hysterectomy with the risk of thyroid cancer were all excluded.

Study selection

We acquired the full texts of all articles that were potentially suitable for this meta-analysis, based on their abstracts. Additionally, we conducted a search for extra articles in the reference lists of the retrieved articles as well as in previously published reviews and meta-analyses. In addition to all observational studies investigating the relationship between hysterectomy and the development of thyroid cancer, retrospective or prospective studies were selected. Studies that developed thyroid cancer after hysterectomy, after hysterectomy and BSO, and after hysterectomy with or without BSO were included in this meta-analysis. No specific year interval was determined for the development of thyroid cancer, and the specified intervals were not considered. Studies in which subgroup thyroid cancers were investigated, except for thyroid cancer in general and patients who underwent BSO alone without hysterectomy, were excluded. Case reports were excluded from this analysis. Additionally, trials that presented results in a manner that obstructed data collection, such as not reporting statistical information, were also excluded. Finally, after the eliminations, we conducted three different meta-analyses with studies that only included patients who underwent TAH, TAH and BSO, and

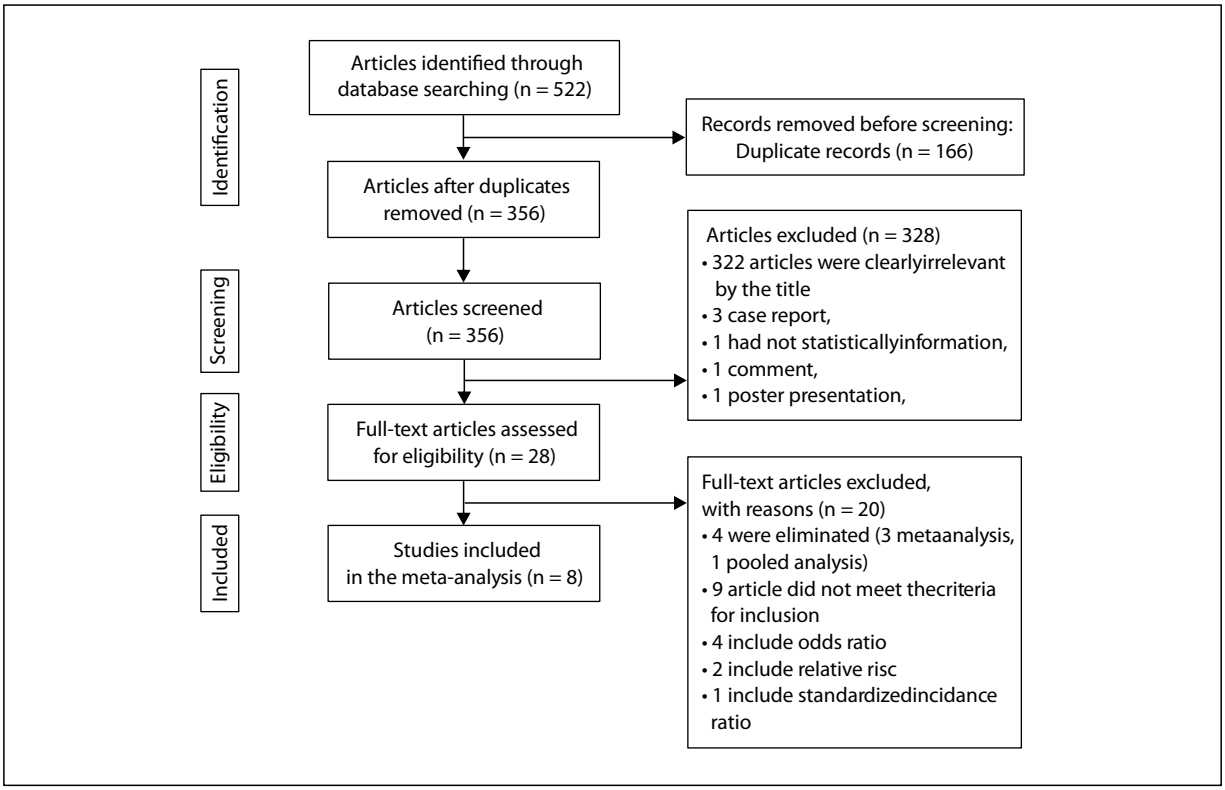


Figure 1. Flow chart

underwent hysterectomy with or without BSO. The articles included in the meta-analysis were those that provided or allowed the estimation of the hazard ratio for the association between hysterectomy and the risk of thyroid cancer among women. These articles also included 95% confidence intervals, standard errors, or variance. No language, time, or geographical restrictions were applied. There was no direct funding for this research.

Quality and risk of bias assessment

Prior to the meta-analysis, the publication bias of the studies was assessed using Begg's and Egger's tests.

Data extraction

The studies were selected through a three-stage process. Initially, the titles and abstracts of all electronic articles were evaluated for eligibility. Subsequently, the decision to include certain studies in this meta-analysis was made after obtaining and reviewing the full texts of articles deemed potentially suitable. Any potential discrepancies in this final stage were resolved through the consensus of all authors.

Summary measures

The primary outcome measure selected for this meta-analysis was to determine whether the risk of thyroid cancer following hysterectomy was significant.

Quantitative data synthesis

In our study, we conducted a meta-analysis using hazard ratios. In some studies included in the meta-analysis, estimates of the hazard ratios were provided, but the variance information was neglected. If there is a $(1 - x_i)$ x 100 percent confidence interval specified, this provides a method for calculating the variance of the logarithmic hazard ratio. In this context, $UPPCI_i$ and $LOWCI_i$ are the values representing the lower and upper limits of the confidence interval for $\ln(HR_i)$ that is, for the logarithmic hazard ratio. Typically, confidence intervals specified for hazard ratios are more common. In this case, $UPPCI_i$ and $LOWCI_i$ are expressed as the logarithms of the upper and lower limits of the hazard ratio [28].

Standard errors were estimated with the formula:

$$\mathrm{var}(\ln(\mathrm{HR_i})) = \left[\frac{\mathrm{UPP\ CI_i} - \mathrm{LOW\ CI_i}}{2\Phi^{-1}(1-\alpha_i/2)}\right]^2$$

$\mathrm{UPP\ CI_i}$ — the value for the upper ends of the confidence interval [28]

$\mathrm{LOW\ CI_i}$ — the value for the lower ends of the confidence interval [28]

$2\Phi^{-1}(1-\alpha_i/2)$ — We note that in practice the 95 percent intervals are usually given, and thus the denominator inside

Table 1. Characteristics of all studies included in our meta-analysis

Authors	Study type /country	Total No. of people included in the study (n)	TAH (n)	TAH and BSO (n)	Hysterectomy ± USO/BSO (n)	Total no. of patients with thyroid Ca (n)
Wilson 2021 [35]	Retrospective-Cohort Australia	838,237	74.056	25.920		1.095
Kim 2021 [36]	Retrospective-Cohort Korea	671,291	42.848	36.113		12.959
Guenego 2018 [37]	Prospective-Cohort France	89.340	7.263	8.918	16,064	412
Falconer 2017 [38]	Retrospective-Cohort Sweden	5,470,078			90,235	2.935
Altman 2016 [39]	Retrospective-Cohort Sweden	5,491,438	90.235	21.360	111,595	6.869
Luo 2016 [19]	Prospective-Cohort USA, China	127,566	10.675	13.880	46,852	344
Braganza 2015 [41]	Prospective-Cohort France	70.047				48
Kabat 2012 [40]	Prospective-Cohort USA	145,007				296
Total		12,903,004				24.958

BSO — bilateral salpingo-oophorectomy; TAH — total abdominal hysterectomy; USO — unilateral salpingo-oophorectomy

the square brackets in expression will usually take the value of 2 x 1.96 [28]

Suppose that there are k trials, and for each trial, i = 1.2, k [28]

When determining the statistical methods, the heterogeneity of the studies was assessed using the Cochran Q test. For the homogeneity and publication bias tests of the studies, the value of α was set at 0.10.

The I^2 index is a more recent approach to quantify heterogeneity in meta-analyses. I^2 provides an estimate of the percentage of variability in results across studies that is due to real differences and not due to chance. The I^2 index measures the extent of heterogeneity by dividing the result of Cochran's Q test and its degrees of freedom by the Q-value itself [29].

When heterogeneity was identified in the studies through Cochran's Q test, the DerSimonian-Laird methodology, based on the random-effects model, was chosen for the analyses. For the statistical evaluations, version 19 of the MedCalc software was employed.

RESULTS

Literature search and study characteristics

Search of the literature yielded 356 articles (refer to Fig. 1). Out of these, 322 were deemed unrelated based on their titles. Among the remaining, three were case reports, with one lacking statistical data [30], another being a commentary, and one more a poster presentation. The full texts of the remaining 28 articles were thoroughly evaluated.

Upon evaluating the full texts of 28 articles, four were omitted from the study. This exclusion included three articles because they were meta-analyses and one due to it being a pooled analysis. Specifically, one of the meta-analyses investigated the relationship between the use of external sex hormones in women and the risk of developing thyroid cancer [31]. The others are about hormonal and reproductive factors in women and thyroid cancer risk [32–33]. So lastly, one pooled analysis of case-control of thyroid cancer [34]. When the full texts were examined, it was seen that nine articles did not meet the inclusion criteria in terms of hysterectomy types. However, when the remaining 15 articles were divided into groups, eight articles [19, 35–41] indicated the hazard ratio for thyroid cancer, four articles the odds ratio, two articles the relative risk, and 1 article the standardized incidence ratio. Thus, eight articles remained to be included in the meta-analysis [19, 35–41]. Table 1 presents the pertinent attributes of the trials that were included.

The meta-analysis incorporated eight articles, published from 2012 through 2021, with study populations varying from 70,047 to 5,491,438 individuals. These studies provided hazard ratios assessing the likelihood of developing thyroid cancer following different types of hysterectomy. Analytical subgroups were categorized into three main sections: Firstly, assessing the risk in women who had TAH only; secondly, those who had both TAH and BSO; and lastly, women who had a hysterectomy, either with or without BSO, evaluating all cases through their respective hazard ratios. Four articles [19, 35–37] for thyroid cancer after TAH, seven articles [19, 35–37, 39–41] for thyroid cancer after TAH and BSO, and six

Table 2. Relevant statistics for meta-analysis in determining the association between total abdominal hysterectomy (TAH) and malign thyroid neoplasm in trials

Study	Ln (HR)	Standard error	HR	95% CI	z	p value	Weight [%]	
							Fixed	Random
Wilson et al., 2021	0.322	0.0755	1.380	1.190 to 1.600			14.02	29.57
Kim et al., 2021	0.519	0.0318	1.680	1.578 to 1.788			78.93	41.22
Guenego et al., 2018	0.673	0.152	1.960	1.455 to 2.641			3.46	14.43
Luo et al., 2016	0.372	0.149	1.450	1.082 to 1.943			3.58	14.78
Total (random effects)	0.461	0.0701	1.586	1.382 to 1.819	6.580	< 0.001	100.00	100.00

HR — hazard ratio; CI — confidence interval

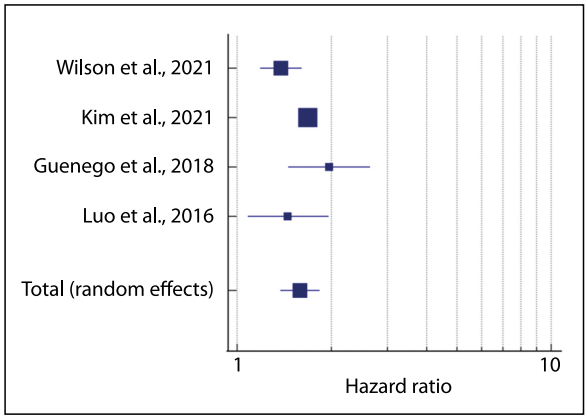


Figure 2. Forest graph in evaluating the association between total abdominal hysterectomy (TAH) and thyroid malignant neoplasm

articles [19, 37–41] for thyroid cancer after hysterectomy with or without BSO were included in the meta-analysis.

Qualitative analysis

Except for three, all studies reported a relation between hysterectomy and the risk of developing thyroid cancer afterward.

Quantitative analysis

In the initial meta-analysis, publication bias was assessed using Egger's test (p = 0.694) and Begg's test (p = 1.000), both indicating its absence. Cochran's Q-test indicated significant heterogeneity (p = 0.049, I^2 = 61.71%). A notable disparity was observed between the patient group and the control group. The risk of developing thyroid cancer later in life was higher in women who TAH, as shown by the hazard ratio (HR = 1.586, 95% CI: 1.382–1.819, p < 0.001) (refer to Tab. 2). Figure 2 illustrates these meta-analysis findings.

The subsequent meta-analysis revealed no publication bias, as demonstrated by Egger's test (p = 0.912) and Begg's test (p = 0.880). Cochran's Q-test showed heterogeneity in the data (p = 0.012, I^2 = 63.23%). A significant variation was found between the patient and control groups. The analysis indicated that women who underwent TAH along with BSO were at a heightened risk (HR = 1.420, 95% CI: 1.205–1.675, p < 0.001) of developing thyroid cancer later (detailed in Tab. 3). Figure 3 displays these results.

In the third meta-analysis, the Egger's test (p = 0.195) and the Begg's test (p = 0.107) ruled out the presence of publication bias. Heterogeneity was confirmed by Cochran's Q-test (p = 0.025, I^2 = 61.05%). There was a marked difference between the control group and patients. Increased risk of thyroid cancer in later life was noted in women who had undergone a hysterectomy, with or without BSO (HR = 1.623, 95% CI: 1.387–1.899, p < 0.001), as detailed in Table 4. The outcomes are depicted in Figure 4.

DISCUSSION

Our meta-analysis, which examined both retrospective and prospective observational studies, investigated the link between hysterectomy and the risk of thyroid cancer. This analysis encompassed over 24,000 cases within a population exceeding 12 million. The findings indicated a statistically significant association between hysterectomy and an increased risk of developing thyroid cancer.

Many studies in the literature investigate the relationship between hormonal and reproductive factors and the risk of thyroid cancer and find conflicting evidence. Hormonal and reproductive factors have been implicated in the development of thyroid cancer, but the molecular mechanisms explaining the exact association have not yet been fully comprehended. Although men have a constant increase in the risk of thyroid cancer throughout their lives, the risk increases in women during puberty and decreases after menopause [42], supporting the idea that hormonal factors are influential in thyroid cancer. It is estimated that estrogen increases the level of TSH and, as a result, causes the growth of thyroid cells [42]. Also, estrogen receptors are highly expressed in thyroid tumor cells [42]. Thyroid carcinogenesis can be influenced by sex steroid hormones, which promote thyroid cell proliferation and interact with

Table 3. Relevant statistics for meta-analysis in determining the association between Total abdominal Hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO) and thyroid malignant neoplasm in trials

Study	Ln (HR)	Standard error	HR	95% CI	z	p value	Weight [%]	
							Fixed	Random
Wilson et al., 2021	0.166	0.137	1.180	0.902 to 1.544			5.95	15.54
Kim et al., 2021	0.322	0.0388	1.380	1.279 to 1.489			74.40	25.09
Guenego et al., 2018	0.854	0.144	2.350	1.773 to 3.115			5.40	14.92
Altman et al., 2016	0.104	0.267	1.110	0.658 to 1.873			1.57	7.20
Luo et al, 2016	0.392	0.137	1.480	1.132 to 1.934			5.99	15.59
Braganza et al., 2015	0.191	0.272	1.210	0.710 to 2.061			1.51	7.02
Kabat et al., 2012	0.239	0.147	1.270	0.952 to 1.694			5.17	14.63
Total (random effects)	0.351	0.0840	1.420	1.205 to 1.675	4.179	< 0.001	100.00	100.00

HR — hazard ratio; CI — confidence interval

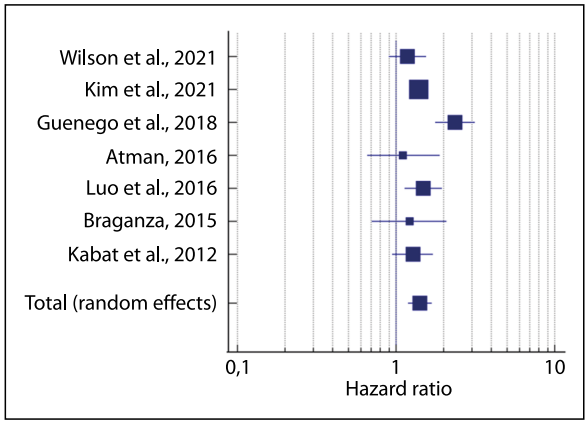


Figure 3. Forest graph in evaluating the association between total abdominal hysterectomy (TAH) + bilateral salpingo-oophorectomy (BSO) and thyroid malignant neoplasm

immune functions. In vitro studies have shown that estradiol enhances metastatic properties such as adhesion, migration, and invasiveness in thyroid cells, thereby facilitating the growth of thyroid tumor cells [16]. Research indicates the presence of progesterone receptors on both normal and cancerous thyroid cells [43], as well as on certain immune system cells [44]. Given the known effect of progesterone in stimulating the growth of uterine fibroids [45], it might also play a crucial role in the initiation and development of thyroid cancers. If BSO has also been performed on women who have had a hysterectomy, hormone replacement therapy will be prescribed. In this regard, we can believe that estrogen and progesterone or only estrogen will stimulate the development of thyroid cancer.

Conversely, the study by Braganza and colleagues found no correlation between menopausal hormone therapy in women, regardless of their hysterectomy history, and thyroid cancer risk [41]. This prospective research highlighted that factors such as a greater number of reproductive years, more frequent ovulation cycles, and the presence of uterine fibroids — all indicative of prolonged exposure to endogenous hormones — were associated with a heightened risk of thyroid cancer [41]. Luo et al. [19], in their study, observed that hysterectomy with or without oophorectomy was linked to an increased risk of thyroid cancer in postmenopausal women. Nevertheless, their findings did not corroborate the theories suggesting that external sources of estrogen increase thyroid cancer risk or that the lack of estrogen acts as a protective agent against this cancer [19]. In addition, Kim et al. [36] similarly did not support this hypothesis in the national cohort of the Korean general population. On the other hand, should elevated estrogen levels be a contributing factor to thyroid cancer, one might anticipate a reduced risk of this cancer in cases of hysterectomy, particularly when accompanied by BSO, due to the abrupt decrease in estrogen levels following BSO. One study showed that women who underwent hysterectomy and did not have an oophorectomy had no increased risk of thyroid cancer, but women with BSO had an increased risk of the disease [20]. It is evident that the hypothesis suggesting external estrogen as a risk factor for thyroid cancers or the absence of estrogen as a protective agent is weak and insufficient.

Several studies have reported that hysterectomy increases the risk of thyroid cancer [20, 46–48], but not all studies have observed this [40, 49–50]. Another study that has confused the literature on the subject is the retrospective cohort of Sweden [39]. Altmann et al. [39] found that the risk of thyroid cancer increases only in women who underwent a hysterectomy. However, the addition of BSO to the operation did not lead to an additional increase in the risk of thyroid cancer. Studies often categorize artificial menopause as resulting from surgical procedures like hysterectomy and/or bilateral oophorectomy, which have been previously linked to a heightened risk of thyroid cancer [13, 34, 50]. In contrast, research by Guonego and colleagues

Table 4. Relevant statistics for meta-analysis in determining the association between hysterectomy with or without bilateral salpingo-oophorectomy (BSO) and thyroid malignant neoplasm in trials

Study	Ln (HR)	Standard error	HR	95% CI	z	p value	Weight [%]	
							Fixed	Random
Guenego et al., 2018	0.765	0.114	2.150	1.719 to 2.689			17.95	17.98
Falconer et al., 2017	0.565	0.0993	1.760	1.449 to 2.138			23.70	19.73
Altman et al., 2016	0.565	0.0993	1.760	1.449 to 2.138			23.70	19.73
Luo et al., 2016	0.378	0.119	1.460	1.156 to 1.844			16.48	17.41
Braganza et al., 2015	0.199	0.215	1.220	0.800 to 1.860			5.04	9.30
Kabat et al., 2012	0.247	0.133	1.280	0.986 to 1.662			13.13	15.86
Total (random effects)	0.484	0.0801	1.623	1.387 to 1.899	6.046	< 0.001	100.00	100.00

HR — hazard ratio; CI — confidence interval

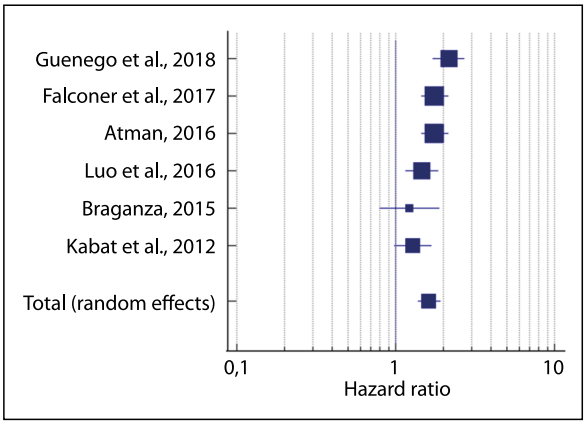


Figure 4. Forest graph in evaluating the association between hysterectomy with or without bilateral salpingo-oophorectomy (BSO) and thyroid malignant neoplasm in trials

indicated that a history of oophorectomy, especially when combined with hysterectomy, did not correlate with an increased risk of thyroid cancer, nor did it significantly alter the relationship between hysterectomy and thyroid cancer risk [37]. These findings align with those from the WHI cohort, where Kabat and team reported no significant link between the risk of thyroid cancer and bilateral oophorectomy.

Although thyroid cancer occurs more frequently in women compared to men, the specific endocrine reasons behind this disparity are yet to be completely understood. Hormone replacement therapy is not given to premenopausal patients unless bilateral oophorectomy is performed in addition to hysterectomy. Therefore, hormone replacement therapy after hysterectomy cannot clearly explain the increased risk of thyroid cancer in women with only a hysterectomy. Dysfunctional menstrual bleeding, one of the most common indications for hysterectomy worldwide, is often associated with thyroid dysfunction [51]. All types of benign thyroid lesions increase the risk of thyroid cancer, and hypothyroidism can also be found in both menopause and metrorrhagia. In this case, hysterectomy may be an intermediary for thyroid cancer that develops due to menstrual disorders, not the cause of thyroid cancer. Research in humans and animals has revealed that uterine factors influence the formation and release of various non-steroidal substances, including neurokinin, substance P, and vasoactive peptides. These factors also play a significant role in the growth of endocrine organs such as the adrenal and thyroid glands [52–53]. In this context, it is considered that hysterectomy may directly affect the thyroid gland, contributing to the carcinogenic transformation of thyroid epithelial or parafollicular cells. However, as previously discussed, there might be a connection between menstrual-related disorders and benign thyroid conditions through the hypothalamic-pituitary-thyroid axis (HPT axis), suggesting that in these cases, hysterectomy might act more as an intermediary factor rather than a direct cause. By this logic, hysterectomy itself has no biological relationship with thyroid cancer risk. Instead, it is a consequence of thyroid dysfunction that manifests in bleeding disorders and eventually results in hysterectomy. The association between a history of hysterectomy and an increased risk of thyroid cancer may be partly due to the common co-occurrence of uterine leiomyomas (a primary reason for hysterectomy) with thyroid nodules [54]. The relationship between hysterectomy and thyroid cancer may also be due to more case detection, as women with dysfunctional uterine bleeding may be greater likely to have thyroid dysfunction leading to ongoing monitoring and further investigative procedures [37].

This meta-analysis has been conducted under several limitations. One of the limitations is that the meta-analysis has not been separated by hormone replacement therapy usage because of the scarce number of previous studies and a very limited amount of information shared in the studies. In addition to this first limitation, it is believed that the distribution of patients in the studies is not homogeneous. We think heterogeneity may be caused by many reasons, such

as differences in surgical procedures or postoperative hormone replacement therapies in the studies, different quality levels, and other methods used to measure the results. Heterogeneity may be due to a known reason, such as that some of the women included in the studies were premenopausal and some were postmenopausal, or it may be due to an unexplained reason. There is a high probability that the hysterectomy performed in premenopausal women and the hysterectomy performed in postmenopausal women are likely to have different risk levels of thyroid cancer. In addition, the studies do not clarify gravida and parity numbers and lactation history, in which estrogen and progesterone balance changes. The presence of familial syndromes with increased risk of thyroid cancer, whether the patients were exposed to radiation in any period of their lives, whether the patients had thyroid nodules in their preoperative lives, and the history of anti-thyroid drug use similarly disrupt the homogeneity of the studies. Thirdly, tumor sizes, invasion of non-thyroid tissues, and metastases to lymph nodes are not known in thyroid cancers developing after hysterectomy. Nevertheless, it is believed that our results deserve careful attention regarding the fact that the findings can have positive effects on public health because of the potential to enlighten the etiological mechanisms leading to thyroid cancer. Within this context, future researches should first aim to explain the underlying mechanisms of developing thyroid cancer after hysterectomy.

Article information and declarations

Author contributions

All authors contributed to the study's conception and design, commented on previous versions of the manuscript, and at the end, read and approved the final manuscript.
Ozkan Balcin — conceptualization, methodology, resources, data curation, writing — original draft, visualization; Ilker Ercan — validation, writing — review and editing, supervision; Arda Uzunoglu — formal analysis, resources.
Each author contributed significantly to the development and design, data analysis and interpretation, and drafting or critical revision of the article for key intellectual content. They also approved the final manuscript. This manuscript is unique to this submission and is not currently under consideration by any other journal or publishing entity. Furthermore, the authors declare no financial interest or affiliation with any organization that could be perceived as influencing the subject matter of this manuscript.

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Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Fitzmaurice C, Dicker D, Pain A, et al. Global Burden of Disease Cancer Collaboration. The global burden of cancer 2013. JAMA Oncol. 2015; 1(4): 505–527, doi: 10.1001/jamaoncol.2015.0735, indexed in Pubmed: 26181261.
2. Lubitz CC, Kong CY, McMahon PM, et al. Annual financial impact of well-differentiated thyroid cancer care in the United States. Cancer. 2014; 120(9): 1345–1352, doi: 10.1002/cncr.28562, indexed in Pubmed: 24481684.
3. Schneider DF, Chen H. New developments in the diagnosis and treatment of thyroid cancer. CA Cancer J Clin. 2013; 63(6): 374–394, doi: 10.3322/caac.21195, indexed in Pubmed: 23797834.
4. Colonna M, Uhry Z, Guizard AV, et al. FRANCIM network. Recent trends in incidence, geographical distribution, and survival of papillary thyroid cancer in France. Cancer Epidemiol. 2015; 39(4): 511–518, doi: 10.1016/j.canep.2015.04.015, indexed in Pubmed: 26003877.
5. Clavel-Chapelon F, Guillas G, Tondeur L, et al. Risk of differentiated thyroid cancer in relation to adult weight, height and body shape over life: the French E3N cohort. Int J Cancer. 2010; 126(12): 2984–2990, doi: 10.1002/ijc.25066, indexed in Pubmed: 19950225.
6. Trésallet C, Seman M, Tissier F, et al. The incidence of papillary thyroid carcinoma and outcomes in operative patients according to their body mass indices. Surgery. 2014; 156(5): 1145–1152, doi: 10.1016/j.surg.2014.04.020, indexed in Pubmed: 24878452.
7. Rahbari R, Zhang L, Kebebew E. Thyroid cancer gender disparity. Future Oncol. 2010; 6(11): 1771–1779, doi: 10.2217/fon.10.127, indexed in Pubmed: 21142662.
8. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5): E359–E386, doi: 10.1002/ijc.29210, indexed in Pubmed: 25220842.
9. Moleti M, Sturniolo G, Di Mauro M, et al. Female Reproductive Factors and Differentiated Thyroid Cancer. Front Endocrinol (Lausanne). 2017; 8: 111, doi: 10.3389/fendo.2017.00111, indexed in Pubmed: 28588554.
10. Derwahl M, Nicula D. Estrogen and its role in thyroid cancer. Endocr Relat Cancer. 2014; 21(5): T273–T283, doi: 10.1530/ERC-14-0053, indexed in Pubmed: 25052473.
11. Bayram C, Valenti L, Britt H. General practice encounters with men. Aust Fam Physician. 2016; 45(4): 171–174, indexed in Pubmed: 27052128.
12. Cordina-Duverger E, Leux C, Neri M, et al. Hormonal and reproductive risk factors of papillary thyroid cancer: A population-based case-control study in France. Cancer Epidemiol. 2017; 48: 78–84, doi: 10.1016/j.canep.2017.04.001, indexed in Pubmed: 28426980.
13. Zamora-Ros R, Rinaldi S, Biessy C, et al. Reproductive and menstrual factors and risk of differentiated thyroid carcinoma: the EPIC study. Int J Cancer. 2015; 136(5): 1218–1227, doi: 10.1002/ijc.29067, indexed in Pubmed: 25041790.
14. Xhaard C, Rubino C, Cléro E, et al. Menstrual and reproductive factors in the risk of differentiated thyroid carcinoma in young women in France: a population-based case-control study. Am J Epidemiol. 2014; 180(10): 1007–1017, doi: 10.1093/aje/kwu220, indexed in Pubmed: 25269571.
15. Manole D, Schildknecht B, Gosnell B, et al. Estrogen promotes growth of human thyroid tumor cells by different molecular mechanisms. J Clin Endocrinol Metab. 2001; 86(3): 1072–1077, doi: 10.1210/jcem.86.3.7283, indexed in Pubmed: 11238488.
16. Rajoria S, Suriano R, Shanmugam A, et al. Metastatic phenotype is regulated by estrogen in thyroid cells. Thyroid. 2010; 20(1): 33–41, doi: 10.1089/thy.2009.0296, indexed in Pubmed: 20067378.
17. Xu S, Chen G, Peng W, et al. Oestrogen action on thyroid progenitor cells: relevant for the pathogenesis of thyroid nodules? J Endocrinol.

2013; 218(1): 125–133, doi: 10.1530/JOE-13-0029, indexed in Pubmed: 23645248.
18. Zane M, Parello C, Pennelli G, et al. Estrogen and thyroid cancer is a stem affair: A preliminary study. Biomed Pharmacother. 2017; 85: 399–411, doi: 10.1016/j.biopha.2016.11.043, indexed in Pubmed: 27899250.
19. Luo J, Hendryx M, Manson JE, et al. Hysterectomy, oophorectomy, and risk of thyroid cancer. J Clin Endocrinol Metab. 2016; 101(10): 3812–3819, doi: 10.1210/jc.2016-2011, indexed in Pubmed: 27459531.
20. Mack WJ, Preston-Martin S, Bernstein L, et al. Reproductive and hormonal risk factors for thyroid cancer in Los Angeles County females. Cancer Epidemiol Biomarkers Prev. 1999; 8(11): 991–997, indexed in Pubmed: 10566554.
21. Wu JM, Wechter ME, Geller EJ, et al. Hysterectomy rates in the United States, 2003. Obstet Gynecol. 2007; 110(5): 1091–1095, doi: 10.1097/01.AOG.0000285997.38553.4b, indexed in Pubmed: 17978124.
22. Tamhane N, Imudia AN, Mikhail E. Contemporary management of adnexa at the time of benign hysterectomy: a review of the literature. J Obstet Gynaecol. 2019; 39(7): 896–902, doi: 10.1080/01443615.2019.1581747, indexed in Pubmed: 31303119.
23. Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, et al. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. J Clin Endocrinol Metab. 2000; 85(2): 645–651, doi: 10.1210/jcem.85.2.6405, indexed in Pubmed: 10690870.
24. Xiangying Hu, Lili H, Yifu S. The effect of hysterectomy on ovarian blood supply and endocrine function. Climacteric. 2006; 9(4): 283–289, doi: 10.1080/13697130600865774, indexed in Pubmed: 16857658.
25. Farquhar CM, Sadler L, Harvey SA, et al. The association of hysterectomy and menopause: a prospective cohort study. BJOG. 2005; 112(7): 956–962, doi: 10.1111/j.1471-0528.2005.00696.x, indexed in Pubmed: 15957999.
26. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021; 372: n160, doi: 10.1136/bmj.n160, indexed in Pubmed: 33781993.
27. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017; 358: j4008, doi: 10.1136/bmj.j4008, indexed in Pubmed: 28935701.
28. Parmar M, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statistics in Medicine. 1998; 17(24): 2815–2834, doi: 10.1002/(sici)1097-0258(19981230)17:24<2815::aid-sim110>3.0.co;2-8, indexed in Pubmed: 9921604.
29. Hoaglin DC. Misunderstandings about Q and ‚Cochran's Q test' in meta-analysis. Stat Med. 2016; 35(4): 485–495, doi: 10.1002/sim.6632, indexed in Pubmed: 26303773.
30. Frentzel-Beyme R, Helmert U. Association between malignant tumors of the thyroid gland and exposure to environmental protective and risk factors. Rev Environ Health. 2000; 15(3): 337–358, doi: 10.1515/reveh.2000.15.3.337, indexed in Pubmed: 11048335.
31. Caini S, Gibelli B, Palli D, et al. Menstrual and reproductive history and use of exogenous sex hormones and risk of thyroid cancer among women: a meta-analysis of prospective studies. Cancer Causes Control. 2015; 26(4): 511–518, doi: 10.1007/s10552-015-0546-z, indexed in Pubmed: 25754110.
32. Mannathazhathu AS, George PS, Sudhakaran S, et al. Reproductive factors and thyroid cancer risk: meta-analysis. Head Neck. 2019; 41(12): 4199–4208, doi: 10.1002/hed.25945, indexed in Pubmed: 31595581.
33. Wang P, Lv L, Qi F, et al. Increased risk of papillary thyroid cancer related to hormonal factors in women. Tumour Biol. 2015; 36(7): 5127–5132, doi: 10.1007/s13277-015-3165-0, indexed in Pubmed: 25669169.
34. Negri E, Dal Maso L, Ron E, et al. A pooled analysis of case-control studies of thyroid cancer. II. Menstrual and reproductive factors. Cancer Causes Control. 1999; 10(2): 143–155, doi: 10.1023/a:1008880429862, indexed in Pubmed: 10231163.
35. Wilson LF, Tuesley KM, Webb PM, et al. Hysterectomy and risk of breast, colorectal, thyroid, and kidney cancer - an Australian data linkage study. Cancer Epidemiol Biomarkers Prev. 2021; 30(5): 904–911, doi: 10.1158/1055-9965.EPI-20-1670, indexed in Pubmed: 33619026.
36. Kim M, Kim BoH, Lee H, et al. Thyroid cancer after hysterectomy and oophorectomy: a nationwide cohort study. Eur J Endocrinol. 2021; 184(1): 143–151, doi: 10.1530/EJE-20-0686, indexed in Pubmed: 33112277.
37. Guenego A, Mesrine S, Dartois L, et al. Relation between hysterectomy, oophorectomy and the risk of incident differentiated thyroid cancer: The E3N cohort. Clin Endocrinol (Oxf). 2019; 90(2): 360–368, doi: 10.1111/cen.13899, indexed in Pubmed: 30390407.
38. Falconer H, Yin Li, Bellocco R, et al. Thyroid cancer after hysterectomy on benign indications: Findings from an observational cohort study in Sweden. Int J Cancer. 2017; 140(8): 1796–1801, doi: 10.1002/ijc.30606, indexed in Pubmed: 28103650.
39. Altman D, Yin Li, Falconer H. Long-term cancer risk after hysterectomy on benign indications: population-based cohort study. Int J Cancer. 2016; 138(11): 2631–2638, doi: 10.1002/ijc.30011, indexed in Pubmed: 26800386.
40. Kabat GC, Kim MY, Wactawski-Wende J, et al. Menstrual and reproductive factors, exogenous hormone use, and risk of thyroid carcinoma in postmenopausal women. Cancer Causes Control. 2012; 23(12): 2031–2040, doi: 10.1007/s10552-012-0084-x, indexed in Pubmed: 23090034.
41. Braganza MZ, Berrington de González A, Schonfeld SJ, et al. Benign breast and gynecologic conditions, reproductive and hormonal factors, and risk of thyroid cancer. Cancer Prev Res (Phila). 2014; 7(4): 418–425, doi: 10.1158/1940-6207.CAPR-13-0367, indexed in Pubmed: 24449056.
42. Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D. Cancer: epidemiology and prevention. Oxford University Press, Oxford 2018.
43. Lewy-Trenda I. Estrogen and progesterone receptors in neoplastic and non-neoplastic thyroid lesions. Pol J Pathol. 2002; 53(2): 67–72, indexed in Pubmed: 12140869.
44. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. Hum Reprod Update. 2005; 11(4): 411–423, doi: 10.1093/humupd/dmi008, indexed in Pubmed: 15817524.
45. Kim JJ, Kurita T, Bulun SE. Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer. Endocr Rev. 2013; 34(1): 130–162, doi: 10.1210/er.2012-1043, indexed in Pubmed: 23303565.
46. Luoto R, Auvinen A, Pukkala E, et al. Hysterectomy and subsequent risk of cancer. Int J Epidemiol. 1997; 26(3): 476–483, doi: 10.1093/ije/26.3.476, indexed in Pubmed: 9222770.
47. Luoto R, Grenman S, Salonen S, et al. Increased risk of thyroid cancer among women with hysterectomies. Am J Obstet Gynecol. 2003; 188(1): 45–48, doi: 10.1067/mob.2003.121, indexed in Pubmed: 12548194.
48. Rossing MA, Voigt LF, Wicklund KG, et al. Reproductive factors and risk of papillary thyroid cancer in women. Am J Epidemiol. 2000; 151(8): 765–772, doi: 10.1093/oxfordjournals.aje.a010276, indexed in Pubmed: 10965973.
49. Wong EY, Ray R, Gao DL, et al. Reproductive history, occupational exposures, and thyroid cancer risk among women textile workers in Shanghai, China. Int Arch Occup Environ Health. 2006; 79(3): 251–258, doi: 10.1007/s00420-005-0036-9, indexed in Pubmed: 16220287.
50. Truong T, Orsi L, Dubourdieu D, et al. Role of goiter and of menstrual and reproductive factors in thyroid cancer: a population-based case-control study in New Caledonia (South Pacific), a very high incidence area. Am J Epidemiol. 2005; 161(11): 1056–1065, doi: 10.1093/aje/kwi136, indexed in Pubmed: 15901626.
51. Lundholm C, Forsgren C, Johansson ALV, et al. Hysterectomy on benign indications in Sweden 1987-2003: a nationwide trend analysis. Acta Obstet Gynecol Scand. 2009; 88(1): 52–58, doi: 10.1080/00016340802596017, indexed in Pubmed: 19140043.
52. Bíró J, Eneroth P, Ritzén EM. Effects of hysterectomy and in-vivo treatment with uterine extracts on plasma concentrations of growth hormone, thyrotrophin and thyroid hormones in rats: a kinetic study. J Endocrinol. 1984; 101(3): 243–248, doi: 10.1677/joe.0.1010243, indexed in Pubmed: 6726104.
53. Patak E, Pinto FM, Story ME, et al. Functional and molecular characterization of tachykinins and tachykinin receptors in the mouse uterus. Biol Reprod. 2005; 72(5): 1125–1133, doi: 10.1095/biolreprod.104.036814, indexed in Pubmed: 15647454.
54. Kim MH, Park YeR, Lim DJ, et al. The relationship between thyroid nodules and uterine fibroids. Endocr J. 2010; 57(7): 615–621, doi: 10.1507/endocrj.k10e-024, indexed in Pubmed: 20467159.