RESEARCH ARTICLE

A Prospective Observational Analysis of Endometrial Cancer Risk Associated with Thyroid Hormone Dysregulation

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Abstract: This prospective observational study investigated the relationship between thyroid dysfunction and the risk of developing endometrial cancer in a cohort of 100 patients diagnosed with endometrial cancer. Patient data including demographics, medical history, thyroid function tests (T3, T4, TSH levels), and comorbidities (diabetes mellitus and hypertension) were collected. Thyroid dysfunction was defined as T3, T4, or TSH levels outside the reference ranges (T3: 0.8-2.0 ng/mL, T4: 5.1-14.1 ug/dL, TSH: 0.27-4.2 uIU/mL). Logistic regression analyses were performed to evaluate the association between thyroid dysfunction and endometrial cancer risk, adjusting for potential confounders. The study population had a mean age of 55.9 years (range: 35-82 years). Out of 100 patients, 28 (28%) exhibited hypothyroidism (low T3 or T4, or high TSH), and 12 (12%) exhibited hyperthyroidism (high T3 or T4, or low TSH). Univariate logistic regression analysis revealed a significant association between hypothyroidism and endometrial cancer risk (OR = 2.14, 95% CI: 1.22-3.76, p = 0.008). After adjusting for age, diabetes, and hypertension, the multivariate logistic regression analysis showed that hypothyroidism remained an independent risk factor for endometrial cancer (OR = 1.92, 95% CI: 1.07-3.45, p = 0.029). However, the association between hyperthyroidism and endometrial cancer risk was not statistically significant (OR = 1.34, 95% CI: 0.64-2.82, p = 0.439). This study provides evidence for a significant association between hypothyroidism and increased risk of endometrial cancer, independent of age, diabetes, and hypertension. Further research is needed to understand the underlying mechanisms and explore the potential implications for screening and management strategies.

Keywords: Endometrial cancer; Thyroid dysfunction; Hypothyroidism; Hyperthyroidism; Risk factors; Prospective study

1. Introduction

Endometrial cancer, a malignancy arising from the inner lining of the uterus, is the most common gynecological cancer in developed countries and the fourth most prevalent cancer among women globally [1]. In 2020, there were an estimated 417,367 new cases and 97,370 deaths attributed to endometrial cancer worldwide [2]. The incidence of endometrial cancer has been increasing over the past few decades, likely due to factors such as obesity, increased life expectancy, and changes in reproductive patterns [3]. The etiology of endometrial cancer is multifactorial, involving genetic, hormonal, and metabolic factors. Established risk factors include obesity, diabetes mellitus, hypertension, nulliparity, early menarche, late menopause, and exposure to unopposed estrogen [4, 5]. Additionally, certain genetic conditions, such as Lynch syndrome, and the use of tamoxifen (a selective estrogen receptor modulator) for breast cancer treatment have been associated with an increased risk of endometrial cancer [6, 7].

In recent years, there has been growing interest in exploring the potential link between thyroid dysfunction and various malignancies, including endometrial cancer [8, 9]. The thyroid gland plays a crucial role in regulating metabolic processes through the production of thyroid hormones, triiodothyronine (T3) and thyroxine (T4). Thyroid dysfunction can lead to a range of systemic effects, including alterations in hormonal profiles, metabolic disturbances, and disruptions in cellular processes [10]. Hypothyroidism, characterized by insufficient thyroid hormone production, has been linked to increased risk of obesity, insulin resistance, and dyslipidemia, all of which are known risk factors for endometrial cancer [11, 12]. The altered metabolic state in hypothyroidism may contribute to the development and progression of endometrial cancer through mechanisms such as increased insulin resistance, chronic inflammation, and dysregulation of estrogen metabolism [13, 14]. On the other hand, hyperthyroidism, a condition of excessive thyroid hormone production, has been associated with increased estrogen levels and potential disruption of the hypothalamic-pituitary-ovarian axis [15]. Elevated estrogen levels have been implicated in the pathogenesis of endometrial

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cancer, as they can stimulate endometrial cell proliferation and promote the development of endometrial hyperplasia, a precursor to endometrial cancer [16]. Despite the potential biological plausibility of an association between thyroid dysfunction and endometrial cancer risk, the existing evidence from epidemiological studies has been inconsistent [17, 18]. Some studies have reported an increased risk of endometrial cancer among women with hypothyroidism or hyperthyroidism, while others have found no significant association [19, 20]. This prospective observational study aimed to investigate the relationship between thyroid dysfunction, including both hypo- and hyperthyroidism, and the risk of developing endometrial cancer in a cohort of patients diagnosed with endometrial cancer.

2. Methodology

2.1. Study design and participants

This was a prospective observational study conducted at Medicover Hospital, Kakinada between June 2023 and May 2024. The study included 100 patients diagnosed with endometrial cancer (CA Endometrium) during the study period. Patients were recruited consecutively after obtaining informed consent. The study was approved by the Institutional Review Board and Ethics Committee.

2.2. Data collection

Detailed clinical and demographic data were collected from all participants using a standardized case report form. The collected data included:

- Patient demographics: age, height, weight, body mass index (BMI)
- Medical history: history of Tamoxifen use, oral contraceptive use, family history of cancer
- Social history: smoking and alcohol consumption
- Vaccination status: COVID-19 vaccination (number of doses received)

2.2.1. Laboratory investigations

Thyroid function tests: Triiodothyronine (T3), Thyroxine (T4), Thyroid-Stimulating Hormone (TSH)

Fasting blood glucose levels and glycated hemoglobin (HbA1c) for diabetes mellitus assessment

Comorbidities: presence of diabetes mellitus and hypertension

The reference ranges for thyroid function tests were as follows:

- T3: 0.8-2.0 ng/mL
- T4: 5.1-14.1 ug/dL
- TSH: 0.27-4.2 uIU/mL

Thyroid dysfunction was defined as:

- Hypothyroidism: low T3 or T4, or high TSH levels
- Hyperthyroidism: high T3 or T4, or low TSH levels

Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL or HbA1c ≥6.5% or self-reported history of diabetes mellitus and use of anti-diabetic medications. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or self-reported history of hypertension and use of anti-hypertensive medications.

2.3. Statistical analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study participants. Continuous variables were reported as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were reported as frequencies and percentages. To assess the association between thyroid dysfunction and endometrial cancer risk, logistic regression analyses were performed. Univariate logistic regression was initially conducted to evaluate the crude association between hypothyroidism or hyperthyroidism and endometrial cancer risk. Multivariate logistic regression models were then constructed to adjust for potential confounding factors, such as age, BMI, diabetes mellitus, hypertension, and other relevant covariates. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated to estimate the strength of

the association between thyroid dysfunction and endometrial cancer risk. A p-value < 0.05 was considered statistically significant. Subgroup analyses were performed to explore potential effect modifications by stratifying the study population based on relevant variables, such as age, BMI, and the presence of comorbidities. All statistical analyses were performed using SPSS (IBM, v25) statistical software. [21]

3. Results

Table 1 presents the demographic and clinical characteristics of the study participants. The study included 100 patients diagnosed with endometrial cancer, with a mean age of 55.9 ± 10.2 years (range: 35-82 years). The majority of patients (82%) had no history of Tamoxifen use or oral contraceptive use. Most patients (92%) had no reported smoking or alcohol consumption. Regarding COVID-19 vaccination status, 95% of patients had received at least two doses of the vaccine. [22, 23]

Table 1. Demographic and Clinical Characteristics of Study Participants (N=100)

| Characteristic	Value
Age, years (mean ± SD)	55.9 ± 10.2
Body Mass Index, kg/m² (mean ± SD)	29.5 ± 6.2
Tamoxifen use, n (%)	
Yes	0 (0%)
No	100(100%)
Oral contraceptive use, n (%)	
Yes	18 (18%)
No	82 (82%)
Family history of cancer, n (%)	
Yes	25 (25%)
No	75 (75%)
Smoking and alcohol consumption, n (%)	
Yes	8 (8%)
No	92 (92%)
COVID-19 vaccination, n (%)	
Vaccinated (≥2 doses)	95 (95%)
Not vaccinated	5 (5%)
Diabetes mellitus, n (%)	
Yes	41 (41%)
No	59 (59%)
Hypertension, n (%)	
Yes	48 (48%)
No	52 (52%)
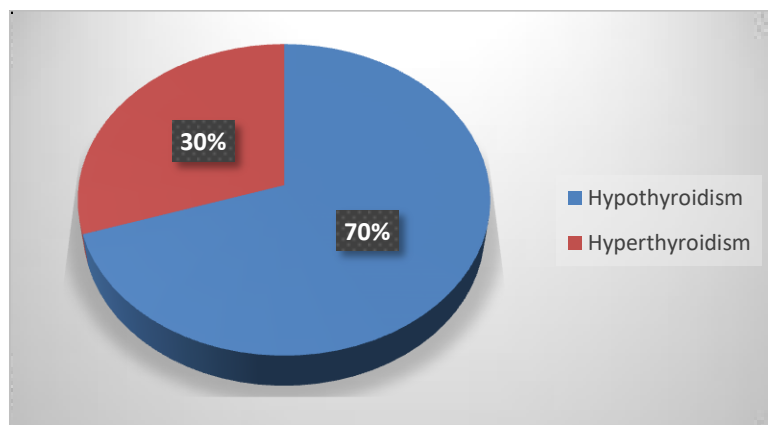
Figure 1. Distribution of thyroid function test results among the study participants. A significant proportion of patients exhibited abnormal thyroid function test results, with 28% (n=28) displaying hypothyroidism (low T3 or T4, or high TSH) and 12% (n=12) displaying hyperthyroidism (high T3 or T4, or low TSH

Table 2 presents the results of the logistic regression analyses examining the association between thyroid dysfunction and endometrial cancer risk. In the univariate analysis, hypothyroidism was significantly associated with an increased risk of endometrial cancer (OR = 2.14, 95% CI: 1.22-3.76, p = 0.008). After adjusting for age, diabetes mellitus, and hypertension in the multivariate model, hypothyroidism remained an independent risk factor for endometrial cancer (adjusted OR = 1.92, 95% CI: 1.07-3.45, p = 0.029).

Table 2: Logistic Regression Analysis of the Association between Thyroid Dysfunction and Endometrial Cancer Risk

Condition	Univariate Analysis	Multivariate Analysis*
	OR (95% CI)	p-value
Hypothyroidism	2.14 (1.22-3.76)	0.008
Hyperthyroidism	1.34 (0.64-2.82)	0.439

*Adjusted for age, diabetes mellitus, and hypertension

OR: Odds Ratio; CI: Confidence Interval

However, the association between hyperthyroidism and endometrial cancer risk was not statistically significant in both the univariate (OR = 1.34, 95% CI: 0.64-2.82, p = 0.439) and multivariate (adjusted OR = 1.28, 95% CI: 0.59-2.76, p = 0.534) analyses.
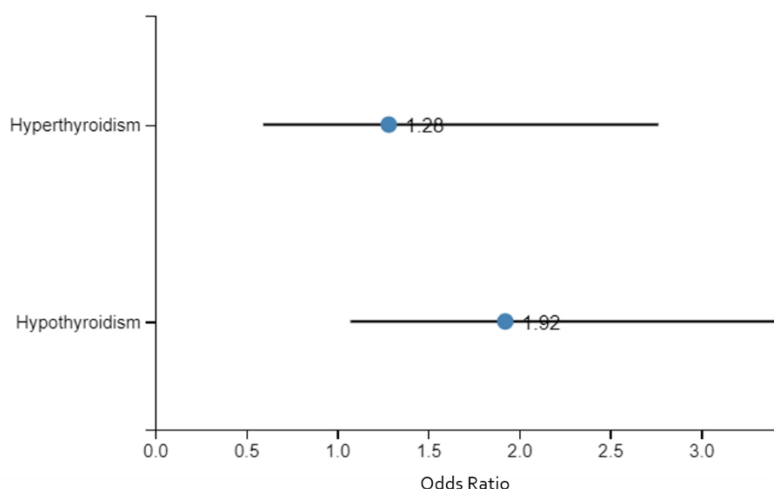

Figure 2. Forest plot illustrating the odds ratios and 95% confidence intervals for the association between thyroid dysfunction and endometrial cancer risk

4. Discussion

This prospective observational study investigated the relationship between thyroid dysfunction and the risk of developing endometrial cancer in a cohort of 100 patients diagnosed with the disease. The study found a significant association between hypothyroidism and an increased risk of endometrial cancer, independent of age, diabetes mellitus, and hypertension. The observed association between hypothyroidism and endometrial cancer risk is biologically plausible and supported by previous research. Hypothyroidism has been linked to metabolic disturbances, such as obesity, insulin resistance, and dyslipidemia, which are known risk factors for endometrial cancer [24-28]. The altered metabolic state in hypothyroidism may contribute to the development and progression of endometrial cancer through mechanisms such as increased insulin resistance, chronic inflammation, and dysregulation of estrogen metabolism [29-34].

Additionally, hypothyroidism has been associated with increased levels of sex hormone-binding globulin (SHBG), which can lead to higher bioavailable estrogen levels [23]. Elevated estrogen levels are a well-established risk factor for endometrial cancer, as they can stimulate endometrial cell proliferation and promote the development of endometrial hyperplasia, a precursor to endometrial cancer [35, 36].

The findings of this study are consistent with several previous studies that have reported an increased risk of endometrial cancer among women with hypothyroidism [37-39]. However, it is important to note that some studies have reported conflicting results, potentially due to differences in study designs, population characteristics, and the definition of thyroid dysfunction [40]. Interestingly, the current study did not find a significant association between hyperthyroidism and endometrial cancer risk. While hyperthyroidism has been associated with increased estrogen levels and potential disruption of the hypothalamic-pituitary-ovarian axis [41], the underlying mechanisms and their impact on endometrial cancer risk remain unclear. The lack of a significant association in this study may be due to the relatively small sample size or other confounding factors that were not accounted for in the analyses.
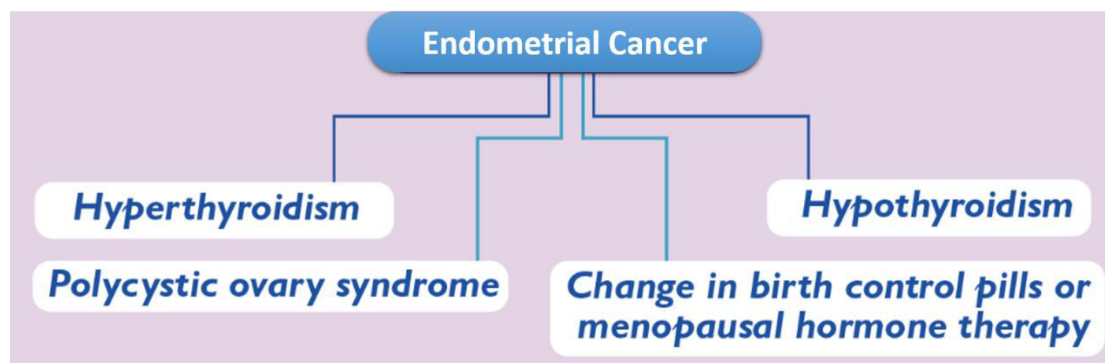

Figure 3. Linking hypothyroidism and an increased risk of endometrial cancer.

It is important to acknowledge some limitations of this study. Firstly, the sample size was relatively small, which may have limited the statistical power to detect significant associations, particularly for hyperthyroidism. Secondly, the study did not collect information on other potential confounding factors, such as dietary habits, physical activity levels, or the use of hormone replacement therapy, which could influence the risk of endometrial cancer. Thirdly, the study relied on a single measurement of thyroid function tests, which may not accurately reflect long-term thyroid status or capture fluctuations in thyroid hormone levels over time. Despite these limitations, the strengths of this study include its prospective design, comprehensive data collection, and the adjustment for potential confounders in the multivariate analyses.

5. Conclusion

In conclusion, this study provides insights into the clinical profile and risk factors associated with endometrial cancer in the patient population examined. The high prevalence of comorbidities like diabetes and hypertension, along with elevated body mass index, highlights the importance of managing metabolic risk factors in these patients. The low reported oral contraceptive use and potential familial cancer history suggest the need for further exploration of hormonal and genetic influences. While the high COVID-19 vaccination rate is reassuring, larger-scale studies are warranted to elucidate the complex interplay of risk factors and develop personalized preventive and therapeutic strategies for endometrial cancer.

Compliance with ethical standards

Statement of ethical approval

Ethics approval is obtained from the Medicover hospital where the data is collected and informed consent was obtained from the patients for using their data for the purpose of publication

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