

Hypothyroidism as a Risk Factor for Cancer: A Systematic Review and Implications for Future Studies

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Received: November 14, 2017; Accepted: December 13, 2017; Published: December 15, 2017,

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Abstract

Background: Hypothyroidism is one of the most common endocrine abnormalities and is often comorbid with additional types of cancer. There has been little study into the manner in which hypothyroidism affects future risk for these various types of cancer.

Purpose: Summarize all published cases of cancer which describe hypothyroidism as a risk or protective factor for developing cancer. From there, we hope to lay groundwork for future study that could further characterize the effect of hypothyroidism on tumorigenesis.

Data Sources: A broad PubMed search was performed on December 21, 2016, and published articles from March 1971 through the search date were included in the initial review. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) were utilized.

Study Selection: Titles were initially screened for relevance. For those that were relevant, full-text articles were reviewed, and studies describing the relationship between hypothyroidism and the development of cancer were included.

Data Extraction and Synthesis: Extracted elements from each article include type of cancer described, number of cases, how hypothyroidism was assessed, possible confounders, and what, if any, association between hypothyroidism and the given cancer was observed. Data were consolidated and stratified by tumor type.

Limitations: Limitations include the low number of studies examining the relationship of hypothyroidism with each tumor type, as well as the heterogeneity of how hypothyroidism was defined across studies.

Conclusions: Hypothyroidism was associated with an increased risk of colorectal cancer and hepatocellular carcinoma, while it was associated with a decreased risk of prostate cancer. Its relationship with breast cancer was mixed. No association was observed with endometrial and ovarian cancers, and there is a possible relationship with parathyroid and esophageal carcinomas.

Key Words: Hypothyroidism; Cancer; Risk Factor

Introduction

Hypothyroidism is one of the most frequently encountered endocrine abnormalities in medical practice [1-3]. There are various causes of hypothyroidism, including autoimmune

disorders like Hashimoto's thyroiditis, the most common cause in the United States, and iodine deficiency, the most common cause in the world [3]. Hypothyroidism can be divided into two categories: overt and subclinical (SCH). Overt hypothyroidism is characterized by a low thyroxine (T4) level (< 57.9 nmol/L) in the presence of a high thyroid stimulating hormone (TSH) level (> 4.5 mIU/L) [1]. It is often accompanied by symptoms such as lethargy, weight gain, cold intolerance, fatigue, and weakness [3-4]. Subclinical hypothyroidism, on the other hand, is characterized by a normal T4 level (57.9-169.9 nmol/L) in the presence of a high TSH level (> 4.5 mIU/L) and is often clinically asymptomatic [1-4]. Both overt and subclinical hypothyroidism is more prevalent in white women, with prevalence increasing with age. The National Health and Nutrition Examination Survey reported a prevalence of 7.9% in ages 12-79 years with that number increasing to 12.1% in those aged 80 years or older [1]. Given its prevalence in the older population, hypothyroidism is often comorbid with a number of additional conditions including various types of cancer. There has therefore been increasing research in associations between cancer and cancer treatments with a number of conditions, including the subsequent development of hypothyroidism. Several studies have demonstrated radiation for head and neck cancer can lead to hypothyroidism, months to years after radiation [5, 6]. In addition, some tyrosine-kinase inhibitors used for treatment of renal cell carcinoma, such as sunitinib and sorafenib, are known to have hypothyroidism as an adverse drug effect, with rates varying from 4-85% [7, 8].

The converse of this association, however – whether hypothyroidism can have any effect on subsequent tumorigenesis – has not been investigated to the same degree. Hypothyroidism, especially in the setting of Hashimoto's thyroiditis, has been well-studied as a potential risk factor for papillary thyroid cancer due to the chronic inflammation of the thyroid gland [9-13]. There have been very few studies, however, focused on the role of hypothyroidism as a risk factor for developing other types of cancer. Thus, the purpose of this systematic review is to evaluate the current knowledge regarding hypothyroidism and its potential relation to the development of other non-thyroid cancers.

Methods

Data Sources and Searches

Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) was followed throughout the course of this review [14]. A broad PubMed search was performed

on December 21, 2016, with the following search criteria: ((hypothyroidism [Title/Abstract]) AND cancer [Title/Abstract]) AND (risk [Title/Abstract] OR association [Title/Abstract] OR relationship [Title/Abstract]). The search was limited to articles written in English and in humans, which yielded a total of 356 articles (Figure 1). Published articles from March 1971 through the search date were included in the initial review.

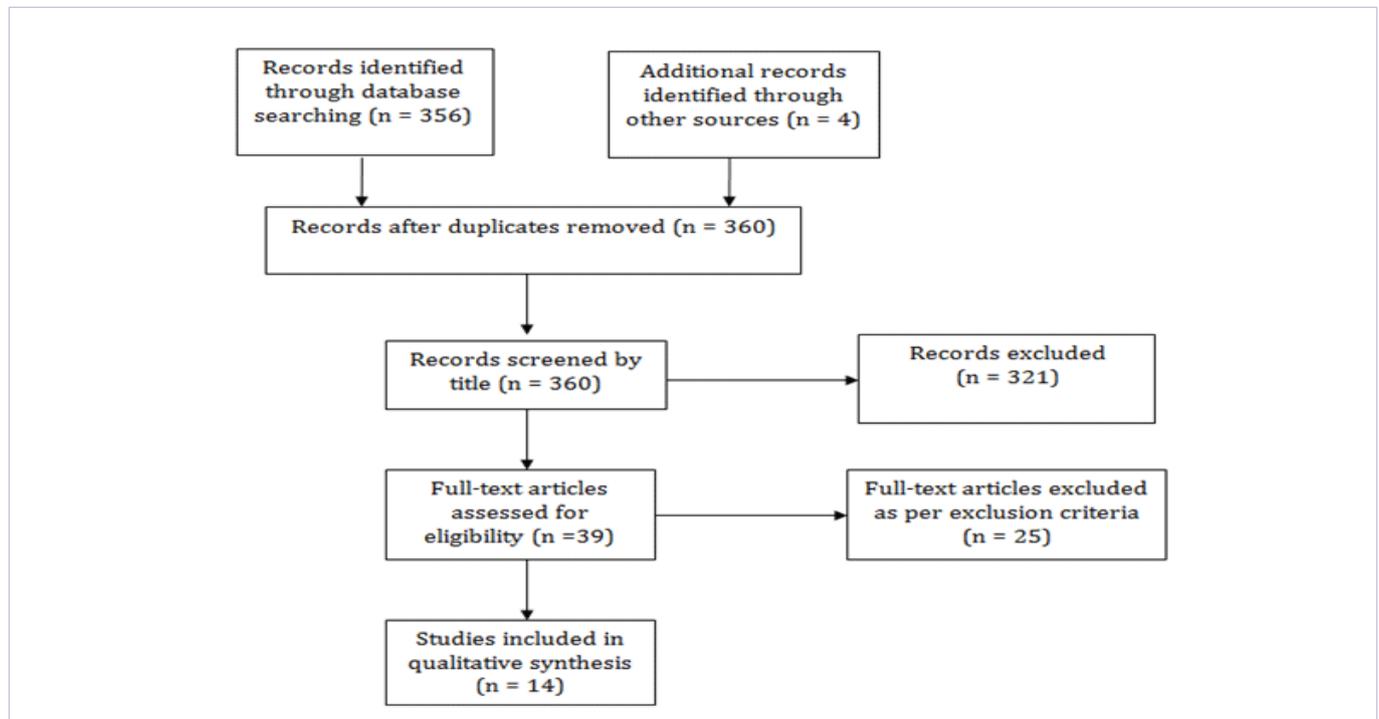


Figure 1: Flow diagram depicting the article selection process for this systematic review

Study Selection

Titles and abstracts were screened for relevance to our review. For those that were relevant, full-text articles were reviewed, and studies that described the relationship between hypothyroidism and the development of cancer were included in this review. Exclusion criteria included studies that described how cancer or cancer treatment is related to the development of hypothyroidism, as well as studies that described hypothyroidism as a risk factor for thyroid cancer. Four articles that also met our search criteria were obtained from the bibliographies of some of the selected articles. Fourteen studies were included in the final analysis [4, 15-27].

Data Extraction and Synthesis

Elements that were extracted from each article include type of cancer described, number of cases, how hypothyroidism was assessed, and what, if any, association between hypothyroidism and the given cancer was observed. Confounding variables were also taken into account and described if available. Data were consolidated from each article and stratified by tumor type. Overall analysis was via summarizing the main outcomes reported from each study.

Results

Hypothyroidism has been reported to have an effect, whether positive or negative, on a number of oncologic processes including hepatocellular, colorectal, gynecological, breast, prostate, esophageal, and parathyroid carcinoma (Table 1).

Hepatocellular Carcinoma

Two articles described hypothyroidism as a potential risk factor for hepatocellular carcinoma (HCC) [18, 23]. In the study by Reddy et al, the group performed a case-control study comparing 54 HCC cases with unknown etiology to 106 HCC cases with a known etiology of either hepatitis C or alcohol, two of the most common causes of HCC [23]. In each patient, history of hypothyroidism was documented either by a TSH of > 5.0 mIU/L (normal range 0.5-5.0 mIU/L), documented history of hypothyroidism before HCC diagnosis, or history of thyroid replacement therapy before HCC diagnosis. When adjusted for age, gender, and smoking status, they found HCC cases with unknown etiology were six times as likely to have a history of hypothyroidism as the HCC cases with known etiology, suggesting that hypothyroidism, similar to alcohol or hepatitis is an independent risk factor for developing HCC. When further

Table 1: Summary of all publications reviewed and included in the analysis [4,15-27]

Cancer Type	Author	Year	Type of Study (Level of Evidence)	Number of Cases	How Hypothyroidism was Assessed	Hypothyroidism Association
Hepatocellular	Reddy et al.	2007	Case Control (3b)	106	TSH >5.0 mIU/L	increased risk
Hepatocellular	Hassan et al.	2009	Case Control (3b)	420	patient interviews	increased risk
Colorectal	Mu et al.	2015	Case Control (3b)	273	TSH>4.2 mIU/L	increased risk
Colorectal	Boursi et al.	2015	Case Control (3b)	20,990	TSH>4.0 mg/dL	increased risk
Endometrial	Kang et al.	2013	Prospective Cohort (2b)	1,314	TSH >4.5 mIU/L	no association
Ovarian	Kang et al.	2013	Prospective Cohort (2b)	1,150	TSH >4.5 mIU/L	no association
Breast	Sandhu et al.	2006	Retrospective Cohort (2b)	89,093	medical records	decreased risk
Breast	Søgaard et al.	2016	Case Control (3b)	61,873	medical records	decreased risk
Breast	Cristofanilli et al.	2005	Retrospective Cohort (2b)	1,136	medical records	decreased risk
Breast	Kuijpers et al.	2005	Prospective Cohort (2b)	2,738	T4<12.5 pmol/L	increased risk
Breast	Simon et al.	2002	Case Control (3b)	4,575	patient interviews	no association
Prostate	Mondul et al.	2012	Case Control (3b)	401	TSH>3.0 mIU/L and T4<4.6 µg/dL	decreased risk
Esophageal	Arnott et al.	1971	Cross-Sectional (4b)	178	patient interviews and medical records	possible association may exist
Esophageal	Turkylmaz et al.	2010	Case Control (3b)	102	patient interviews	no association
Parathyroid	Loviselli et al.	1997	Case Report (5)	1	TSH 39.1 mIU/L and T4 0.40 pmol/L	possible association may exist

adjusted for other metabolic syndrome variables such as diabetes, BMI, and hypertension, the risk increased to twelve fold, further implicating hypothyroidism as an HCC risk factor.

Similar to the study by Reddy et al, Hassan et al performed a case-control study, comparing 420 HCC cases to 1,104 healthy controls [18]. All patients were interviewed for history of thyroid disorders, including hypothyroidism. They found that women with a history of hypothyroidism for greater than 10 years had a threefold increased risk for developing HCC, whereas there was no statistically significant association in men with the same history. Furthermore, when only patients without HCC risk factors such as alcoholism, hepatitis, diabetes, and smoking were included in the analysis, a two to threefold increase in HCC risk was still found in women with history of hypothyroidism, further implicating hypothyroidism as a possible independent risk factor for HCC.

Colorectal Cancer

There were two articles describing an association between hypothyroidism and the development of colorectal cancer (CRC), both of which demonstrate an increased risk of cancer in the setting of hypothyroidism [4,16]. In a study by Mu et al, the group performed a case-control study comparing 273 colorectal neoplasm cases with 819 healthy controls [4]. Subclinical hypothyroidism, which was present prior to CRC diagnosis, was defined as a TSH > 4.2 mIU/L with free T3 and T4 levels between

3.1–6.8 pmol/L (normal range 3.5-6.5 pmol/L) and 12–22 pmol/L (normal range 10-23 pmol/L) respectively. Subclinical hypothyroidism was found to be present in significantly more patients with colorectal neoplasm's (34.9%) versus the control group (24.1%). In the CRC group, a greater proportion of cancer cases were associated with SCH when compared to non-cancer cases, 2.6% versus 0.8%. Although causation cannot be determined, these data suggest that there is an association between the two disease processes.

Boursi et al also examined the relationship between hypothyroidism and CRC on a larger scale [16]. They included 20,990 colorectal cancer cases and 82,054 healthy controls, and defined hypothyroidism as a TSH > 4.0 mg/dL. They found that patients with untreated clinical or SCH had a higher risk of developing CRC with an odds ratio of 1.16 (95% CI 1.08-1.24). They also found that patients with hypothyroidism treated with thyroid replacement therapy had a lower risk of CRC when compared to those with untreated hypothyroidism, with an odds ratio of 0.92 (95% CI 0.86-0.98) Furthermore, they demonstrated a statistically significant protective association between hypothyroidism treatment and CRC that became stronger as thyroid replacement therapy duration increased, with an odds ratio of 0.88 when treated for 5 to 10 years, and 0.62 when treated for more than 10 years.

Gynecological Cancers

One article examining the association between hypothyroidism and endometrial and ovarian cancers found no association between the endocrine imbalance and these tumors [19]. Kang et al conducted a cohort study of 1,314 endometrial cancer cases and 1,150 ovarian cancer cases. They assessed for the presence of hypothyroidism via patient questionnaire, in which patients were asked about a history of physician-diagnosed hypothyroidism. The diagnosis was confirmed with a TSH level > 4.5mIU/L. A history of hypothyroidism was not found to be significantly associated with either endometrial or ovarian cancer, although a nonsignificant inverse association was found between hypothyroidism histories of more than eight years with both tumor types. The authors speculate that the nonsignificant results may have been due to an underrepresentation of the proportion of women with hypothyroidism. As hypothyroid status was determined by patient-report, it is prone to recall bias and is possible that some women did not reveal their diagnosis, thereby leading to fewer women with both hypothyroidism and cancer included in the analysis.

Breast Cancer

There have been several studies that have investigated hypothyroidism as a risk factor for breast cancer with heterogeneity among the findings [17, 20, 24-26]. In one study by Sandhu et al, authors retrospectively compared 89,093 hypothyroid patients with an equal number of euthyroid patients matched for age, income level, urban vs. rural residence location, and hormone replacement therapy status [24]. Thyroid status was determined by presence of levothyroxine on patients' medication list in the medical records. They found that hypothyroidism served a protective role in development of breast cancer in women aged 66 or older. Specifically, they report a statistically significant decrease in the incidence of breast cancer in the hypothyroid group – 0.86% versus 0.97% in the control group. In addition, they found a significant decrease in all-cause mortality among the hypothyroid women who developed breast cancer – 43.9% versus 56.1% in the breast cancer patients in the euthyroid group.

Similar to the study by Sandhu et al, a Danish study by Sogaard et al demonstrated a decreased risk of breast cancer in the setting of hypothyroidism [26]. Patients with hypothyroidism were identified using a nation-wide hospital registry with 61,873 women included. The exact definition of hypothyroidism, however, was not specified further than the recorded diagnoses obtained from medical records. Using standardized incidence ratios (SIRs), they compared expected breast cancer incidence with observed breast cancer incidence over a median follow-up time of 4.9 years. The 970 observed breast cancer cases compared to the expected 1,031 breast cancer cases yielded a SIR of 0.94, signifying a decreased risk of developing breast cancer when hypothyroidism is present. Of note, it was found that hyperthyroidism was associated with an increased risk of breast cancer, with a SIR of 1.11.

Another study describing hypothyroidism as a protective factor for breast cancer was conducted by Cristofanilli et al [17]. This retrospective chart review included 1,136 women with breast cancer and 1,088 healthy controls. Controls were matched for possible confounders such as age, family history of breast cancer, and hormone replacement therapy status. Thyroid status was obtained from medical records as laboratory values for TSH although cutoffs were not specified and free T4 values were not available. They found that the prevalence of hypothyroidism in the control group was 14.9%, whereas it was 7% in the breast cancer group, demonstrating a statistically significant negative association between hypothyroidism and breast cancer. Their results indicated that women with breast cancer were 57% less likely to have a history of hypothyroidism than healthy women were, further supporting the idea that hypothyroidism may protect against this tumor. Despite matching to eliminate possible confounders, however, absolute causation cannot be determined, but rather, an association between hypothyroidism and breast cancer can be implied.

Contrary to the above studies, one study suggested hypothyroidism increased risk for breast cancer in peri- and post-menopausal women [20]. Kuijpers et al included 2,738 women in their prospective study, following them for 8 years for the development of breast cancer. Thyroid hormone levels were obtained at time of study initiation. They found that women in the lowest 10th percentile of free T4 level (< 12.5 pmol/L) had a significantly higher risk of developing breast cancer over the observation period, with an odds ratio of 2.3.

Finally, one study performed by Simon et al failed to demonstrate an association between hypothyroidism and breast cancer [25]. They examined 4,575 breast cancer cases and 4,677 healthy controls. Thyroid status was determined via patient interviews, but no laboratory values were obtained to validate the history. Although there was an increased risk of breast cancer associated with a history of thyroid cancer (odds ratio 2.7), there was found to be no statistically significant relationship between a history of hypothyroidism and the presence of breast cancer.

Prostate Cancer

In regards to prostate cancer, one article demonstrated an association between hypothyroidism and a decreased risk for prostate cancer [22]. In this study by Mondul et al, 401 prostate cancer cases were matched to 800 healthy controls, and thyroid measurements were obtained at baseline. Men were defined as hypothyroid if both TSH was >3.0 mIU/L and T4 was <4.6 µg/dL. Initially, they found that men in the top 20th percentile of TSH had a decreased risk of prostate cancer with an odds ratio of 0.70, regardless of T4 level. More importantly, they found that when both TSH was elevated and T4 was reduced – meeting their full definition of the endocrine imbalance – hypothyroidism further served as a protective factor with an odds ratio of 0.48.

Esophageal Cancer

Two articles described the relationship between thyroid abnormalities and esophageal cancer, but no conclusive

association between the two was ascertained [15, 27]. In the first by Arnott et al in 1970, they looked at 178 patients with Squamous cell carcinoma of the esophagus [15]. They found that three of the patients had hypothyroidism diagnosed before the esophageal cancer, but no statistical analysis was performed to determine a significant causal relationship between the two. As there were few prior studies examining hypothyroidism and esophageal cancer together, and the incidence of hypothyroidism in the general population was unknown at the time, the authors considered that a possible relationship between the two could exist. Forty years later, a study by Turkyilmaz et al examined the relationship between thyroid disorders and esophageal cancer [27]. They examined 102 patients with esophageal cancer and 160 healthy controls, assessing for thyroid status via patient interviews with questions regarding past diagnoses of thyroid disorders. Although they found a statistically significant higher incidence of hyperthyroidism in the cancer patients, they did not report any association between hypothyroidism and esophageal cancer.

Parathyroid Carcinoma

Of note is one case report describing the possible association between hypothyroidism and parathyroid carcinoma [21]. This patient presented to the hospital with symptoms of hypercalcemia and confirmatory lab values, echo and CT of the neck suggested a parathyroid carcinoma. Thyroid function tests at the time were also consistent with hypothyroidism, with TSH of 39.1 mIU/L (reference range 0.5-5.5 mIU/L), free T3 of 3.28 pmol/L (reference range 3.34-7.14 pmol/L), and free T4 of 0.40 (reference range 1.08-2.39 pmol/L). Causal relationships between hypothyroidism and parathyroid carcinoma, however, remain unclear.

Conclusions

From our review, it is apparent that there appears to be an association between hypothyroidism and the risk of cancer although the direction of these relationships is variable. Hypothyroidism was consistently associated with an increased risk of colorectal cancer and hepatocellular carcinoma, while it was consistently associated with a decreased risk of prostate cancer. Its relationship with breast cancer was mixed, with some studies showing an increased risk, others showing a decreased risk, and others showing no association at all. No association was observed with endometrial and ovarian cancers, and there is a possible relationship between hypothyroidism with parathyroid and esophageal carcinomas, although there was no statistically significant data available.

There are several mechanisms that may explain the effect of hypothyroidism on cancer risk. One possibility is via its effect on thyroid hormone receptors. Thyroid hormone receptors have been shown to play important roles in cellular proliferation and malignant transformation [28-30]. Activation of these receptors prevents the ras oncogene from initiating the transcription of cyclin D1.30In the hypothyroid state, fewer thyroid hormone receptors are bound, and thus there is unopposed activation of cyclin D1 by the ras oncogene, leading to uncontrolled cellular

growth [28-30]. In this manner, thyroid hormone can be seen as a tumor suppressor, and without sufficient thyroid hormone, tumorigenesis can ensue.

Another plausible explanation is via thyroid hormones effect on the immune system, primarily through the increased generation of reactive oxidative species in the hypothyroid state [31, 32]. In addition, as lack of thyroid hormone is associated with lipid peroxidation and hyperlipidemia, progressive liver damage can result in the form of nonalcoholic steatohepatitis (NASH) [18, 33, 34]. The chronic inflammation and DNA damage that ensues from excess oxidative stress can lead to the progression of NASH to cirrhosis and later to the development of HCC. Similar to in HCC, the increased oxidative stress induced by hypothyroidism can lead to a chronic inflammatory state in the colon, thereby increasing risk of CRC [35].

In prostate cancer, a possible mechanism explaining the relationship with hypothyroidism is thyroid hormones' action on the prostate-specific integrin $\alpha\beta3$. It has been shown that thyroid hormone binds to integrin $\alpha\beta3$ on the plasma membrane, which is then responsible for increasing cell proliferation and angiogenesis, both of which are involved in cancer development [36]. With hypothyroidism, therefore, it is hypothesized that a decrease in activation of this receptor leads to less tumorigenic activity. In addition, thyroid hormone has been shown to increase the expression of androgen receptor in prostatic epithelial cell lines, which can induce cellular proliferation and subsequent cancer development [37, 38]. A lack of thyroid hormone, on the other hand, has been reported to decrease overall steroidogenesis and cellular proliferation [39]. Moreover, thyroid hormone has been shown to induce the expression of the PSA gene, which is further implicated in prostate cancer [40]. In the setting of hypothyroidism, therefore, it is plausible that the lack of thyroid hormone leads to less proliferation of prostate cells, less expression of PSA, and an overall decreased risk of developing prostate cancer.

Studies with breast cancer and thyroid hormone have suggested a similar rationale for hypothyroidism's predominantly protective effect. It has been shown *in vitro* that thyroid hormone acts on receptors in the breast to stimulate cell proliferation, which may lead to uncontrolled growth [41, 42]. Further studies *in vivo* demonstrated that thyroid hormone acts on mammary tissue to promote ductal branching and alveolar budding [42]. Through cross-recognition of thyroid hormone and estrogen by the estrogen receptor, thyroid hormone has been reported to have estrogen-like effects, thereby increasing cellular proliferation [44-46]. Similar effects of thyroid hormone with the progesterone receptor have also been demonstrated, which again leads to increased cellular growth in breast tissue [47]. As such, a decrease in the amount of thyroid hormone may reduce risk of developing breast cancer via decreased activity of these pathways. Due to the similarity of breast and prostate cancers in that both are hormonally driven, it appears that hypothyroidism may play a significant protective role in hormonally sensitive cancers. Further study into this area is warranted. In regards to the one study which described an increased risk of breast

cancer associated with hypothyroidism, however, the mechanism remains less clear.

There are some limitations of this review that can be noted. The first is the relatively low number of studies examining the relationship of hypothyroidism with each tumor type. Aside from breast cancer, which comprised five of the articles reviewed, other types of cancer had only one or two relevant studies. The power to draw strong conclusions regarding the association of hypothyroidism and the development of different cancers was thus limited. Although the initial literature search yielded several studies discussing the relationship between hypothyroidism and cancer, many of these pertained to hypothyroidism after radiation or chemotherapy or discussed basic science mechanisms. Another drawback is the heterogeneity of how hypothyroidism was defined across studies. Hypothyroid status was determined via various methods – obtaining a TSH level, obtaining thyroid hormone levels, interviewing patients about their medical history, using medical records, or some combination thereof. Even for the laboratory values of TSH and thyroid hormone, the cutoff values that were used to classify a patient as hypothyroid were not consistent across studies. The variation of the definition could have led to either an underestimate or overestimate of the true patient population with hypothyroidism, skewing the results.

Despite these limitations, this review generates a comprehensive summary of the studies to date regarding hypothyroidism as a risk factor for the development of non-thyroid cancer. It sheds light on which tumor types have been studied extensively, minimally, and not at all. Given that hypothyroidism appears to affect the risk for various tumors, further study into these relationships is warranted. For example, there have not been any studies on the association between hypothyroidism and skin cancer, the most common cancer in the United States. If it is found that skin cancer, or other common cancers, are associated with hypothyroidism, we could recommend regular early screening and correction of causal endocrine imbalances.

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