A SCOPING REVIEW OF RISK FACTORS FOR PREGNANCY-ASSOCIATED THYROID CANCER

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ABSTRACT

Background: Pregnancy-associated cancers affect 1 in 1000 women globally with breast cancer, melanoma, and thyroid cancer being the most diagnosed. While extensive research exists on pregnancy-associated breast cancer, studies on pregnancy-associated thyroid cancer (PATC) remain limited. This scoping review aimed to summarize existing evidence on PATC risk factors, and whether these risk factors differed from thyroid cancer (TC) not diagnosed during pregnancy, as well as identify gaps in current knowledge to guide future research. Peer-reviewed studies published in English-language journals investigating exposures in females aged 15 to 50 years old with thyroid cancer were eligible for inclusion in the review.

Methods: A PubMed search was not confined by a specific publication date range. The 185 identified articles published between 1987 and 2024 were imported into Covidence for review and extraction. The 'Title and Abstract' review, 'Full Text' review, and data extraction were completed in duplicate by three reviewers. Conflicts were resolved through discussion until a consensus was reached. Thirteen studies were included in the scoping review eligible for extraction. Post-extraction consensus was reached by one reviewer per the rules of Covidence Extraction Tool 1, which allowed for pre-extraction control and update of the data template. Qualitative analyses were performed. Synthesis followed.

Results: Three studies showed significant odds for developing PATC with the presence of palpable goiter or thyroid nodule (OR=20.5), history of gestational diabetes (GDM) (OR=1.24-4.3), and positive blood tests for thyroid peroxidase antibody (TPO-Ab) (OR=3.32) and thyroid globulin antibody (Tg-Ab) (OR=2.03). Only four variables were evaluated in relation to both PATC and TC; parity, history of infertility, history of miscarriage or abortion, and oral contraceptive (OC) use. None were associated with PATC; they were mixed factors with TC. For TC, parities had an increasing significant trend (OR=1.19-3.0), history of infertility were nonsignificant (OR=1.6), history of miscarriage or abortion were nonsignificant (OR=1.1-2.7), and OC use had a mixed protective (OR=0.74) or risk (OR=1.72-3.8).

Conclusions: Although, the risk factors for PATC and TC are similar according to the American Thyroid Association (ATA), findings from this review suggest palpable goiter/thyroid nodule, GDM, and autoimmunity markers as an additional PATC risk factor.

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LIST OF ABBREVIATIONS

ATA	American Thyroid Association
BMI	Body Mass Index
GDM	Gestational Diabetes
NICU	Neonatal Intensive Care Unit
OC	Oral Contraceptive
PAC	Pregnancy-Associated Cancer
PATC	Pregnancy-Associated Thyroid Cancer
PPROM	Preterm Premature Rupture of Membranes
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses – Scoping Review
TC	Thyroid Cancer
TE	Thromboembolism
WHO	World Health Organization

INTRODUCTION

Pregnancy-associated cancer (PAC) is defined as cancer diagnosed during pregnancy or within one year postpartum [2, 6]. Although relatively rare, occurring in 1 in 1000 pregnancies, its global incidence has been increasing over the past two decades [7, 9]. The timing of diagnosis presents a significant clinical challenge, as treatment decisions must account for both maternal and fetal well-being. As a result, managing PAC requires a delicate balance between ensuring optimal maternal cancer treatment and minimizing potential harm to the developing fetus. Published studies about pregnancy-associated cancer have examined the types of cancer being diagnosed, the possible exposures linked to PAC diagnosis, maternal and fetal outcomes after PAC, PAC treatment options, as well as overall PAC survival [1-42].

While the one-year postpartum period, whether that delivery is through abortion, stillbirth, or live birth [1-3, 5-6, 8-12, 14-18, 20-24], is widely accepted as part of the PAC definition, some studies extend this timeframe to two years [18, 27]. The types of cancer being diagnosed are various, possibly masking the symptoms of cancer behind the obvious pregnancy [31]. Notably, three types of cancer represent most PACs, which are breast, melanoma, and thyroid.

Current literature cites increased maternal age at first pregnancy as the primary risk factor for PAC [6]. Other possible risk factors examined over time include body mass index (BMI), maternal comorbidities, geographic region, immigration status, calendar year, family history, age at menarche, and parity [1-3, 5-6, 8-12, 14-18, 20-24]. There is evidence of an increasing trend in PAC over time [7, 9, 10]. According to a systematic review by Dalmartello et al. (2020), the incidence of PAC diagnosed per year varies from 107.1 per 100,000 in Denmark, 109.1 per 100,000 in the United States, and 145.4 per 100,000 in Australia. It should be noted that the variation in PAC could be evidence of a wide range of genetic and epigenetic influences, and/or environmental and lifestyle factors [27]. It should also be noted that most PAC studies use European, American, or Australian datasets.

Maternal and fetal obstetric outcomes in relation to PAC have been explored in prior studies. A meta-analysis conducted by Walters et al (2024) concluded that PAC made it 1.5X more likely for preterm premature rupture of the placental membrane (PPROM), 3X more potential for the pregnancy to end in preterm birth, almost 7X more likely to experience a venous thromboembolic (TE) episode, and 41X more likely to end in maternal death. Findings from

other studies have suggested a significant association between PAC and maternal outcomes including delivery by cesarian section (CS) (aOR = 1.4 to 2.08), postpartum hemorrhage (aOR = 1.1 to 1.5), and placenta previa (aOR = 1.49) [20, 22, 41]. Non-significant associations between PAC and other outcomes including GDM (aOR [95% CI]= 1.2 [0.9, 1.5]), pre-eclampsia (aOR = 1.14 to 1.3), and stillbirth (aOR = 1.02 to 1.2) have been observed in prior studies [20, 22, 41]. PAC has been associated with fetal outcomes including low birthweight (aOR = 1.2 to 1.52) and fetal growth restriction (aOR = 1.5 to 4.77), although associations were not statistically significant [20, 21, 24]. All these exposures and outcomes have been measured primarily in relation to all PACs combined.

Pregnancy-associated breast cancer (PABC) has received the most extensive attention due to it being the most commonly diagnosed PAC. According to Borges et al. (2020), there was an estimated 150,000 to 350,000 cases of PABC diagnosed during the postpartum timeframe annually around the world. Therefore, there three articles that were found during this research in the epidemiological literature regarding the exposures, treatment options, and outcomes of the mother and baby [4, 12, 18, 43]. In contrast, significantly less research has been conducted on pregnancy-associated thyroid cancer, despite ranking among the top three PACs.

Thyroid tissue, like breast tissue, is influenced by hormonal fluctuations. During pregnancy, human chorionic gonadotropin (HCG) is produced, causing progesterone and estrogen to be upregulated to downshift the immune system, support the developing fetus by allowing for uterine tissue growth and loosening ligaments, and prepare the breast tissue for lactation [13]. Studies have linked the upregulation of these sex steroids and remodeling of breast tissue for lactation to the development of breast cancer. There is clinical evidence of increased production and secretion of thyroid-stimulating hormone (TSH) during pregnancy, which may be directly stimulated by HCG, much like estrogen and progesterone [24]. However, TSH is not only increased in pregnancy; there is evidence of increased production during puberty, delivery, and during oral contraceptive use [24]. There is also evidence that thyroid cancers have estrogen receptors that influence histological diagnosis and prognosis [24].

Problem Statement

While pregnancy-associated breast cancer has been well studied, there is a lack of comprehensive research on pregnancy-associated thyroid cancer (PATC). Given the increasing incidence of PAC and the unique hormonal and biological changes during pregnancy that may influence thyroid cancer development, a deeper understanding of its risk factors, diagnostic challenges, and clinical outcomes is needed. This gap in knowledge limits the ability to develop effective screening strategies and optimize treatment protocols for affected patients. Thus, this study aims to address these gaps by summarizing the existing evidence characterizing risk factors for PATC and identifying areas for future research.

OBJECTIVE

Using a preliminary search of MEDLINE and the Cochrane Database of Systematic Reviews, no current systematic or scoping reviews on PATC were identified. Thus, we conducted a scoping review of the literature on PATC with the following objectives:

1. Identify and characterize risk factors for PATC.
2. Compare PATC risk factors to risk factors of TC diagnosed outside of pregnancy to investigate similarities and differences to identify inconsistencies.
3. Identify gaps in current knowledge to guide future research.

METHODS

Study Design

The proposed scoping review was conducted following the PRISMA-ScR Checklist [30].

Eligibility Criteria

Due to the nature of the sex-specific life event, the population of interest was restricted to females of reproductive age, defined as 15-50 years old, which aligns with the WHO [16]. Eligibility was not restricted to a specific geographic region. Those excluded from the participant population were males and females younger than 15 and older than 50.

The study focused on capturing all the risk factors that have been studied as it pertains to the outcome of pregnancy-associated thyroid cancer. This includes risk factors of external and internal origin. External factors included environmental exposures associated with thyroid disease such as radiation. Internal factors included reproductive factors, as well as biological and hormonal changes due to pregnancy. Furthermore, other measured variables considered by the eligible studies were considered.

Types of sources

PubMed was exclusively used to search for studies. PubMed is an excellent source for peer-reviewed studies, fulfilling the criteria of being peer-reviewed. Studies that were not peer-reviewed were excluded. All results were used in the initial search to get the full breadth of all available studies. No time constraints were used for the same reason of capturing all possible results regardless of when the study was published. Studies published in English were included; studies published in any other language were excluded.

This scoping review considered experimental and quasi-experimental study designs, including randomized controlled trials, non-randomized controlled trials, before-and-after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, were considered for inclusion. This review also considered descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies.

Studies that focus on qualitative data were also considered, including, but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, action research, and feminist research. Systematic reviews that met the inclusion criteria were also

considered, depending on the research question. Text and opinion papers were also considered for inclusion in this scoping review.

Search strategy

The search strategy aimed to locate published studies in publicly available databases. First, an initial limited search of PubMed was undertaken to identify articles on the topic. An academic librarian was consulted regarding how to approach the search and assist with the appropriate keywords and index terms. The search strategy was adapted for PubMed, including all identified keywords and index terms. The reference list of all included sources of evidence was screened for additional studies – none were included in this way. Keywords used to search in PubMed were (pregnancy OR pregnant OR gestational OR prenatal OR postnatal OR “post partum” OR postpartum OR parity) AND (“thyroid cancer” OR “thyroid neoplasm” OR “thyroid tumor” OR “thyroid tumour” OR “thyroid carcinoma” OR “thyroid adenoma” OR "Thyroid Neoplasms"[Mesh]) AND (“risk factor*” OR “protective factor*” OR "Risk Factors"[Mesh]). Due to the scarcity of literature on this subject, all results were used in the initial search to gather as many articles as possible. All results were imported into Covidence for review and data abstraction. Covidence is a web-based collaboration software platform that streamlines the production of systematic and other literature reviews (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.).

Study/Source of Evidence Selection

Following the search, all identified citations were collated and uploaded into Covidence, and duplicates were removed. Titles and abstracts were screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant sources were retrieved in full, and their citation details were imported into Covidence. Two independent reviewers assessed the full text of selected citations in detail against the inclusion criteria. Reasons for excluding sources of evidence in full text that do not meet the inclusion criteria were recorded and reported in the scoping review. Any disagreements between the reviewers at each stage of the selection process were resolved through discussion or with an additional reviewer or reviewers. The search results and the study inclusion process were reported in full in the final scoping review and presented in a PRISMA flow diagram [30].

Data extraction

Two independent reviewers used Covidence to extract data from sources included in the scoping review. The data included specific details about the participants, concept, context, study methods, and key findings relevant to the review question/s.

A standardized data extraction sheet was used to extract data from included studies. The reviewers discussed differences until a consensus was reached.

The data extracted included:

- Authors(s)
- Year of Publication
- Study Start and End Dates
- Study Type
- Sample Size
- Location of Study
- Age Range of Participants
- Race/Ethnicity Distribution
- Main Risk Factors Considered
- Other Risk Factors Observed
- Measurement of the Exposure/Risk Factors
- Cancer Diagnosis During Pregnancy or Postpartum

During the Covidence set-up, Extraction Tool 1 was chosen. According to the Covidence application, Extraction Tool 1 is recommended by Cochrane, which is ideal for intervention reviews. This tool choice required one of the two extraction reviewers to complete the consensus. Therefore, one of the extraction reviewers determined the consensus between the two extractions. The draft data extraction template was piloted using four eligible studies. Modifications were made to the extraction template, then published after a suitable design was created. One main feature was creating 15 blank risk factor placeholders in the Intervention section to capture all measured variables of the population of interest without prejudice. Any reviewer disagreements were resolved through discussion or with an additional reviewer.

Data analysis and presentation

After extraction, a descriptive analysis of the risk factors was completed. Data charting was completed to aid in identifying concepts and themes regarding the risk factors. The thirteen eligible studies were classified as focusing on PATC or TC. Table 1 focused on the eligible PATC studies and summarized the age ranges for maternity and age at diagnosis of the study populations. Table 2 summarized the similar variables measured in both study types describing the name of the variable and the finding for each variable, typically measured as an OR. Figure 1 and 2 were graphs created with PATC risk factors in one graph and TC risk factors another. They provide visual representations of all the measured variables within each study. They took count of how many studies measured a variable and what kind of association was found, either positive, protective, or null. Gaps in knowledge were identified and summarized.

RESULTS

The PubMed search resulted in 185 studies. All 185 study titles and abstracts were downloaded and imported into Covidence from PubMed. Two reviewers (SB, XL) sorted all 185 references by title and abstract. Neither Covidence nor the reviewers removed duplicates, and none were marked irrelevant by the automation tools in the Covidence platform. The reviewers excluded 123 studies due to their relevance to the study, leaving 62 studies to be assessed for eligibility by the inclusion and exclusion criteria.

Before full-text screening, approximately 20 full manuscripts were available in Covidence. Those unavailable manuscripts through Covidence were retrieved and downloaded to Covidence by SB. Two reviewers (SB, XL) completed the full text screening. Conflict resolution was discussed in 37 of the 62 studies. Out of the 62 articles, 49 were excluded for having the wrong outcome (n=10), wrong intervention (n=2), wrong study design (n=1), wrong patient population (n=31), or were printed in a language other than English (n=5). This left 13 studies to be reviewed for data extraction.

Data extraction occurred through Covidence on the 13 studies that fulfilled the eligibility criteria. Two reviewers (SB, JO) extracted the data separately, then one reviewer (SB) completed the consensus. The remaining studies were published between 1987 and 2024. The study designs were either case-control, retrospective cohort, or meta-analysis. Five of the 13 studies had outcomes that examined multiple pregnancy-associated cancers and included pregnancy-associated thyroid cancer or explicitly focused on pregnancy-associated thyroid cancer. The other studies examined thyroid cancer, but performed analyses that stratified by age, singling out women of reproductive age. Regardless of the timing of diagnosis of thyroid cancer, all studies investigated the association of reproductive factors with the outcome of thyroid cancer.

There were three meta-analyses in total. Between the three meta-analyses, four of the studies used were eligible in this scoping review. Negri et al (1999) and Zhou et al (2015) used Preston-Martin et al (1987) and Galanti et al (1995) in their pooled analyses. Mannathazhathu et al (2019) used Sakoda et al (2002) and Neale et al (2005) in their pooled analysis.

The five studies that examined PATC were two retrospective and three case-control studies. Women in the PATC studies had their ages reported as medians or mean, which was between 30-32 years old. Two studies considered PATC only within the 9 months of pregnancy. Jiskra et al (2022) evaluated the association of thyroid nodules or goiter discovered during

thyroid disease screening during pregnancy and PATC in two iodine sufficient populations of the Czech Republic between 1999-2012. Kitahara et al (2024) evaluated pre-diagnostic, early pregnancy blood serum sex steroid and thyroid function hormone levels and their association with PATC in the Finnish Maternity Cohort. They used blood samples drawn during the 1st and early 2nd trimester of pregnancy from the study participants between 1987 and 2015. In their analysis, they controlled for smoking, parity, and sex of the neonate.

The other three PATC studies considered PATC diagnosed postpartum up to 5 years. Bejaimal et al (2016) assessed the relationship between gestational diabetes and multiple types of PAC including PATC in a Canadian Cohort from Ontario between 1995-2008. During analysis, they adjusted for income and number of physician visits in the 3 years prior to delivery. Andersen et al. (2016) evaluated the prevalence of maternal thyroid disease, including PATC, and its association with risk factors using the Danish National Birth Cohort with records dated 1997-2003. They looked at not only PATC incidence, but also other thyroid disease incidence that could be detected during pregnancy such as hyperthyroidism, hypothyroidism, and benign goiter or nodules. Their multivariate logistic analysis focused mainly on thyroid disease. This was most likely due to the small number of thyroid cancer cases (n=45) in the cohort of 77,445 pregnant women. Finally, Chen et al (2018) assessed the association between recent pregnancy and a specific type of PATC, which is well-differentiated TC, in California in records dated from 1999 to 2012. The concentration of analysis was on tumor characteristics during which they controlled for age and ethnicity.

Table 1: ***Comparison of Age at Maternity and Age at Diagnosis in PATC Studies***

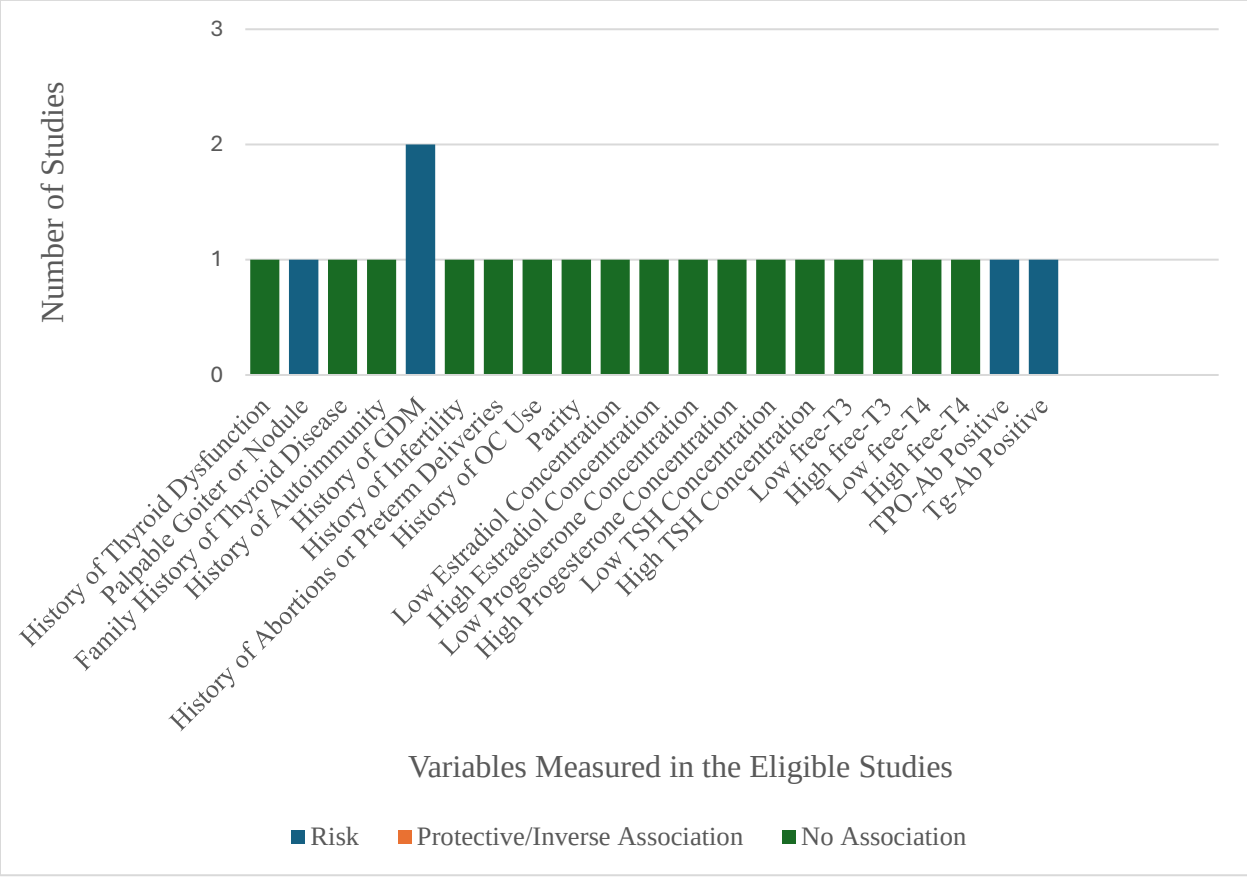
PATC	
Author (Year)	*Age at Maternity and TC Diagnosis*
Jiskra (2022)	Median (IQR) = 30.5 (27.0-33.0) *Only considered diagnosis during pregnancy
Kitahara (2024)	Median (IQR) = 30.7 (27.9-34.2) *Only considered diagnosis during pregnancy
Chen (2018)	Mean (SD) = 30.8 +/- 5.4 *PATC 5year PP Window
Andersen (2016)	Did not disclose age range *PATC 5year PP Window
Bejaimal (2015)	Maternity Median (IQR) = 32 (28-35) Diagnosis Median (IQR) = 39 (34-43) *PATC 5year PP Window

The other eight studies were included because even though they did not exclusively consider TC diagnosed during pregnancy, they measured the association of factors during the age range of interest – the reproductive age range. Seven of the eight evaluated the association of several measured variables throughout the reproductive years and through post-menopause however they were included because the authors conducted a separate analysis stratified by age, capturing the age range of eligibility for this scoping review.

Neale et al (2005) evaluated the incidence of a variety of cancers among women who delivered twins versus singletons in a Swedish cohort of women who were pregnant between 1961 and 1999. During their analysis, they controlled for twin pregnancy, parity, and mother's birth date. Negri et al (1999) sought to clarify the role of sex steroids in TC development through a meta-analysis of publication printed between 1980 and 1997. Galanti et al (1995) evaluated the association between parity and TC development in a case-control study utilizing the Swedish Birth Cohort with women aged 15-59. During analysis, they controlled for exact age of the participant and parity. He et al (2021) evaluated the association between a broad range of reproductive factors and TC in a case-control study utilizing hospital records from specific facilities in the Anhui Province in China. During their analysis, they stratified by age and controlled for BMI, income, physical activity, history of x-ray exposure, history of thyroid

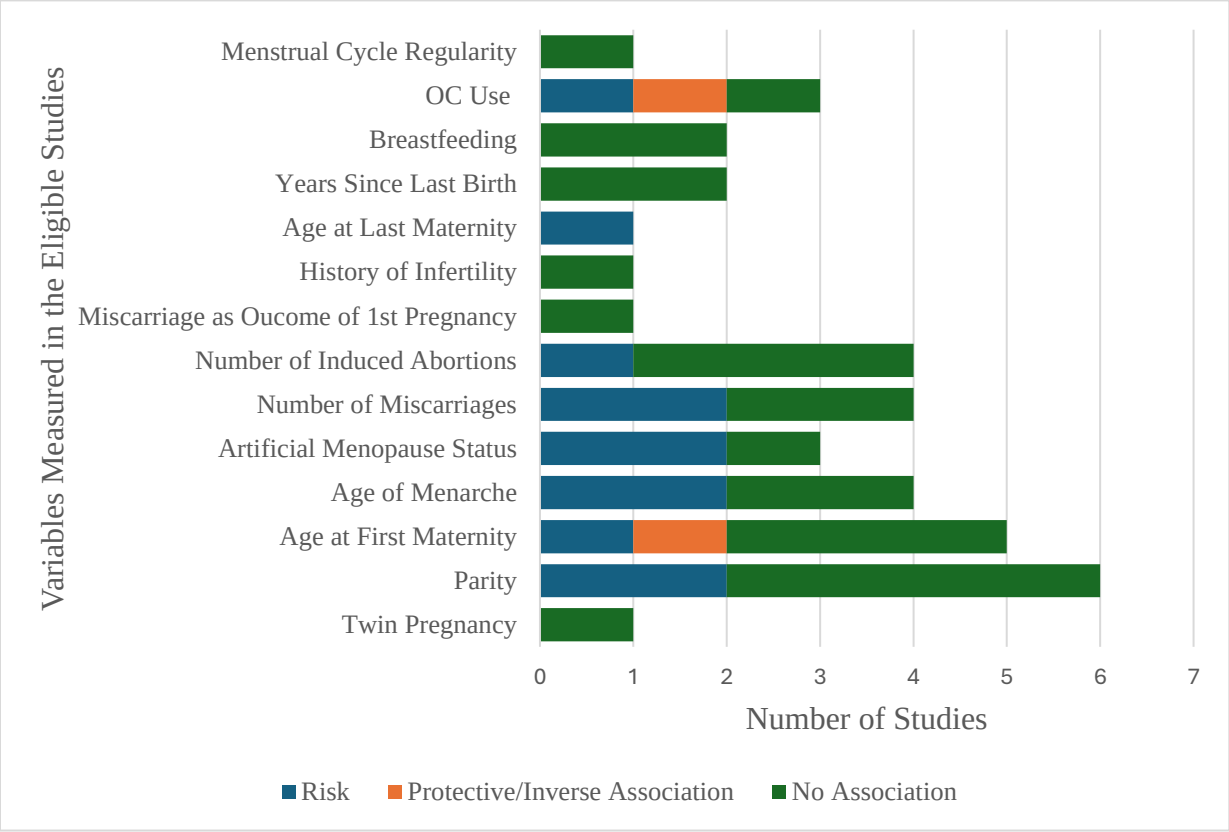
cancer or disease, parity, age at menarche, and regularity of menstruation. Sakoda et al (2002) evaluated the association between blood serum sex steroids levels and other reproductive factors and the development of TC with a case-control study design. The records they used were from women registered in the Greater Bay Area Cancer registry in California. During their analysis, they controlled for age, race/ethnicity, education level, history of goiter or nodules, history of radiation of the head or neck, history of thyroid disease, parity, and OC use. Zhou et al (2015) and Mannathazhutha et al (2019) used the meta-analysis design to investigate the association between reproductive factors and TC. Finally, Preston-Martin et al (1987) evaluated the association between elevated blood serum sex steroid and thyroid hormone levels and TC development using a case-control study design. Participants were registered with the University of Southern California Cancer Surveillance Program between 1980-1981 and were Caucasian women between 15-40 years old. They controlled for prior diagnosis of thyroid hyperplasia and non-menstruating cases.

Figure 1: ***Measured Variables and Their Frequency of Measurement in the Eligible Pregnancy-Associated Thyroid Cancer Studies***



The measured variables in the studies that examined PATC (Figure 1) included history of thyroid disease (e.g. personal and/or family), history of autoimmunity (e.g. Type I Diabetes), obstetric history (e.g. GDM, abortion, preterm deliveries, overall parity, age at first pregnancy), pre-diagnostic, and early pregnancy blood hormone levels (e.g. estradiol, progesterone, TSH, free-T3, free-T4, TPO-Ab, Tg-Ab). There were 21 measured variables considered in the five eligible PATC studies. Of these variables, palpable goiter or nodule during pregnancy, history of GDM, high estradiol, high free-T3 and high freeT-4 blood levels, and low TSH, low free-T4 blood levels, and positive blood serum results for TPO-Ab and Tg-Ab were associated with increased odds of PATC. There were four variables that a significant increase in odds of being diagnosed with PATC was observed: history of GDM (OR = 1.24 - 4.3), palpable goiter or nodule (OR = 20.5), positive TPO-Ab blood test (OR = 3.32), and positive Tg-Ab blood test (OR =2.03) [3, 17, 19]. The other variables did not reach statistical significance. The lack of significance in the majority of the measured variables could stem from the smaller sample sizes in both Jiskra et al (2021) that had an N of 397 and Kitahara et al (2023) whose case-control study compared 605 cases and 1185 controls.

Figure 2: ***Measured Variables and Their Frequency of Measurement in the Eligible Thyroid Cancer in Reproductive-Aged Women Studies***



The measured variables in the studies that examined TC diagnosed in reproductive age women included reproductive history (e.g. age at menarche, artificial menopause status, history of infertility, OC use, menstrual cycle regularity) and obstetric history (twin pregnancy, parity, age at first pregnancy and last pregnancy, history of miscarriage, history of induced abortion, years since last birth, and history of breastfeeding). There were 14 variables considered in the eight studies evaluating factors that either increase or decrease risk for TC in reproductive-aged women.

Depending on the risk factor, the strength of association for increased risk varied with the study. There were six variables with a range of OR's and number of studies reporting a risk factor as statistically significant. One of four studies measured the number of induced abortions as a significant risk (OR =1.29). The study that considered induced abortions a significant risk was Mannathazhathu et al (2019), and that measurement was a result of a pooled OR of seven studies. One of four studies measured the number of miscarriages as a significant risk (OR =

1.29). This one significant result for number of miscarriages was also from the Mannathazhathu et al (2019) study, and that measurement was also the result of a pooled OR of seven studies. Two of four studies measured age at menarche as a significant risk factor (OR = 1.1-1.34). The two studies that reported significance of age of menarche were both meta-analyses – Mannathazhathu et al (2019) and Negri et al (1999). Mannathazhathu et al (2019) measured significance for late age at menarche from a pooled OR of 10 studies, and Negri et al (1999) measured significance of each additional year leading to late age of menarche stratified by age from a pool of 14 case-control studies. One of five studies measured age at first maternity as a significant risk (OR = 3.3). Sakoda et al (2002) measured the significant odds ratio for age at first maternity for the ages 25 to 29 in a California-based case-control study that had 336 cases between the ages of 20-44 and 327 controls between 20-44. Two of six studies measured parity of three or more to be a significant risk factor (OR = 1.39 – 3.0). The two studies that measured of 3 or more parities, which were Zhou et al (2015) and Preston-Martin et al (1987). Zhou et al (2015) reported a significant risk from a pooled analysis of 8 studies. Preston-Martin et al (1987) reported a significant risk from a California-based case-control study of 108 white cases and 108 white controls. Two of three studies measured artificial menopause status to be a significant risk factor (OR = 1.4 -2.1). Both of the studies that reported significant odds were from pooled ORs from Mannathazhathu et al (2019) and Negri et al (1999).

Of the studies with protective associations, prolonged OC use of five or more years was associated with lower odds of TC in one study [OR = 0.74 (0.65, 0.84)] (Mannathazhathu, 2019) and age at first maternity under 24 was associated with lower odds of TC in another [OR = 0.54 (0.31, 0.94)] (He, 2021).

Table 2: ***Similar Measured Variables - PATC vs TC***

Measured Variable	PATC	Number of PATC Studies	TC	Number of TC Studies
History of Infertility	OR = NS (p=0.179)	1	OR (p-value) = 1.6 (p= 0.17)	1
History of Abortions or Preterm Deliveries	OR = NS (p=0.782)	1	OR (95% CI) Range = 1.1 (0.69, 1.8) – 2.7 (1.1, 7.0)*	4
History of OC Use	OR = NS (p=0.540)	1	Prolonged Use OR (95% CI) = 0.74 (0.65, 0.84) 24 Months or Less OR (95% CI) Range = 1.72 (0.76, 3.9) – 3.8 (1.5, 10.8)	3
Parity	OR = NS (p=0.506)	1	OR (95% CI) Range = 1.14 (0.66, 1.99) - 3.0 (1.3, 7.0)*	6

Only four variables that were assessed in both PATC and TC studies. These variables were history of infertility, number of abortions or miscarriages, history of OC use, and parity. There were no significant associations for history of infertility in relation to both PATC and TC. For history of abortion or miscarriage, there was no significance in PATC and no significance in three TC studies, but a significant increase of odds was reported in Mannathazhathu (2019) with a 29X higher for developing TC [1.15, 1.44 (95% CI)]. For history or current OC use, there was no significance in PATC, no significance in the He (2021) TC study [OR = 1.72 (0.76, 3.9)], significant increased protection with prolonged use in the Mannathazhathu (2019) TC study [OR = 0.74 (0.65, 0.84)], and significant increased risk with use less than 2 years in the Preston-Martin (1987) TC study [OR = 3.8 (1.5, 10.8)]. For parity, there was no significance in PATC and in three of the four studies in TC. Two TC studies observed a significant increased risk for parity

three and over, with Zhou (2015) reporting an OR of 1.39 (1.21, 1.59) and Preston-Martin (1987) reporting an OR of 3.0 (1.3, 7.0).

DISCUSSION

In 1987, Preston-Martin et al published a study investigating why females worldwide had a higher incidence of thyroid cancer that was two to three times higher than that of men [33]. Before this study, the common conclusion was that the prevalent risk factor for thyroid cancer was ionizing radiation [33]. However, they hypothesized that because most diagnosed cases were in pre-menopausal females between 20 and 50 years old, there was an association between female sex steroids and thyroid cancer [33]. Their findings provided evidence that pregnancy increases the risk of thyroid cancer, even after excluding women with prior thyroid disease diagnosis and women whose first pregnancy ended in miscarriage. The studies that follow chronologically attempted to discover other thyroid cancer risk factors within the scope of the biology of pregnancy.

Overall global PAC incidence is 100 cases per 100,000 women, compared to PATC incidence of 14 cases per 100,000 women [6, 7, 44]. In this scoping review, identified PATC risk factors from prior studies were ones of physical, clinically-verifiable evidence – palpable goiter or thyroid nodules (OR = 20.5), blood serum measurements of autoimmune antibodies TPO-Ab (OR = 3.32) and Tg-Ab (OR = 2.03), as well as having a history of gestational diabetes (OR = 1.24 – 4.3). There was a wide range of reproductive and demographic risk factors that were evaluated in the eligible studies in this scoping review. However, there were not multiple studies assessing consistency of associations between each risk factor of PATC. Most factors were assessed in a single study, as illustrated in Figure 1.

The American Thyroid Association (ATA) published 2017 guidelines addressing clinical risk factors for TC on whom to follow up with further clinical testing [5,17]. These risk factors include a personal or family history of thyroid disease or current apparent symptoms of thyroid dysfunction, past radiation exposure of the head and neck, being over 30 years old, history of autoimmune diseases (e.g. diabetes mellitus), obstetric history of miscarriage, preterm delivery, infertility, multiparity, morbid obesity, use of amiodarone or lithium, recent use of iodinated radiologic contrast, or long residency in an area of notable iodine insufficiency [17]. These clinical risk factors would be more apparent in a woman during pregnancy when clinical examinations are more regular during approximately 9 months.

Within the eligible studies, not all studies controlled for iodine and radiation. Dietary iodine and ionizing radiation exposure are two risk factors measured by global surveillance, both

of which can injure thyroid tissue and cause disease and carcinogenesis. More than half of these studies utilize datasets of women who live in Northern Europe who the Iodine Global Network (IGN) in collaboration with the WHO has recorded as being iodine insufficient.

According to the IGN, iodine sufficiency as a public health issue was not embraced until the 1990s. About a decade later, improvements were made that decreased the number of iodine-insufficient countries by about 50. For example, the Andersen et al (2016) study utilizes the Danish National Birth Cohort, including 101,032 pregnancies that occurred between 1997 and 2003. In their multivariate logistic regression, they controlled for residing in a mild to moderate iodine deficiency area. By contrast, Galanti et al (1995) used a Swedish cohort of women diagnosed with TC between 1960 and 1981. Their analysis did not control for iodine exposure, but, given that dietary iodine sufficiency was not being studied at the time of the study, it should not be held against them. However, when looking at older publications regarding TC, iodine sufficiency, and the area of study should be considered.

A knowledge gap that has become apparent while searching literature on PAC and, more specifically, PATC is that there is no consensus on the timespan to consider whether a cancer is associated with pregnancy or not. For most studies, PAC is limited to pregnancy from 3 months of gestation to 9 months of gestation plus 1 year postpartum. However, there is currently one known PAC that has evidence and consensus of current studies to extend the postpartum window to 10 years, and that is pregnancy-associated breast cancer (PABC). Out of the 13 eligible studies, one study provided evidence for extending the timeframe of PATC diagnosis, and three studies utilized a five-year postpartum window to consider TC as PATC. Beyond the timeframe, comparing the five PATC studies is difficult because there is little overlap of measured variables considered besides the one variable, GDM, which was reported by two studies. Each of the five studies took a different approach to the outcome of PATC.

Chen et al (2018), while investigating the association between pregnancy and well-differentiated thyroid cancer, chose a postpartum period of five years as the inclusion criterion in their case-control study. Five years was selected based on a study on radiation and thyroid cancer incidence following the Chernobyl nuclear accident [5]. The rationale was that the full “insult” of pregnancy has a time delay of five years [5]. Though the ATA states that the current prognosis of TC is similar whether diagnosis occurs within or outside of the pregnancy or the postpartum

timeframe, it may still be essential to differentiate the time of diagnosis because of treatment change or progression.

Within the eligible studies, not all studies controlled for iodine intake and radiation exposure especially during childhood. From the PATC studies, Jiskra et al (2021) was the only to control for iodine exposure by choosing to enroll participants from 2 hospitals within iodine sufficient regions in the Czech Republic. Chen et al (2018) noted the reason for extending the exposure period of pregnancy by 5 years postpartum was due to studies on radiation exposure and TC incidence, but they did not report controlling for it in their analysis. It is hard to compare how controlling for iodine exposure affected the OR because each study measured different risk factors. From the TC studies, Sakoda et al (2002) and He et al (2021) reported controlling for a history of radiation exposure to the head and neck or a history of x-ray exposure.

Compared to other eligible TC studies, Sakoda et al (2002) measured variables with a similar categorical scheme to at least one other study in the eligible TC study group. For the age at first maternity of 25 to 29, Sakoda et al (2002) reported an aOR of 3.3 [95% CI (1.5, 7.4)] whereas Neale et al (2005) reported an aOR 1.18 [95% CI (0.96, 1.44)]. For the risk factor of having a miscarriage, Sakoda (2002) reported an aOR of 1.4 (95% CI (0.74, 2.6)] and Preston-Martin et al (1987) reported an aOR of 2.7 [95% CI (1.1, 7.0). For the risk factor of having an induced abortion, Sakoda (2002) reported an aOR of 1.1 [95% CI (0.69, 1.8)] and Preston-Martin et al (1987) reported an aOR of 1.9 [95% CI (0.9, 4.2). In comparing Sakoda et al (2002) and Preston-Martin et al (1987), there is a pattern of the aOR becoming lower when adjusting for radiation exposure. This pattern of how the aOR is affected would have to be studied further.

Dietary iodine and ionizing radiation exposure are two risk factors measured by global surveillance, both of which can injure thyroid tissue and cause disease and carcinogenesis. According to the IGN, iodine sufficiency as a public health issue was not embraced until the 1990s [13]. About a decade later, improvements were made that decreased the number of iodine-insufficient countries by about 50 [13]. For example, the Andersen et al (2016) study utilizes the Danish National Birth Cohort, including 101,032 pregnancies that occurred between 1997 and 2003. In their multivariate logistic regression, they controlled for residing in a mild to moderate iodine deficiency area. By contrast, Galanti et al (1995) used a Swedish cohort of women diagnosed with TC between 1960 and 1981. Their analysis did not control for iodine exposure, but, dietary iodine sufficiency was not being studied at the time of the study. It would not be until

2001 that the WHO, the United Nation's Children Fund (UNICEF), and IGN would systematically and consistently monitor global dietary iodine intake [21]. However, when looking at older publications regarding TC, iodine sufficiency, and the area of study should be considered.

There were discrepancies in the findings between the reported measured variables that were similar between the PATC and TC studies. The similar variables were history of infertility, history of abortions or preterm deliveries, history of OC use, and parity. One issue with the comparison was that all the PATC measurements came from one study – Jiskra et al (2021) which stated 'NS' for no significance in place of the numerical values for the ORs. In Jiskra et al (2021), the sample size of PATC cases, or what they considered 'Malignant Nodules' could have been a contributor because a separate analysis that combined the cases of 'Benign Nodules' and 'Malignant Nodules' the total n=397 in which history of infertility [OR= 3.343 (p=0.002)]and parity [OR=2.446 (p=0.002)] were significant risks. A comparison in numerical ORs could not be made. If this were not the case, the possibility of a better comparison between similar risk factors measured in PATC and TC could be made.

The strength of this study is that it is a novel contribution to science. There have been no other scoping reviews looking specifically at PATC to date. This opens the door to further research with study designs, such as meta-analyses focusing on PATC.

The study's limitations included the limited literature search. PubMed was the only search engine utilized. This may have impacted the frequency of measured variables in PATC studies, which mostly yielded one study per variable. An extensive set of initial studies using the exact search keywords would have likely added more studies to the eligibility pool, either strengthening the associations of the measured variables already found or adding new ones to the list. The results are not generalizable as they are not representative of various ethnic and racial populations. The only regions represented are China, Northern Europe, Eastern Europe, and North America. A potential solution may be using multiple search engines and including race and ethnicity in the search keywords.

Future research should assess the timing of PATC during the postpartum period, for instance, a one-to-five-year time frame. This would facilitate comparison with other PAC studied cancers, such as melanoma where 1-year post-partum is the usual definition for PAC and breast where 10-years postpartum is the new definition. More importantly, more studies are needed

assessing the risk factors that the PATC studies in this review. Future studies should utilize clinical data for blood serum drawn during pregnancy for sex steroid and thyroid hormone assays and thyroid ultrasound performed during pregnancy. From a public health perspective, reproductive-aged women who are not pregnant should be encouraged to go to annual medical physicals in order to detect thyroid cancer and other thyroid diseases.

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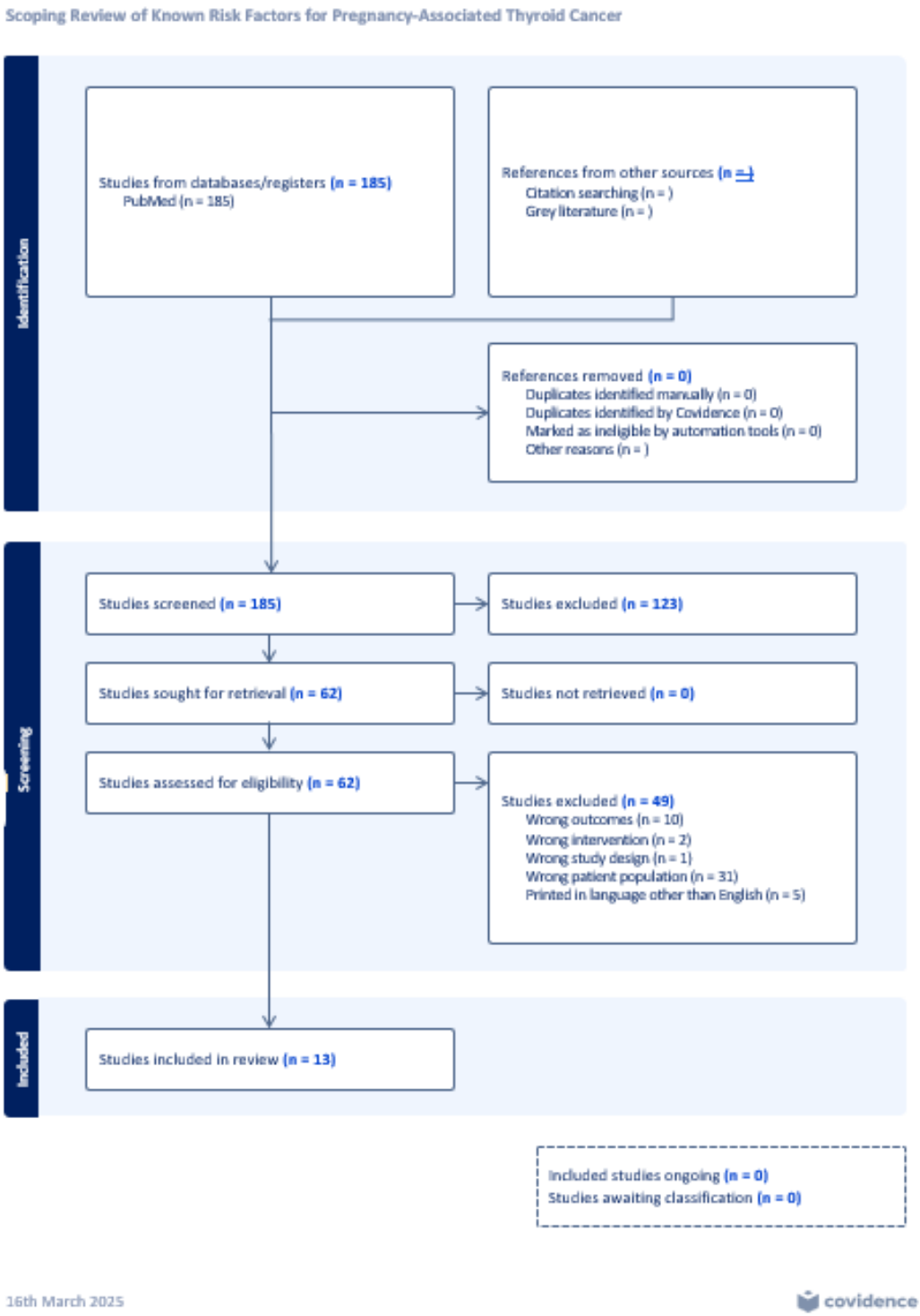
APPENDIX 1:

Figure 3: *Eligibility Flowchart*



APPENDIX 2:

Table 3: *PRISMA-ScR Checklist*

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	i
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	ii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	1-3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5-6
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	7
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	7
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	8
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	8
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	8

Table 3 (cont'd)

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	8
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	9
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	10-11
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	12-13
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	14-17
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	18
Limitations	20	Discuss the limitations of the scoping review process.	20
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	21-22
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

APPENDIX 3:

Table 4: ***Table of Selected Studies***

Author (Year)	Study Design	Objective	Participants	Sample Size	Outcomes
Jiskra (2022)	Retrospective Cohort	Evaluate associations between thyroid nodules and TC diagnosed during pregnancy	Reproductive-aged women in the Czech Republic who were pregnant between January 2004 and December 2009	N=397	PATC
Neale (2005)	Retrospective Cohort	Evaluate incidence of a variety of cancers among women who delivered twins versus singletons	Reproductive-aged women in Sweden who were pregnant between 1961 and 1996	Thyroid Cancer Cases (n=986)	Multiple cancer types, including TC
Kitahara (2024)	Case-Control	Evaluate pre-diagnostic, early pregnancy sex steroid and thyroid function hormone and autoimmunity	Participant in Finnish Maternity Cohort between 18-44 years old between 1987-2015	Cases (n=605) + Controls (n=1,185)	PATC
Negri (1999)	Meta-Analysis	Clarify female sex steroids role in TC development	Female cases and controls from pulled from publications printed between 1980 and 1997	14 case-control studies [case n=2,247, control n=3,699]	TC
Galanti (1995)	Case-Control	Evaluate the association between parity and thyroid cancer	Women aged 15-59 whose record could be link between the Swedish Birth Cohort and Swedish Cancer Registry	Cases (n=1,409) + Controls (n=7,019)	TC
Bejaimal (2016)	Case-Control	Evaluate the relationship between gestational diabetes (GDM) and cancer	Canadian women 20-50 who had given birth between 1995 and 2008	Thyroid Cancer Cases (n=592) [per 1000 person-years] =	PAC (Multiple Types, including Thyroid)

Table 4 (cont'd)

				GDM Cases (n=226) + No Diabetes (n=366)	
He (2021)	Case-Control	Evaluate the association between reproductive factors and TC	Chinese women in the Anhui Province (separate analysis done for women 50 and under)	Cases (n=335) + Controls (n=335)	TC
Sakoda (2002)	Case-Control	Evaluate the association between female sex steroids, reproductive factors and thyroid cancer	Women registered in the Greater Bay Area Cancer Registery (CA, USA) aged 20-74 (separate analysis done for reproductive age 20-44)	Cases (n=817) + Controls (n=793)	TC
Zhou (2015)	Meta-Analysis	Investigate the association between reproductive factors and TC	Case-control studies published between 1984 and 2011	21 studies	TC
Mannathazhathu (2019)	Meta-Analysis	Investigate the association between reproductive factors and TC during the past 2 decades	Case-control and cohort studies published between 1996 and 2017	17 studies	TC
Andersen (2016)	Retrospective Cohort	Evaluate the prevalence of maternal thyroid disease (diagnosed during pregnancy + 5 years postpartum) and associations of risk factors	Women recruited in the Danish National Birth Cohort between 1997 and 2003	N=77,445	Thyroid Disease (including PATC)
Preston-Martin (1987)	Case-Control	Evaluate the association between elevated female sex steroids and TSH levels and TC	Participant of University of Southern California Cancer Surveillance Program who	Cases (n=108) + Control (n=108)	TC

Table 4 (cont'd)

			were white women between 15-40 years old in 1980-1981		
Chen (2018)	Case-Control	Evaluate the association between recent pregnancy and well-differentiated TC	Participant in California Cancer Registry between 1999-2013	Cases (n=301) + Controls (n=903)	PATC

APPENDIX 4:

Table 5: ***Measured Variables and Association with Pregnancy-Associated Thyroid Cancer (Risk, Protection/Inverse Association, No Association)***

Measured Variable	Authors that Measured the Association	Sample Size	aOR (95% CI or p-value)	Association
History of Thyroid Dysfunction	Jiskra (2022)	Yes (2 of 75 participants)	NS (p=0.513)	No association
Palpable Goiter or Nodule	Jiskra (2022)	Yes (11 of 25 participants)	20.5 (p=<0.001)	Risk*
Family History of Thyroid Disease	Jiskra (2022)	Yes (2 of 51 participants)	NS (p=0.967)	No association
History of Autoimmunity	Jiskra (2022)	Yes (0 of 8 participants)	NS (p=0.845)	No association
History of GDM	Jiskra (2022)	Yes (4 of 23 participants)	4.3 (p=0.016)	Risk*
	Bejaimal (2016)	226 GDM of 592 TC cases	1.24 (1.05, 1.46)	Risk*
History of Infertility	Jiskra (2022)	Yes (4 of 38 participants)	NS (p=0.179)	No association
History of Abortions or Preterm Deliveries	Jiskra (2022)	Yes (4 of 84 participants)	NS (p=0.782)	No association
History of OC Use	Jiskra (2022)	Yes (5 of 141 participants)	NS (p=0.540)	No association
Parity	Jiskra (2022)	Yes (9 of 149 participants)	NS (p=0.506)	No association
Low Estradiol Concentration	Kitahara (2024)	29 cases/59 controls	0.96 (0.60, 1.55)	No association
High Estradiol Concentration	Kitahara (2024)	36 cases/60 controls	1.24 (0.77, 1.99)	No association
Low Progesterone Concentration	Kitahara (2024)	28 cases/59 controls	0.93 (0.58, 1.50)	No association
High Progesterone Concentration	Kitahara (2024)	25 cases/60 controls	0.78 (0.47, 1.29)	No association
Low TSH Concentration	Kitahara (2024)	41 cases/59 controls	1.40 (0.93, 2.13)	No association
High TSH Concentration	Kitahara (2024)	30 cases/60 controls	1.00 (0.64, 1.58)	No association

Table 5 (cont'd)

Low free-T3	Kitahara (2024)	20 cases/57 controls	0.69 (0.41, 1.16)	No association
High free-T3	Kitahara (2024)	36 cases/61 controls	1.11 (0.72, 1.71)	No association
Low free-T4	Kitahara (2024)	33 cases/52 controls	1.28 (0.81, 2.02)	No association
High free-T4	Kitahara (2024)	38 cases/64 controls	1.17 (0.77, 1.79)	No association
TPO-Ab Positive	Kitahara (2024)	515 cases/1123 controls	3.32 (2.33, 4.72)	Risk*
Tg-Ab Positive	Kitahara (2024)	544 cases/1124 controls	2.03 (1.41, 2.93)	Risk*

***=significant**

APPENDIX 5:

Table 6: ***Measured Variables and Association with Thyroid Cancer Diagnosed in Women During Reproductive Age (15-50 Years Old) (Risk, Protective/Inverse Association, No Association)***

Measured Variable	Authors that Measured the Association	Sample Size	aOR (95% CI)	Association
Twin Pregnancy	Neale (2005)	23 TC cases	1.10 (0.73, 1.66)	No association
Parity	Negri (1999)	[i]	1.3 (p=0.46)	No association
	Neale (2005) [3]	240 TC cases	1.19 (0.98, 1.45)	No association
	He (2021) [2 or less]	63 cases/64 controls	1.14 (0.66, 1.99)	No association
	Sakoda (2002) [Yes]	220 cases/ 189 controls	1.4 (0.98, 2.1)	No association
	Zhou (2015) [3+]	8 studies	1.39 (1.21, 1.59)	Risk*
	Preston-Martin (1987) [3+]	29 cases/ 20 controls	3.0 (1.3, 7.0)	Risk*
Age at First Maternity	Negri (1999) [per 5 year delay]	[i]	1.3 (p=0.14)	No association
	Neale (2005) [25-29]	307 TC cases	1.18 (0.96, 1.44)	No association
	He (2021) [24 or less]	72 cases/90 controls	0.54 (0.31, 0.94)	Protective*
	Sakoda (2002) – 25-29	84 cases/ 50 controls	3.3 (1.5, 7.4)	Risk*
	Preston-Martin (1987) [24+]	16 cases/ 13 controls	1.6 (0.5, 4.9)	No association
Age of Menarche	Negri (1999)	[i]	1.1 (p=0.10)	Risk*
	He (2021) [less than 13]	11 cases/9 controls	1.26 (0.48, 3.33)	No association
	Mannathazhathu (2019) – Late Age	10 studies	1.34 (1.13, 1.59)	Risk*
	Preston-Martin (1987) [12 and 13]	12 yo: 25 cases/ 27 controls 13 yo: 24 cases/ 26 controls	1.3 (0.5, 3.2)	No association
Artificial Menopause Status	Negri (1999)	[i]	1.4 (p=0.02)	Risk*
	He (2021) [Menopause by abnormal]	1 case/2 controls	0.94 (0.07, 11.95)	No association
	Mannathazhathu (2019)	6 studies	2.1 (1.58, 2.79)	Risk*
Number of Miscarriages	Negri (1999) [per miscarriage]	[i]	1.1 (p=0.6)	No association

Table 6 (cont'd)

	Sakoda (2002)	32 cases/ 25 controls	1.4 (0.74, 2.6)	No association
	Mannathazhathu (2019)	7 studies	1.29 (1.15, 1.44)	Risk*
	Preston-Martin (1987) [Ever]	17 cases/ 10 controls	2.7 (1.1, 7.0)	Risk*
Number of Induced Abortions	Negri (1999) [per abortion]	[i]	1.2 (p=0.7)	No associations
	Sakoda (2002)	65 cases/ 61 controls	1.1 (0.69, 1.8)	No associations
	Mannathazhathu (2019)	7 studies	1.29 (1.15, 1.44)	Risk*
	Preston-Martin (1987) [Ever]	22 cases/ 18 controls	1.9 (0.9, 4.2)	No associations
Miscarriage as Outcome of 1st Pregnancy	Negri (1999)	[i]	2.1 (p=0.7)	No associations
History of Infertility	Negri (1999) [Yes]	[i]	1.6 (p=0.17)	No association
Age at Last Maternity	Negri (1999) [per 5 years increase]	[i]	1.4 (p=0.03)	Risk*
Years Since Last Birth	Negri (1999) [per 5 years increase]	[i]	0.8 (p=0.37)	No association
	Galanti (1995) [uniparous within 1st year]	47 cases/ 113 controls	2.5 (1.1, 5.9)	Risk
Breastfeeding	Negri (1999) [per 12 months]	[i]	0.9 (p=0.57)	No association
	He (2021) [less than 6 months]	23 cases/14 controls	1.63 (0.75, 3.54)	No association
OC Use	He (2021) [Yes]	12 cases/11 controls	1.72 (0.76, 3.90)	No association
	Mannathazhathu (2019) [Yes, Prolonged]	12 studies	0.74 (0.65, 0.84)	Protective*
	Preston-Martin (1987) [Yes, 24 months or less]	29 cases/ 20 controls	3.8 (1.5, 10.8)	Risk
Menstrual Cycle Regularity	Preston-Martin (1987) [never regular]	7 cases/ 6 controls	1.6 (0.5, 6.2)	No association

=significant

[i]=N of cases and controls not provided in the age stratified analysis