Master's Thesis of Medicine

Reproductive and Hormonal Factors and the Risk of Thyroid Cancer in Women – A Pooled Analysis of Prospective Studies in the Asia Cohort Consortium

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Abstract

Background: Thyroid cancer is a common malignancy of the endocrine system worldwide, with a significant gender disparity in its incidence. Females are affected about three times more frequently than men, and this female predominance in thyroid cancer incidence is particularly observed in the reproductive age group. Despite the suggested mechanisms of female sex hormones in thyroid cancer etiology, the role of reproductive factors on thyroid cancer development remains unclear. Prior studies investigating this association have yielded inconsistent findings, possibly due to limited power, differences in study design or population characteristics. Additionally, there is a scarcity of population-based prospective studies specifically examining reproductive-aged women, particularly from Asian countries, which limits the interpretation of previous results on the role of reproductive factors in thyroid cancer risk among Asian women.

Objectives: This study aimed to explore the association between reproductive and hormonal factors and thyroid cancer among females in an Asian population using a large sample size. The associations were investigated both overall and for the most common histological subtype, papillary thyroid cancer. Additionally, the study examined whether the association between reproductive factors and thyroid cancer incidence differed by smoking status, body mass index (BMI), birth years, country, and thyroid cancer age of diagnosis.

Methods: A pooled analysis was conducted using individual data from ten prospective cohort studies participating in the Asia cohort consortium, that provided information on female reproductive factors and thyroid cancer follow-up. Exposure variables included age at menarche, parity status, number of children/deliveries, age at first delivery, breastfeeding status, menopausal status, age at menopause, Oral contraceptive and hormone replacement therapy

use, and hysterectomy status. Incident primary thyroid cancer cases were identified by linkage to local cancer registries and defined using the ICD-10 code C73. Histological thyroid cancer subtypes were defined based on ICD-O-3 codes. Potential covariates included baseline smoking status, alcohol drinking status, and BMI (kg/m^2). Exclusions were males, missing gender information at baseline, missing data on age at baseline, missing information on parity status/number of deliveries at baseline, those with a prior thyroid cancer diagnosis at baseline, and those with missing or invalid diagnosis or follow-up.

Statistical analyses: Descriptive statistics were used to summarize the baseline characteristics of each participating cohort. To investigate the association between reproductive factors and thyroid cancer risk, HRs and 95% CIs were calculated using Cox proportional hazards regression models by different reproductive factors for each cohort. Age was used as the time scale, and person-time accrued from baseline to the date of thyroid cancer incidence, death, or end of follow-up, whichever occurred first. Cox models were adjusted for potential covariates. The proportional hazards assumption was tested by examining the Schoenfeld residuals. Linear trends across categories of reproductive variables and thyroid cancer were tested, and *p*-value for trend reported. Pooling was conducted using a random-effects model, combining cohort-specific HRs. Heterogeneity was assessed with Cochran's *Q*-test and quantified with the I^2 statistic. Stratified analyses by smoking status, BMI, country, and birth years were conducted to examine modification of associations between reproductive factors and thyroid cancer risk. Significance of interaction was examined by the likelihood ratio test and reported as a *p*-value for interaction. Also, the study examined thyroid cancer risk based on younger (<55 years) and older (≥55 years) age at diagnosis.

Results: After exclusions, the final study population included 289,707 females from the 10 cohorts [7 from Japan (JPHC1, JPHC2, JACC, Miyagi, 3pref. Miyagi, Ohsaki, LSS), 1 from China (SWHS)

and 2 from South Korea (KMCC, KNCC)] who participated in the study. The SWHS cohort had the largest number of females (n=74,930) and KMCC cohort had the least (n=11,423). Overall, the mean (SD) age at baseline was 54 (10.6) years. The Japanese cohorts predominantly included older females, while the SWHS and Korean cohorts comprised younger females. At baseline, 7% of females were ever smokers (n=20,230), and 19% were ever alcohol drinkers (n=56,091). The mean BMI at baseline for all females was 23.4 (6.4) kg/m^2. Over a mean follow-up of 17.2 (6.6) years, a total of 1,519 incident thyroid cancer cases were identified. The KNCC (n=421) and SWHS (n=306) cohorts had the highest number of cases. Overall, the mean age at baseline and at diagnosis for thyroid cancer cases was 50.6 (9.7) and 60.2 (12.5) years, respectively. Among the 1,519 cases, 1,294 had available histological data, of which 88% (n=1,140) were papillary. Due to a considerable amount of missing information on reproductive factors and histology, the LSS cohort was excluded from the main analysis.

Older age at first delivery (≥26 vs 21-25 years) was significantly associated with thyroid cancer risk [HR 1.16 (95% CI 1.03-1.31), *p*-trend 0.003]. Non-significant positive associations were observed between number of children/deliveries, breastfeeding status, being menopausal and age at menopause and thyroid cancer risk. Age at menarche, parity status, oral contraceptive and hormone replacement therapy use were not associated with thyroid cancer risk. Similar associations were seen for papillary thyroid cancer. Advanced age at first delivery significantly increased thyroid cancer risk if diagnosed at a later age (≥55 years) [HR 1.19 (95% CI:1.02-1.39), *p*-trend 0.003], this association was weaker for diagnosis at an earlier age (<55 years). Stratified analyses by countries revealed significant interactions for the relationship between number of deliveries/children and thyroid cancer risk (*p*-interaction 0.002). Korea showed a significant positive association [HR 1.89 (95% CI 1.21-2.94), *p*-trend 0.0008 (≥5 vs 1-2 children)], while China

and Japan showed inverse non-significant associations. Birth years significantly modified the association between number of deliveries/children and thyroid cancer risk (p-interaction 0.002), with significant positive association seen in younger cohorts, especially for women born in 1950s or later [HR 2.40 (95% CI 1.12-5.18), p-trend 0.0001 (≥5 vs 1-2 children)] and no substantial trend in older cohorts.

Conclusions: To the best of my knowledge, this is the first large, pooled analysis exploring the relationship between reproductive factors and thyroid cancer risk in Asian women. Findings show that older age at first delivery was significantly associated with increased thyroid cancer risk, particularly when diagnosed later in life, posing challenges for healthcare providers due to the rising trend of delayed childbearing. Distinct patterns were observed for the number of deliveries/children and thyroid cancer risk across countries, with a significant positive association for Korea. Younger birth cohorts, mainly composed of Korean cohorts also showed increased risk with more number of deliveries/children. These findings provide additional evidence of a consistent association between the number of deliveries/children and thyroid cancer risk among Korean populations. Overall, this study fills a knowledge gap and provides valuable insights into the association between reproductive factors and thyroid cancer risk in Asian women. The study findings underscore the importance of considering country-specific, birth year-specific and thyroid cancer age of diagnosis analyses, highlighting the need for a comprehensive approach. Further research is crucial to understand the potential role of hormone status as a risk factor, especially in women, for better thyroid cancer management.

Keywords: pooled analyses of prospective studies, thyroid cancer incidence, reproductive factors, Asia cohort consortium, country-specific, birth years

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List of abbreviations

TC – thyroid cancer,
IARC – International Agency for Research on Cancer
GLOBOCAN – Global Cancer Incidence, Mortality and Prevalence, (The Global Cancer Observatory)
BMI – body mass index
TSH – thyroid stimulating hormone
ERα – estrogen receptor alpha
ERβ – estrogen receptor alpha
HCG – human chorionic gonadotropin
OC – oral contraceptive pill
HRT – hormone replacement therapy
ACC – Asia Cohort Consortium
WG – Working Group
SWHS – Shanghai Women's Health Study
JPHC1 – Japan Public Health Center-based prospective Study 1
JPHC2 – Japan Public Health Center-based prospective Study 2
JACC – Japan Collaborative Cohort Study
Miyagi – Miyagi Cohort
3pref. Miyagi – 3-Prefecture Miyagi Cohort
Ohsaki – Ohsaki National Health Insurance Cohort Study
LSS – Life Span Study Cohort
KMCC – Korean Multi-center Cancer Cohort Study
KNCC – Korean National Cancer Center Cohort
ICD-10 – International Classification of Diseases, tenth edition
ICD-O-3 – ICD for Oncology, third edition
WHO – World Health Organization
SD – standard deviation
HR(s) – hazard ratio(s)
CI(s) – confidence interval(s)

Chapter 1. Introduction

1.1. Background

1.1.1 The thyroid gland

The thyroid is a small butterfly shaped endocrine gland situated just below the larynx at the front of the lower neck (1). The structural and functional unit of the thyroid gland is the follicle, which consists of a single layer of epithelial cells surrounding a central colloid-filled cavity (Figure 1). There are two kinds of epithelial cells: follicular and parafollicular. Follicular cells produce the hormones triiodothyronine (T3) and thyroxine (T4), which are essential for the proper functioning and regulation of metabolic processes throughout the body. Parafollicular cells (or C cells) produce a hormone called calcitonin, which may play a role in bone metabolism.

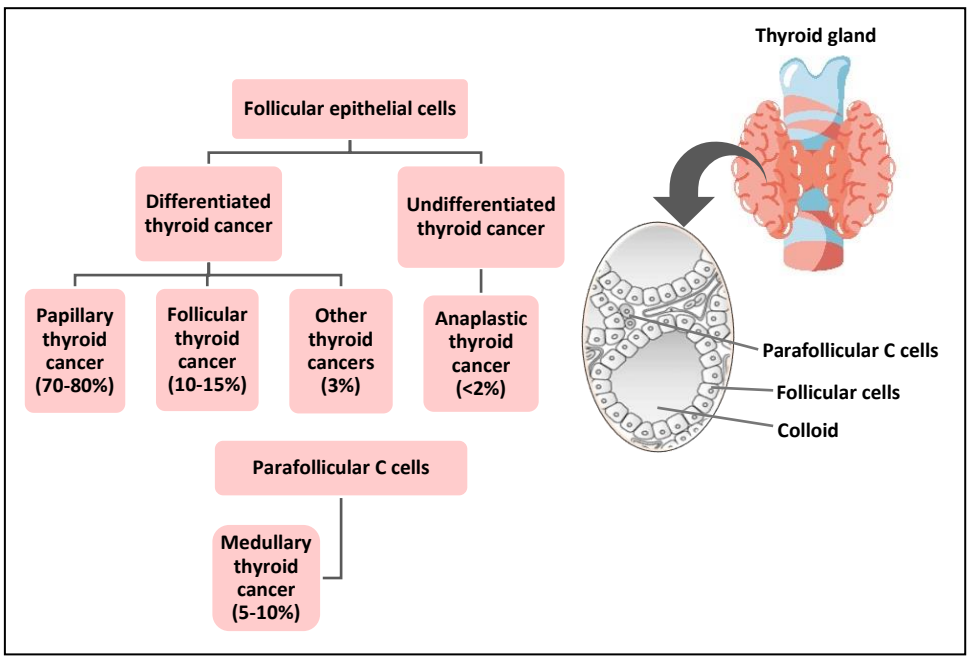

Figure 1: Thyroid gland and classification of thyroid cancer

1.1.2 Thyroid cancer – Histological types

Cancers of thyroid gland can be classified according to the origin of cells and the rate of cancer division (Figure 1)(2, 3). About 95% of all thyroid cancers arise from cells derived from the follicular epithelium, and among them differentiated papillary thyroid cancer is the most common type (70–80%). Follicular thyroid cancers also originate from the follicular cells and account for about 10–15% of cases. It tends to grow more slowly than papillary thyroid cancer. The undifferentiated anaplastic thyroid cancer is a rare and aggressive type of thyroid carcinoma that is follicular cell–derived and accounts for 2–3% of all thyroid cancers. A small proportion of thyroid cancers (about 5–10%) arise from the parafollicular cells and are known as medullary thyroid cancer (4, 5). The outlook for thyroid cancer is generally good, with a five–year survival rate of over 98% for early–stage papillary and follicular thyroid cancers, but advanced cases can be more difficult to treat and have a lower survival rate. In comparison, the anaplastic type has a much poorer prognosis and accounts for a considerable proportion of thyroid cancer deaths (6).

1.2. Epidemiology of Thyroid Cancer

1.2.1 Global incidence and trends – An overview

Thyroid carcinoma is the most common malignant cancer of the endocrine system (6–8), with a worldwide incidence that ranks ninth place among all cancers (Supplementary Figure 1).

The epidemiology of thyroid cancer is characterized by its relatively low incidence and increasing trend in many countries over the past few decades. According to the International Agency for Research on Cancer (IARC), thyroid cancer accounts for only a small proportion of all cancer cases globally, with an estimated 586,202 new cases in 2020 (Supplementary Figure 1). However, its incidence has been increasing globally in recent years, especially for papillary thyroid cancer (9). Developed countries have seen a

rapid rise in thyroid cancer cases (10, 11), and the disease is projected to become the fourth leading type of cancer across the globe (12). This trend has been observed in many countries, including the United States, Japan, South Korea, and several European countries (13).

Several factors have been explored in an attempt to explain the growing incidence of thyroid cancer worldwide, but it remains debatable whether this increase is due to increased diagnostic testing, improved access to healthcare or other genetic, lifestyle and environmental influences such as diet and obesity or exposure to radiation (14–17). However, recent global efforts have been made to tackle the impact of overdiagnosis for thyroid cancers and has led to modifications of international and national clinical practice guidelines which recommend against screening for thyroid cancer (5, 18), and the subsequent significant decline in incidence rates may indicate the mitigating harmful effects of increased diagnostic scrutiny (14, 19–21).

1.2.2 Geographical distribution and demographics

Previous studies have shown the incidence of thyroid cancer to vary by geographic area, age, and sex (12, 14).

Geographic variation in thyroid cancer incidence:

Thyroid cancer incidence rates differ substantially within and across continents. Asia has, by far, the highest observed incidence of thyroid carcinoma among all continents (Supplementary Figure 2) and the age–standardized incidence is higher in more developed countries (14.3 and 2.6 /100,000 in women and men, respectively) as compared with less developed countries (4.3 and 0.92 /100,000 in women and men, respectively)(11). The cancer is more common in certain regions of the world, such as the Pacific Islands, where there is high volcanic activity (22). Moreover, differences in radiation exposure or iodine status in populations are also suggested to play a role in the geographic variations of incidence(5).

Age distribution of thyroid cancer:

In comparison to most other types of adult cancers, thyroid cancer occurs most frequently at younger ages. especially in women, who are commonly diagnosed between 30 to 50 years old. According to the cancer statistics for adolescents and young adults (aged 15–39 years) as defined by the National Cancer Institute, thyroid cancer has been reported as the most commonly diagnosed cancer in adolescents and young adults aged 20–29 years in both sexes combined (23).

Gender differences:

Thyroid cancer is nearly three times more common in women than in men, with a global age-standardized incidence rate of 10.1 /100,000 in females and 3.1 /100,000 in males (12). The cancer accounts for 1 in every 20 cancers that is diagnosed in women (12),

1.2.3 East & West variations: Insights on risk factors

The epidemiology of thyroid cancer varies between Eastern and Western countries, reflecting differences in risk factors, genetics, and environmental or lifestyle influences. Some of the key differences are as follows, particularly with an insight on risk factors:

East-West variation of incidence: The incidence of thyroid cancer is generally higher in East Asian countries, such as South Korea, Japan, and China, compared to Western countries, such as the United States and Canada. In fact, South Korea has the highest incidence of thyroid cancer in the world with an annual percent change of about 24%–25%, which has been suggested to be almost entirely due to increased detection and diagnosis (24). However, it is worth noting that, while increased diagnostic testing may have been the primary driver of the rapid increase in incidence in Eastern populations, there is evidence suggesting that etiologic risk factors may have also contributed to the rise in thyroid cancer, particularly among Korean adolescents and young adults who are

unlikely to participate in thyroid cancer screening, as highlighted in an age–period–cohort analysis (25).

Sex–specific incidence: detailed in Chapter 1.3.

Age–specific incidence: In Asian countries, the incidence of thyroid cancer peaks in the third and fourth decades of life(26), while in Western countries, the peak incidence occurs in the fifth and sixth decades of life. This age–specific incidence pattern has been attributed to variations in risk factor exposure.

Iodine Intake: Differences in iodine intake and iodine status between populations might be one explanation. In some parts of East Asia, such as Japan and South Korea (27, 28), iodine intake is high due to the consumption of seaweed, which may contribute to the earlier age of peak incidence of thyroid cancer. Another factor that might contribute to the earlier onset of thyroid cancer in East Asian countries is differences in genetic mutations or environmental exposures to radiation or other carcinogens(5, 29).

Radiation Exposure: While ionizing radiation exposure is a well–established risk factor for thyroid cancer in both East and the West, the extent and sources of radiation exposure can vary between regions. For instance, in Japan, exposure to ionizing radiation from the atomic bombings (30) and from the Fukushima nuclear disaster (31) has been a concern, whereas in some Western countries, exposure to medical radiation is a more common source of ionizing radiation exposure (32). Furthermore, in addition to ionizing radiation, the carcinogenic effect due to exposure to the radiofrequency electromagnetic fields (RF–EMFs) from mobile and cordless phones have also been considered in the context (33).

Genetic Factors and benign thyroid disease: Several genetic and epigenetic alterations contribute to thyroid cancer development, with *BRAF* and *RET* mutations frequently observed in papillary thyroid cancer. Recent discoveries have implicated *NTRK* and *ALK* mutations to the cancer. These gene mutations may be more common in some regions than others (34). Having first–degree relatives with thyroid cancer has also been linked to an increased

likelihood of developing the disease. Moreover, a history of benign thyroid disease is associated with an increased risk of the cancer, and the prevalence of these disorders may vary regionally.

Body Mass Index: Greater adiposity has consistently been linked to an increased risk of thyroid cancer in both Eastern and Western populations. Several studies have shown a positive correlation between body mass index (BMI), weight, waist and hip circumference and waist-to-hip ratio and thyroid cancer in a dose-dependent manner (35, 36). Interestingly, higher BMI during childhood and adolescence has shown a stronger association with adult thyroid cancer compared to adult BMI (37). While the positive association between BMI and thyroid cancer risk is reported in both Eastern and Western countries, the strength of the association and the specific subtypes of thyroid cancer affected may vary. These differences can be attributed to variations in the prevalence of obesity and overweight between these populations (38). Western populations tend to have higher average BMIs compared to Eastern populations, which can be attributed to differences in dietary patterns, lifestyle, and cultural norms surrounding body weight. As a result, the effects of BMI on thyroid cancer risk in the two populations may lead to different patterns of risk.

Cigarette Smoking: Epidemiological observations demonstrate a reduced risk of thyroid cancer among individuals who smoke, in both sexes (39-43). This inverse association has been observed in studies conducted in Western populations; however, the findings among Asian populations have been less conclusive. Proposed explanations include anti-inflammatory effects of nicotine, a major component of cigarette smoke, and reduced levels of thyroid-stimulating hormone (TSH) due to smoking (44, 45). However, the evidence supporting these hypotheses is not yet definitive. Furthermore, it is challenging to determine whether the observed trends in thyroid cancer incidence are directly attributable to or caused by the decrease in smoking prevalence in the West and elsewhere around the world.

1.3. Gender Disparity in Thyroid Cancer

1.3.1 Overview and in relation to histology

Uniquely, despite being a non-reproductive cancer, thyroid cancer exhibits a strong female tendency, with women having an incidence rate approximately three-fold higher than that of men (**Figure 2**). with a global age-standardized incidence rate of 10.1 per 100,000 in females and 3.1 per 100,000 in males. The gender difference in thyroid cancer is also specific to the histologic subtype. The more aggressive types of thyroid cancer, anaplastic and medullary, have similar incidence rates in males and females. While differentiated thyroid cancers, such as the follicular thyroid cancer and papillary thyroid cancer, are more common in woman (46).

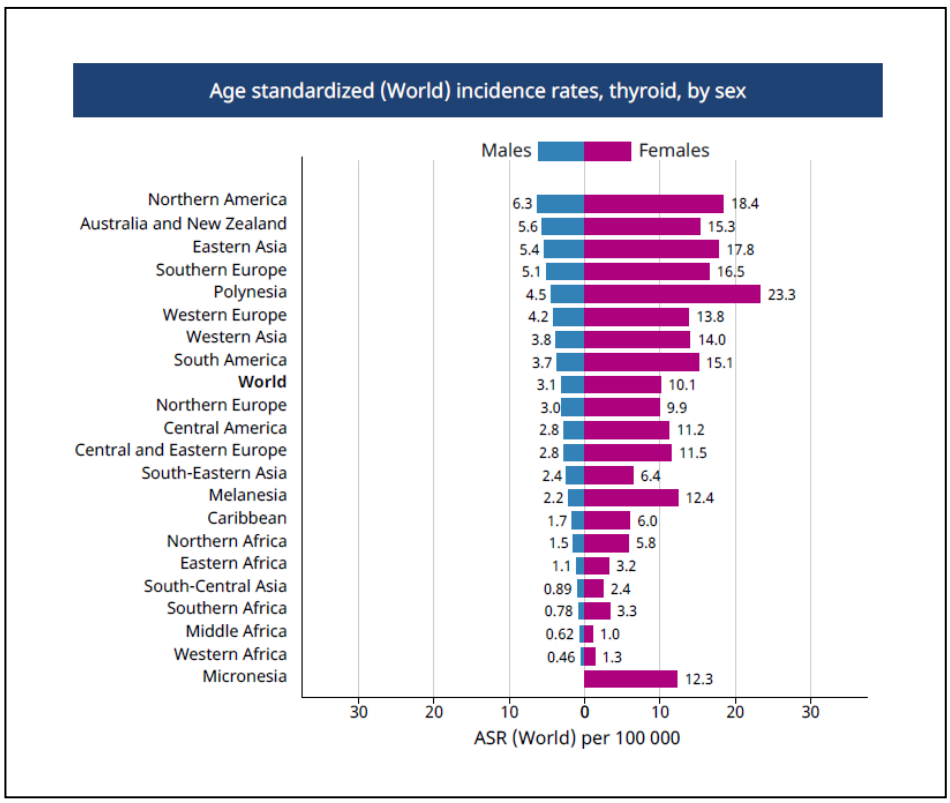

Figure 2: Gender disparity in thyroid cancer incidence, worldwide
Source: GLOBOCAN, IARC https://gco.iarc.fr/today/

1.3.2 Across age groups and geographic regions

The significant gender disparity in thyroid cancer incidence, with a female predominance has been observed particularly in the reproductive age group (46). According to The Global Cancer Observatory, thyroid cancer is the third most common cancer in women between the ages of 25 and 45, after breast and cervical cancer (Supplementary Figure 3). Furthermore, this gender difference in incidence is consistently evident across various geographic regions in both Eastern and Western countries, suggesting that it is not solely driven by factors such as environmental exposure or genetic predisposition. In some East Asian countries, the gender disparity is even more pronounced, for example, in South Korea, the incidence of thyroid cancer in women is more than five times higher than in men (47).

1.3.3 Possible reasons for gender disparity

Given the female predominance in thyroid cancer incidence compared to men, especially during the reproductive age, female sex hormones have been suggested to play a role in thyroid cancer etiology. Also, although radiation exposure, diet, and nutritional factors (48–50) are all well-known risk factors for thyroid cancer, there is no conclusive evidence that these factors contribute to the significant gender disparities. Alternately, differences in healthcare-seeking behavior, with greater use of medical care by women as compared to men more so during reproductive years may increase the opportunity for incidental diagnosis and contribute to the gender difference in incidence. However, this is unlikely to fully explain the gender disparity in thyroid cancer incidence, as studies have shown that the gender difference persists even after accounting for differences in healthcare-seeking behavior (9).

1.4. Reproductive Factors And Thyroid Cancer

Considering reproductive and hormonal factors as potential risk factors to account for gender disparity, a major effort has focused on examining their association with thyroid cancer (38-40, 51-82).

1.4.1 Literature review: Inconsistent findings

Factors such as age at menarche, age at menopause, having given birth, parity or number of children, age at first birth, breastfeeding, exogenous hormone use have been correlated with thyroid cancer incidence. While several lines of evidence suggest that these factors may contribute to the increased risk of thyroid cancer in women, others have demonstrated reduced risks or no associations(83).

Age at menarche, menopause, and age at menopause:

Both early menarche and late age at menarche have been associated with increased risk of thyroid cancer. While several studies suggested early menarche to be associated with greater risk, a meta-analysis of 9 prospective cohort and 10 case-control studies showed positive association between late menarche (≥ 14 years) and risk of thyroid cancer (summary OR = 1.49 95% CI: 1.19 – 1.86)(52).

A number of studies have assessed whether menopausal status, age at menopause and type of menopause were associated with thyroid cancer risk. A meta-analysis of 24 prospective studies suggested a reduced risk for post-menopausal women (summary RR = 0.79, 95% CI: 0.62 – 1.01)(61) and a meta-analysis of 13 cohort and 12 case-control studies report an increased risk for older age at menopause (summary RR = 1.24, 95% CI 1.00 1.53)(60). Hysterectomy (surgical removal of uterus) has been consistently associated with an increased risk of thyroid cancer.

Pregnancy, number of children, age at childbirth and breastfeeding:

Some studies have suggested that nulliparous women have similar risk of thyroid cancer compared to parous women. While several meta-analyses demonstrated positive associations between number of pregnancies/children and thyroid cancer(52, 59).

Women who have their first child at a later age (after age 30) have been shown to have an increased risk of thyroid cancer(61, 76), while some other studies did not report any association.

Findings from a meta-analysis of 13 cohort and 12 case-control studies suggested that breastfeeding has a protective role against developing thyroid cancer(60).

Exogenous hormone use:

More than a few studies have investigated he role of oral contraceptive pills (OC) and post-menopausal hormonal therapy with the risk of thyroid cancer. Results have shown association in both directions. A meta-analysis of case-control and cohort studies suggested a protective effect in thyroid cancer among prolonged OC users (summary OR = 0.78, 95% CI: 0.65 – 0.92).

It should be noted that while these reproductive factors have been linked to an increased risk of thyroid cancer in women(84), the precise mechanisms by which they may increase the risk are not fully understood. Further research is needed to fully understand the complex interplay of factors that contribute to the development of thyroid cancer.

1.4.2 Summary of literature search

Table 1 contains details on the literature search related to reproductive factors and thyroid cancer.

Table 1: Summary of previous studies for reproductive factors and thyroid cancer risk

Author, Year	Country	Study design	Findings, Association with thyroid cancer risk
Schubart JR, et al. 2021	USA (Nurses' Health Study II)	Prospective Study	620 cases Significant linear trends toward an increased thyroid cancer for advancing **age at first birth** and later **age at menopause**. Longer reproductive years increased risk of thyroid cancer (≥41 vs ≤30 years, RR = 2.20; 95% CI 1.19–4.06). **Parity number**, months of **breastfeeding**, **age at menarche**, **menopausal status**, and **postmenopausal hormone therapy** were not associated with the risk of thyroid cancer
Wang M, et al. 2021	Zhejiang, China	Hospital-based 1:1 matched case–control study	2261 pairs of female subjects Decreased occurrence of thyroid cancer with later **age at first pregnancy** (> 25 vs. ≦ 20 years, OR= 0.47, 95% CI 0.23–0.96) and longer duration of **breast feeding** (6–12 vs. ≦ 6 months, OR= 0.49, 95% CI 0.24–0.98
He JL, et al. 2021	Anhui Province, China	Hospital-based case-control study	335 papillary thyroid cancer cases Early **age at menarche** (OR ≤13 vs >13years = 2.40, 95 % CI 1.12−5.13), shorter **breastfeeding** duration (OR <6 months vs ≥6 months = 1.99, 95 % CI 1.11−3.55) and **premenopausal** (OR premenopausal vs Menopause by natural = 2.34, 95 %CI 1.03−5.28) increased risk of papillary thyroid cancer. Early **age at first pregnancy** (OR ≤24years vs >24 years = 0.66, 95 % CI 0.44−0.98) decreased the risk
Mannathazhathu AS, et al. 2019	Worldwide	Meta-analysis of 10 case-control and 9 cohort studies	Case-control studies - 3389 cases and approximately 2500 controls Cohort studies *Summary OR for case-control studies* Increased risk on thyroid cancer with ORs of 1.43 (95% CI: 1.16-1.77) for **age at menarche** >14 years, 1.49 (95% CI: 1.19-1.86) for **parity** >2, 1.38 (95% CI: 1.18-1.61) for **miscarriage/ abortion**, and 2.05 (95% CI: 1.39-3.01) for **artificial menopause.** A protective effect (ORs: 0.85; 95% CI: 0.72-0.99) for prolonged use of **OCs**. *RR for cohort studies* Increased risk on thyroid cancer with RR of 1.17 (95% CI: 0.90-1.57) for **age at menarche** >14 years, 1.10 (95% CI: 0.94-1.27) for **parity** >2, 1.20 (95% CI: 1.03-1.40) for **miscarriage/abortion**, and 2.16 (95% CI: 1.41-3.31) for artificial **menopause** and protective effect (RR: 0.78; 95% CI: 0.65-0.92) for prolonged use of **OCs**.

Shin S, et al. 2018	Japan (JPHC I and II study)	Prospective Study	187 cases Early **age at menarche** for premenopausal women (≥16 vs ≤13 years HR: 0.83 per 1 year increase, 95% CI: 0.70–0.98, P trend=0.03) and surgical **menopause** (surgical vs natural menopause HR: 2.34, 95% CI: 1.43–3.84), and late **age at** natural **menopause** for postmenopausal women may be related to increased risk of thyroid cancer.
Kim H, et al. 2018	Korea	Cross - sectional study	210 cases **Pregnancy** (nulliparous vs parous OR= 6.12, 95 % CI 2.93−12.71), parity (having 4 **number of pregnancies** had the highest risk vs 1 OR= 4.51, 95 % CI 1.77−11.59) and **number of reproductive years** (OR 1.08 95 % CI 1.06, 1.11) were significantly associated with increased risk of thyroid cancer. Duration of **breastfeeding** (OR 0.87 95 % CI 0.80, 0.96) and number of babies breastfed (OR 0.69 95 % CI 0.57, 0.83) significantly decreased the risk for thyroid cancer.
Cordina-Duverger E et al. 2017	France	Population-based case-control study	430 cases and 505 controls Late **age at menarche** (≥15 vs <12 years, OR 1.55 95% CI 0.96-2.5) and **postmenopausal status** (either natural or artificial, OR 1.69 and 2.52, respectively) were associated with increased incidence of *papillary* thyroid cancer. Exposure to **exogenous hormones** (ever OC vs never (OR 0.69, 95% CI 0.48-1.01) as well as **breastfeeding** (ever vs never, OR 0.73, 95% CI 0.55–0.97) were inversely associated with thyroid cancer.
Zhu J, et al. 2016	Worldwide	Meta-analysis of 23 studies (10 prospective, 12 case-control and 1 pooled analysis)	Significant association between **parity** (parous vs nulliparous: RR 1.09, 95% CI 1.03-1.15; I2=33.4%) and **parity number** (2 vs nulliparous, 3 vs nulliparous: RR=1.11, 95% CI 1.01-1.22; I2=31.1% and RR=1.16, 95% CI 1.01-1.33; I2=19.6% respectively) for increased risk of thyroid cancer.
Zhou YQ, et al. 2015	Worldwide	Meta-analysis of 21 studies (2 prospective and 19 case-control)	406,329 cases Risk of thyroid cancer was increased with **multiple pregnancies** (≥3 pregnancies (OR=1.39, 95% CI: 1.21-1.59) and an interval of ≤5 years between pregnancies (OR=1.53, 95% CI: 1.29-1.81)
Cao Y, et al. 2015	Worldwide	Meta-Analysis of 25 studies (13 cohort, 12 case-control)	**OC** and **HRT** use did not alter the risk of thyroid cancer. Older **age at menopause** (RR = 1.24, 95% CI 1.00–1.53, P = 0.049) and **parity** (parous vs nulliparous RR = 2.30, 95% CI 1.31–4.04, P = 0.004) are risk factors for thyroid cancer while longer duration of **breastfeeding** (RR = 0.7, 95% CI 0.51–0.95, P = 0.021) plays a protective role against this cancer

Caini S, et al. 2015	Worldwide	meta-analysis of 24 prospective studies	5,434 thyroid cancer cases Increasing **age at first pregnancy**/birth (SRR 1.56, 95 % CI 1.01–2.42) and **hysterectomy** (SRR 1.43, 95 % CI 1.15–1.78) were associated with increased thyroid cancer risk. Reduced risk was associated with **menopause** (SRR 0.79, 95 % CI 0.62–1.01). No associations were seen with **age at menarche, age at menopause, Parity, OC or HRT use**.
Wang P, et al. 2015	Western countries	Meta analysis of 6 cohort and 3 case–control studies	increased risk of papillary thyroid cancer with late **age at menopause** (RR=1.39, 95 % CI 1.03–1.89, P=0.032). No significant association **OC** or **HRT use, age at menarche, parity, age at first birth, menopausal status,** and **breast feeding.**
Xhaard C, et al. 2014	France	Population-Based Case-Control Study	633 cases and 677 controls Increased risk of thyroid cancer with higher **number of pregnancies** (3 vs 0 OR 1.4 95%CI 0.7- 2.9 p trend 0.05) and early **age at menarche** (OR 1.3 95%CI 1.0-1.8). Lower risk of thyroid cancer with **breastfeeding** duration (≥months vs none OR: 0.3 95%CI 0.1-0.7 p-trend <0.01), **OC** use duration (> 7years vs never OR 0.7 95%CI 0.4-1.0), and late **age at first pregnancy** (≥25 vs <25 years OR: 0.5 95%CI 0.3, 0.9).
Braganza M Z, et al. 2014	(Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial)	Prospective study	127 cases Increased risk of thyroid cancer was with older age at natural **menopause** (≥55 vs. <50 years; HR, 2.24; 95% CI, 1.20–4.18), greater lifetime number of ovulatory cycles (≥490 vs. <415 cycles; HR, 2.40; 95% CI, 1.33– 4.30) and greater **number of live births** (≥5 vs. 1–2; HR, 1.72; 95% CI, 1.05–2.82), Earlier **age at menarche** was non significantly associated with increased thyroid cancer risk. No associations were observed for **OC or HRT use**
Sungwalee W, et al. 2013	Thailand	Prospective Cohort Study	17 cases High incidence rate per 100,000 person-year associated with early **age of menarche** (<14 vs≥14 = 51.0 vs 9.6), **nulligravida** women (Never vs Ever 28.9 vs 10.3), and **OC** users (Never vs Ever 10.2 vs 11.4),
Peterson E, et al. 2012	Worldwide	Systematic Review of 37 studies	Weak and equivocal associations for ever **being pregnant/parous**, **number of pregnancies/births**, **use of prescription hormones** and **menopausal status**.

Schonfeld S J, et al. 2011	USA (NIH-AARP Diet and Health Study)	Prospective study	312 cases Thyroid cancer was not associated with **ages at menarche** or **menopause, menopause type,** or **parity**. **OC use** (≥10 years vs. never use) was inversely associated with thyroid cancer risk (HR, 0.48; 95%CI, 0.28–0.84; P-trend = 0.01) **HRT use** had an increased thyroid cancer risk (current vs. never HR 1.38; 95% CI: 1.07–1.79)
Horn-Ross P L, et al, 2011	California (California Teachers Study cohort)	Prospective study	Later age at menarche (age ≥14 years) was associated with increased risk (RR=1.88, 95% CI: 1.13–3.13)
Shin A, et al. 2011	Korea	Retrospective cohort, Prospective study	327 cases No significant associations were seen with **age at menarche** or **age at menopause**.
Pham TM, et al. 2009	Japan (JACC study)	Prospective Cohort Study	86 cases Nonsignificant reduced risk of thyroid cancer was observed for women who had experienced **pregnancy** (HR 0.56 95% CI 0.25–1.24) or a **live birth** (HR 0.52 95% CI 0.24–1.16). No associations with **age at menarche**, **age at menopause**, **age at first birth**, or **hormone use**.
Brindel P, et al. 2008	French Polynesia	Population-based Case-Control	201 cases and 324 controls The risk of thyroid cancer increased with **menopause** (premenopausal vs natural OR= 1.9, or artificial menopause OR= 4.5) and with **number of births** (nulliparous vs having ≥8 children p for trend = 0.03). No association was observed with **age at menopause**, **age at first pregnancy**, or **breastfeeding**.
Wong EY, et al. 2006	Shanghai, China (Shanghai female textile workers cohort)	Nested Case-cohort study	130 cases and 3,187 sub cohort non-cases No associations between **number of live births**, **age at menarche** or **menopause**, **gravidity**, **breastfeeding**, **OC** use and thyroid cancer were observed in this study. Nonsignificant increased risk of thyroid cancer was observed for women with later **age at first birth** (30+ vs 20-29 years HR 1.40 95% CI: 0.88-2.22).

Truong T, et al. 2005	New Caledonia, South Pacific	Population-based Case-Control Study	293 cases and 354 controls Increased risk of thyroid cancer was associated with later **age at menarche** (≤12 vs ≥15 years OR 1.2 95% CI 0.7- 1.9), **hysterectomy** (no vs yes OR 1.5 95% CI 0.8- 2.8), and **number of pregnancies** (nulliparous vs ≥8 OR 2.2 (95% CI 1.1-4.3, p-trend 0.01). **OC** and **HRT** use were unrelated to thyroid cancer.
Zivaljevic V, et al. 2003	Serbia	Hospital based 1:1 matched case-control study	204 pairs **OC use** increased the risk of thyroid cancer (OR = 2.34, 95% CI = 1.31–4.18) but was not independently related to risk after adjusting for well-established thyroid cancer risk factors.
Negri E, et al. 2002	Europe, North America, and Asia	Pooled analysis of 14 case – control studies	67 cases and 335 controls Reduction in medullary thyroid cancer risk with **age at first birth** before 25years (< 25 vs 25-29 and 30+ years, ORs = 2.2, 95% CI 0.74-6.4 and 5.6, 95% CI 1.7-18 respectively) No associations with **age at menarche, menopausal status, number miscarriages/induced abortions**. Non-significant positive association with **nulliparous** vs parous (OR 1.3) inverse association with number of births (OR 0.85)
Memon A, et al. 2002	Kuwait, Middle East	Population based 1:1 matched case-control study	238 pairs No associations with thyroid cancer risk with **age at menarche, pregnancy, menopausal status** and **age at menopause**. Increased risk among women who had **>5 children** (OR51.5; 95% CI: 0.9–2.5). childbearing during the latter half of reproductive life had a substantial effect on the incidence of thyroid cancer; for any given level of parity, there was about a 2-fold increased risk if the age at last pregnancy was >30 years.
Iribarren C, et al. 2001	San Francisco, CA, USA	Population based cohort study	196 incident thyroid cancers **Number of children, Age at menarche, OC** and hormone use did not show statistically significant relations to thyroid cancer.
Mack WJ, et al. 1999	Los Angeles County	1:1 matched case-control study	292 pairs **Age at menarche, pregnancy, menopausal status, use of OC** and other exogenous estrogens were not associated with thyroid cancer. Decreased risk with duration of **breastfeeding** (P trend 0.04).
Rossing MA, et al. 1998	Washington, USA	Population based case control study	410 cases and 574 controls Reduced risk of papillary thyroid cancer among women <45 years with ever **OC use** (OR = 0.6 95%CI 0.4-0.9)

Galanti MR, et al. 1996	Norway and Sweden	Population based case control study	191 cases and 341 controls No clear association was found with **number of live births/pregnancies**, **OC or HRT** use. Increased risk of thyroid cancer was seen with **early first childbirth** (before 20 years of age) and **menopausal status** (artificial vs spontaneous menopause OR 2.52; 95% CI 0.96-6.62)
Levi F, et al. 1993	Switzerland	Hospital based Case control study	91 cases and 306 controls Non-significant increase in cancer risk with an **increasing number of full-term pregnancies** (> 3 vs. 0 OR = 1.6, 95% CI: 0.7–3.6) and **menopausal status** (artificial menopause vs. premenopausal women, OR = 6.3 95% CI: 1.7–23.2). No associations with **age at first birth** and **age at menarche.**
La Vecchia C, et al. 1993	Italy	integrated series of case-control studies	Several reproductive factors were investigated with several cancers. There were no significant results for thyroid cancer
Akslen LA, et al. 1992	Norway	Prospective study	124 cases No strong associations with **parity, age at first birth, age at menarche** and **menopause**. A long reproductive period was related to increased risk of papillary carcinomas,
Franceschi S, et al. 1990	Italy	Hospital-based case control study	165 cases and 214 controls Late **age at menarche** (≥ 14 vs ≤11, RR = 2.8), late **age at first birth** (≥ 28 vs ≤21 years, RR = 2.4) significantly increased risk of thyroid cancer

1.5. Estrogen and thyroid cancer

1.5.1 Plausible mechanisms for gender disparity

Understanding the possible explanations for the gender disparity in thyroid cancer incidence has been an area of active research, and differences in hormonal status and hormonal receptor mediation have been proposed to contribute to the disparities in thyroid cancer in males and females (85). It is well established that sex hormone effects are mediated by hormone-specific nuclear receptors that regulate gene expression and tumor cell biology (86). Several lines of evidence suggest a role of estrogen in the pathogenesis of thyroid cancer in women (**Figure 3**).

1.5.2 Estrogen receptor-mediated signaling

The strongest support comes from experimental studies that have demonstrated estrogen receptors in thyroid tissue, and some studies show higher levels of estrogen receptors in neoplastic versus normal thyroid cells (87). The action of estrogen occurs through two types estrogen receptors, called alpha (ERα) and beta (ERβ) which are members of a large family of nuclear transcription factors that regulate transcriptional activation of genes. Studies suggest that thyroid cancer cells exhibit differential expression of estrogen receptors, with an increase in ERα and a decrease in ERβ, which in turn promote tumorigenesis and reduce tumor suppression respectively (88, 89).

1.5.3 Estrogen receptor as a growth factor

In addition, estrogen has been suspected to affect growth-factor dependent signaling pathways in thyroid cancer. Recent studies have elucidated molecular mechanisms by which estrogen affects the cell cycle regulatory system to promote cellular proliferation, such as 17β-Estradiol has been shown to stimulate cell cycle progression by inducing the expression of the cyclin D1 gene during early G1 phase(90). Experimental evidence suggests

in-vivo direct growth promoting effect of estrogen (17β-Estradiol) in differentiated FRTL-5 rat thyroid cells (91).

1.5.4 Pregnancy and thyroid cancer

Similar molecular observations have been seen during pregnancy, where the increase of human chorionic gonadotropin (HCG) which has close homology to TSH have stimulating effects on the thyroid tumors (92). In addition, increased estrogen levels in pregnancy were associated with increased size of thyroid tumors, supported by the observation that up to 87.5% of females who developed thyroid cancer during pregnancy had an estrogen receptor-α-positive tumor (93).

1.6 Reproductive Patterns in Females – East Vs West

There is evidence to suggest that reproductive patterns may differ for Asian and Western women.

Age at menarche: Studies have found that on average, Asian women tend to experience menarche at a younger age compared to Western women (94). For example, studies from East Asia found that the average age at menarche was around 12.5 years (95, 96), while studies from Western countries showed an average age of around 13 years (94, 97). A certain degree of downward trend of age at menarche has been reported in both Eastern and Western countries. A decline in the mean age at menarche from 13.4 to 12.4 years between 2001 and 2010/2011 was reported in Korea(98) and similar findings were highlighted from Japan (drop in mean age at menarche from 13.8 to 12.2 years)(99); and the average age at menarche decreased remarkably from 17 years to under 14 years between the mid-19th and the mid-20th century in United States and in some countries in Western Europe(100).

Parity: Although according to the United Nations World Fertility Report, generally Asian women tend to have higher parity rates (i.e.,

more children) compared to Western women(101), but in recent decades parity has been declining worldwide(102). East Asian countries, such as South Korea, Japan, and China, have relatively low parity, with total fertility rates ranging from 1 to 1.7, and is comparable to western nations (total fertility rate in United States and Europe is from 1.5 to 1.7).

Age at first delivery: In many parts of the world, including Asia, there has been a trend toward delayed childbearing, with women waiting longer to have their first child(103) and the median age of women has increased from 26.8 to 33.2 years in developed countries(104). In East Asian countries, there has been a particularly pronounced trend toward delayed childbearing where the average age at first birth is over 30 years, while the average age at first birth among women in the United States is currently around 26 years,

Menopause and age at menopause: There is evidence to suggest that the age at menopause may be slightly earlier in Asian women compared to Western women(105). Studies have reported that the age at menopause in Asia ranges from 42.1−49.5 years (106−108), while studies from Western countries have reported an average age of around 51−52 years(97, 109).

Breastfeeding: In general, Asian women tend to breastfeed for longer durations compared to Western women(110). However, breastfeeding rates vary widely across both Eastern and Western countries, with some countries having higher rates than others(111).

OC use and HRT use: Between 1994 and today, OC use in the world overall grew by 8.3% and every continent saw an increase. There is evidence to suggest that Western women have a higher prevalence of OC use compared to Asian women.

As for hormone replacement therapy (HRT), studies have suggested that Asian women tend to have a lower prevalence of HRT use compared to Western women(112, 113).

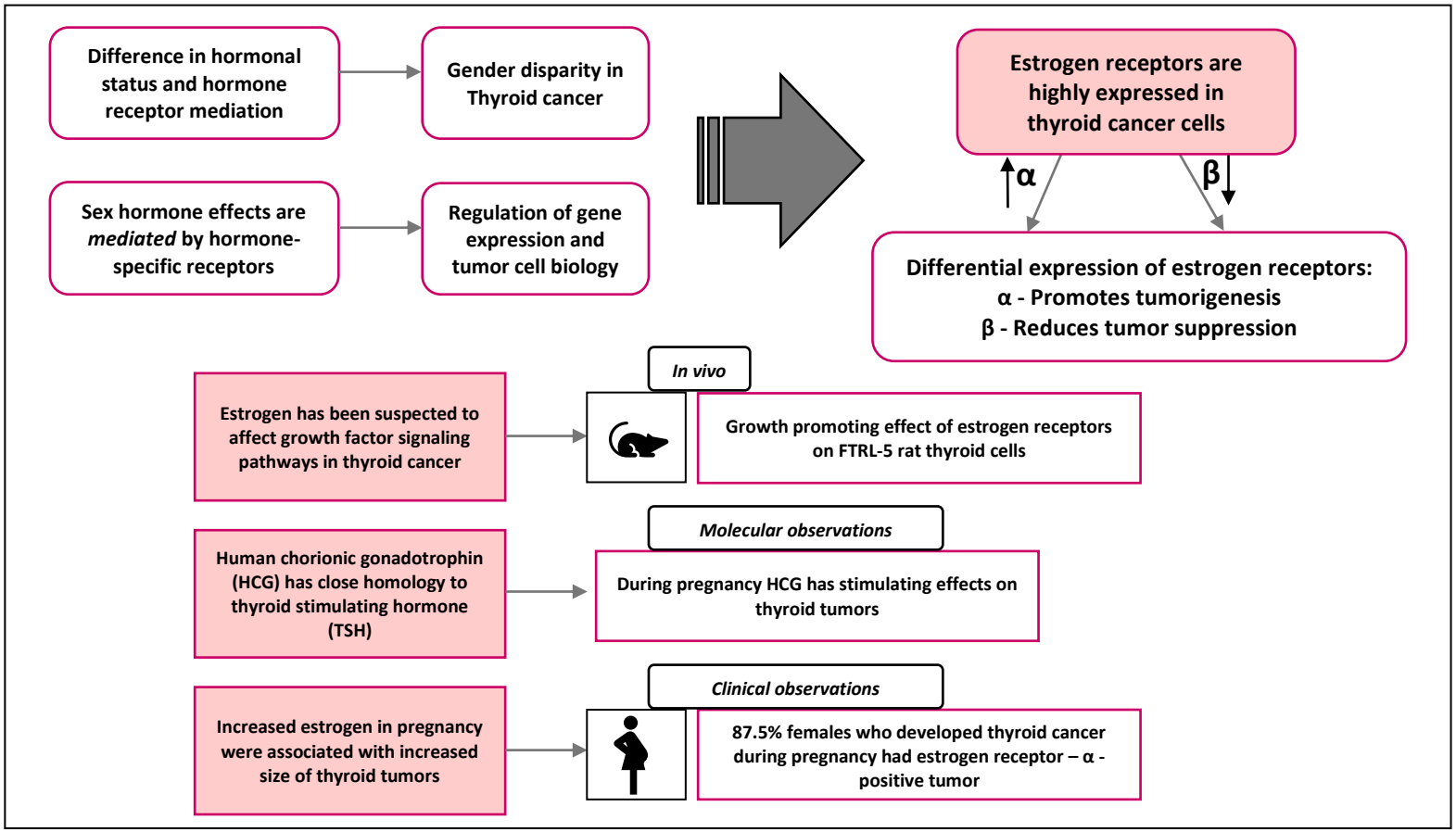

Figure 3: Plausible mechanisms of estrogen in thyroid cancer

Chapter 2. Specific Aim and objectives

2.1. Significance and Rationale of the Study

Since thyroid cancer incidence is substantially higher in females, and it rises dramatically during their early reproductive years peaking between the ages of 40 and 49 which corresponds to menopause. This trend of age-specific incidence in women has been linked to fluctuations in female sex hormones during the menstrual cycle and pregnancy.

Therefore, one may speculate that reproductive, and hormonal factors may serve as potential risk factors for thyroid cancer, reflecting lifetime estrogen exposure (**Figure 4**)(2).

Exploring whether female reproductive or hormonal factors have a role in the striking female predominance in thyroid cancer incidence could offer valuable insights into the underlying causes of gender disparities in thyroid cancer. This exploration could also aid in identifying subpopulations with a higher risk of developing thyroid cancer.

2.2. Knowledge Gap

2.2.1 Current state of the field

Several previous studies have investigated the association between female reproductive factors and thyroid cancer; however, their findings vary considerably. Factors such as, early menarche, late menopause, having given birth or higher parity, which contribute to a longer reproductive life span, have been correlated with developing thyroid cancer in females(52, 54-60, 62-64, 66, 68, 73, 77, 81) However, some studies(39, 65, 80) (67-70, 72, 74, 75, 77), pooled analyses(76), systematic reviews(38) and metanalyses(61, 73) found either inverse, none or weak associations.

Apart from this, the impact of exogenous sex hormones, such as, OCs and post-menopausal hormonal therapy, on thyroid cancer risk remains inconclusive. Several studies suggest protective effects(52, 56, 57, 71, 75), while findings from other studies reveal conflicting results (60, 63, 69, 70, 73-75).

2.2.2 Barriers and challenges

These inconsistent associations could be attributed to the limited power of most studies and heterogeneous study designs. Most of the previous studies have case-control study designs and are vulnerable to biases. There also seems to be a paucity in population-based prospective studies specifically examining reproductive-aged women, with only few studies from Asian countries (26, 51, 54-56, 63, 65, 72, 79, 82). The existing meta-analyses predominantly include studies from Europe and United States, which may not adequately elucidate the impact of reproductive factors on the risk of thyroid cancer in Asian populations.

The possible role of comorbidities, lifestyle factors and reproductive factors in the thyroid cancer risk association has also been poorly investigated. Yet multiple conditions such as diabetes and obesity are direct risk factors of thyroid cancer.

Furthermore, the reproductive patterns for Western and Asian females show differences in the onset of menarche and menopause, essentially shifting the reproductive age, which somewhat limits the interpretation of previously available literature on the role of reproductive factors on the risk of thyroid cancer in Asian women.

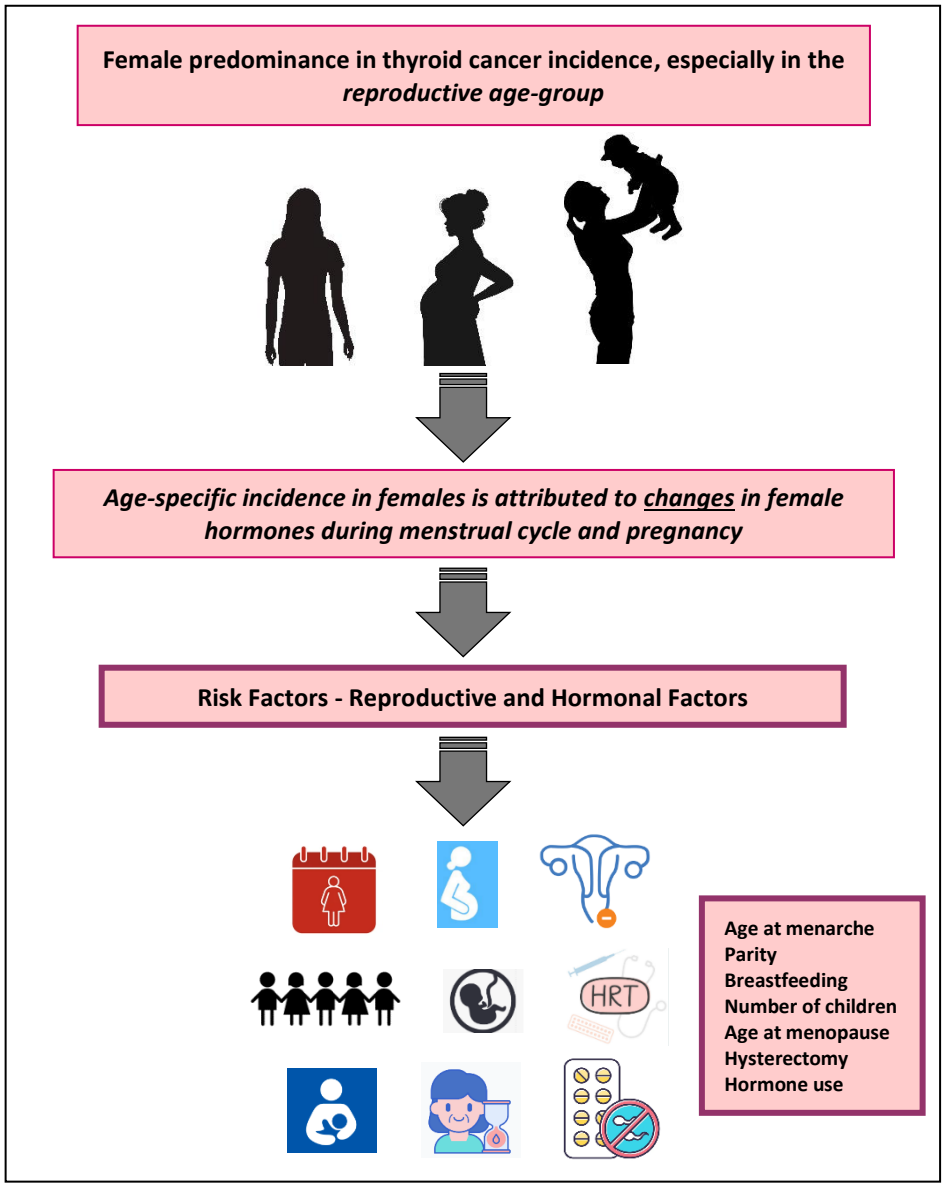

Figure 4: Significance and rationale of the study

2.3. Research Hypotheses and Objectives

2.3.1 Hypothesis

It was hypothesized that, are female reproductive and hormonal factors associated with an increased risk of thyroid cancer, and whether these associations can be influenced by changes in lifestyle and environmental exposures.

2.3.2 Objectives

Accordingly, the primary objective of this thesis project was to investigate the associations between reproductive and hormone related risk factors with the risk of thyroid cancer in females, overall and by histological subtypes, while investigating possible confounding and modifying effects of potential risk factors.

2.3.3 Specific aims

The specific aims were to:

- Examine overall associations between reproductive factors and thyroid cancer incidence in females by a pooled analyses of individual–level data from prospective cohort studies.
- Examine the association by histological subtype (papillary)
- Assess effect modification of potential risk factors on this association. It was examined if any association observed between reproductive variables with thyroid cancer incidence differed by smoking status and BMI.
- Investigate the effects of birth year, country, and thyroid cancer age of diagnosis on the association between reproductive factors and thyroid cancer, which is a unique and important aspect of the research.

Chapter 3. Materials and Methods

3.1. Study Design

Pooled analysis of data collected from prospective cohort studies in the Asia Cohort Consortium (ACC).

Data for the current study were obtained from cohort studies participating in the ACC, containing information on female reproductive factors.

3.2. Data Source

3.2.1 The Asia Cohort Consortium – Overview

History And Organization of the ACC: The ACC is a collaborative effort of a total of 44 cohort studies from 10 countries across Asia, aimed at sharing resources to conduct large-scale epidemiological studies on a variety of health-related issues in the region (114). The total number of cohort participants is around 1 million Asians (115). The ACC comprises about 50 active members from Asia and the United States, as well as prominent cancer research institutes including the National Cancer Institute (NCI) in Bethesda, Maryland. Each member is involved in helping developing cohorts in Asia in some way. Members are faculty at their respective institutions, and others have positions in their respective national health ministries. These researchers from China, India, Bangladesh, Japan, Korea, Malaysia, Singapore, Taiwan, Thailand, the United States, and other countries and economies meet biannually to report on the progress of new and existing cohorts, discuss issues related to the development of common protocols, and establish collaborative projects (116, 117).

Available data: Each individual cohort study provided data of participants that was collected at baseline regarding various risk factors, demographic characteristics, lifestyle, and medical history

(Table 2), using questionnaires, anthropometric measurements, and laboratory tests, respectively, and followed up on new cancer cases according to individual ascertainment system in each country. The data collected are harmonized centrally by the ACC's coordinating center.

Table 2: Available baseline data in Asia Cohort Consortium

Available Data*	
Sociodemographic	Age, Sex, Birth year, Education, Marital status, Ethnicity,
Environmental factors	Occupation, Population density, Sleep (Sleep duration, night shift work), Living arrangement, Stress
Lifestyle	Tobacco use (frequency, amount, smoking status), Tea and Coffee intake (amount and frequency), Alcohol intake (types, frequency, alcohol consumption status) Physical activity (Metabolic Equivalent of Task (METS) Height, Weight, BMI, Waist measurements Dietary intake (Total energy intake, quantity, and frequency of diet)
Health status	Medical condition (Age at diagnosis of diseases, Age at surgery), Menopause status, Reproductive factors, Family history (Number family members diagnosed with cancer, Age at diagnosis of family member)
Cancer incidence, Death and Censoring data	Vital status (Cause of death (ICD-9/10)), Time under surveillance, Cancer diagnosis (ICD codes), Tumor histology (ICD-O) Time to cancer incidence, Age at death, Age at end of follow up,

*Depends on availability of data in each cohort (all variables not shown)

Data harmonization: Data harmonization for the ACC is done centrally by the ACC Coordinating Center. Once a project proposal has been accepted by the ACC Executive Committee, the ACC Coordinating Center requests data from each participating cohort. All cohorts that were relevant for the current project (decided by

the availability of exposure and outcome measures) receive an invitation to participate. The number of cohorts participating in each project varies depending on the research question and availability of data. The ACC Coordinating Center then collects and harmonizes the collected data. Data can be analyzed remotely using a virtual private network (Figure 5).

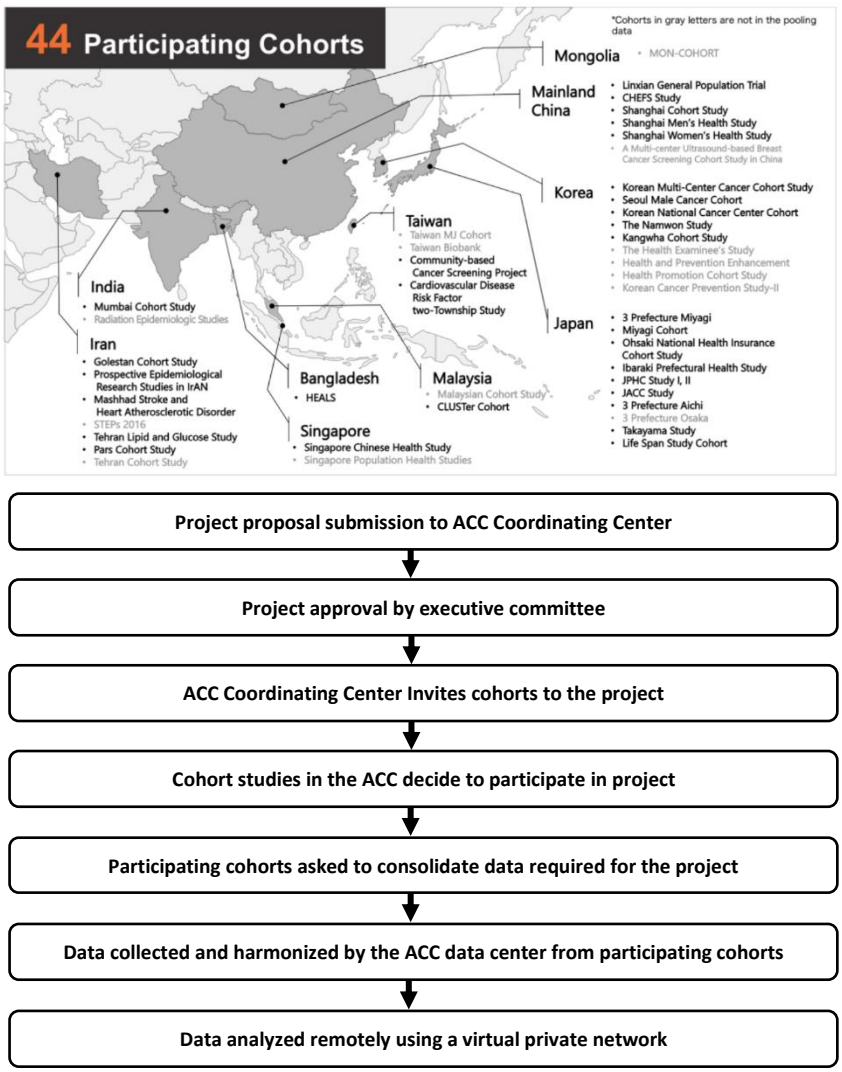

Figure 5: Asia Cohort Consortium cohort participation
https://www.asiacohort.org/index.html

3.2.2 ACC reproductive factor working group

In 2020, the ACC established the Reproductive Factor Working Group (WG) as a response to the growing interest in the relationship between reproductive factors and chronic diseases such as cancer, cardiovascular disease, and osteoporosis. The primary objective of this WG is to promote a common understanding of reproductive variables and their appropriate use in data analyses, which can help to ensure consistency and accuracy in research, and ultimately accelerate the pace of scientific progress. Specifically, the Reproductive Factor WG is a group of researchers from various countries in Asia who have established a standardized set of reproductive factor variables that are common across all participating studies. The group ensures that data collected from different cohorts is consistent, comparable, accurate and can be combined and analysed in a consistent and meaningful way. This helps to generate high-quality epidemiological data that can support research to provide important insights into the health of populations in Asia and beyond.

Development of Reproductive Factor WG protocol: A specific process for harmonizing reproductive factor variables across studies within the ACC was followed. At the beginning, after approval by the ACC executive committee, the aims of the proposed Reproductive Factor WG were circulated. Subsequent Zoom meetings, E-mails, intensive collaboration, and communication among all involved members led to the development of a Reproductive Factor WG protocol, specifying the analysis plan, and requested variables.

Identification of core variables: Along with the WG leaders, Coordinating Center (CC) staff identified a set of core variables related to reproductive factors that are common and/or available across all studies. A data request template was sent to participating cohorts, soliciting information on reproductive and hormonal variables for each cohort (baseline questionnaire data only).

The core variables identified were: Parity status, Number of deliveries/pregnancies, Age at first delivery/pregnancy, Age at menarche, Menopausal status & Age at menopause, Breastfeeding, Use of OC, Use of postmenopausal hormones and Hysterectomy.

Identification of cohorts having reproductive variables: At the timepoint when data harmonization was planned, there were 13 cohorts within the ACC who had reproductive factor variables available, as follows:

SWHS: Shanghai Women's Health Study
JACC: Japan Collaborative Cohort Study
JPHC1: Japan Public Health Center-based prospective Study 1
JPHC2: Japan Public Health Center-based prospective Study 2
Miyagi: Miyagi Cohort
Ohsaki: Ohsaki National Health Insurance Cohort Study
LSS: Life Span Study Cohort
Takayama: Takayama Study
3 Pref Miyagi: 3-Prefecture Miyagi Cohort
KMCC: Korean Multi-center Cancer Cohort Study
KNCC: Korean National Cancer Center Cohort
Namwon: The Namwon Study
SCHS: Singapore Chinese Health Study

Standardization of variable definitions: Comparability of reproductive variables from participating cohorts was assessed and how to devise a standardized definition for each reproductive variable was examined. Details are as follows:

Parity status: Parity status at baseline was available for all cohorts except for LSS.

Number of deliveries/pregnancies: Except for LSS, data on number of deliveries/pregnancies were available for all cohorts. Not all cohorts had a single variable to describe number of deliveries/pregnancies information. Many cohorts had more than one variable for the same data. Except for SCHS, all the cohorts provided number of deliveries/pregnancies information as continuous values.

Age at first delivery/pregnancy: For age at first delivery/pregnancy, all cohorts except Takayama had continuous values. JACC and LSS only had data on age at first pregnancy and this value may refer to a pregnancy that is not full-term. Plausible values for age at first delivery/pregnancy were considered in the range of 10-49 years (values outside of this range were set as missing), 49 was selected as the upper cut-off because it is the median menopausal age for both Japan and Korea cohorts.

Age at menarche: All cohorts had age at menarche data as continuous values except for Takayama and SCHS.

Menopausal status & age at menopause: There was a modest amount of missing data for menopausal status, particularly in LSS, JACC and KNCC. Implausible values for menopausal status were judged by comparing it with a participant's baseline age and/or their age at menopause (if available), such as premenopausal women reporting an age at menopause or reporting very high baseline age such as >55 years. Implausible values for age at menopause were considered <20 years. Age at menopause was available as continuous values for all cohorts except SCHS and Takayama.

Breastfeeding: Only 7 cohorts had data on breastfeeding status (JPHC1, JPHC2, Miyagi, Ohsaki, KMCC, KNCC, Namwon); three of these cohorts also had data on breastfeeding duration (KMCC, KNCC, Namwon) at baseline. Breastfeeding duration was the cumulative duration of breastfeeding (sum for all children in months). Implausible values for breastfeeding duration would be considered as those inconsistent with the number of deliveries data.

Use of OCs: Only a few cohorts had OC use status (Ohsaki, KMCC, KNCC, Namwon, SCHS; OC use status was computed for Miyagi using data from the OC use duration variable) and/or OC use duration (Miyagi, Ohsaki, KNCC, Namwon) reported at the study baseline. Data for OC start age were available for KNCC and Namwon and OC stop age for only Namwon. Implausible values were noted after comparing with baseline age.

Use of postmenopausal hormones: Data on HRT use were not

available for JACC, JPHC 1, JPHC 2, LSS and 3 Pref Miyagi. Different variables were available with different categorizations for baseline HRT. In Takayama, data on both HRT current use and HRT ever use were available.

Hysterectomy: Hysterectomy at baseline information was available for Takayama, KMCC and KNCC from two variables with overlapping data.

(**Supplementary table 1** details the Questionnaire items of the reproductive variables from each cohort)

3.2.3 Data cleaning and harmonization of variables

The coding for each reproductive variable as well as other core variables was developed by the coordinating center. This included providing instructions on the original variables that were collected in the ACC database (baseline questionnaire data) followed by any re-coding or data processing that was necessary to create derived variables, and any relevant exclusions or exceptions. Thus, allowing data from different cohorts to be combined and analysed in a consistent way. A thorough data cleaning and processing was also performed to identify and correct any errors or inconsistencies, including checking for missing data, outliers, and logical inconsistencies in the data. Details for data cleaning, processing, and harmonization of each reproductive variable is as follows:

Parity status: Derived variables were created for parity status (nulliparous, parous, missing). When parity status at baseline was missing, it was assigned using processed data on number of deliveries/pregnancies. Women who reported stillbirth/miscarriages were also set as parous (when this information was available). The LSS study only had data on age at first pregnancy, therefore women in this study were assigned as parous if they had reported their age at first pregnancy.

Number of deliveries/pregnancies: Variables that described full term pregnancies were preferentially used when available. A derived variable was created for number of children/deliveries with

categorical values (no child, 1−2, 3−4, 5+ children, missing) which included nulliparous women. A separate derived variable for number of children/deliveries was created that excluded nulliparous women.

Age at first delivery/pregnancy: The derived variable for age at first delivery/pregnancy was created to have categorical values (≤ 20, 21−25, 26−30, 31+ years, missing) and was restricted to parous women. Therefore, missing included nulliparous women as well as parous women with missing age at first delivery/pregnancy. If women were missing parity status, they were also assigned missing age at first delivery/pregnancy. This is to maintain consistency across the derived variables, and we also believe that information on parity status should be more reliable than information on age at first pregnancy. A second derived variable for age at first delivery was also created that had continuous values.

Age at menarche: A derived variable for age at menarche were created with categorical values (<13, 13−14, 15−16, 17+ years, missing). Plausible values for age at menarche were considered in the range of 10−23 years (values outside of this range were set as missing) as a consensus of the WG. A variable for age at menarche with continuous values was also created but it was missing for Takayama and SCHS cohorts who had only categorical values.

Menopausal status & age at menopause: Menopausal status was assigned (when missing) using data on age at menopause (when available). When age at menopause was missing or implausible, menopausal status was assigned using data on baseline age. Considering the median menopausal age for both Japan and Korea is 49, the following baseline age cut−offs were used to assign menopausal status: Age 54+ years: postmenopausal, Age 44 years or less: premenopausal, Ages 45−53 years: perimenopausal/ unknown. A derived variable for age at menopause (<45, 45−49, 50−54, 55+, missing) was created with categorical values. Premenopausal women, those missing menopausal status or those with implausible age of menopause < 20 years were set as missing age at menopause. Another derived variable for age at menopause

was created with continuous values and medians of categories were assigned for SCHS (only categorical age at menopause data was available in SCHS).

Breastfeeding: New variables for breastfeeding status (never, ever, missing) and duration were computed. The derived breastfeeding duration variable was measured in months and had continuous values. Missing values on breastfeeding status and duration were assigned to participants who were missing information on breastfeeding status and/or breastfeeding duration (when relevant), nulliparous women and participants who were missing parity. Implausibly high values for breastfeeding duration for a small number of KMCC participants were set as missing after identifying inconsistencies after cross checking with number of deliveries.

Use of OCs: OC start/stop age variables were not cleaned because very few cohorts had those data. New variables were derived for OC ever use status (never, ever, missing) and for OC ever use duration (as continuous values). For OC ever use status, missing was assigned to missing OC use status. Conflicting information of OC use and duration, such as never users reporting duration or ever users reporting no duration or implausible values after cross checking with baseline age were assigned as missing.

Use of postmenopausal hormones: New variables were derived for HRT ever use status (never, ever, missing) and postmenopausal HRT ever use status (restricted to postmenopausal women). Those participants with missing values were those with missing information on HRT ever use status.

Hysterectomy: A derived variable for hysterectomy status was created (never, ever, missing). Missing was set for participants with missing/unknown information on hysterectomy status and if data gave a conflicting answer.

Common exclusion criteria: As a consensus of the WG, the common exclusion criteria for reproductive factors focused data analysis included males, missing data on gender, missing age at baseline and

missing information on pregnancy and number of deliveries at baseline.

3.3. Study Population

3.3.1 Participating cohorts in the study

Of these, 10 cohorts (7 from Japan, 1 from China and 2 from South Korea) agreed to participate in the current study (n=507,487) which provided information on reproductive variables as well as follow-up data on TC incidence (**Figure 6**).

This study was approved by the ACC executive committee, the ethical committee of the National Cancer Center Japan, the institutional review board of Seoul National University Hospital (E-2303-037-1410) and by respective ethics committees overseeing the participating studies. Informed consent was obtained from all participants. All data were de-identified.

3.3.2 Eligibility criteria

Following are the details of exclusions :

- males (n=195,055),
- missing information on gender at baseline (n=5),
- women with missing data on age at baseline (n=2,416),
- women with missing data on parity status/number of deliveries at baseline (n=18,925)

In addition, the following individuals were considered ineligible and excluded from the study if they

- had a prior thyroid cancer diagnosis at baseline (n=24)
- had missing or invalid information on diagnosis or follow-up (n=1,355).

Details of exclusions considering each participating cohort are provided in **Table 3**.

After these exclusions, the final study population comprised 289,707 females (**Figure 6**).

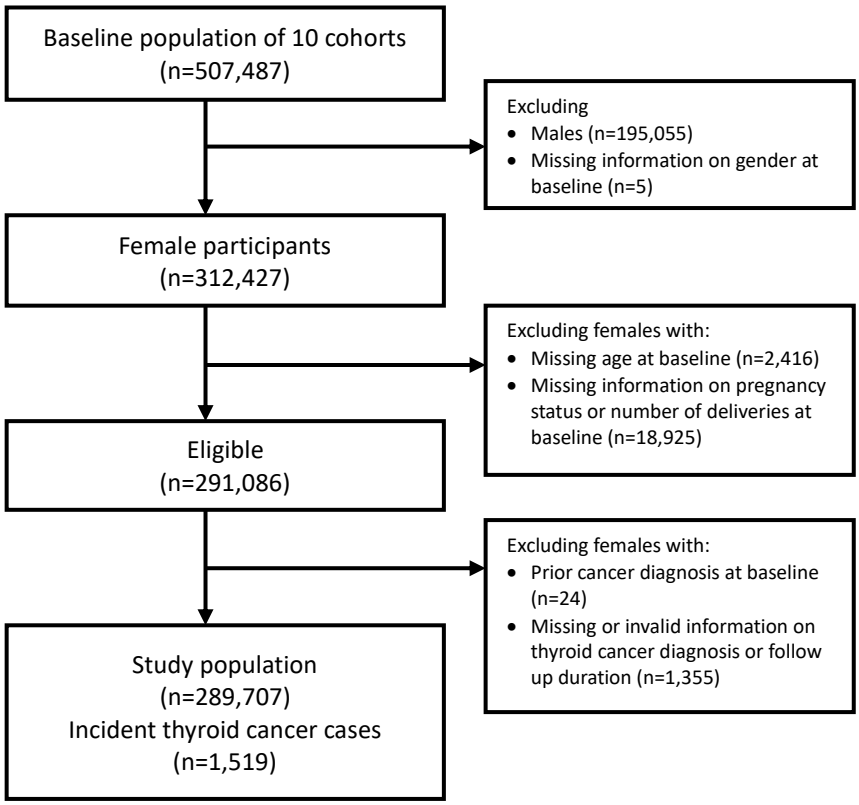

Figure 6: Study flowchart of participant inclusion and exclusion

3.4. Assessment of Exposure and Outcome

3.4.1 Exposure measurement

All reproductive and hormonal variables reported by participants at baseline were examined as follows:

- age at menarche (<13, 13−14, 15−16, ≥17 years)
- parity status (nulliparous women, parous women who had ≥1 deliveries/children)
- number of children/deliveries (1, 2, 3, 4, 1−2, 3−4, ≥5 children)
- age at first delivery/pregnancy (≤ 20, 21−25, ≥26 years)
- breastfeeding status (never, ever)
- menopausal status (premenopausal ≤44, postmenopausal ≥54 years)

- age at menopause (<45, 45–49, 50–54, ≥55 years)
- OC use (never, ever)
- HRT use (no, yes)
- hysterectomy status (no, yes)

During harmonization, it was noted that the LSS cohort did not report number of children/deliveries, and only age at first pregnancy was available which may have referred to pregnancy that was not full-term. Also, no information was collected on parity status and women were classified as parous if they reported their age at first pregnancy; thus, in the LSS cohort the proportion of parous women was likely underestimated.

For this study, following cohorts did not have information for the following variables:

Breastfeeding status – SWHS, JACC, LSS, 3 pref Miyagi;
OC use – SWHS, JPHC1, JPHC2, JACC, LSS, 3 pref Miyagi;
HRT use – JPHC1, JPHC2, LSS, 3 pref Miyagi;
Hysterectomy status – SWHS, JPHC1, JPHC2, JACC, Miyagi, Ohsaki, LSS, 3 pref Miyagi.

3.4.2 Outcome ascertainment

In each cohort, incident thyroid cancer cases during the follow-up duration were identified by linkage to local cancer registries of participating cohorts. Only primary thyroid cancer cases were included as incident cases.

Thyroid cancer cases were defined using the International Classification of Diseases (ICD) 10th revision code C73. The histological subtypes for thyroid cancer were defined based on the ICD for Oncology, third edition (ICD-O-3) (Supplementary table 2). Information on histological thyroid cancer subtypes was available from 9 out of 10 cohorts (all cohorts except LSS).

Table 3: Exclusion criteria and final study population

Before exclusion		Exclusion 0			Exclusion 1		Exclusion 2		Exclusion 3			**After exclusion**	
Cohort	**Cohort Participants**	*Missing data on gender at BL*	*Males*	**Females**	*Missing data on age at BL*	**Remaining females after Exclusion 1**	*Missing information on pregnancy status and/or number of deliveries at BL*	**Remaining females after Exclusion 2**	*Diagnosed with TC at BL*	*Missing data on diagnosis at BL*	*Missing data on follow up duration*	**Final study population**	**TC cases**
	N	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**
ACC, Total	**507,487**	5	195,055	312,427	2,416	310,011	18,925	291,086	24	–	1,355	**289,707**	**1,519**
China													
SWHS	**74,940**	–	–	74,940	-	74,940	-	74,940	-	–	10	**74,930**	**306**
Japan													
JPHC1	**43,050**	–	20,609	22,441	-	22,441	963	21,478	3	–	10	**21,465**	**108**
JPHC2	**56,520**	–	26,799	29,721	-	29,721	1,988	27,733	1	–	17	**27,715**	**77**
JACC	**86,505**	–	36,199	50,306	-	50,306	4,647	45,659	-	–	-	**45,659**	**89**
Miyagi	**47,605**	–	22,836	24,769	-	24,769	1,931	22,838	1	–	-	**22,837**	**167**
Ohsaki	**51,252**	–	24,573	26,679	-	26,679	4,488	22,191	-	–	-	**22,191**	**57**
LSS	**52,883**	–	20,390	32,493	2,416	30,077	-	30,077	19	–	–	**30,058**	**166**
3pref. Miyagi	**31,345**	–	13,992	17,353	-	17,353	829	16,524	-	–	-	**16,524**	**27**
Korea													
KMCC	**20,636**	5	8,232	12,399	-	12,399	961	11,438	-	–	15	**11,423**	**101**
KNCC	**42,751**	–	21,425	21,326	-	21,326	3,118	18,208	–	1303	1303	**16,905**	**421**

BL – baseline, TC–thyroid cancer

3.5. Potential Confounders

The following variables collected at baseline were considered potential confounders:

- Smoking status (never, ever, missing),
- Alcohol drinking status (never, ever, missing),
- BMI (kg/m^2) (<18.5, 18.5−22.9, 23−24.9, ≥25)

Other factors suggested to be associated with thyroid cancer risk, such as education, occupation, radiation history, infertility, family history of thyroid cancer, and history of benign thyroid disease, were mostly unavailable for the participating cohorts.

3.6. Statistical Analyses

- Considering LSS cohort had the greatest number of reproductive variables and histology data missing it was excluded from the main analyses.
- Analyses for number of children/deliveries, age at first delivery/pregnancy and breastfeeding status were conducted among parous women.
- The specifics of how the reproductive variables and potential covariates were derived and/or categorized are described in the relevant sections; however, in general, standard groupings or categories mentioned in literature were used.

An overview of the different statistical methods for the data analyses used in this thesis is presented below.

3.6.1 Descriptive statistics

Descriptive statistics were used to summarize the baseline characteristics. The mean and standard deviation (SD) were calculated for age at baseline and follow−up duration for the total study population and for each participating cohort.

3.6.2 Cox proportional hazard models

The Cox proportional hazards model is essentially a regression model used for investigating the association between survival/time-to-event and one or more independent variables(118).

In this study, Cox proportional hazards regression models were used to examine the association between reproductive factors and the risk of thyroid cancer among females in the ACC participating cohorts overall, and for the most common histologic subtype papillary thyroid cancer.

Defining the Models

Using the Cox models, hazard ratios (HRs) and 95% confidence intervals (CIs) of thyroid cancer incidence were calculated according to reproductive factors for each cohort (cohort-specific HRs). Age was used as the time scale, such that person-time was accrued from baseline to the date of thyroid cancer incidence, death, or end of follow-up of each cohort, whichever occurred first. The proportional hazard assumptions were graphically tested by examining the Schoenfeld residuals. No evidence of non-proportionality was observed.

The reference category of each reproductive factor was defined as follows: ≥17 years (age at menarche), parous (parity status), 1 child or 1-2 children (number of children/deliveries), 21-25 years (age at first delivery/pregnancy), never (breastfeeding status), no (menopausal status), <45 years (age at menopause), never (OC use), no (HRT use) and no (hysterectomy status).

Model building

The following model building strategy was implemented:

Covariate analyses: To identify potential covariates, Cox regression analyses were performed, where each potential risk factor was tested separately to see if it had a significant association with the outcome of interest. This was done by computing HRs and its

associated CIs (Table 5). Covariates with a significant association were selected for further analysis in the adjusted Cox models.

Age-adjusted Cox model: Unadjusted Cox models with age as time-scale.

Multivariable-adjusted Cox model: Cox models adjusted for potential covariates – BMI, alcohol drinking and smoking status.

Assessment of confounding and test for trend

The potential confounding effect was assessed by evaluating the changes in adjusted HRs for thyroid cancer risk exceeding 10%.

Regression analyses are commonly used to test for trend of the effect of the exposure on the outcome, and reported as a *p*-value for trend (118, 119). This is done to determine whether increasing or decreasing levels of exposure are associated with increasing or decreasing risk of outcome. In this study, linear trends across categories of reproductive variables and thyroid cancer were tested and *p*-value for trend reported (*p* – trend).

3.6.3 Pooled analyses

Pooled analyses were conducted using DerSimonian and Laird random-effect models (120) by combining cohort-specific HRs and 95% CIs and computing pooled risk estimates.

Random-effects model

For each reproductive variable, cohort-specific risk estimates were pooled using a random-effects model that employs a weighting scheme based on the inverse of the cohort-specific variance. This type of model allows errors both within study and between studies.

Heterogeneity test

Heterogeneity was assessed by Cochran's *Q*-test and quantified with the I^2 statistic (121).

The presence of heterogeneity across studies was evaluated using the Cochran's *Q*-test. A low *p*-value (<0.1) of the test provides evidence of heterogeneity. In addition to testing whether

heterogeneity is present, it was quantified by calculating the I^2 statistic(122), which examines the proportion (%) of total variance in the estimates that is due to between-study heterogeneity. An I^2 of 0-40% might not be important, 30-60% represents moderate heterogeneity, 50-90% indicates substantial heterogeneity and 75-100% represents considerable heterogeneity (123).

3.6.4 Stratified analyses

To account for a modifying effect, analyses were conducted on data stratified by

- Smoking status
- BMI (kg/m^2)
- Birth years
- Country

These analyses examined whether the above factors modified the associations between reproductive and hormonal factors and risk of thyroid cancer incidence. Significance of interaction was examined by the likelihood ratio test and reported as a *p*-value for interaction (*p* - interaction).

For stratified analyses by smoking: Females were grouped as ever smokers and never smokers.

For stratified analyses by BMI: BMI was categorized using the World Health Organization (WHO) recommendation for adult Asians(124) and a BMI of $\geq$23 kg/m^2 was considered as being at risk in the ACC (Supplementary table 3). Therefore, BMI cutoff at 23 kg/m^2 was chosen and participants grouped as those with BMI < 23 kg/m^2 and with BMI $\geq$ 23 kg/m^2.

For stratified analyses by birth years: Participants were grouped as those born before and after the 1940s. Birth year cut-off at 1940s was chosen considering the birth cohort effects on thyroid cancer incidence in females in three East Asian countries(125). Further analyses were conducted on those grouped as those born in the 1920s or earlier, in the 1930s, 1940s and 1950s or later.

For stratified analyses by country: Cohorts were grouped according to the country as China, Japan, Korea.

Stratified Analysis by age of diagnosis

To evaluate the association between reproductive variables and thyroid cancer in relation to age of diagnosis, a cutoff of age 55 years was implemented to delineate two separate age groups. Analyses were conducted by employing Cox models to examine thyroid cancer risk among cases diagnosed before age 55 by censoring follow up at age 55 years. A similar approach was applied for those diagnosed after age 55. Age at diagnosis cutoff at 55 years was chosen considering the age cohort effects on thyroid cancer incidence in females in three East Asian countries(125) and the median age at diagnosis of cases in this study was 60.2 (12.5) years.

3.6.5 Sensitivity analyses

In this study, menopausal status serves a dual purpose: it provides information about hormone status and also defines age, as women were categorized based on age at baseline. By considering menopausal status, women were divided into two groups: those younger than 54 years and those aged 54 years and older. This division allows us to calculate HRs and corresponding CIs and compare the results of the follow-up periods up to age 54 and those after 54 years. This analysis helps assess if young and old females differ in the risk of developing thyroid cancer due to reproductive or hormonal factors, thereby providing insights into its biological plausibility (Supplementary table 4).

3.6.6 Statistical software

In all analyses, statistical significance was determined using a two-sided p-value threshold of 0.05. Analyses were performed using SAS (SAS Inc., Cary, NC) and STATA (StataCorp LP, College Station, TX, USA) software.

Chapter 4. Results

4.1. Study Population Characteristics

4.1.1 Baseline characteristics of participating cohorts

The baseline characteristics of each participating cohort are shown in Table 4. Cohort enrolment was initiated from 1963 to 2002, and the follow-up of the final cohort ended in 2015. After exclusions, the final study population comprised a total of 289,707 females across the 10 participating cohorts. Among them, the greatest number of females was from the SWHS cohort (n=74,930) and the least were from the KMCC cohort (n=11,423). From the Japanese cohorts, JACC contributed the most number of participants (n=45,659).

Overall, the mean (SD) age at baseline was 54 (10.6) years. Among the total study population, a similar number of participants were born in the different decades: 1920s or earlier (25%), 1930s (30%), 1940s (25%) and 1950s or later (19%). However, when examining each birth year cohort separately, a higher proportion of females from the Japanese cohorts were older, and the SWHS and Korean cohorts mainly consisted of younger females born in the 1950s or later.

At baseline, 7% of females were ever smokers (n=20,230), and 19% were ever alcohol drinkers (n=56,091). The mean (SD) BMI at baseline for all females was 23.4 (6.4) kg/m^2.

During a mean (SD) follow-up of 17.2 (6.6) years in the 10 prospective cohorts, a total of 1,519 incident thyroid cancer cases were identified. The greatest number of cases came from the KNCC (n=421) and SWHS (n=306) cohorts. Overall, the mean (SD) age at baseline and at diagnosis for the thyroid cancer cases were 50.7 (9.7) and 60.2 (12.5) years respectively.

Table 4: Baseline characteristics of participating cohorts

(continued on next page)

Cohort	Number of women after exclusion	Enrolment (years)	Age at baseline (years)	Follow-up duration (years)	Birth years			
					1920s or earlier	*1930s*	*1940s*	*1950s and above*
	N	**Start-end**	**Mean (SD)**	**Mean (SD)**	**N (%) ***	**N (%) ***	**N (%) ***	**N (%) ***
ACC, Total	**289,707**	**1963-2015**	**54.0 (10.6)**	**17.2 (6.6)**	**71,729 (25)**	**85,945 (30)**	**73,666 (25)**	**55,812 (19)**
China								
SWHS	74,930	1996-2000	52.6 (9.1)	17.3 (3.1)	2,640 (4)	19,852 (26)	19,738 (26)	32,700 (44)
Japan								
JPHC1	21,465	1990-1992	49.6 (5.9)	21.5 (3.8)	0	11,109 (52)	10,356 (48)	0
JPHC2	27,715	1993-1995	54.3 (8.8)	18.3 (3.5)	6,370 (23)	9,196 (33)	9,003 (32)	3,146 (11)
JACC	45,659	1988-1990	57.4 (9.9)	16.3 (5.6)	20,349 (45)	14,503 (32)	10,684 (23)	123 (0)
Miyagi	22,837	1990	52.2 (7.4)	22.1 (5.5)	3,903 (17)	9,358 (41)	8,452 (37)	1,124 (5)
Ohsaki	22,191	1996	60.5 (10.0)	10.9 (4.2)	8,403 (38)	7,854 (35)	3,988 (18)	1,946 (9)
LSS	30,058	1963-1992	52.1 (15.1)	23.4 (10.3)	19,572 (65)	6,081 (20)	4,405 (15)	0
3pref. Miyagi	16,524	1984	57.4 (11.3)	11.7 (4.9)	9,578 (58)	5,161 (31)	1,785 (11)	0
Korea								
KMCC	11,423	1993-2005	54.0 (14.2)	14.5 (4.5)	901 (8)	2,534 (22)	2,290 (20)	3,143 (28)
KNCC	16,905	2002-2015	49.8 (9.0)	9.0 (3.4)	13 (0)	297 (2)	2,965 (18)	13,630 (81)

* – % calculated from total participants of each cohort.

Table 4: Baseline characteristics of women in the participating cohorts
(continued from previous page)

Cohort	Number of women after exclusion	Ever smokers at baseline	Ever alcohol drinkers at baseline	BMI at baseline (kg/m²)	TC cases	Age at baseline of TC cases (years)	Age at diagnosis of TC cases (years)
	N	N (%) *	N (%) *	Mean (SD)	N (%) #	Mean (SD)	Mean (SD)
ACC, Total	**289,707**	**20,230 (7)**	**56,091 (19)**	**23.4 (6.4)**	**1,519**	**50.7 (9.7)**	**60.2 (12.5)**
China							
SWHS	74,930	2,113 (3)	1,678 (2)	24.0 (3.4)	306 (20)	49.0 (7.7)	59.0 (7.8)
Japan							
JPHC1	21,465	1,602 (7)	4,938 (23)	23.6 (3.1)	108 (7)	48.1 (6.0)	58.2 (9.1)
JPHC2	27,715	2,125 (8)	6,021 (22)	23.4 (3.2)	77 (5)	52.5 (9.0)	63.3 (11.1)
JACC	45,659	2,606 (6)	10,704 (23)	22.9 (3.6)	89 (6)	55.4 (7.9)	60.7 (8.2)
Miyagi	22,837	1,873 (8)	5,544 (24)	23.7 (3.1)	167 (11)	52.2 (6.7)	64.1 (9.3)
Ohsaki	22,191	1,860 (8)	5,050 (23)	23.8 (3.4)	57 (4)	59.5 (8.3)	65.8 (8.6)
LSS	30,058	4,410 (15)	7,831 (26)	22.2 (17.0)	166 (11)	52.0 (14.9)	76.8 (17.0)
3pref. Miyagi	16,524	1,435 (9)	4,296 (26)	23.4 (3.6)	27 (2)	58.0 (9.3)	62.6 (9.7)
Korea							
KMCC	11,423	965 (8)	2,305 (20)	23.9 (3.4)	101 (7)	49.4 (11.6)	59.2 (10.8)
KNCC	16,905	1,241 (7)	7,724 (46)	23.1 (3.0)	421 (28)	48.6 (8.8)	52.0 (8.9)

* – % calculated from total participants of each cohort

– % calculated from total thyroid cancer cases (n=1519) to indicate % TC cases contributed by each cohort

TC–thyroid cancer

Table 5: Risk factor association with incident thyroid cancer

Covariate	HR (95% CI)	*p*-value
Smoking		
Ever	0.81 (0.65-1.01)	0.06
Never	*reference*	
Alcohol drinking		
Ever	0.91 (0.79-1.04)	0.16
Never	*reference*	
Body Mass Index (kg/m^2)		
Underweight <18.5	1.08 (0.84-1.39)	0.56
Normal 18.5–22.9	*reference*	
Overweight 23.0–24.9	**1.16 (1.02-1.32)**	***0.03***
Obese ≥25	**1.22 (1.07-1.38)**	***0.002***

Body mass index categorized using categories recommended by the WHO for adult Asians

HR – Hazard ratio, CI – confidence interval

p−values indicated in bold show significant association.

4.1.2 Characteristics of cohorts by reproductive factor

Details of the characteristics of women in the participating cohorts according to reproductive factor are available in Tables 6 to 15.

Age at menarche (Table 6)

All thyroid cancer cases (n=1,519) in the participating cohorts had age at menarche information available. A greater proportion of women (n=122,592) and thyroid cancer cases (n=656) had their menarche between the ages of 13−14 years, while least were seen for <13 years (n=17,702, cases=108). The KMCC cohort had no case for the <13 years category.

Parity status (Table 7) and Number of children/deliveries (Table 8)

All thyroid cancer cases (n=1,519) had information for parity status. A major proportion of them (n=269,810, cases=1,426) were parous. Being parous included women that reported stillbirth or miscarriages.

Number of children/deliveries was categorized in two different ways as shown in Table 8. LSS cohort did not have data on number of deliveries/pregnancies. Most women in the participating cohorts had 1−2 children (n=138,752, cases=822), more specifically 2 children (n=82,996, cases=502). Having no children did not include parous women that reported stillbirth or miscarriages.

Age at first delivery/pregnancy (Table 9)

Table 9 shows that a comparable number of women were between the ages of 21−25 years (n=133,978, cases=631) or ≥ 26 years (n=102,295, cases=662) when they first gave birth.

Table 6: Cohort−specific characteristics by age at menarche

Reproductive Characteristic		Total	SWHS	JPHC1	JPHC2	JACC	Miyagi	Ohsaki	LSS	3pref. Miyagi	KMCC	KNCC
Age at menarche												
	N	**17,702**	4,683	1,891	2,483	2,860	1,771	483	1,322	888	136	1,185
<13 years	*Person years*	**322,273**	82,965	40,886	46,445	47,299	39,478	5,435	36,996	10,076	2,342	10,351
	TC cases	**108**	26	16	9	5	13	2	9	2	0	26
	N	**122,592**	27,385	9,040	11,115	17,942	10,913	14,137	16,862	6,354	1,906	6,938
13-14 years	*Person years*	**2,112,142**	479,265	195,244	205,685	294,422	243,410	154,500	376,298	73,352	28,532	61,435
	TC cases	**656**	107	53	31	34	79	35	95	11	20	191
	N	**99,309**	29,548	7,500	9,046	16,661	7,137	5,024	8,243	6,345	3,703	6,102
15-16 years	*Person years*	**1,711,937**	511,684	160,552	165,157	271,203	157,218	54,999	205,473	75,744	53,380	55,528
	TC cases	**510**	119	25	23	41	53	16	42	11	39	141
	N	**50,104**	13,314	3,034	5,071	8,196	3,016	2,547	3,631	2,937	5,678	2,680
≥17 years	*Person years*	**827,222**	225,344	64,069	90,780	130,176	65,382	27,349	83,210	34,749	81,230	24,935
	TC cases	**245**	54	14	14	9	22	4	20	3	42	63

* Women with age at menarche less than 10 years or greater than 23 years, TC−thyroid cancer

Table 7: Cohort−specific characteristics by parity status

Reproductive Characteristic		Total	SWHS	JPHC1	JPHC2	JACC	Miyagi	Ohsaki	LSS	3pref. Miyagi	KMCC	KNCC
Parity status												
	N	**19,897**	2,506	1,186	1,609	1,773	567	742	8,802	1,609	532	571
Nulliparous	*Person years*	**335,142**	42,633	24,622	28,644	28,222	11,893	8,270	157,824	17,562	9,027	6,447
	TC cases	**93**	8	3	2	7	2	5	43	1	3	19
	N	**269,810**	72,424	20,279	26,106	43,886	22,270	21,449	21,256	14,915	10,891	16,334
Parous	*Person years*	**4,638,432**	1,256,625	436,128	479,424	714,877	493,594	234,013	544,153	176,359	157,458	145,802
	TC cases	**1,426**	298	105	75	82	165	52	123	26	98	402

TC−thyroid cancer

Table 8: Cohort−specific characteristics by number of children/deliveries

Reproductive Characteristic		Total	SWHS	JPHC1	JPHC2	JACC	Miyagi	Ohsaki	LSS	3pref. Miyagi	KMCC	KNCC
Number of children/deliveries												
	N	**11,095**	2,506	1,186	1,609	1,773	567	742	0	1,609	532	571
No child	*Person years*	**177,276**	42,633	24,622	28,644	28,222	11,893	8,270	0	17,562	9,026	6,447
	TC cases	**50**	8	3	2	7	2	5	0	1	3	19
	N	**138,752**	56,689	8,975	11,189	20,319	11,050	9,176	0	6,595	2,525	12,234
1-2 children	*Person years*	**2,304,082**	1,003,382	192,554	206,267	336,215	244,075	101,470	0	77,373	36,424	106,595
	TC cases	**822**	269	47	37	45	90	24	0	8	27	275
	N	**86,398**	12,515	9,254	10,883	19,865	10,323	10,026	0	5,644	4,111	3,777
3-4 children	*Person years*	**1,436,822**	204,049	200,094	200,247	327,132	230,388	110,023	0	70,195	59,380	35,771
	TC cases	**398**	25	49	25	34	70	25	0	11	46	113
	N	**55,756**	40,792	1,614	2,125	3,440	1,679	1,635	0	1,659	543	2,269
1 child	*Person years*	**951,569**	727,201	34,167	38,321	53,246	35,905	18,067	0	17,784	7,811	19,068
	TC cases	**320**	219	9	8	6	14	5	0	0	4	55
	N	**82,996**	15,897	7,361	9,064	16,879	9,371	7,541	0	4,936	1,982	9,965
2 children	*Person years*	**1,352,785**	276,181	158,387	167,946	282,969	208,170	83,403	0	59,589	28,613	87,527
	TC cases	**502**	50	38	29	39	76	19	0	8	23	220
	N	**60,307**	7,870	6,545	7,367	14,589	7,883	7,087	0	3,847	2,079	3,040
3 children	*Person years*	**1,014,650**	130,080	141,876	135,950	244,523	176,968	78,381	0	48,305	30,071	28,497
	TC cases	**283**	17	35	16	28	48	20	0	7	30	82
	N	**26,091**	4,645	2,709	3,516	5,276	2,440	2,939	0	1,797	2,032	737
4 children	*Person years*	**422,627**	73,969	58,218	64,297	82,608	53,421	31,642	0	21,890	29,309	7,273
	TC cases	**115**	8	14	9	6	22	5	0	4	16	31
	N	**22,510**	3,220	1,854	3,703	3,702	897	2,247	0	2,676	3,888	323
≥5 children	*Person years*	**335,943**	49,194	39,418	67,062	51,531	19,131	22,520	0	28,792	54,859	3,436
	TC cases	**80**	4	9	12	3	5	3	0	7	23	14
	N	**30,952**	0	196	331	0	0	0	30,058	0	367	0
Missing	*Person years*	**718,680**	0	4,062	5,849	0	0	0	701,977	0	6,793	0
	TC cases	**169**	0	0	1	0	0	0	166	0	2	0

TC−thyroid cancer

Table 9: Cohort−specific characteristics by age at first delivery/pregnancy

Reproductive Characteristic		Total	SWHS	JPHC1	JPHC2	JACC	Miyagi	Ohsaki	LSS	3pref. Miyagi	KMCC	KNCC
Age at first delivery/pregnancy												
	N	**26,639**	8,530	1,680	1,887	2234	1,641	1,848	4761	1,526	2,172	360
≤ 20 years	*Person years*	**459,570**	138,089	35,967	34,425	33,582	36,129	19,614	111,213	16,858	30,243	3,449
	TC cases	**100**	20	8	4	7	12	6	24	3	6	10
	N	**133,978**	22,908	10,777	14,579	23721	14,785	14,574	11772	8,954	6,062	5,846
21-25 years	*Person years*	**2,322,4773**	392,101	231,963	269,127	379,060	330,675	159,314	309,048	108,887	87,947	54,354
	TC cases	**631**	72	55	37	35	110	28	75	18	58	143
	N	**102,295**	40,981	7,360	8,586	15,032	5,689	4,266	4,723	4,049	2,006	9,603
≥ 26 years	*Person years*	**1,74,501**	726,351	158,521	156,998	250,355	123,419	47,002	123,891	46,550	28,716	83,693
	TC cases	**662**	206	42	32	30	43	16	24	5	31	233
	N	**6,898**	5	462	1,054	2,899	155	761	0	386	651	525
Missing*	*Person years*	**110,883**	83	9,676	18,873	51,880	3,370	8,082	0	4,064	10,551	4,305
	TC cases	**33**	0	0	2	10	0	2	0	0	3	16
	N	**19,897**	2,506	1,186	1,609	1,773	567	742	8,802	1,609	532	571
Missing**	*Person years*	**335,142**	42,633	24,622	28,644	28,222	11,893	8,270	157,824	17,562	9,026	6,447
	TC cases	**93**	8	3	2	7	2	5	43	1	3	19

* Parous women with missing information on age at first delivery/pregnancy

** Nulliparous women with missing information on age at first delivery/pregnancy

TC−thyroid cancer

Breastfeeding status (Table 10)

A larger proportion of women had ever breastfed (n= 97,139, cases= 727), however a comparable amount were missing breastfeeding information (n= 176,902, cases= 682).

Postmenopausal status (Table 11)

Table 11 demonstrates that more women were postmenopausal than premenopausal, and this was most evident in the Ohsaki, 3pref. Miyagi and KMCC cohorts.

Age at menopause (Table 12)

The age at menopause was generally between 50−54 years for most cohorts (n= 67,966, cases= 296).

OC use (Table 13) and HRT use (Table 14)

Among the four cohorts that had OC use data, most of them were never users (n= 60,358, cases= 570), but a majority of data was missing (n= 220,995, cases= 838).

Similarly, in Table 14 a high majority of the women were never HRT users (n= 163,306, cases= 792) and equivalent number of women had no information for this factor (n= 114,749, cases= 616).

Hysterectomy status (Table 15)

None of the women in any of the cohorts had had hysterectomy (n= 0, cases= 0). Except KMCC and KNCC, all cohorts were missing information on hysterectomy status (n= 272,211, cases= 1,202).

Table 10: Cohort−specific characteristics by breastfeeding status

Reproductive Characteristic		Total	SWHS	JPHC1	JPHC2	JACC	Miyagi	Ohsaki	LSS	3pref. Miyagi	KMCC	KNCC
Breastfeeding status												
	N	**15,666**	0	2,841	2,900	0	4,013	3,040	0	0	431	2,441
Never	*Person years*	**263,564**	0	60,764	53,270	0	89,243	33,352	0	0	5,902	21,083
	TC cases	**110**	0	11	7	0	23	8	0	0	5	56
	N	**97,139**	0	17,085	22,527	0	17,570	18,008	0	0	9,444	12,505
Ever	*Person years*	**1,606,615**	0	367,820	414,189	0	389,222	196,336	0	0	134,004	105,823
	TC cases	**727**	0	94	67	0	142	44	0	0	83	297
	N	**176,902**	74,930	1,539	2,288	45,659	1,254	1,143	30,058	16,524	1,548	1,959
Missing*	*Person years*	**3,102,406**	1,299,258	32,166	40,609	743,100	27,022	12,596	701,977	193,921	26,577	25,343
	TC cases	**682**	306	3	3	89	2	5	166	27	13	68

TC−thyroid cancer

Table 11: Cohort−specific characteristics by postmenopausal status

Reproductive Characteristic		Total	SWHS	JPHC1	JPHC2	JACC	Miyagi	Ohsaki	LSS	3pref. Miyagi	KMCC	KNCC
Postmenopausal status												
	N	**102,470**	37,102	9,603	8,971	11,575	8,791	3,832	11,913	4,407	289	5,987
No	*Person years*	**1,975,458**	665,197	208,613	169,932	208,397	199,138	41,994	362,924	52,696	4,724	61,845
	TC cases	**639**	192	63	30	26	57	9	73	6	1	182
	N	**179,555**	37,824	11,813	18,699	33,933	13,808	18,279	16,066	11,751	8,554	8,828
Yes	*Person years*	**2,879,776**	634,005	251,088	337,272	532,437	301,050	199,423	292,453	136,383	119,828	75,838
	TC cases	**796**	114	45	46	63	109	48	87	20	66	198
	N	**7,682**	4	49	45	151	238	80	2,079	366	2,580	2,090
Missing	*Person years*	**118,339**	57	1049	864	2266	5299	866	46599	4843	41,932	14565
	TC cases	**84**	0	0	1	0	1	0	6	1	34	41

TC−thyroid cancer

Table 12: Cohort−specific characteristics by age at menopause

Reproductive Characteristic		Total	SWHS	JPHC1	JPHC2	JACC	Miyagi	Ohsaki	LSS	3pref. Miyagi	KMCC	KNCC
Age at menopause												
	N	**25,467**	6,266	1,851	2,629	4,241	2,040	1,957	2,446	1,181	1,562	1,294
<45 years	*Person years*	**417,630**	105,452	38,969	47,546	65,366	44,101	21,051	48,736	13,595	21,103	11,712
	TC cases	**128**	24	8	9	12	17	6	13	1	9	29
	N	**57,351**	16,414	4,262	5,936	10,320	3,668	4,384	5,081	2,673	2,001	2,612
45-49 years	*Person years*	**945,648**	274,827	90,812	107,141	163,837	80,235	48,093	97,819	31,748	28,098	23,039
	TC cases	**246**	48	16	11	16	31	14	31	4	11	64
	N	**67,966**	13,232	5,046	8,564	14,985	4,695	6,538	5,421	3,150	2,429	3,906
50-54 years	*Person years*	**1,098,554**	221,697	107,689	154,707	236,827	102,742	72,479	98,515	37,254	34,011	32,636
	TC cases	**296**	37	18	22	26	44	17	26	8	19	79
	N	**7,837**	1,440	301	941	1,656	453	861	562	325	550	748
≥55 years	*Person years*	**116,223**	23,765	6,258	16,840	24,182	9,696	9,536	8,899	3,689	7,144	6,214
	TC cases	**43**	4	2	3	4	3	0	5	0	6	16
	N	**28,616**	476	402	674	2,882	3,190	4,619	4,635	4,788	4,592	2,358
Missing	*Person years*	**420,059**	8,320	8,409	11,902	44,492	69,576	49,131	85,084	54,940	71,403	16,803
	TC cases	**167**	1	1	2	5	15	11	18	8	55	51
	N	**102,470**	37,102	9,603	8,971	11,575	8,791	3,832	11,913	4,407	289	5,987
Not postmenopausal	*Person years*	**1,975,458**	665,197	208,613	169,932	208,397	199,138	41,994	362,924	52,696	4,724	61,845
	TC cases	**639**	192	63	30	26	57	9	73	6	1	182

TC−thyroid cancer

Table 13: Cohort−specific characteristics by oral contraceptive use

Reproductive Characteristic		Total	SWHS	JPHC1	JPHC2	JACC	Miyagi	Ohsaki	LSS	3pref. Miyagi	KMCC	KNCC
Oral contraceptive use												
	N	**60,358**	0	0	0	0	21,637	19,140	0	0	7,496	12,085
Never	*Person years*	**902,138**	0	0	0	0	479,108	210,086	0	0	105,994	106,950
	TC cases	**570**	0	0	0	0	153	49	0	0	66	302
	N	**8,354**	0	0	0	0	732	949	0	0	3,573	3,100
Ever	*Person years*	**109,753**	0	0	0	0	16,089	10,253	0	0	55,931	27,479
	TC cases	**111**	0	0	0	0	10	1	0	0	32	68
	N	**220,995**	74,930	21,465	27,715	45,659	468	2,102	30,058	16,524	354	1,720
Missing*	*Person years*	**3,961,684**	1,299,258	460,750	508,068	743,100	10,290	21,943	701,977	193,921	4,558	17,819
	TC cases	**838**	306	108	77	89	4	7	166	27	3	51

* Missing includes cohorts with no data on OC use and OC use duration , TC−thyroid cancer

Table 14: Cohort−specific characteristics by hormone replacement therapy use

Reproductive Characteristic		Total	SWHS	JPHC1	JPHC2	JACC	Miyagi	Ohsaki	LSS	3pref. Miyagi	KMCC	KNCC
Hormone replacement therapy												
	N	**163,306**	72,279	0	0	37,313	19,113	18,404	0	0	10,359	5,838
No	*Person years*	**2,690,336**	1,252,199	0	0	614,348	423,352	201,384	0	0	148,972	49,181
	TC cases	**792**	294	0	0	77	146	46	0	0	94	135
	N	**11,652**	2,651	0	0	1,975	1,446	1,652	0	0	1,064	2,864
Yes	*Person years*	**171,179**	47,059	0	0	31,769	31,781	17,926	0	0	16,522	26,033
	TC cases	**111**	12	0	0	6	11	3	0	0	7	72
	N	**114,749**	0	21,465	27,715	6,371	2,278	2,135	30,058	16,524	0	8,203
Missing	*Person years*	**2,112,058**	0	460,750	508,068	96,982	50,354	22,973	701,977	193,921	0	77,035
	TC cases	**616**	0	108	77	6	10	8	166	27	0	214

TC−thyroid cancer

Table 15: Cohort−specific characteristics by hysterectomy status

Reproductive Characteristic		Total	SWHS	JPHC1	JPHC2	JACC	Miyagi	Ohsaki	LSS	3pref. Miyagi	KMCC	KNCC
Hysterectomy status												
	N	**17,496**	0	0	0	0	0	0	0	0	8,083	9,413
No	*Person years*	**200,527**	0	0	0	0	0	0	0	0	113,029	87,498
	TC cases	**317**	0	0	0	0	0	0	0	0	72	245
	N	**0**	0	0	0	0	0	0	0	0	0	0
Yes	*Person years*	**0**	0	0	0	0	0	0	0	0	0	0
	TC cases	**0**	0	0	0	0	0	0	0	0	0	0
	N	**272,211**	74,930	21,465	27,715	45,659	22,837	22,191	30,058	16,524	3,340	7,492
Missing	*Person years*	**4,773,047**	1,299,258	460,750	508,068	743,100	505,487	242,283	701,977	193,921	53,455	64,751
	TC cases	**1,202**	306	108	77	89	167	57	166	27	29	176

TC−thyroid cancer

4.2. Reproductive factors & Thyroid cancer

4.2.1 Overall pooled analyses

Table 16 demonstrates the pooled HRs and 95% CIs for the association between reproductive factors and the risk of overall thyroid cancer risk. Supplementary Figures 4 to 12 demonstrate forest plots of the pooled analyses with cohort specific HRs and 95% CIs for each reproductive variable.

After adjusting for potential covariates, a significant positive association was observed with older age at first delivery/pregnancy. Non-significant positive associations were seen for a higher number of children/deliveries, ever breastfeeding, being menopausal and later age at menopause. Age at menarche, parity status, OC and HRT use were not associated with the risk of thyroid cancer.

4.2.2 Age at first delivery/pregnancy

Older age at first delivery/pregnancy was significantly associated with the risk of thyroid cancer. When compared to 21-25 years (reference), the HR (95% CIs) for ≥ 26 years was 1.16 (1.03-1.31) and that for ≤20 years was 1.09 (0.85-1.39) with a significant *p* for trend [*p*-trend 0.003]. Inter-study heterogeneities were low (I^2 0-4%).

4.2.3 Parity status, Number of children/deliveries

Compared to nulliparous, parous women did not show a significant association, the HR with 95% CI was 0.97 (0.73-1.30). The inter-study heterogeneities were moderate (I^2 55%).

Considering the low number of cases of nulliparous women (cases=93), the association between number of children/deliveries and thyroid cancer risk was sought among parous women (cases=1,426). When compared to the lowest category of number deliveries (1-2 children), the HRs (95% CIs) for 4-5 and ≥5 children were 1.05 (0.92-1.20) and 1.15 (0.87-1.51) respectively (*p*-trend 0.72).

To clearly see the number of children/deliveries that were associated with thyroid cancer risk, the reference was set to 1 child and the corresponding HRs (95% CIs) for 2, 3, 4 and ≥5 children, were 0.92 (0.76−1.11), 0.96 (0.77−1.21), 1.15 (0.87−1.52) and 1.07 (0.75−1.51) respectively, with a *p* for trend 0.84. Having 4 children showed the highest risk of thyroid cancer risk, though statistically nonsignificant. The heterogeneity was low (I^2 0−39%).

4.2.4 Breastfeeding status

Compared to never breastfeeding, the HR and 95% CI for ever breastfeeding was 1.15 (0.97−1.36), with low heterogeneity (I^2 0).

4.2.5 Postmenopausal status, Age at menopause

The HR (95% CI) for postmenopausal women [vs being premenopausal (reference)] was 1.19 (0.99−1.42)].

On setting the youngest category of age at menopause (<45 years) as reference, the corresponding HRs (95% CIs) for 45−49 years, 50−54 years and ≥55 years were 1.00 (0.79−1.26), 1.04 (0.82−1.31) and 1.30 (0.87−1.93) with *p*−trend 0.28. The heterogeneities were low for both menopausal status and age at menopause.

4.2.6 Age at menarche

Compared to later age at menarche (≥17 years), the HRs (95% CIs) for <13 years, 13−14 years and 15−16 years were 1.04 (0.80−1.34), 0.99 (0.84−1.17) and 1.00 (0.85−1.18) respectively, *p*−trend 0.81. The I^2 (0−27%) represented low heterogeneity.

4.2.7 OC use, HRT use

Ever (vs never) OC use and yes (vs no) HRT use had HRs (95% CIs) 0.95 (0.79−1.14) and 1.05 (0.84−1.32) respectively. The I^2 (57%) showed moderate heterogeneity for OC use and there was low heterogeneity for HRT use.

Table 16: Pooled relative risks for reproductive factors & incident thyroid cancer risk, Overall

(continued on next page)

Reproductive characteristic	Number of women	Person-years	Number of TC cases	HR[a] (95% CI)	Heterogeneity		*p*-trend	HR[b] (95% CI)	Heterogeneity		*p*-trend
					I^2 (%)	*p*			I^2 (%)	*p*	
Age at menarche											
<13 years	17,702	322,273	108	1.05 (0.81-1.35)	0	0.87		1.04 (0.80-1.34)	0	0.88	
13-14 years	122,592	2,112,142	656	1.00 (0.84-1.18)	0	0.66	0.80	0.99 (0.84-1.17)	0	0.63	0.81
15-16 years	99,309	1,711,937	510	1.00 (0.85-1.18)	25	0.23		1.00 (0.85-1.18)	27	0.21	
≥17 years	50,104	827,222	245	*reference*				*reference*			
Parity status											
Nulliparous	19,897	335,142	93	*reference*				*reference*			
Parous	269,810	4,638,432	1,426	1.00 (0.75-1.33)	55	0.02*		0.97 (0.73-1.30)	55	0.03*	
Number of children/deliveries											
1-2 children	138,752	2,304,354	822	*reference*				*reference*			
3-4 children	86,398	1,437,278	398	1.08 (0.94-1.23)	56	0.02*	0.65	1.05 (0.92-1.20)	52	0.03*	0.72
≥5 children	22,510	335,943	80	1.19 (0.90-1.56)	46	0.06		1.15 (0.87-1.51)	44	0.07	
1 child	55,756	951,569	320	*reference*				*reference*			
2 children	82,996	1,352,785	502	0.94 (0.77-1.13)	0	0.97		0.92 (0.76-1.11)	0	0.98	
3 children	60,307	1,014,650	283	1.01 (0.81-1.26)	21	0.27	0.93	0.96 (0.77-1.21)	16	0.31	0.84
4 children	26,091	422,627	115	1.22 (0.92-1.61)	41	0.10		1.15 (0.87-1.52)	39	0.12	
≥ 5 children	22,510	335,943	80	1.13 (0.80-1.60)	38	0.12		1.07 (0.75-1.51)	37	0.13	
Age at first delivery/pregnancy											
≤ 20 years	26,639	459,570	100	1.07 (0.84-1.37)	26	0.21		1.09 (0.85-1.39)	24	0.23	
21-25 years	133,978	2,322,477	631	*reference*			**0.005***	*reference*			**0.003***
≥ 26 years	102,295	1,745,501	662	**1.14 (1.02-1.27)**	9	0.36		**1.16 (1.03-1.31)**	9	0.36	
Breastfeeding status											
Never	15,666	263,613	110	*reference*				*reference*			
Ever	97,139	1,607,394	727	1.17 (0.96-1.44)	0	0.88		1.15 (0.97-1.36)	0	0.88	
Postmenopausal status											
No	102,470	1,975,458	639	*reference*				*reference*			
Yes	179,555	2,879,776	796	1.20 (1.00-1.44)	20	0.26		1.19 (0.99-1.42)	21	0.26	

Table 16: Pooled relative risks for reproductive factors & incident thyroid cancer risk, Overall

(continued from previous page)

Reproductive characteristic	Number of women	Person-years	Number of TC cases	HR[a] (95% CI)	Heterogeneity		*p*-trend	HR[b] (95% CI)	Heterogeneity		*p*-trend
					I^2 (%)	*p*			I^2 (%)	*p*	
Age at menopause											
<45 years	25,467	417,630	128	*reference*				*reference*			
45-49 years	57,351	945,648	246	1.00 (0.79-1.26)	0	0.91		1.00 (0.79-1.26)	0	0.91	
50-54 years	67,966	1,098,554	296	1.05 (0.83-1.32)	0	0.92	0.28	1.04 (0.82-1.31)	0	0.92	0.28
≥55 years	7,837	116,223	43	1.33 (0.89-1.98)	0	0.95		1.30 (0.87-1.93)	0	0.95	
Oral contraceptive use											
Never	60,358	902,138	570	*reference*				*reference*			
Ever	8,354	109,753	111	0.97 (0.79-1.20)	48	0.12		0.95 (0.79-1.14)	57	0.07	
Hormone replacement therapy use											
No	163,306	2,690,336	792	*reference*				*reference*			
Yes	11,652	171,179	111	1.06 (0.85-1.32)	0	0.89		1.05 (0.84-1.32)	0	0.89	
Hysterectomy status											
No	17,496	200,527	317	-				-			
Yes	0	-	0	-				-			

HR[a] – Unadjusted Cox proportional hazard model with age as time-scale,

HR[b] – Adjusted Cox proportional hazard model for smoking status, alcohol drinking status and BMI

Heterogeneity – Cochran's *Q* test *p*-value (<0.1) provides evidence of heterogeneity. I^2 statistic of 0-40% indicates low heterogeneity, 30-60% moderate, 50-90% substantial and 75-100% considerable heterogeneity.

p-trend – *p* value for trend

LSS cohort was not included

4.3. Reproductive factors & Papillary thyroid cancer

4.3.1 Thyroid cancer cases in the cohorts by histology

Among the 1,519 thyroid cancer cases, a total of 1,294 cases had histological data available, of whom 88% (n=1,140) were the papillary histological type, while the medullary, follicular and anaplastic types were 1% (n=7), 3% (n=37) and 1% (n=11) respectively (Table 17).

Table 18 details the distribution of thyroid cancer cases among participating cohorts according to the histological subtype. No histological information was available for the LSS cohort. Papillary thyroid cancer cases were present in all cohorts except 3pref Miyagi. Most of the papillary thyroid cancer cases came from the KNCC (n=410) and SWHS (n=256) cohorts.

4.3.2 Pooled analyses, papillary thyroid cancer

Similar associations were seen for papillary thyroid cancer as the overall thyroid cancer pooled analyses (Table 19).

Table 17: Distribution of total thyroid cancer cases by histological subtype

	Total TC cases	Total TC cases with histological data available	Papillary	Medullary	Follicular	Anaplastic	Specified	Unspecified
	N	N	N (%) *	N (%) *	N (%) *	N (%)	N (%) *	N (%) *
Total	**1,519**	**1,294**	**1,140 (88)**	**7 (1)**	**37(3)**	**11 (1)**	**9 (1)**	**90 (7)**

* % calculated from total cases with histological data available(n=1294)

Table 18: Cohort-specific distribution of thyroid cancer cases by histological subtype

Cohort	Total	TC cases with histological data available	Papillary	Medullary	Follicular	Anaplastic	Specified	Unspecified
	N	N	N (%) *	N (%) *	N (%) *	N (%)	N (%) *	N (%) *
Total	**1,519**	**1,294**	**1,140**	**7 (1)**	**37(3)**	**11 (1)**	**9 (1)**	**90 (7)**
China								
SWHS	306	296	256 (22)	4 (57)	14 (38)	0	0	22 (24)
Japan								
JPHC1	108	106	99 (9)	0	1 (3)	1 (9)	0	5 (6)
JPHC2	77	70	56 (5)	0	8 (22)	1 (9)	0	5 (6)
JACC	89	82	62 (5)	0	3 (8)	1 (9)	0	16 (18)
Miyagi	167	160	144 (13)	1 (14)	3 (8)	6 (55)	0	6 (7)
Ohsaki	57	56	49 (4)	0	3 (8)	2 (18)	0	2 (2)
LSS	166	0	0	0	0	0	0	0
3pref. Miyagi	27	27	0	0	0	0	0	27 (30)
Korea								
KMCC	101	76	64 (6)	2 (29)	3 (8)	0	2 (22)	5 (6)
KNCC	421	421	410 (36)	0	2 (5)	0	7 (78)	2 (2)

* % calculated from total cases to indicate % of cases that each cohort contributed to a certain histological type

Table 19: Pooled relative risks for reproductive factors & incident thyroid cancer risk, Papillary type

(continued on next page)

Reproductive characteristic	Number of women	Person-years	Number of papillary TC cases	HR[a] (95% CI)	*p*-trend	HR[b] (95% CI)	*p*-trend
Age at menarche							
<13 years	16,340	763	89	1.03 (0.79-1.34)		1.03 (0.79-1.33)	
13-14 years	105,642	3,489	473	0.96 (0.79-1.14)	0.98	0.95 (0.79-1.13)	0.94
15-16 years	90,989	2,513	391	0.97 (0.81-1.16)		0.96 (0.81-1.15)	
≥17 years	46,435	1,082	187	*reference*		*reference*	
Parity status							
Nulliparous	11,085	177,215	40	*reference*		*reference*	
Parous	248,351	4,091,901	1,100	1.12 (0.89-1.69)		1.18 (0.85-1.62)	
Number of children/deliveries							
1-2 children	138,641	2,303,256	711	*reference*		*reference*	
3-4 children	86,331	1,436,325	331	1.07 (0.93-1.24)	0.53	1.05 (0.91-1.22)	0.61
≥5 children	22,488	335,650	58	1.03 (0.76-1.39)		1.03 (0.76-1.39)	
1 child	55,709	951,103	273	*reference*		*reference*	
2 children	82,932	1,352,153	438	0.94 (0.71-1.01)		0.92 (0.69-0.99)	
3 children	60,259	1,014,027	235	0.99 (0.73-1.11)	0.77	0.97 (0.71-1.08)	0.88
4 children	26,072	422,298	96	1.07 (0.82-1.40)		1.03 (0.79-1.35)	
≥ 5 children	22,488	335,650	58	0.91 (0.65-1.27)		0.89 (0.64-1.25)	
Age at first delivery/pregnancy							
≤ 20 years	21,863	348,238	61	1.08 (0.83-1.39)		1.07 (0.83-1.38)	
21-25 years	122,119	2,012,167	469	*reference*	0.07	*reference*	**0.05**
≥ 26 years	97,479	1,620,684	545	1.11 (0.96-1.26)		1.11 (0.98-1.25)	
Breastfeeding status							
Never	15,657	263,527	101	*reference*		*reference*	
Ever	97,050	1,605,981	638	1.19 (0.96-1.47)		1.18 (0.95-1.45)	
Postmenopausal status							
No	90,498	1,611,951	507	*reference*		*reference*	
Yes	163,360	2,585,834	580	1.18 (0.98-1.42)		1.17 (0.97-1.41)	

Table 19: Pooled relative risks for reproductive factors & incident thyroid cancer risk, Papillary type

(continued on next page)

Reproductive characteristic	Number of women	Person-years	Number of papillary TC cases	HR[a] (95% CI)	*p*-trend	HR[b] (95% CI)	*p*-trend
Age at menopause							
<45 years	23,000	368,672	94	*reference*		*reference*	
45-49 years	52,237	847,499	182	1.10 (0.85-1.42)		1.10 (0.85-1.41)	
50-54 years	62,499	999,499	224	1.16 (0.90-1.51)	0.19	1.14 (0.88-1.48)	0.2
≥55 years	7,267	107,235	30	1.29 (0.83-1.98)		1.26 (0.81-1.93)	
Oral contraceptive use							
Never	60,296	901,198	508	*reference*		*reference*	
Ever	8,340	109,383	97	0.97 (0.77-1.21)		0.97 (0.77-1.22)	
Hormone replacement therapy use							
No	163,168	2,688,486	654	*reference*		*reference*	
Yes	11,642	171,044	101	1.12 (0.89-1.41)		1.11 (0.89-1.40)	
Hysterectomy status							
No	17,462	199,846	283	-		-	
Yes	0	-	0	-		-	

HR[a] – Unadjusted Cox proportional hazard model with age as time−scale,

HR[b] – Adjusted Cox proportional hazard model for smoking status, alcohol drinking status and BMI

p−trend – *p* value for trend

4.4. Stratified Analyses by Body Mass Index

Age at first delivery/pregnancy

Table 20 (and Figure 7) show a significant interaction effect for the association between age at first delivery/pregnancy and thyroid cancer modified by BMI (p−interaction 0.02).

For low BMI (<23 kg/m^2), the risk of developing thyroid cancer was relatively higher for women with older age at first delivery/pregnancy, while for high BMI (≥23 kg/m^2) the risk of thyroid cancer was relatively higher for women who had their first delivery/pregnancy at a younger age.

For women with BMI <23 kg/m^2, the HRs (95% CIs) for ≤20 years and ≥ 26 years [vs 21−25 years (reference)] were 1.14 (0.66−1.96) and 1.17 (0.97−1.41) respectively. The trend for this association was also significant (p−trend 0.007). While for women with BMI ≥23 kg/m^2, the corresponding HRs (95% CIs) were 1.23 (0.92−1.64) and 1.14 (0.96−1.34).

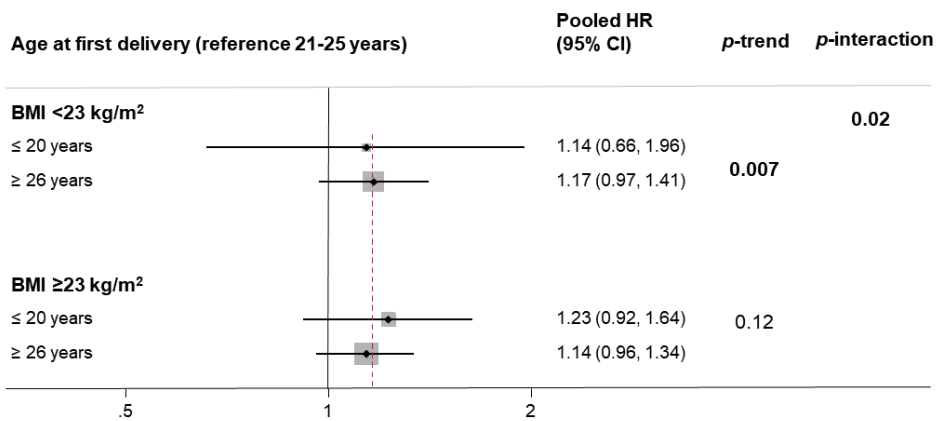

Figure 7: Pooled relative risks for age at first delivery/pregnancy and thyroid cancer, stratified by BMI

* Pooled HRs (95% CIs) generated by combining cohort−specific HRs (95% CIs) for each category of age at first delivery/pregnancy (see supplementary figure 13)

Table 20: Characteristics of participating cohorts by age at first delivery/pregnancy, stratified by BMI

	BMI <23 kg/m^2			BMI ≥23 kg/m^2		
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**
Age at first delivery/pregnancy						
≤ 20 years	10,265	182,036	28	15,862	270,101	71
21-25 years	61,327	1,083,273	266	70,495	1,206,570	356
≥ 26 years	51,755	885,443	327	49,645	847,155	327

TC – thyroid cancer

OC use

Effect modification by BMI was also seen for the association between OC use and thyroid cancer risk (p–interaction 0.02). An inverse association was seen among females with BMI<23 kg/m^2 (HR 0.8, 95% CI: 0.57–1.13), while those with BMI >23 kg/m^2 had a positive association (HR 1.14, 95% CI: 0.87–1.50) (Table 27). But it must be noted that very few cohorts contributed to this variable.

Other reproductive factors

No effect modification by BMI was observed for the associations between thyroid cancer and age at menarche (p–interaction 0.14) (Table 21), parity status (p–interaction 0.81) (Table 22), or number of children/deliveries (p–interaction 0.12) (Table 23), or breastfeeding status (p–interaction 0.54) (Table 24), or postmenopausal status (p–interaction 0.80) (Table 25), or age at menopause (p–interaction 0.50) (Table 26) or HRT use (p–interaction 0.16) (Table 28).

Table 21: Pooled relative risks for age at menarche and thyroid cancer, stratified by BMI

	BMI <23 kg/m²				BMI ≥23 kg/m²				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Age at menarche									0.13
< 13 years	8,165	149,895	49	0.88(0.61-1.28)	9449	170,860	59	1.15(0.83-1.61)	
13-14 years	59,693	1,041,465	303	0.85(0.66-1.09)	61097	1,044,983	341	1.09(0.88-1.37)	
15-16 years	47,302	826,578	220	0.83(0.65-1.06)	50887	868,158	284	1.13(0.91-1.41)	
≥ 17 years	23,144	385,309	115	*reference*	25949	426,328	129	*reference*	
***p*-trend**				0.48				0.53	

HR[b] – Adjusted Cox proportional hazard model for smoking status and alcohol drinking status, TC – thyroid cancer

Table 22 Pooled relative risks for parity status and thyroid cancer, stratified by BMI

	BMI <23 kg/m²				BMI ≥23 kg/m²				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Parity status									0.80
Nulliparous	11,895	204,341	53	*reference*	7,818	128,292	39	*reference*	
Parous	126,409	2,198,907	634	1.32(0.88-2.00)	1,395,694	2,382,038	774	1.01(0.67-1.53)	

HR[b] – Adjusted Cox proportional hazard model for smoking status and alcohol drinking status, TC – thyroid cancer

Table 23: Pooled relative risks for number of children/deliveries and thyroid cancer, stratified by BMI

	BMI <23 kg/m²				BMI ≥23 kg/m²				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Number of children/deliveries									0.23
1-2 children	67,301	1,109,764	390	*reference*	70,207	1,175,957	422	*reference*	
3-4 children	35,969	596,145	144	1.06(0.86-1.32)	48,819	815,645	246	1.02(0.86-1.22)	
≥ 5 children	8,544	121,905	20	0.84(0.51-1.38)	13,021	201,315	60	1.17(0.86-1.60)	
p-trend				0.98				0.42	
1 child	27,887	473,613	160	*reference*	27,555	474,031	157	*reference*	
2 children	39,414	636,151	230	0.81(0.64-1.04)	42,652	701,926	265	0.87(0.69-1.1)	
3 children	25,857	434,269	103	0.85(0.63-1.15)	33,493	564,765	178	0.93(0.71-1.2)	
4 children	10,112	161,876	41	1.11(0.74-1.65)	15,326	250,879	68	0.89(0.65-1.25)	
≥ 5 children	8,544	121,905	20	0.73(0.42-1.25)	13,021	201,315	60	1.04(0.72-1.50)	
***p*-trend**				0.74				0.80	

HR[b] – Adjusted Cox proportional hazard model for smoking status and alcohol drinking status, TC – thyroid cancer

Table 24: Pooled relative risks for breastfeeding status and thyroid cancer, stratified by BMI

	BMI <23 kg/m²				BMI ≥23 kg/m²				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Breastfeeding status									0.51
Never	7679	127,308	58	*reference*	7,701	131,663	49	*reference*	
Ever	42,400	696,232	292	1.07(0.80-1.42)	52,175	870,494	421	1.36(1.01-1.84)	

HR[b] – Adjusted Cox proportional hazard model for smoking status and alcohol drinking status, TC – thyroid cancer

Table 25: Pooled relative risks for postmenopausal status and thyroid cancer, stratified by BMI

	BMI <23 kg/m²				BMI ≥23 kg/m²				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Postmenopausal status									0.80
No	54,868	1,076,537	339	*reference*	47,141	890,723	297	*reference*	
Yes	79,426	1,265,059	310	1.15(0.88-1.50)	96,789	1,566,672	472	1.19(0.95-1.50)	

HR[b] – Adjusted Cox proportional hazard model for smoking status and alcohol drinking status, TC – thyroid cancer

Table 26: Pooled relative risks for age at menopause and thyroid cancer, stratified by BMI

	BMI <23 kg/m²				BMI ≥23 kg/m²				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Age at menopause									0.51
<45 years	11,557	188,976	61	*reference*	13,556	223,385	67	*reference*	
45-49 years	25,931	426,386	103	0.90(0.63-1.29)	30,779	509,511	142	1.08(0.80-1.47)	
50-54 years	29,579	473,975	103	0.85(0.59-1.22)	37,588	612,186	189	1.18(0.87-1.59)	
≥55 years	3,092	44,972	15	1.12(0.58-2.17)	4,603	69,285	27	1.25(0.77-2.02)	
***p*-trend**				0.70				0.18	

HR[b] – Adjusted Cox proportional hazard model for smoking status and alcohol drinking status, TC – thyroid cancer

Table 27: Pooled relative risks for oral contraceptive use and thyroid cancer, stratified by BMI

	BMI <23 kg/m²				BMI ≥23 kg/m²				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Oral contraceptive use									0.02*
Never	26,675	388,820	249	*reference*	31,712	481,714	307	*reference*	
Ever	3,453	44,548	39	0.80(0.57-1.13)	4,497	58,616	71	1.14(0.87-1.50)	

HR[b] – Adjusted Cox proportional hazard model for smoking status and alcohol drinking status, TC – thyroid cancer

Table 28: Pooled relative risks for hormone replacement therapy use and thyroid cancer, stratified by BMI

	BMI <23 kg/m2				BMI ≥23 kg/m²				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Hormone replacement therapy use									0.16
No	72,570	1,194,625	326	*reference*	88,683	1,463,000	454	*reference*	
Yes	5,283	77,251	41	0.94(0.67-1.34)	6,208	91,745	70	1.23(0.94-1.62)	

HR[b] – Adjusted Cox proportional hazard model for smoking status and alcohol drinking status, TC – thyroid cancer

4.5. Stratified Analyses by Smoking

Given that only 7% of females were ever smokers at baseline, when stratified analyses for each reproductive factor were conducted by smoking status, few cohorts contributed to the stratum of ever smokers with limited number of participants (Tables 29-37).

No statistically significant differences in the association between any of the reproductive factors and thyroid cancer risk by smoking status was observed.

Table 29: Pooled relative risks for age at menarche and thyroid cancer, stratified by smoking status

	Never Smokers				Ever Smokers				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Age at menarche									0.73
< 13 years	15,632	285,840	101	1.17(0.84-1.61)	1,308	23,658	4	0.40(0.07-2.30)	
13-14 years	103,366	1,803,789	562	0.89(0.70-1.12)	8,902	147,775	44	0.95(0.40-2.27)	
15-16 years	85,227	1,481,910	444	0.94(0.75-1.19)	6,286	105,634	21	0.73(0.31-1.73)	
≥ 17 years	42,207	701,608	208	*reference*	3,734	59,048	15	*reference*	
***p*-trend**				0.74				0.79	

HR[b] – Adjusted Cox proportional hazard model for alcohol drinking status and BMI, TC – thyroid cancer

Table 30: Pooled relative risks for parity status and thyroid cancer, stratified by smoking status

	Never Smokers				Ever Smokers				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Parity status									0.60
Nulliparous	15,939	273,953	75	*reference*	2,794	43,661	12	*reference*	
Parous	230,493	3,999,194	1,240	0.95(0.70-1.29)	17,436	292,453	72	1.26(0.35-4.61)	

HR[b] – Adjusted Cox proportional hazard model for alcohol drinking status and BMI, TC – thyroid cancer

Table 31: Pooled relative risks for number of children/deliveries and thyroid cancer, stratified by smoking status

	Never Smokers				Ever Smokers				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Number of children/deliveries									0.09
1-2 children	122,339	2,050,500	739	*reference*	7,599	116,627	41	*reference*	
3-4 children	71,883	1,207,118	330	1.01(0.87-1.17)	5,016	79,676	13	1.53(0.76-3.08)	
≥ 5 children	18,407	281,835	69	1.17(0.87-1.57)	1,859	25,566	3	2.78(0.58-13.27)	
***p*-trend**				0.98				0.79	
1 child	51,673	892,382	298	*reference*	2,540	37,502	15	*reference*	
2 children	70,666	1,158,118	441	0.91(0.74-1.12)	5,059	79,125	26	0.97(0.46-2.02)	
3 children	50,342	853,741	242	0.94(0.74-1.20)	3,346	53,748	8	1.30(0.46-3.61)	
4 children	21,541	353,377	88	1.02(0.74-1.39)	1,670	25,928	5	11.86(2.51-56.1)	
≥ 5 children	18,407	281,835	69	1.07(0.73-1.55)	1,859	25,566	3	1.53(0.14-16.32)	
***p*-trend**				0.43				0.96	

HR[b] – Adjusted Cox proportional hazard model for alcohol drinking status and BMI, TC – thyroid cancer

Table 32: Pooled relative risks for age at first delivery/pregnancy and thyroid cancer, stratified by smoking status

	Never Smokers				Ever Smokers				***p*-interaction**
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	
Age at first delivery/pregnancy									0.58
≤ 20 years	21,323	372,176	80	0.92(0.70-1.19)	3,269	55,234	10	0.70(0.24-2.08)	
21-25 years	111,718	1,958,664	533	*reference*	8,526	145,047	30	*reference*	
≥ 26 years	91,959	1,578,700	600	1.19(1.05-1.36)	5,059	83,726	29	1.14(0.63-2.05)	
***p*-trend**				**0.006***				0.43	

HR[b] – Adjusted Cox proportional hazard model for alcohol drinking status and BMI, TC – thyroid cancer

Table 33: Pooled relative risks for breastfeeding status and thyroid cancer, stratified by smoking status

	Never Smokers				Ever Smokers				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Breastfeeding status									0.81
Never	12,514	210,815	88	*reference*	1,658	26,649	9	*reference*	
Ever	81,161	1,345,876	616	1.24(0.99-1.55)	6,832	108,481	37	1.18(0.55-2.40)	

HR[b] – Adjusted Cox proportional hazard model for alcohol drinking status and BMI, TC – thyroid cancer

Table 34: Pooled relative risks for postmenopausal status and thyroid cancer, stratified by smoking status

	Never Smokers				Ever Smokers				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Postmenopausal status									0.55
No	91,116	1,759,599	561	*reference*	6,887	134,472	39	*reference*	
Yes	148,750	2,414,447	674	**1.25(1.03-1.52)**	12,763	192,780	43	0.94(0.40-2.18)	

HR[b] – Adjusted Cox proportional hazard model for alcohol drinking status and BMI, TC – thyroid cancer

Table 35: Pooled relative risks for age at menopause and thyroid cancer, stratified by smoking status

	Never Smokers				Ever Smokers				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Age at menopause									0.89
<45 years	21,175	350,176	111	*reference*	2,400	37,636	7	*reference*	
45-49 years	48,916	813,636	208	0.98(0.76-1.26)	4,099	63,857	19	0.90(0.18-4.45)	
50-54 years	58,144	947,785	256	1.02(0.80-1.31)	4,021	61,231	10	-	
≥55 years	6,640	99,553	36	1.31(0.85-1.31)	524	7,164	3	-	
***p*-trend**				0.39				0.83	

HR[b] – Adjusted Cox proportional hazard model for alcohol drinking status and BMI, TC – thyroid cancer

Table 36: Pooled relative risks for oral contraceptive use and thyroid cancer, stratified by smoking status

	Never Smokers				Ever Smokers				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Oral contraceptive use									0.35
Never	46,362	670,514	472	*reference*	4,754	68,089	34	*reference*	
Ever	7,025	91,570	95	1.04(0.82-1.31)	801	9,982	6	0.62(0.25-1.51)	

HR[b] – Adjusted Cox proportional hazard model for alcohol drinking status and BMI, TC – thyroid cancer

Table 37: Pooled relative risks for hormone replacement therapy use and thyroid cancer, stratified by smoking status

	Never Smokers				Ever Smokers				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Hormone replacement therapy use									0.34
No	143,169	2,369,361	705	*reference*	8,553	129,223	29	*reference*	
Yes	9,883	145,603	89	1.04(0.81-1.32)	761	10,625	5	1.57(0.54-4.51)	

HR[b] – Adjusted Cox proportional hazard model for alcohol drinking status and BMI, TC – thyroid cancer

4.6. Stratified Analyses by Country

Number of children/deliveries

A significant interaction was observed for the relationship between number of children/deliveries and thyroid cancer risk, stratified by countries (*p*−interaction 0.002).

The association between the number of children/deliveries and thyroid cancer risk varies across the different countries. For China and Japan, non−significant reduced risks were observed with increasing number of children/deliveries for the risk of thyroid cancer. In contrast, a significant positive association was seen between number of children/deliveries and thyroid cancer for Korea.

Figure 8a shows, when compared to the lowest category of number children/deliveries (1−2 children), the HRs (95% CIs) for 3−4 and ≥5 children were 0.84 (0.51−1.39) and 0.66 (0.23−1.88) respectively (*p*−trend 0.32) for China, 0.87 (0.72−1.04) and 0.88 (0.62−1.26) respectively (*p*−trend 0.22) for Japan, and 1.46 (1.18−1.80) and 1.89 (1.21−2.94) respectively (*p*−trend 0.0008) for Korea.

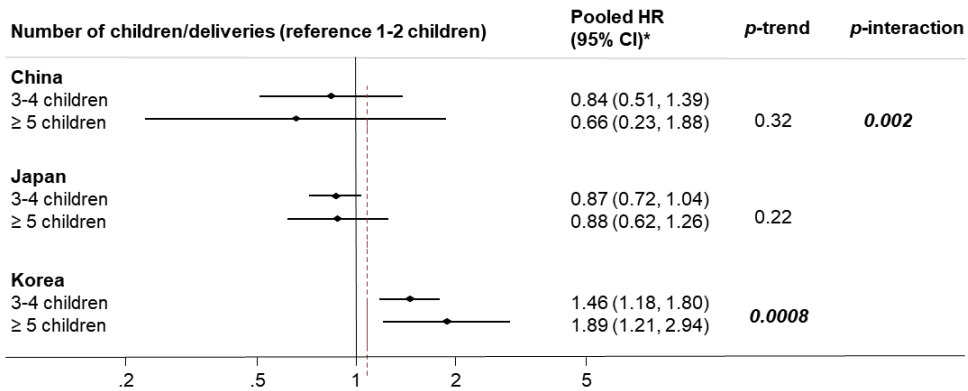

Figure 8a: Pooled relative risks for number of children/deliveries and thyroid cancer, stratified by country

* Pooled HRs (95% CIs) generated by combining cohort−specific HR (95% CIs) of following cohorts from each country − China: SWHS, Japan: JPH1, JPH2, JACC, Miyagi, Ohsaki, 3pref Miyagi, Korea: KNCC, KMCC.

To clearly see the number of children/deliveries that were associated with thyroid cancer risk, the reference was set to 1 child and the corresponding HRs (95% CIs) for 2, 3, 4 and ≥5 children, were generated. Figure 8b shows the forest plot.

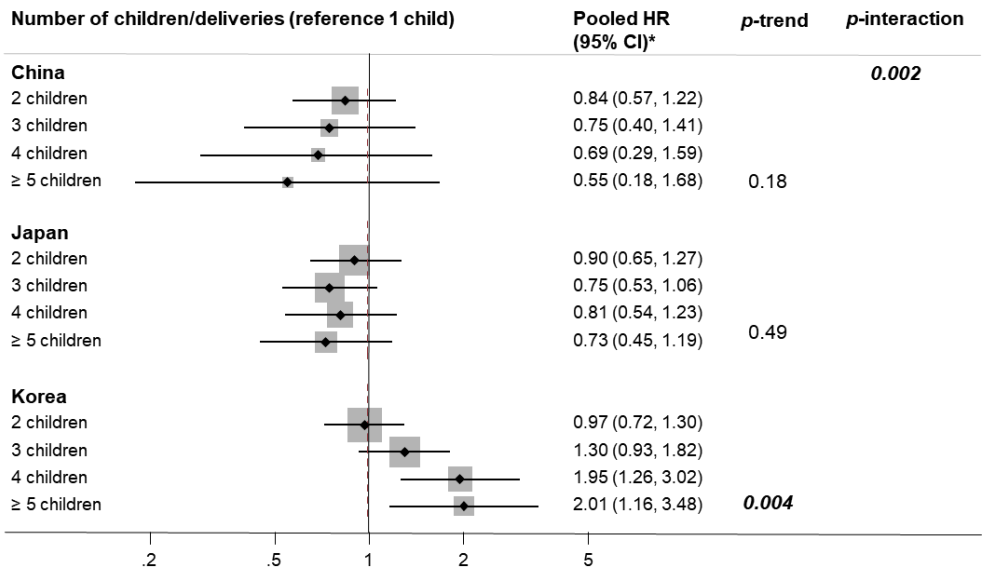

Figure 8b: Pooled relative risks for number of children/deliveries and thyroid cancer, stratified by country

* Pooled HRs (95% CIs) generated by combining cohort-specific HR (95% CIs) of following cohorts from each country – China: SWHS, Japan: JPH1, JPH2, JACC, Miyagi, Ohsaki, 3pref Miyagi, Korea: KNCC, KMCC.

Table 38: Characteristics of participating cohorts by number of children/deliveries, stratified by country

	China			Japan			Korea		
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**
Number of children/deliveries									
1-2 children	56,689	1,003,382	269	67,304	1,157,952	251	14,759	142,747	302
3-4 children	12,515	204,049	25	65,995	1,138,078	214	7,888	94,694	159
1 child	40,792	727,201	219	12,152	197,489	42	2,812	26,879	59
2 children	15,897	276,181	50	55,152	960,463	209	11,947	116,140	243
3 children	7,870	130,079	17	47,318	826,002	154	5,119	58,568	112
4 children	4,645	73,969	8	18,677	312,075	60	2,769	36,582	47
≥ 5 children	3,220	49,193	4	15,079	228,454	39	4,211	58,109	37

TC – thyroid cancer

Age at first delivery/pregnancy

A significant interaction was observed for the relationship between age at first delivery/pregnancy and thyroid cancer risk, stratified by countries (*p*−interaction = 0.002).

For China and Japan, there appeared to be no significant difference with younger (≤20 years) or older (≥26 years) age at delivery. While an increasing risk of thyroid cancer was observed with older age at first delivery/pregnancy for Korean cohorts. Though all values and *p*−trends were statistically non−significant

Figure 9 shows, that with ≤20 years as reference, the HRs (95% CIs) for older (≥26 years) age at first delivery/pregnancy for China and Japan were 1.04 (0.61−1.76) and 1.01 (0.71−1.43) respectively, and 0.88 (0.52−1.48) and 0.81 (0.58−1.13) for 21−25 years. Whereas for Korea, the corresponding HRs (95% CIs) for ≥26 years and 21−25 years were 1.38 (0.82, 2.33) and 1.30 (0.78, 2.16).

Age at menarche, Breastfeeding status

Significant *p*−values for interaction were also observed for stratified analyses by country for the associations between thyroid cancer and age at menarche (*p*−interaction 0.004) (Figure 10) and breastfeeding status (*p*−interaction 0.03) (Figure 11).

For age at menarche, <13 years (vs ≥ 17 years) was associated with relatively increased thyroid cancer risk (HRs 95% CI) for China (1.07; 0.66−1.69) and for Japan (1.30; 0.88−1.93) but reduced risk for Korea (0.82; 0.52−1.29).

For breastfeeding status, the stratified analyses consisted of cohorts from only Japan and Korea. Ever breastfeeding (vs never) showed increased risk (HRs 95% CI) for Japan (1.33; 0.98, 1.79) and no association (1.09; 0.83, 1.43) for Korea.

Other reproductive factors

No significant effect modification by country was observed for the rest of the reproductive factors and the risk of thyroid cancer (Figures 12−16).

Table 39: Characteristics of participating cohorts by age at first delivery/pregnancy, stratified by country

	China			Japan			Korea		
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**
Age at first delivery /pregnancy									
≤ 20 years	8,530	138,089	20	15,577	287,789	64	2,532	33,647	16
21-25 years	22,908	392,101	72	99,162	1,788,074	358	11,908	141,737	201
≥ 26 years	40,981	726,351	206	49,705	906,740	192	11,609	112,118	264

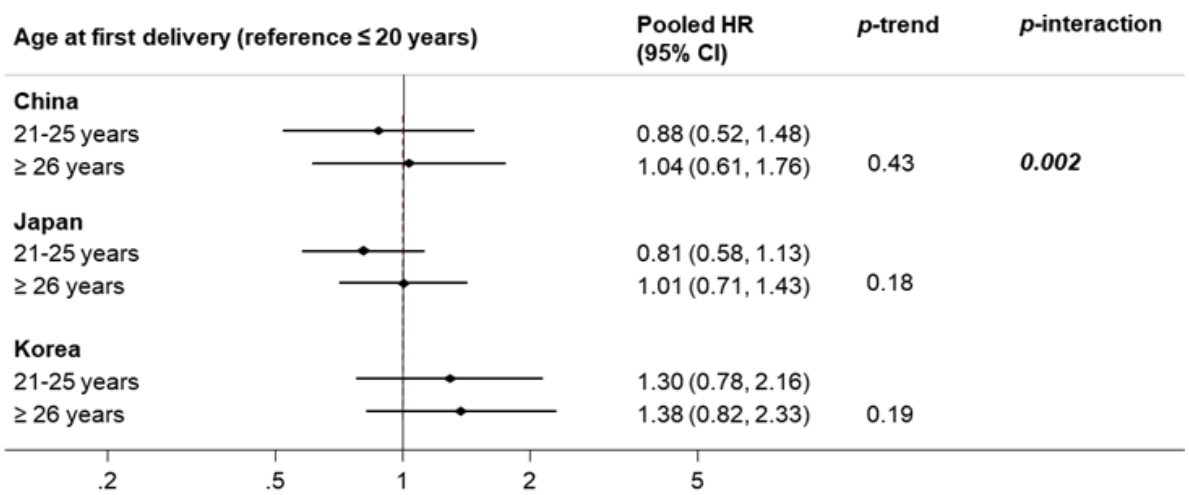

Figure 9: Pooled relative risks for age at first delivery/pregnancy and thyroid cancer, stratified by country

* Pooled HRs (95% CIs) generated by combining cohort-specific HR (95% CIs) of following cohorts from each country – China: SWHS, Japan: JPH1, JPH2, JACC, Miyagi, Ohsaki, 3pref Miyagi, Korea: KNCC, KMCC.

Table 40: Characteristics of participating cohorts by age at menarche, stratified by country

	China			Japan			Korea		
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**
Age at menarche									
< 13 years	4,683	82,965	26	11,698	226,614	56	1,321	12,693	26
13-14 years	27,385	479,265	107	86,363	1,542,910	338	8,844	89,757	211
15-16 years	29,548	511,684	119	59,956	1,090,345	211	9,805	109,522	180
≥ 17 years	13,314	225,343	54	28,432	495,714	86	8,358	105,769	105

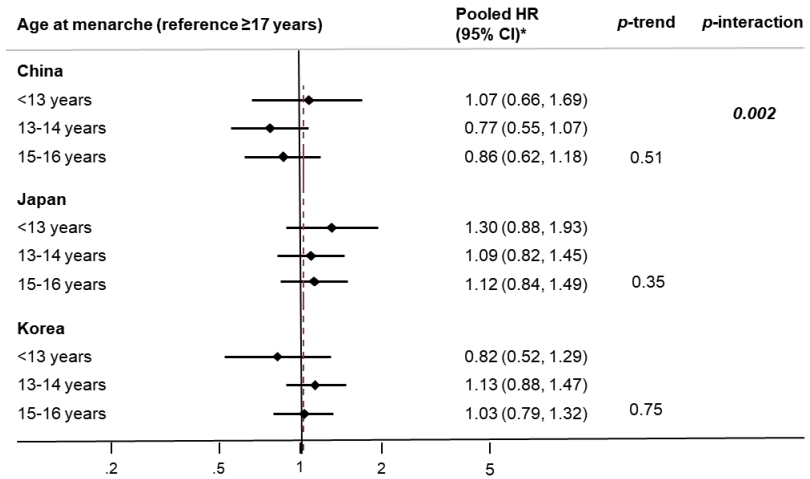

Figure 10: Pooled relative risks for age at menarche and thyroid cancer, stratified by country

* Pooled HRs (95% CIs) generated by combining cohort-specific HR (95% CIs) of following cohorts from each country – China: SWHS, Japan: JPH1, JPH2, JACC, Miyagi, Ohsaki, 3pref Miyagi, Korea: KNCC, KMCC.

Table 41: Characteristics of participating cohorts by breastfeeding status, stratified by country

	China			Japan			Korea		
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**
Breastfeeding status									
Never	0	0	0	12,794	236,628	49	2,872	26,935	61
Ever	0	0	0	75,190	1,367,566	347	21,949	239,048	380

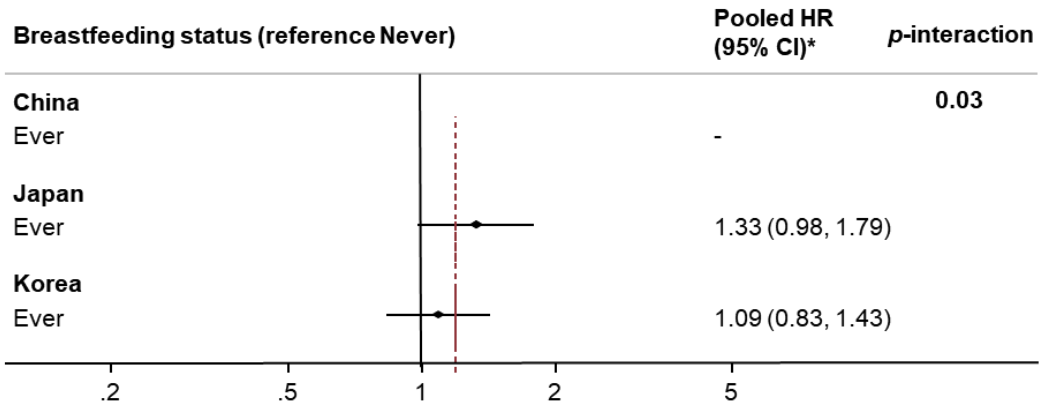

Figure 11: Pooled relative risks for breastfeeding status and thyroid cancer, stratified by country

* Pooled HRs (95% CIs) generated by combining cohort-specific HR (95% CIs) of following cohorts from each country – China: none, Japan: JPH1, JPH2, Miyagi, Ohsaki, Korea: KNCC, KMCC.

Table 42: Characteristics of participating cohorts by postmenopausal status, stratified by country

	China			Japan			Korea		
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**
Postmenopausal status									
No	37,102	665,196	192	59,092	1,243,692	264	6,276	66,559	183
Yes	37,824	634,004	114	124,349	2,050,105	418	17,382	195,071	264

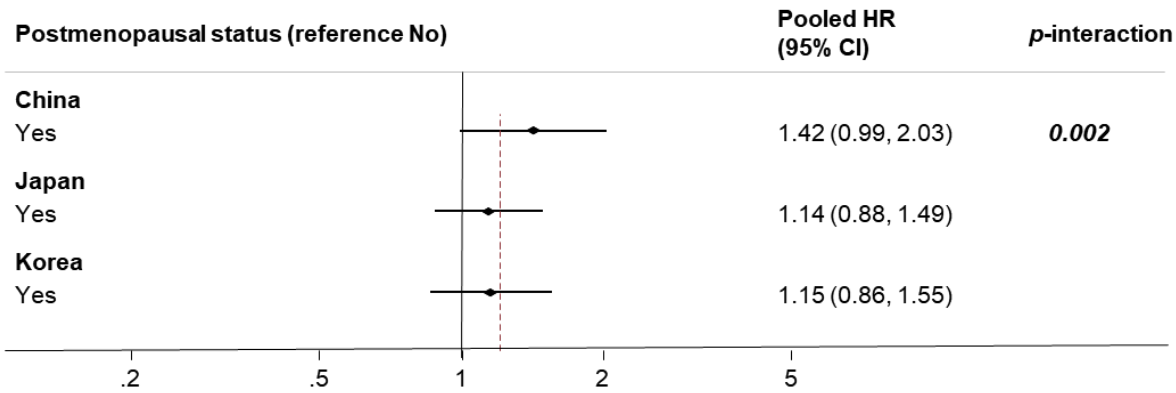

Figure 12: Pooled relative risks for postmenopausal status and thyroid cancer, stratified by country

* Pooled HRs (95% CIs) generated by combining cohort-specific HR (95% CIs) of following cohorts from each country – China: SWHS, Japan: JPH1, JPH2, JACC, Miyagi, Ohsaki, 3pref Miyagi, Korea: KNCC, KMCC.

Table 43: Characteristics of participating cohorts by parity status, stratified by country

	China			Japan			Korea		
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**
Parity status									
Nulliparous	2,506	42,633	8	16,288	277,035	63	1,103	15,431	22
Parous	72,424	1,256,625	298	170,161	3,078,548	628	27,225	302,311	500

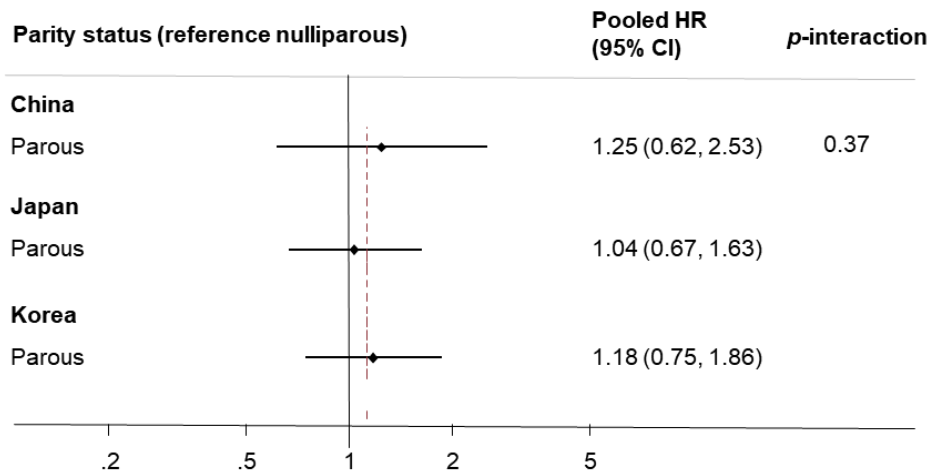

Figure 13: Pooled relative risks for parity status and thyroid cancer, stratified by country

* Pooled HRs (95% CIs) generated by combining cohort-specific HR (95% CIs) of following cohorts from each country – China: SWHS, Japan: JPH1, JPH2, JACC, Miyagi, Ohsaki, 3pref Miyagi, Korea: KNCC, KMCC.

Table 44: Characteristics of participating cohorts by age at menopause, stratified by country

	China			Japan			Korea		
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**
Age at menopause									
<45 years	6,266	105,452	24	16,345	279,363	66	2,856	32,734	38
45-49 years	16,414	274,827	48	36,324	619,683	123	4,613	51,055	75
50-54 years	13,232	221,696	37	48,399	810,211	161	6,335	66,468	98
≥55 years	1,440	23,765	4	5,099	79,099	17	1,298	13,328	22

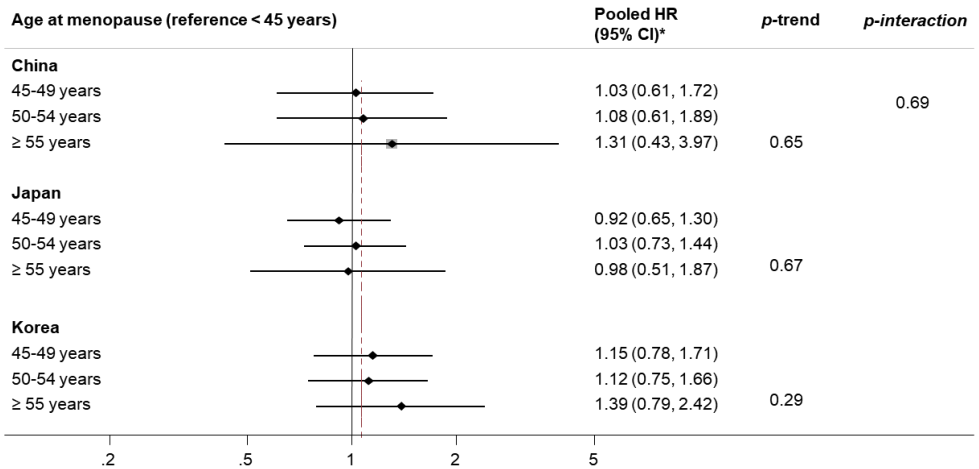

Figure 14: Pooled relative risks for age at menopause and thyroid cancer, stratified by country

* Pooled HRs (95% CIs) generated by combining cohort−specific HR (95% CIs) of following cohorts from each country − China: SWHS, Japan: JPH1, JPH2, JACC, Miyagi, Ohsaki, 3pref Miyagi, Korea: KNCC, KMCC.

Table 45: Characteristics of participating cohorts by oral contraceptive use, stratified by country

	China			Japan			Korea		
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**
Oral contraceptive use									
Never	0	0	0	40,777	689,193	202	19,581	212,333	368
Ever	0	0	0	1,681	26,342	11	6,673	83,066	100

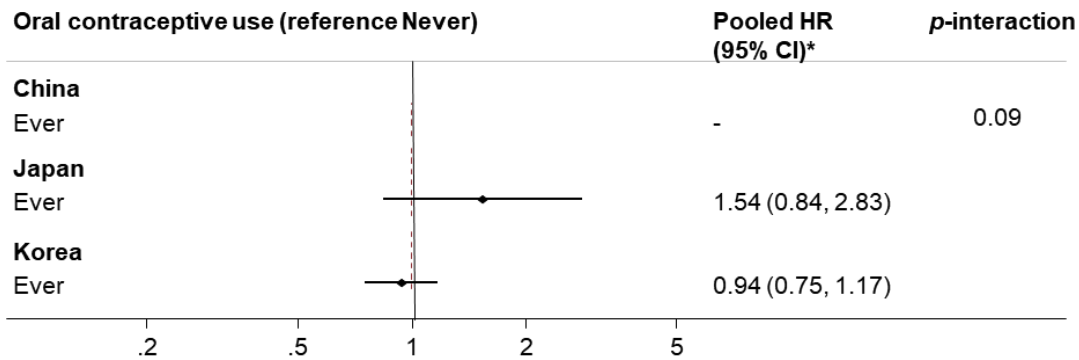

Figure 15: Pooled relative risks for oral contraceptive use and thyroid cancer, stratified by country

* Pooled HRs (95% CIs) generated by combining cohort-specific HR (95% CIs) of following cohorts from each country – Japan: JACC, Miyagi, Ohsaki, Korea: KNCC, KMCC.

Table 46: Characteristics of participating cohorts by hormone replacement therapy use, stratified by country

	China			Japan			Korea		
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**
Hormone replacement therapy									
No	72,279	1,252,199	294	74,830	1,239,083	269	16,197	198,153	229
Yes	2,651	47,059	12	5,073	81,476	20	3,928	4,255	79

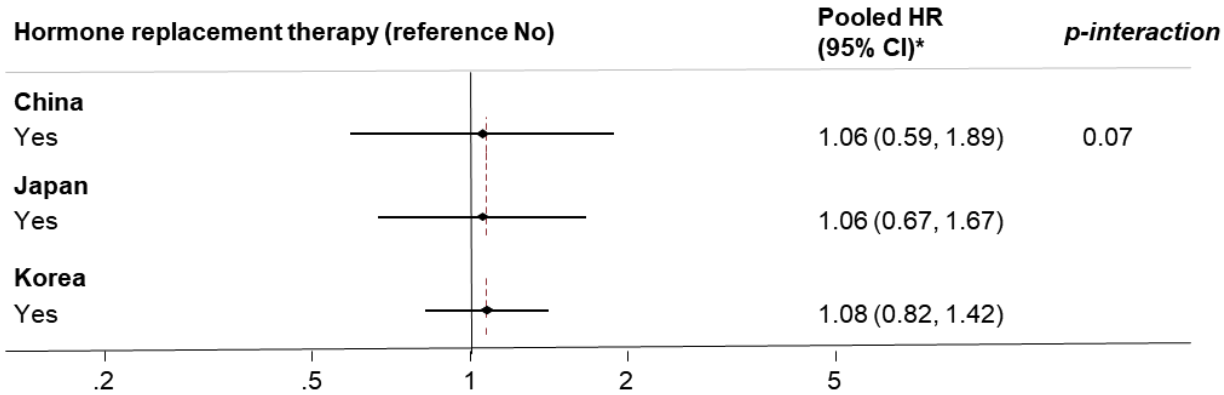

Figure 16: Pooled relative risks for hormone replacement therapy use and thyroid cancer, stratified by country

* Pooled HRs (95% CIs) generated by combining cohort-specific HR (95% CIs) of following cohorts from each country – China: SWHS, Japan: JACC, Miyagi, Ohsaki, Korea: KNCC, KMCC.

4.7. Stratified Analyses by Birth Years

Number of children/deliveries

Birth years modified the association between number of children/deliveries and thyroid cancer risk (p-interaction <0.05).

For stratified by those born before and after the 1940s (**Figure 17a**), there was no significant trend across categories for women born before the 1940s. While among women born after the 1940s, increasing number of children was significantly associated with an increased risk of thyroid cancer (p-trend = 0.03). Compared to 1-2 children, the HR (95% CI) for ≥5 children was 1.57 (1.06-2.33).

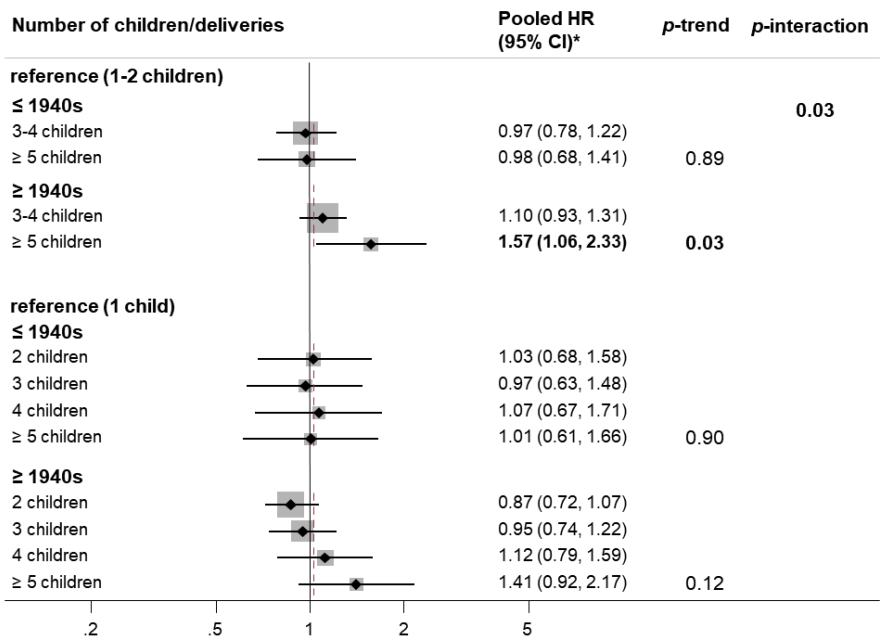

Figure 17a: Pooled relative risks for number of children/deliveries and thyroid cancer, stratified by birth years

* Pooled HRs (95% CIs) generated by combining cohort-specific HR (95% CIs)

On further grouping women as those born in 1920s or earlier, 1930s, 1940s and later than 1950s (**Figure 17b**), a significant trend of increasing risk of thyroid cancer with increasing number of

children was observed for women born in 1950s or later (p-trend 0.001). The HRs (95% CIs) were 0.92 (0.70-1.21), 1.27 (0.90-1.78), 2.12 (1.29-3.47) and 2.29 (1.03-5.1) for 2, 3, 4, and ≥5 children respectively, compared to 1 child (reference).

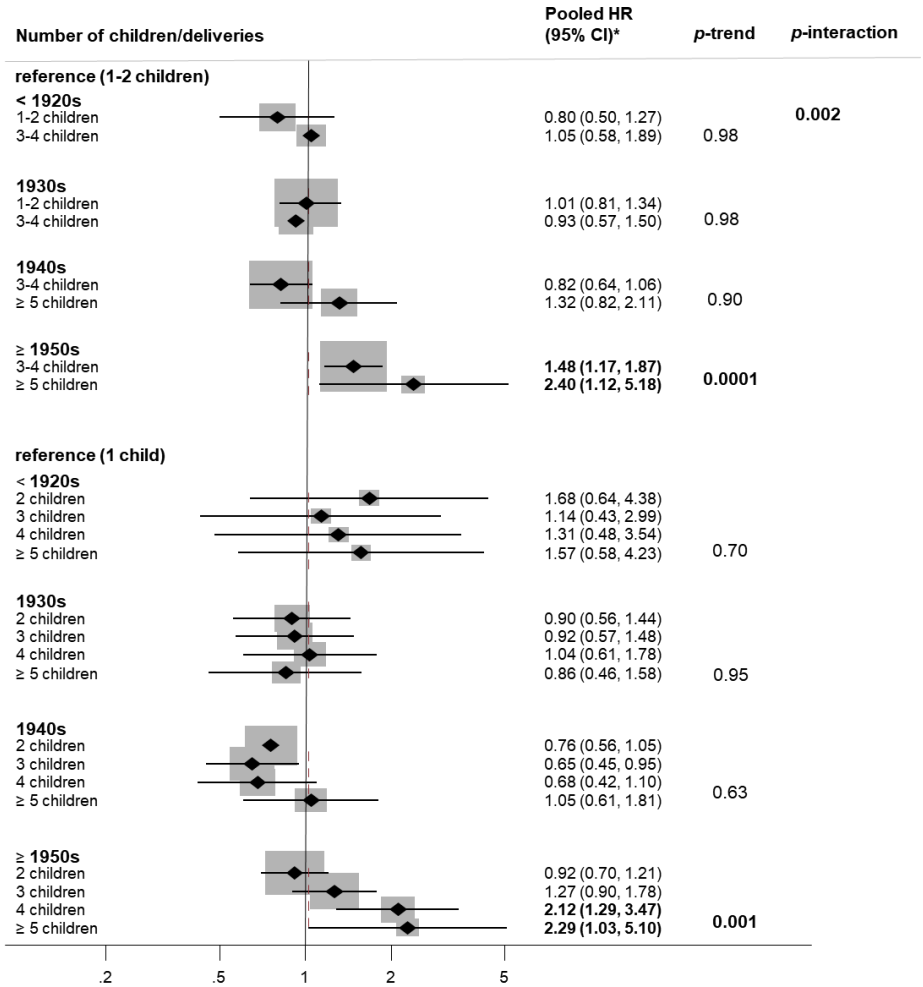

Figure 17b: Pooled relative risks for number of children/deliveries and thyroid cancer, stratified by birth years

* Pooled HRs (95% CIs) generated by combining cohort-specific HR (95% CIs)

Other reproductive factors

No significant effect modification by birth years was observed for the rest of the reproductive factors and the risk of thyroid cancer (Tables 48-55).

Table 47: Characteristics of participating cohorts by number of children/deliveries, stratified by birth years

	<1940s			≥1940s		
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**Number of women**	**Person-years**	**TC Cases**
Number of children/deliveries						
1-2 children	48,749	797,082	150	89,547	1,498,635	667
3-4 children	58,003	948,672	170	27,495	472,599	214
1 child	10,019	154,640	26	45,622	794,802	294
2 children	38,730	642,441	124	43,925	703,832	373
3 children	38,122	632,292	112	21,728	374,072	162
4 children	19,881	316,380	58	5,767	98,527	52
≥ 5 children	18,906	275,124	46	2,655	44,975	31

	<1920s		1930s		1940s		≥1950s	
Reproductive variable	**Number of women**	**TC Cases**	**Number of women**	**TC Cases**	**Number of women**	**TC Cases**	**Number of women**	**TC Cases**
Number of children/deliveries								
1-2 children	14,096	31	34,653	119	42,300	208	47,247	459
3-4 children	23,665	43	34,338	127	21,801	112	5,694	102
1 child	3,850	5	6,169	21	12,659	70	32,963	224
2 children	10,246	26	28,484	98	29,641	138	14,284	235
3 children	14,040	25	24,082	87	17,018	83	4,710	79
4 children	9,625	18	10,256	40	4,783	29	984	23
≥ 5 children	11,392	21	7,514	25	2,325	24	330	7

Table 48: Pooled relative risks for age at menarche and thyroid cancer, stratified by birth years

	<1940s				≥1940s				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Age at menarche									0.77
< 13 years	5,482	98,492	19	1.00(0.56-1.81)	12,185	2,233,134	89	1.08(0.81-1.45)	
13-14 years	60,055	1,030,071	219	0.99(0.75-1.31)	62,178	1,075,451	431	1.02(0.83-1.26)	
15-16 years	57,546	1,002,087	183	1.04(0.79-1.36)	40,910	694,571	320	0.99(0.80-1.22)	
≥ 17 years	34,591	579,788	104	*reference*	14,205	22,654	130	*reference*	
***p*-trend**				0.93				0.51	

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 49: Pooled relative risks for parity status and thyroid cancer, stratified by birth years

	<1940s				≥1940s				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Parity status									0.58
Nulliparous	13,136	216,335	51	*reference*	6,757	118,689	42	*reference*	
Parous	144,538	2,494,103	474	0.98(0.57-1.67)	122,721	2,099,122	928	1.2(0.85-1.69)	

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 50: Pooled relative risks for age at first delivery/pregnancy and thyroid cancer, stratified by birth years

	<1940s				≥1940s				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Age at first delivery/pregnancy									0.62
≤ 20 years	20,380	349,951	64	1.10(0.78-1.56)	5,727	100,958	36	1.02(0.71-1.46)	
21-25 years	79,601	1,368,758	269	*reference*	53,027	929,966	351	*reference*	
≥ 26 years	39,874	699,662	131	1.09(0.86-1.38)	62,039	1,038,936	521	1.16(0.99-1.34)	
***p*-trend**				0.79				0.07	

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 51: Pooled relative risks for breastfeeding status and thyroid cancer, stratified by birth years

	<1940s				≥1940s				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Breastfeeding status									0.64
Never	5,430	95,520	18	*reference*	10,206	167,591	90	*reference*	
Ever	50,313	863,099	220	1.38(0.85-2.24)	44,553	704,414	487	1.15(0.92-1.45)	

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 52: Pooled relative risks for postmenopausal status and thyroid cancer, stratified by birth years

	<1940s				≥1940s				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Postmenopausal status									0.66
No	15,099	375,094	73	*reference*	87,321	1,599,439	566	*reference*	
Yes	140,550	2,286,574	446	1.25(0.76-2.04)	37,099	560,654	333	1.08(0.88-1.33)	

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 53: Pooled relative risks for age at menopause and thyroid cancer, stratified by birth years

	<1940s				≥1940s				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Age at menopause									0.49
<45 years	16,292	266,287	53	*reference*	8,799	145,110	73	*reference*	
45-49 years	43,060	718,447	132	1.00(0.68-1.45)	13,800	218,818	111	0.97(0.71-1.32)	
50-54 years	56,271	936,285	186	1.12(0.79-1.60)	11,145	152,718	106	0.91(0.65-1.27)	
≥55 years	6,697	104,127	22	1.04(0.59-1.85)	1,052	10,608	21	1.35(0.78-2.33)	
***p*-trend**				0.39				0.92	

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 54: Pooled relative risks for oral contraceptive use and thyroid cancer, stratified by birth years

	<1940s				≥1940s				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Oral contraceptive use									0.25
Never	29,468	466,650	144	*reference*	29,667	141,990	414	*reference*	
Ever	1,642	24,248	15	1.76(0.98-3.13)	5,403	61,119	85	0.89(0.70-1.13)	

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 55: Pooled relative risks for hormone replacement therapy use and thyroid cancer, stratified by birth years

	<1940s				≥1940s				
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	***p*-interaction**
Hormone replacement therapy use									0.26
No	77,956	1,237,080	238	*reference*	83,476	1,419,974	532	*reference*	
Yes	3,860	59,156	20	0.97(0.57-1.64)	7,111	99,980	89	1.08(0.84-1.38)	

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

4.8. Stratified Analyses by Age of Diagnosis of Cases

Parity status

Women diagnosed with thyroid cancer at a younger age (<55 years) and who were parous had a significantly increased risk of developing thyroid cancer compared to those who were nulliparous. The HR (95% CI) was 1.75 (1.11−2.76). While diagnosis at an older age (≥55 years) showed a reduced risk, with an HR (95% CI) of 0.74 (0.50−1.08) (Table 56).

Age at first delivery

Among women diagnosed at an older age (≥55 years), an increasing risk of thyroid cancer was seen with older age at first delivery (p−trend 0.003). The HRs (95% CI) for ≤20 years and ≥26 years were 0.81 (0.61−1.07) and 1.19 (1.02−1.39) respectively, compared to age at first delivery 21−25 years. While when diagnosed a younger age (<55 years), the association between age at first delivery and thyroid cancer risk was weaker (Table 57).

Postmenopausal status

There was a clear contrast in the association between postmenopausal status and thyroid cancer risk based on age at diagnosis of thyroid cancer. Diagnosis <55 years showed being menopausal (vs not postmenopausal) is associated with a significantly reduced risk of thyroid cancer (HR 0.7, 95% CI 0.51−0.96). However, for women diagnosed >55 years, being menopausal was significantly associated with a higher risk of thyroid cancer (HR 1.79, 95% CI 1.42−2.24) (Table 58).

Age at menopause

For those diagnosed ≥55 years, an increasing risk of thyroid cancer was seen with older age at menopause (p−trend 0.003). The HRs (95% CI) for 45−49 years, 50−54 years and ≥55 years were 1.15 (0.87−1.51), 1.35 (1.04−1.77) and 1.56 (1.04−2.33) respectively, compared to <45 years. While for diagnosis <55 years, age at menopause 45−49 years was non significantly associated with highest risk (HR 1.39, 95% CI 0.81−2.37) (Table 59).

Table 56: Pooled relative risks for parity status and thyroid cancer, by thyroid cancer age of diagnosis

	TC diagnosed < 55 years				TC diagnosed ≥ 55 years			
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**
Parity status								
Nulliparous	1,359	15,460	27	*reference*	18,538	319,681	66	*reference*
Parous	13,518	106,729	525	**1.75 (1.11-2.76)**	256,292	4,531,703	901	0.74 (0.50-1.08)

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer (see supplementary Figure 14)

Table 57: Pooled relative risks for age at first delivery/pregnancy and thyroid cancer, by thyroid cancer age of diagnosis

	TC diagnosed < 55 years				TC diagnosed ≥ 55 years			
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**
Age at first delivery/pregnancy								
≤ 20 years	537	4,034	18	1.01(0.60-1.69)	26,102	455,536	82	0.81(0.61-1.07)
21-25 years	5,694	43,460	187	*reference*	128,284	2,279,017	444	*reference*
≥ 26 years	6,784	53,504	307	1.12(0.92-1.38)	95,511	1,691,996	355	**1.19(1.02-1.39)**
***p*-trend**				0.22				***0.003***

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 58: Pooled relative risks for postmenopausal status and thyroid cancer, by thyroid cancer age of diagnosis

	TC diagnosed < 55 years				TC diagnosed ≥ 55 years			
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**
Postmenopausal status								
No	10,193	81,296	385	*reference*	92,277	1,894,162	254	*reference*
Yes	1,795	7,973	101	**0.7(0.51-0.96)**	177,760	2,871,803	695	**1.79(1.42-2.24)**

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 59: Pooled relative risks for age at menopause and thyroid cancer, by thyroid cancer age of diagnosis

	TC diagnosed < 55 years				TC diagnosed ≥ 55 years			
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**
Age at menopause								
<45 years	805	4,991	40	*reference*	24,662	412,638	88	*reference*
45-49 years	605	2,091	39	1.39(0.81-2.37)	56,746	943,556	207	1.15(0.87-1.51)
50-54 years	248	480	14	0.66(0.31-1.42)	67,718	1,098,074	282	**1.35(1.04-1.77)**
≥55 years	1	-	0	-	7,836	116,222	43	**1.56(1.04-2.33)**
***p*-trend**				0.23				***0.003***

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 60: Pooled relative risks for number of children/deliveries and thyroid cancer, by thyroid cancer age of diagnosis

	TC diagnosed < 55 years				TC diagnosed ≥ 55 years			
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**
Number of children/deliveries								
1-2 children	9,866	77,379	398	*reference*	128,886	2,226,975	424	*reference*
3-4 children	3,045	22,139	104	0.99(0.79-1.27)	83,353	1,415,138	294	0.99(0.84-1.17)
≥ 5 children	135	878	7	0.69(0.32-1.51)	22,375	335,064	73	0.84(0.63-1.13)
***p*-trend**				0.68				0.47
1 child	2,468	18,590	155	*reference*	53,288	932,979	165	*reference*
2 children	7,398	58,789	243	0.95(0.74-1.22)	75,598	1,293,996	259	**0.76(0.61-0.94)**
3 children	2,559	18,903	80	0.92(0.66-1.27)	57,748	995,747	203	0.81(0.63-1.02)
4 children	486	3,236	24	1.15(0.71-1.86)	25,605	419,391	91	0.79(0.59-1.06)
≥ 5 children	135	878	7	0.67(0.30-1.51)	22,375	335,064	73	**0.68(0.49-0.95)**
***p*-trend**				0.77				0.15

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 61: Pooled relative risks for age at menarche and thyroid cancer, by thyroid cancer age of diagnosis

	TC diagnosed < 55 years				TC diagnosed ≥ 55 years			
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**
Age at menarche								
< 13 years	1,564	12,861	52	0.99(0.66-1.49)	16,138	309,411	56	1.00(0.72-1.40)
13-14 years	8,234	65,919	268	1.13(0.83-1.55)	114,358	2,046223	388	0.93(0.76-1.13)
15-16 years	4,093	34,676	177	1.13(0.83-1.55)	95,216	1,677,260	333	0.97(0.79-1.17)
≥ 17 years	986	8,734	55	*reference*	49,118	818,488	190	*reference*
***p*-trend**				0.93				0.65

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 62: Pooled relative risks for breastfeeding status and thyroid cancer, by thyroid cancer age of diagnosis

	TC diagnosed < 55 years				TC diagnosed ≥ 55 years			
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**
Breastfeeding status								
Never	2,055	16,265	63	*reference*	13,611	247,348	47	*reference*
Ever	7,153	57,908	286	1.06(0.80-1.39)	89,986	1,549,485	441	1.27(0.94-1.73)

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 63: Pooled relative risks for oral contraceptive use and thyroid cancer, by thyroid cancer age of diagnosis

	TC diagnosed < 55 years				TC diagnosed ≥ 55 years			
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**
Oral contraceptive use								
Never	7,757	67,715	261	*reference*	52,601	834,422	309	*reference*
Ever	1,609	16,903	51	0.87(0.64-1.19)	6,745	92,850	60	1.11(0.82-1.49)

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

Table 64: Pooled relative risks for hormone replacement therapy use and thyroid cancer, by thyroid cancer age of diagnosis

	TC diagnosed < 55 years				TC diagnosed ≥ 55 years			
Reproductive variable	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**	**Number of women**	**Person-years**	**TC Cases**	**HR[b] (95%CI)**
Hormone replacement therapy use								
No	6,706	62,534	273	*reference*	156,600	2,627,802	519	*reference*
Yes	491	3,160	25	0.84(0.54-1.29)	11,161	168,019	86	**1.36(1.06-1.75)**

HR[b] – Adjusted Cox model for smoking status, alcohol drinking status and BMI, TC – thyroid cancer

4.9 Sensitivity analyses

Menopausal status serves a dual purpose: it provides information about hormone status and defines age, as women were categorized based on age at baseline.

By considering menopausal status, women were divided into two groups: those younger than 54 years (n=110,152) and those aged 54 years and older (n=179,555) and HRs (95% CIs) generated for the follow-up periods up to age 54 (cases=723) and those after 54 years (cases=796).

On keeping females younger than 54 years as reference, the adjusted HR (95% CI) for females aged 54 years and older was 1.01 (0.87-1.19) (Supplementary table 4).

It can be implied that both young and old females have similar risk of developing thyroid cancer due to reproductive or hormonal factors, thereby providing insights into its biological plausibility.

Chapter 5. Discussion

5.1. Main Findings

A range of reproductive and hormonal factors were examined in relation to thyroid cancer risk in this large-scale pooled analysis of 289,707 ACC female participants enrolled in 10 prospective cohort studies from three Asian countries. To my knowledge, this is first large-scale study to explore reproductive and hormone-related factors on thyroid cancer risk in Asian women.

Older age at first delivery/pregnancy was significantly associated with the risk of thyroid cancer, overall (Table 16). Other childbearing factors such as higher number of children/deliveries and ever breastfeeding showed non-significant positive associations. Age at menarche, oral contraceptive and hormone replacement therapy use were not associated with the risk of thyroid cancer. Similar associations were seen for the papillary subtype as for overall thyroid cancer (Table 19).

Stratified analyses by countries unveiled significant interactions for the relationship between thyroid cancer risk and number of deliveries/children, age at first delivery/pregnancy, age at menarche and breastfeeding status, A significant positive association with more number of deliveries/children was observed for Korea, in contrast inverse associations were seen for China and Japan (Figures 8a and 8b). For age at first delivery/pregnancy, younger or older age at first delivery/pregnancy did not show any association for China and Japan, while a nonsignificant positive association with older age at first birth was seen for Korean cohorts (Figure 9). For age at menarche, earlier age at menarche demonstrated nonsignificant increased risk for China and Japan but reduced risk for Korea (Figure 10). Ever breastfeeding showed nonsignificant increased risk for Japan and no association for Korea (Figure 11).

Birth years appeared to significantly modify the association between number of deliveries/children and thyroid cancer risk, with a significant positive association in younger birth cohorts, especially for those born after the 1950s (**Figures 17a and 17b**).

A significant interaction effect by BMI was observed for the association between age at first delivery/pregnancy and thyroid cancer risk, where an older age at first delivery/pregnancy showed relatively increased risk among women of BMI <23 kg/m^2, whereas a younger age at first delivery/pregnancy was seen to increase the risk among those with BMI <23 kg/m^2 (**Figure 7**).

No statistically significant differences in the association between any of the reproductive factors and thyroid cancer risk by smoking status was observed.

The risk of thyroid cancer diagnosed at an earlier (<55 years) or older age (≥55 years) differed considerably with parity status, age at first delivery/pregnancy, postmenopausal status and age at menopause. While parous women diagnosed at an older age had reduced risk of developing the cancer, those diagnosed at an earlier age had a significantly increased risk (**Table 56**). Advanced age at first delivery/pregnancy significantly increased the risk for thyroid cancer if diagnosed at an older age, this association was weaker for thyroid cancer diagnosis at an earlier age (**Table 57**). The association between postmenopausal status and risk of thyroid cancer showed clear contrast based on earlier or older age at diagnosis, with significantly reduced risk for earlier age and increased risk for older age (**Table 58**).

5.2. Comparison with Previous Literature

Age at first delivery/pregnancy

This study's finding of a significantly increased risk of thyroid cancer with older age of women when they first gave birth [HR (95% CIs): 1.16 (1.03−1.31) for ≥26 years, 1.09 (0.85−1.39) for ≤20 years compared to 21−25 years (reference), p−trend 0.003] is

consistent with a previous prospective study from United States that reported similar associations of a significant linear trend toward an increased thyroid cancer for advancing age at first birth (53), and also with a pooled analysis of 14 case-control studies from North America, Europe, and Asia, in which the only significant reproductive risk factor that revealed a lower risk of thyroid cancer was younger age at first birth (<25 years)(76). Similarly, an Italian study of 379 women discovered that older age at first birth was associated with a doubled risk of thyroid cancer. The relative risk was 2.4 (95% CI: 1.2-5.0) for women who gave birth at age 28 or older versus those who gave birth at age 21 or younger(126). Additionally, a recent case-control study from China observed early age at first pregnancy (≤24 years vs >24 years) decreased the risk of thyroid cancer (OR 0.66, 95% CI 0.44-0.98) (54). While in another Chinese study, (65) non-significant increased risk of thyroid cancer was reported for later age at first birth (>30 vs 20-29 years; HR 1.40, 95% CI: 0.88-2.22).

The underlying mechanisms for the potential association between older age at delivery and thyroid cancer risk are not well understood, but may be because a later age at first birth is associated with a longer period of hormonal exposure, including exposure to estrogen(127). Experimental and molecular studies indicate that estrogen may influence thyroid carcinogenesis by promoting the growth and proliferation of thyroid cells, potentially increasing the risk of cancer(85, 87). Other factors like delayed childbearing(103) or obesity may also contribute to this association.

It is worth noting that there are previous studies which have demonstrated reduced(39, 51), or no risk(64, 67, 68, 72, 73) associated with age at first delivery and thyroid cancer. However, most of these studies often had limited statistical power or utilized case-control study designs and focused on Western countries.

Parity, number of deliveries/pregnancies

In this study, having a greater number of children/deliveries

(compared to 1 or 1-2 children) was associated with a non-significant increased risk of thyroid cancer, especially with >4 children.

While some studies have found that women who have had more pregnancies have no or slightly decreased risk(53, 65, 76), this study, along with several previous meta-analysis (58-60) supports a positive association between parity number and thyroid cancer risk. Also, consistent with the finding of this study are results from a Korean cross-sectional study that reported having 4 pregnancies had the highest risk compared to having 1 child (OR 4.51, 95% CI 1.77-11.59)(56).

This may be because pregnancy and childbirth are associated with changes in hormonal levels and may have some effects in the development of thyroid cancer. During pregnancy, increased levels of estrogen and human chorionic gonadotropin which has close homology to TSH have been suggested to have stimulating effects on thyroid tumors(92). Moreover, Estrogen receptor-α-positive tumors have been observed in up to 87.5% of females who developed TC during pregnancy(93).

The reasons for the mixed findings regarding the association between parity and thyroid cancer risk may be due to the influence of other factors, such as age at first pregnancy, breastfeeding, and hormonal factors, which vary between populations and regions.

Breastfeeding

While ever breastfeeding showed non-significant positive associations for thyroid cancer in this study, previous studies and meta-analyses have mostly documented reduced risk or no association (60, 62, 64, 65, 70, 73). For example, a hospital-based case-control study in China involving 2261 matched pairs of cases and controls demonstrated a decreased risk of thyroid cancer associated with longer duration of breastfeeding (6-12 months vs. 6 months, OR 0.49, 95%CI 0.24 0.98) and a meta-analysis revealed that women who breastfed for a longer duration had a 0.7-fold

lower risk of thyroid cancer.

While some studies suggest that breastfeeding may be a potential protective factor for thyroid cancer, the evidence is limited, and more research is required to better comprehend the underlying mechanisms and direction of association.

Age at menarche

This study and a previous large study from Korea (82) showed no significant difference of associations with thyroid cancer among women with early and late age at menarche, consistent with findings from other large prospective studies from USA(53) and China(72), pooled analyses of 14 case-control studies(76), and meta-analyses of 24 prospective studies (61).

Nevertheless, there is some evidence from previous studies that both early(≤13 years) (54, 55) and later age at menarche (>14 years) (52) are associated with an increased risk of thyroid cancer. The underlying mechanisms for this association are not fully understood, but it is believed that the hormonal changes that occur during puberty and early adolescence may play a role in the development of the cancer. Specifically, it is thought that the increased levels of estrogen that occur during this time may contribute to the growth and proliferation of thyroid cell growth(85, 87).

It should be noted, however, that not all studies have found an association between age at menarche and thyroid cancer risk, and the findings may vary depending on the population and region being studied. Additionally, the magnitude of the association between age at menarche and thyroid cancer risk appears to be relatively small, and other risk factors(94, 100, 128) such as variations in environment, lifestyle, genetics and differences in average age of menarche between Asian (~12.5 years)(95, 96) and Western (~13 years)(97) women are possibly to play a larger role in the development of thyroid cancer.

OC and HRT use

Consistent with previous studies (60, 69, 70, 73) this study found no association of hormone use in the form of OC and HRT with thyroid cancer risk. A meta-analysis of 6 cohort and 3 case-control studies from Western countries(73), as well as another metanalyses including 25 studies worldwide(60) also reported OC and HRT use did not alter the risk of thyroid cancer.

OC use has been investigated as a potential risk factor for thyroid cancer, considering these pills contain synthetic hormones that may affect the growth and function of the thyroid gland. However, the evidence on the association between OC use and thyroid cancer risk remains inconsistent(84).

The inconsistent findings may be due in part to the complexity of the hormonal pathways involved in thyroid cancer development, as well as the potential confounding effects of other risk factors. There is also some evidence to suggest that the associations between OC use and thyroid cancer may differ between Asian(112) and Western(113) women. However, conclusions relating to OC and HRT use should be made with caution for this study considering limited cohort contributions to the risk analyses.

5.3. Stratified Analyses

5.3.1 Effect of birth years

The effect of birth year on the association between reproductive factors and thyroid cancer risk refers to the idea that the relationship between reproductive factors and thyroid cancer risk may have changed over time, possibly due to changes in lifestyle, environmental factors, or medical practices. This study using data from the Asia Cohort Consortium was able to investigate this by looking at how the association between reproductive factors and thyroid cancer risk varied across different birth cohorts.

The study found that the risk of thyroid cancer by number of children/deliveries did vary by birth years in Asian women, with a

positive association observed to be stronger in younger birth cohorts than in older ones. These findings suggest that changes in lifestyle and environmental factors over time may have influenced the relationship between number of deliveries and thyroid cancer risk.

Possible explanations for these changes include changes in dietary patterns such as adopting Westernized diet(50, 129), changes in the prevalence of obesity and changes in reproductive patterns such as decline in fertility rates or older age at first delivery(101, 102) or other risk factors such as cultural factors like the one-child policy from 1979-2015 in China, as well changes in medical practices, such as increased use of ultrasound imaging and fine needle aspiration biopsy, which may have led to the earlier detection of thyroid cancer in women with a history of childbirth.

Overall, the findings of the study suggest that the relationship between reproductive factors and thyroid cancer risk may be influenced by birth cohort, and that future studies should take into account the potential effects of birth year when investigating this relationship.

5.3.2 Effect of country

Stratified analyses by country provide an additional layer of information to stratified analyses by birth year, enabling the examination of cross-country differences in the association between reproductive variables and thyroid cancer risk. It allows for the exploration of potential geographic or cultural influences that may contribute to the observed variations in the associations.

This study revealed that the associations between number of deliveries/children and thyroid cancer risk varied significantly across countries. A significant positive association was observed for Korea, indicating a higher risk with more deliveries/children, in contrast inverse associations were seen for China and Japan. In the stratified analyses by birth years, younger birth cohorts were primarily composed of Korean cohorts, while older birth cohorts

were predominantly from Japan. And an increased risk of thyroid cancer was observed among the younger birth cohorts in association with number of deliveries. This finding aligns with the observations from the younger birth cohorts, indicating additional evidence of a consistent association between the number of deliveries and thyroid cancer risk among Korean populations.

In the stratified analyses by country, distinct patterns emerged when examining the association between age at first delivery/pregnancy or age at menarche and thyroid cancer risk. For China and Japan, the risk estimates for younger and older age at first delivery/pregnancy were close to null, indicating no significant association. However, the 21-25 years age group showed a reduced risk of thyroid cancer. On the other hand, in Korea, there was a noticeable increasing risk of thyroid cancer with older age at first delivery/pregnancy. For China and Japan, an earlier age at menarche was associated with an increased risk of thyroid cancer. In contrast, in Korea, an earlier age at menarche was associated with a reduced risk of thyroid cancer.

Now, turning to the stratified analyses by birth years, no significant associations were found between age at first delivery/pregnancy or age at menarche and thyroid cancer risk. Although statistically non-significant, these country-specific associations were not observed when examining the entire study population grouped by birth years. Moreover, the lack of significant associations in the stratified analyses by birth years suggests that the observed associations in the stratified analyses by country are not simply a result of overall population trends but reflect distinct patterns within each country.

Another significant interaction that was observed was for the relationship between breastfeeding status and thyroid cancer risk, stratified by countries, where ever breastfeeding showed non-significant increased risk for Japan and no association for Korea. The combined evidence from the stratified analyses by birth cohorts (ever breastfeeding showed non-significant increased risk

for thyroid cancer in older birth year groups) and country suggests that older birth cohorts, primarily composed of Japanese women, exhibit a higher risk of thyroid cancer in relation to breastfeeding.

These findings underscore the importance of considering both country-specific and birth year-specific analyses to gain a comprehensive understanding of the relationship between reproductive factors and thyroid cancer risk.

5.3.3 Effect of age at diagnosis of thyroid cancer

Women diagnosed at an earlier age and who were parous demonstrated a significantly higher risk of thyroid cancer (HR 1.75, 95%CI 1.11-2.76). This is an interesting finding considering in the stratified analysis by birth years, nonsignificant increased risk was observed in younger birth cohorts (HR 1.2, 95% CI 0.85-1.69) for ever being parous. Therefore, it is possible that the higher risk observed in younger birth cohorts and in thyroid cancer diagnosis at an earlier age may reflect a screening or detection bias. It may be influenced by increased medical surveillance or diagnostic testing, as women have generally increased exposure to healthcare because of reproductive and perimenopausal factors leading to enhanced thyroid gland scrutiny.

Advanced age at first delivery/pregnancy significantly increased the risk for thyroid cancer if diagnosed at an older age (HR 1.19, 95% CI 1.02-1.39, p-trend=0.003). This association was weaker for thyroid cancer diagnosis at an earlier age. In stratified analysis by birth years, no significant associations were found between age at first delivery/pregnancy and thyroid cancer risk. Interestingly in the specific context of Korea, there was a noticeable increasing risk of thyroid cancer with older age at first delivery/pregnancy. Overall, these findings suggest advanced age at first delivery/pregnancy may be a potential risk factor for thyroid cancer, particularly among women diagnosed at an older age, and the divergent patterns observed across countries may be influenced by cultural, genetic, or environmental factors unique to each region.

An earlier age of diagnosis of thyroid cancer was significantly associated with a reduced risk in relation to menopausal status (HR 0.7, 95% CI 0.51−0.96). Conversely, later age at diagnosis was associated with an increased risk. Additionally, the study also revealed that when stratified analysis by birth years, among older cohorts, there was a non−significant increased risk of thyroid cancer associated with menopausal status. These associations highlight the difference in screening methods or country−specific patterns. Similar findings were seen for age at menopause.

5.3.4 Effect of BMI

In this study, BMI was found to modify the association between age at first delivery/pregnancy and thyroid cancer risk, specifically for Asian women. Older age at first delivery/pregnancy showed relatively increased risk among women of BMI <23 kg/m^2, whereas younger age at first delivery showed increased risk among those with BMI ≥23 kg/m^2

The relationship between BMI, reproductive factors, and thyroid cancer risk is still an area of active research. There is evidence to suggest that BMI is a major lifestyle related factor that affects the development of thyroid cancer in both Eastern and Western populations (38, 69, 130−132). However, there may be variation in the strength of the association and the specific subtypes of thyroid cancer affected.

The exact mechanisms by which BMI may increase the risk of thyroid cancer in women with certain reproductive factors are not fully understood. However, one plausible mechanism could be that obesity leads to a state of chronic inflammation, which can promote the development of cancer. Another hypothesis is that obesity may affect the levels of sex hormones such as estrogen and progesterone, which may in turn influence the development and progression of thyroid cancer. In addition, obesity is also associated with insulin resistance and hyperinsulinemia, which can stimulate the growth of cells and contribute to the development of cancer.

Insulin and insulin-like growth factor-1 (IGF-1) have been shown to promote the growth of thyroid cells in vitro. (133)

For the effect of BMI on the association between age at delivery/pregnancy and thyroid cancer, the exact mechanisms may differ between Asian and Western women due to differences in genetics, dietary patterns, lifestyle factors, and cultural norms surrounding body weight. There are several potential reasons why this interaction may differ between the two populations. One possibility is differences in the prevalence of obesity and overweight(38); Asian populations tend to have lower BMI on average compared to Western populations, and so the effects of BMI on thyroid cancer risk in the two populations may lead to different patterns of risk.

Additionally, differences in childbearing trends between Asian and Western women could contribute to varying interaction between BMI and age at first delivery on thyroid cancer risk.

5.3.5 Effect of smoking

In this study, a small proportion of females (7%) were identified as ever smokers at baseline and when analyzing the data by smoking status and examining the relationship between reproductive factors and thyroid cancer, the number of cohorts that contributed to the ever smokers' group was limited. Consequently, no significant associations between reproductive factors and thyroid cancer risk were observed by smoking status.

To my knowledge, there is currently no evidence to suggest that smoking reduces the risk of thyroid cancer in women with certain reproductive factors. While some studies have reported a reduced risk of thyroid cancer among smokers, (39-43) these findings are not consistent and may be likely due to other factors such as the healthy smoker effect or differences in thyroid cancer screening practices between smokers and non-smokers.

Proposed explanations include anti-inflammatory effects of nicotine, a major component of cigarette smoke, and reduced levels

of TSH due to smoking(44, 45). However, the evidence supporting these hypotheses is not yet definitive. Furthermore, there is limited research on the interaction of smoking with reproductive factors on the risk of thyroid cancer in Asian women compared to Western women.

5.4. Clinical Implications

In many parts of the world, including Asia, there has been a trend toward delayed childbearing,(103) where the median age of women at first childbirth has increased from 26.8 to 33.2 years(104). This presents a challenge for healthcare providers as more women are having children at older ages, and there will be a higher risk of thyroid cancer in women who desire pregnancy.

The study findings from stratified analyses underscore the importance of considering country-specific, birth year-specific and thyroid cancer age of diagnosis analyses to gain a comprehensive understanding of the relationship between reproductive factors and thyroid cancer risk.

A better understanding of the association between reproductive and hormonal factors and thyroid cancer risk in both Asian and Western women would have important clinical implications. For instance, if certain reproductive and hormonal factors are more strongly associated with thyroid cancer risk in Asian women compared to Western women, healthcare providers could use this information to develop more appropriate counseling for women in Asian countries.

In addition, in recent years, the emerging management of thyroid cancer is shifting towards a more parsimonious approach. Considering thyroid cancer ranks third among women aged 25-45, following breast and cervical cancer, it becomes imperative to conduct more rigorous research to determine whether hormone status is a potential risk factor or not. This is particularly important for women, aiming to minimize risks and maximize patient benefits.

5.5. Strengths and Limitations

5.5.1 Strengths

There are several strengths of this study:

- Large sample size with a prospective study design
- Plausibly the first pooled analyses to explore associations of reproductive factors with thyroid cancer risk in Asian women.
- Due to pooling data of several cohorts, a larger number of thyroid cancer cancers were available, which allowed conducting subgroup analyses with greater statistical power.
- In addition, because the analyses were limited to prospective studies, recall and selection biases were minimized.
- Standardized categorizations of reproductive, hormonal variables and other covariates across studies.
- Furthermore, by standardizing the categorizations of exposure and other covariates across studies, potential sources of heterogeneity between studies were minimized.

5.5.2 Limitations

This study has some limitations:

- Any change in exposure status during follow-up cannot be addressed in this study because reproductive and hormonal variables were measured only at baseline.
- Confounding cannot be completely ruled out; however, it is probably of minor importance as potential risk factors for thyroid cancer were adjusted in the models, and the age-adjusted and multivariable models yielded similar results.
- Further adjustment by radiation exposure, iodine intake, family history of thyroid cancer was not possible due to unavailability of data across studies.
- Although pooled data increased the sample size, it was still not enough to calculate certain reproductive factors

associations.

- No differences in the associations between reproductive factors and thyroid cancer risk stratified by smoking may be the result of the relatively small number of ever smoker within each study (range of the number of thyroid cases in ever smokers = 4 to 72).
- Women have generally increased exposure to healthcare because of reproductive and perimenopausal factors leading to enhanced thyroid gland scrutiny.
- Generalizability of findings may be limited to the Chinese, Japanese, and Korean populations included in the study.
- Stratification by BMI was conducted using baseline information. To address the potential interaction with reproductive factors, BMI during early adulthood or before pregnancy may be more relevant.(38, 134-136)

Chapter 6. Conclusion

To the best of my knowledge, this is the first large, pooled analysis to explore the relationship between reproductive factors and thyroid cancer risk in Asian women.

Findings revealed a significantly increased risk of thyroid cancer for older age at first delivery/pregnancy, which poses a new challenge for healthcare providers, as the proportion of women having children at the end of their reproductive years has been on the rise, and there will be a higher risk of thyroid cancer in women who delay pregnancy.

Additionally, older age at first delivery/pregnancy significantly increased thyroid cancer risk, particularly when diagnosed later in life (≥55 years). Among the countries, a positive association was seen in Korean cohorts and no significant associations observed for China and Japan. Furthermore, the lack of significant associations when stratified by birth year suggest that these observed associations reflect country-specific patterns.

Birth years modified the association between number of children/deliveries and thyroid cancer risk, with a significant positive association in younger cohorts, which mainly consisted of Korean populations. Moreover, when stratified by countries, a significant positive association was observed for Korea, while inverse associations were seen for China and Japan, further emphasizing the evidence of a consistent association between the number of children/deliveries and thyroid cancer risk among Korean populations.

An elevated risk of thyroid cancer in parous women diagnosed at an earlier age and non-significant increased risk in younger birth cohorts may be indicative of heightened medical surveillance or increased diagnostic testing. An increased risk at later age at diagnosis in relation to menopausal status was observed, in addition to non-significant increased risk among older cohorts. These

associations highlight the differences in country-specific screening methods or patterns.

BMI modified the association between age at first delivery/pregnancy and thyroid cancer risk, especially in Asian women. This interaction may differ between Asian and Western women, due to variations in genetics, dietary patterns, lifestyle factors, BMI prevalence and childbearing trends.

Overall, this study fills a knowledge gap and offers valuable insights into the association between reproductive factors and thyroid cancer risk in Asian women. However, further studies that include genetic, reproductive, and environmental factors should be conducted to better understand the complex interplay between these factors and thyroid cancer risk.

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Abstract in Korean

연구 배경: 갑상선암은 전 세계적으로 흔한 내분비계 악성 종양이며, 성별 간 발생률 차이가 크게 나타난다. 남성보다 여성에서 갑상선암 발생률이 약 3배 높으며, 특히 가임기 연령의 여성이 갑상선암 발생에 취약하다. 갑상선암 병리와 관련하여 여성 호르몬의 작용이 갑상선암 발생 기전으로서 언급되고 있지만, 생식 요인(reproductive factor)의 영향력에 대해서는 명확히 밝혀진 바가 없다. 갑상선암 발생 위험과 여성 생식 요인 간의 연관성에 대한 선행 연구들의 결과가 서로 일치하지 않다. 이는 각 연구들의 제한된 검정력과 연구 설계 및 특성 차이에서 기인하였을 가능성이 있다. 특히, 아시아 국가의 생식 연령 여성 대상 인구 기반 전향적 연구가 부족하므로, 아시아 여성의 생식 요인 작용에 따른 갑상선암 발생 위험 해석에 있어 제약이 따른다.

연구 목표: 본 연구는 대규모 아시아 여성을 대상으로, 여성의 생식 및 호르몬 요인과 갑상선암 발생 간의 연관성을 평가하였다. 추가적으로, 갑상선암 중 조직학적으로 가장 흔한 유두상 갑상선암(papillary thyroid cancer)과 여성의 생식 및 호르몬 요인 연관성을 탐색하였다. 더 나아가, 흡연 여부 및 체질량지수(BMI, body mass index), 국가, 출생 연도, 갑상선암 진단 시 연령에 따른 생식 요인과 갑상선암 발생 위험 연관성 차이를 탐구하였다.

연구 방법: 아시아 코호트 컨소시엄에 참여한 코호트 중, 여성 생식 요인과 갑상선암 발생 정보 제공에 동의한 10개 코호트의 개인 수준 연구 자료를 사용하여 통합분석을 수행하였다. 생식 및 호르몬 요인은 초경 연령, 출산 경험, 분만/자녀 수, 초산 연령, 모유 수유 경험, 폐경 여부, 폐경 연령, 경구 피임약 복용 및 호르몬 대체요법 경험여부, 자궁 절제 여부로 정의하였다. 갑상선암 발생 여부는 국제질병분류 10차 개정판(ICD-10)의 'C73' 을 사용하여 각 코호트별 국가 암등록자료와 연계 후 식별되었다. 갑상선암의 조직학적 분류는 종양학 국제질병분류 3차 개정판(ICD-O-3)에 기반하여 진행되었다. 교란요인으로 흡연 여부, 음주 여부, BMI(kg/m^2)를 보정하였다. 연구대상자 선정시 1) 남성 또는 성별 정보가 없는 경우, 2) 연령 정보가 없는 경우, 3) 출산 경험/출산 횟수 정보가 없는 경우, 4) 코호트 입적 이전에 갑상선암 진단 이력이 있는 경우 또는 갑상선암 진단·발생 추적 정보가 누락되었거나 유효하지 않은 경우를

제외하였다.

통계 분석: 기술 통계량은 각 코호트의 특성을 요약하기 위해 사용되었다. 생식 요인과 갑상선암 발생 위험 연관성 평가를 위하여, 각 참여 코호트의 생식 요인에 대한 Cox 비례 위험 회귀 모형으로 위험도(HR)와 95% 신뢰구간(CIs)을 추정하였다. 시간 척도로서 연령을 사용하였으며, 입적 연령부터 갑상선암 발생 또는 사망, 각 코호트 추적 관찰 종료일까지의 인년(person-years)을 계산하였다. 또한, 잠재적 교란요인에 대하여 보정하였다. 비례 위험 가정은 Schoenfeld 잔차를 이용하여 평가하였다. 갑상선암 발생 위험에 대한 생식 요인 변수의 선형추세 통계적 유의성을 조사하였고, 각 코호트의 위험도 통합 분석은 무작위 효과 모형으로 수행하였다. 코호트간 이질성은 Cochran의 Q-검정과 I^2 통계량으로 평가하였다. 출생 연도와 국가, 흡연 여부, BMI별 층화 분석을 수행하여 해당 요인에 따른 생식 및 호르몬 요인과 갑상선암 발생 위험 간의 연관성에 차이가 있는지 관찰하였다. 상호작용의 유의성은 우도비 검정을 통하여 상호작용에 대한 p-값으로 평가하였다. 갑상선암 진단 시 연령별(<55세, 55세≤) 생식 요인에 따른 갑상선암 발생 위험 분석을 추가로 실시하였다.

연구 결과: 최종 연구대상자는 본 연구에 참여를 동의한 10개의 코호트로부터 289,707명의 여성으로 선정되었다. 본 연구에 포함된 코호트는 각 일본 7개(JPHC1, JPHC2, JACC, Miyagi, 3pref. Miyagi, Ohsaki, LSS), 한국 2개(KMCC, KNCC), 중국 1개(SWHS)이었다. SWHS 코호트에서 가장 많은 대상자(74,930명), KMCC 코호트에서 가장 적은 대상자(11,423명)가 본 연구에 포함되었다. 코호트 입적 평균(표준편차)연령은 54(10.6)세이었다. 일본 코호트는 주로 연령대가 높은 편이었으며, 한국과 중국 코호트는 상대적으로 연령대가 낮았다. 전체 연구대상자에서 흡연자는 총 7%(20,230명), 음주자는 총 19%(56,091명)이었다. 입적 시 BMI 평균(표준편차)은 23.4(6.4)kg/m^2이었다. 평균(표준편차) 17.2(6.6)년의 추적 관찰 결과, 총 1,519명의 갑상선암 환자가 발생하였다. KNCC 코호트(421명)와 SWHS 코호트(306명)에서 가장 많은 갑상선암 환자가 발생하였다. 갑상선암 환자의 코호트 입적 시 평균(표준편차) 연령 은 50.6(9.7)세, 갑상선암 진단 시 연령은 60.2(12.5)세이었다. 총 1,519명 갑상선암 환자 중 조직학적 분류 정보가 있는 환자는 1,294명이었으며, 이 중 88%(1,140명)가 유두상 갑상선암 유형이었다. LSS 코호트의 경우, 생식

요인과 조직학적 분류 정보가 다수 누락되어 주요 분석에서 제외하였다.

초산 연령이 높을수록(≥26세 vs 21−25세) 갑상선암 발생 위험이 유의하게 증가하였다[HR 1.16 (95% CI 1.03−1.31), *p*−trend 0.003]. 자녀 수, 모유 수유 경험, 폐경, 폐경 연령은 갑상선암 발생 위험 증가와 연관성이 관찰되었으나, 통계적으로 유의하지 않았다. 초경 연령, 출산 경험, 경구피임약 복용, 호르몬 대체요법 경험은 갑상선암 발생 위험과 유의한 연관성이 없는 것으로 나타났다. 유두상 갑상선암 발생에 있어서도 비슷한 연관성이 관찰되었다. 갑상선암 진단 시 연령별 분석 결과, 55세 이후 갑상선암 진단을 받은 경우 높은 초산 연령은 갑상선암 발생 위험 증가와 유의한 연관성 [HR 1.19(95% CI: 1.02−1.39), *p*−trend=0.003]을 가지었다. 국가별 층화 분석 결과, 분만/자녀 수와 갑상선암 발생 위험 간의 유의한 상호 작용이 관찰되었다(*p*−interaction=0.002). 한국의 경우 분만/자녀 수가 많을수록 유의한 양의 연관성[HR 1.89 (95% CI 1.21−2.94), *p*−trend 0.0008 (≥5명 vs 1−2명)]이 관찰된 반면, 일본과 중국에서는 유의하지 않은 음의 연관성이 관찰되었다. 출생 연도에 따라 분만/자녀 수와 갑상선 암 발생 위험 간의 연관성이 크게 달랐다(*p*−interaction=0.002). 1950년대 또는 그 이후 출생한 여성에서 분만/자녀 수가 증가함에 따라 갑상선암 발생 위험이 유의하게 증가하는 경향성[HR 2.40 (95% CI 1.12−5.18), *p*−trend 0.0001 (≥5명 vs 1−2명)]을 보였으나, 그 이전에 태어난 경우 유의한 경향성이 없었다.

결론: 본 연구는 아시아 여성의 생식 요인과 갑상선암 발생 위험 간의 연관성을 탐구한 최초의 대규모 통합분석이다. 본 연구 결과, 초산 연령이 높아질수록 갑상선암 발생 위험이 유의하게 증가하였다. 이는 출산 시기가 늦어지는 사회적 현상에 따라 의료 서비스 제공자들에게 도전과제로서 대두된다. 분만/자녀 수와 갑상선암 발생 위험 간의 연관성에 대하여 국가별 다른 패턴을 보였으며, 한국은 유의한 양의 연관성을 가지었다. 주로 한국인으로 구성된 후기 출생 연도 코호트에서도 분만/자녀 수가 많을수록 갑상선암 발생 위험이 증가하는 것으로 나타났다. 이는 한국 여성의 분만/자녀 수와 갑상선암 발생 위험 간의 일관된 연관성을 뒷받침한다. 본 연구는 기존 연구 결과의 간극을 줄이고, 아시아 여성의 생식 요인과 갑상선 암 발생 위험 간의 연관성에 대한 주요한 통찰력을 제공함에 의의가 있다. 또한, 생식 요인과 갑상선암 발생 간의 연관성을 더욱 포괄적으로 탐색하기 위하여, 국가 및 출생 연도, 갑상선암 진단 시

연령까지 분석에 고려하였음을 강조하고자 한다. 여성의 갑상선암 관리 향상을 위하여 위험요인으로서 생 식 및 호르몬 요인에 대한 추후 연구가 중요하다.

키워드: 전향적 연구 통합분석, 갑상선암 발생률, 생식 요인, 아시아 코호트 컨소시엄. 국가별, 출생 연도
학번: 2021-23035

Appendix

Supplementary tables

Supplementary Table 1: Questionnaire items of the reproductive variables from each cohort

	SWHS	JHPC1	JHPC2	JACC	Miyagi	Ohsaki	LSS	3 Pref Miyagi	Takayama	KMCC	KNCC	Namwon	SCHS
Pregnancy status	Date when pregnancy ended (year / month)								Have you ever been pregnant? No / Yes	Have you ever been pregnant? No / Yes / Do not know		Have you ever been pregnant? No / Yes	Have you ever been pregnant? No / Yes
Age at first delivery/ pregnancy	Date when pregnancy ended (year / month)	At what age was your first pregnancy? __years old	At what age was your first pregnancy? __years old	Age at first live birth			At what age was your first pregnancy? __years old / At what age was your first delivery? __years old		How old were you at your first pregnancy? Age=<14 / 15-17 / 18-20 / 21-25 / 26-30 / 31-35 / 36=<	How old were you at your first pregnancy? Age__ / Do not know	What is the age at first pregnancy ?	How old were you at your first pregnancy ? Age__	
Number of deliveries/ pregnancies	How many times have you been pregnant?	In total, how many pregnancies have you had? __ times	In total, how many pregnancies have you had? __ times	Number of times you have been pregnant/ Number of times you have given birth	How many times have you been pregnant? __ times	How many times have you been pregnant? __ times	How many times have you been pregnant? __ times				Age in years / Do not know		

Breastfeeding	If you breast fed the baby, how many months you nursed	Did you breastfeed your children? No / Yes	Did you breastfeed your children? No / Yes		What kind of feeding method did you use? Breast milk only / Artificial nutrition (milk) only / a combination (or both)	What kind of feeding method did you use? Breast milk only / Artificial nutrition (milk) only / a combination (or both)	How many children did you breastfeed ? / Artificial nutrition (milk) only / a combination (or both)? How long did you breastfeed			Have you ever breastfed? No /Yes		Have you ever breastfed? No /Yes	
Age at menarche	At what age did you have your first period (menarche) (please fill in your actual age): ___years old	How old were you when you first started menstruat-ing? __years old	How old were you when you first started menstruati ng? __years old	Age when menstrual periods started	How old were you when you had your first period? __ years of age	How old were you when you had your first period? __ years of age	How old were you when you had your first period? __ years of age	At what age did menstruat ion begin (first menstruat ion) full __ years of age	How old were you when you had your first menstrual period? Age=< 10 years / 11-12 years / 13-14 years / 15-16 years / 17 years =<	When did you have your first menstru at-ion? Age__ / Do not know / No	What is the age at first childbearin g?	When did you have your first menstruat-ion? Age__ / No	How old were you when you had your first menstrual period? Less than 11 years / 11-12 years / 13-14 years / 15-16 years / 17 years or more
Menopausal status	Do you still have periods? Yes/no	Do you still menstruat e? Yes / Natural menopaus e / Artificial menopaus e	Do you still menstruat e? Yes / Natural menopaus e / Artificial menopaus e	Age of menopaus e	Do you menstruat e (have menses) currently? Yes / I Have had menopaus e (naturally) / I Have had	Do you menstruat e (have menses) currently? Yes / I Have had menopaus e (naturally) / I Have had		Is menstruat ion still continuing ? Yes / No	Is menstruatio n still continuing? Yes / No	When did you have your menopa use? Age___ / Do not know / doesn't apply	Age in years / Do not know	Do you still menstruat e? No, menopaus e, age__ / Yes	Have your menstrual periods stopped permanent ly? No / Yes

					menopause (surgically)	menopause (surgically)							
Age of menopause	What was the date of your last period? 19__year __month	If you are no longer menstruate, how old were you when menopause began? __years old	If you are no longer menstruate, how old were you when menopause began? __years old	Age of menopause	Around what age were you when you had menopause? __years of age	Around what age were you when you had menopause? __years of age	What age were you when you had menopause? __years of age / Not applicable	Did it stop naturally? Yes (full __years of age) / No (full __years of age)	If you are no longer menstruate, how old were you when menopause began? Age=<39 / 15-17 / 18-20 / 21-25 / 26-30 / 31-35 / 36=<	When did you have your menopause? Age___/ Do not know/ doesn't apply		Do you still menstruate? No, menopause, age__ / Yes	How old were you when this happened? Less than 40 years / 40-44 years / 45-59 years / 50-54 years / 55 years or more
OC use status	Have you ever taken OC? Yes / No	Have you ever taken female hormone drugs? No / Yes	Have you ever taken hormone therapy for dysmenorrh-ea, contracept-ion or for menopausal problems?		Have you ever used contracept-ive medications? No / Yes	Have you ever used contracept-ive medications? No / Yes				Have you ever used OC? No / Yes	What is the age at first delivery?	Have you ever used OC? No / Yes	Did you ever take birth control pills for one month or longer? No / Yes and I am currently taking them / Yes but I no longer take them
Duration of OC use	How long did you take/have you been taking OC? __year/ __month				Have you ever used contracept-ive medications? No / Yes (The time period __months or __ years)	Have you ever used contracept-ive medications? No / Yes (The time period __months or __ years)				How long have you been using? __year __month / Do not know	Age in years / Do not know	How long have you been using? __year __months	How many years did you take them in total? Less than one year / 1-2 years / 3-5 years / 6-9 years /10-14 years /

													15-19 years / 20 years or more
HRT status	Have you ever used female hormones to treat climacteric melancholia, sterility, mulleriosis, acne, etc? Yes / No	Have you ever taken female hormone drugs? No/Yes	Have you ever taken hormone therapy for dysmenorrh-ea, contracept-ion or for menopausal problems?	Have you ever used sex hormone agents?	Have you ever used female hormones other than contracept-ive medications? Yes / No	Have you ever used female hormones other than contracept-ive medications? Yes / No			Have you ever taken female hormones by pill or injection for menopausal disorder or other reasons? No / Yes still currently / Yes but not currently	Have you ever taken female hormones by pill, injection, or patch for menopause or other reasons? No / Yes still currently / Yes but not currently	What is the total number of pregnancies?	Have you ever taken female hormones by pill, injection, or patch for menopause or other reasons? No / Yes	Did you ever take estrogens (female hormones) by pill, or injections, for one month or longer for menopause or other reasons? Don't know or No / Yes and I am currently taking them / Yes but I no longer take them
Hysterectomy status	Hysterect-omy? Yes / no				Have you ever had abdominal surgery? Yes / No	Have you ever had abdominal surgery? Yes / No			Have you ever had a hysterect-omy? No / Yes	Have you ever had a hysterect-omy? No / Yes age __ or __years ago	Did you do breast feeding?	Have you ever had a hysterect-omy? No / Yes age (___)	Have you ever had a hysterect-omy? No / Yes

Supplementary Table 2: Histological subtypes of thyroid cancer based on ICD−O−3 codes available from cohorts

Papillary	Medullary	Follicular	Anaplastic	Specified	Unspecified
8050	8345	8290	≥8020≤8030	8337	≥8000≤8005
8260	8510	8330-35		8346-47	
8340-44	8511-13				
8350					
8450-60					

Supplementary Table 3: Different categorizations of BMI and its associations with incident thyroid cancer

	HR (95% CI)	*p* value
BMI (East)*		
Underweight <18.5	1.08 (0.84-1.39)	0.56
Normal 18.5–22.9	reference	
Overweight 23.0–24.9	**1.16 (1.02-1.32)**	***0.02***
Obese ≥25	**1.22 (1.08-1.38)**	***0.002***
BMI (West)**		
Underweight <18.5	1.03 (0.80-1.32)	0.84
Normal 18.5–24.9	reference	
Overweight 25.0–29.9	**1.19 (1.06-1.34)**	***0.004***
Obese ≥30	0.88 (0.66-1.21)	0.42

* BMI categorized using categories recommended by the WHO for adult Asians

** BMI categorized using categories recommended by the WHO for adults

BMI – body mass index (kg/m2)

HR – Hazard ratio, CI – confidence interval

p−values indicated in bold show significant association.

Supplementary Table 4: Sensitivity analyses

Using menopausal status to make groups of women according to baseline age

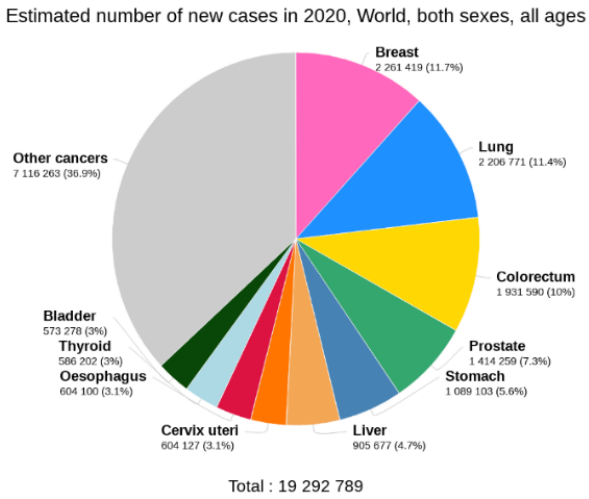
Cohort	Females aged younger than 54 years			Females aged 54 years and older		
	Number of women	Number of TC cases	Person years at risk	Number of women	Number of TC cases	Person years at risk
Total	110,152	723	2,093,403	179,555	796	2,879,182
China						
SWHS	37,106	192	665,235	37,824	114	634,005
Japan						
JPHC1	9,652	63	209,662	11,813	45	251,088
JPHC2	9,016	31	170,796	18,699	46	337,272
JACC	11,726	26	210,663	33,933	63	532,437
Miyagi	9,029	58	204,437	13,808	109	301,050
Ohsaki	3,912	9	42,860	18,279	48	199,423
LSS	13,992	79	409,523	16,066	87	292,453
3pref. Miyagi	4,773	7	57,539	11,751	20	136,383
Korea						
KMCC	2869	35	46262	8,554	66	119,233
KNCC	8,077	223	76,410	8,828	198	75,838

	Number of TC cases	Person years	HR[a] (95% CI)	HR[b] (95% CI)
Females aged younger than 54 years	723	2,093,403	1.00 (0.86-1.17)	1.01 (0.87-1.19)
Females aged 54 years and older	796	2,879,182	*reference*	*reference*

HR[a] – Cox proportional hazard model adjusted for baseline age, HR[b] – Cox proportional hazard model additionally adjusted for smoking status, alcohol drinking status and BMI

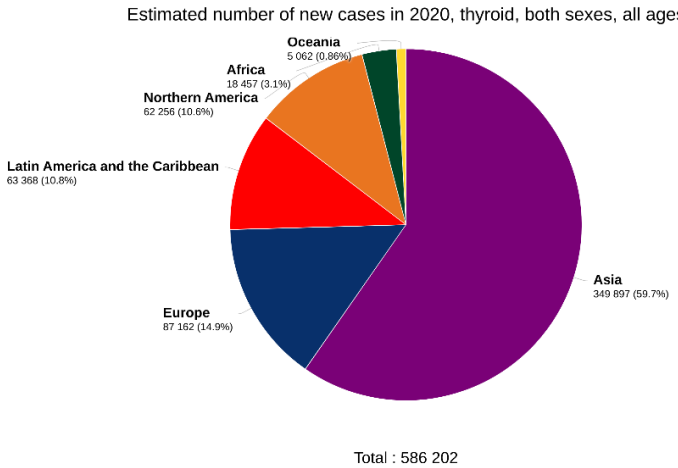
Supplementary figures

Supplementary Figure 1: Global cancer incidence – Thyroid cancer ranks 9th



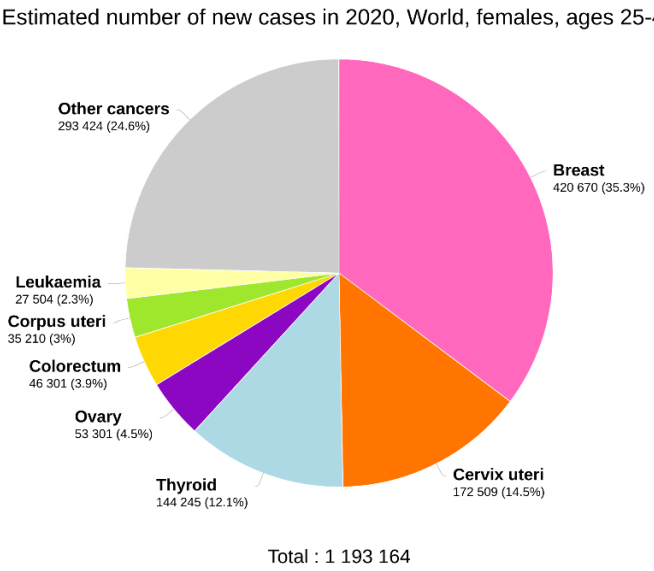
Source: GLOBOCAN, IARC https://gco.iarc.fr/today/

Supplementary Figure 2: Thyroid cancer incidence among continents



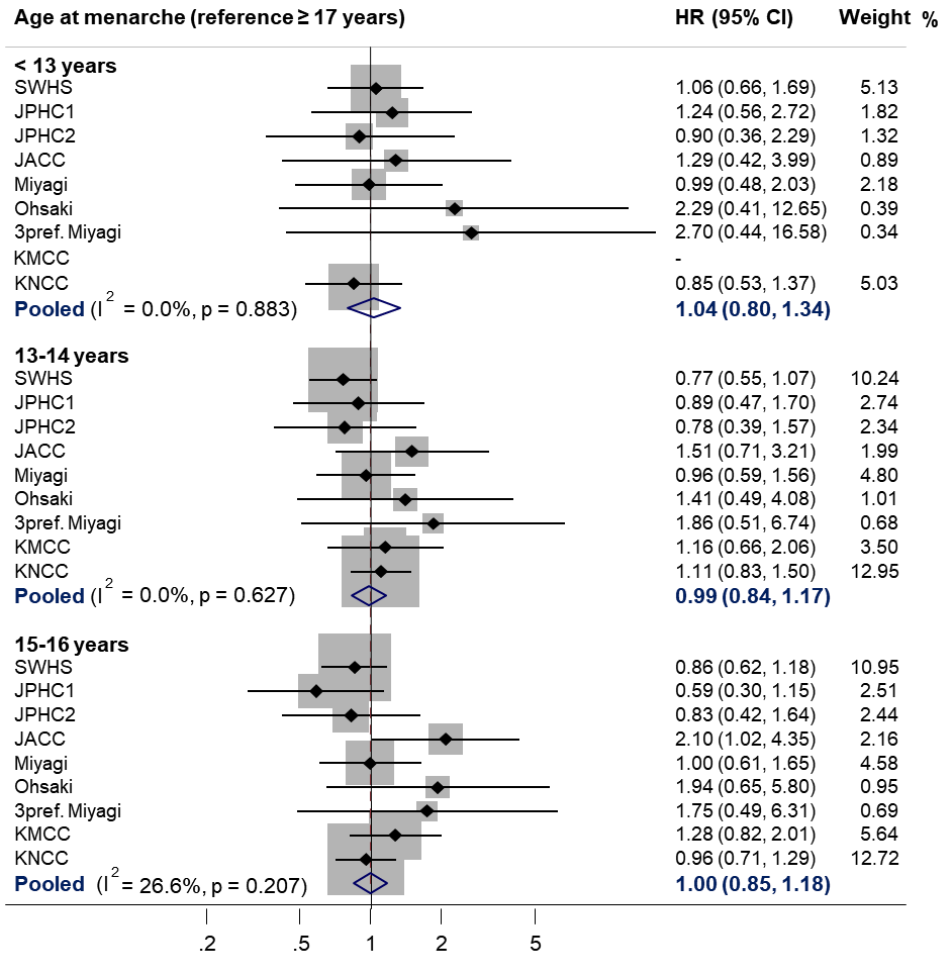
Source: GLOBOCAN, IARC https://gco.iarc.fr/today/

Supplementary Figure 3: Global cancer incidence in females aged 25–44 years

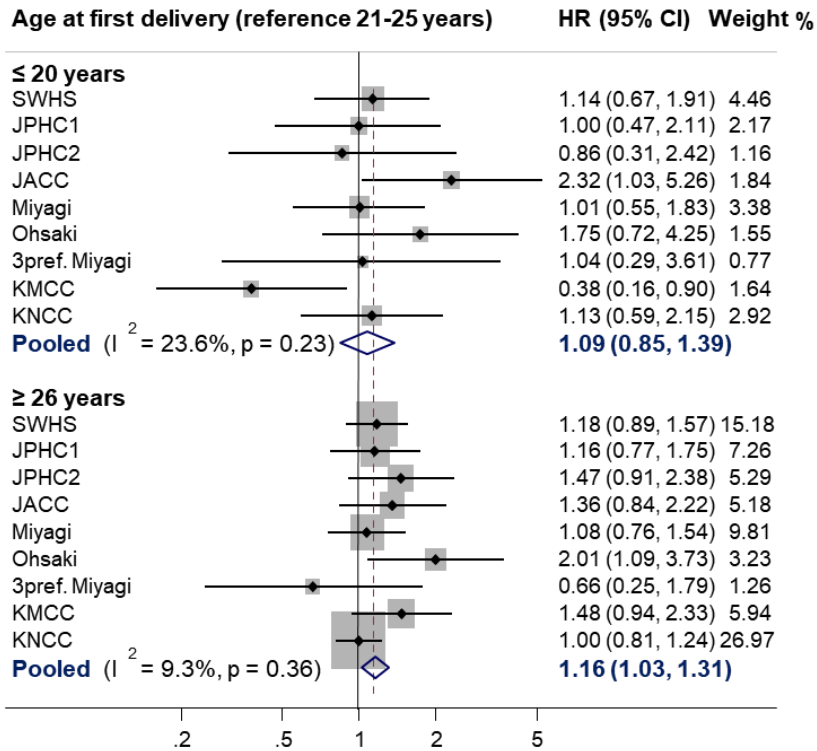


Source: GLOBOCAN, IARC https://gco.iarc.fr/today/

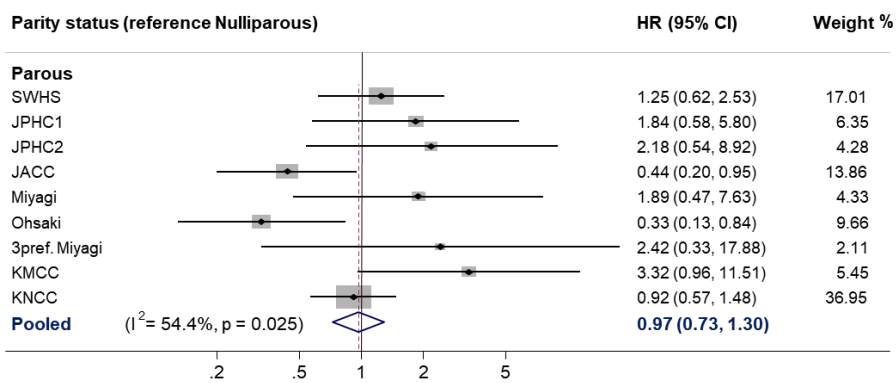
Supplementary Figure 4: Forest plot for the pooled HRs and CIs for age at menarche and thyroid cancer risk, overall



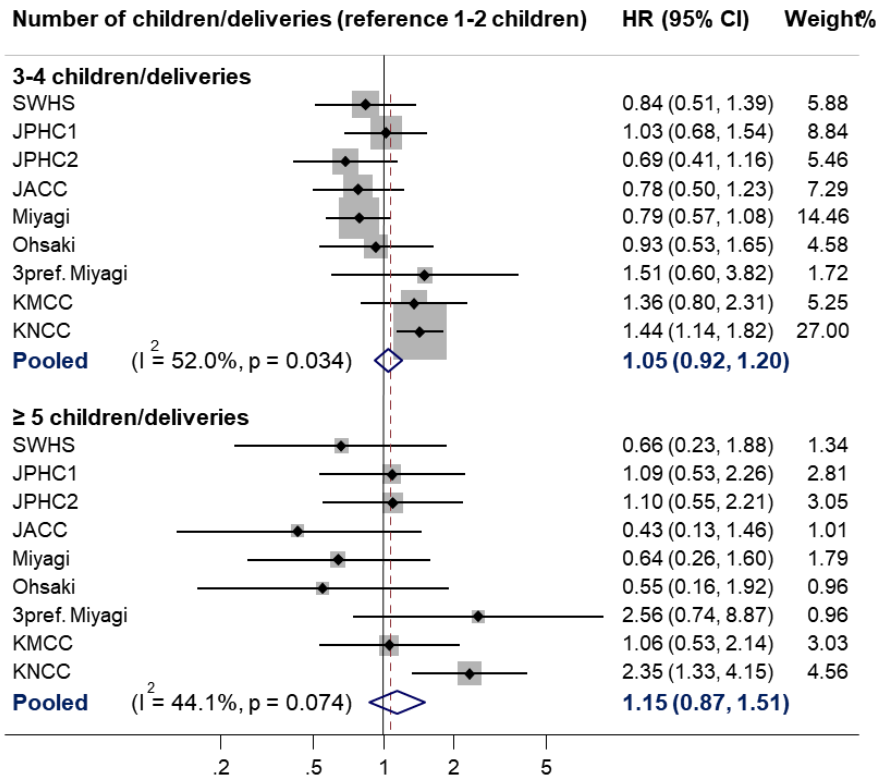
Supplementary Figure 5: Forest plot for the pooled HRs and CIs for age at first delivery and thyroid cancer risk, overall

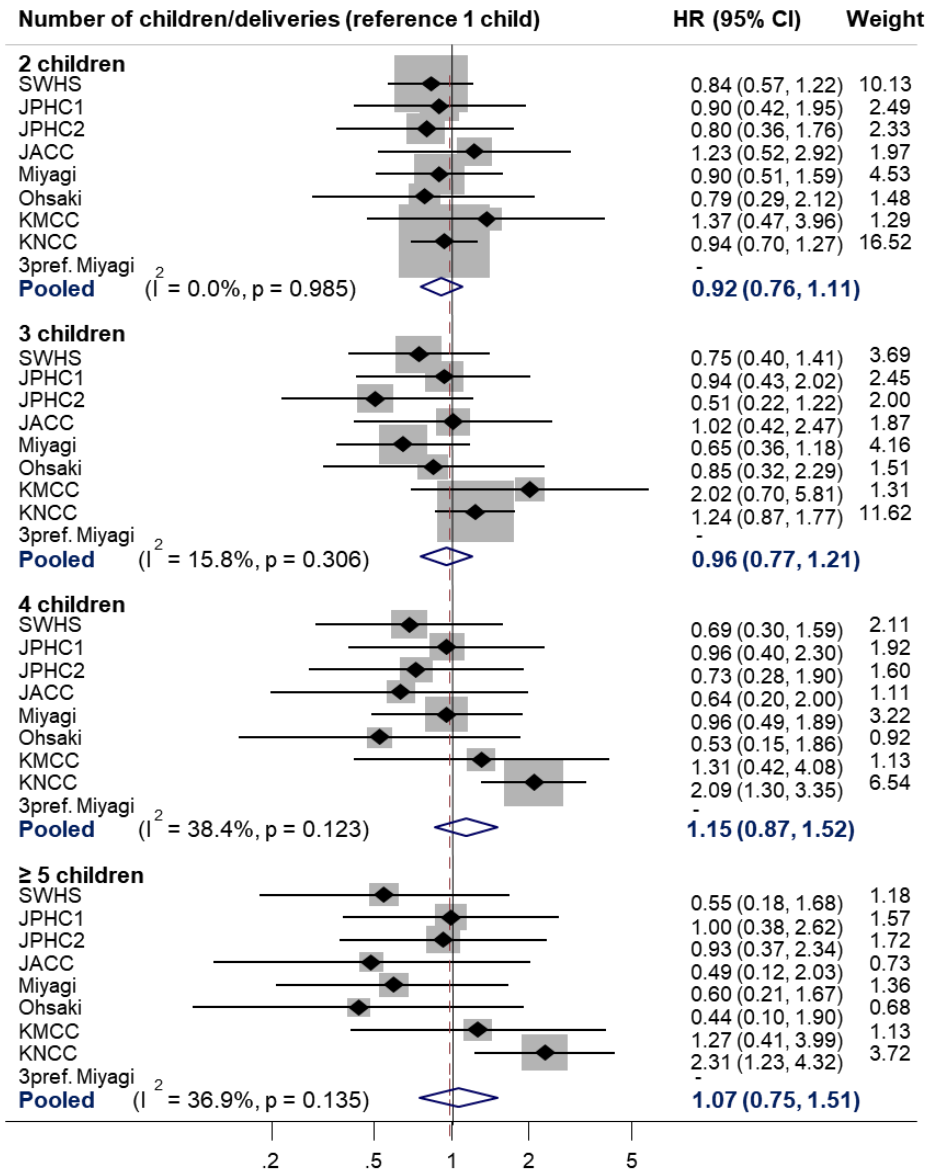


Supplementary Figure 6: Forest plot for the pooled HRs and CIs for parity status and thyroid cancer risk, overall

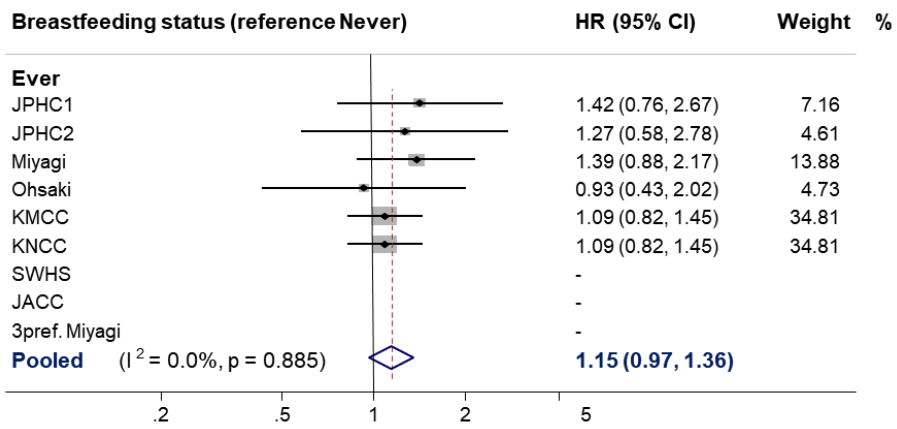


Supplementary Figure 7: Forest plot for the pooled HRs and CIs for number of children/deliveries and thyroid cancer risk, overall

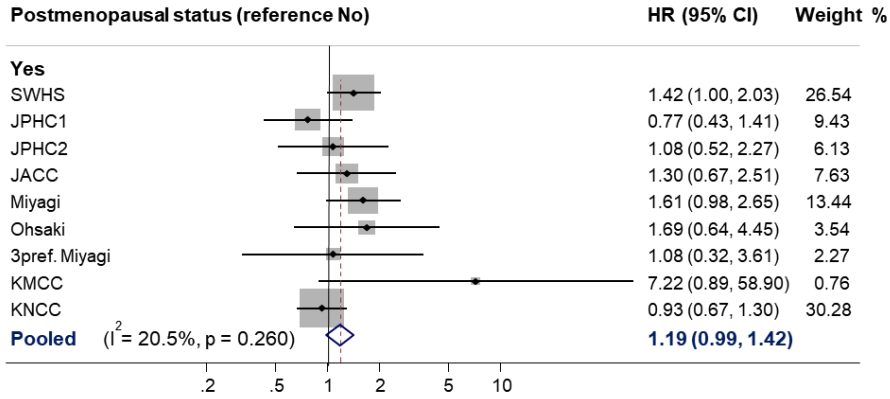



Number of children/deliveries (reference 1 child)
HR (95% CI)
Weight %
2 children
SWHS 0.84 (0.57, 1.22) 10.13
JPHC1 0.90 (0.42, 1.95) 2.49
JPHC2 0.80 (0.36, 1.76) 2.33
JACC 1.23 (0.52, 2.92) 1.97
Miyagi 0.90 (0.51, 1.59) 4.53
Ohsaki 0.79 (0.29, 2.12) 1.48
KMCC 1.37 (0.47, 3.96) 1.29
KNCC 0.94 (0.70, 1.27) 16.52
3pref. Miyagi -
Pooled (I^2 = 0.0%, p = 0.985) 0.92 (0.76, 1.11)
3 children
SWHS 0.75 (0.40, 1.41) 3.69
JPHC1 0.94 (0.43, 2.02) 2.45
JPHC2 0.51 (0.22, 1.22) 2.00
JACC 1.02 (0.42, 2.47) 1.87
Miyagi 0.65 (0.36, 1.18) 4.16
Ohsaki 0.85 (0.32, 2.29) 1.51
KMCC 2.02 (0.70, 5.81) 1.31
KNCC 1.24 (0.87, 1.77) 11.62
3pref. Miyagi -
Pooled (I^2 = 15.8%, p = 0.306) 0.96 (0.77, 1.21)
4 children
SWHS 0.69 (0.30, 1.59) 2.11
JPHC1 0.96 (0.40, 2.30) 1.92
JPHC2 0.73 (0.28, 1.90) 1.60
JACC 0.64 (0.20, 2.00) 1.11
Miyagi 0.96 (0.49, 1.89) 3.22
Ohsaki 0.53 (0.15, 1.86) 0.92
KMCC 1.31 (0.42, 4.08) 1.13
KNCC 2.09 (1.30, 3.35) 6.54
3pref. Miyagi -
Pooled (I^2 = 38.4%, p = 0.123) 1.15 (0.87, 1.52)
≥ 5 children
SWHS 0.55 (0.18, 1.68) 1.18
JPHC1 1.00 (0.38, 2.62) 1.57
JPHC2 0.93 (0.37, 2.34) 1.72
JACC 0.49 (0.12, 2.03) 0.73
Miyagi 0.60 (0.21, 1.67) 1.36
Ohsaki 0.44 (0.10, 1.90) 0.68
KMCC 1.27 (0.41, 3.99) 1.13
KNCC 2.31 (1.23, 4.32) 3.72
3pref. Miyagi -
Pooled (I^2 = 36.9%, p = 0.135) 1.07 (0.75, 1.51)
.2
.5
1
2
5

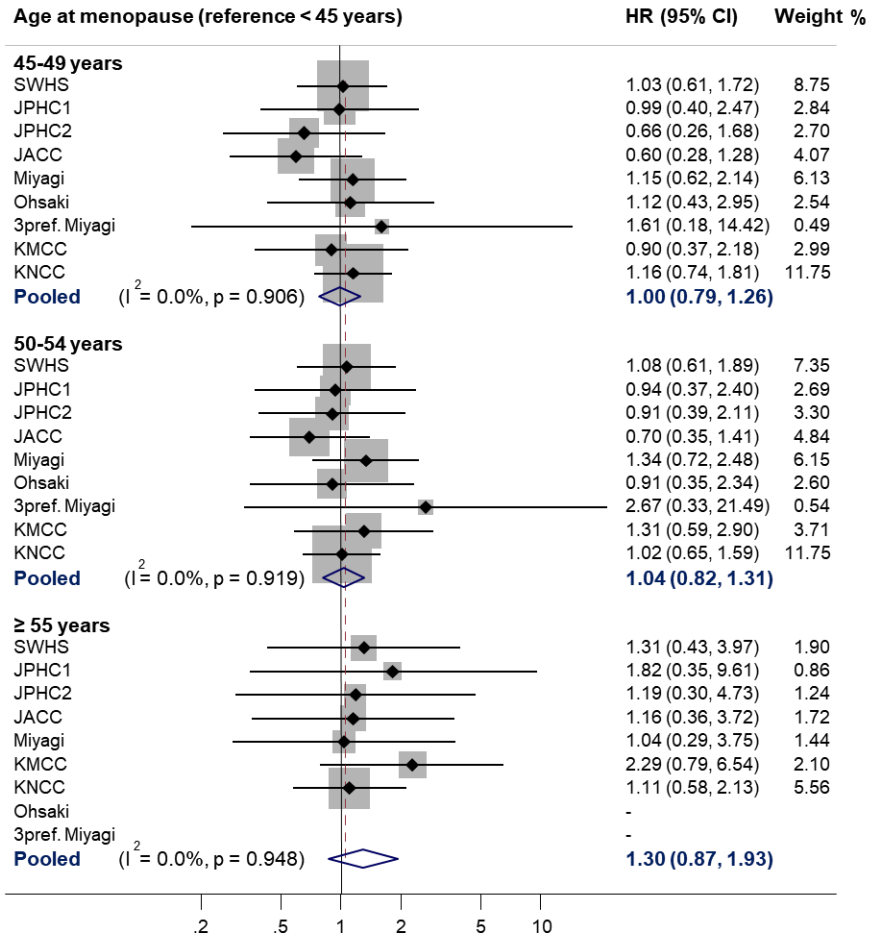
Supplementary Figure 8: Forest plot for the pooled HRs and CIs for breastfeeding status and thyroid cancer risk, overall



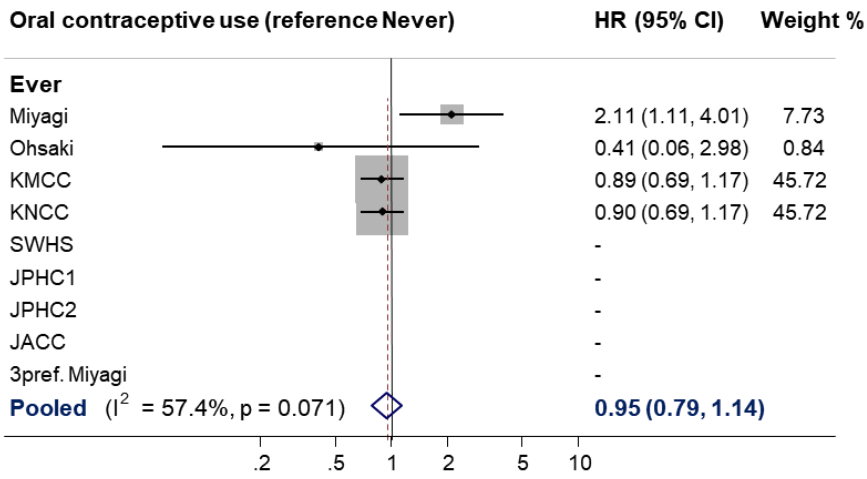
Supplementary Figure 9: Forest plot for the pooled HRs and CIs for postmenopausal status and thyroid cancer risk, overall



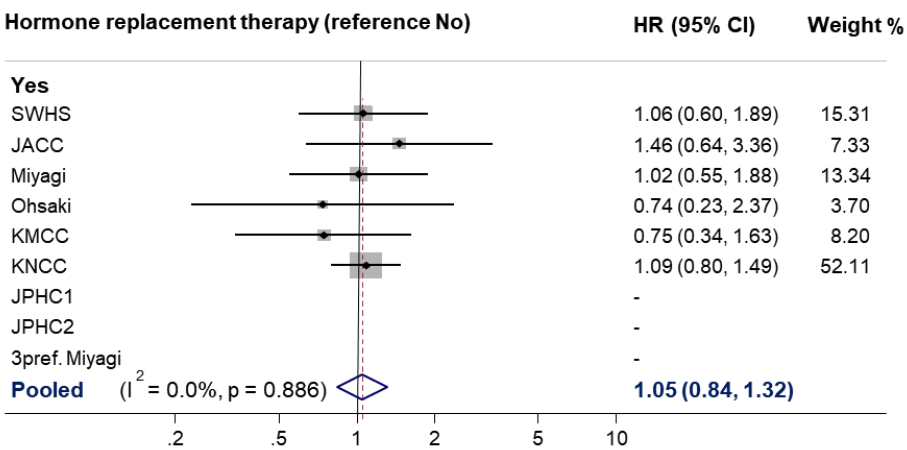
Supplementary Figure 10: Forest plot for the pooled HRs and CIs for age at menopause and thyroid cancer risk, overall



Supplementary Figure 11: Forest plot for the pooled HRs and CIs for oral contraceptive use and thyroid cancer risk, overall



Supplementary Figure 12: Forest plot for the pooled HRs and CIs for hormone replace therapy use and thyroid cancer risk, overall



Supplementary Figure 13: Forest plot for the pooled HRs and CIs for age at first delivery and thyroid cancer risk, stratified by BMI