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Parity and thyroid cancer risk: a meta-analysis of epidemiological studies

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Abstract

Although observational studies have assessed the relationship between parity and thyroid cancer risk, the findings are inconsistent. To quantitatively assess the association, we conducted a systematic review and meta-analysis. PubMed and Embase were searched up to January 2015. Prospective or case–control studies that evaluated the association between parity and thyroid cancer risk were included. We used the fixed-effects model to pool risk estimates. After literature search, 10 prospective studies, 12 case-control studies and 1 pooled analysis of 14 case-control studies including 8860 patients were identified. The studies had fair methodological quality. Pooled analysis suggested that there was a significant association between parity and risk of thyroid cancer (RR for parous versus nulliparous: 1.09, 95% CI 1.03-1.15; I2=33.4%). The positive association persisted in almost all strata of subgroup analyses based on study design, location, study quality, type of controls, and confounder adjustment, although in some strata statistical significance was not detected. By evaluating the number of parity, we identified that both parity number of 2 versus nulliparous and parity number of 3 versus nulliparous demonstrated significant positive associations (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). The dose-response analysis suggested neither a non-linear nor linear relationship between the number of parity and thyroid cancer risk. In conclusion, this meta-analysis suggests a potential association between parity and risk of thyroid cancer in females. However, the lack of detection of a dose-response relationship suggests that further studies are needed to better understand the relationship.

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Introduction

As the most common type of the endocrine malignancies, thyroid cancer causes a large number of deaths that is higher than the combined number of all other endocrine cancers [1]. It is estimated that in the US, 15,220 males and 47,230 females will newly develop thyroid cancer in 2015 [2]. A large proportion of etiology for certain subtypes of thyroid cancer, such as medullary thyroid cancer and familial papillary thyroid cancer, can be attributed to genetic factors [3, 4]. Research also has demonstrated that exposure to ionizing radiation, iodine availability, body mass index (BMI), height, vegetable consumption, smoking, alcohol drinking, diabetes, and obesity can influence individual's risk of developing thyroid cancer [5–11]. However, to date, a large proportion of the etiology of thyroid cancer has not been fully understood. Considering a huge difference in incidence of thyroid cancer between males and females, it may be warranted to hypothesize that reproductive factors may play roles in the etiology. This hypothesis is also aligned with the fact that the incidence rate of thyroid cancer in females is highest during the reproductive years [12]. Oral contraceptives (OC) use has been suggested to be associated with thyroid cancer risk in a dose–response relationship, based on evidence from prospective studies [13]. As another representative reproductive factor, parity is also hypothesized to be associated with thyroid cancer risk. To date, numerous studies have investigated the association between parity and risk of thyroid cancer, but yielded inconsistent findings. It was demonstrated that ever giving birth to children conferred a higher risk of developing thyroid cancer in women by Mctiernan et al. [14]. Several other studies also supported that a higher number of parity was associated with increased risk [15, 16]. However, a study conducted in Japan supported an inverse conclusion [17] and many other studies revealed nonsignificant associations [12, 18–22]. We thus conducted this systematic review and meta-analysis for summarizing available evidence from epidemiological studies to assess the association between parity and thyroid cancer risk in females, including evaluating the dose–response relationship.

Methods

This meta-analysis was performed in accordance with the MOOSE guideline [23].

Data sources and search strategies

A search of PubMed (MEDLINE) and Embase was conducted from each database's inception to January 2015 for studies of humans published in English. We used the following search keywords and Medical Subject Heading terms: (parity OR pregnancy OR livebirth OR reproductive OR reproduction OR reproductive factors) AND (papillary OR follicular OR thyroid) AND (cancer OR neoplasm OR carcinoma OR tumor OR adenoma OR cancers OR neoplasms OR carcinomas OR tumors OR adenomas). We also reviewed references of relevant review articles to identify additional potential studies.

Study selection

Studies were eligible if they (1) were case–control studies or prospective studies; (2) evaluated the association between parity and risk of thyroid cancer; (3) presented odds ratio (OR), relative risk (RR), or hazard ratio (HR) estimates with 95% confidence intervals (CI) or data necessary to calculate them. Studies were excluded if they used a cross-sectional study design. Studies primarily focusing on subjects with extensive exposure to radiation were not included because exposure to radiation is the most well-established risk factor for thyroid cancer, and it would make the studied population significantly different from more general population and might induce bias for the research question of interest. Studies were included regardless of publication status, sample size and length of follow-up. If multiple publications from the same study were identified, we included the study with the largest number of cases and most relevant information, like previous studies [24–27].

Data extraction and quality assessment

A pair of investigators independently carried out the abstract screening, full-text screening, data extraction, and quality assessment. Disagreements were resolved by consensus. Data extracted from each study included: the first author's last name, year of publication, study region, study design, characteristics of study population (sample size, age, length of follow-up, measures and numbers of parity, and effect sizes). If multiple estimates of the association for the same outcome were reported, we extracted the estimate that adjusted for the most appropriate covariates, like previous studies [28, 29]. In cases when only

unadjusted estimates were presented, we included the crude estimates. When the eligible studies did not present enough data, corresponding authors were contacted.

To assess the study quality, we used the Newcastle–Ottawa Quality Assessment Scale [30] in terms of population and sample methods, exposure and outcome descriptions, and statistical matching/adjustments of the data. This scale was used to assign a maximum of nine points for each study. Studies with score of seven or above were categorized as high-quality studies, and those with score of 6 or below were categorized as low-quality studies.

Statistical methods

The RRs and corresponding 95% CIs from each of the included studies were used as the measure of association across studies. Due to the rarity of thyroid cancer, ORs and HRs were deemed equivalent to RRs and we used RRs to represent measures. We used the I^2 to assess the heterogeneity across the included studies, where $I^2 > 50\%$ suggests substantial heterogeneity [31]. We pooled the log-transformed RR using either the fixed-effects model [32, 33] when there was no considerable heterogeneity or the random-effects model [34] when there was substantial heterogeneity. Besides pooling results for parous versus nulliparous, we further conducted analyses summarizing effect sizes according to different number of parity. Based on the available data, we analyzed parity number of one versus nulliparous, parity number of two versus nulliparous, and parity number of three versus nulliparous, respectively. Subgroup analyses were conducted based on study design (case–control vs. prospective studies), geographic location (America, Europe, Asia, or Oceania), study quality (high vs. low), type of controls (population-based vs. hospital-based), and whether the study was adjusted for confounders (yes vs. no). We also conducted sensitivity analyses excluding one study at a time to explore whether any specific study strongly influenced the results.

For the dose–response analysis, we explored potential nonlinear and linear relationship between the number of parity and risk of thyroid cancer [35, 36]. If studies reported the parity number by ranges, we set the midpoint of each category by averaging the lower and upper bound. If the highest category did not have an upper bound, we assumed that the open ended interval's width was as same as the adjacent interval's width. We examined a potential nonlinear dose–response relationship between parity and thyroid cancer with fractional polynomial models, using restricted cubic splines with three knots at fixed percentiles (10, 50, and 90%) of the distribution [37]. We conducted a likelihood ratio test to evaluate the difference between the linear and nonlinear models.

Publication bias was evaluated via Egger's test [40] and Begg's test [38]. A *P*-value of 0.05 was used as the threshold for determining significant publication bias. All statistical analyses were performed with Stata (version 13; StataCorp, College Station, TX).

Results

Literature search and study characteristics

The detailed steps of the literature search were shown in Figure 1. After excluding 34 studies during the assessment of whole contents of 50 potential articles due to various

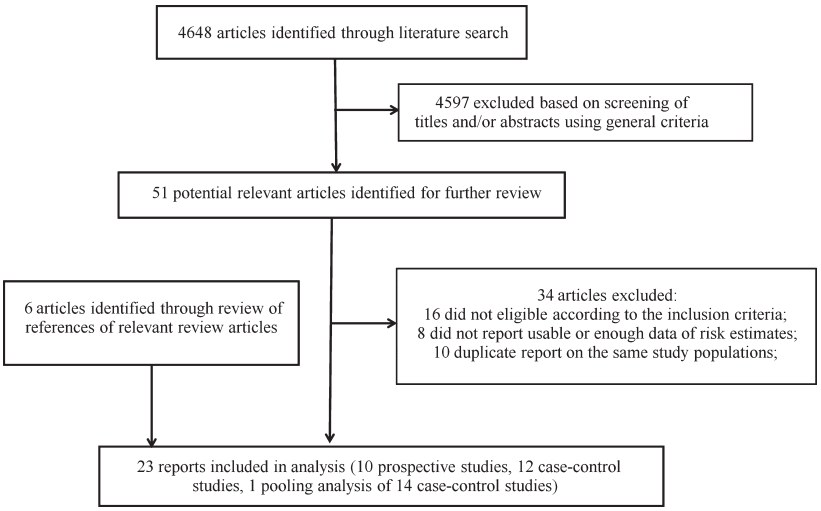

Figure 1. Flowchart for selection of eligible studies.

Table 1. Characteristics of studies of parity and thyroid cancer risk.

First author, publication year, country, study design	Cases/subject (age), duration of follow-up	Parity categories (exposure/case assessment)	RR (95% CI)	Matched/Adjusted factors
Case–control studies				
Xhaard (2014), France, PC-CS	633/679 (10–40 years)	Nulliparous	1.0 (ref)	Ethnic group, level of education, height, BMI, smoking status, sex, age, region of residence
		1	0.9 (0.6–1.2)	
		2	1.1 (0.8–1.7)	
		≥3	1.5 (0.7–3.0)	
		(Trained interviewer/Cancer registry + pathology record)		
Truong (2005), New Caledonia, PC-CS	293/354 (N/A)	Nulliparous	1.0 (ref)	Age, ethnic, gender, reference/diagnosis year
		Parous	1.2 (0.7–1.9)	
		1	1.0 (0.5–1.9)	
		2	0.7 (0.4–1.4)	
		3	1.4 (0.7–2.6)	
		4–5	1.1 (0.6–2.1)	
		6–7	1.6 (0.8–3.3)	
		≥8	2.2 (1.1–4.3)	
Zivaljevic (2003); Serbia, HC-CS	204/204 (14–87 years)	Nulliparous	1.0 (ref)	Sex, age, place of residence, time of hospitalization
		1	0.65 (0.29–1.43)	
		2	1.12 (0.81–1.55)	
		≥3	1.16 (0.84–1.60)	
		(Trained interviewer/histological confirmed)	Individuals <45 years	
Sakoda (2002); USA, PC-CS	608/558 (20–74 years)	Nulliparous	1.0 (ref)	Age, race/ethnic, history of radiation to the head or neck, history of goiter or nodules, family history of proliferative thyroid disease, education level, OC use, recency of last FTP, and birthplace
		Parous	1.4 (0.98–2.1)	
		1	1.2 (0.75–1.9)	
		2	1.7 (1.1–2.7)	
		≥3	1.4 (0.82–2.4)	
			Individuals ≥45 years	
		Nulliparous	1.0 (ref)	
		Parous	0.73 (0.42–1.3)	
		1	0.7 (0.34–1.5)	
		2	0.87 (0.47–1.6)	
		≥3	0.62 (0.34–1.2)	
		(Trained interviewer/Cancer registry)		
Memon (2002); Kuwait, PC-CS	238/238 (10–65 years)	Nulliparous	1.0 (ref)	Age, gender, nationality, district of residence
		1–2	0.9 (0.5–1.8)	
		3–4	1.3 (0.6–2.5)	
		5–6	1.4 (0.7–2.8)	
		7–8	1.2 (0.6–2.6)	
		9–10	1.9 (0.8–4.9)	
		≥11	2.0 (0.7–5.8)	
		(Trained interviewer/medical record)		

(*Continued*)

Table 1. Continued.

First author, publication year, country, study design	Cases/subject (age), duration of follow-up	Parity categories (exposure/case assessment)	RR (95% CI)	Matched/Adjusted factors
Rossing (2000), Washington, USA, PC-CS	410/574 (18–64 years)	Nulliparous	1.0 (ref)	Age, county of residence, race, marital status, cigarette smoking, alcohol consumption, history of radiation treatment to the head or neck as a child or adolescent, family history of thyroid cancer, use of oral contraceptives, history of benign thyroid disease
		1	0.9 (0.6–1.5)	
		2	0.9 (0.6–1.4)	
		3	1.2 (0.7–2.0)	
		≥4	1.1 (0.5–2.3)	
		(Trained interviewer/Cancer registry)		
Negri (1999), International, pooled analysis of case- control studies	2247/3699 (NA)	Nulliparous	1.0 (ref)	Study, age, history of radiation, oral contraceptive use
		Parous	1.2 (1.0–1.4)	
		1	1.3 (1.0–1.6)	
		2	1.2 (1.0–1.4)	
		3	1.1 (0.9–1.4)	
		≥4	1.2 (1.0–1.6)	
Brindel (2008), French Polynesia, PC-CS	201/324 (NA)	Nulliparous	1.0 (ref)	Age
		Parous	1.7 (0.8–3.5)	
		1	0.9 (0.3–2.3)	
		2	1.6 (0.7–3.8)	
		3	2.3 (1.0–5.5)	
		4–5	2.2 (0.9–5.2)	
		6–7	2.7 (1.0–7.6)	
		≥8	1.7 (0.7–4.4)	
		(Trained interviewer/Cancer registry + pathology review)		
Kalezic (2013), Serbia, PC-CS	98/196 (NA)	Nulliparous	1.0 (ref)	Age, place of residence
		Parous	0.7 (0.47–1.05)	
		(Trained interviewer/histopathological finding)		
Lee (2010), Korea, HC-CS	260/259 (NA)	Nulliparous	1.0 (ref)	Age
		Parous	1.27 (0.88–1.84)	
		(Self-questionnaire/unclear)		
Przybylik-Mazurek (2012), Poland, HC-CS	99/51 (mean 41/37)	Nulliparous	1.0 (ref)	Age, age of menarche, breastfeeding, estradiol, progesterone level
		Parous	1.52 (1.03–2.23)	
		1–2	3.03 (0.89–10.37)	
		≥3	6.16 (1.41–26.88)	
		(Self-questionnaire/unclear)		
Takezaki (1996), Japan, HC-CS	94/22666 (20–79)	Nulliparous	1.0 (ref)	Age, year of visit
		Parous	2.09 (1.05–4.15)	
		1–2	1.8 (0.9–3.7)	
		≥3	2.5 (1.1–5.7)	
		(Self-questionnaire/histology confirmation)		

(*Continued*)

Table 1. Continued.

First author, publication year, country, study design	Cases/subject (age), duration of follow-up	Parity categories (exposure/case assessment)	RR (95% CI)	Matched/Adjusted factors
Lence-Anta (2014), Cuba, PC-CS	179/173 (17–60)	Nulliparous	1.0 (ref)	Age, smoking status, ethnic group, level of education, height, and BMI
		Parous	2.31 (1.22–4.39)	
		1	1.3 (0.5–3.4)	
		2	2.5 (1.1–6.1)	
		≥3	3.8 (1.7–8.3)	
		(Trained interviewer/Cancer registry + pathology register)		
Prospective studies				
Zamora-Ros (2014), Europe, CS	508/345,157 (mean 51 years), 11 years	Nulliparous	1.0 (ref)	Age, study center, age at recruitment
		Parous	0.87 (0.66–1.15)	
		1	0.85 (0.61–1.20)	
		2	0.91 (0.66–1.22)	
		≥3	0.82 (0.59–1.12)	
		(Self-questionnaire/Cancer registry)		
Kabat (2012), USA, CS	296/145,007 (50–79), 12.7 years	Nulliparous	1.0 (Ref)	Age, education, ethnicity, age at menarche, BMI, age at menopause, hormone therapy, physical activity, height, OC/CT, alcohol intake, pack-years of smoking, and history of goiter/nodules, randomization status in each CT
		Parous	1.15 (0.72–1.85)	
		1–2	0.88 (0.53–1.47)	
		3–4	1.30 (0.89–1.89)	
		≥5	1.19 (0.77–1.84)	
		(Self-questionnaire//Medical record and pathology report)		
Schonfeld (2011), USA, CS	312/187,865 (median 62.2), mean 9.3 years	Nulliparous	1.0 (Ref)	Unadjusted
		Parous	1.03 (0.74–1.45)	
		1–2	1.20 (0.84–1.71)	
		≥3	1.02 (0.72–1.45)	
		(Self-questionnaire/Cancer registry)		
Pham (2009), Japan, CS	86/110,792 (40–79 years), 9 years	Nulliparous	1.0 (Ref)	Unadjusted
		1	0.45 (0.14–1.41)	
		2	0.59 (0.26–1.35)	
		3	0.55 (0.24–1.27)	
		≥4	0.32 (0.12–0.87)	
		(Self-questionnaire/Cancer registry)		
Navarro Silvera (2005), Canada, CS	169/89,835 (40–59 years), 15.9 years	Nulliparous	1.0 (Ref)	Age, study center, randomization group, age at first live birth
		1–2	0.65 (0.35–1.23)	
		3–4	0.85 (0.47–1.54)	
		≥5	0.65 (0.32–1.33)	
		(Self-questionnaire/cancer database)		

(*Continued*)

Table 1. Continued.

First author, publication year, country, study design	Cases/subject (age), duration of follow-up	Parity categories (exposure/case assessment)	RR (95% CI)	Matched/Adjusted factors
Galanti (1995), Sweden, NC-CS	1409/7019 (15–59 years), 21 years	Nulliparous	1.0 (Ref)	Age
		1	1.2 (1.0–1.4)	
		2	1.1 (0.9–1.3)	
		3	1.2 (1.0–1.5)	
		≥4	1.1 (0.8–1.4)	
		(Registry/Cancer registry)		
Akslen (1992) Norway, CS	124/63,090 (32–74 years), 28 years	Nulliparous	1.0 (Ref)	Unadjusted
		Parous	0.97 (0.61–1.54)	
		1–2	0.98 (0.60–1.60)	
		≥3	0.99 (0.60–1.63)	
		(Trained interviewer/Cancer registry)		
Wong (2006), China, Case cohort study	130/3187 (30–69), 10 years	Nulliparous	1.0 (ref)	Age
		1	1.35 (0.20, 9.06)	
		≥2	0.32 (0.05, 2.15)	
		(Trained interviewer/Cancer registry)		
Hannibal (2008), Denmark, Case cohort study	29/54362 (median 30 years), median 8.8 years	Nulliparous	1.0 (ref)	Unadjusted
		Parous	0.75 (0.35–1.62)	
		1	0.83 (0.35–1.97)	
		≥2	0.68 (0.27–1.71)	
		(Trained interviewer/Cancer registry)		
Horn-Ross (2011), USA, CS	233/117,646 (NA),~11 years	Nulliparous	1.0 (ref)	Unadjusted
		Parous	1.07 (0.80–1.44)	
		1–2	1.18 (0.86–1.60)	
		≥3	0.86 (0.59–1.26)	
		(Self-questionnaire/Cancer registry)		

BMI: body mass index; CI: confidence interval; CS: cohort study; HC-CS: hospital-based case–control study; N/A: not available; NC-CS: nested case–control study; OR: odds ratio; PC-CS: population-based case–control study; Ref: reference; RR: relative risk.

reasons (the list of the 34 studies is available upon request), a total of 23 reports met the inclusion criteria and were included in this study [12, 15, 17, 18, 20–22, 39, 41–55]. Since one study reported the risk estimates separately according to the age category (<45 years old or ≥45 years old) [12] and the combined effect size was unable to determine based on available data, we treated the two estimates as from two separate studies and incorporated both in the pooled analysis. The detailed characteristics of the included studies were shown in Table 1. In total, 10 prospective studies (seven cohort studies, one nested case–control study and two case cohort studies), 12 case–control studies and one pooling analysis of 14 case–control studies were available. Overall, eight studies were conducted in Europe, seven in America, five in Asia, two in Oceania, and one was conducted internationally. The studies enrolled 8860 patients and had a median follow-up of 11 years (range 8.8–28 years). The detailed quality ratings for each study were listed in Tables 2 and 3. Overall, the studies had fair methodological quality. Fourteen studies had scores of seven or above and were categorized as high-quality studies; eight studies were categorized as low-quality studies. Parity was defined as full-term pregnancies in 17 included studies [12, 15, 17, 18, 20–22, 39, 41, 43, 44, 47–50, 53, 54], defined as pregnancies in three studies [42, 52, 55], defined as pregnancies lasting greater than 4 months in one study [45], and unspecified in two studies [46, 51]. With regards to the histopathological types of thyroid cancer, in 18 studies, various subtypes of thyroid cancer were included [15, 17, 18, 20–22, 41–49, 52, 54, 55]; in three studies, only papillary thyroid cancer was assessed [12, 39, 51]; in one study, only sporadic medullary thyroid cancer was assessed [50]; and in another study, it was unclear which subtypes of thyroid cancer were evaluated [53].

Parous versus nulliparous

After pooling results from all available studies, there was a significant positive association between risk of thyroid cancer and parity for parous versus nulliparous (RR = 1.09, 95% CI 1.03–1.15), with no considerable heterogeneity (I^2 = 33.4%; Table 4 and Fig. 2). There was no significant publication bias as indicated by Egger's test (P for bias: 0.878) and Begg's test (P for bias: 1.000). Sensitivity analysis revealed that the 23 study-specific RRs of parous versus nulliparous ranged from a low of 1.07 (95% CI 1.01–1.14; I^2 = 33.4%) after omission of the study by Negri et al. [22] to a high of 1.10 (95% CI 1.04–1.17; I^2 = 32.4%) after omission of the study by Rossing et al. [39]. The subgroup analyses revealed that the significant positive association persisted in almost all strata, although the statistical significance was only achieved in some of them (Table 4).

Different number of parity

We assessed the associations between different number of parity (1, 2 or 3) and risk of thyroid cancer, respectively (Table 5). Parity number of one versus nulliparous was positively associated with risk of thyroid cancer (RR = 1.08, 95% CI 0.98–1.21; I^2 = 3.6%), although the association was not statistically significant. On the other hand, both parity number of two versus nulliparous and parity number of three versus nulliparous demonstrated significant positive association with the risk of thyroid cancer (RR = 1.11, 95% CI 1.01–1.22; I^2 = 31.1% and RR = 1.16, 95% CI 1.01–1.33; I^2 = 19.6%, respectively).

Dose–response meta-analysis

Based on the dose–response analysis, we did not detect a nonlinear dose–response relationship between the number of parity and risk of thyroid cancer. Assuming a linear dose–response relationship, the combined RR per live birth was 1.01 (95% CI 0.96–1.07; P = 0.69 for the linear trend), with significant heterogeneity (P for heterogeneity: <0.0001). There seemed not be a clear dose–response relationship between the number of parity and thyroid cancer risk.

Discussion

Main findings

We performed a comprehensive systematic review and meta-analysis to assess the association between parity and risk of thyroid cancer. After summarizing available evidence from observational studies, ever giving birth to children was identified to be significantly associated with an increased risk of developing thyroid cancer. Analyses assessing different numbers of parity (1, 2 and 3) demonstrated that such a significant positive association with thyroid cancer risk persisted for both parity number of two versus nulliparous and parity number of three versus nulliparous. However, the dose–response analysis did not suggest a significant nonlinear or linear relationship between the number of parity and thyroid cancer risk. Overall, these findings suggested that parity might be associated with risk of thyroid cancer in females, while the exact relationship needs exploration and clarification in further studies.

Interpretation

Although the exact biological mechanism underlying the potential association between parity and risk of thyroid cancer has not been completely established, plausible explanations have been suggested by basic research. During pregnancy estrogens are elevated, which potentially

Table 2. Quality assessment of reviewed case–control studies.

Study	Case defined with independent validation	Representativeness of the cases	Selection of controls from community	Statement that controls have no history of outcome	Cases and controls matched and/or adjusted by factors	Ascertain exposure by blinded structured interview	Same method of ascertainment for cases and controls	Same response rate for both groups
Sakoda (2002)	0	1	1	0	2	0	1	1
Memon (2002)	1	1	1	1	2	1	1	1
Rossing (2000)	1	1	1	0	2	1	1	1
Truong (2014)	1	1	1	1	2	1	1	1
Xhaard (2014)	1	1	1	1	2	1	1	1
Zivaljevic (2003)	1	1	0	0	2	1	1	1
Brindel (2008)	1	1	1	0	1	1	1	1
Kalezic (2013)	1	1	1	0	2	1	1	1
Lee (2010)	0	1	0	1	1	0	1	1
Przybylik-Mazurek (2012)	0	0	0	1	2	0	1	1
Takezaki (1996)	1	1	0	1	2	0	1	1
Lence-Anta (2014)	1	1	1	0	2	1	1	1

1 means study adequately fulfilled a quality criterion (2 for case–control fully matched and adjusted), 0 means it did not. Quality scale does not imply that items are of equal relevant importance.

Table 3. Quality assessment of reviewed prospective studies.

Study	Exposed cohort represents average in community	Selection of the nonexposed cohort from same community	Ascertain exposure through records or structured interviews	Demonstrate that outcome not present at study start	Exposed and nonexposed matched and/or adjusted by factors	Ascertain outcome via independent blind assessment or record linkage	Follow-up long enough for outcome to occur	Loss to follow-up <20%
Akslen (1992)	1	1	1	0	0	1	1	1
Galanti (1995)	1	1	1	1	1	1	1	1
Kabat (2012)	1	1	0	0	2	1	1	1
Navarro Silvera (2005	1	1	0	0	2	1	1	1
Pham (2009)	1	1	0	1	0	1	1	1
Schonfeld (2011)	1	1	0	1	0	1	1	1
Zamora-Ros (2014)	1	1	0	1	2	1	1	1
Wong (2006)	1	1	1	0	1	1	1	1
Hannibal (2008)	0	1	1	0	0	1	1	1
Horn-Ross (2011)	1	1	0	1	0	1	1	1

1 means study adequately fulfilled a quality criterion, 0 means it did not. Quality scale does not imply that items are of equal relevant importance.

Table 4. Summary risk estimates of the association between parity and thyroid cancer risk (parous vs. nulliparous).

	No of reports	RR (95% CI)	I^2	*P* for heterogeneity
Overall	24	**1.09 (1.03–1.15)**	33.4%	0.058
Subgroup analysis				
Study design				
Prospective	10	1.03 (0.94–1.13)	0.0%	0.558
Case–control	14	**1.12 (1.05–1.20)**	47.0%	0.027
Study quality				
High	14	**1.07 (1.00–1.14)**	38.4%	0.071
Low	9	1.11 (0.96–1.27)	31.8%	0.164
Location				
Europe	8	1.07 (0.996–1.15)	36.4%	0.139
America	8	1.04 (0.93–1.17)	41.7%	0.100
Asia	5	1.15 (0.94–1.41)	47.9%	0.104
Oceania	2	1.34 (0.89–2.02)	0.0%	0.444
International	1	**1.20 (1.00–1.40)**	–	–
Type of controls				
Population-based	9	1.07 (0.99–1.17)	52.5%	0.032
Hospital-based	4	**1.32 (1.08–1.60)**	10.7%	0.339
Confounder adjustment				
Yes	19	**1.10 (1.04–1.16)**	39.6%	0.039
No	5	0.98 (0.81–1.18)	0.0%	0.496

significant associations are bolded.

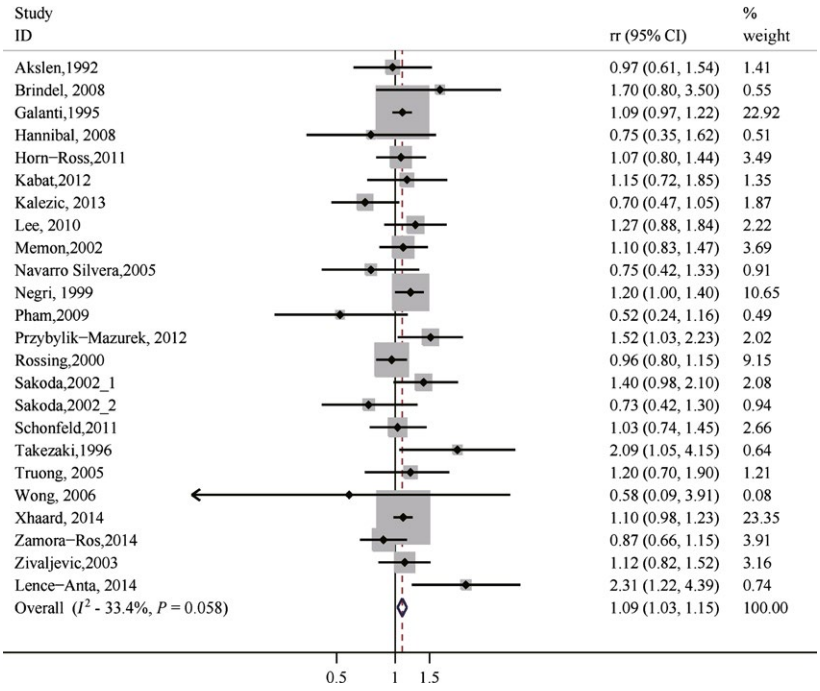

Figure 2. Forest plot (fixed-effects model) of parity (parous vs. nulliparous) and thyroid cancer risk.

Table 5. Summary risk estimates of the associations between different number of parity and thyroid cancer risk.

	No of reports	RR (95% CI)	I^2	*P* for heterogeneity
Parity number of one versus nulliparous	14	1.08 (0.98–1.21)	3.6%	0.411
Parity number of two versus nulliparous	12	1.11 (1.01–1.22)	31.1%	0.142
Parity number of three versus nulliparous	6	1.16 (1.01–1.33)	19.6%	0.285

influence the proliferation as well as enhance the adhesion, migration, and invasiveness of malignant thyroid cells [56–58]. Estrogens are also known to interact with estrogen receptors and alter apoptotic pathways, which are suggested to be linked to tumor development [59–61].

In the subgroup, analyses of the association between thyroid cancer risk and parity for parous versus nulliparous, significant positive association was also detected in subgroups of studies with a case–control design, case–control studies with hospital-based controls, high–quality studies, and studies with confounder adjustments. We acknowledge that studies with a case–control design are more susceptible to bias compared with studies with a prospective design. Similarly, case–control studies with hospital-based controls may be more susceptible to bias compared with those with population-based controls. On the other hand, even though the detected associations in many other subgroups did not reach statistical significance, the directions of the associations tend to be positive. The trend of a positive association was also suggested for parity number of one versus nulliparous. These suggest that the detected positive association between parity and thyroid cancer risk may be real and warrants further clarification.

Several reasons may explain the inconsistencies of the association between parity and thyroid cancer across included studies. For example, not all included studies sufficiently adjust for relevant covariates. Besides parity, several other reproductive factors like age at first pregnancy, OC use, and age at menopause are suggested to influence thyroid cancer risk as well [13, 43, 62]. These relevant factors may vary across different countries where the included studies were conducted. This may partially explain some of the inconsistencies of the association of interest.

Strengths and limitations

Our study has several strengths. To the best of our knowledge, this is the most comprehensive meta-analysis evaluating the association between parity and thyroid cancer risk. A systematic review previously assessed the association [6]; however, instead of quantitatively evaluating the evidence, they just briefly discussed the risk estimate trends. After the conduction of this study, several meta-analysis studies evaluating a similar research question were published [63, 64]. We think this study has advantages compared with those studies: for the study by Zhou et al. [64], the literature was only updated through April 2013, and a couple of more recent studies were not included in their analysis [43, 47, 50]; for the study by Caini et al. [63], evidence from case–control studies were not included. Furthermore, ours is the first study assessing the dose–response relationship to better characterize the relationship. Our study quantitatively summarized all available evidence from epidemiological studies and might have sufficient power to assess the association of interest. Besides conducting subgroup analyses and sensitivity analyses, we also assessed associations according to different numbers of parity and conducted dose–response analysis with the aim of fully understanding the relationship.

Several potential limitations must be acknowledged for the interpretation of our findings. First, we did not have access to the individualized primary data from the included studies, and the risk estimates used in pooling might not be fully adjusted for. Relevant covariates including age, BMI, iodine intake, use of OC, HRT, and fertility treatment were not always adjusted for in the included studies. Residual confounding may thus be an issue for our findings. Further well-designed studies with full adjustments are needed. Second, during the dose–response analysis, the highest levels of number of parity in different studies have wide range of values, which may cause the exposure values to not be accurately assigned. This may be one reason that we did not detect a linear or nonlinear dose–response relationship between the number of parity and risk of thyroid cancer, which seemed to be suggested based on the increasing risks over parity of 1, 2, and 3 (Table 2). However, this is a known shortcoming for determining the dose–response relationship with aggregate data. The dose–response relationship of parity and thyroid cancer risk is thus warranted to be further explored in well-designed studies.

Conclusion

Based on a summarization of relevant evidence from epidemiological studies, parous versus nulliparous was positively associated with risk of thyroid cancer. A similar positive association was also detected for both parity number of two versus nulliparous and parity number of three versus nulliparous. However, no linear or nonlinear relationship between the number of parity and thyroid cancer risk was detected. Although parity might be associated with the risk of thyroid cancer in females, further studies are warranted to better clarify the relationship.

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Conflict of Interest

There are no competing interests to declare.

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