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Reproductive Factors and Disease Progression in Differentiated Thyroid Cancer: A Large Retrospective Cohort Study of 1,098 Chinese Women

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Abstract

Background: Differentiated thyroid carcinoma (DTC) shows a marked female predominance, particularly during reproductive years, implicating sex hormones and reproductive factors in its pathogenesis. However, evidence regarding the impact of reproductive variables—such as age at menarche, parity, and pregnancy history—on disease progression remains inconsistent, especially in Chinese women. Large-scale studies addressing this issue are limited. This study aimed to evaluate the association between reproductive history and clinicopathological aggressiveness in female patients with DTC.

Methods: We conducted a single-center retrospective cohort study of 1,098 female patients with DTC who underwent surgical resection between June 2014 and February 2024. Data on reproductive history and tumor characteristics were collected. Group comparisons were performed using standard statistical tests, and multivariable logistic regression was applied to adjust for confounders and estimate odds ratios (ORs) with 95% confidence intervals (CIs). The study was performed in accordance with the ethical principles of the Declaration of Helsinki and relevant institutional guidelines.The study was approved by the Institutional Review Board of Sichuan Cancer Hospital (SCCHEC-02-2025-148), with informed consent waived.

Results: Multivariable analysis identified early (≤11 years) and late menarche (≥15 years) as independent predictors of advanced clinical stage (OR=7.60, 95%CI:2.76–20.92; OR=3.10, 95%CI:1.31–7.35, respectively). Parity demonstrated a dose-response relationship with disease severity, with ≥3 births being the strongest predictor of advanced stage (OR=23.19, 95%CI:11.00–59.64). Nulliparity showed protective effects against advanced staging (OR=0.03, 95%CI:0.01–0.23).Reproductive factors exhibited compartment-specific nodal metastasis patterns: nulliparity associated with central compartment involvement (OR=1.69, 95%CI:1.25–2.28), while ≥5 pregnancies linked to lateral neck metastasis (OR=2.37, 95%CI:1.29–4.36). Parity ≥3 correlated with both local invasion (T3/T4: OR=4.12, 95%CI:2.13–7.97) and metastases in central (OR=3.81, 95%CI:1.67–8.69) and lateral neck compartments (OR=4.24, 95%CI:2.24–8.00).

Conclusion: Abnormal menarche timing, multiple pregnancies, and high parity independently predict more advanced and aggressive DTC in Chinese women, with clear dose–response relationships. Incorporating reproductive history into clinical risk stratification may improve identification of high-risk patients and guide individualized management.

1. Introduction:

Thyroid cancer has emerged as one of the fastest growing malignancies worldwide, with its prevalence rising sharply over the past two decades[1–3]. In China, this trend is particularly striking, as the age-standardized incidence rate nearly tripled from 3.21 to 9.61 per 100,000 between 2005 and 2015, a pace that exceeds the global average[4]. A notable epidemiological feature of thyroid cancer is its pronounced gender disparity: women are affected approximately three times more often than men[5]. This difference

is most evident during reproductive years (20–49 years), when the female-to-male ratio may reach 4.1:1, suggesting that sex hormones and reproductive factors could play a critical role in the onset and progression of differentiated thyroid carcinoma (DTC) [6–8][25] .

Estrogen is widely recognized as a key factor underlying the gender disparity in thyroid cancer. By binding to estrogen receptors on thyroid cells, estrogen activates oncogenic signaling cascades such as MAPK and PI3K/Akt, which promote cellular proliferation, migration, and invasion [11–14]. In parallel, improvements in nutritional status have led to earlier pubertal onset, thereby extending the cumulative duration of estrogen exposure across the lifespan [15][16]. Moreover, many Chinese women born in the 1960s and 1970s—shaped by historical fertility policies—experienced multiple pregnancies, each accompanied by repeated surges in estrogen levels [24]. Together, these elements create a distinctive reproductive hormone exposure profile in Chinese women, which may contribute to heightened susceptibility to differentiated thyroid carcinoma. .

Despite plausible molecular mechanisms linking reproductive factors to thyroid cancer, epidemiological evidence remains inconsistent and fragmented, underscoring the need for further investigation. While several studies have identified early menarche, high parity, and multiple pregnancies as potential risk factors [17–20], large-scale cohort analyses in European populations, including Norway and Sweden, have failed to confirm these associations [21–23]. Such discrepancies may reflect differences in population characteristics, study design, and approaches to confounder adjustment. Importantly, most prior research has focused on disease etiology, leaving the determinants of disease progression largely unexplored. Although differentiated thyroid carcinoma (DTC) generally carries a favorable prognosis, its clinical behavior is heterogeneous; a subset of patients develops aggressive features such as nodal or distant metastases and extrathyroidal extension, which significantly worsen outcomes. This highlights a critical knowledge gap regarding the influence of reproductive history on tumor aggressiveness, particularly in relation to advanced TNM stage and lymph node burden.

To address this critical gap, we conducted a large hospital-based retrospective cohort study of Chinese women who underwent surgical treatment for differentiated thyroid carcinoma (DTC) at a tertiary academic center between 2014 and 2024. The primary objective was to examine the associations between key reproductive factors—including age at menarche, parity, and pregnancy history—and indicators of tumor aggressiveness, specifically advanced clinical stage and lymph node metastasis.

2. Materials and Methods

2.1 General Data

2.1.1 Study Population

A retrospective cohort analysis was performed on female patients with differentiated thyroid carcinoma (DTC) who underwent surgical treatment at the Department of Head and Neck Surgery of Sichuan

Cancer Hospital between June 2014 and February 2024. Clinical data were extracted from medical records to ensure accuracy and minimize recall bias(Figure 1).

2.1.2 Inclusion Criteria

(1) Patients admitted for thyroid nodules; (2) Treated in the Department of Head and Neck Surgery at Sichuan Cancer Hospital; (3) Pathological diagnosis of differentiated thyroid carcinoma; (4) Age ≥ 18 years; (5) Female patients.

2.1.3 Exclusion Criteria

(1) Missing or incomplete clinical information; (2) No surgical treatment performed; (3) Histopathological diagnosis other than DTC.

2.1.4 Grouping Information

Collected reproductive variables included age at menarche, number of pregnancies, and parity. Menarche age ranged from 7 to 19 years (SD = 1.3). National survey data indicate that the mean age of menarche among Chinese female students declined from 12.8 years in 2005 to 12.3 years in 2014 [27]. For analysis, menarche was categorized as: (1) ≤ 11 years (early), (2) 12–14 years (normal), and (3) ≥ 15 years (late). Pregnancy history ranged from 0 to 9, and parity from 0 to 6. These distributions reflect historical fertility trends in China, where average pregnancies per woman decreased from 5.37 in 1982 to 1.62 in 2015, with current total fertility rates between 1.0 and 1.3 [28–30]. Clinical staging is classified into early-stage (Stages I and II) and advanced-stage (Stages III and IV); TNM staging, tumor size, and local invasion are categorized into a low-risk group (T1-T2) and a medium-high-risk group (T3-T4)[31] .

2.2 Research Methods

A retrospective clinical study was conducted on female patients diagnosed with differentiated thyroid carcinoma (DTC) who underwent surgical treatment in the Department of Head and Neck Surgery at Sichuan Cancer Hospital between June 2014 and February 2024. Clinical data were collected from medical records, including demographic information (age, body mass index [BMI]), reproductive history (age at menarche, pregnancy and delivery history), and tumor characteristics (TNM stage, clinical stage, postoperative pathology, and lymph node metastasis).

Associations between reproductive variables (menarche age, number of pregnancies, and parity) and clinicopathological outcomes (lymph node metastasis, clinical stage, tumor size, and local invasion) were analyzed. The objective was to determine whether reproductive history was significantly correlated with disease progression in female patients with DTC.

2.3 Statistical Methods

A database was established using Excel 2019 to organize and clean the collected data. Quantitative variables were expressed as mean ± standard deviation, while categorical variables were presented as

frequency and percentage. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corporation, Armonk, NY, USA).

Group comparisons were conducted using appropriate statistical tests: t-tests for normally distributed quantitative data, Mann–Whitney U tests for non-normally distributed quantitative data, and chi-square or Fisher's exact tests (when expected frequency < 5) for categorical variables.

Multivariable logistic regression models were applied to evaluate associations between reproductive factors (age at menarche, number of pregnancies, and parity) and clinicopathological features of differentiated thyroid carcinoma, including TNM stage, T stage, and lymph node metastasis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate effect sizes. All hypothesis tests were two-tailed, and statistical significance was defined as $P < 0.05$.

3. Results and Analysis

3.1 Correlation between Age at Menarche and Disease Advancement in Differentiated Thyroid Carcinoma

3.1.1 Correlation between Age of Menarche and Clinical Staging.

A univariate rank-sum test revealed significant differences in clinical stage distribution among patients with varying menarcheal ages ($\chi^2 = 23.45$, $P = 0.003$) (Table 3-1). Multivariate logistic regression analysis of 981 patients demonstrated that, after adjustment for age and BMI, early menarche (≤11 years) was independently associated with advanced disease stage (III/IV), conferring a 7.60-fold increased risk compared with the reference group (12–14 years) (OR = 7.60, 95% CI: 2.76–20.92, $P < 0.001$). Similarly, late menarche (≥15 years) was significantly correlated with disease progression, with patients exhibiting a 3.10-fold higher risk of advanced-stage disease relative to the reference group (OR = 3.10, 95% CI: 1.31–7.35, $P = 0.010$) (Table 3-1).

Table 3-1: Impact of Different Menarche Timing on Tumor Staging

Age at menarche	Clinical Stage		χ^2	P	OR（95% CI）	P-value
	Stage I and II	Stage III and IV				
Early	47 (4.93)	6 (21.43)	23.45	0.003	7.60（2.76–20.92）	<0.001
Normal(ref)	714 (74.92)	12 (42.86)			1.00	-
Late	192 (20.15)	10 (35.71)			3.10（1.31–7.35）	0.010

3.1.2 Correlation between Age at Menarche and Lymph Node Metastasis

Chi-square analyses revealed no significant differences in the distribution of central compartment lymph node metastasis ($\chi^2 = 1.755$, $P = 0.416$) or lateral neck lymph node metastasis ($\chi^2 = 0.240$, $P = 0.887$)

among patients stratified by age at menarche (Table 3-2). These findings indicate that menarcheal age was not correlated with the occurrence of lymph node metastasis in differentiated thyroid carcinoma (DTC), suggesting that reproductive timing does not influence nodal involvement in this cohort.

Table 3-2: Effect of Different Menarche Timing on Lymph Node Metastasis

Age at menarche	Central Zone Lymph Node Metastasis		Lateral Neck Lymph Node Metastasis	
	Yes	No	Yes	No
Early	29 (4.74)	24 (6.50)	17 (5.86)	36 (5.99)
Normal	465 (75.98)	261 (70.73)	213 (73.45)	513 (85.36)
Late	118 (19.28)	84 (22.76)	60 (20.69)	142 (23.63)
Total	612	369	290	601
χ^2	1.755		0.240	
P	0.416		0.887	

3.1.3 Correlation Between Age at Menarche and T Staging

T staging in DTC reflects disease advancement by assessing tumor size and local invasion, thereby guiding surgical planning, adjuvant therapy, and follow-up strategies. Chi-square analysis demonstrated no significant differences in T stage distribution among patients stratified by age at menarche (χ^2 = 2.145, P = 0.342) (Table 3-3). These findings indicate that menarcheal age was not associated with tumor dimensions or local invasiveness in this cohort.

Table 3-3: Effect of different menarche timing on tumor size and local invasion

Menarche Stage	T Stage		Total	χ^2	P
	T1+T2	T3+T4			
Early	48 (5.71)	5 (3.57)	53 (5.40)	2.145	0.342
Normal	625 (74.32)	101 (72.14)	726 (74.01)		
Late	168 (19.98)	34 (24.29)	202 (20.59)		
Total	841	140	981		

3.2 Correlation Between Pregnancy Count and Patients Diagnosed with Differentiated Thyroid Carcinoma

3.2.1 Correlation Between Various Pregnancy Counts and Tumor Clinical Staging

Univariate analysis revealed a significant association between pregnancy count and clinical stage of DTC (χ^2 = 40.520, P < 0.001; Table 3-4). Patients with stage III/IV disease had markedly higher rates of 3–4 pregnancies (39.29% vs. 13.35%) and ≥5 pregnancies (28.57% vs. 4.79%). Multivariate logistic

regression, adjusted for age, BMI, and menarcheal age, confirmed that 3–4 pregnancies (OR = 5.91, 95% CI: 2.54–13.74, P < 0.001) and ≥5 pregnancies (OR = 18.56, 95% CI: 6.43–53.58, P < 0.001) were independent risk factors for advanced-stage disease, demonstrating a clear dose–response relationship. Conversely, nulliparity was associated with a significantly reduced risk compared with 1–2 births (OR = 0.08, 95% CI: 0.01–0.60, P = 0.014) (Table 3-4). These findings underscore parity as a key reproductive determinant of DTC progression, warranting closer monitoring in patients with three or more pregnancies.

Table 3-4: Impact of different numbers of pregnancies on thyroid cancer staging

Number of Pregnancies	Tumor Stage		χ^2	P	OR(95% CI)	P-value
	Stage I and II	Stage III and IV				
0 times	282 (29.90)	1 (3.57)	40.52	<0.001	0.08（0.01 - 0.60）	0.014
1 - 2 times(ref)	505 (53.55)	8 (28.57)			-	-
3 - 4 times	120 (12.73)	11 (39.29)			5.91（2.54 - 13.74）	<0.001
5 times or more	39 (4.14)	8 (28.57)			18.56（6.43 - 53.58）	<0.001

3.2.2 Correlation Between Number of Pregnancies and Lymph Node Metastasis

Pregnancy count was significantly associated with lymph node metastasis in DTC. The central compartment showed the highest metastasis rate in nulliparous patients (70.6%, 207/293), compared with 57.4% in the 1–2 pregnancies group, 62.6% in the 3–4 group, and 63.8% in the ≥5 group(Table 3-5). Multivariable analysis confirmed that nulliparity independently increased central metastasis risk relative to 1–2 pregnancies (OR = 1.69, 95% CI: 1.25–2.28, P < 0.001), whereas 3–4 and ≥5 pregnancies were not significant(Table 3-6).

In the lateral neck, metastasis rates rose with pregnancy count (31.7% in nulliparous patients, 25.5% in 1–2, 35.1% in 3–4, and 44.7% in ≥5). Adjusted models indicated that only ≥5 pregnancies were significantly associated with lateral metastasis (OR = 2.37, 95% CI: 1.29–4.36, P = 0.0052)(Table 3-6). These findings suggest a compartment-specific pattern: central metastasis risk is elevated in nulliparous women, while lateral metastasis requires very high pregnancy exposure.

Table 3-5 Effect of Number of Pregnancies on Lymph Node Metastasis

Number of Pregnancies	Central Zone Lymph Node Metastasis		Lateral Neck Metastasis	
	Yes	No	Yes	No
0 times	207 (33.82)	86 (23.31)	93 (32.07)	200 (33.28)
1 - 2 times	293 (47.88)	217 (58.81)	130 (44.83)	380 (63.23)
3 - 4 times	82 (13.40)	49 (13.28)	46 (15.86)	85 (14.14)
5 times or more	30 (4.90)	17 (4.61)	21 (7.24)	26 (4.33)
Total	612	369	290	601
χ^2	15.32		9.76	
P	0.002		0.021	

Table 3-6 Association Between Pregnancy Count and Lymph Node Metastasis

Number of Pregnancies	Central Compartment Metastasis OR（95% CI）	P-value	Lateral Neck Metastasis OR (95% CI)	P-value
0 times	1.69 (1.25–2.28)	<0.001	1.13 (0.82–1.56)	0.44
1 - 2 times(ref)	1.00	-	1.00	-
3 - 4 times	1.25 (0.84–1.85)	0.27	1.28 (0.84–1.95)	0.25
5 times or more	1.31 (0.72–2.39)	0.38	2.37 (1.29–4.36)	0.0052

3.2.3 Correlation Between Pregnancy Count and T Staging

Pregnancy number was significantly associated with tumor T stage (χ^2 = 16.75, P < 0.001; Table 3-7). Multivariate analysis confirmed that ≥5 pregnancies independently increased the risk of T3/T4 disease (OR = 3.28, 95% CI: 1.73–6.21, P < 0.001), while other groups showed no significant differences compared with 1–2 pregnancies (Table 3-7). These results highlight high parity as a risk factor for local tumor invasiveness in DTC.

Table 3-8: Impact of Varying Pregnancy Counts on Tumor Dimensions and Extent of Local Invasion

Pregnancy Grading	T Stage		χ^2	P	OR(95% CI)	P-value
	T1+T2	T3+T4				
0 times	250 (29.73)	43 (30.71)	16.75	<0.001	0.81（0.53 - 1.23）	0.32
1 - 2 times(ref)	446 (53.03)	64 (45.71)			1.00	-
3 - 4 times	114 (13.56)	17 (12.14)			0.95（0.54 - 1.67）	0.86
5 times or more	31 (3.69)	16 (11.43)			3.28（1.73 - 6.21）	<0.001

3.3 Correlation between Birth Rate and Incidence of Differentiated Thyroid Carcinoma

3.3.1 Correlation between Parity and Tumor Stage

Chi-square analysis revealed a significant correlation between parity and clinical stage in DTC (χ^2 = 63.58, P < 0.001; Table 3-9). Multivariate logistic regression of 981 patients, adjusted for pregnancy count, demonstrated that ≥3 births were independently associated with progression to advanced stages (III/IV) (OR = 23.19, 95% CI: 11.00–59.64, P < 0.001). Conversely, nulliparous women exhibited a markedly reduced risk compared with those having 1–2 births (OR = 0.03, 95% CI: 0.01–0.23, P < 0.001), suggesting a protective effect of nulliparity against disease advancement (Table 3-9). These findings underscore high parity (≥3 births) as a robust independent risk factor for advanced-stage DTC.

Table 3-9: Effect of Different Birth Counts on Thyroid Cancer Tumor Staging

Number of births	Tumor Staging		χ^2	P	OR (95% CI)	P-value
	Stage I and II	Stage III and IV				
0 times	300 (31.81)	1 (3.57)	63.58	<0.001	0.03 (0.01–0.23)	<0.001
1 - 2 times(ref)	624 (66.17)	13 (46.43)			1.00	-
3 - 4 times and 5 times or more	29 (2.76)	14 (42.86)			23.19 (10.56–50.93)	<0.001

3.3.2 Correlation between Birth Rate and Lymph Node Metastasis

Parity was also significantly correlated with nodal involvement. Central compartment metastasis rates were 69.8% in nulliparous women, 57.5% in the 1–2 births group, and 81.6% in the ≥3 births group (χ^2 = 22.72, P < 0.001)(Table 3-10). Multivariable regression confirmed that ≥3 births independently increased central metastasis risk (OR = 3.81,95% CI: 1.67–8.69, P = 0.0028)(Table 3-11).

For the lateral neck, metastasis rates were 31.6% in nulliparous women, 26.5% in the 1–2 births group, and 60.5% in the ≥3 births group (χ^2 = 9.01, P = 0.011)(Table 3-10).Adjusted models demonstrated a strong association between ≥3 births and lateral metastasis (OR = 4.24, 95% CI: 2.24 - 8.00, P < 0.001) (Table 3-11).These results highlight parity as a robust predictor of nodal involvement, with both central and lateral compartments significantly affected when ≥3 births are present.

Table 3-10 Correlation between Various Parity Levels and Lymph Node Metastasis

Lymph Nodes Metastasis	Outcome	Number of Parities					
		0 times	1 - 2 times	≥3 times	Total	χ²	P
Central Zone Lymph Node Metastasis	Yes	210(69.76)	366(57.46)	36(81.58)	612 (62.39)	22.72	<0.001
	No	91(30.23)	271(42.54)	7(18.42)	369 (37.61)		
Lateral Neck Lymph Node Metastasis	Yes	95(31.56)	169(26.53)	26 (60.53)	290 (29.56)	9.01	0.011
	No	206(68.44)	468(73.47)	17 (39.48)	691 (70.44)		

Table 3-11 Association Between Parity Count and Lymph Node Metastasis

Number of parities	Central Compartment Metastasis OR（95% CI）	P-value	Lateral Neck Metastasis OR (95% CI)	P-value
0 times	1.71 (1.28–2.29)	<0.001	1.28 (0.95–1.72)	0.11
1 - 2 times(ref)	1.00	-	1.00	-
≥3 times	3.81 (1.67–8.69)	0.0028	4.24 (2.24–8.00)	<0.001

3.3.3 Correlation between Pregnancy Count and T Staging

Chi-square analysis revealed a significant correlation between parity and tumor T stage, reflecting tumor size and local invasion ($\chi^2 = 19.75$, $P < 0.001$; Table 3-13). Multivariate logistic regression, adjusted for age, BMI, and menarcheal age, demonstrated that ≥3 births were independently associated with advanced T3/T4 staging (OR = 4.12, 95% CI: 2.13–7.97, $P < 0.001$), corresponding to a more than fourfold increased risk compared with the 1–2 birth group (Table 3-12). No significant differences were observed between nulliparous women and the reference cohort.

Table 3-12: Effects of different parity levels on tumor size and degree of local invasion

Parity Grading	T Stage		X2	P	OR（95% CI）	P-value
	T1+T2	T3+T4				
0 times	257 (30.56)	44 (31.43)	19.75	<0.001	1.19（0.80–1.77）	0.39
1-2 times(ref)	557 (66.23)	80 (57.14)			1	-
3-4 times	27 (3.21)	16 (11.42)			4.12（2.13–7.97）	<0.001

4. Results

4.1 Association Between Reproductive Factors and Clinical Stage

Multivariate logistic regression analysis revealed that several reproductive factors were significantly associated with advanced clinical stage (III/IV) in DTC patients. As shown in Figure A, early menarche (≤11 years) was strongly linked to advanced disease (OR = 7.60, 95% CI: 2.76–20.92, P < 0.001), and late menarche (≥15 years) also conferred increased risk (OR = 3.10, 95% CI: 1.31–7.35, P = 0.010). Among all variables, high parity (≥3 births) emerged as the strongest predictor (OR = 23.19, 95% CI: 11.00–59.64, P < 0.001), followed by ≥5 pregnancies (OR = 18.56, 95% CI: 6.43–53.58, P < 0.001) and 3–4 pregnancies (OR = 5.91, 95% CI: 2.54–13.74, P < 0.001). Conversely, nulliparity exerted a significant protective effect (OR = 0.03, 95% CI: 0.01–0.23, P < 0.001). These findings demonstrate a clear dose–response relationship between reproductive history and disease progression.

4.2 Association Between Reproductive Factors and Local Invasion

As illustrated in Figure B, parity and pregnancy count were independently associated with local tumor invasion (T3/T4 stage). Women with ≥3 births had a significantly elevated risk of local invasion (OR = 4.12, 95% CI: 2.13–7.97, P < 0.001), and ≥5 pregnancies showed similar effects (OR = 3.28, 95% CI: 1.73–6.21, P < 0.001). In contrast, nulliparity (OR = 0.81, 95% CI: 0.53–1.23, P = 0.32) and menarcheal age (≤11 or ≥15 years) were not significantly associated with T3/T4 stage (P > 0.05). These results suggest that reproductive burden, particularly high parity and multiple pregnancies, is a robust predictor of tumor invasiveness, whereas pubertal timing does not appear to influence local extension.

4.3 Association with lymph node metastasis

Compartment-specific effects of reproductive factors on lymph node metastasis were observed, as shown in Figure C. Nulliparity was independently associated with increased central compartment metastasis (OR = 1.69, P < 0.001), while lateral neck metastasis was significantly elevated only in patients with ≥5 pregnancies (OR = 2.37, P = 0.0052). In contrast, parity ≥3 births was strongly associated with both central (OR = 3.81, P = 0.0028) and lateral metastasis (OR = 4.24, P < 0.001). Menarcheal age showed no significant correlation with lymph node involvement or T stage (P > 0.05). These findings indicate that reproductive history influences nodal spread in a compartment- and

measure-specific manner: central metastasis risk is elevated in nulliparous and high-parity patients, whereas lateral metastasis is driven by heavy reproductive exposure.

4.4 Dose–response relationship

Taken together, reproductive factors demonstrated a consistent dose–response relationship with disease progression. Increasing numbers of pregnancies and births were associated with progressively higher risks of advanced clinical stage, local invasion, and lymph node metastasis. Conversely, nulliparity consistently conferred a protective effect across multiple analyses.

5. Discussion

5.1 Correlation Between Age at Menarche and Differentiated Thyroid Carcinoma

Our study demonstrated that both early menarche (≤ 11 years) and late menarche (≥ 15 years) were independently associated with advanced-stage DTC, while no significant associations were observed with lymph node metastasis. These findings suggest that reproductive timing primarily influences overall stage progression rather than nodal dissemination.

Prior studies have reported inconsistent results. He et al. [27] and Xhaard et al. [32] identified early menarche as a risk factor, whereas Sakoda et al. [33] and Wang et al.[36]suggested increased risk or protective effects with later onset. Other investigations, including Galanti et al.[35]and a meta-analysis by Cao et al.[34], found no correlation. Such discrepancies may reflect differences in population genetics, study design, and whether endpoints assessed incidence or progression.

Mechanistically, early menarche extends cumulative estrogen exposure, activating ER-mediated pathways such as MAPK/ERK and PI3K/Akt [9][10], while delayed menarche may reflect endocrine dysregulation[11]. Estrogen also remodels the tumor microenvironment, promoting angiogenesis, immune modulation, and fibroblast activation [40], and enhances tumor stemness via lncRNA H19 [38] or proliferation through suppression of miR-570-3p[39]. Future studies integrating molecular pathology, including BRAF mutations, are warranted to clarify these associations and improve risk stratification

5.2 Correlation Between Pregnancy Count and Thyroid Carcinoma

Our study demonstrated that pregnancy count was strongly correlated with disease progression in DTC, showing a clear dose–response relationship. Women with 3–4 pregnancies and those with ≥ 5 pregnancies had significantly higher risks of advanced-stage disease (OR = 5.91, 95% CI: 2.54–13.74, P < 0.001; OR = 18.56, 95% CI: 6.43–53.58, P < 0.001, respectively). Moreover, increasing pregnancy

frequency was positively associated with both central and lateral cervical lymph node metastases, underscoring the role of reproductive history in tumor aggressiveness.

These findings are consistent with international reports. Messuti et al.[43]observed that patients diagnosed with DTC during pregnancy or shortly postpartum had a significantly higher risk of disease persistence or recurrence (OR = 1.1, P = 0.023). Similarly, Moleti et al. [44] and Preston-Martin et al. [45] reported that multiple pregnancies were associated with a 3–4.2-fold increased risk of thyroid cancer. Collectively, this evidence suggests that repeated endocrine fluctuations during pregnancy may promote tumor growth through continuous activation of oncogenic signaling pathways such as MAPK and PI3K/Akt.

Interestingly, while multiple pregnancies increase aggressiveness and recurrence risk, prior studies have shown no significant impact on long-term survival [42]. This paradox likely reflects the generally favorable prognosis of DTC, indicating that reproductive factors primarily influence local tumor behavior rather than overall mortality. Based on these findings, we propose that a history of ≥ 3 pregnancies should be considered in risk stratification models, with closer surveillance warranted in this subgroup. Future research should aim to clarify the mechanistic links between pregnancy-related hormonal changes and driver mutations in thyroid cancer progression.

5.3 Correlation Between Pregnancy Count and Differentiated Thyroid Carcinoma

Our study identified parity as the reproductive factor most strongly associated with DTC progression. Women with ≥ 3 live births had a markedly increased risk of advanced-stage disease (OR = 23.19, 95% CI: 10.56–50.93, P < 0.001) and locally invasive tumors (T3/T4 stage; OR = 4.12, 95% CI: 2.13–7.97, P < 0.001). A clear dose–response relationship was observed, with central lymph node metastasis rates reaching 81.58% in the 3–4 births group and 100% in the ≥ 5 births group.

These findings extend prior research on reproductive factors and thyroid cancer. While some studies, such as those conducted in Scandinavian populations [35], reported no significant association, and others failed to establish a dose–response relationship [52], our results align with reports emphasizing the impact of completed pregnancies. Previous studies have linked higher parity to increased thyroid cancer risk [51] and malignant nodule formation[47], suggesting that full-term gestation may impart lasting physiological effects beyond pregnancy itself. The underlying mechanisms likely involve profound endocrine and immune remodeling during delivery [48]. The postpartum and lactation periods, characterized by elevated prolactin and declining estrogen/progesterone[49], may exert persistent influences on the thyroid microenvironment. Moreover, the frequent co-expression of estrogen (ERα), progesterone (PR), and prolactin (PRLR) receptors in thyroid cancer tissues [50] supports the hypothesis that abnormal activation of sex hormone signaling pathways contributes to aggressive tumor phenotypes[37][50].

In conclusion, parity is a significant predictor of DTC progression. Women with ≥ 3 births, particularly those with ≥ 5, should be considered at exceptionally high risk, warranting comprehensive preoperative evaluation and intensified postoperative surveillance. Future studies should further clarify the synergistic effects of full-term pregnancies and other carcinogenic drivers in thyroid cancer progression.

6. Conclusion

This study demonstrated that abnormal menarche age, multiple pregnancies, and high parity are independent predictors of advanced DTC, with a distinct dose–response relationship. Nulliparity was protective. These reproductive traits should inform clinical risk assessment and management, including enhanced preoperative evaluation and postoperative monitoring. Future multicenter studies should validate these associations and investigate hormonal–genetic interactions to support precision prevention and treatment.

Abbreviations

DTC (Differentiated Thyroid Carcinoma)

OR (Odds Ratio)

CI (Confidence Interval)

BMI (Body Mass Index)

IRB (Institutional Review Board)

TNM (Tumor, Node, Metastasis)

ER (Estrogen Receptor)

PR (Progesterone Receptor)

PRLR (Prolactin Receptor)

MAPK (Mitogen-Activated Protein Kinase)

PI3K/Akt (Phosphoinositide 3-Kinase/Protein Kinase B)

lncRNA (Long Non-Coding RNA)

miRNA/miR (MicroRNA)

Declarations

Ethics approval and consent to participate

Ethics approval This retrospective study involved the analysis of anonymized clinical data and was formally approved by the Institutional Review Board (IRB) of Sichuan Cancer Hospital (**Approval No.: SCCHEC-02-2025-148**).

Consent to participate All procedures performed in this study were in strict accordance with the ethical standards of the responsible institutional and national committees on human experimentation and with the principles of the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study prior to their enrollment. The need for informed consent was waived by the IRB of Sichuan Cancer Hospital due to the retrospective nature of the study.

Consent for publication

Not Applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Yong-Cong Cai: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

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Declaration of AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with the language polishing and editing of the cover letter. Since the authors' native language is Chinese, the tool was employed solely to improve the clarity and fluency of the English text. After using this tool, the authors carefully reviewed and edited the content, and take full responsibility for the final version and the scientific integrity of the manuscript.

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Figures

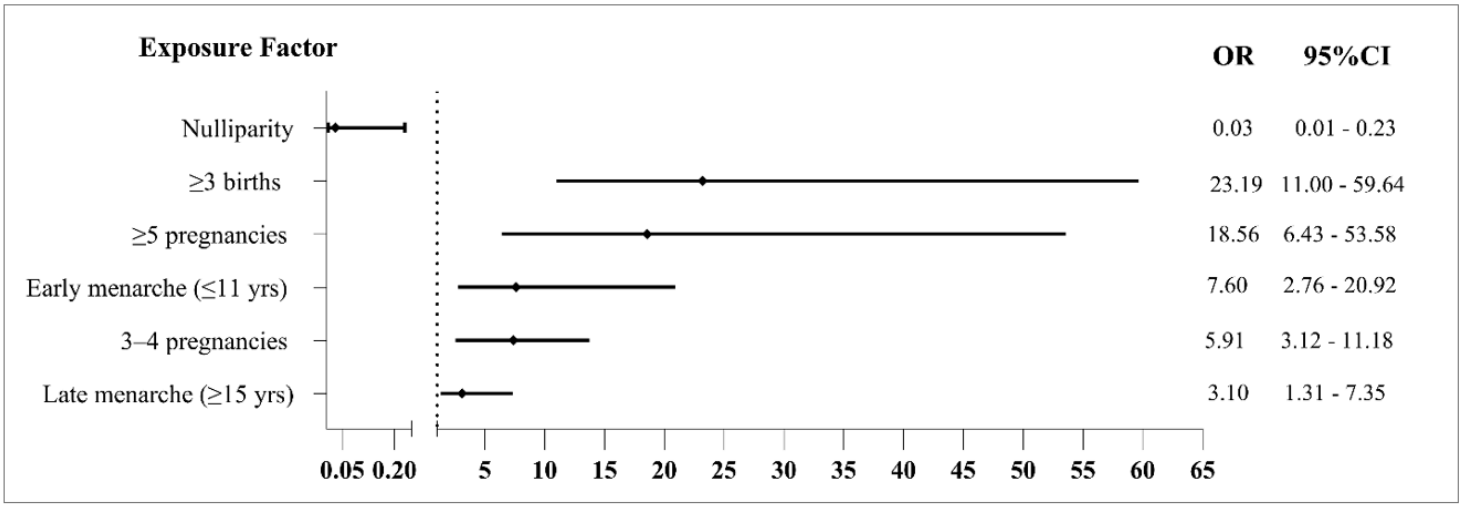


Figure 1

Figure A. Forest plot of reproductive factors associated with advanced clinical stage (III/IV) in differentiated thyroid carcinoma (DTC). Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from multivariate logistic regression models adjusted for age and BMI. Red markers indicate significant risk factors (OR > 1, P < 0.05), blue markers indicate protective factors (OR < 1, P < 0.05), and the vertical dashed line represents the null value (OR = 1).

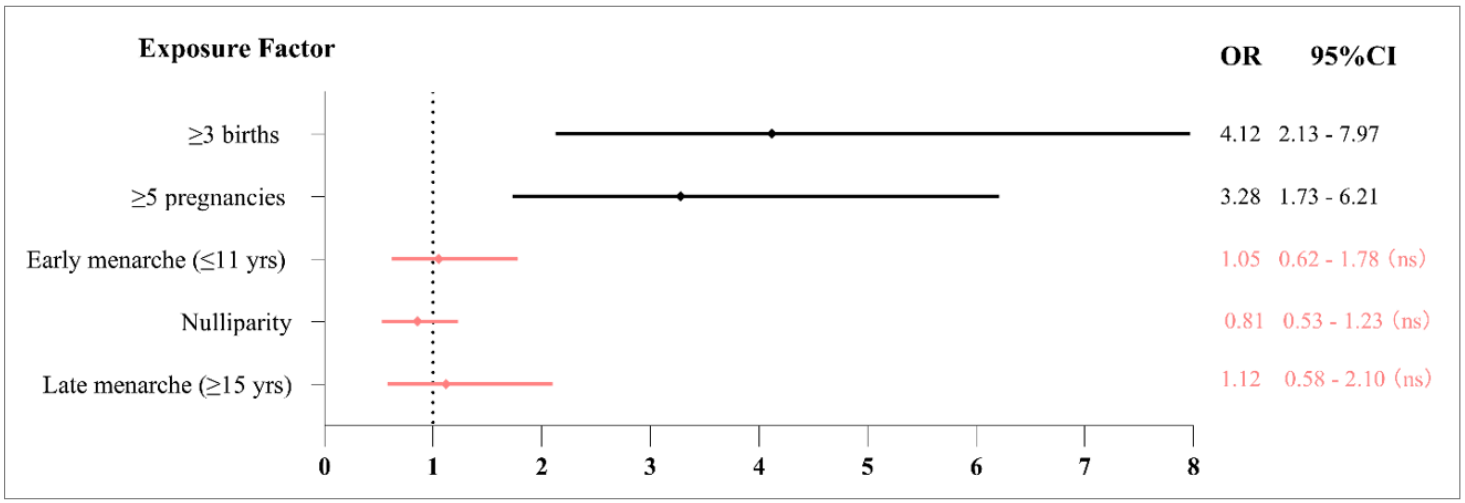


Figure 2

Figure B. Forest plot of reproductive factors associated with local invasion (T3/T4 stage) in differentiated thyroid carcinoma (DTC). Odds ratios (ORs) and 95% confidence intervals (CIs) were

derived from multivariate logistic regression models adjusted for age and BMI. Red markers indicate significant risk factors, blue markers indicate protective factors, and gray markers represent non-significant associations (P > 0.05). The vertical dashed line represents the null value (OR = 1).

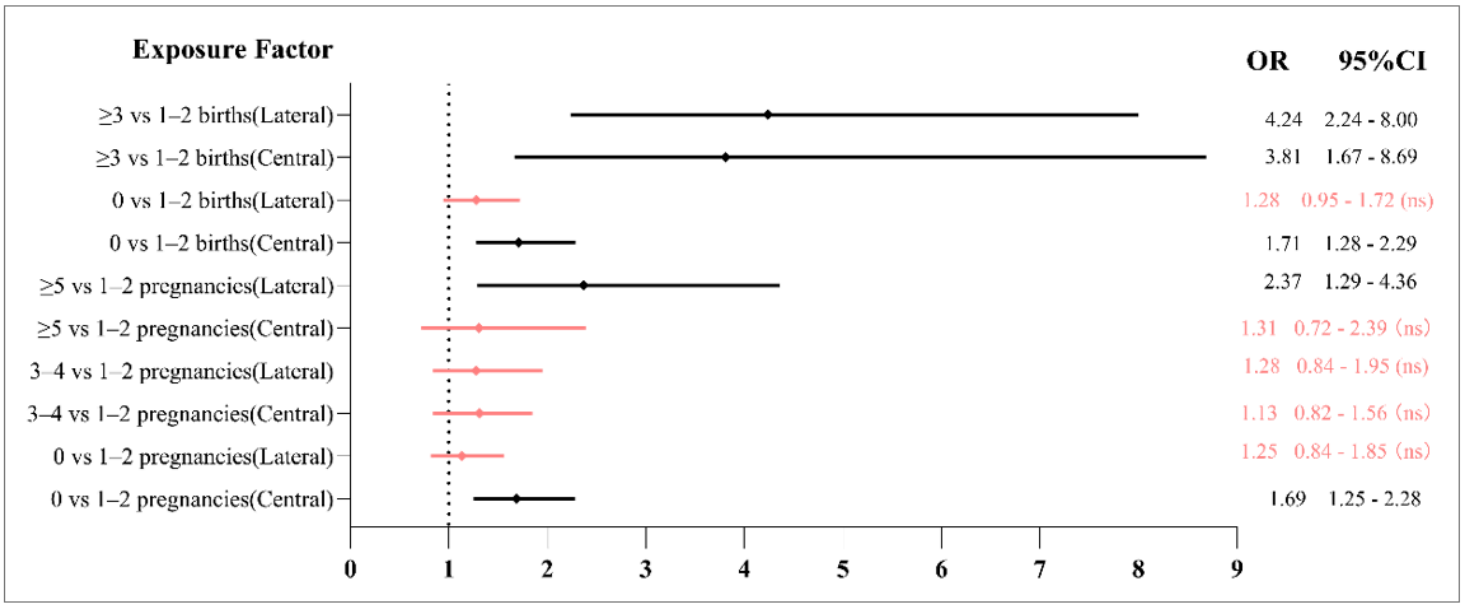


Figure 3

Figure C. Forest plot of reproductive factors associated with lymph node metastasis in DTC.Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from crude 2×2 comparisons. Red markers indicate significant risk factors (P < 0.05), gray markers indicate non-significant associations. The vertical dashed line represents the null value (OR = 1).

Supplementary Files

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- datas.xlsx