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Original Article

A protective factor against lymph node metastasis of papillary thyroid cancer: Female gender

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ABSTRACT

Objective: Papillary thyroid carcinoma (PTC) is the most common pathological type of thyroid cancer, with good prognosis, but the rate of lymph node metastasis (LNM) is high, and the difference between men and women is significant. Therefore, the related risk factors for LNM of PTC based on gender were examined in this study in order to draw attention to gender factor in PTC.

Methods: We retrospectively analyzed the clinicopathological data of 2103 patients with surgically confirmed PTC at the Fourth affiliated Hospital of Hebei Medical University West Side between January 2016 and December 2019.

Results: LNM was detected in 1124 of the 2103 cases of PTC. Logistic regression analysis showed that LNM was associated with age ($p < 0.001$, OR:0.547), gender ($p < 0.001$, OR:2.609), tumor diameter ($p < 0.001$, OR:2.995), bilaterality (p=0.003, OR:1.683), and extrathyroid extension ($p < 0.001$, OR:1.657). After propensity score matching, female gender ($p < 0.001$, OR: 0.393) remained an independent factor of LNM in patients with PTC. LNM in men was only associated with diameter ($p < 0.001$, OR: 3.246). LNM in woman was associated with menopausal history ($p = 0.012$, OR=0.684), reproductive history ($p < 0.001$, OR=0.360), abortion history ($p = 0.011$, OR=0.725), tumor diameter >1 cm ($p < 0.001$, OR=2.807), bilaterality (p =0.006, OR:1.728), and extrathyroid extension ($p < 0.001$, OR=1.879).

Conclusion: Although the invasion is high in female patients, the rate of LNM is significantly reduced due to the influence of sex hormones and reproductive factors. For female patients of childbearing age who were not pregnant and did not have children, it is suggested to take a positive attitude towards their lymph nodes.

1. Introduction

The incidence of thyroid carcinoma (TC) has the most rapidly increased in many country over recent years [1,2]. In the endocrine system, TC is one of the most common

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malignancies, which may be caused by radiation exposure, sex hormone levels, gene mutation, family heredity and other factors. Compared with other TC types, papillary thyroid carcinoma (PTC) is known to be the most common pathological type and counts for more than 80% [3] of TCs. PTC is less malignant and has a good prognosis with 10-years survival rates of 27–90% [4]. However, the recurrence rate and cervical lymph node metastasis (LNM) rate are high. LNM is the main way for the metastasis of PTC, but the mechanism is not clear. Previous study [5,6] have reported that LNM has a significant effect on the recurrence rate of PTC. Another study [7] showed that the presence of LNM increased the distant metastasis rate by 11.2 times. Therefore, LNM is one of the main factors affecting the prognosis of patients. It is particularly important to make accurate preoperative assessment of lymph node status for PTC patients.

In recent years, the role of gender in the occurrence and development of thyroid cancer has become a research hotspot. Gender differences in PTC have been explored over the past decade [8]. Many scholars have found significant differences between the genders in many aspects, such as diameter, bilateralilty, multifocality, HT, lymphatic vascular invasion, recurrence and death [9–11]. In women, the incidence of PTC is about three times higher than in men [12]. However, the rate of LNM was significantly lower than that of men [13–15]. Hence, the following questions need to be answered:1: Are the risk factors for LNM consistent between men and women? 2. What factors reduce LNM in women? 3. Which patients require preventive neck dissection? There are few studies on the clinically relevant individual and independent risk factors of LNM in different genders. Therefore, this study analyzed the LNM in PTC patients of different genders in order to identify the critical risk factors, and facilitate more reasonable and individualized surgical plans for PTC patients of different genders.

2. Methods

2.1. Patients

A total of 2120 hospitalized patients who underwent neck surgery for the first time between January 2016 and December 2019 at the Fourth affiliated Hospital of Hebei Medical University West Side were enrolled in this study. There were 499 males and 1621 females, aged 9-78 (45.18±12.03) years.

2.2. Clinicopathological characteristics

Clinical features of PTC such as gender, age, height, weight, body mass index (BMI), family history of malignant tumor, chronic diseases, hypertension history, type 2 diabetes mellitus (T2DM) history, benign tumor history, malignant tumor history, reproductive history (women only), menopause history (women only), abortion history (women only), menarche time (women only), smoking history (men only), alcohol history (men only) were recorded. Among them, the occurrence of pregnancy, whether full term or not, is defined as the reproductive history. The patient's menopausal age $\leq$ the age at onset of PTC was defined as a history of menopause. Pathological features of PTC such as maximal diameter of tumor, multifocality, bilaterality, only capsular invasion, extrathyroid extension (ETE), combined with Hashimoto's thyroiditis (HT), lymph node metastasis (LNM), and Thyroid Stimulating Hormone(TSH) level were also recorded. The retrospective study protocol was approved by the Clinical Research Ethics Review Committee of the Fourth Hospital of Hebei Medical University.

2.3. Inclusion and exclusion criteria

Inclusion criteria: ① The postoperative pathology of all cases were PTC, ② Unilateral lobectomy or total thyroidectomy + neck dissection (including central dissection ± lateral neck dissection), ③ Without history of thyroid and neck surgery, ④ Patients with complete clinical and pathological data. Exclusion criteria: ① Type 1 diabetes mellitus and ② Patients with serious cardiovascular and cerebrovascular diseases or heart, liver, lung and renal insufficiency. PTC was confirmed by postoperative pathology. Tumor size was defined as the greatest diameter of each lesion. The diagnosis of Hashimoto's thyroiditis was only made based on the postoperative pathology. Extrathyroidal extension (ETE) is characterized by involvement of the sternothyroid muscle or the subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.The diagnosis of T2DM was approved by American Diabetes Association (ADA), the diagnosis of basic chronic diseases included hypertension, coronary heart diseases, arrhythmia, etc., meets the latest research criteria of the World Health Organization (WHO).

2.4. Propensity score matching process

Accroding to the recommendations by Lonjon *et al* [16], propensity score matching was applied to minimize the effects of potential confounding factors at baseline. Based on this, age, height, weight, BMI, family history of malignant tumor, chronic diseases, hypertension history, T2DM history, benign tumor history, malignant tumor history, maximal diameter of tumor, multifocality, bilaterality, only capsular invasion, ETE, combined with HT, and TSH were included as covariables. Then patients with LNM were matched at a 1:1 ratio to patients without LNM owing to observed heterogeneity in baseline characteristics in the original cohort. The propensity score with a standard caliper width of 0.2. Propensity score matching was performed by SPSS software, version 24.0.

2.5. Statistical methods

SPSS 24.0 statistical software was used for data processing. Normally distributed measurement data were expressed as X ± SD, t-test for the group comparison; the counting data were expressed as cases or percentages, $\chi 2$ test and Fisher's exact probability method were used for comparison between groups. After propensity score matching, the characteristics were compared between the 2 groups as matched

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Table 1. Patients' demographics features and clinicopathological characteristics.

Variables	Number of patients	%
Male/Female	496/1607	23.6/76.4
Age (mean ± SD, years)	45.18±12.03	–
Groups (<55 years vs >55 years)	1601/502	76.1/23.9
BMI (<25 vs >25 Kg/m 2)	1097/1006	52.2/47.8
Family history of cancer (yes/no)	61/2042	2.9/97.1
Hashimoto's thyroiditis (yes/no)	139/1964	6.6/93.4
Chronic basic disease (yes/no)	442/1661	21.0/79.0
Hypertension (yes/no)	391/1712	18.6/81.4
Type 2 Diabetes Mellitus(yes/no)	133/1970	6.3/93.7
Benign tumor history(yes/no)	183/1920	8.7/91.3
Malignant tumor history(yes/no)	62/2041	2.9/97.1
Smoke (yes/no)	159/1944	7.6/92.4
Alcohol use(yes/no)	53/2050	2.5/97.5
TSH level (mIU/L, mean ± SD)	2.17±1.82	–
Tumor size (<10 mm vs >10 mm)	1357/746	64.5/35.5
Tumors size (mean ± SD, cm)	1.12±0.83	–
Multifocality (yes/no)	724/1396	34.1/65.9
Bilaterality (yes/no)	495/1608	23.5/76.5
Capsular invasion only (yes/no)	482/1621	22.9/77.1
Extrathyroid extension (yes/no)	418/1685	19.9/80.1
Lymph node metastasis (yes/no)	1124/979	53.4/46.6
Variables	Number of patients (Female)	%
Case number	1607	–
Post-menopause (yes/no)	621/986	38.6/61.4
Pregnancy history (yes/no)	135/1472	8.4/91.6
Age of menarche(mean ± SD, years)	14.34±1.56	–
Age of menopause(mean ± SD, years)	48.9±4.35	–

BMI: body-mass index; TSH:Thyroid Stimulating Hormone.

pairs. Logistic analysis was used for univariate and multivariate analysis. All statistical tests were two-sided probability tests, and p <0.05 was considered to be statistically significant.

3. Results

3.1. Patients' characteristics

A total of 2021 eligible patients were included. There were 496 males (23.6%) and 1607 females (76.4%). The average age was 45.18±12.03 years (mean ± SD). The average tumor size was about 1.12±0.83 cm (mean ± SD). Among them, 724 cases (34.1%) showed multifocality, 495 cases (23.5%) showed bilaterality, 482 cases (22.9%) had capsular invasion, and 418 cases (19.9%) had ETE. A total of 1124 patients (53.4%) developed LNM at the time of the first operation. Table 1 describes the details of the patients.

3.2. Univariate analysis and multivariate logistic regression analysis for LNM

The univariate analysis showed no significant difference in BMI, family history of malignant tumor, basic chronic disease, HT, hypertension history, T2DM history, benign tumor history, malignant tumor history, TSH level and only capsular invasion. The rates of age <55 years, male, tumor diameter >1 cm, multifocality, bilaterality and ETE in patients with LNM were higher than in patients without LNM (Table 2). Based on the results of univariate analysis, the significant variables were included in the multivariable analysis. The multivariate logistic regression analysis found that all the above variables, including age <55 years (p < 0.001, OR: 0.547),female (p < 0.001, OR: 0.412), diameter >1 cm (p < 0.001, OR: 2.995), bilaterality (p=0.003, OR: 1.683) and ETE (p < 0.001, OR: 1.657), except multifocality, were independent factors (Table 3).

3.3. Gender differences between PTC patients with and without LNM

The relationship of LNM with gender was examined in the original cohort. There was a significantly lower risk of LNM in patients with female (N=779) than in male(N=345) (48.4% vs 69.6%; p < 0.001). Thus, using the propensity score matching method, patients with and without

LNM were also matched at a 1:1 ratio. In this way, 747 patients were assigned to each group. The baseline demographics features and clinicopathologic characteristics of the patients with and without LNM were presented in Table 2. In the matched cohort, the baseline variables of patients in the LNM group was compared with those of patients in the no LNM group (all p > 0.05). A lower risk of LNM in female (44.9% vs 67.5%; p < 0.001) were observed in the LNM group. Logistic analysis also revealed that gender was a critical factor in LNM and LNM were significantly lower in female than in male patients. (p < 0.001, OR:0.412; p < 0.001, OR: 0.383; p < 0.001, OR: 0.393) (Table 3).

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Table 2. The baseline demographics features and clinicopathologic characteristics of 2103 patients with PTC by LNM before and after propensity score matching.

Variables	Original cohort LNM(+)(n=1124)	LNM(-)(n=979)	P-Value	Matched cohort LNM(+)(n=747)	LNM(-)(n=747)	P-Value
Gender			<0.001[a]			<0.001[a]
female	779(48.4%)	828(51.5%)		519(44.9%)	637(55.1%)	
male	345(69.6%)	151(30.4%)		228(67.5%)	110(32.5%)	
Age(years)			<0.001[a]			0.497
<55	898(56.1%)	703(43.9%)		583(50.5%)	572(49.5%)	
>55	226(45.0%)	276(55.0%)		164(48.4%)	175(51.6%)	
BMI (kg/m2)			0.771			0.918
≤25	583(53.1%)	514(46.9%)		384(50.1%)	382(49.9%)	
>25	541(53.8%)	465(46.2%)		363(49.9%)	365(50.1%)	
Family history of cancer	31(50.8%)	30(49.2%)	0.676	21(48.8%)	22(51.2%)	0.877
HT	74(53.2%)	65(46.8%)	0.959	54(51.9%)	50(48.1%)	0.684
Chronic basic disease	228(51.6%)	214(48.4%)	0.377	154(49.0%)	160(51.0%)	0.703
Hypertension	205(52.4%)	186(47.6%)	0.576	138(49.6%)	140(50.4%)	0.894
T2DM	62(46.6%)	71(53.4%)	0.103	48(43.6%)	62(56.4%)	0.165
Benign tumor history	88(48.1%)	95(51.9%)	0.128	66(50.4%)	65(49.6%)	0.927
Malignant tumor history	27(43.5%)	35(56.5%)	0.113	21(61.8%)	13(38.2%)	0.165
TSH level(uIU/mL)			0.813			0.747
<2.17	714(53.6%)	617(46.4%)		270(49.5%)	276(50.5%)	
>2.17	410(53.1%)	362(46.9%)		477(50.4%)	471(49.7%)	
Tumor size(cm)			<0.001[a]			0.275
<1	586(43.2%)	771(56.8%)		526(49.1%)	545(50.9%)	
>1	538(72.1%)	208(27.9%)		221(52.2%)	202(47.8%)	
Multifocality	451(62.9%)	266(37.2%)	<0.001[a]	217(47.8%)	237(52.2%)	0.261
Bilaterality	336(67.9%)	159(32.1%)	<0.001[a]	131(46.1%)	153(53.9%)	0.147
Capsular invasion only	268(55.6%)	214(44.4%)	0.280	179(48.8%)	188(51.2%)	0.589
ETE	284(67.9%)	134(32.1%)	<0.001[a]	111(46.1%)	130(53.9%)	0.181

All calculated using chi-square test.

LNM+: lymph nodes metastasis positive, LNM-: lymph nodes metastasis negative;BMI: body-mass index; TSH: Thyroid Stimulating Hormone; HT:Hashimoto's thyroiditis; T2DM: Type 2 Diabetes Mellitus; ETE: Extrathyroidal extension.

[a] Statistically significant ($p < 0.05$). All Calculated using two-tailed student t test.

Table 3. Logistic regression analysis by LNM.

Variables	Univariate analysis (N=2103)			Multivariate Analysis (N=2103)			Matched cohort Analysis (N=1494)		
	OR	95%CI	P-Value	OR	95%CI	P-Value	OR	95%CI	P-Value
Gender(Female,male)	0.412	0.332-0.510	<0.001[a]	0.383	0.305-0.481	<0.001[a]	0.393	0.305-0.507	<0.001[a]
Age (<55 or >55, years)	0.641	0.524-0.784	<0.001[a]	0.547	0.439-0.682	<0.001[a]			
BMK «25 or >25, kg/m2)	1.025	0.864-1.218	0.771						
Family history of cancer	0.897	0.539-1.493	0.676						
HT	0.991	0.702-1.399	0.959						
Chronic basic disease	0.910	0.737-1.122	0.377						
Hypertension T2DM	0.951	0.763-1.185	0.655						
	0.747	0.525-1.062	0.104						
Benign tumor history	0.790	0.583-1.071	0.129						
Malignant tumor history	0.664	0.399-1.105	0.115						
TSH level(<2.17 or >2.17, uIU/mL)	0.979	0.819-1.169	0.813						
Tumor size(cm)	3.403	2.807-4.126	<0.001[a]	2.995	2.438-3.679	<0.001[a]			
Multifocality	1.796	1.494-2.160	<0.001[a]	1.158	0.855-1.567	0.344			
Bilaterality	2.199	1.778-2.720	<0.001[a]	1.683	1.190-2.382	0.003[a]			
Capsular invasion only	1.119	0.912-1.373	0.280						
ETE	2.132	1.700-2.674	<0.001[a]	1.657	1.289-2.129	<0.001[a]			

OR: odds ratio; CI: confidence interval; BMI: body-mass index; TSH: Thyroid Stimulating Hormone; HT:Hashimoto's thyroiditis; T2DM: Type 2 Diabetes Mellitus; ETE: Extrathyroidal extension.

[a] Statistically significant ($p < 0.05$).

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Table 4. Univariate and multivariate analysis for LNM in 496 Male with the statistically significant variables.

Variables	Univariate analysis			Multivariate analysis		
	LNM(+)(n,%)	X2 value	P-Value	OR	95%CI	P-Value
Age(years)		1.530	0.216			
<55	269(71%)					
>55	76(65%)					
BMI (kg/m2)		1.295	0.255			
≤25	128(72.7%)					
>25	217(67.8%)					
HT	12(75.0%)	0.231	0.631[b]			
T2DM	29(64.4%)	0.611	0.435			
Tumor size		32.878	<0.001[a]	3.246	2.032-5.187	<0.001[a]
≤1	185(60.3%)					
>1	160(84.7%)					
Multifocality	141(81.0%)	15.493	<0.001[a]	1.567	0.782-3.140	0.205
Bilaterality	105(82%)	12.679	<0.001[a]	1.566	0.695-3.531	0.279
Capsular invasion only	70(76.9%)	2.856	0.091			
ETE	61(81.3%)	5.787	0.016[a]	1.385	0.721-2.662	0.328
Smoke history	107(69.0%)	0.029	0.864			
Alcohol history	35(66.0%)	0.347	0.556			

LNM+: lymph nodes metastasis positive. HT:Hashimoto's thyroiditis; T2DM: Type 2 Diabetes Mellitus; ETE: Extrathyroidal extension. OR: odds ratio; CI: confidence interva.

[a] Statistically significant ($p < 0.05$).All Calculated using two-tailed student t test.

[b] Calculated using Fisher exact test, others calculated using chi-square test.

3.4. Univariate analysis and multivariate logistic regression analysis for LNM in male PTC patients

The univariate analysis showed no significant difference in age, BMI, HT, T2DM, only capsular invasion, smoking history, and alcohol history. There were significant differences in tumor diameter ($p < 0.001$), multifocality ($p < 0.001$), bilaterality ($p < 0.001$) and ETE (p=0.016). The multivariate logistic regression analysis found that among all the above variables, only tumor diameter ($p < 0.001$, OR=3.426) was an independent factor (Table 4).

3.5. Univariate analysis and multivariate logistic regression analysis for LNM in female PTC patients

The univariate analysis revealed significant differences in age ($p < 0.001$), T2DM (p=0.034), post-menopause ($p < 0.001$), reproductive history ($p < 0.001$), abortion history ($p < 0.001$), age of menarche (p=0.032), tumor diameter ($p < 0.001$), multifocality ($p < 0.001$), bilaterality ($p < 0.001$) and ETE ($p < 0.001$), but no significant differences in BMI (p=0.389), HT (p=0.656) and only capsular invasion (p=0.203) among female PTC patients with or without LNM. In female patients with LNM, the proportion of age <55 years, without T2DM, pre-menopause, nullipara, without abortion history, age of menarche <14 years, tumor diameter >1 cm, multifocality, bilaterality and ETE were higher than in patients without LNM. Based on the results of univariate analysis, the significant variables were included in the multivariable analysis. The multivariate logistic regression analysis found that post-menopause (p=0.012, OR=0.684), reproductive history ($p < 0.001$,OR=0.360), abortion history (p=0.011, OR=0.72), tumor diameter >1 cm ($p < 0.001$, OR=2.807), bilaterality (p=0.006, OR: 1.728), and ETE ($p < 0.001$, OR=1.879) were independent factors. Among them, the first three factors were negatively correlated with LNM, and the last three were positively correlated with LNM (Table 5).

3.6. Analysis of menopause and reproductive factors for LNM in females

Further analysis indicated that the age of menarche was younger in PTC patients with LNM than without LNM, and the difference was statistically significant (t=2.382, p=0.017). The difference between spontaneous menopause and artificial menopause showed no significance in LNM, but the rates were lower than pre-menopause. Compared with nullipara females (75.4%), the rate of LNM in females without abortion history (48.3%) was lower, and the lowest rate (40.3%) was in females with abortion history. The difference was statistically significant ($\chi 2$=47.188, $p < 0.001$). The rate of LMN in females with pregnancy history was lower than those without pregnancy history, but there was no significant difference between the number of pregnancies ($\chi 2$=33.840, $p < 0.001$). Similarly, the rate of LMN in females with full-term pregnancy was lower than those without full-term pregnancy, but there was no significant difference between the number of live births ($\chi 2$=31.081, $p < 0.001$). Comparatively, the rate of LNM in females with ≥3 pregnancies (41.6%) was significantly decreased ($\chi 2$=4.722, p=0.030) (Table 6A). For removing the influence of age on reproductive factors, the data of adult females aged 20-49 years of childbearing age was analyzed again. There was no significance in age of menarche. The rate of females with ≥3 pregnancies was also significantly less than others ($\chi 2$=6.754, p=0.005). The rate of LNM in females with artificial menopause (75%) was higher than those with spontaneous menopause (25%). The rate of

Table 5. Univariate and multivariate analysis for LNM in 1607 Femalewith the statistically significant variables.

Variables	Univariate analysis			Multivariate analysis		
	LNM(+)(n,%)	x2 value	P-Value	OR	95%CI	P-Value
Age(years)		18.350	<0.001[a]	0.791	0.565-1.109	0.174
<55	629(51.5%)					
>55	150(39.0%)					
BMI (kg/m2)		0.743	0.389			
≤25	455(49.4%)					
>25	324(47.2%)					
HT	62(50.4%)	0.199	0.656			
T2DM	33(37.5%)	4.490	0.034[a]	0.763	0.472-1.234	0.271
Post-menopause	251(40.4%)	26.303	<0.001[a]	0.684	0.508-0.921	0.012[a]
Reproductive history	684 (47.3%)	36.902	<0.001[a]	0.360	0.231-0.560	<0.001[a]
Abortion history	160(40.3%)	47.188	<0.001[a]	0.725	0.565-0.930	0.011[a]
Age of menarche (mean±MD, years)	14.24±1.59	2.382	0.017[a]			
Age of menarche (years,n)		4.576	0.032[a]	0.890	0.708-1.120	0.320
<14	537(50.4%)					
>14	242(44.7%)					
Tumor size		128.29	<0.001[a]	2.807	2.224-3.542	<0.001[a]
<1	401(38.2%)					
>1	378(67.9%)					
Multifocality	310(57.2%)	24.899	<0.001[a]	1.132	0.801-1.600	0.491
Bilaterality	231(62.6%)	38.268	<0.001[a]	1.728	1.167-2.560	0.006[a]
Capsular invasion only	198(51.3%)	1.617	0.203			
ETE	223(65.0%)	47.759	<0.001[a]	1.879	1.425-2.477	<0.001[a]

All Calculated using two-tailed student t test.
All calculated using chi-square test.
LNM+: lymph nodes metastasis positive. HT: Hashimoto's thyroiditis; T2DM: Type 2 Diabetes Mellitus; ETE: Extrathyroidal extension. OR: odds ratio; CI: confidence interva.
[a] Statistically significant ($p < 0.05$).

LNM in female with ≥3 full-term pregnancies (43.7%) was also significantly decreased. However, the difference of those were not statistically significant (Table 6B).

4. Discussion

The prognosis for PTC is good. However, the lymph node metastasis rate is very high, reaching 40-80% [6,17,18]. In the 8th AJCC TNM staging, LNM is the third most important prognostic factor, which is the main reason for local recurrence and threatening patients' lives [19,20]. The incidence of LNM between males and females is significantly different [10,11,21]. The incidence in men was 50-80%, but in women was 40-60%. Male gender is an independent risk factor for LNM, which is predictive of more invasion and poor prognosis of PTC [10,11] in male. However, the reason for the difference in LNM between men and women with PTC remains uncertain. Hence, in order to reveal the key factors leading to this difference, we not only analyzed the usual influence factors [9–11,22–24] include age, tumor diameter, multifocality, bilaterality, and extrathyroid extension, but also extensively analyzed many other factors, such as BMI, basic chronic diseases, T2DM history, male smoking history, female reproductive history, etc., in this study.

Our results indicated that gender was a crucial factor for the LNM of PTC. Female gender was a protective factor for PTC patients in LNM. Absolutely, age, tumor diameter, multifocality, bilaterality, extrathyroid extension were the influencing factors in all patients, which were consistent with previous studies. But the roles of these factors in LNM are not uniform between the genders. Age as a factor has shown controversial results in previous studies. Liu et al. [25] found no relationship between age and LNM, but another study reported that 45 years of age [13] was a risk factor for central LNM. Chen et al. [26] indicated that 55 years of age was a risk factor. In this study, we found that the rate of LNM was inversely associated with age, and 55 years was the cutoff age, which was an independent risk factor for LNM. Moreover, when we analyzed by gender again, the difference was more obvious in females. The rate of LNM was obviously lower in patients ≥55 years.Therefore, we recommend that more attention should be paid to patients under 55 years old, especially women, who are more susceptible to LNM. Tumor size has been considered as an important predictor of LNM in PTC, but the cutoff value was different. Yan et al. [27] mentioned that the diameter was 0.25 cm, while Ahn et al. [14] found that size 1 cm was an independent risk factor for CLNM. Some studies have shown a positive correlation between LNM and primary tumor size. The incidence of LNM increased with the increase of tumor size [9,13,27]. We also found that the diameter of 1 cm was a critical factor. Among males, this was the only independent factor. However in females, the rate of patients with tumor diameter <1 cm in LNM was obviously declined. So females with tumor diameter <1 cm may not be susceptible to LNM. Multifocality and ETE were the risk factors for

Table 6A. Analysis reproductive factors associated with LNM of female PTC. (A-B) A.Analysis reproductive factors associated with LNM of 1607 female PTC.

Variab les	LNM(+) (n,%)	LNM(-) (n,%)	t/x2 value	P-Value
Total patients	779(48.5%)	828(51.5%)		
Age of menarche (mean±MD, years)	14.24±1.59	14.42±1.52	2.382	0.017[a,b]
Menopausal status			26.303	<0.001[a]
Premenopausal	528(53.5%)	458(46.5%)		
Postmenopausal	251(40.4%)	370(59.6%)		
Type of menopausal		0.324	<0.001[a]	
Nature	33(43.4%)	43(56.6%)		
Artificial	218(40%)	327(60%)		
Age of menopause(mean ± SD, years)	48.80±4.42	48.9±4.31	0.465	0.642[b]
Number of full-term pregnancies			31.081	<0.001[a]
0	97(71.3%)	39(28.7%)		
1	316(46.1%)	369(53.9%)		
2	290(46.5%)	333(53.5%)		
>3	76(46.6%)	87(53.4%)		
Number of Pregnancies			33.840	<0.001[a]
0	95(74.2%)	33(25.8%)		
1[a]	237(47.5%)	262(52.5%)	0.125[ab]	0.723[ab]
2[b]	274(48.9%)	290(51.4%)	4.722[bc]	0.030[bc,a]
>3[c]	173(41.6%)	243(58.4%)		
Abortion History			47.188	<0.001[a]
Yes	160(40.3%)	237(59.7%)		
No	524(48.3%)	560(51.7%)		
Unpregnancy	95(75.4%)	31(24.6%)		

All Calculated using two-tailed student t test.
LNM+:lymph nodes metastasis positive, LNM-:lymph nodes metastasis negative
[a] Statistically significant ($p < 0.05$).
[b] Calculated using t- test, others calculated using chi-square test.
[ab] Number of Pregnancies 1 time vs Number of Pregnancies 2 times
[bc] Number of Pregnancies 2 times vs Number of Pregnancies >3 times.

LNM in numerous studies [23,24,27]. However, the role of bilaterality is controversial [9,23,24]. Our study showed that bilaterality and ETE were independent risk factors of LNM, especially in females, but not in males. The rate of ETE in women was 21.4%, which was obviously higher than in men (14.2%). However, only 65% of ETE was susceptible to LNM in women, which was up to 81.3% in men. The results indicated that there may be some factors in women that lower the role of ETE. Our results showed that multifocality is not an independent factor. The possible reason is multifocality increases the possibility of bilaterality and further increases the probability of LNM. For male patients of any age, female patients aged <55 years, tumor diameter >1 cm, or male patients with bilaterality or ETE, it is recommended to monitor the lymph nodes and perform preventive neck dissection if necessary.

In addition to the above common factors, we also conducted individual factor analysis for gender characteristics. For males, HT, T2DM, smoking history and alcohol history were analyzed, but none of these factors had any influence on LNM. However, for females, in addition to tumor diameter, bilaterality and extrathyroid extension, we found that T2DM history, menopausal history, reproductive history, and abortion history were negatively correlated with LNM, the last three of which were also independent factors. The role of menopause, reproductive history, and abortion history in LNM has been rarely reported before.

Based on epidemiological data, hormonal and reproductive factors (including age at menarche, age at menopause, age at birth or age at the end of life) were thought to play a role in determining or regulating the risk of thyroid cancer [28]. Although previous studies [29–31] showed no significant correlation between hormones, reproductive factors and the occurrence of thyroid cancer. However, recent studies [32–36] have shown that hormones and reproductive factors were significantly associated with the risk of thyroid cancer. Among them, Caini S et al. [32] found that menopausal women have a reduced risk of thyroid cancer. Wang et al. [33] found that women who had their first pregnancy later in life or who had breastfed longer were less likely to develop thyroid cancer. Sungwalee et al. [34] found significantly higher rates among women with early menarche, non-pregnant women and oral contraceptive users. In this study, hormones and reproductive factors were also found to play an important role in PTC LNM. In postmenopausal women, LNM decreased significantly. This may explain the reason why the rate of LNM was obviously lowered in patients aged ≥55 years. The influence of pregnancy and full-term pregnancies on LNM of PTC is obvious. Among women with no full-term pregnancy, the lymph nodes metastasis rate of PTC was 71.3%, which was similar to that of men (69.7%). However, in women who had the reproductive history, the rate of LNM was significantly decreased, which had no significant correlation with the number of births. The rate of LNM was 74.2% in non-pregnant his-

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Table 6B. Analysis reproductive factors associated with LNM of 20 to 49 years old female.

Variables	LNM(+) (n,%)	LNM(-) (n,%)	t/x2 value	P-Value
Total patients	512(53.9%)	438(46.1%)	–	–
Age of menarche (mean±MD, years)	14.01±1.30	14.07±1.34	0.747	0.455[b]
Age of menarche				
<14 years	389(54.9%)	320(45.1%)	1.061	0.303
>14 years	123(51.0%)	118(49.0%)		
Menopausal status			0.761	0.383
Premenopausal	486(54.2%)	410(45.8%)		
Postmenopausal	26(48.1%)	28(51.9%)		
Type of menopausal			–	0.135[c]
Nature	20(43.5%)	26(56.5%)		
Artificial	6(75.0%)	2(25.0%)		
Age of menopause(mean ± SD, years)	44.12±4.04	44.46±3.83	0.325	0.746[b]
Number of full-term pregnancies			23.186	<0.001[a]
0[a]	86(69.9%)	37(30.1%)	14.489[ab]	<0.001[ab,a]
1[b]	230(50.7%)	224(49.3%)	0.547[bc]	0.460[bc]
2[c]	176(53.3%)	154(46.7%)	0.710[cd]	0.399[cd]
>3[d]	20(46.5%)	23(53.5%)		
Number of Pregnancies			15.606	0.001[a]
0[e]	85(72.6%)	32(27.4%)	15.348[ef]	<0.001[ef,a]
1[f]	178(51.9%)	165(48.1%)	0.902[fg]	0.342[fg]
2[g]	162(55.7%)	129(44.3%)	6.754[gh]	0.009[gh,A]
>3[h]	87(43.7%)	112(56.3%)		
Abortion History			25.558	<0.001[A]
Yes	106(44.7%)	131(55.3%)		
No	321(53.8%)	276(46.2%)		
Unpregnancy	85(73.3%)	31(26.7%)		

All Calculated using two-tailed student t test.
LNM+:lymph nodes metastasis positive, LNM-:lymph nodes metastasis negative
[a] Statistically significant ($p < 0.05$).
[b] Calculated using t- test, others calculated using chi-square test.C Calculated using Fisher exact test.
[ab] Number of full-term Pregnancies 0 time vs Number of full-term Pregnancies 1 time
[bc] Number of full-term Pregnancies 1 time vs Number of full-term Pregnancies 2 times
[cd] Number of full-term Pregnancies 2 times vs Number of full-term Pregnancies >3 times.
[ef] Number of Pregnancies 0 time vs Number of Pregnancies 1 time
[fg] Number of Pregnancies 1 time vs Number of Pregnancies 2 times
[gh] Number of Pregnancies 2 times vs Number of Pregnancies >3 times.

tory women, but the rate was significantly decreased in pregnant history women. The same results were observed when we further analyzed women of appropriate child-bearing age. Moreover, irrespective of age, the rate of LNM was obviously lowered in females with ≥3 pregnancies. Interestingly, women who had abortion history had a greater decrease in LNM than women who had not. This may be because more abortions also mean more pregnancies. However, the influence of menarche age had some difference between all women and women of child-bearing age. For women of childbearing age, artificial menopause resulted in higher LNM. For all of those results, we acknowledged that PTC was an estrogen-dependent tumor [32,36]. Prolonged exposure to estrogen increased the risk of thyroid cancer [30,34]. And then, Magri et al. [37] have confirmed that estrogen is significantly correlated with T stage. Vannucchi et al. [38] also found that tumors expressing ER and PR had a higher prevalence of local metastasis and more aggressive behavior. The studies verified that estrogen promoted thyroid cancer cell growth through estrogen receptor α (ER-A) and β (ER-B) mediated pathways [37,39]. The effect of this action depended on the equilibrium between ERα and ERβ [37]. Among the ERα-negative expression PTC, lower ERβ_1 expression was associated with disease progression [40]. So we thought the abnormal expression of ER and PR was the crucial key. In addition, the biological response of estrogen to PTC in female was different from the male-mediated pathway [41]. That may be related with some proteins which can inhibite the development of tumor in female. This difference may also contribute to the difference in the incidence of PTC and LNM between men and women.

The causes of LNM are varied, and the gender differences in LNM are obvious. According to these study, the main reasons for these differences were hormonal, reproductive factors and abnormalities in related protein pathways. Based on these findings, we consider that in the female this special group, estrogen occurrence, influence and action system is more complex. The total estrogen exposure time and the level of estrogen may be two crucial factors of LNM for female in clinic. The level of women are abnormal during artificial

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menopause, and the level is obviously lowered after delivering a baby and after natural menopause. Many reproductive factors will lead to shorter estrogen exposure time and lower the estrogen level, which weakened the positive and synergistic effects of estrogen on promoting the development of thyroid cancer. These may be the reasons why the rate of LNM in females declined with higher ETE and longer diameter. More basic research is needed to clarify this issue.

However, these series results refer to a surprisingly small sized lesions and should be taken with caution regarding this fact. There were still some limitations in this paper. First of all, this was a single-center retrospective study. Secondly, lymph node metastasis had not been further defined, such as the combination of central and lateral neck lymph node metastasis. Thirdly, comprehensive assessment was not carried out in conjunction with prognosis. Based on the above contents, our center had already been actively summarizing the data and conducting further analysis and research, and the results would continue to be followed up.

5. Conclusion

For male patients with tumor diameter >1 cm and suspicious nodules indicated by preoperative ultrasound, vigilance should be increased, central lymph node dissection should be performed, and lateral neck dissection should be performed as appropriate. Meanwhile, for female patients, due to the influence of sex hormones and reproductive factors, although the invasion is high, the rate of lymph node metastasis is significantly reduced. For women of childbearing age who were not pregnant and did not have children, it is recommended to monitor and take a positive attitude towards their lymph nodes.

Authors' contributions

(I) Conception and design: Ping Shi, Yanzhao Wu; (II) Administrative support: Shanghua Jing, Huijing Shi; (III) Provision of study materials or patients: Shanghua Jing, Yanzhao Wu, Huijing Shi, Junjian Song, Zhijun Zhao; (IV) Collection and assembly of data: Ping Shi, Dongqiang Yang; (V) Data analysis and interpretation: Ping Shi, Dongqiang Yang, Yan Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Data availability statement

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request

Statement of ethics

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of The Fourth Hospital of Hebei Medical University and Hebei Tumor Hospital (2021KS028). All participants fully understood the experimental protocol and signed informed consent forms. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Patient consent for publication is not applicable.

Declaration of Competing Interest

The authors have no conflicts of interest to declare. The authors do not have financial interests or conflicts to report.

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