Research Article

Clinicopathological Characteristics and Prognosis of Papillary Thyroid Carcinoma in Naturally Menopausal Women with Various Durations of Premenarche, Reproductive Periods, and Postmenopausal Stages

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Background. Papillary thyroid cancer (PTC) exhibits a higher incidence in women. Due to various ages at menarche and menopause, estrogen levels vary, which may account for the differences in the occurrence, development, and prognosis of female patients with PTC. Objective. The aim of this study was to investigate the association between various durations in different estrogen levels and PTC and to provide important information to guide clinical management and treatment of this disease.

Methods. First, we selected naturally menopausal female study subjects diagnosed with PTC at Zhejiang Cancer Hospital from 2007 to 2012 and then compared the differences in clinicopathological characteristics and prognosis among subjects with various lengths of premenarche, reproductive periods, and postmenopausal stages.

Results. We found that all patients showed a significantly higher incidence of tumor multicentricity and intrathyroidal dissemination as the time after menopause increased. Additionally, women with shorter (<30) or longer (>38) reproductive lives had increased recurrence rates of PTC.

Conclusions. In this study, we did not find any relationship of self-reported menarche and menopausal ages with the prognosis of PTC patients. More importantly, natural postmenopausal PTC patients with shorter or longer reproductive life, compared to the normal groups, had a higher rate of cancer recurrence and the patients with these characteristics could be recommended a more aggressive surgical treatment.

1. Introduction

Thyroid cancer is a more predominant malignancy in women than in men [1], which is likely due to the more variable hormonal environments in women than in men [2]. Additionally, the incidence of thyroid cancer is equal in prepubertal girls and boys and increases in females by up to 14 times after the onset of menstruation [3]. Jonklaas et al. [4] found that postmenopausal women diagnosed with papillary thyroid cancer (PTC) had worse outcomes than premenopausal women and suggested that menopause-associated hormonal alterations may be the cause of this outcome, which was supported by other studies [5, 6]. Some studies have focused on the role of estrogen receptors and estradiol in PTC, which have suggested that estradiol can stimulate the proliferation of PTC cells [7–9]. These data showed that the occurrence, development, and prognosis of PTC are significantly influenced by the levels of sex hormones during a woman’s life.

Understanding the relationship between menstrual characteristics and PTC could be beneficial for better surgical management and treatment of PTC patients. Menarche and menopause are two peculiar aspects of a woman’s menstrual characteristics. Therefore, a woman’s lifespan can be divided...
into three stages (the premenarche stage, reproductive period, and postmenopausal stage), and each stage can be divided into three parts, depending on standard references. The most important indicator is the length of each stage, measured in years, which is a measure of exposure to estrogen. Most studies have addressed the relationship between PTC and the common parameters of menstrual characteristics such as age at menarche or menopause [10–12], but few studies have evaluated varying durations of estrogen exposure, especially among female Chinese patients.

In this retrospective study, we enrolled patients who had undergone natural menopause among 3790 female patients diagnosed with PTC at Zhejiang Cancer Hospital between 2007 and 2012. We investigated differences in the clinico-pathological characteristics and prognosis among female patients with various estrogen exposures to provide important information to guide clinical management and treatment.

2. Methods

2.1. Ethics Statement. All participants provided written informed consent, and the study protocol was approved by the Ethics Committee at Zhejiang Cancer Hospital.

2.2. Study Population. Between January 2007 and December 2012, 3790 female patients underwent initial treatment for PTC in the Department of Head and Neck Surgery of Zhejiang Cancer Hospital. In total, 429 patients who experienced natural menopause, underwent primary surgical treatment in our hospital, and were diagnosed with PTC were enrolled in this study. The operation was performed by a surgical team, and at least two pathologists reviewed the pathological findings. Individuals who had previous and recent histories of neck surgeries, artificial menopause, hysterectomy, ovariectomy, and drug intake for a long period of time were excluded, as these factors can influence hormone levels. Patients with diseases affecting natural menstruation (e.g., oophoroma or chronic diseases such as tuberculosis and malignancy) were also excluded from this study.

2.3. Menstrual Variables. The length of premenarche was established by the age at menarche. The age at the time of each patient’s first period was considered the age at menarche; the time from menarche to menopause was defined as a woman’s natural reproductive span (also called length of reproductive life), and the number of years since menopause was calculated from the age at menopause to the age at diagnosis. The judgment of menopausal status depended on the definition of the World Health Organization, which specifies cessation of menstruation for at least 12 months. All information about menstruation was reconfirmed by telephone.

Each stage was divided into three portions; the length of premenarche and the reproductive span was divided based on the Shanghai Women’s Health Study, which is a large, population-based cohort study conducted in China. No standard was provided for the number of years since menopause, and the criteria for the three grades of the other categories were as follows: below the 25th percentile, between the 25th and 75th percentiles, and above the 75th percentile of the total population.

Based on this information, the menstrual variable categories used as the reference groups in our analyses were as follows: aged 14–16 years at menarche, 30–38 reproductive years, and 4–14 years after menopause.

2.4. Outcome Definition. The evaluation of clinico-pathological features was performed by professional pathologists. The tumor/node/metasitasis (TNM) classification was estimated according to the 2010 AJCC criteria. Follow-up was performed after treatment was completed in our hospital and before December 31, 2015. Clinical examinations, blood parameter tests, and ultrasonography (USG) were performed in all patients every 3 months during the first year and every 6 months during the second year. A chest X-ray or CT scan was performed once each year. Recurrence was confirmed by FNAB and reoperation if any suspicion of a malignancy was found by imaging. Information on the disease-specific survival of patients or patients who did not undergo subsequent treatment in our hospital was confirmed by phone contact or letters.

2.5. Measurement of Selected Potential Confounders. Information regarding baseline conditions was collected from the medical record data in our hospital and included age (years), TNM stages (I, II, III, and IV), tumor size (≤1 cm, >1 cm), multicentricity (solitary, multiple), bilaterality (unilateral, bilateral), intrathyroidal dissemination (present, absent), thyroid nodular goiter (present, absent), Hashimoto’s thyroiditis (present, absent), operation on primary tumor (total thyroidectomy, subtotal thyroidectomy), and lymph node dissection (not done, central node dissection, and total node dissection), iodine radiotherapy (done, not done), and time of pregnancy (age at first birth, age at last birth).

2.6. Statistical Analysis. The chi-square test and Fisher’s exact test were used to compare clinico-pathological characteristics among the subgroups, and the Kaplan-Meier method and log-rank test were used to analyze the time-dependent variables. Prognostic factors that were significant in the univariate analysis were further evaluated using the multivariate Cox model test for independent significance. These analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). P values < 0.05 were considered significant.

3. Results

Table 1 shows the characteristics of the study population. At the time of diagnosis, the age of our study subjects ranged from 44 to 80 years, with a median of 57 years. The median premenarche period, length of reproductive span, and number of years since menopause were 15, 35, and 8 years, respectively. The age at first birth and last birth of our study subjects ranged from 16 to 35 years and from 18 to 44 years, with a median of 24 and 30 years. The follow-up periods ranged from 36 to 107 months (median, 54 months). The incidences of cancer recurrence and diseases were 4.0% and 0.6%, respectively. Additionally, the recurrence rates of metastasis to the cervical lymph
age increased, age at last birth increased (result, we further analyzed the clinicopathological features of patients died of the disease in our study. Based on this postmenopause period (patients in the three stages of the reproductive span and the following were found in the three stages of postmenopause. As the postmenopausal period increased, age at first birth, the proportion of patients with multiple nodules, intrathyroidal dissemination, and the recurrence of diseases also increased \( P_{\text{trend}} < 0.05 \). Significant differences related to multicentricity, intrathyroidal dissemination, and recurrence of disease were found in the three stages of postmenopause. As the postmenopausal period increased, age at first birth, the proportion of patients with multiple nodules, intrathyroidal dissemination, and the recurrence of diseases also increased \( P_{\text{trend}} < 0.05 \). As the length of reproductive life increased, age at last birth increased \( P_{\text{trend}} < 0.05 \). Few patients died of the disease in our study. Based on this result, we further analyzed the clinicopathological features of PTMC patients in three menstrual stages. The differences in age at first birth, age at last birth, intrathyroidal dissemination, and recurrence among subjects in the three postmenopausal stages were not significant, and the other outcomes were similar to those of the PTC patients.

Table 4 represents univariate and multivariable-adjusted HRs of the recurrence according to the multicentricity, intrathyroidal dissemination, age at menarche, length of reproductive life, years after menopause, age at first birth, and age at last birth. A shorter (<30 years) or longer (>38 years) reproductive span was associated with recurrence in PTC patients. Compared to the reference group, the HRs and 95% CIs were 3.4 (1.0, 11.3) for women with a span of <30 years and 4.6 (1.5, 13.9) for women with a span of >38 years in the univariate model. The HRs and 95% CIs were 4.2 (1.2, 13.9) for women with a span of <30 years and 5.6 (1.7, 17.2) for women with a span of >38 years in the multivariable model. In PTMC patients, compared to the reference group, the HRs and 95% CIs were 4.5 (1.2, 16.9) for women with an older age at menarche and 4.4 (1.1, 18.7) for a span of <30 years in the univariate model, and the HRs and 95% CIs were 4.5 (1.2, 16.9) for women with an older age at menarche and 4.3 (0.8, 23.1) for a span of <30 years in the multivariable model. The age at menarche and length of reproductive span were not significant independent factors \( P > 0.05 \) in PTMC patients. The reproductive span \( (P = 0.00) \) was the independent factor that influenced the recurrence of the disease, and no other factors were found to be significant in PTC patients in the current study. The interaction between menstrual stages and other factors in PTC patients was not significant (data not shown).

The Kaplan-Meier survival analysis revealed that compared to the reference values, a significant difference in recurrence existed \((10.3\% \text{ versus } 2.4\% \text{ versus } 9.4\% ; P < 0.05; \text{Figure 1})\), and women with a shorter (<30 years) or longer (>38 years) reproductive span had a higher risk of PTC recurrence.

### 4. Discussion

In this study, all patients showed a significantly higher incidence of tumor multicentricity and intrathyroidal dissemination with increasing time after menopause. Additionally, our results demonstrated that the reproductive span length was an independent factor that influenced the prognosis of PTC. Women with shorter or longer reproductive spans had a higher risk of recurrence than the reference group.

The incidence of tumor multifocality and intrathyroidal dissemination, which represented invasive behavior by a tumor and led to a worse prognosis and the need for more aggressive treatments than unilateral tumors [13], was increased as the number of years after menopause increased in our study. However, we found that they were not the factors that influenced the prognosis of PTC.

It was controversial whether there were positive associations between thyroid cancer and time of pregnancy. Memon et al. [14] found increasing tendency of risk with increasing age at last pregnancy; on the other hand, Kabat et al. [12] found that women who had a first live birth with age between 20 and 24 years also had a significant risk of papillary thyroid cancer. Actually, according to many published reports [12, 14–16] along with our present study, we did not get any significant positive associations between time of pregnancy and PTC.

Although many studies [17–19] have suggested that older age, tumor size, and advanced stage are risk factors of cancer recurrence, we found only a positive association of reproductive span with the prognosis of PTC in our study, and we did not find other factors that influence the prognosis of PTC.

Although epidemiological and experimental studies have suggested a potential association between the development of thyroid malignancies and estrogen, this conclusion is not
Table 2: Clinicopathological characteristics, treatment modalities, and outcome characteristics of PTC patients at various menstrual stages.

| Variables                                      | Total (n = 429) | Total (n = 429) | Total (n = 429) | P* for trend |
|------------------------------------------------|----------------|----------------|----------------|--------------|
|                                                | Group 1 (n = 37): <14 | Group 2 (n = 291): 14–16 | Group 3 (n = 101): >16 |                |
| Age at menarche, years                         |                |                |                |              |
| (mean, range)                                  |                |                |                |              |
|                                                | 55.8 (37–78) 58.6 (42–80) 56.9 (47–74) | NS 54.2 (37–74) 57.9 (46–78) 60.7 (54–80) | 0.00 51.8 (46–70) 56.3 (46–78) 66.7 (46–77) | 0.00 |
| Length of reproductive life, years             |                |                |                |              |
| (mean, range)                                  |                |                |                |              |
|                                                | 24.1 (16–33) 24.3 (16–35) 25.1 (18–35) | NS 23.0 (16–34) 24.6 (16–35) 24.8 (16–34) | NS 23.4 (16–35) 24.8 (16–35) 24.7 (16–35) | 0.04 |
| Years after menopause, years                   |                |                |                |              |
| (mean, range)                                  |                |                |                |              |
|                                                | 29.2 (18–36) 29.8 (17–44) 30.7 (21–43) | NS 27.9 (17–39) 30.2 (17–44) 29.8 (18–42) | 0.03 29.1 (17–41) 30.1 (18–43) 30.5 (17–44) | NS |
| Maximal tumor diameter                         |                |                |                |              |
| ≤1 (cm)                                        | 27 194 70 | NS 26 229 36 | NS 68 156 67 | NS |
| >1 (cm)                                        | 10 97 31 | NS 13 108 17 | NS 26 69 43 | NS |
| Multicentricity                                |                |                |                |              |
| Solitary                                       | 23 199 65 | NS 23 230 34 | NS 69 154 64 | 0.02 |
| Multiple                                       | 14 92 36 | NS 16 107 19 | NS 25 71 46 | NS |
| Bilaterality                                   |                |                |                |              |
| Unilateral                                     | 29 225 75 | NS 30 262 37 | NS 77 172 80 | NS |
| Bilateral                                      | 8 66 26 | NS 9 75 16 | NS 17 53 30 | NS |
| Extrathyroidal extension                       |                |                |                |              |
| Present                                        | 9 127 42 | NS 13 149 16 | NS 34 92 52 | NS |
| Absent                                         | 28 164 59 | NS 26 188 37 | NS 60 133 58 | NS |
| Intrathyroidal dissemination                   |                |                |                |              |
| Present                                        | 2 15 6 | NS 5 15 3 | NS 2 10 11 | 0.01 |
| Absent                                         | 35 276 95 | NS 34 322 50 | NS 92 215 99 | NS |
| Thyroid nodular goiter                         |                |                |                |              |
| Present                                        | 22 173 58 | NS 17 205 31 | NS 54 136 63 | NS |
| Absent                                         | 15 118 43 | NS 22 132 22 | NS 40 89 47 | NS |
| Hashimoto’s thyroiditis                        |                |                |                |              |
| Present                                        | 3 9 6 | NS 2 15 1 | NS 7 10 1 | NS |
| Absent                                         | 34 282 95 | NS 37 322 52 | NS 87 215 109 | NS |
| TNM stage                                      |                |                |                |              |
| I                                              | 23 173 59 | NS 27 198 30 | NS 58 135 62 | NS |
| II                                             | 1 10 2 | NS 1 9 2 | NS 2 6 4 | NS |
| III                                            | 8 57 18 | NS 8 66 10 | NS 17 45 22 | NS |
| IV                                             | 5 51 22 | NS 3 64 11 | NS 17 39 22 | NS |
| Variables                      | Total (n = 429) | Total (n = 429) | Total (n = 429) | Total (n = 429) |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
|                               | Age at menarche, years | Length of reproductive life, years | Years after menopause, years | P* for trend |
| T staging                     |                 |                 |                 |                 |
| T1                            | 29 (n = 37): <14 | 32 (n = 39): <30 | 79 (n = 94): <4 | NS |
| T2                            | 2 (n = 229): 14–16 | 1 (n = 337): 30–38 | 6 (n = 225): 4–14 | NS |
| T3                            | 4 (n = 101): >16 | 6 (n = 53): >38 | 9 (n = 110): >14 | NS |
| T4                            | 2 (n = 37): <14 | 0 (n = 39): <30 | 0 (n = 94): <4 | NS |
| N staging                     |                 |                 |                 |                 |
| N0/Nx                         | 25 (n = 37): <14 | 28 (n = 39): <30 | 63 (n = 94): <4 | NS |
| N1a                           | 9 (n = 229): 14–16 | 7 (n = 337): 30–38 | 16 (n = 225): 4–14 | NS |
| N1b                           | 3 (n = 101): >16 | 4 (n = 53): >38 | 15 (n = 110): >14 | NS |
| M staging                     |                 |                 |                 |                 |
| M0                            | 37 (n = 37): <14 | 39 (n = 39): <30 | 93 (n = 94): <4 | NS |
| M1                            | 0 (n = 229): 14–16 | 0 (n = 337): 30–38 | 1 (n = 225): 4–14 | NS |
| Operation of primary tumor    |                 |                 |                 |                 |
| Total thyroidectomy           | 11 (n = 37): <14 | 18 (n = 39): <30 | 32 (n = 94): <4 | NS |
| Subtotal thyroidectomy        | 26 (n = 229): 14–16 | 21 (n = 337): 30–38 | 62 (n = 225): 4–14 | NS |
| Lymph node dissection         |                 |                 |                 |                 |
| Not done                      | 3 (n = 37): <14 | 6 (n = 39): <30 | 12 (n = 94): <4 | NS |
| Central node dissection       | 27 (n = 229): 14–16 | 29 (n = 337): 30–38 | 63 (n = 225): 4–14 | NS |
| Total node dissection         | 7 (n = 101): >16 | 4 (n = 53): >38 | 19 (n = 110): >14 | NS |
| Iodine radiotherapy           |                 |                 |                 |                 |
| Done                          | 6 (n = 37): <14 | 5 (n = 39): <30 | 12 (n = 94): <4 | NS |
| Not done                      | 31 (n = 229): 14–16 | 34 (n = 337): 30–38 | 82 (n = 225): 4–14 | NS |
| Recurrence of disease         |                 |                 |                 |                 |
| Present                       | 2 (n = 37): <14 | 4 (n = 39): <30 | 0 (n = 94): <4 | 0.02 |
| Absent                        | 35 (n = 229): 14–16 | 35 (n = 337): 30–38 | 94 (n = 225): 4–14 | 0.02 |
| Disease-specific survival (DSS) |                |                 |                 |                 |
| Dead                          | 1 (n = 37): <14 | 1 (n = 39): <30 | 0 (n = 94): <4 | NS |
| Alive                         | 36 (n = 229): 14–16 | 38 (n = 337): 30–38 | 94 (n = 225): 4–14 | NS |

*ANOVA for continuous variables and chi-square test for categorical variables. NS: not significant. Bold values are less than or close to 0.05.
Table 3: Clinicopathological characteristics, treatment modalities, and outcome characteristics of PTMC patients at various menstrual stages.

| Variables                              | Total (n = 291) | Total (n = 291) | Total (n = 291) |
|----------------------------------------|-----------------|-----------------|-----------------|
|                                        | Group 1 (n = 27) | Group 2 (n = 194) | Group 3 (n = 70) | P* for trend |
|                                        | Group 1 (n = 26) | Group 2 (n = 229) | Group 3 (n = 36) |               |
|                                        | Group 1 (n = 68) | Group 2 (n = 156) | Group 3 (n = 67) |               |
|                                        |                 |                 |                 |               |
| Age (mean, range)                      | 54.9 (37–68)    | 57.9 (44–77)    | 56.8 (45–74)    | NS            |
|                                        | Group 1 < 14    | Group 2 14–16   | Group 3 >16     |               |
|                                        | Group 1 < 30    | Group 2 30–38   | Group 3 >38     | 0.02          |
|                                        | Group 1 4–63    | Group 2 37–68   | Group 3 55–77   | 0.00          |
| Age at menarche, years                 | 24.5 (16–33)    | 24.1 (16–35)    | 24.6 (18–35)    | NS            |
| Length of menstrual life, years        | 22.8 (16–32)    | 24.4 (16–35)    | 24.8 (16–34)    | NS            |
| Years after menopause, years           | 23.3 (16–35)    | 24.6 (16–35)    | 24.7 (16–35)    | NS            |
|                                        | 27.2 (17–37)    | 29.8 (17–43)    | 30.2 (18–42)    | NS            |
|                                        | 29.0 (17–40)    | 29.6 (18–43)    | 30.3 (17–41)    | NS            |
| Multicentricity                        | 17              | 140             | 47              | NS            |
|                                        | 14              | 165             | 25              | NS            |
|                                        | 52              | 110             | 42              | 0.02          |
| Bilaterality                           | 22              | 160             | 55              | NS            |
|                                        | 21              | 190             | 26              | NS            |
|                                        | 58              | 126             | 53              | NS            |
| Extrathyroidal extension               | 7               | 52              | 21              | NS            |
|                                        | 20              | 142             | 49              | NS            |
|                                        | 58              | 126             | 53              | NS            |
| Intrathyroidal dissemination           | 1               | 4               | 2               | NS            |
|                                        | 26              | 190             | 68              | NS            |
|                                        | 5              | 69              | 6               | NS            |
|                                        | 18              | 45              | 17              | NS            |
| Thyroid nodular goiter                 | 19              | 125             | 44              | NS            |
|                                        | 8               | 69              | 26              | NS            |
|                                        | 46              | 99              | 43              | NS            |
| Hashimoto’s thyroiditis                | 1               | 8               | 4               | NS            |
|                                        | 26              | 186             | 66              | NS            |
|                                        | 5              | 7               | 1               | NS            |
| TNM stage                              | I               | 20              | 154             | NS            |
|                                        | II              | 0               | 0               | NS            |
|                                        | III             | 7               | 28              | NS            |
|                                        | IV              | 0               | 12              | NS            |
|                                        | 20              | 154             | 49              | NS            |
|                                        | 0               | 0               | 0               | NS            |
|                                        | 3               | 39              | 6               | NS            |
|                                        | 5               | 16              | 3               | NS            |
|                                        | 22              | 174             | 27              | NS            |
|                                        | 0               | 0               | 0               | NS            |
|                                        | 3               | 39              | 6               | NS            |
|                                        | 1               | 16              | 3               | NS            |
|                                        | 53              | 114             | 56              | NS            |
|                                        | 0               | 0               | 0               | NS            |
|                                        | 10              | 32              | 6               | NS            |
| T staging                              | T1              | 26              | 187             | NS            |
|                                        | T2              | 0               | 0               | NS            |
|                                        | T3              | 1               | 6               | NS            |
|                                        | T4              | 0               | 1               | NS            |
|                                        | 26              | 221             | 36              | NS            |
|                                        | 0               | 0               | 0               | NS            |
|                                        | 0               | 0               | 0               | NS            |
|                                        | 0               | 0               | 0               | NS            |
|                                        | 0               | 0               | 0               | NS            |
Table 3: Continued.

| Variables                           | Total (n = 291) | Group 1 (n = 27): <14 | Group 2 (n = 194): 14–16 | Group 3 (n = 70): >16 | P* for trend | Total (n = 291) | Group 1 (n = 26): <30 | Group 2 (n = 229): 30–38 | Group 3 (n = 36): >38 | P* for trend | Total (n = 291) | Group 1 (n = 68): <4 | Group 2 (n = 156): 4–14 | Group 3 (n = 67): >14 | P* for trend |
|-------------------------------------|----------------|------------------------|---------------------------|----------------------|--------------|----------------|------------------------|------------------------|----------------------|--------------|----------------|------------------------|------------------------|------------------------|--------------|
| **N staging**                       |                |                        |                           |                      |              |                |                        |                        |                      |              |                |                        |                        |                        |              |
| N0/Nx                               | 20             | 157                    | 50                        | NS                   |              | 54             | 117                    | 56                     | NS                   |              | 177            | 28                     | 31                      | 6                        | NS           |
| N1a                                 | 7              | 27                     | 13                        | NS                   |              | 3              | 37                     | 7                      | NS                   |              | 37            | 7                      | 31                      | 6                        | NS           |
| N1b                                 | 0              | 10                     | 7                         | NS                   |              | 1              | 15                     | 1                      | NS                   |              | 4              | 8                      | 5                        | NS          |
| **M staging**                       |                |                        |                           |                      |              |                |                        |                        |                      |              |                |                        |                        |                        |              |
| M0                                  | 27             | 193                    | 70                        | NS                   |              | 26             | 229                    | 35                     | NS                   |              | 68             | 155                    | 67                      | NS          |
| M1                                  | 0              | 1                      | 0                         | NS                   |              | 0              | 0                      | 1                      | NS                   |              | 0              | 1                      | 0                        | NS          |
| **Operation of primary tumor**      |                |                        |                           |                      |              |                |                        |                        |                      |              |                |                        |                        |                        |              |
| Total thyroidectomy                 | 6              | 54                     | 25                        | NS                   |              | 10             | 64                     | 11                     | NS                   |              | 23             | 42                     | 47                      | NS          |
| Subtotal thyroidectomy              | 21             | 140                    | 45                        | NS                   |              | 16             | 165                    | 25                     | NS                   |              | 45             | 114                    | 20                      | NS          |
| **Lymph node dissection**           |                |                        |                           |                      |              |                |                        |                        |                      |              |                |                        |                        |                        |              |
| Not done                            | 2              | 31                     | 9                         | NS                   |              | 4              | 34                     | 4                      | NS                   |              | 12             | 20                     | 10                      | NS          |
| Central node dissection             | 22             | 148                    | 53                        | NS                   |              | 21             | 173                    | 29                     | NS                   |              | 51             | 122                    | 50                      | NS          |
| Total node dissection               | 3              | 15                     | 8                         | NS                   |              | 1              | 22                     | 3                      | NS                   |              | 5              | 14                     | 7                       | NS          |
| **Iodine radiotherapy**             |                |                        |                           |                      |              |                |                        |                        |                      |              |                |                        |                        |                        |              |
| Done                                | 2              | 7                      | 2                         | NS                   |              | 1              | 8                      | 2                      | NS                   |              | 2              | 6                      | 3                       | NS          |
| Not done                            | 25             | 187                    | 68                        | NS                   |              | 25             | 221                    | 34                     | NS                   |              | 66             | 150                    | 64                      | NS          |
| **Recurrence of disease**           |                |                        |                           |                      |              |                |                        |                        |                      |              |                |                        |                        |                        |              |
| Present                             | 1              | 5                      | 4                         | NS                   |              | 3              | 5                      | 2                      | NS                   |              | 0              | 8                      | 2                       | NS          |
| Absent                              | 26             | 189                    | 66                        | NS                   |              | 23             | 224                    | 34                     | NS                   |              | 68             | 148                    | 65                      | NS          |
| **Disease-specific survival (DSS)** |                |                        |                           |                      |              |                |                        |                        |                      |              |                |                        |                        |                        |              |
| Dead                                | 0              | 1                      | 0                         | NS                   |              | 1              | 0                      | 0                      | NS                   |              | 0              | 0                      | 1                       | NS          |
| Alive                               | 27             | 193                    | 70                        | NS                   |              | 25             | 229                    | 36                     | NS                   |              | 68             | 156                    | 66                      | NS          |

*ANOVA for continuous variables and chi-square test for categorical variables. NS: not significant. Bold values are less than or close to 0.05.
| Variables | PTC | PTMC |
|-----------|-----|------|
| Multicentricity | | |
| Solitary | 11/318 | 9/228 |
| Multiple | 6/94 | 1/53 |
| Univariate | | |
| HR | 1.8 | 0.5–4.9 |
| | 0.7–4.9 | NS |
| | 1.6 | 0.5–5.5 |
| | 0.5–5.5 | NS |
| Multivariate | | |
| HR | 4.9 | NS |
| | 0.5 | NS |
| PP | 1.6 | 0.7–5.5 |
| | 0.5 | 0.7–5.5 |
| trend | NS | NS |
| trend | NS | NS |
| Intrathyroidal dissemination | | |
| Absent | 9/242 | 6/205 |
| Present | 8/170 | 4/76 |
| Univariate | | |
| HR | 1.1 | 0.4–3.1 |
| | 1.1 | 0.4–3.1 |
| Multivariate | | |
| HR | 2.8 | 1.2–6.2 |
| | 1.2–6.2 | NS |
| PP | 0.5 | 0.7–2.8 |
| | 0.7–2.8 | NS |
| trend | NS | NS |
| trend | NS | NS |
| Age at menarche (years) | | |
| <14 | 2/35 | 1/26 |
| 14–16 | 11/280 | 5/189 |
| >16 | 4/97 | 4/66 |
| Univariate | | |
| HR | 1.3 | 0.2–7.6 |
| | 0.2–7.6 | NS |
| Multivariate | | |
| HR | 4.9 | NS |
| | 0.5–4.9 | NS |
| PP | 0.5 | NS |
| trend | 0.5 | NS |
| trend | 0.5 | NS |
| Length of reproductive life (years) | | |
| <30 | 4/35 | 3/23 |
| 30–38 | 8/329 | 5/224 |
| >38 | 5/48 | 4/66 |
| Univariate | | |
| HR | 4.2 | 1.2–13.9 |
| | 1.2–13.9 | 0.00 |
| Multivariate | | |
| HR | 1.4 | 0.7–11.6 |
| | 0.7–11.6 | NS |
| PP | 2.8 | 1.2–6.2 |
| | 1.2–6.2 | NS |
| trend | 2.8 | 1.2–6.2 |
| trend | 1.2–6.2 | NS |
| Years after menopause | | |
| <4 | 0/77 | 0/52 |
| 4–14 | 11/243 | 8/176 |
| >14 | 6/92 | 5/73 |
| Univariate | | |
| HR | 0.3 | 0.0–2.9 |
| | 0.0–2.9 | NS |
| Multivariate | | |
| HR | 0.0 | 0.0–1.8 |
| | 0.0–1.8 | NS |
| PP | 0.0 | 0.0–1.8 |
| | 0.0–1.8 | NS |
| trend | 0.0 | 0.0–1.8 |
| trend | 0.0 | 0.0–1.8 |
| Age at first birth | | |
| <21 | 3/75 | 2/57 |
| 21–28 | 9/241 | 6/161 |
| >28 | 5/96 | 2/63 |
| Univariate | | |
| HR | 1.0 | 0.2–4.2 |
| | 0.2–4.2 | NS |
| Multivariate | | |
| HR | 1.4 | 0.3–6.8 |
| | 0.3–6.8 | NS |
| PP | 1.2 | 0.7–1.9 |
| | 0.7–1.9 | NS |
| Age at last birth | | |
| <26 | 4/91 | 3/70 |
| 26–34 | 9/238 | 5/161 |
| >34 | 4/83 | 2/50 |
| Univariate | | |
| HR | 1.4 | 0.3–5.6 |
| | 0.3–5.6 | NS |
| Multivariate | | |
| HR | 1.2 | 0.2–6.1 |
| | 0.2–6.1 | NS |
| PP | 0.9 | 0.6–1.4 |
| | 0.6–1.4 | NS |
| trend | 0.9 | 0.6–1.4 |
| trend | 0.6–1.4 | NS |

PTC: papillary thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; HR: hazard ratio; CIs: confidence intervals; P: P value for each variable; P trend: P value for the trend. *Adjusted for age, TNM stages, tumor size (except for ††), bilateral cancer, thyroid nodular goiter, Hashimoto’s thyroiditis, surgery for primary tumor, lymph node dissection, multicentricity (except for a), intrathyroidal dissemination (except for b), age at menarche (except for c), length of reproductive span (except for d), years after menopause (except for e), age at first birth (except for f), and age at last birth (except for g).
The main limitation of this study was that the information about menstrual history was self-reported and may be influenced by recall bias. However, previous studies have shown that the recall of ages at menarche and menopause is relatively reliable [36–38]. Additionally, differences were observed between individuals due to environment and lifestyle, and the findings of our study may not be generalizable to other populations. Another limitation was the small number of patients studied; due to the excellent prognosis of PTC patients, the numbers of cases of recurrence or death are particularly small. Therefore, extensive research on a larger population is required to confirm our conclusions and to develop a more precise standard for naturally postmenopausal patients.
5. Conclusion

In this study, we did not find any relationship of self-reported menarche and menopausal ages with the prognosis of PTC patients. More importantly, natural postmenopausal PTC patients with shorter or longer reproductive life, compared to the normal groups, had a higher rate of cancer recurrence, and the patients with these characteristics could be recommended a more aggressive surgical treatment.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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