Secular trends in the prognostic factors for papillary thyroid cancer

Hoonsung Choi[1], Jung Ah Lim[1], Hwa Young Ahn[2], Sun Wook Cho[1,3], Kyu Eun Lee[4],
Kyung Won Kim[1], Ka Hee Yi[1], Myung-Whun Sung[5], Yeo-Kyu Youn[4,6],
June-Key Chung[7], Young Joo Park[1], Do Joon Park[1] and Bo Youn Cho[2]

[1]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea, [2]Department of
Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea, [3]Department of Internal Medicine,
National Medical Center, Seoul, Korea, [4]Department of Surgery and Cancer Research Institute, Seoul National
University College of Medicine, Seoul, Korea, [5]Department of Otorhinolaryngology and Head and Neck Surgery,
Seoul National University College of Medicine, Seoul, Korea, [6]Department of Surgery, National Medical Center,
Seoul, Korea and [7]Department of Nuclear Medicine, Seoul National University College of Medicine, Seoul, Korea

Correspondence
should be addressed to
Y J Park or D J Park
Email
yjparkmd@snu.ac.kr or
djpark@snu.ac.kr

Abstract

Objective: With the recent increasing rates of screening for thyroid cancer, the cancers now tend to be smaller and less aggressive than those that are diagnosed when presented with symptoms, suggesting changes in the clinical validity of conventional prognostic factors for outcomes. We performed the retrospective study to identify the secular trends in the prognostic factors of thyroid cancer.

Methods: We used medical records of 3147 patients diagnosed with papillary thyroid cancer (PTC) at the Seoul National University Hospital Thyroid Cancer Clinic between 1962 and 2009.

Results: During the median 5.1-year follow-up, the overall recurrence rate was 13.3%, and male sex, tumor size, lymph node (LN) involvement, and extrathyroidal extension (ETE) were the significant prognostic factors for recurrence. Thyroid cancer-specific mortality was 1.4%, and the associated prognostic factors were older age, male sex, and LN involvement. For tumor recurrence, the hazard ratio (HR) for male sex decreased from 2.809 (95% CI, 1.497–5.269) in the pre-1989 period to 1.142 (95% CI, 0.736–1.772) in the post-1999 period. The pathologic characteristics, such as tumor size, LN involvement, and ETE, showed similar or increasing HRs over the time periods. For cancer-specific mortality, the HR for male sex decreased from 6.460 (95% CI, 1.714–24.348) in the pre-1990 period to 0.781 (95% CI, 0.083–7.379) in the post-1999 period.

Conclusion: The risk for poor outcomes in PTC associated with male sex decreased over time; in contrast, the risk associated with pathologic characteristics remained the same or increased over time. These trends might be associated with recent changes in the characteristics of patients with thyroid cancer.

Introduction

Among thyroid cancers, well-differentiated thyroid cancer is associated with better prognosis with lower recurrence and mortality rates than other solid tumors (1, 2). However, some thyroid cancer patients still experience aggressive clinical outcomes (3, 4, 5, 6); thus, it is important to understand the prognostic factors for a poor prognosis. Previous studies have reported older age, male sex, large tumor size, lymph node (LN) involvement, extrathyroidal extension (ETE), and distant metastasis as poor prognostic factors (7).

The recent, rapid increase in the prevalence of thyroid cancer might be attributed to the increasing rates of screening for thyroid cancer in the healthy, asymptomatic population in addition to the improvement of cytologic and pathologic diagnoses (8). As the proportion of patients diagnosed through screening tests has increased,

epidemiologic studies have also indicated an increase in the proportion of smaller tumors (<1 cm diameter), a decrease in LN involvement, a decrease in ETE, and improved prognostic outcomes (4, 9). These changes might also be related with temporal changes in the previously well-known prognostic factors. In fact, several recent studies have reported changes in the effect of age and gender on the risk and prognosis of thyroid cancer (10, 11). We aimed at investigating the changes in the impact of prognostic factors for thyroid cancer during a long-term follow-up.

In this study, we used retrospective data from the previous four decades at one tertiary hospital and compared the effects of each prognostic factor according to specific time periods within that duration. We report that the impact of male sex has decreased, while the impact of age and pathologic characteristics have remained the same or increased over time.

Methods

Subjects

Among the 4500 thyroid cancer patients who underwent thyroidectomy from 1962 to 2009 in the Seoul National University Hospital Thyroid Clinic, 4074 patients had confirmed papillary thyroid cancer (PTC) (4). We included 3149 patients, excluding those who were followed up <12 months without evidence of recurrence. The patients were classified into three groups by the calendar year of diagnosis: pre-1990 ($n = 248$), 1990–1999 ($n = 839$), and post-2000 ($n = 2030$). This study was conducted according to the guidelines of the Declaration of Helsinki, and the Institutional Review Board of Seoul National University Hospital (IRB no. H-0912-009-302) approved the research protocol.

Biochemical tests

During the study period, biochemical test methodologies were changed several times, as described in our previous study (4). Serum thyroglobulin (Tg) was measured using a commercial IRMA Kit (Diasorin, Saluggia, Italy) until 2004; thereafter, it was measured by a specific, high-sensitivity IRMA (Tg-plus; BRAHMS Diagnostica GmbH, Berlin, Germany). Starting in July 1997, anti-Tg antibody (Ab) was measured using specific RIA Kits (anti-Tg; BRAHMS Diagnostica GmbH). The measurements of serum thyroid-stimulating hormone (TSH) were carried out using a commercially available kit (Daiichi Radioisotope Labs, Tokyo, Japan) from August 1998 to February 2007; thereafter, the Liaison TSH Kit (Diasorin) was used. Serum total thyroxine (T_4) was measured using a commercial RIA Kit (Monobind, Costa Mesa, CA, USA) and was later replaced by the measurement of free T_4 using GammaCoatTM Free T_4 (Diasorin) until March 2003. Free T_4 was then measured using a commercial kit (RIA-gnost FT4; CISbio International, Gif-Sur-Yvette, Cedex, France) until completion of the study.

Treatment and follow-up

As described in our previous study (4), the use of total thyroidectomy has gradually increased from 22.5% (pre-1990) to 49.1% (1990–1999) and, finally, 94.3% (post-1999) (Table 1). The use of prophylactic central or anterior neck LN dissection began in 2003 and has been increasingly performed in most patients with PTC ≥1 cm in our hospital starting in 2007. Postoperative radioactive iodine (RAI) remnant ablation therapy has also been increasingly conducted over time: 45.3% (pre-1990), 62.4% (1990–1999), and 62.7% (post-1999).

The follow-up evaluations included a physical examination, measurement of serum Tg and anti-Tg Ab levels every 6–12 months, and periodic neck ultrasonography (USG) every 1–3 years. Periodic monitoring of serum Tg levels started in the mid-1990s and neck USG in 2000. Levothyroxine was administered to maintain undetectable serum TSH level during the first 5–10 years after the initial treatment. In patients without any evidence of recurrence for 5–10 years, the target of TSH suppression was less strict to maintain a substitutive level of serum TSH.

Definition of recurrence and mortality

Recurrence was pathologically confirmed by FNA or surgical excision. Even though pathologic confirmation was not made, patients with highly suspicious lesions on imaging modalities, such as an RAI whole body scan (WBS), computed tomography (CT), a bone scan, magnetic resonance imaging (MRI), or positron emission tomography (PET), were considered as cases with tumor recurrence. In our institute, serum Tg and anti-Tg Ab levels had not been routinely monitored before the mid-1990s, and it became widely used for regular monitoring for recurrence from the early 2000s. A high-resolution USG also had been widely used since the early 2000s. Owing to the limited usage of serum Tg and anti-Tg Ab levels or USG in a regular follow-up, we could not include cases with an isolated elevation of serum Tg and anti-Tg Ab levels or

Table 1 Clinicopathological characteristics of patients with papillary thyroid cancer (1962–2009).

	Total	Pre-1990	1990–1999	Post-1999	*P*
Cases	3147	278	840	2029	
Follow-up duration (years)					
Median (min–max)	5.1 (1–43)	19.0 (1–43)	11.1 (1–20)	3.7 (1–10)	
Age (years)	46.5±12.5	38.9±12.8	44.5±12.8	48.4±11.8	<0.001
<45	1383 (44.0)	188 (67.9)	438 (52.2)	757 (37.3)	<0.001
45–54	940 (29.9)	58 (20.5)	205 (24.4)	677 (33.4)	
≥55	824 (26.2)	32 (11.6)	197 (23.4)	595 (29.3)	
Gender, *n* (%)					0.020
Men	496 (15.8)	37 (13.3)	115 (13.7)	344 (17.0)	
Women	2651 (84.2)	241 (86.7)	725 (86.3)	1685 (83.0)	
Total thyroidectomy, *n* (%)	2363 (76.2)	59 (22.5)	404 (49.1)	1900 (94.3)	<0.001
Tumor size (cm)	1.6±1.2	2.7±1.7	2.3±1.4	1.3±0.9	<0.001
<1	962 (32.6%)	18 (8.8%)	84 (11.1%)	860 (43.3%)	<0.001
1–1.9	1028 (34.9%)	55 (26.8%)	236 (31.1%)	737 (37.1%)	
2–3.9	796 (30.0%)	90 (43.9%)	363 (47.9%)	343 (17.3%)	
≥4	163 (5.5%)	42 (20.5%)	75 (9.9%)	46 (2.3%)	
Extrathyroidal extension, *n* (%)					<0.001
None	1335 (44.8)	125 (62.8)	339 (43.2)	871 (43.7)	
Micro	1335 (44.8)	12 (6.0)	310 (39.5)	1013 (50.8)	
Gross	308 (10.4)	62 (31.2)	135 (17.3)	111 (5.5)	
LN involvement, *n* (%)					<0.001
N0	1139 (37.9)	25 (11.6)	232 (29.3)	882 (44.1)	
N1	1200 (39.9)	106 (49.3)	341 (43.0)	753 (37.6)	
Nx	670 (22.2)	84 (39.1)	219 (27.7)	367 (18.3)	
Recurrence rate, *n* (%)					
Overall	418 (13.3)	100 (36.1)	164 (19.6)	154 (7.6)	<0.001
5 years	206 (6.6)	29 (10.6)	59 (7.0)	118 (5.8)	0.004
10 years	180 (16.2)	53 (19.4)	127 (15.2)	–	0.097
Disease-specific mortality rate, *n* (%)					
Overall	44 (1.4)	17 (6.1)	22 (2.6)	5 (0.3)	<0.001
5 years	17 (0.5)	4 (1.5)	9 (1.1)	4 (0.2)	<0.001
10 years	34 (3.1)	13 (4.8)	21 (2.5)	–	0.060

P values were calculated using one-way ANOVA for continuous variables or χ^2 tests for dichotomous variables.

abnormal findings detected only in USG without structural recurrence defined by pathological confirmation or another imaging methods described earlier, despite their role as sensitive markers for recurrence. The specific mortality from thyroid cancer was obtained from the Statistics Korea national database for each patients up to the year 2009.

Statistical analyses

We categorized the patients into three age groups for analyses relating to recurrence: <45, 45–54, and ≥55 years. In the univariate analyses for mortality, the difference between the age groups was most significant around the age of 53 years; consequently, a dichotomous variable based on an age of 53 years was entered into the multivariate analyses for mortality.

Continuous variables were analyzed using independent *t*-tests or one-way ANOVA, and dichotomous variables using χ^2 tests or logistic regression analysis. Kaplan–Meier analysis and Cox-hazard regression analysis were used for the survival analyses. Statistical analyses were performed using STATA 12.1 (StataCorp., College Station, TX, USA), and all *P* values are two-tailed with *P* values <0.05 being considered significant.

Results

Clinicopathological characteristics of the subjects

For the entire study period, the mean age at diagnosis was 46.5±12.5 years, and there was an increasing trend in age over time (*P*<0.001). The percentage of patients aged >45 years was 32.1% in the pre-1990 period, and this proportion increased to 62.7% in the post-1999 period (*P*<0.001). The proportion of men was 15.8% for the entire study period, and this also increased from 13.3% in the pre-1990 period to 17.0% in the post-1999 period

($P=0.02$). Table 1 shows an increase in the proportion of small tumors and a decrease in gross ETE and LN involvement, as reported in our previous study (4). There was an increasing trend in the proportion of microscopic ETE, perhaps owing to a previous lack of discrimination from total ETE, which included both microscopic and gross ETE.

During the median follow-up of 5.1 years (1–43 years), 13.3% of the patients experienced tumor recurrence, and 1.4% died from PTC. There was a significant decrease in the recurrence rates and cancer-specific mortality rates over the three time periods (pre-1990, 1990–1999, and post-1999) and at 5 years, with only a marginal decrease at 10 years (Table 1). However, the survival analyses did not result in a considerable improvement in the recurrence-free survival ($P=0.438$) and disease-specific survival ($P=0.344$) rates between the three periods.

Changes in the prognostic factors associated with recurrence between the three time periods

Over the entire study period, the Cox proportional hazard regression analysis resulted in older age (≥ 55 years), male sex, larger tumor size, LN involvement, and ETE (both gross and microscopic) as significant prognostic factors for recurrence. Younger age (<45 years) was associated with a marginal risk of recurrence (data not shown). Multivariate analyses also implicated older age (≥ 55 years), male sex, larger tumor size, LN involvement, and microscopic ETE as significant prognostic factors, while gross ETE was only a marginally significant factor (Table 2).

The multivariate analyses were then conducted to determine the changes in the effect of each prognostic factor between the time periods (Fig. 1A). Younger age (<45 years) was not a significant prognostic factor in any of the periods, whereas older age (≥ 55 years) resulted in significant hazard ratios (HRs) in the pre-1990 (HR, 2.987; 95% CI, 1.233–7.234) and 1990–1999 (HR, 1.755; 95% CI, 1.077–2.859) periods. In the post-1999 time period, the effect of older age (≥ 55 years) on the risk was marginally significant (HR, 1.549; 95% CI, 0.955–2.510). Male sex resulted in a significant HR in the pre-1990 (HR, 2.809; 95% CI, 1.497–5.269) and 1990–1999 (HR, 2.191; 95% CI, 1.457–3.294) periods; however, the HR was not significant in the post-1999 period (HR, 1.142; 95% CI, 0.736–1.772).

There was a gradually increasing risk of recurrence related to the pathological characteristics; the HRs related to tumor size increased from 0.946 (95% CI, 0.778–1.150) in the pre-1990 period to 1.355 (95% CI, 1.180–1.555) in the post-1999 period. The HRs for LN involvement increased from 2.672 (95% CI, 1.444–4.943) in the pre-1990 period to 3.038 (95% CI, 2.028–4.552) in the post-1999 period. Both microscopic and gross ETE also demonstrated an increasing trend in the HRs; however, this was not statistically significant.

To account for the possible effect of the extent of surgery on prognosis (12, 13), we stratified the sample into two groups: total thyroidectomy and non-total thyroidectomy (Supplementary Table 1, see section on supplementary data given at the end of this article). In the total thyroidectomy group, similar trends were observed as described earlier. In the non-total thyroidectomy group, appropriate analyses could not be performed

Table 2 Cox-HRs for each risk factor for outcomes in papillary thyroid cancer determined using multivariate analyses and reported for the entire period (1962–2009). HRs were calculated by Cox-hazard regression and adjusted for all risk factors. Age was categorized into three groups in the analyses for recurrence-free survival and into two groups for disease-specific survival.

	Recurrence		Cancer-specific mortality	
	HR (95% CI)	P	HR (95% CI)	P
Age <45 years	1.178 (0.880–1.578)	0.272	–	–
Age ≥55 years	1.748 (1.274–2.398)	0.001	–	–
Age ≥53 years	–	–	11.498 (5.114–25.852)	<0.001
Men	1.684 (1.292–2.193)	<0.001	3.374 (1.661–6.855)	0.001
Tumor size (cm)	1.217 (1.135–1.305)	<0.001	1.225 (1.002–1.498)	0.048
LN involvement	2.783 (2.173–3.565)	<0.001	3.096 (1.367–7.016)	0.007
Microscopic ETE	1.325 (1.016–1.738)	0.038	1.208 (0.496–2.938)	0.677
Gross ETE	1.362 (0.981–1.891)	0.065	1.223 (0.519–2.877)	0.645

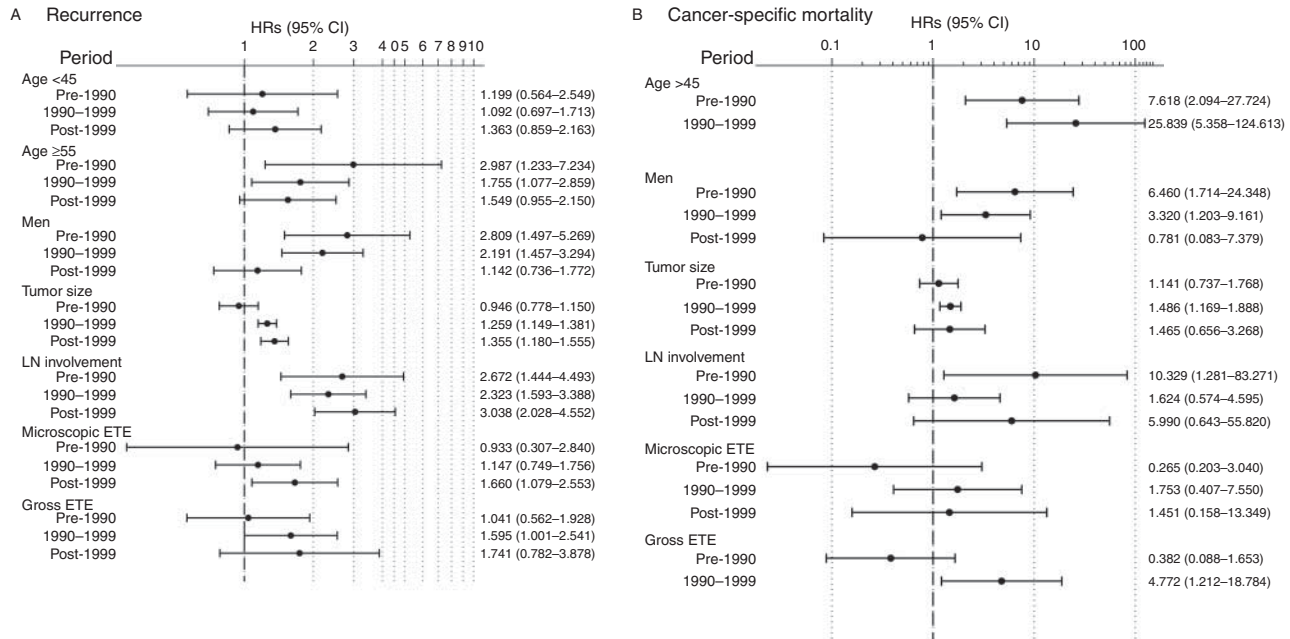LN, lymph node; ETE, extra-thyroidal extension; HR, hazard-ratio.

Figure 1

Changes in the Cox-HRs for each prognostic factor for papillary thyroid cancer prognosis between three time periods. (A) For the tumor recurrence, older age and male sex, showed decreasing risk effect whereas the pathologic characteristics showed increasing risk effect. (B) For the cancer-specific mortality, older age showed persistent risk effect, whereas the effect of male sex was not significant in the post-1999 period.

The risk effects of pathologic characteristics were gradually increased without statistical significances. HRs were calculated by Cox-hazard regression and adjusted for all prognostic factors. Age was categorized into three groups in the analyses for recurrence-free survival (A) and into two groups for disease-specific survival (B). HR, hazard ratio; LN, lymph node; ETE, extra-thyroidal extension.

because of the small number of cases. To examine the effects of RAI therapy, we also performed multivariate analyses for RAI therapy with adjustment for other prognostic factors and surgery extent; however, statistical significances were not observed (data not shown).

Prognostic factors associated with mortality and their changes over time

For cancer-specific mortality, univariate analysis resulted in significantly high HRs related to older age (≥ 53 years), male sex, larger tumor size, LN involvement, and gross ETE during the entire study period (data not shown). In the multivariate analysis, older age (≥ 53 years), male sex, and LN involvement remained as significant prognostic factors (Table 2). Despite only a few mortality events, we observed similar trends with the results in the analyses for recurrence (Fig. 1B). In particular, male sex resulted in significant risks in both the pre-1990 (HR, 6.460; 95% CI, 1.714–24.348) and 1990–1999 (HR, 3.320; 95% CI,

1.203–9.161) periods; the effect of male sex was not significant in the post-1999 period (HR, 0.781; 95% CI, 0.083–7.379). Tumor size, LN involvement, and ETE resulted in a gradually increasing risk of mortality; however, the presence of few mortality records and incomplete medical records for pathologic data limited our ability to find a significant effect. Older age (≥ 53 years) demonstrated significant risk for mortality in the 1990–1999 (HR, 25.839; 95% CI, 5.358–127.613) and pre-1990 (HR, 7.618; 95% CI, 2.094–27.724) periods. Stratified analyses by the extent of surgery were difficult to perform because of the limited number of mortality cases (Supplementary Table 2, see section on supplementary data given at the end of this article).

Comparison of the clinicopathological characteristics between male and female patients in each time period

The mean age of the male patients was older than that of the female patients in every time period; however, the

Table 3 Comparisons of the clinicopathological characteristics relating to papillary thyroid cancer between the sexes, according to the three time periods. Values are represented by mean ± S.D. or n (%).

	Pre-1990			1990–1999			Post-1999			P for trend	
	Male	Female	P	Male	Female	P	Male	Female	P	Male	Female
Cases	37 (13.4)	240 (86.6)	–	115 (13.7)	724 (86.3)	–	344 (17.0)	1684 (83.0)	–	0.021	
Age (years)	40.6±14.7	38.7±12.6	0.398	49.0±13.0	43.7±12.6	<0.001	49.3±12.8	48.2±11.6	0.135	0.499	0.020
TT	8 (21.6)	51 (21.3)	0.959	59 (51.3)	346 (47.8)	0.484	326 (94.8)	1574 (93.5)	0.366	<0.001	<0.001
Tumor size (cm)	3.2±2.0	2.5±1.5	0.111	2.7±1.9	2.2±1.3	0.019	1.3±1.0	1.3±0.9	0.669	<0.001	<0.001
ETE (micro/gross)	3/11 (10.7/39.3)	9/51 (5.3/29.8)	0.256	44/18 (40.7/16.7)	266/117 (39.4/17.3)	0.961	156/21 (46.2/6.2)	857/90 (51.7/5.4)	0.174	0.090/ <0.001	<0.001/ <0.001
LN involvement	19 (61.3)	87 (47.3)	0.149	56 (51.4)	285 (41.7)	0.059	154 (45.4)	599 (36.2)	0.001	0.062	<0.001
5RR, n (%)	7 (18.9)	22 (9.4)	0.080	15 (13.2)	44 (6.1)	0.006	26 (7.6)	92 (5.5)	0.125	0.009	0.039
5MR, n (%)	1 (2.7)	3 (1.3)	0.503	4 (3.5)	5 (0.7)	0.007	0 (0)	4 (0.2)	0.367	0.003	0.014

P values were calculated using Student's t-tests or one-way ANOVA for continuous variables or using χ^2 tests or Wilcoxon rank-sum tests for dichotomous variables. TT, total thyroidectomy; ETE, extra-thyroidal extension; LN, lymph node; 5RR, 5-year recurrence rate; 5MR, 5-year disease specific mortality rate.

difference between the sexes became smaller over time (Table 3). LN involvement and ETE were also more prevalent in male patients than in female patients in the earlier time periods; however, these differences also became smaller over time. In the same manner, average tumor size was larger in male patients than in the female patients in the earlier time period, and there was no difference in the most recent time period. The differences in the 5-year recurrence and mortality rates between the sexes decreased with time.

In contrast, the differences between two age gruops (<53 years and ≥53 years) did not show significant changes both in the clinicopathological characteristics and long term prognosis (Supplementary Table 3, see section on supplementary data given at the end of this article).

Discussion

Our results indicate that the prognostic factors for PTC have changed over time. The risk associated with male sex for recurrence and mortality decreased over time, while the pathologic characteristics, including tumor size, LN involvement, and ETE, demonstrated a gradually increasing risk. Although our retrospective study could not clarify the reason of secular changes in risk effects of prognostic factors, we focus on the several changes over time. Even though we did not consider the biochemical abnormality in the definition of recurrence throughout the whole periods, the ability to detect earlier recurrence might be higher after post-1999, when serum Tg or anti-Tg Ab levels and high resolution ultrasound of neck, and RAI therapy started to be used widely. Therapeutic strategies also changed to be more comprehensive through time, such as total thyroidectomy or prophylactic central LN dissection and increasing RAI treatment, which were able to make differences in outcomes of the patients with similar risk for poor prognosis. Consequently, these thorough evaluations by diagnostic or therapeutic modalities might be able to augment the statistical risk effects of pathological parameters, because there exists a possibility that the characteristics of the recurred patients were somewhat different among the three periods. In addition, in the stratified analyses and the multivariate analyses using the Cox-hazard regression about beneficial effect of total thyroidectomy or RAI treatment, we could not find significant beneficial effects with the limitation of sample size in each subgroup. To compare the effect according to treatment strategies, we need well-designed prospective studies.

Several studies have reported that male sex is a significant prognostic factor for mortality, suggesting a

protective effect of being female owing to hormonal effects (14). Experimental studies have revealed inhibitory effects of the estrogen receptor beta on the development of thyroid cancer (15, 16). A recent epidemiologic study has also demonstrated a better prognosis in younger female patients (<55 years), before menopause, and those aged >55 years had similar outcomes to those of male patients, suggesting a sex disparity in thyroid cancer outcomes (10). However, the beneficial effect of hormones in female patients remains unclear (14), and our results are not consistent with the results mentioned above; in our study, improved prognosis in female patients was observed in those <65 years, and in the patients in the post-1999 time period, the differences in the prognostic outcomes between the sexes were no longer observed for any age group (data not shown).

Although we were not able to determine the reason for a decreasing effect of male sex, increases in health examinations might be related to these changes. In the past, men tended to visit the hospital at more advanced stages of thyroid cancer; this is supported by our observations that male patients were older in addition to having larger tumor sizes and higher rates of LN involvement and ETE in the earlier time period. With the increases in thyroid cancer screening in our country, especially in male employees financially supported by their employers for health examinations, the rates of male participants increased at higher rates than did the rates of female participants. Furthermore, because male participants are likely to have more cardiovascular risks, they may have more opportunities for carotid neck USG, which might lead to the detection of incidental thyroid nodules (17). Consequently, the number of male patients with incidentally detected early thyroid cancer from health examinations increased at higher rates than female patients in the most recent time period, which might contribute to the decreasing effect of male sex.

Recently, Elisei et al. (9) have reported similar trends of the prognostic effect of pathological parameters, such as age, sex, histotype, tumor size, LN metastasis, ETE, and distant metastases. In light of the risk effect of male sex, our results were in conflict with that study, while our study showed sustained risk effects of the other prognostic factors. Although we cannot readily account for the cause of the differences, it might be associated with the possible differences in racial, geographic, or medical environment, and especially the proportion of patients detected by health checkup or screening examination. In the future, we need the previous epidemiologic study for the changes in characteristics of the patient population with thyroid cancer.

Similar to previous studies, our study demonstrated that patient age was a significant factor for prognosis of thyroid cancer. This effect was present in a bimodal distribution of age; the recurrence rate was higher with ages <45 and ≥55 years, which has also been reported in a previous study (18). We observed that the effect of age on recurrence was attenuated with time, possibly owing to increasing health examinations, as with the decreasing effect of male sex. Compared with recurrence rates, mortality rates increased steadily with age, and the risk associated with age was significant over time. Older patients are likely to have more comorbidities; consequently, older age is likely to remain a significant prognostic factor. However, we also observed that cancer-related mortality increased sharply around 53 years old, older than 45 years, which is the age identified in the TNM staging system (19). Although we could not determine the exact reason for this discrepancy, it might also result from an increase in early diagnoses with the recent increase in health examinations. In Korea, the rates of thyroid USG screening in health examinations are highest (28.8%) in those aged 50–59 years (MK Hyun, J-W Kwon, JH Kim, JM Kim, JI Shim, NR Lee, KW Kim, YJ Park, HY Ahn & MS You, unpublished observations), potentially resulting in more early diagnoses and improved prognoses in that age group through early treatment and evaluation; this may explain the increase in the age at which there is a significant effect on prognosis. However, because these inferences are not based on direct analyses for that issue, further epidemiologic studies are needed to reach a conclusion about the influence of health examinations on the age at which prognosis is affected.

Tumor size was a significant prognostic factor for thyroid cancer in a number of previous studies (6, 12). Interestingly, the effect of tumor size on the risk of recurrence and cancer-related mortality increased and became significant in the most recent time period (Fig. 1). With the recent increase in earlier diagnoses of thyroid cancer using neck USG, the expected proportion of patients with a good prognosis has also grown (20, 21), possibly augmenting the statistical effect of large tumors compared with the improved prognosis associated with small tumors. In addition, the pathologic reports with comprehensive and detailed description, such as microscopic ETE or nodal metastasis, might enable pathologic characteristics to predict clinical outcomes more exactly. However, our retrospective study was limited by the fact that thyroid examinations did not occur using the same neck USG and

by insufficient data in the pathologic reports. In the future, well-designed prospective studies are warranted.

Our retrospective study used medical records, resulting in inherent limitations. First, a considerable number of cases had missing data in the pathology reports, especially in the older records. The proportion of missing data in the pre-1989 period was 22.4% for both LN involvement and ETE, leading to ascertainment bias. Despite this fundamental limitation, the results from the recent time periods (1989–1999 and post-1999) had little missing data (5.6 and 1.3% in LN involvement and 6.6 and 1.6% in ETE respectively), and similar trends were observed in all of the study periods, indicating that the missing data might not have influenced the relevance of the study. Second, we defined the recurrence only to structural disease, not to the isolated elevation of Tg or anti-Tg Ab level, because of the limited usage in the past. In practice, serum Tg or anti-Tg Ab levels have an important role in surveillance for tumor recurrence (22). Given the importance of serum Tg or anti-Tg Ab concentration during a follow-up in thyroid cancer patients, omitting isolated elevation of Tg or anti-Tg Ab level from the definition of recurrence would make it possible to underestimate recurrence rates. However, in our subjects, only five patients showed elevation of serum Tg or anti-Tg Ab level without evidence of structural disease, and the effect from these limitation of our study might be restricted (data not shown). Lastly, our study included only patients who were diagnosed and treated in one tertiary hospital; therefore, our results may not be generalizable to the general population in Korea.

Our results present gradual changes over recent decades in the effects of well-known prognostic factors, including age, sex, tumor size, LN involvement, and ETE. Male sex was a prognostic factor in all of the time periods; however, the effect decreased over time. Conversely, the effect of pathologic characteristics (tumor size, LN involvement, and ETE) increased over time. In light of these changes in prognostic factors, there might be an increase in the number of patients with good prognoses as a result of detection through health examinations and more accurate evaluations and treatments associated with advances in thyroid cancer management. To clarify the changes in the prognostic factors associated with thyroid cancer outcomes, further prospective studies are warranted.

References

1 Lin J-D, Chen S-T, Hsueh C & Chao T-C. A 29-year retrospective review of papillary thyroid cancer in one institution. *Thyroid* 2007 **17** 535–541. (doi:10.1089/thy.2006.0160)

2 Jung K-W, Won Y-J, Kong H-J, Oh C-M, Seo HG & Lee J-S. Cancer statistics in Korea: incidence, mortality, survival and prevalence in 2010. *Cancer Research and Treatment* 2013 **45** 1. (doi:10.4143/crt.2013.45.1.1)

3 Eustatia-Rutten CFA, Corssmit EPM, Biermasz NR, Pereira AM, Romijn JA & Smit JW. Survival and Death Causes in Differentiated Thyroid Carcinoma. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 313–319. (doi:10.1210/jc.2005-1322)

4 Cho BY, Choi HS, Park YJ, Lim JA, Ahn HY, Lee EK, Kim KW, Yi KH, Chung J-K, Youn YK et al. Changes in the clinicopathological characteristics and outcomes of thyroid cancer in Korea over the past four decades. *Thyroid* 2013 **23** 797–804. (doi:10.1089/thy.2012.0329)

5 Hamzany Y, Soudry E, Strenov Y, Lipschitz N, Segal K, Hadar T, Hilly O & Feinmesser R. Early death from papillary thyroid carcinoma. *American Journal of Otolaryngology* 2012 **33** 104–108. (doi:10.1016/j.amjoto.2011.04.002)

6 Tzvetov G, Hirsch D, Shraga-Slutzky I, Weinstein R, Manistersky Y, Kalmanovich R, Lapidot M, Grozinsky-Glasberg S, Singer J, Sulkes J et al. Well-differentiated thyroid carcinoma: comparison of microscopic and macroscopic disease. *Thyroid* 2009 **19** 487–494. (doi:10.1089/thy.2008.0228)

7 Sipos JA & Mazzaferri EL. Thyroid cancer epidemiology and prognostic variables. *Clinical Oncology* 2010 **22** 395–404. (doi:10.1016/j.clon.2010.05.004)

8 Davies L & Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *Journal of the American Medical Association* 2006 **295** 2164–2167. (doi:10.1001/jama.295.18.2164)

9 Elisei R, Molinaro E, Agate L, Bottici V, Masserini L, Ceccarelli C, Lippi F, Grasso L, Basolo F, Bevilacqua G et al. Are the clinical and pathological features of differentiated thyroid carcinoma really changed over the last 35 years? Study on 4187 patients from a single Italian institution to answer this question. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 1516–1527. (doi:10.1210/jc.2009-1536)

10 Jonklaas J, Nogueras-Gonzalez G, Munsell M, Litofsky D, Ain KB, Bigos ST, Brierley JD, Cooper DS, Haugen BR, Ladenson PW et al. The impact of age and gender on papillary thyroid cancer survival. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E878–E887. (doi:10.1210/jc.2011-2864)

11 Mazurat A, Torroni A, Hendrickson-Rebizant J, Benning H, Nason RW & Pathak KA. The age factor in survival of a population cohort of well-differentiated thyroid cancer. *Endocrine Connections* 2013 **2** 154–160. (doi:10.1530/EC-13-0056)

12 Konturek A, Barczyński M, Nowak W & Richter P. Prognostic factors in differentiated thyroid cancer – a 20-year surgical outcome study. *Langenbeck's Archives of Surgery* 2012 **397** 809–815. (doi:10.1007/s00423-011-0899-z)

13 Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS & Sturgeon C. Extent of surgery affects survival for

papillary thyroid cancer. *Annals of Surgery* 2007 **246** 375–384. (doi:10.1097/SLA.0b013e31814697d9)

14 Rahbari R, Zhang L & Kebebew E. Thyroid cancer gender disparity. *Future Oncology* 2010 **6** 1771–1779. (doi:10.2217/fon.10.127)

15 Chen GG, Vlantis AC, Zeng Q & van Hasselt CA. Regulation of cell growth by estrogen signaling and potential targets in thyroid cancer. *Current Cancer Drug Targets* 2008 **8** 367–377. (doi:10.2174/156800908785133150)

16 Kumar A, Klinge CM & Goldstein RE. Estradiol-induced proliferation of papillary and follicular thyroid cancer cells is mediated by estrogen receptors α and β. *International Journal of Oncology* 2010 **36** 1067–1080. (doi:10.3892/ijo_00000588)

17 Steele SR, Martin MJ, Mullenix PS, Azarow KS & Andersen CA. The significance of incidental thyroid abnormalities identified during carotid duplex ultrasonography. *Archives of Surgery* 2005 **140** 981–985. (doi:10.1001/archsurg.140.10.981)

18 Mazzaferri EL & Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *American Journal of Medicine* 1994 **97** 418–428. (doi:10.1016/0002-9343(94)90321-2)

19 Egner JR. AJCC cancer staging manual. *Journal of the American Medical Association* 2010 **304** 1726. (doi:10.1001/jama.2010.1525)

20 Pellegriti G, Frasca F, Regalbuto C, Squatrito S & Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. *Journal of Cancer Epidemiology* 2013 **2013** 1–10. (doi:10.1155/2013/965212)

21 Enewold LR, Zhou J, Devesa SS, de Gonzalez AB, Anderson WF, Zahm SH, Stojadinovic A, Peoples GE, Marrogi AJ, Potter JF *et al*. Thyroid cancer incidence among active duty U.S. military personnel, 1990-2004. *Cancer Epidemiology, Biomarkers & Prevention* 2011 **20** 2369–2376. (doi:10.1158/1055-9965.EPI-11-0596)

22 American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Hauger BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B *et al*. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009 **19** 1167–1214. (doi:10.1089/thy.2009.0110)