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Epidemiology Note

Thyroid Cancer is the Most Common Cancer in Women, Based on the Data from Population-based Cancer Registries, South Korea

Sun-Seog Kweon[1,2], Min-Ho Shin[1,*], Ik-Joo Chung[2,3], Young-Jin Kim[4] and Jin-Su Choi[1]

[1]Department of Preventive Medicine, Chonnam National University Medical School, Gwangju, [2]Jeonnam Regional Cancer Center, Chonnam National University Hwasun Hospital, Hwasun, [3]Department of Internal Medicine, Division of Hemato-Oncology, Chonnam National University Medical School, Gwangju and [4]Department of Surgery, Chonnam National University Medical School, Gwangju, South Korea

*For reprints and all correspondence: Min-Ho Shin, Department of Preventive Medicine, Chonnam National University Medical School, 160, Baekseok-ro, Dong-gu, Gwangju, South Korea. E-mail: mhshinx@paran.com

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Similar to worldwide trends, the incidence of thyroid cancer in South Korea has increased steadily in recent decades. We examined the trends in thyroid cancer incidence in Gwangju and Jeonnam provinces between 1996 and 2010, and identified 19 881 cases (men 3282/16.5%; women 16 599/83.5%) from the Gwangju Cancer Registry and Jeonnam Cancer Registry databases, which are population-based cancer registries. Age-standardized incidence rates per 100 000 persons, using hypothetical world standard population (Segi), increased from 1.9 in 1996 to 27.0 in 2010 in men, and from 10.6 to 111.3 in women, respectively. The estimated annual percentage changes (95% confidence interval) of age-standardized incidence rates were 27.1% (24.6–29.6) and 19.7% (16.4–23.2) for men and women, respectively, during the same period. The proportion of papillary-type thyroid cancer increased from 74.2 and 75.4% in 1996 to 97.9 and 98.3% in 2010 for men and women, respectively. We found the most prominent increasing trends and the highest incidence rate of thyroid cancer among those that have ever been reported. Thyroid cancer has been the leading cancer in women since 2003 and is now the fifth most common cancer in men in Gwangju and Jeonnam, South Korea.

Key words: thyroid cancer – incidence – registries

INTRODUCTION

The thyroid gland is the most common site of all primary endocrine cancers globally, comprising 2.7% of all female cancers, ranking as the ninth most common cancer affecting women (1). Thyroid cancer (TC) incidence has increased greatly over recent decades. Although TC is perceived as a cancer with a high survival rate, this sustained increase in TC incidence worldwide has recently attracted considerable attention (2–5). TC treatment employs a three-tiered approach including surgery, radioactive iodine treatment and long-term exogenous hormone replacement (6). Therefore, despite its relatively favorable clinical prognosis, TC care places an inevitable demand on social health care resources and economic burden. The annual TC incidence differs considerably according to the race and lifestyle. During 1998–2002, the highest incidence in males were reported in Ferrara in Italy, District of Columbia (White) in the USA, Modena in Italy and in Hawaiian Filipinos, with age-adjusted incidence rates per 100 000 persons using the WHO world standard population (age-standardized incidence rates, ASRs) of 6.4, 6.3, 5.9 and 5.7, respectively. The highest rates of incidence of TC in females were reported in French Polynesia, Hawaiian Filipinos, Gwangju in Korea and Ferrara in Italy, with ASRs of 37.4, 22.5, 21.4 and 20.4, respectively (7).

Many previous studies have suggested that the cause of increasing TC incidence is associated with increased diagnostic scrutiny, improvements in ultrasonography (US) and other medical imaging tests, and the increased use of fine-needle aspiration biopsy (FNAB). Neck radiation remains an undisputed risk factor for TC development. The Gwangju metropolitan city and Jeonnam province have relatively higher TC incidence than those reported in other South Korean provinces (8). In a worldwide report, the TC incidence described from nine South Korean cancer registries ranked as being relatively high in both the genders. Above all Korean registries, the Gwangju Cancer Registry (GCR) and the Jeonnam Cancer Registry (JCR) showed the highest TC incidence in both the genders (7).

In this paper, we report on TC incidence based on the GCR and JCR databases of past 15 years.

PATIENTS AND METHODS

Area and Population

Gwangju and Jeonnam are located in the south-western end of the Korean Peninsula. These regions span an area of 12 574 km^2, and had a population of ~3.37 million at the end of 2010. Gwangju is a metropolitan city with 1.4 million people, and is geographically located in the middle portion of Jeonnam, which is a province consisting of 5 cities and 17 counties (called ‘gun’). In certain manufacturing industries, including automobile assembly plants, the majority of the Gwangju population is engaged in service industries. The largest nuclear power plant complexes in South Korea and a large petrochemical complex are located in Jeonnam province. However, farming, fishing and service industries remain the major occupation of residents in Jeonnam province. Because of their geographic proximity, Gwangju and Jeonnam have similar medical service utilizing patterns. We selected a sample region, Yeosu City, where the increasing trend of TC was first identified, to evaluate the secular trends according to the clinical information, such as mass size and presence of clinical symptoms at diagnosis.

Data Collection Process

The GCR is a population-based cancer registry system, established in 1997, and certified as holding data being of sufficient quality to appear in the Cancer Incidence in Five Continents (CI5) Vol. IX. The JCR also has a population-based cancer registry system, established in 2000 and initiated the data collection processes for TC incidence in 1996. The GCR and JCR are operated by the same tumor registrars and epidemiologists, and have identical data collection and quality control processes. These two registries employed four specific main data sources which are as follows: (i) Korea Central Cancer Registry data, a hospital-based cancer registry system that is reported from major hospitals throughout the nation; (ii) clinical data including electronic files of pathological findings from almost all the pathology laboratories within the catchment areas; (iii) the cancer claims data for National Health Insurance and (iv) death certificate data, which are obtained from the National Statistical Office (NSO) of Korea. TC cases diagnosed in Yeosu City ($n = 3101$) were also classified according to the presence of symptoms at initial diagnosis and the nodule size ($\leq$1, 1–2 and >2 cm). Asymptomatic cases were defined as TC cases detected by US screening without any related symptoms or a previous history of thyroid disease.

Statistical Analyses

We calculated the crude incidence rate (CR) per 100 000 persons by sex and age-specific incidence rates (ASIRs) in 5-year age groups ranging from 0 to 4 through to 85 and over by sex, using the year-end population data that are released annually from the NSO of Korea. The ASIRs for years 1996–2010 were also calculated for combined age groups (0–19, 20–39, 40–59, 60–79 and $\geq$80 years). ASRs and TC-specific mortality rates were calculated by a direct method with hypothetical WHO world standard population (9). To describe the incidence trend by calendar year and to calculate the estimated annual percentage changes (EAPCs) of ASRs, we carried out a joinpoint regression analysis using the Joinpoint Regression Program (version 4.0; Statistical Research and Applications Branch, NCI) (6,10–13). The analysis included logarithmic transformation of the rates, standard error, maximum number of two joinpoints and minimum of 4 years between the joinpoints. All other program parameters were set to default values. To evaluate the relative frequency of TC among total cancer cases, we employed the GCR dataset from 1997 to 2010 and a JCR dataset from 1999 to 2010. All statistics were calculated based on data pooling of cancer cases from the two registries and populations.

RESULTS

A total of 19 981 cases (men 3282/16.5%; women 16 599/83.5%) were registered in two regional registry systems between 1996 and 2010. Among them, 1345 (15.7%) men and 7240 (84.3%) women cases were extracted from the GCR, and 1947(17.1%) men and 9359 (82.9%) women cases extracted from the JCR. The mean age ± standard deviation (SD) at diagnosis was 48.6 ± 12.6 years in men and 47.9 ± 12.5 years in women. The mean age at diagnosis was significantly lower for papillary thyroid carcinoma (PTC) patients (men 48.2 ± 12.3 years; women 47.7 ± 12.3 years) when compared with non-PTC patients (men 54.9 ± 15.6; women 53.6 ± 16.9) in both sexes ($P < 0.001$). Among all TC cases, the mean age ± SD at diagnosis did not differ between registries, nor during the periods 1996–2000, 2001–05 and 2006–10 in either sex (data not shown).

Table 1 presents the overall TC incidence trend of the number of cases, CR, annual ASRs and age-standardized mortality for all TC types according to sex over the 15-year study period, and statistically significant increasing trends were

Table 1. Thyroid cancer incidence and mortality trend by sex in Gwangju and Jeonnam, 1996–2010

	Men				Women			
	Incidence			Death	Incidence			Death
	Cases	CR	WASR	Mortality	Cases	CR	WASR	Mortality
Year								
1996	31	1.8	1.9	0.0	183	10.5	10.6	0.4
1997	28	1.6	1.5	0.2	211	12.0	10.7	0.3
1998	43	2.5	2.3	0.4	284	16.1	13.9	0.4
1999	56	3.2	2.9	0.3	326	18.5	15.9	0.7
2000	56	3.2	2.8	0.4	345	19.6	16.6	0.9
2001	78	4.5	3.9	0.2	423	24.2	20.3	0.7
2002	97	5.7	4.8	0.3	562	32.4	26.8	0.7
2003	159	9.4	7.7	0.5	901	52.5	42.7	0.8
2004	191	11.3	9.4	0.5	1227	72.1	58.3	0.8
2005	282	16.8	13.3	0.3	1489	88.0	70.1	0.6
2006	308	18.5	14.2	0.4	1546	91.8	71.6	0.9
2007	390	23.4	18.0	0.4	1984	118.2	92.6	0.7
2008	458	27.5	20.9	0.2	2224	132.6	102.4	0.8
2009	490	29.4	21.7	0.6	2441	145.3	110.8	0.4
2010	615	36.6	27.0	0.3	2453	144.9	111.3	0.4
Period								
1996–2000	214	2.5	2.3	0.3	1349	15.4	13.5	0.5
2001–05	807	9.5	8.0	0.4	4602	53.5	44.3	0.7
2006–10	2,261	27.1	21.0	0.4	10 648	126.6	100.0	0.6
EAPC (%)	26.6[a]	27.1[a]	22.5[a]	17.6	23.1[a]	23.6[a]	19.7[a]	2.4

CR, crude incidence rate; WASR, age-standardized incidence rate (world standard) per 100 000; Mortality, age-adjusted mortality using the WHO standard population; EAPC, estimated annual percentage change; TC, thyroid cancer.
*The EAPC is significantly different from zero ($P < 0.05$).

observed in both sexes. The annual ASRs per 100 000 person of TC increased from 1.9 and 10.5 in 1996 to 27.0 and 111.3 in 2010 for men and women, respectively. The EAPCs [95% confidence interval (CI)] of the ASR over this period were 22.5% (95% CI 19.7–25.4) and 19.7% (95% CI 16.4–23.2) for men and women, respectively. No significant increasing trends of mortality were observed in both sexes (Table 1).

Table 2 shows the findings from the joinpoint regression analysis over the period 1996–2010 for the number of cases, ASIRs of five categories, CRs and ASRs by sex. In men, the total TC cases increased by 21.8% (95% CI 11.8–32.7) between 1996 and 2001, by 38.8% (95% CI 14.6–68.1) between 2001 and 2005 and by 16.9% (95% CI 7.3–27.3) between 2006 and 2010, respectively. ASIRs from 20 to 39, 40 to 59 and 60 to 79 years were increased by 25.8% (95% CI 22.2–29.5), 27.5% (95% CI 24.1–31.0) and 22.2% (95% CI 16.9–27.6), respectively, without any joinpoint. A similar trend with case counts was observed in the results of CR and ASR in men with two without any joinpoints. In women, we found two joinpoints for all parameters, except for ASIR from 0 to 19, 60 to 79 and ≥80 years. The largest increases in trends by >45% were found in the second joinpoints segment for the parameters (Table 2).

Typically, PTC is the most common histologic type of TC. Out of 3282 TC cases in men, 3093 cases (94.2%) were PTC and only 189 cases (5.8%) were of non-papillary type. The trend was similar among women, with 15 949 (96.1%) PTC cases and 650 non-PTC cases (3.9%) among the total of 16 599 TC diagnoses. The proportion of PTC increased steadily from 74.2 and 75.4% in 1996 to 97.9 and 98.3% in 2010 for men and women, respectively (data not shown). Fig. 1 gives the trends of ASRs for PTC and non-PTC, and age-standardized mortality rates between 1996 and 2010 by sex. An obvious increase in the trend of incidence was found for PTC in both sexes, whereas no significant increasing trends were found for non-PTC and mortality in both sexes (Fig. 1).

Table 2. Joinpoint analysis of TC incidence by sex in Gwangju and Jeonnam, 1996–2010

	Trend 1		Trend 2		Trend 3	
	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)
Males						
Case number	1996–2001	21.8 (11.8–32.7)	2001–2005	38.8 (14.6–68.1)	2005–2010	16.9 (7.3–27.3)
Age-specific rate						
0–19 years	1996–2010	NA				
20–39 years	1996–2010	25.8 (22.2–29.5)				
40–59 years	1996–2010	27.5 (24.1–31.0)				
60–79 years	1996–2010	22.2 (16.9–27.6)				
80+ years	2002–2010	0.9 (−14.5–19.1)				
Total CR	1996–2001	21.8 (11.8–32.6)	2001–2005	40.3 (15.9–69.7)	2005–2010	16.8 (7.2–27.2)
WASR	1996–2000	14.1 (−5.7–38.1)	2000–2005	35.1 (21.0–50.9)	2005–2010	15.3 (10.7–20.1)
Females						
Case number	1996–2001	17.3 (11.3–23.6)	2001–2004	44.9 (14.4–83.4)	2004–2010	13.2 (8.7–17.8)
Age-specific rate						
0–19 years	1996–2010	8.7 (3.1–14.6)				
20–39 years	1996–2001	19.7 (12.1–27.8)	2001–2004	46.2 (9.1–95.9)	2004–2010	12.6 (7.1–18.3)
40–59 years	1996–2001	13.9 (7.0–21.2)	2001–2004	49.5 (13.0–97.7)	2004–2010	12.0 (6.8–17.4)
60–79 years	1996–2010	19.8 (17.6–22.1)				
80+ years	1997–2010	2.1 (−3.9–8.4)				
Total CR	1996–2001	17.2 (11.1–23.6)	2001–2004	46.7 (15.6–86.2)	2004–2010	13.3 (8.8–18.0)
WASR	1996–2001	13.5 (0.7–27.8)	2001–2004	46.9 (6.4–102.8)	2004–2010	11.8 (8.1–15.5)

95% CI, 95% confidence interval; NA, not applicable due to insufficient number of cases.

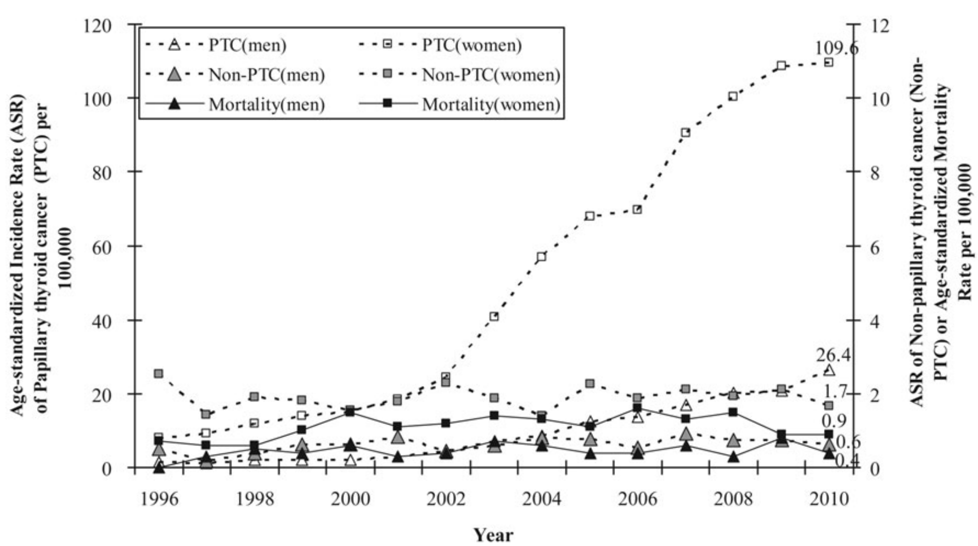

Figure 1. Trends in age-standardized incidence and mortality rate of thyroid cancer (TC) by sex and histologic type in Gwangju and Jeonnam, South Korea, 1996–2010.

Figure 2 shows the trend of ASRs of TC and five most common cancers based on the 2006–10 period in Gwangju and Jeonnam, Korea. Stomach, lung, liver and colorectal cancers in men and breast, stomach, colorectal and lung cancers in women showed similar ASRs during the period, and TC increased notably in both sexes (Fig. 2).

Among 3101 cases registered in Yeosu City, information regarding the exact diagnostic pathway and the presence of

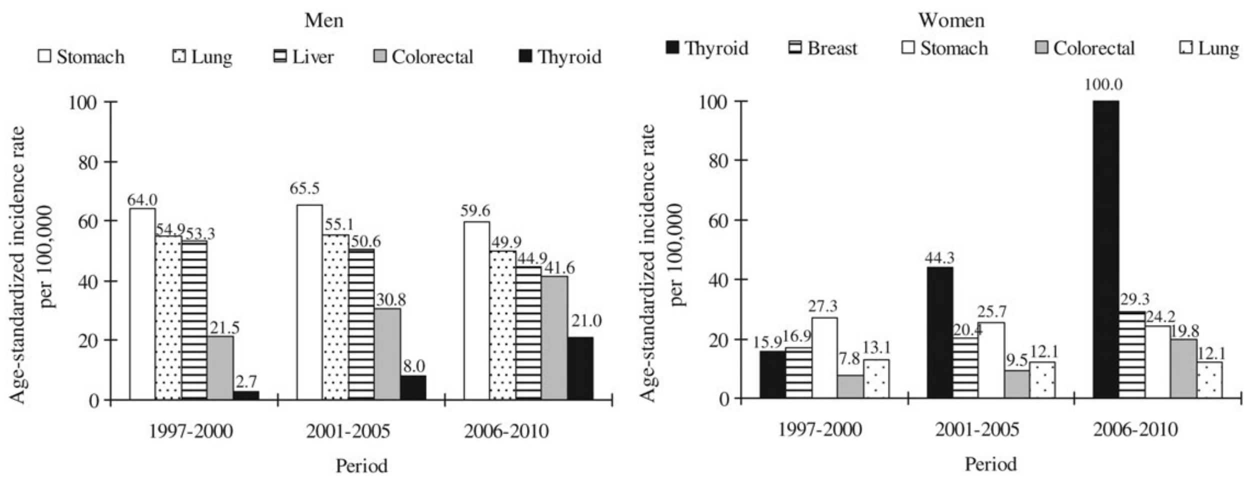

Figure 2. Incidence trend of five most common cancers in 2006–2010 by sex and 5-year period in Gwangju and Jeonnam, South Korea, 1997–2010.

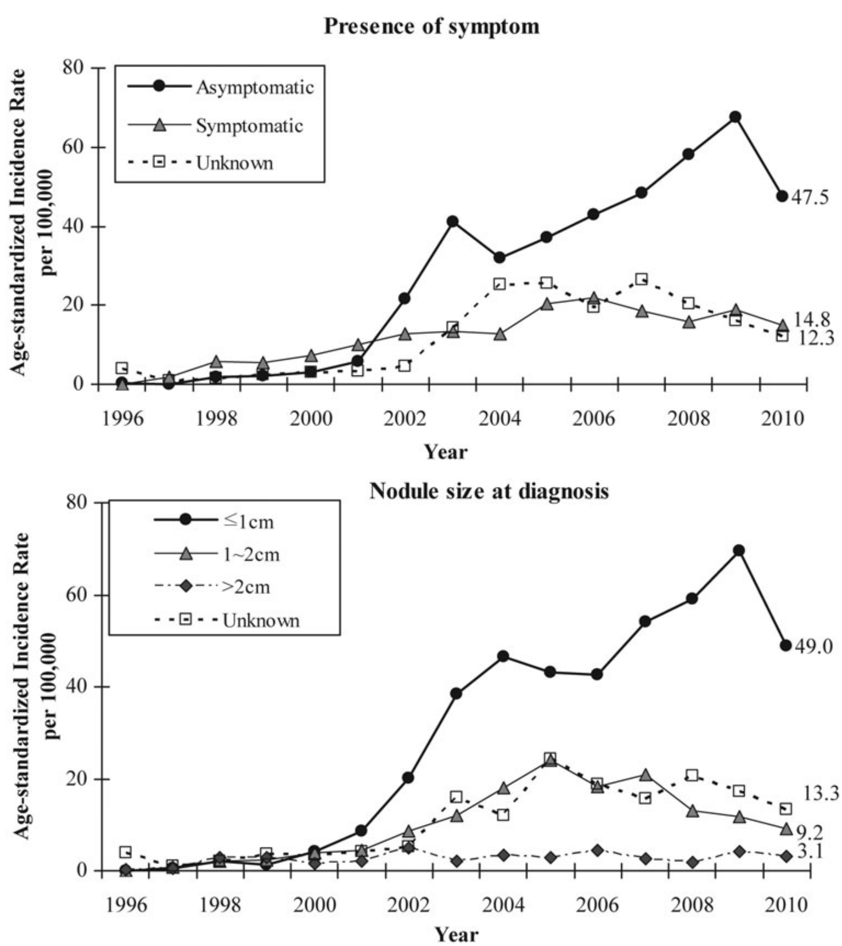

Figure 3. Incidence trend of TC according to the status at incidental diagnosis and the nodule size among the cases registered in Yeosu City ($n = 3101$), 1996–2010.

related symptoms at initial diagnosis was available in 2407 cases (77.6%), and information on the nodule size was available in 2480 cases (80.0%). Fig. 3 shows that the bulk increase was the result of increased detection of asymptomatic cases by screening and small cancers (≤1 cm) (Fig. 3).

DISCUSSION

Significant increases in TC incidence were observed in both sexes and registries between 1996 and 2010. Despite the increasing incidence, mortality from TC remained stable in both sexes. The discrepancy between the increasing incidence of

TC and stable mortality in our study also supports the screening effect rather than real epidemics. However, the longer lag time between the increase in incidence and the increase in mortality compared with other cancers should be considered; this reasoning is thus still controversial.

An increasing trend in TC incidence is not a new phenomenon, but has been sustained for several decades in many countries, though the present study presents the most dominant increasing trend among those that have ever been reported in both sexes. To the best of our knowledge, the highest reported TC incidence rates thus far are 7.7 and 62.9 per 100 000 men and women, respectively, in New Caledonia, a French territory in the South Pacific between 1995 and 1999 (14). The ASRs calculated from our registries in 2010 were ∼1.8- to 3.5-fold higher in both sexes than the previously documented highest rates. Increasing trends in TC incidence were also found in data from Korean National Cancer Registry and from other population-based cancer registries. In 2010, ASRs of TC in Korean population were 18.3 and 87.4 for men and women, respectively (15). The Seoul Cancer Registry reported the women ASR for TC to be 18.8 in 2002 (12). Between 1998 and 2002, the women ASRs for TC were 14.1 and 13.1 in Seoul and Jejudo, respectively (7). When compared with the data from other registries or other countries in the similar period, we found that TC incidence in Gwangju and Jeonnam was higher and increased earlier than those from other population-based cancer registries (Table 3). Moreover, TC has been the most common female cancer among women in our registries, GCR and JCG, as reported consistently since 2003. The ASRs of stomach and breast cancers from 1998 to 2002, which were the most common cancers in Korea, were 27.5 and 21.2 per 100 000 females, respectively, in the GCR (7). In our regions, these values were exceeded by those for TC in 2003, with ASRs of 42.7 per 100 000 women. In the case of men, TC is the fifth most common cancer with an ASR over 21.0 per 100 000 men in the past 5 years (2006–10).

A number of previous studies have reported increasing trends in TC worldwide, which may have several possible explanations as follows: (i) more comprehensive strategy to ensure the quality of registered data may impact time trends (4), (ii) high historical radiation exposure in geographically confined regions, such as those adjacent to Chernobyl (16) or increase in other types of radiation exposure, such as head and neck radiation therapy used to treat benign childhood conditions (17) and occupational exposure (18), (iii) ethnic differences and (iv) changes in medical practice patterns (3,11,19,20). However, the first three possible factors cannot explain the sharp increase in TC in Gwangju and Jeonnam. Guidelines for TC registry or criteria were not modified during the period, and the given environmental factors seldom change over time in the same area.

Table 3. Incidence trend of TC by sex and countries or registries

Registries	Year or period 1	ASR 1 (men, women)	Year or period 2	ASR 2 (men, women)	Annual percentage change (men, women)
Gwangju–Jeonnam	1996–2000	2.3, 13.5 (W)	2006–2010	21.0, 100.0	22.5, 19.7
Korea (15)	2002	2.7, 15.7	2010	18.3, 87.4	NA
Seoul (Korea) (12,35)	1993–1997	NA, 8.9 (W)	1998–2002	NA, 14.1	NA, 5.8
Japan (36,37)	1985	NA	2007	2.2, 7.9	3.0, [8.5 (1985–91); −0.3 (1991–2002); 4.5 (2002–07)]
Hong Kong (38)	1983	1.2, 5.3 (W)	2008	2.5, 10.6	2.0, [6.5 (1983–89); 0.1 (1989–2004); 7.3 (2004–08)]
USA, SEER (39)	1999	3.9, 10.6 (US)	2004–2008	7.0, 21.0	6.2, 7.3
Canada (40)	1970	1.5, 3.9 (C)	2007	5.2, 18.0	3.6, 4.3
The Netherlands (41)	1989	2.0, 3.1 (E)	2009	2.9, 4.1	1.7, 1.7
Denmark	1996	1.4 (W)[a]	2008	2.2	NA
South East England (42)	1987	1.0, 2.6 (W)	2006	1.7, 4.5	0.7, 0. 8
UK (43)	1976–1986	3.0, 8.9 (UK)	1997–2005	5.2, 17.3	NA
Italy (44)	1991–1995	1.8, 4.8 (E)	2001–2005	4.1, 13.6	8.7, 9.6
France (45)	1983–1988	0.8, 2.7 (W)[b]	1995–2000	1.8, 7.5	8.1, 9.0
Lithuania (46)	1978	0.7, 1.5 (E)	2003	2.5, 11.4	4.6, [5.2 (1978–2000); 29.8 (2000–03)]
Germany (47)	1970	1.5, 2.9 (CR)	2002	2.9, 7.7	2.2, 3.0

ASR, age standardized incidence rate adjusted to world population (W) or US standard population (US) or Canada standard population (C) or European standard population (E) or UK standard population(UK).
[a]Rate in men and women.
[b]Rate of papillary TC only.

In addition, no catastrophic accidents in the study area, which might be associated with thyroid pathogenesis, have been reported during the period and within the previous incubation period. In general, geographic or ethnic differences in cancer incidence patterns are also likely influenced by genetic–environmental interactions. However, in a Korean immigration study, TC incidence in Korean Americans was lower than in white Americans and slightly higher than native Koreans for both sexes (21). These data support the accord that Korean traditional dietary habits, environmental exposure and genetic susceptibility do not play a key role in current increase in TC among native Koreans. Recently, several research groups suggested that the increasing incidence in TC is due to the changes in medical practice patterns. The range of more sophisticated diagnostic tools, such as US and US-guided FNAB, and the increased application of confirmative practices, such as surgical biopsy and the removal of solitary nodules, have been suggested as possible contributors to the observed increase in TC diagnosis and reporting. In South Korea, the use of US is widespread and common, even at the primary care level, as are routine US-based check-ups for thyroid masses (22). Notably, thyroid US screening carried out in parallel with prenatal US examination (25) or breast cancer screening (26) is common in Korean medical facilities. In our study, the relatively prominent increasing trends in 20- to 39-year-old and 40- to 59-year-old females (Table 2) could be explained by the thyroid US screening of females of childbearing age and breast cancer screening examinees. The geographic variation in physician's preference for thyroid US and medical behaviors of the inhabitants provide insights into the positive trends in TC incidence and its geographic differences. Indeed, we found geographic differences in time trend in TC incidence within the catchment area (data not shown). In both sexes, the earliest increasing trend with the highest rate was observed in Yeosu City and might be closely associated with the presence of medical facilities, which performed US thyroid screening and FNAB. This small area variation was weakened, because the similar increasing trend was also evident in the rest of the area, even in Gwangju metropolitan city. Such a behavior could also be explained by the extension of attributable medical practice patterns, such as physician-induced US thyroid screening for healthy person without any thyroid problem. Indeed, the use of US thyroid screening for a health screening examinee or breast US examinee was spreading rapidly over the past decade (23,24). We strongly believe that changes in medical practice patterns could better explain the increasing trend of TC in our study, because genetic susceptibility to TC and dietary habits are less likely to change with time and differ from place to place than the tendency of medical practices. There are two prerequisites for the hypothesis of this 'nodule management effects' (20), the existence of sufficient latent pool of TC in populations and existence of detection activities (25). A recent study from South Korea reported that the TC prevalence in health examinees with thyroid nodules was 23.6% in females and 11.9% in males, respectively (10). Another study reported that the prevalence of incidental thyroid nodules was 27.4 and 7.0% in men and women, respectively. Among these incidental nodules, the prevalence of malignant TC was 11.5 and 12.8% in men and women, respectively (26). The reported prevalence of thyroid nodule and malignancy in Korean studies is similar to the reported studies in other countries, and the prevalence of thyroid nodule ranged from 9.2 to 13.0% (27–29). Moreover, a Korean nationwide survey reported that a total of 13.2% of adults (8.4% in men and 16.4% in women) underwent US thyroid screening during their lifetime (22).

Numerous recent studies have suggested that the marked increase in cancer incidence, including thyroid, prostate and breast, may be due in part to the early detection of latent tumors, which may have otherwise never progressed into symptomatic cancers during the patient's lifetime. Abrupt increases in cancer incidence are seldom observed in reality without the concomitant occurrence of a catastrophic accident, such as nuclear bomb testing or exposure to high doses of toxic pollutants. A recent study from the USA suggested that the increasing incidence of TC was related to the increased detection of small subclinical papillary cancers (2). Based on the magnitude of the latent TC pool in South Korea, we speculate that these increases in TC incidence will be sustained for some time in the future. Although the use of thyroid US is routine in our study area, its usage may eventually spread nationwide. Indeed, TC incidence from the Korean National Cancer Registry in 2009 was also increased up to 15.4 and 79.6 persons per 100 000 men and women, respectively (30). Recently, a study reported an evidence for the association between the incidence of TC and the status of economic level or characteristics of healthcare system (31). The study predicted that an upward trend of TC is dominantly present in developed countries. In such an event, we can refer to this occurrence as the 'thyroid US screening era' in the near future, and these usage trends will also likely spread to other developed countries.

In general, the main causes of cancer are reportedly related to lifestyle factors. Moreover, some studies suggest that the enhanced detection cannot fully explain the increase in TC (32–34). Therefore, more detailed epidemiological data are needed to determine whether the increased TC incidence is not simply the result of altered medical practice patterns, but also due to increased exposure to certain environmental risk factors. To clarify the factors underlying these unfortunate trends, further research on the distributions of cancer stages, mass sizes, symptoms and diagnosis opportunity is ongoing in the study area.

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Conflict of interest statement

None declared.

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