Cancer Causes Control (2009) 20:525–531
DOI 10.1007/s10552-008-9260-4

ORIGINAL PAPER

International patterns and trends in thyroid cancer incidence, 1973–2002

Briseis A. Kilfoy · Tongzhang Zheng · Theodore R. Holford · Xuesong Han · Mary H. Ward · Andreas Sjodin · Yaqun Zhang · Yana Bai · Cairong Zhu · Grace L. Guo · Nathaniel Rothman · Yawei Zhang

Received: 12 June 2008 / Accepted: 27 October 2008 / Published online: 19 November 2008

Abstract During the past several decades, an increasing incidence of thyroid cancer has been reported in many parts of the world. To date, no study has compared the trends in thyroid cancer incidence across continents. We examined incidence data from cancer incidence in five continents (CI5) over the 30-year period 1973–2002 from 19 populations in the Americas, Asia, Europe, and Oceania. Thyroid cancer rates have increased from 1973–1977 to 1998–2002 for most of the populations except Sweden, in which the incidence rates decreased about 18% for both males and females. The average increase was 48.0% among males and 66.7% among females. More recently, the age-adjusted international thyroid cancer incidence rates from 1998 to 2002 varied 5-fold for males and nearly 10-fold for females by geographic region. Considerable variation in thyroid cancer incidence was present for every continent but Africa, in which the incidence rates were generally low. Our analysis of published CI5 data suggests that thyroid cancer rates increased between 1973 and 2002 in most populations worldwide, and that the increase does not appear to be restricted to a particular region of the world or by the underlying rates of thyroid cancer.

Keywords International trends · Thyroid cancer · Papillary thyroid cancer

B. A. Kilfoy · T. Zheng · T. R. Holford · X. Han · Y. Zhang · Y. Bai · C. Zhu · Y. Zhang (✉)
Yale School of Public Health, Yale University, 60 College Street, LEPH 440, P.O. Box 208034, New Haven, CT 06520, USA
e-mail: yawei.zhang@yale.edu

B. A. Kilfoy · M. H. Ward · N. Rothman
Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, US Department of Health and Human Services, Rockville, MD, USA

A. Sjodin
Division of Laboratory Sciences (DLS), Organic Analytical Toxicology Branch (OATB), National Center for Environmental Health (NCEH), Centers for Disease Control and Prevention (CDC), 4770 Buford Highway NE, Atlanta, GA 30341, USA

Y. Zhang
Gansu Provincial Design and Research Institute of Environmental Science, Lanzhou, Gansu, China

Y. Bai
School of Public Health, Lanzhou University, Lanzhou, Gansu, China

C. Zhu
School of Public Health, Sichuan University, Chengdu, Sichuan, China

G. L. Guo
Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Cancer, Kansas City, KS, USA

Introduction

Thyroid cancer is a relatively rare neoplasm worldwide, accounting for approximately 1–5% of all cancers in females and <2% in males [1]. Although the incidence of thyroid cancer is relatively rare, it is the most common endocrine malignancy worldwide [1]. While the international incidence varies considerably, a fairly consistent female-to-male ratio of 3:1 is observed in almost all geographic areas and ethnic groups [1].

During the past several decades, an increasing incidence of thyroid cancer has been reported in some European countries, the United States, and some parts of the China [2–7]; however, no study has provided a comparison of trends in thyroid cancer incidence across continents. The

International Agency of Research on Cancer (IARC) has published rates for time periods spanning three decades for 95 registries around the world, enabling the analysis of trends over a relatively longer time period. In order to understand how thyroid cancer incidence has changed over time across different populations and what factors may be responsible for the observed change, we examined incidence data over the 30-year period 1973–2002 from 19 populations in the Americas, Asia, Europe, and Oceania.

Materials and methods

Incidence data

In order to examine the secular trends in the incidence of thyroid cancer, age-standardized (World Population) incidence rates were obtained from Vols. 4–9 of cancer incidence in five continents (CI5). The CI5 volumes include incidence data reported by selected population-based cancer registries covering areas within Asia, Oceania, Africa, Europe, and the Americas. Volumes 4–9 generally provided data for the 5-year periods: 1973–1977, 1978–1982, 1983–1987, 1988–1992, 1993–1997, and 1998–2002. The classification of thyroid cancer was based on ICD-8, ICD-9, and ICD-10 for Vols. 4, 5–8, and 9, respectively. There were no changes in the coding of thyroid cancer among the 8th, 9th, and 10th revisions (193). Incidence rates for different histologic subtypes (follicular, papillary, medullar, anaplastic, and other/unspecified) were abstracted from Vol. 9, as incidence rates for specific subtypes was not provided in the earlier volumes.

Populations were chosen for inclusion in our analysis on the basis of the following criteria: (1) availability of rates in the CI5 for time periods at least, as far back as 1978–1982; (2) an absence of changes in population coverage or of warnings regarding data quality; and (3) a sufficiently large number of registered cases in CI5 Vol. 9 to enable analyses of recent rates by histologic subtype (trends by histologic subtype are not included in our study). Only one registry from each country was selected; if more than one registry met the basic criteria, the registry with the largest population was included in the analysis. A total of 19 populations were selected: four from the Americas, four from Asia, four from Scandinavia, five from elsewhere in Europe and two from Oceania. No African or South Asian populations met all the inclusion criteria. However, five African countries included in CI5 Vol. 9 (Algeria, Setif; Egypt, Gharbiah; Tunisia, Center, Sousse; Uganda, Kyadondo Country; and Zimbabwe, Harrare) and the registry of Mumbai, India, had rates available which allowed for a broader geographic comparison for recent years.

Data analysis

Thyroid cancer incidence is presented overall and by histologic subtype for males and females separately for selected populations for the time period 1998–2002. Trends in age-standardized (world standard) incidence rates were examined for the time periods 1973–1977, 1978–1982, 1983–1987, 1988–1992, 1993–1997, and 1998–2002. The percentage change in thyroid cancer rates between 1973–1977 and 1998–2002 was calculated for each population to show the relative change in incidence between these two periods for males and females separately.

Results

The 1998–2002 age-adjusted thyroid cancer incidence rates varied 5-fold for males and nearly 10-fold for females (Table 1), with the highest rates in the US and Israel for males (3.5 per 100,000 for both countries) and for females (10.0 per 100,000 and 12.1 per 100,000, respectively), and the lowest rates in Uganda for males (0.5 per 100,000) and for females (1.5 per 100,000). Neither the highest rates nor the lowest rates were concentrated in one continent for either males or females. Considerable variation in thyroid cancer incidence was present within every continent with the exception of Africa, in which the incidence rates were generally low. Based on the rates from 1998 to 2002, the incidence of papillary was the highest, followed by follicular, medullar and anaplastic subtypes (Figs. 1, 2).

Thyroid cancer rates increased from 1973–1977 to 1998–2002 (Table 1) for most populations. On average, the populations with increasing rates experienced about a 58.1% increase. The average increase was 48.0% among males and 66.7% among females with the largest increase in New South Wales, Australia for both males (177.8%) and females (252.2%). In contrast, the incidence rates decreased for males in Sweden (18.8%) and for females in Norway, Sweden, and Spain (5.8%, 18.2%, and 25.9%, respectively).

The thyroid cancer rates among each population during the 30-year period 1973–2002 are shown in Fig. 2a, b. Fairly consistent increasing trends in rates were apparent for most populations, and positive trends were generally stronger among females. There has been, however, a leveling off for trends in the Scandinavian countries.

Discussion

During the period 1973–2002, the incidence rates of thyroid cancer increased among most populations examined. Thyroid cancer incidence among the 19 populations

Table 1 International variation in thyroid cancer incidence rates, from 1973–1977 to 1998–2002

	1973–1977				1998–2002					
	Males		Females		Males		Females		Males	Females
	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	% Change	% Change
Europe, Scandinavian Countries										
Denmark	168	1	330	1.6	210	1.2	524	2.9	20.0	81.3
Norway	182	1.4	558	4.4	247	1.6	649	4.2	14.3	−5.8
Sweden	463	1.6	1,158	3.9	407	1.3	1,031	3.3	−18.8	−18.2
Finland	221	1.7	684	4.3	384	2.2	1,281	7.0	29.4	62.8
Europe, Other										
France, Bas-Rhin	25	0.9	85	2.8	75	2.3	198	5.8	155.6	107.1
Switzerland, Geneva	18	1.9	43	3.5	27	2.0	98	6.5	5.3	85.7
UK, Thames, England	134	0.6	391	1.5	433	0.9	1,133	2.3	50.0	53.3
Italy, Varese	45	2.0	105	3.8	45	2.9	123	7.1	45	86.8
Spain, Zaragoza	28	1.2	134	5.4	37	1.4	123	4.0	16.7	−25.9
Oceania										
New Zealand	108	1.2	285	3.1	181	1.6	598	5.1	33.3	64.5
Australia, New South Wales	116	0.9	315	2.3	506	2.5	1,639	8.1	177.8	252.2
Americas										
USA, SEER: White	997	2.3	2,491	5.4	2,216	3.5	6,306	10.0	52.2	85.2
Canada, BC	104	1.5	252	3.6	271	2.1	733	5.6	40	55.6
Colombia, Cali	20 (1972–1976)	1.5	104 (1972–1976)	6.1	85	2.2	450	9.4	46.7	54.1
USA, SEER: Black	47	1.2	173	3.8	121	1.6	494	5.2	33.3	36.8
Asia										
China, Hong Kong	126 (1974–1977)	1.6	352 (1974–1977)	4.2	447	2.2	1,557	7.2	37.5	71.4
Japan, Osaka Prefecture	129	0.7	432	2.1	432	1.3	1,194	3.2	85.7	52.4
Singapore	43	1.3	141	3.8	180	2	636	6.6	53.8	73.7
Israel: Jews	193	2.6	472	6.2	474	3.5	1,747	12.1	34.6	95.2
Africa										
Algeria, Setif					32	1.4	88	3.6		
Egypt, Gharbiah					53	1.1	151	2.6		
Tunisia, Center, Sousse					14	1.3	34	3.1		
Uganda, Kyadondo County					11	0.5	26	1.5		
Zimbabwe, Harare					14	1	45	3.1		

Rate is age-standardized to the world population, per 100,000 person-years. Counts, rate for 1978–1982 period. These registries were excluded from the trends analysis due to an absence of data for early time periods, changes in population coverage, and/or data quality issues

varied more than 5-fold in both males and females. The variation was mainly attributed to papillary thyroid carcinoma. Despite the wide intercountry variation in age-adjusted incidence rates, a consistent female-to-male ratio of 3:1 is observed within most of the countries included in both the earlier (1973–1977) and later (1998–2002) data (Figs. 3, 4).

It is currently unclear whether the observed increases in thyroid cancer are real or are due to increased diagnosis. The common use of fine needle aspiration technology in the late 1980s in combination with thyroid ultrasound has facilitated the diagnosis of smaller thyroid tumors [8] in areas with access to these technologies. Previously, investigators concluded that the increase in the incidence rates reflects the increased detection of subclinical disease, not an increase in the true occurrence of thyroid cancer due to the increase in microcarcinomas [8]. Since, information on tumor size is not available for majority of the registries, we were unable to assess whether the international incidence rates increased for all sizes of thyroid cancer tumors or mainly in cases with smaller size tumors. However, we observed a substantial percent change from 1988–95 to 1996–2005 in the incidence of thyroid cancer for both smaller size tumors and larger size tumors in the SEER 9

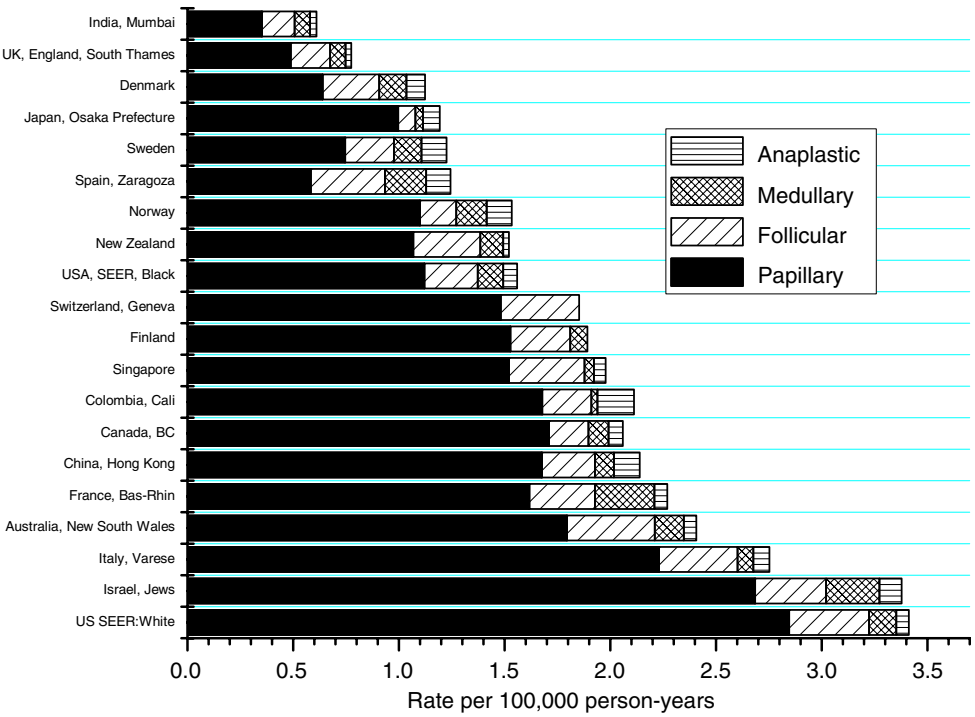

Fig. 1 Rates for males from selected populations for the time period 1998–2002. Incidence rates of thyroid cancer for males (per 100,000 person-years) age standardized to the world population for selected populations for the time period 1998–2002

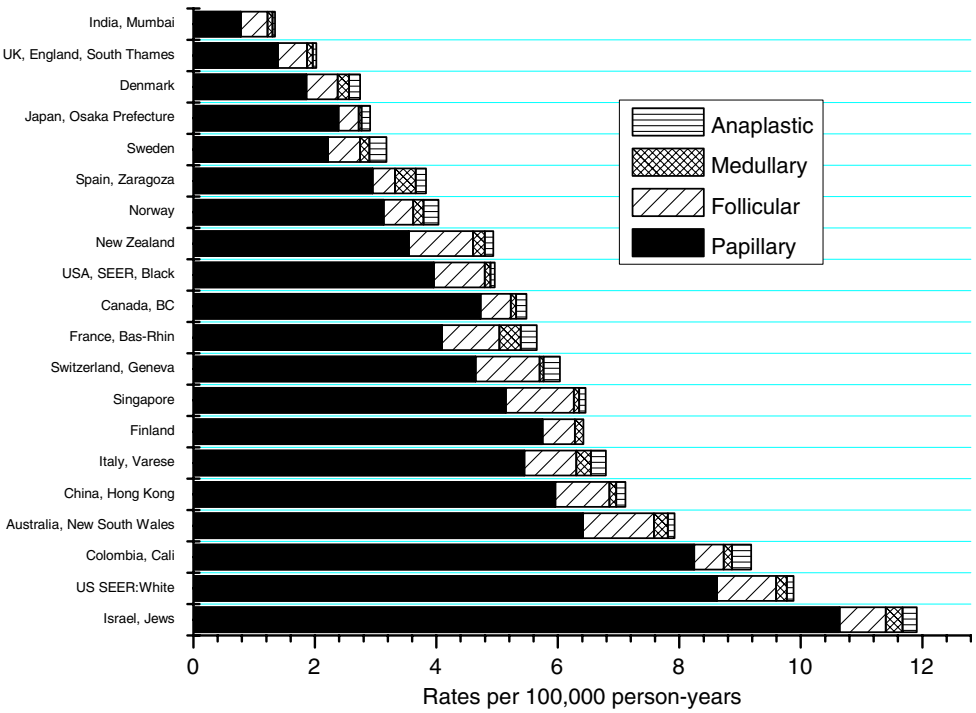

Fig. 2 Rate for females from selected populations for the time period 1998–2002. Incidence rates of thyroid cancer for females (per 100,000 person-years) age standardized to the world population for selected populations for the time period 1998–2002

database [9], with a 120.85% increase in thyroid microcarcinomas < 1 cm, and a 56.2% increase for thyroid tumors > 4 cm. This argues against advanced diagnostic techniques or increased attention to small nodules as the only explanation for the observed increasing trend of thyroid cancer.

The histopathologic classification system for thyroid cancer has evolved over time. In 1988, the World Health Organization (WHO) revised its classification when it was recognized that nuclear features (particularly nuclear inclusions and nuclear folds) are more important than architectural patterns in classifying thyroid cancer [10]. As

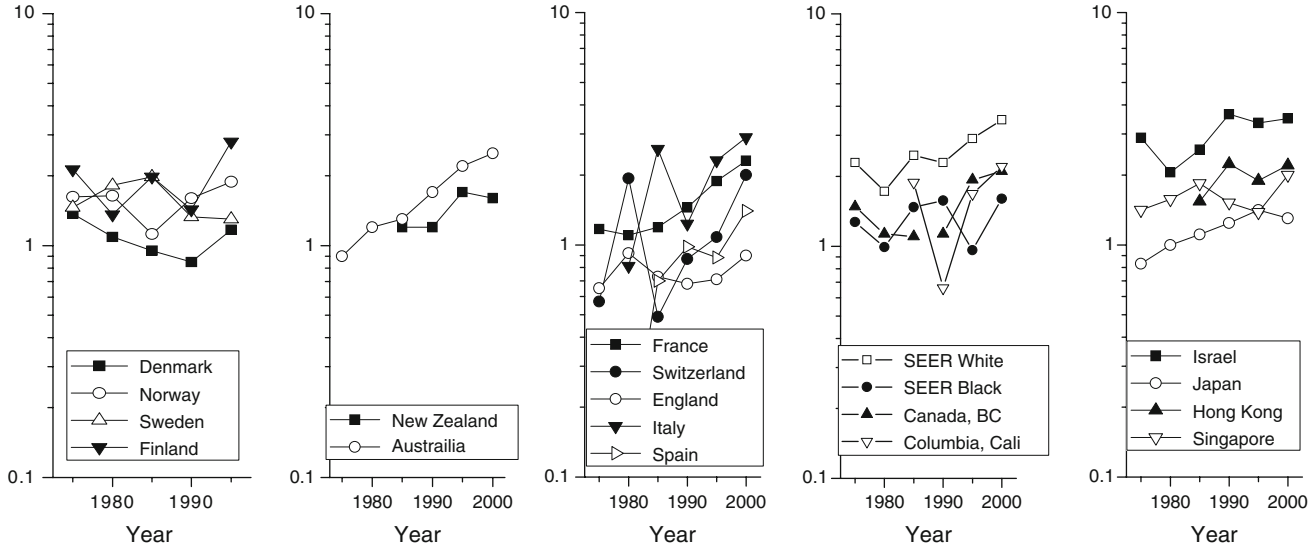

Fig. 3 Trends in age-standardized thyroid cancer rates for males by continent and area for the time periods 1973–2002

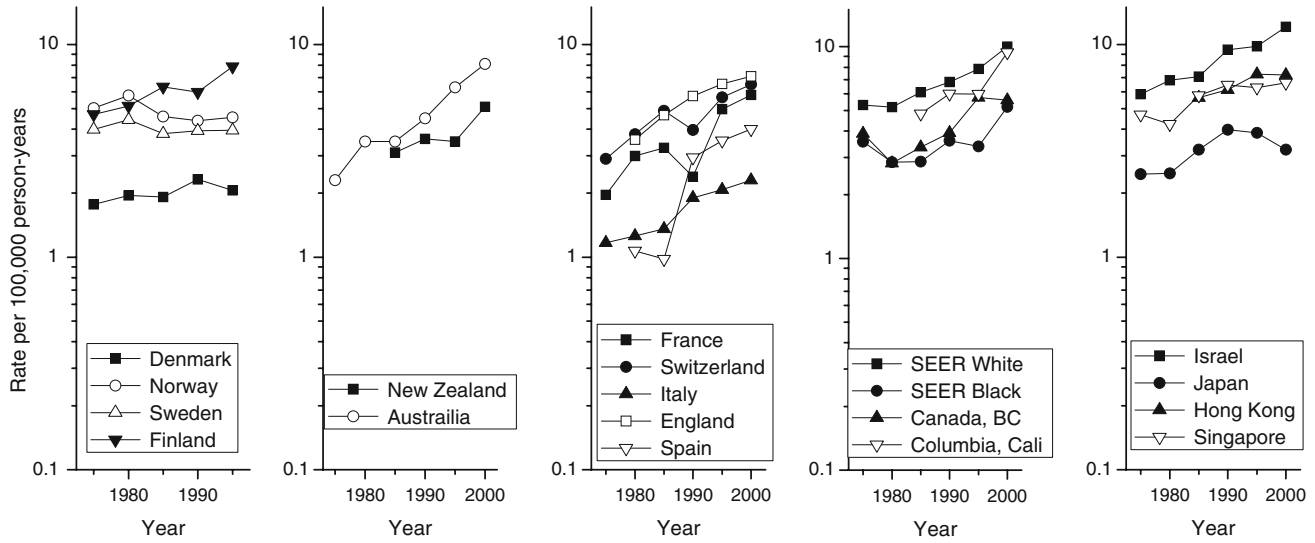

Fig. 4 Trends in age-standardized thyroid cancer rates for females by continent and area for the time periods 1973–2002

a result, many cancers previously classified as follicular are now categorized as follicular variants of papillary cancer [11]. Although changes in classification could impact the distribution of cases by subtype, this point does not undermine our findings as the total number of cases diagnosed should not be significantly affected.

Most countries have introduced nationwide iodization measures, but there are regional differences in the year iodine supplementation was implemented. In 1990, iodine deficiency affected almost one-third of the world population [12]. Following a resolution adopted by the World Summit for Children in 1990, major programs of iodine supplementation were implemented by the governments of the affected countries. By April 1999, 68% of the affected populations had access to iodized salt. It has been noted that when iodine supplementation occurs in iodine deficient regions, the proportion of papillary thyroid cancers often increases although the overall rates tend to stay the same [13, 14]. According to the World Health Organization, of the countries included in this study with available iodine intake data, Denmark, France, Italy, Australia, New Zealand, and Algeria are reported to be iodine deficient [15].

The differences in thyroid cancer rates, particularly among women, in the Scandinavian countries are notable because similar standards of medical care and reporting in the Scandinavian countries reduce the limitations associated with intercountry comparisons. The age-adjusted incidence rate among women in Finland is over twice that reported in Denmark in both time periods of interest (1973–1977 and 1998–2002). Furthermore, the wide

variation in percent change over the past three decades in these countries is striking. This suggests that these populations may be experiencing different levels of environmental exposure to a significant risk factor/set of risk factors.

It is also notable that despite the wide intercountry variation in age-adjusted incidence rates, according to the GloboCan 2002 database [16], there is a small variation in sex-specific mortality rates by geographic region. Among females, the current thyroid cancer mortality rates for the European, Oceanic, American, and Asian countries included in this analysis is between 0.2 and 1.0 per 100,000 person-years. Similarly, for males, the range in thyroid cancer mortality rates is from 0.1 to 0.7 per 100,000 person-years. Such consistency in the mortality burden suggests that differences in incidence may be a function of detection methods. However, as thyroid cancer is known to have a high rate of survival, the intercountry consistency in mortality rate may not necessarily be evidence for artificially inflated rates.

There is emerging evidence that PBDEs alter thyroid hormone homeostasis and cause thyroid dysfunction, and may subsequently play a role in the global increase in thyroid tumorigenesis [17]. The use of PBDEs has increased rapidly during the last three decades in the US and other parts of the world, doubling in some areas in less than a decade [18], reaching a global demand of 200,000 tons in 2003 [19]. PBDEs are widely used as flame retardants in polyurethane foam, textiles, and hard plastics used in applications such as carpet pads, furniture, curtains, televisions, computers, and seats in automobiles and airplanes. The impact of these hormone disrupting agents in the etiology of thyroid cancer is of interest, as there is strong animal data and evidence for increasing and widespread global exposure. The European Union banned the use of two PBDEs (Penta- and OctaBDE) in 2004 due to increasing evidence that PBDEs may result in thyroid toxicity, liver toxicity, and neurodevelopmental toxicity, and because PBDEs accumulate in human breast milk [20]. The State of Washington also passed a bill banning the use of PBDEs in 2007 [21]. However, these compounds, like the other previously banned PHAHs (such as PCBs, DDT, and HCB), will remain ubiquitous in the environment due to their stability, persistence, and their ability to bioaccumulate.

It is also notable that despite the wide intercountry variation in age-adjusted incidence rates, a consistent female-to-male ratio of 3:1 is observed within most of the countries included in the international comparison in both the earlier (1973–1977) and later (1998–2002) data. Possible explanations for the disparities between males and females with sporadic thyroid cancers are biological sex differences, differential screening patterns, or gender-specific behavioral differences. One hypothesized mechanism is that increased levels of female hormones during reproductive years, due to pregnancy which increases thyroid stimulating hormone (TSH) levels, potentially lead to thyroid dysplasia and then to cancer [22–25]. Experimental evidence shows that TSH stimulation of the thyroid gland leads to proliferative changes in follicular cells including hypertrophy and hyperplasia, as well as ultimately neoplasia in rodents [26]. Our results confirm the previously observed gender disparity and support the need for future research in this area.

In summary, our analysis of published CI5 data suggests that thyroid cancer rates increased between 1973 and 2002 in most populations worldwide, for males and females, and that the increase does not appear to be restricted to a particular region of the world or by the underlying rates of thyroid cancer. There is also some indication that the rates may be leveling off in some populations. The worldwide increase in thyroid cancer incidence may be due to changes in the prevalence of important risk factors; epidemiologic investigations describing between population differences and within population trends in the prevalence of suspected risk factors may yield important insights into the causes of the widespread increase in thyroid cancer.

Acknowledgment This research was supported by the National Institutes of Health training grant TU2CA105666 and National Institutes of Health Fogarty training grant 2043TW007864-01.

References

1. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P (eds) (2007) Cancer incidence in five continents, vol IX. IARC Scientific Publications, Lyon, IARC, p 160
2. Akslen LA, Haldorsen T, Thoresen SO, Glattre E (1993) Incidence pattern of thyroid cancer in Norway: influence of birth cohort and time period. Int J Cancer 53:183–187. doi:10.1002/ijc.2910530202
3. Colonna M, Grosclaude P, Remontet L et al (2002) Incidence of thyroid cancer in adults recorded by French cancer registries (1978–1997). Eur J Cancer 38:1762–1768. doi:10.1016/S0959-8049(02)00110-7
4. Dos Santos Silva I, Swerdlow AJ (1993) Thyroid cancer epidemiology in England and Wales: time trends and geographical distribution. Br J Cancer 67:330–340
5. Montanaro F, Pury P, Bordoni A, Lutz JM (2006) Unexpected additional increase in the incidence of thyroid cancer among a recent birth cohort in Switzerland. Eur J Cancer Prev 15:178–186. doi:10.1097/01.cej.0000197450.94980.36
6. Pettersson B, Adami HO, Wilander E, Coleman MP (1991) Trends in thyroid cancer incidence in Sweden, 1958–1981, by histopathologic type. Int J Cancer 48:28–33
7. Qian B, He M, Dong S, Wang J, Chen K (2005) Incidence and mortality of thyroid cancers in Tianjin from 1981 to 2001. Chin J Endocrinol Metab 21:432–434
8. Davies L, Welch HG (2006) Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA 295:2164–2167. doi:10.1001/jama.295.18.2164
9. Surveillance, Epidemiology, and End Results (SEER) Program (November 2007 submission). Public-use database (1973–2005).

National Cancer Institute DCCPS, Suveillance Research Program, Cancer Statistics Branch, Released April 2008, based on the November 2007 submission
10. World Health Organization (1998) In: Hedinger CWE, Sobin LH (eds) Histological typing of thyroid tumours, 2nd edn. Springer, Berlin
11. LiVolsi VA, Asa SL (1994) The demise of follicular carcinoma of the thyroid gland. Thyroid 4:233–236
12. Delange F, Lecomte P (2003) Iodine supplementation: benefits outweigh risk. Drug Saf 22:89–95. doi:10.2165/00002018-200022020-00001
13. Harach HR (2003) Sporadic versus familial medullary thyroid microcarcinoma. Am J Surg Pathol 27:136–137. doi:10.1097/00000478-200301000-00016
14. Huszno B, Szybinski Z, Przybylik-Mazurek E, Stachura J, Trofimiuk M, Buziak-Bereza M, Gollowski F, Pantoflinski J (2003) Incidence of thyroid cancer in the selected areas of iodine deficiency in Poland. J Endocrinol Invest 26:57–62
15. World Health Organization (2004). In: de Benoist B, Andersson M, Egli I, Takkouche B, Allen H (eds). Iodine status worldwide: WHO global database on iodine deficiency. Department of Nutrition for Health and Development. World Health Organization, Geneva
16. Ferlay J, Bray F, Pisani P, Parkin DM (2004) GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5. Version 2.0. IARC Press, Lyon
17. Zhang Y, Guo G, Han X, Zhu C, Kilfoy BA, Zhu Y, Boyle P, Zheng T (2008) Do polybrominated diphenyl ethers (PBDEs) increase the risk of thyroid cancer? Biosci Hypothesis 1:195–199. doi:10.1016/j.bihy.2008.06.003
18. Schecter A, Päpke O, Tung KC, Joseph J, Harris TR, Dahlgren J (2005) Polybrominated diphenyl ether flame retardants in the U.S. population: current levels, temporal trends, and comparison with dioxins, dibenzofurans, and polychlorinated biphenyls. J Occup Environ Med 47(3):199–211. doi:10.1097/01.jom.0000158704.27536.d2 Mar
19. Guvenius DM, Aronsson A, Ekman-Ordeberg G, Bergman A, Noren K (2003) Human prenatal and postnatal exposure to polybrominated diphenyl ethers, polychlorinated biphenyls, polychlorobiphenylols, and pentachlorophenol. Environ Health Perspect 111:1235–1241
20. Directive 2003/11/EC of the European Parliament and of the Council of 6 February 2003 amending for the 24th time Council Directive 76/769/EEC relating to restrictions on the marketing and use of certain dangerous substances and preparations (pentabromodiphenyl ether, octabromodiphenylether). http://eur-x.europa.eu/LexUriServ/site/en/oj/2003/l_042/l_04220030215en00450046.pdf
21. "Chemical ban puts industry on the defensive." State of Washington bans use of PBDEs. http://seattlepi.nwsource.com/local/311845_pbdes17.html
22. Memon A, Darif M, Al-Saleh K, Suresh A (2002) Epidemiology of reproductive and hormonal factors in thyroid cancer: evidence from a case–control study in the Middle East. Int J Cancer 97:82–89. doi:10.1002/ijc.1573
23. Negri E, Dal Maso L, Ron E et al (1999) A pooled analysis of case-control studies of thyroid cancer. II. Menstrual and reproductive factors. Cancer Causes Control 10:143–155. doi:10.1023/A:1008880429862
24. Zivaljevic V, Vlajinac H, Jankovic R et al (2003) Case–control study of female thyroid cancer—menstrual, reproductive and hormonal factors. Eur J Cancer Prev 12:63–66. doi:10.1097/00008469-200302000-00010
25. Goodman MT, Kolonel LN, Wilkens LR (1992) The association of body size, reproductive factors and thyroid cancer. Br J Cancer 66:1180–1184
26. Smith P, Williams ED, Wynford-Thomas D (1987) In vitro demonstration of a TSH-specific growth desensitising mechanism in rat thyroid epithelium. Mol Cell Endocrinol 51:51–58. doi:10.1016/0303-7207(87)90118-3