Major Evolution in Clinical Detection of Thyroid Cancer Since 2000

Potential Impact on Findings and Analyses

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Medullary Thyroid Carcinoma Registry

MTC Registry Background

- In mice and rats, long-acting GLP-1 receptor agonists (GLP-1 RAs)caused proliferative and neoplastic changes in the thyroid C-cells

- As a Post Marketing PhV requirement the FDA requested the sponsor of the first LA-GLP-1 RA (NN) to design and conduct an observational MTC Registry Study for at least 15 years

- Subsequently all sponsors with FDA approved LA GLP-1 RAs have been required to conduct a similar 15 year registry of MTC incident cancers.

MTC REGISTRY CONSORTIUM

Kristine Harper, MD
March 22, 2016

Formation of the MTC Registry Consortium

- As all sponsors would be pulling from the same very limited source, FDA suggested all Sponsors with LA GLP-1 RAs collaborate on 1 registry to minimize inconvenience to patients, physicians, and state cancer registries
- Thus the MTC Registry Consortium was formed
- United BioSource Corporation (UBC) is managing the MTC registry on behalf of the Sponsors

MTC REGISTRY CONSORTIUM

Kristine Harper, MD
March 22, 2016

Consortium Sponsors

- Consortium Sponsors include those companies with an FDA approved long-acting GLP-1RA and who have a contractual agreement to participate in the MTC Registry

- Current Members
  - Novo Nordisk (2010)
  - AstraZeneca (2/2014) (Amylin, 6/2012; BMS&AZ, 4/2013)
  - GlaxoSmithKline (10/2014)
  - Eli Lilly (2/2015)

- Other companies with long-acting GLP-1 RAs developed in the future could potentially join the Consortium

MTC REGISTRY CONSORTIUM

Kristine Harper, MD
March 22, 2016

Medullary Thyroid Carcinoma Registry

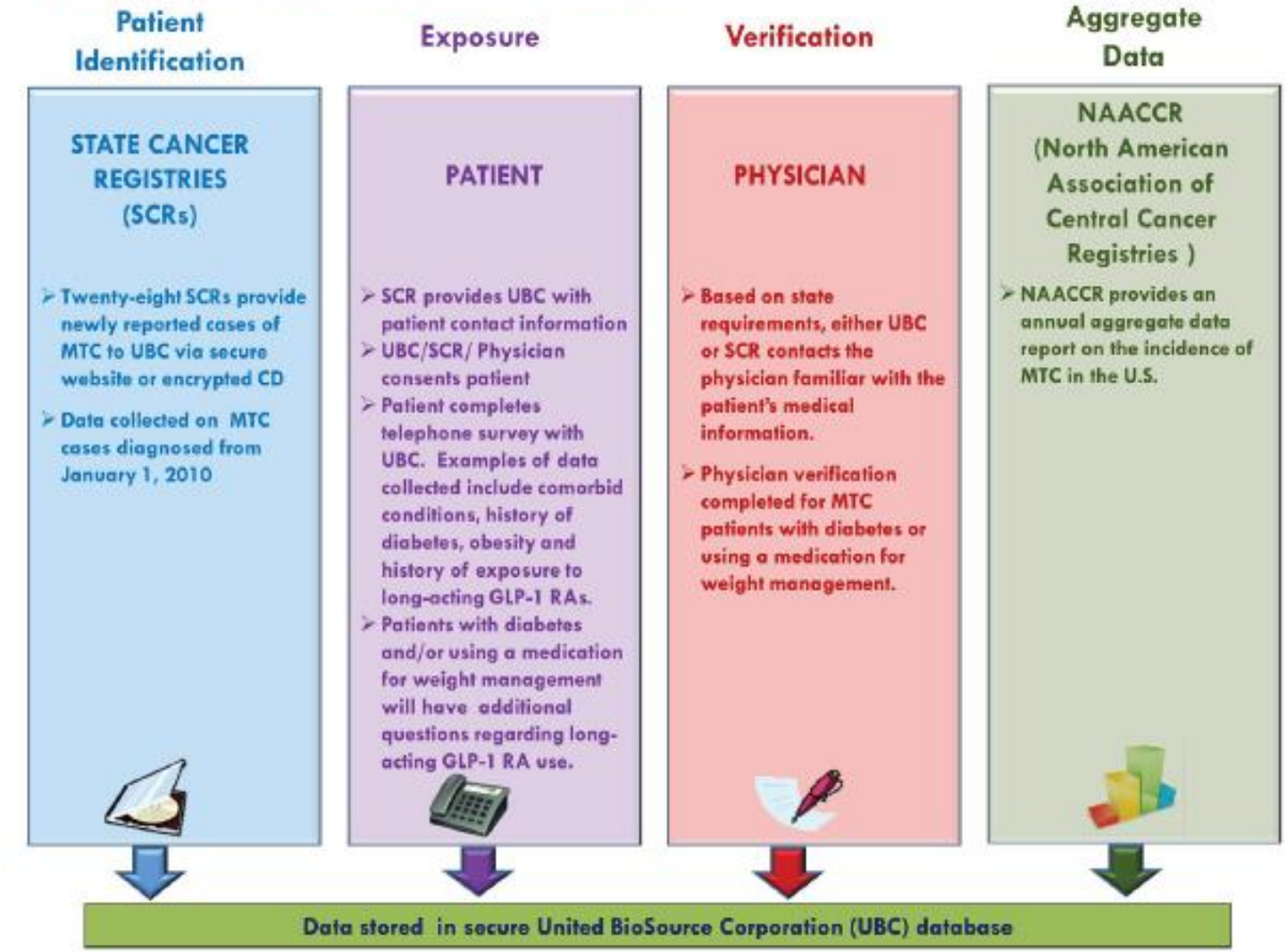
OBJECTIVES

1. To systematically monitor the annual incidence of MTC in the US through the North American Association of Central Cancer Registries (NAACCR) to identify any possible increase related to the introduction of long-acting GLP-1 RAs into the US market.
2. To establish a registry of incident cases of MTC in adults in the US to characterize their medical histories and possible risk factors, including history of long-acting GLP-1 RAs treatment.

MTC REGISTRY CONSORTIUM

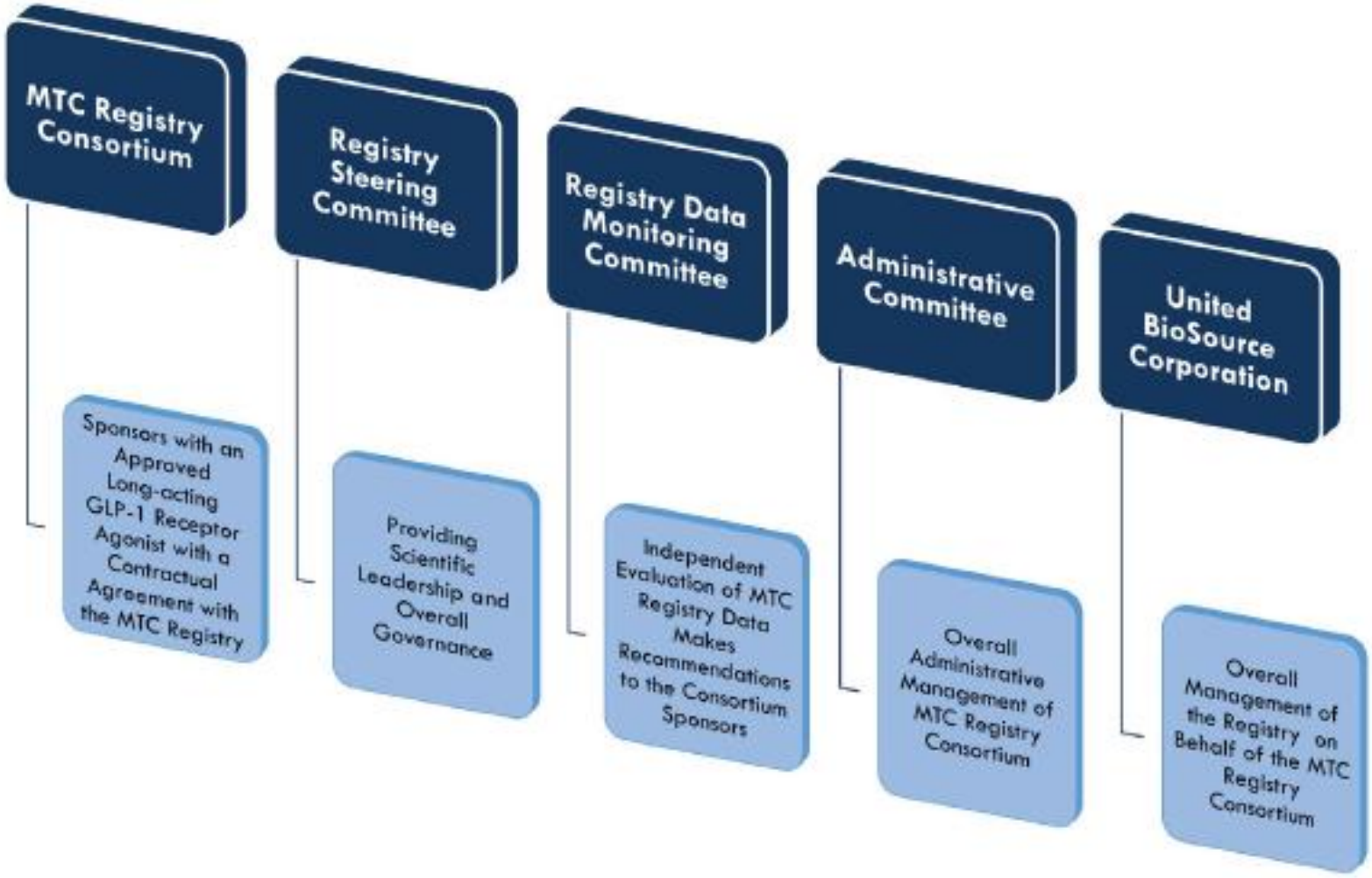
Medullary Thyroid Carcinoma Registry

Figure 2.MTC Registry Paths to Collect Patient Data



Medullary Thyroid Carcinoma Registry

Figure 1. MTC Committees and Corporations Involved in the Conduct of the Registry



Medullary Thyroid Carcinoma Registry

METHODS/CASE PRESENTATION

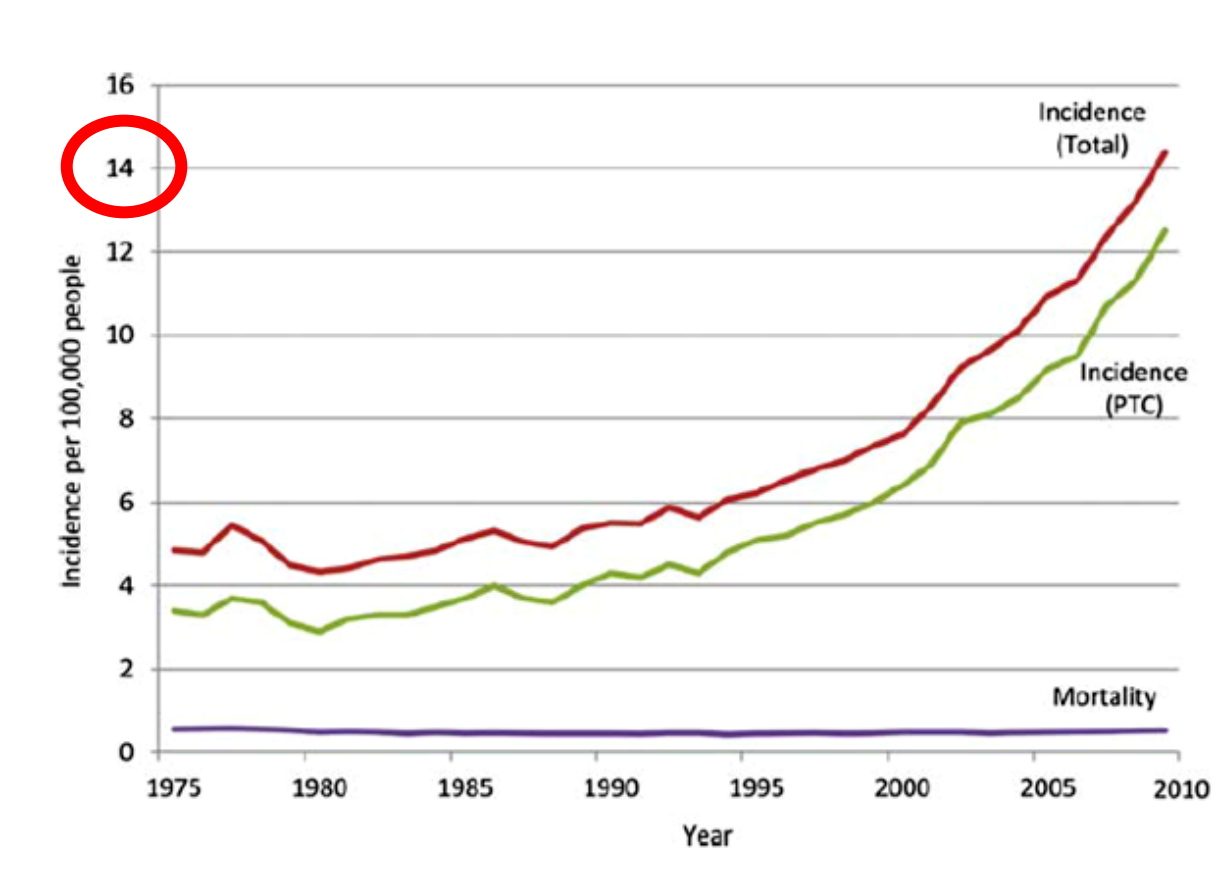
As seen in Figure 1, the sponsors have formed the MTC Registry Consortium and partnered with the American Thyroid Association to conduct this registry under the management of the United BioSource Corporation. The Registry Committees provide scientific leadership and overall governance (Steering), an independent review of collected case data (Data Monitoring), and daily operational oversight (Administrative). To meet objective 1, annual MTC incidence rates are obtained from the North American Association of Central Cancer Registries (NAACCR). The time period prior to the introduction of long-acting GLP-1 RAs into the marketplace is used as the baseline (January 1, 2001 to December 31, 2009).

1. To meet objective 1, annual MTC incidence rates are obtained from the North American Association of Central Cancer Registries (NAACCR) using January 1, 2001 to December 31, 2009 as a baseline as it reflects the time period prior to the introduction of long-acting GLP-1 RAs into the marketplace.
2. To meet objective 2, new (or incident) cases of MTC after January 1, 2010 are identified by participating State Cancer Registries (SCRs). Once informed consent is obtained from the patient or proxy, a telephone interview is conducted to collect possible risk factors including comorbid conditions, history of diabetes, obesity, and history of exposure to long-acting GLP-1 RAs. If a patient was treated with a long-acting GLP-1 RA or had a diabetes diagnosis, attempts are made to contact the treating physician to obtain verification of diagnosis and medications prescribed.

Increasing Diagnosis of Subclinical Thyroid Cancers Leads to Spurious Improvements in Survival Rates

Allen S. Ho, MD[1]; Louise Davies, MD[2,3]; Iain J. Nixon, MD[1]; Frank L. Palmer, MD[1]; Laura Y. Wang, MD[1]; Snehal G. Patel, MD[1]; Ian Ganly, MD[1]; Richard J. Wong, MD[1]; R. Michael Tuttle, MD[4]; and Luc G. T. Morris, MD, MSc[1]

Cancer 2015



SEER 1975-2009
Age adjusted incidence rates per 100,000

Cancer Res Treat. 2014 Dec 2 [Epub ahead of print] http://dx.doi.org/10.4143/crt.2014.110

Original Article Open Access

Age-Period-Cohort Analysis of Thyroid Cancer Incidence in Korea

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Young-Joo Won, PhD[1]
Aesun Shin, MD, PhD[12]
Hyun-Joo Kong, MS[1]
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Table 1. Age-standardized incidence rates per 100,000 population and annual percent change (APC) of thyroid cancer according to histologic type and sex in Korea, 1997-2011

Gender	Histologic type	Year														APC[a)]	Difference
		1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	
Men	Follicular	0.20	0.19	0.20	0.15	0.21	0.20	0.24	0.29	0.26	0.33	0.36	0.31	0.34	0.45	0.42	6.78 (5.00 to 8.60)	0.22
	Papillary	1.11	1.38	1.46	1.41	1.84	2.17	3.00	4.12	5.13	6.52	8.77	12.10	14.49	17.63	19.22	25.10 (22.73 to 27.52)	18.11
	Medullary	0.04	0.05	0.05	0.06	0.08	0.10	0.07	0.09	0.11	0.10	0.13	0.07	0.16	0.15	0.18	9.51 (6.49 to 12.62)	0.14
Women	Follicular	0.66	0.63	0.68	0.75	1.00	0.98	1.12	1.01	1.08	1.12	1.08	1.16	1.20	1.36	1.26	5.17 (3.82 to 6.54)	0.60
	Papillary	6.53	7.09	8.85	8.58	11.42	14.37	19.65	27.03	32.54	39.86	51.11	64.77	77.00	86.09	94.15	23.72 (21.93 to 25.54)	87.62
	Medullary	0.11	0.11	0.09	0.16	0.13	0.16	0.14	0.19	0.15	0.21	0.26	0.24	0.29	0.32	0.30	8.82 (6.79 to 10.88)	0.19

Medullary Thyroid Microcarcinoma

A Population-Level Analysis of 310 Patients

Hadiza S. Kazaure, BSc, Sanziana A. Roman, MD; and Julie A. Sosa, MD, MA

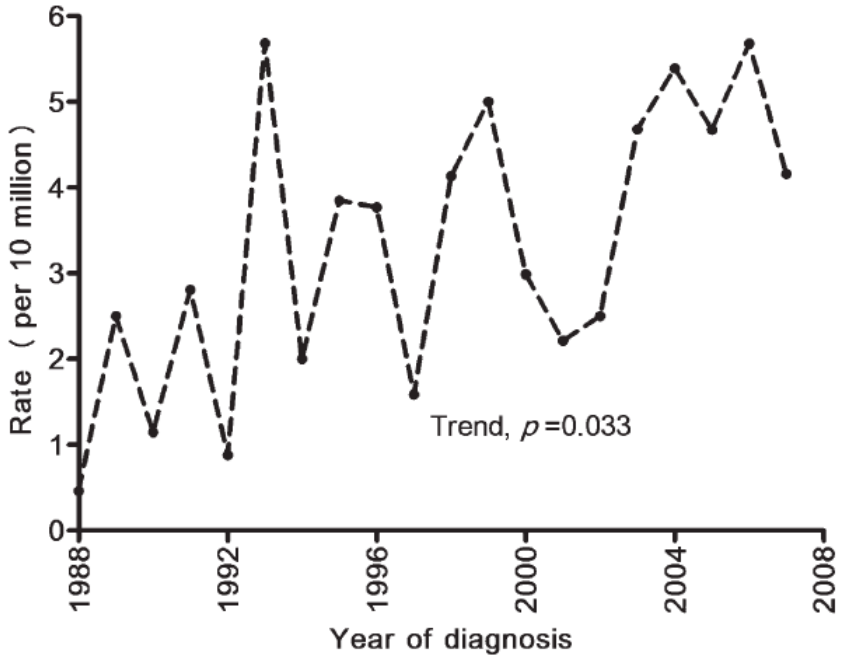

Figure 1. Age-adjusted incidence per 10 million population is illustrated for medullary thyroid microcarcinoma (Surveillance, Epidemiology, and End Results [SEER] Program, 1988-2007). Incidence data were based on the population of the SEER-9 registries(Connecticut, Hawaii, Iowa, New Mexico, Utah, Atlanta, Detroit, San Francisco, and Seattle).

310 patients had microMTC; its incidence increased during the study period (p trend= .033), and microMTC as a proportion of all MTCs increased by 39%. The mean tumor size was 5.7 mm

The Prevalence of Occult Medullary Thyroid Carcinoma at Autopsy

Laticia A. Valle and Richard T. Kloos

MTC Prevalence at Autopsy
0.42%

If entire gland examined with Calcitonin Immunostain

J Clin Endocrinol Metab, January 2011, 96(1):E109–E113

TABLE 1. Breakdown of prevalence, age, size, and country

No. autopsy cases	No. MTC cases	% MTC	% PTC	Country (state)
100	0	0.0	24.0	U.S. (HI)
157	1	0.6	5.1	U.S. (MN)
274	1	0.4	2.9	Chile
1167	0	0.0	12.0	Intl[b]
600	0	0.0	1.0	Portugal
500	4	0.8	6.4	Sweden
260	0	0.0	4.2	Israel
101	0	0.0	35.6	Finland
1020	1	0.1	6.1	Germany
138	1	0.7	2.9	U.S. (WI)
300	0	0.0	1.0	Brazil
100	0	0.0	11.0	Argentina
408	0	0.0	15.7	Japan
199	1	0.5	6.0	Iceland
444	0	0.0	9.0	Singapore
625A	1	0.2	4.6	Spain
100B	0	0.0	22.0	Spain
215	1	0.5	8.8	Belarus
162	0	0.0	10.8	Ukraine
118	0	0.0	8.6	Austria
160	0	0.0	5.6	Greece
150	0	0.0	2.0	Guatemala
433	0	0.0	5.0	Hungary
166	0	0.0	7.8	Brazil

A and B denote two series done by Martinez-Tello *et al.* (28) to compare two
NA, not applicable.

[a] Entire gland sent for microscopy.

[b] Canada, Poland, Columbia, Japan, and U.S. (Hawaii).

Incidentally Discovered Medullary Thyroid Cancer: Diagnostic Strategies and Treatment

Shabina R. Ahmed and Douglas W. Ball

Division of Endocrinology and Metabolism (S.A., D.W.B.), and Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (D.W.B.), Johns Hopkins University School of Medicine, Baltimore, Maryland 21287

J Clin Endocrinol Metab, May 2011, 96(5):1237–1245

Composite Prevalence In Post-Surgical Nodular Goiters 0.3%

15,992 patients
12 series

TABLE 1. Incidence of occult MTC in postsurgical multinodular goiter specimens

First author (Ref.)	Year	Total no. of thyroid specimens	No. of occult MTC (%)
Atli (44)	2006	815	3 (0.4)
Bertazzo (45)	1981	917	1 (0.1)
Cerci (46)	2007	294	1 (0.3)
Costante (47)[a]	2007	5,817	15 (0.26)
Fernando (48)	2009	32	1 (3.1)
Gandolfi (49)	2004	81	0 (0.0)
Hahm (31)[a]	2001	1,448	10 (0.6)
Niccoli (25)[a]	1997	1,167	16 (1.3)
Pelizzo (50)	1996	539	2 (0.3)
Pezzolla (51)	2010	1,507	0 (0.0)
Rieu (29)[a]	1995	469	1 (0.2)
Tezelman (52)	2009	1,695[b]	0 (0.0)
Tezelman (52)	2009	1,211[c]	1 (0.08)
Surgical total		15,992	51 (0.31)

[a] Studies with routine calcitonin screening.

[b] Bilateral subtotal thyroidectomy.

[c] Total or near-total thyroidectomy.

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http://dx.doi.org/10.4143/crt.2014.110

Original Article

Open Access

Age-Period-Cohort Analysis of Thyroid Cancer Incidence in Korea

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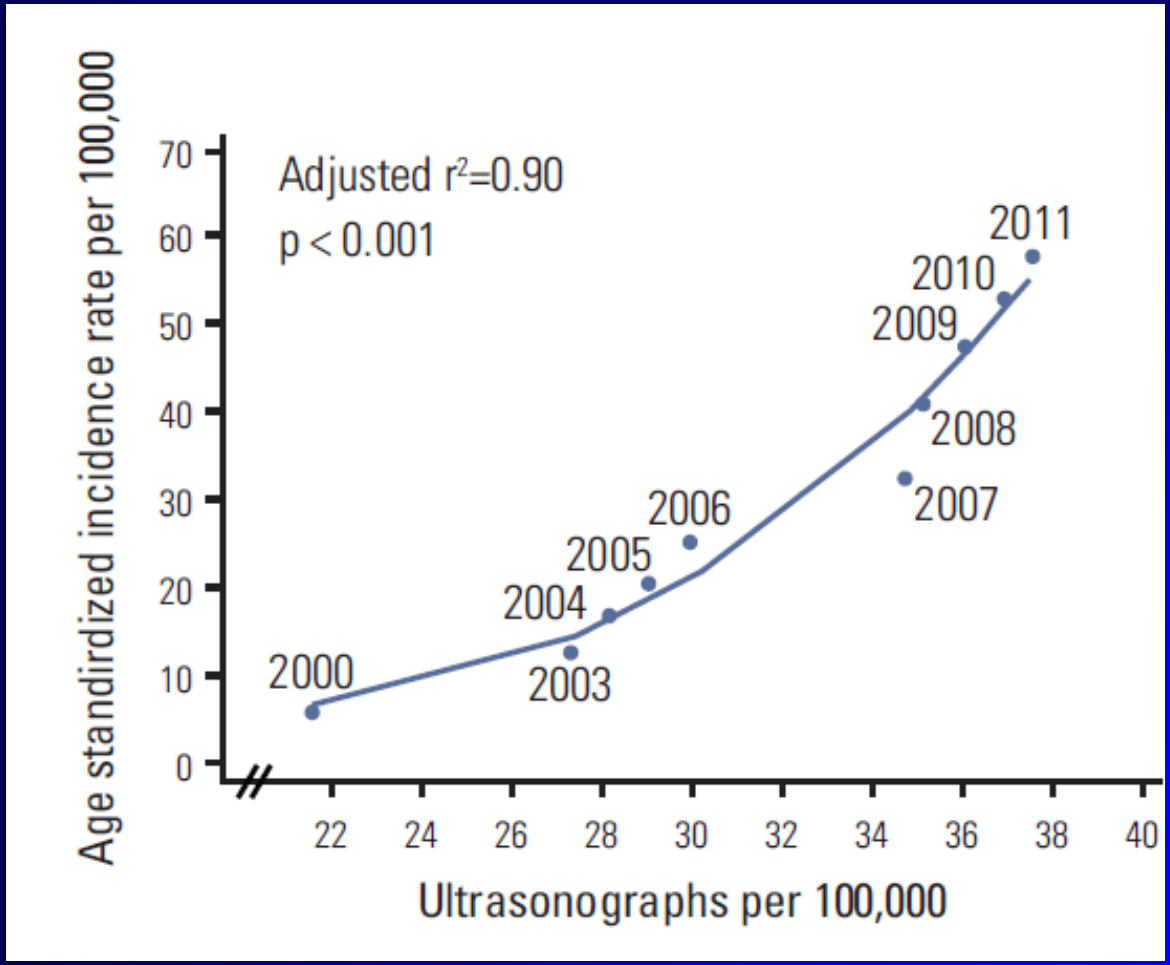
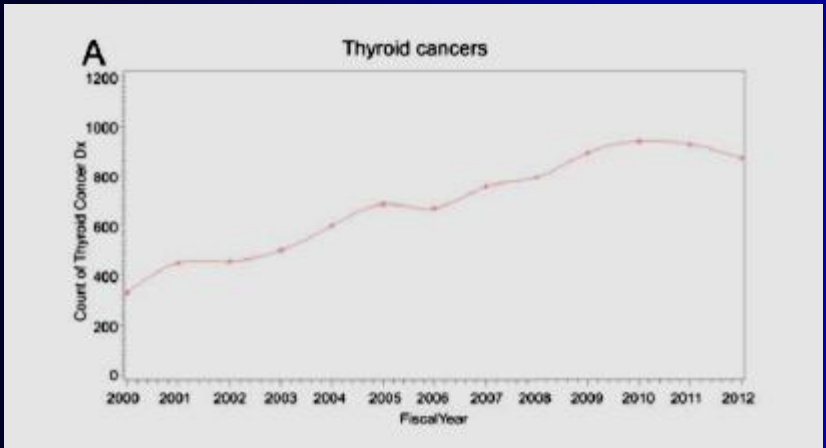


Increased Thyroid Cancer Incidence Corresponds to Increased Use of Thyroid Ultrasound and Fine-Needle Aspiration: A Study of the Veterans Affairs Health Care System

Jose P. Zevallos, MD, MPH[1]; Christine M. Hartman, PhD[2]; Jennifer R. Kramer, MPH, PhD[2,3]; Erich M. Sturgis, MD, MPH[4,5]; and Elizabeth Y. Chiao, MD, MPH[2,3]



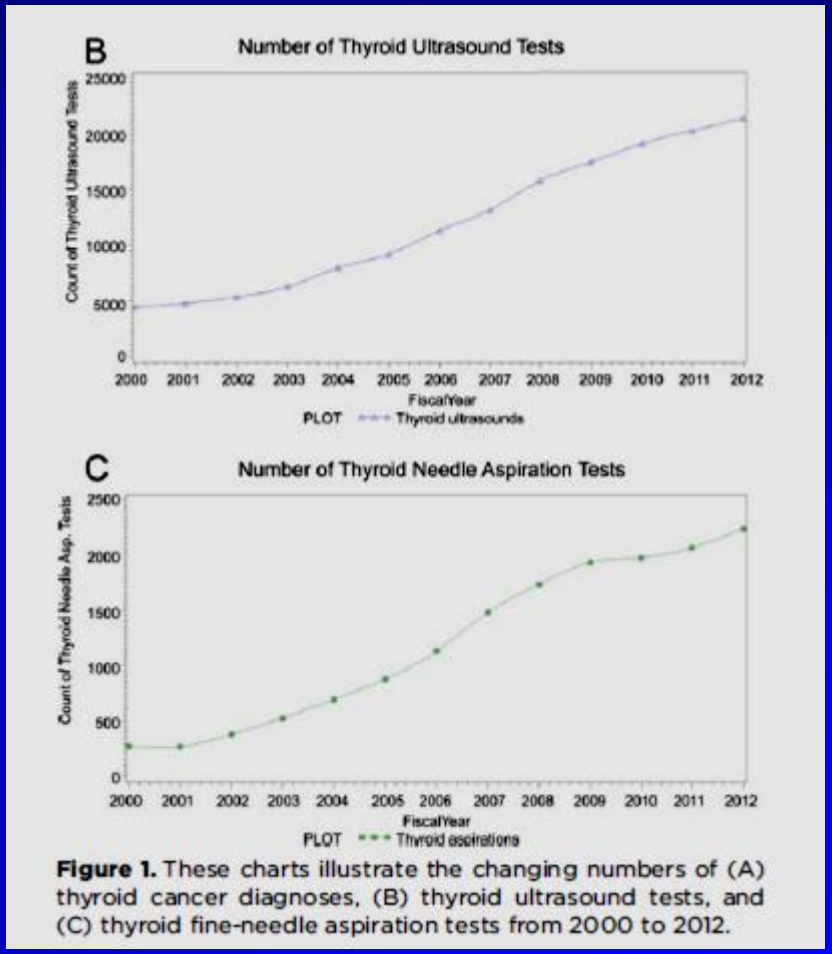
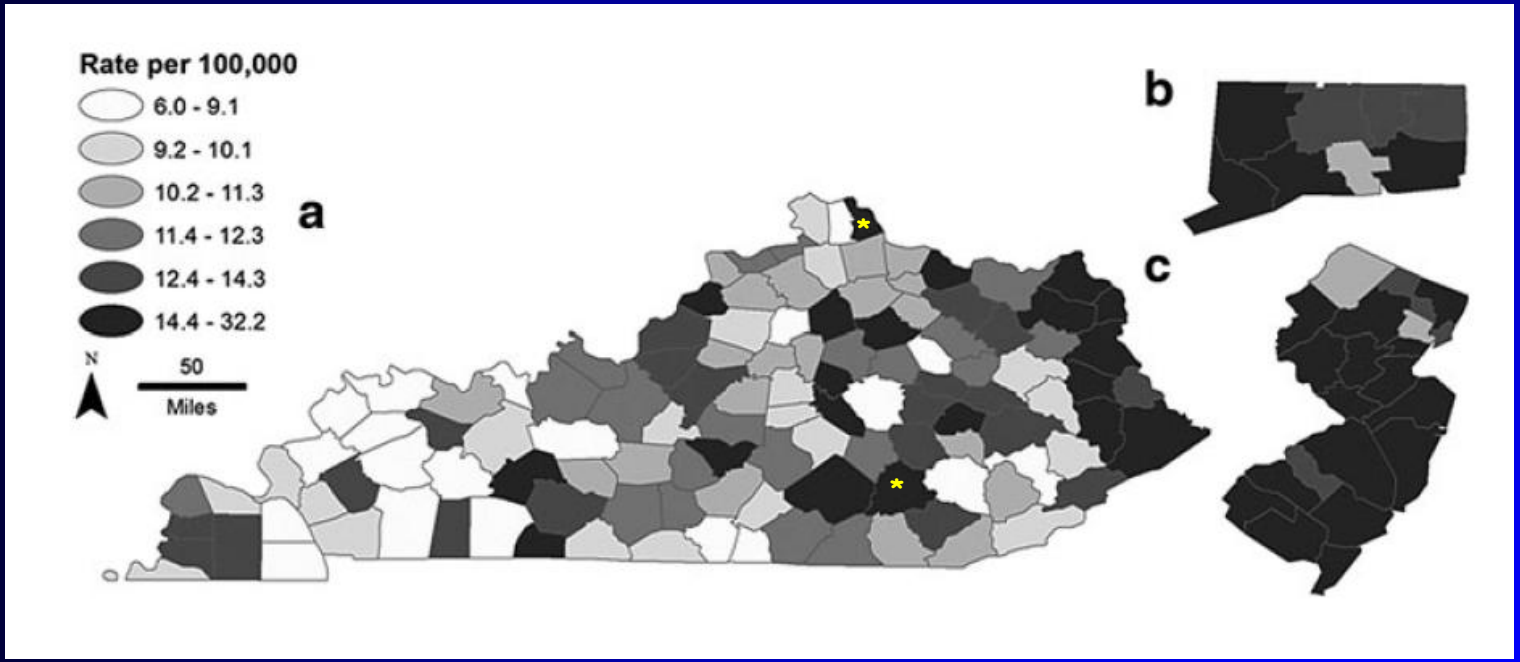


Figure 1. These charts illustrate the changing numbers of (A) thyroid cancer diagnoses, (B) thyroid ultrasound tests, and (C) thyroid fine-needle aspiration tests from 2000 to 2012.

Cancer 2015;121:741-6

Increased Detection in the US

The Increasing Incidence of Thyroid Cancer: The Influence of Access to Care



Luc Morris et al, Thyroid 2013.

Increased Detection in the US

The Epidemic of Thyroid Cancer in the United States:
The Role of Endocrinologists and Ultrasounds

Age standardized incidence rates correlated
Density of Endocrinologists
Use of Neck Ultrasonography

Explained ≈ 50% of the state level incidence

Udelsman and Zhang, Thyroid 2014

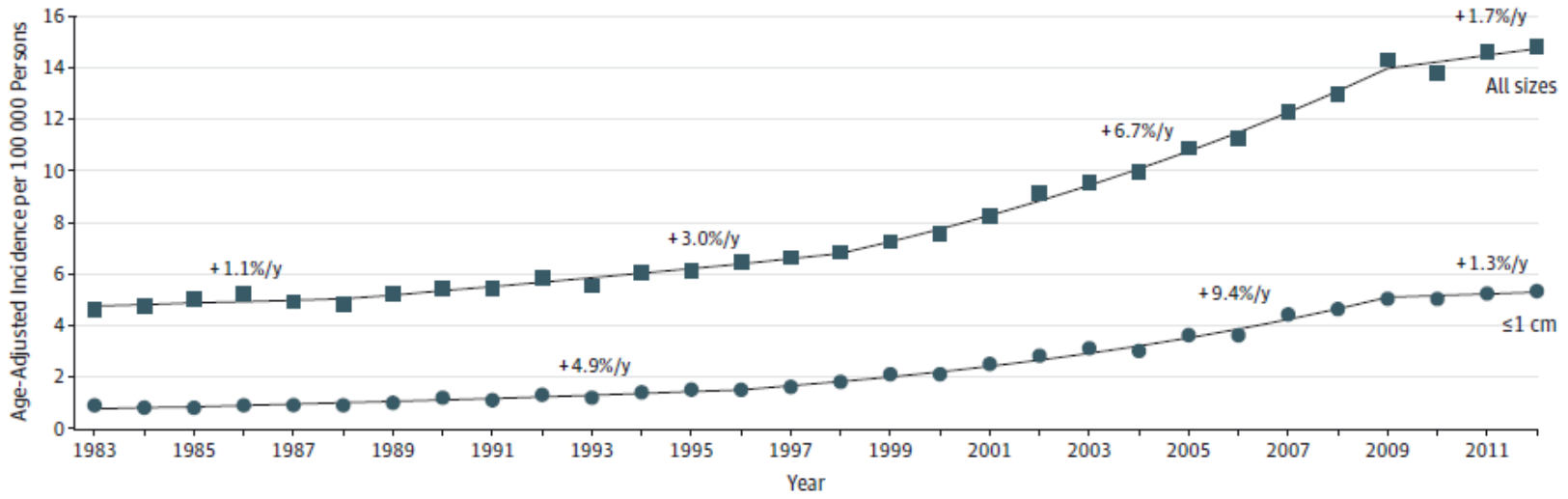
Letters

RESEARCH LETTER

Changing Trends in the Incidence of Thyroid Cancer in the United States

Luc G. T.Morris, MD,MSc
R. Michael Tuttle,MD
Louise Davies,MD, MS

Figure. Time Trends in Incidence of Thyroid Cancer for All Sizes and Those of 1 cm or Less



Data are expressed per 100 000 persons and age-adjusted to the 2000 US population. Data markers represent observed incidence rates; lines, the joinpoint-modeled regression lines; and percentages, the annual percentage change (Table).

South Korea's Thyroid-Cancer "Epidemic" — Turning the Tide

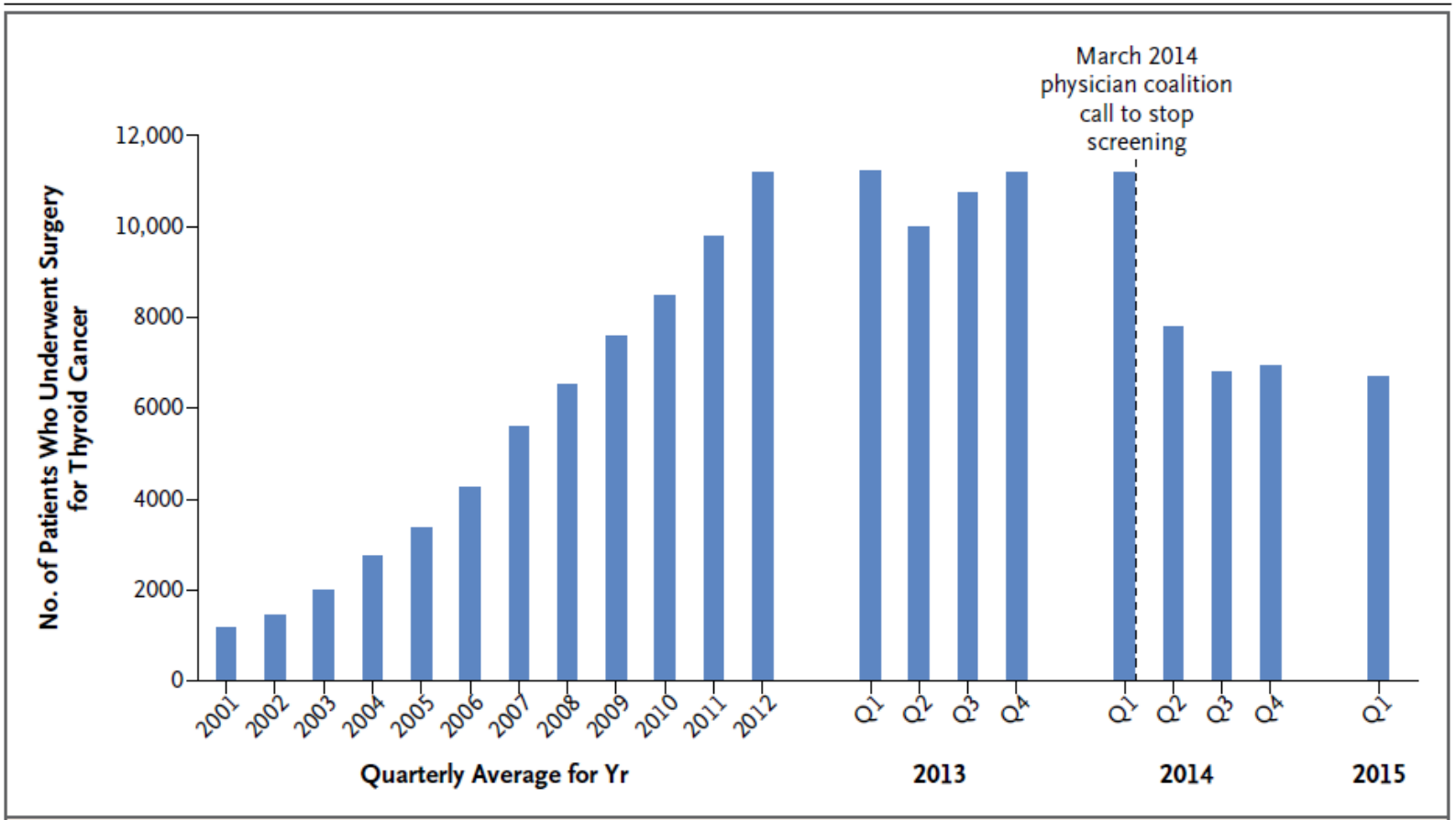


Figure 1. Trend in the Number of Operations for Thyroid Cancer in South Korea, 2001–2015.
Data are from the Health Insurance Review and Assessment Service, South Korea.

NEJM 373;24, 2015

Impact of Thyroid Cancer Guidelines

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer*

Bryan R. Haugen,[1,†] Erik K. Alexander,[2] Keith C. Bible,[3] Gerard M. Doherty,[4] Susan J. Mandel,[5] Yuri E. Nikiforov,[6] Furio Pacini,[7] Gregory W. Randolph,[8] Anna M. Sawka,[9] Martin Schlumberger,[10] Kathryn Schuff,[11] Steven I. Sherman,[12] Julie Ann Sosa,[13] David L. Steward,[14] R. Michael Tuttle,[15] and Leonard Wartofsky[16]

Decrease in FNA diagnosis of Papillary Microcarcinoma
Observation of Papillary Microcarcinoma

No surgery, no pathology report,
not counted in tumor registries

Haugen, Thyroid 2015

Original Investigation

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD; Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD; Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD; Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Gooding, MS; Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD; Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD; Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. LiVolsi, MD; Gregory W. Randolph, MD; Ronald A. Ghossein, MD

Non-invasive follicular variant papillary thyroid cancer

Renamed

Non-invasive thyroid follicular neoplasm with papillary like nuclear features (NIFT-P)

Clinically evident thyroid cancer
60,000 cases/year
Prevalence 600,000

Previously subclinical thyroid cancer

US Population
10-15% have PTC
0.4% have MTC

US Guided FNA

Ultrasound