# Current Controversies in the Diagnosis and Management of Thyroid Cancer: Cases from the Clinic


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# Disclosures

- Writing group member, planned update to the American Thyroid Association differentiated thyroid cancer guidelines (in progress)
- Board of Directors, American Thyroid Association

# Learning Objectives

- Review the current understanding and recommendations for the monitoring of NIFTP tumors.
- Discuss the available evidence weighing the pros and cons of active surveillance in patients with low-risk thyroid cancers.
- Describe the role of serum thyroglobulin measurements in patients who undergo either a partial thyroidectomy, or a total thyroidectomy without subsequent radioactive iodine ablation.
- Analyze the potential reasons for the escalating rise in the incidence of thyroid cancer as observed over recent decades.

# Case 1

- 44 year-old female
- Found to have **two incidental thyroid nodules** on a neck MRI, done for breast cancer surveillance
  - 1.6 cm hyperechoic, circumscribed solid nodule in the right mid gland without associated calcifications or internal Doppler flow (**TIRADS 3**)
  - 8 mm spongiform nodule in the left mid gland without associated calcifications or internal Doppler flow (**TIRADS 2**)
- FNA biopsy, right thyroid nodule
  - Follicular Neoplasm (Bethesda class IV)
  - Veracyte Afirma GEC suspicious

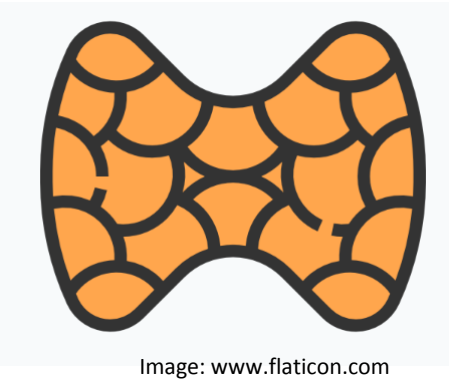


Image: www.flaticon.com

# Surgical Pathology

## November 2015, RIGHT HEMITHYROIDECTOMY:

- **Encapsulated follicular variant of papillary thyroid carcinoma**
- Tumor size: 1.8 cm located mid-pole abutting posterior capsule
- Cytomorphology: classic
- Architecture: follicular
- Capsular invasion: not identified
- Lymphovascular invasion: not identified
- Extrathyroidal extension: not identified
- Pathologic stage: pT1b Nx
- Uninvolved thyroid unremarkable

# ARS Question 1

Given this surgical pathology, what is your estimate for the risk of cancer recurrence in the next 5-10 years?

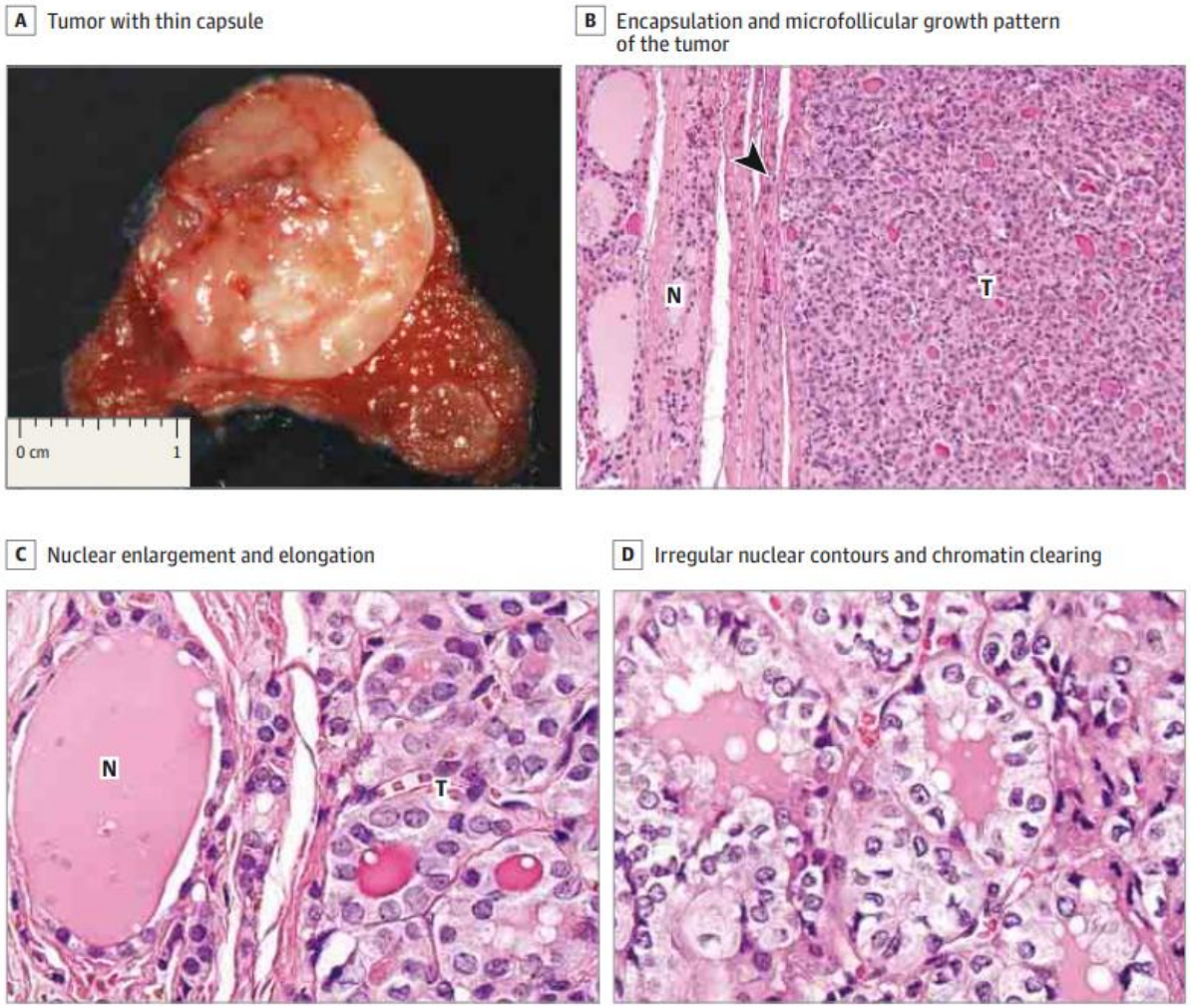
A. Zero
B. Less than 1%
C. 1-5%
D. 5-10%
E. 10-15%
F. More than 15%

# NIFTP
# (Non-Invasive Follicular-Cell Derived Thyroid Neoplasm)

- A pathologic definition **first described in 2016** by Nikiforov et al, reported in *JAMA Oncology*
  - A neoplasm with very low malignant potential
  - N=109, followed for median 13 years [range 10-26] and **zero** adverse outcomes seen
  - In contrast, adverse outcomes were seen in **12 of 101** invasive EFVPTCs
- Initial definition excluded tumors ≤1 cm, and required <1% papillae
  - Subsequent reclassification has been expanded to also include micro-NIFTPs, oncocytic-NIFTPs, and exclusion of any papillae
- 2017: NIFTP tumors added as a distinct category in the revised WHO Classification of Tumors of Endocrine Organs
- Comprises **~2.1 - 9.6%** of follicular cell-derived thyroid neoplasms
  - Lower incidences seen in Asia
  - Higher incidences in North America and Europe

Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors. JAMA Oncol 2016; 2:1023-1029.

# Requirements for the Definition of NIFTP




**Major Features**

Encapsulation or clear demarcation

Follicular growth pattern

Nuclear features of papillary thyroid carcinoma (PTC)[a]:

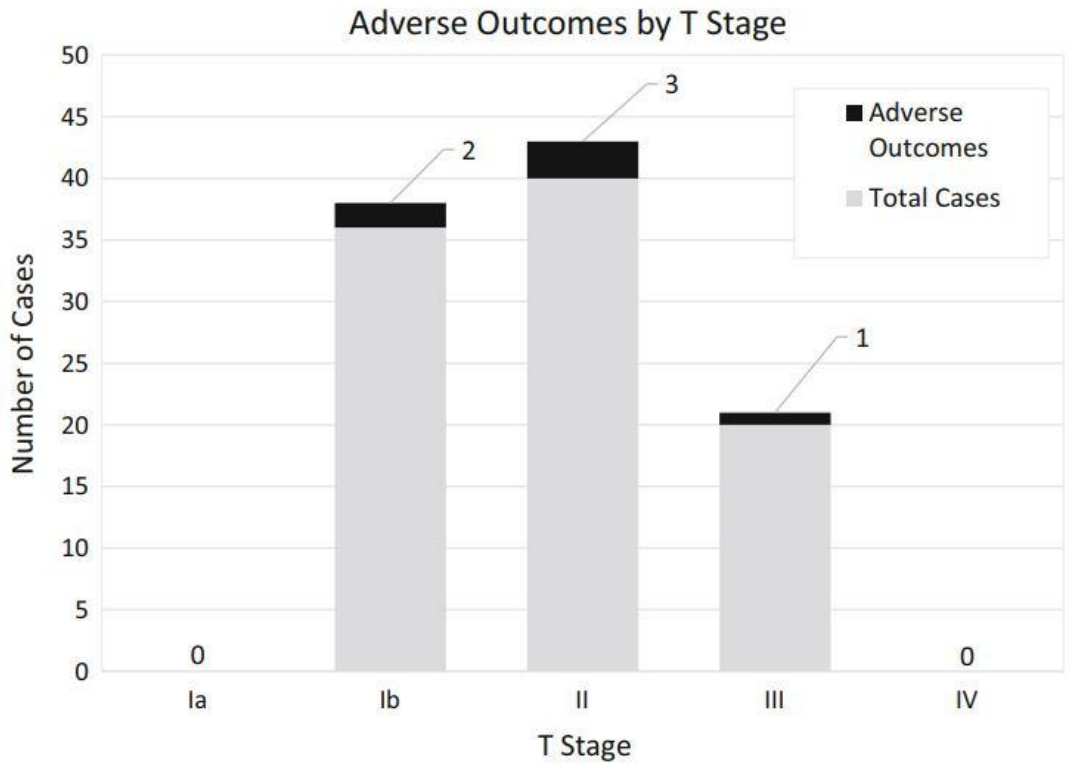
- Enlargement, crowding/overlapping
- Elongation
- Irregular contours
- Grooves
- Pseudoinclusions[b]
- Chromatin clearing[c]

Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors. JAMA Oncol 2016; 2:1023-1029.

# Parente et al, 2018: Follow-Up of NIFTP

- Several cohort studies show **0% malignant potential** in series spanning up to 7.5 years

- However, one single-institution study by Parente (2018) has since demonstrated a **6% malignant potential**
  - Total n=102
  - Mean follow-up of 5.7 years (range, 0-11 years)
  - 5 patients developed nodal metastases and 1 with lung metastases




Parente DN, Kluijfhout WP, Bongers PJ, Verzijl R, Devon KM, Rotstein LE, Goldstein DP, Asa SL, Mete O, Pasternak JD. Clinical Safety of Renaming Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: Is NIFTP Truly Benign? World J Surg. 2018 Feb;42(2):321-326.

# Molecular Profile of NIFTP Tumors

- NIFTPs are **clonal neoplasms**
- Molecular alterations are present in ~78% of cases
  - 30-54% have some type of *RAS* mutation
  - **Mostly *NRAS*,** also *HRAS* and rarely *KRAS* mutations

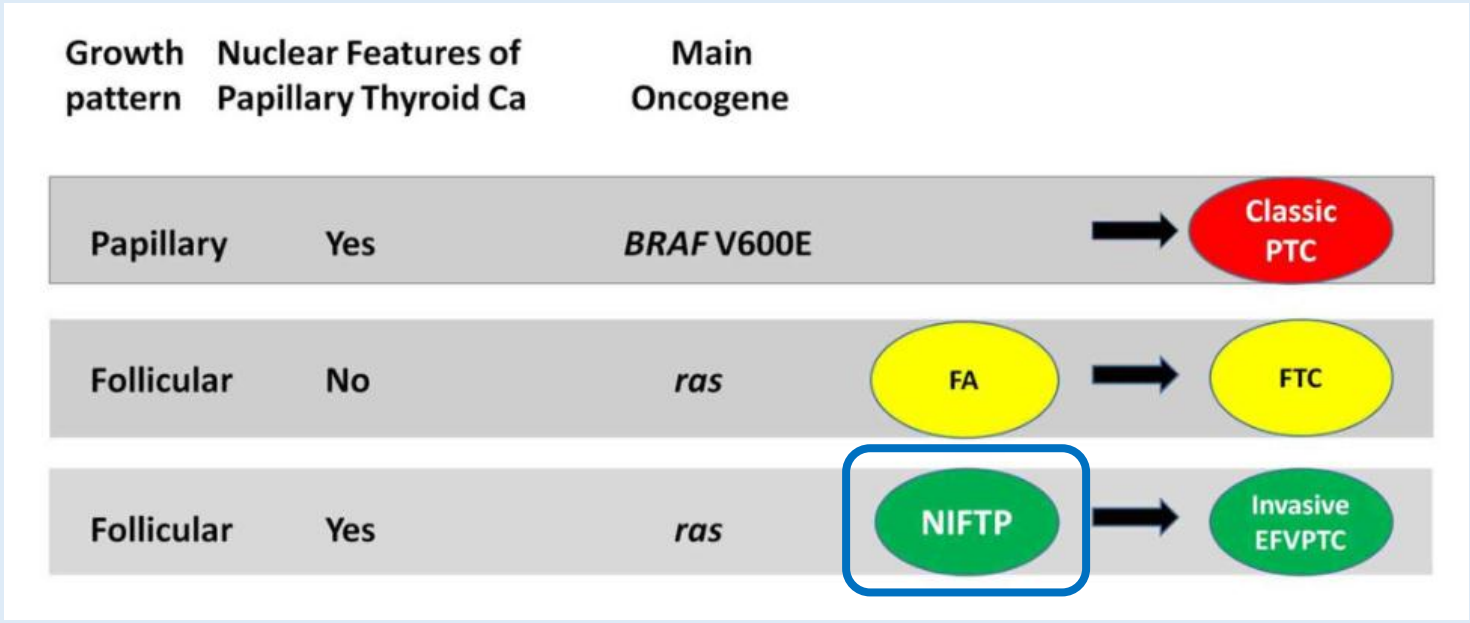
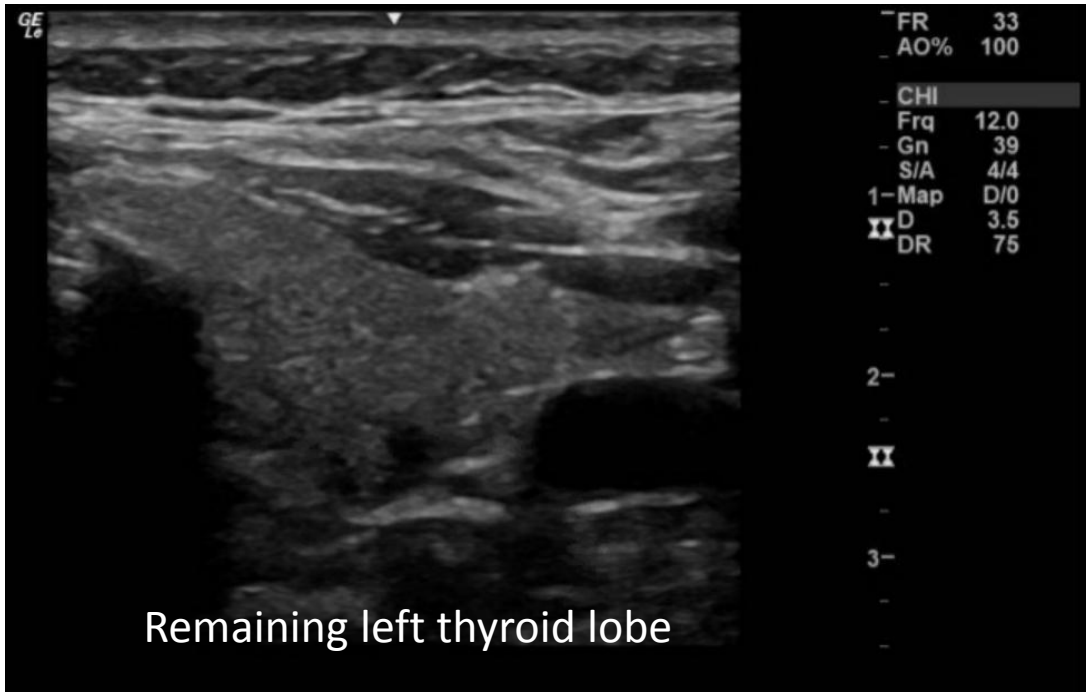



Figure contributed by Poller D.
Jug R, Poller D, Jiang X. NIFTP. PathologyOutlines.com website.
https://www.pathologyoutlines.com/topic/thyroidglandNIFTP.html. Accessed August 12th, 2022

Chu YH, Sadow PM. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): Diagnostic updates and molecular advances. Semin Diagn Pathol 2020; 37:213-218.

# Back to the Case

- 2022:  Seven years of follow-up thus far, now age 52 years
- TSH have been maintained between 0.5-2.0 mIU/L with levothyroxine 100 mcg daily
- Neck ultrasounds every 1-2 years have been unremarkable
- Serum thyroglobulins have ranged 5.8-10.8 ng/mL (Tg Ab are negative)



Remaining left thyroid lobe

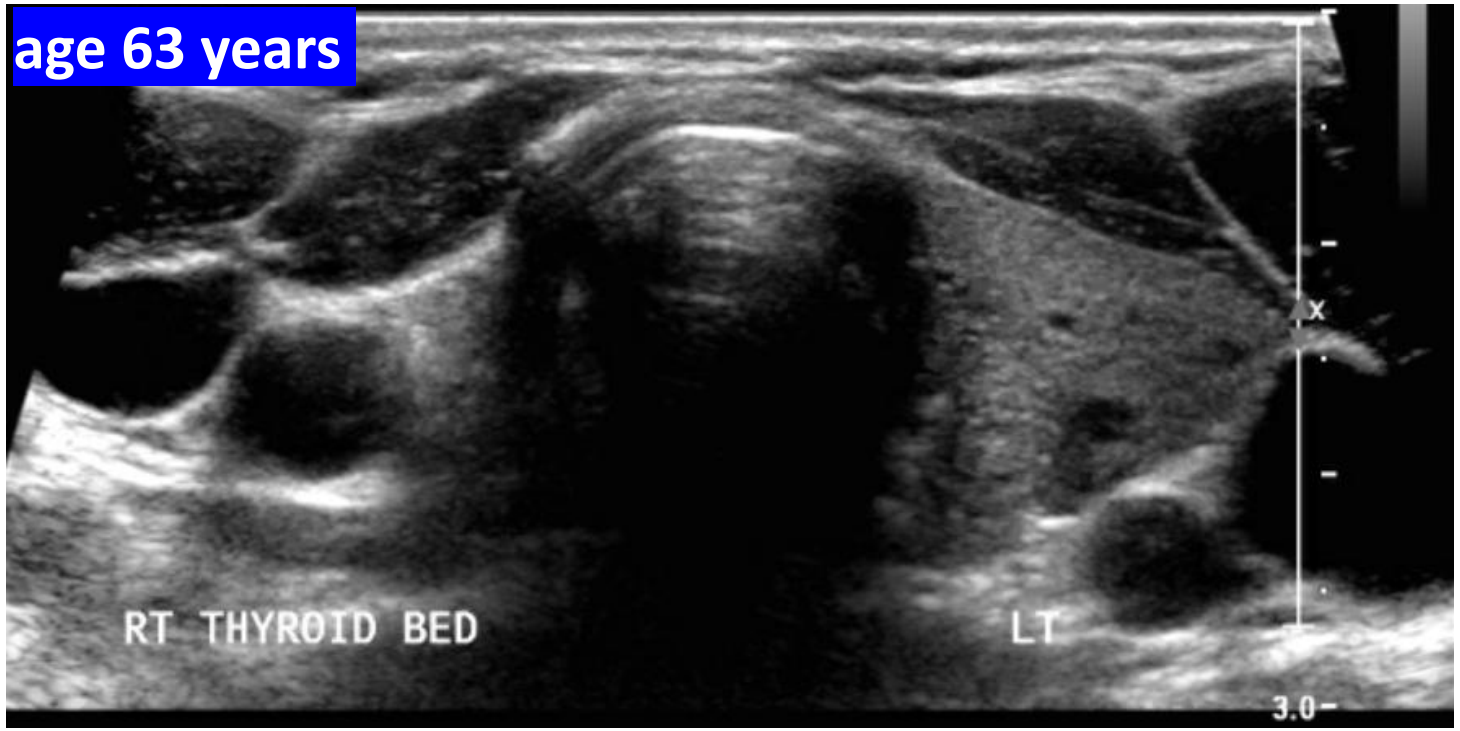
# Key Takeaway Points

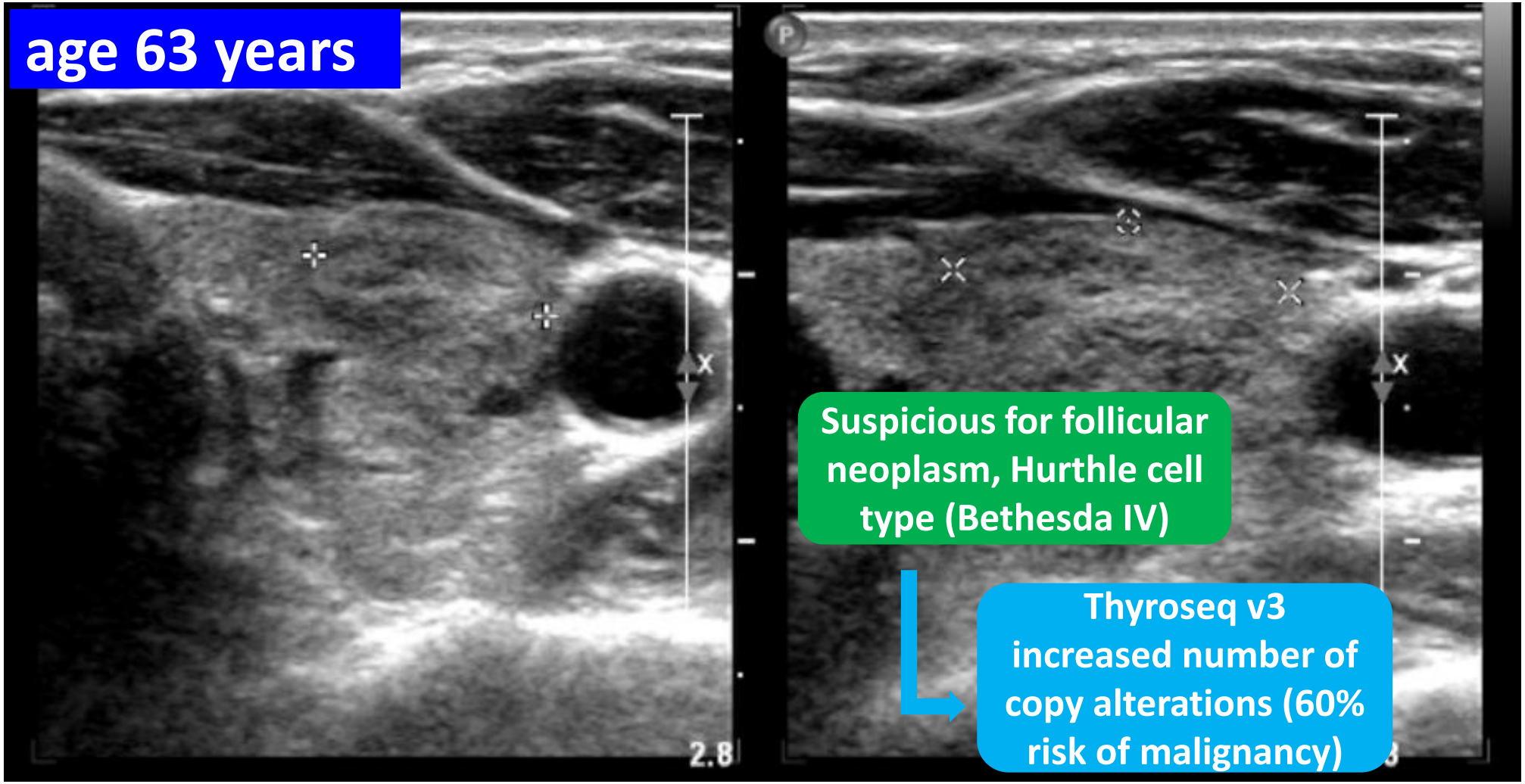
## NIFTP Tumors

- Diagnosed pathologically
- “Very low” malignant potential
- Continued monitoring, but at decreased frequency than that for DTCs, is suggested
- The optimal duration of long-term monitoring of NIFTP tumors is unknown

# Case 2

- 63 year-old woman who was noted to have 2 left thyroid nodules
- Previously undergone a right hemithyroidectomy at age 47 years (unclear why), for which the surgical pathology showed 2 benign nodules






9 mm left superior nodule

10 mm left inferior nodule

# ARS Question 2

Given this cytology, what would you recommend as the next course of action?

A. Completion left thyroid lobectomy
B. Observation (active surveillance)

# Consideration of Active Surveillance for Low-Risk Thyroid Cancers

### Candidate Characteristics[a]

- Solitary intrathyroidal papillary thyroid tumor ≤1.0 cm in greatest diameter, surrounded by 2 mm of normal thyroid parenchyma (ie, no local invasion)
- No suspicious lymph nodes
- No high-grade cytologic findings
- Age ≥60 years[b]
- Life-threatening comorbidities
- Committed to regular follow-up examinations

### Health System Characteristics[a]

- Sophisticated patient tracking/reminders in the health record system
- Capability for high-quality neck ultrasonography
- Multidisciplinary team with experience managing thyroid cancer

### Counseling Points

- Requires repeat ultrasonography examinations every 6 months to demonstrate stability, usually for 2 years, then every 1 to 2 years
- Approximately 15% of patients undergo surgery during long-term follow-up, usually for growth of primary thyroid tumor
- No significant morbidity or mortality associated with delayed surgical treatment of ideal candidates
- No head-to-head randomized trial data comparing surgery vs active surveillance

[a] Adopted from patient, tumor, and medical team characteristics of ideal candidates for observation described by Brito et al.[9]

[b] Younger patients are also reasonable candidates, realizing that progression to clinical disease is higher in younger age groups.

Zanocco KA, Hershman JM, Leung AM. Active Surveillance of Low-Risk Thyroid Cancer. JAMA. 2019 May 28;321(20):2020-2021.

| Country, Year, Institution | Study design | Number of patients | Follow-up time mean, median* | Tumor growth rate (maximum diameter ≥3 mm) | Tumor growth rate (tumor volume ≥50%) | Lymph node metastasis rate | Extrathyroidal extension rate | Distant metastasis rate |
|---|---|---|---|---|---|---|---|---|
| Japan 2014[90] Kuma Hospital | Prospective cohort | 1,235 | 60 months (range 18–227) | 4.6%<br>4.9%/5 years<br>8.0%/10 years | ND | 1.5%<br>1.7%/5 years<br>3.8%/10 years | 0.16% | 0% |
| Japan 2016[92] Cancer Institute Hospital | Prospective cohort | 409 | 6.8 years* (range 1–23) | 6.0%<br>6.3%/5 years<br>7.3%/10 years | ND | 1.0% | 0% | 0% |
| United States 2017[91] Memorial Sloan Kettering Cancer Center | Prospective and retrospective cohort | 291<br><15 mm | 25 months (range 6–166) | 3.8%<br>2.5%/2 years<br>12.1%/5 years | 12.4%<br>11.5%/2 years<br>24.8%/5 years | 0% | 0% | 0% |
| Korea 2018[99] Asan Medical Center, Samsung Medical Center, Seoul St. Mary's Hospital | Retrospective study | 370 | 32.5* (IQR 21.5–47.6) | 3.5% | 23.2% | 1.4% | ND | 0% |
| Japan 2019[196] Cancer Institute Hospital | Prospective and retrospective cohort | T1a:360<br>T1b:61 | 7.3 years (range 0.5–25)<br>7.9 years (range 1–17) | 8%<br>7% | 21%<br>11% | 1%<br>3% | ND<br>1.6% | ND<br>ND |
| Italy 2019[101] University Hospital of Pisa | Prospective study | 93 | 19 months* (range 6–54) | 2.1% | 16% | 1.1% | ND | 0% |
| Japan 2019[102] Nagoya University | Retrospective study | 41<br>(T1b:7) | 62 months (range 7–180) | 4.8% | ND | 0% | ND | 0% |
| Colombia 2020[103] Neck Cancer Center in Medellin | Prospective study | 102<br>Almost <15 mm | 13.9 months* (range 0.2–112) | 10.8% | 25.5% | ND | ND | ND |

ND, no data; IQR, interquartile range

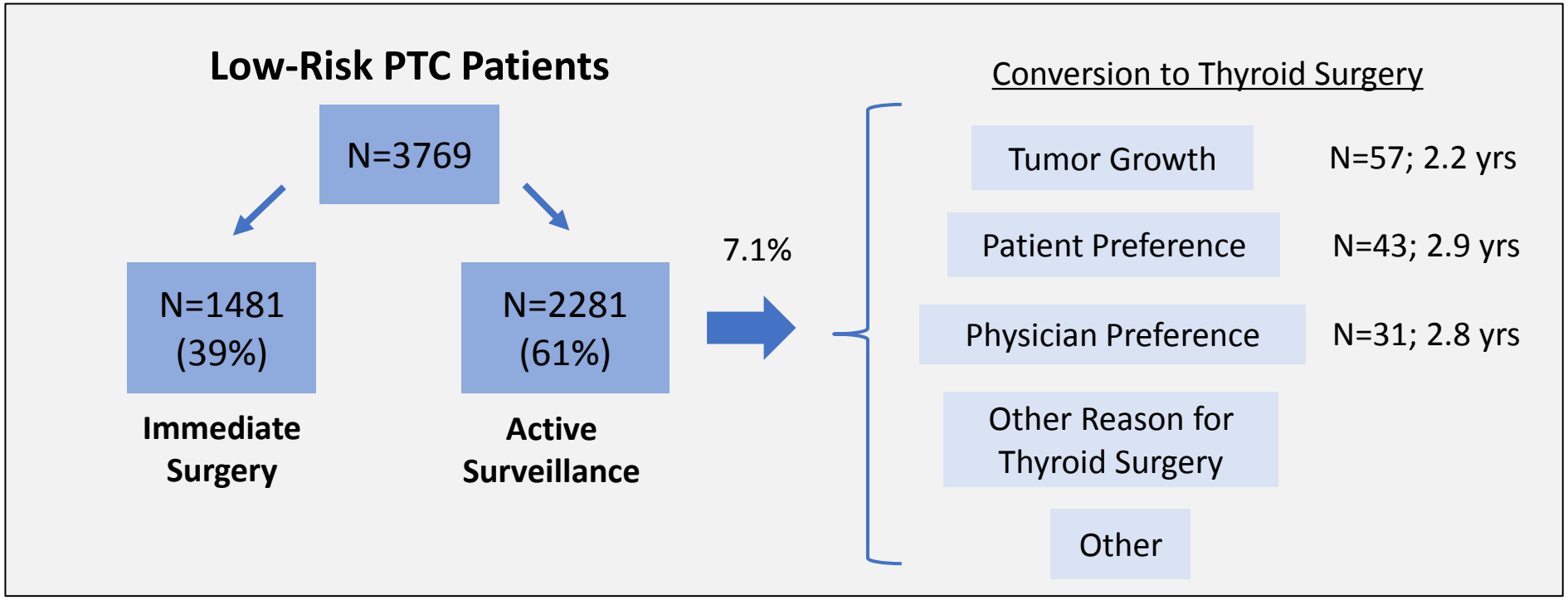
## Active Surveillance Cohorts, 1993-present

- **Mean follow-up duration, 1.1-6.8 years (maximal 23 years)**
- **N = 41-1235 patients**
- **Tumor growth, 2.1-10.8%**
- **LN metastases, 1-3%**
- **Distant metastases, 0% or no data**

Horiguchi K, Yoshida Y, Iwaku K, Emoto N, Kasahara T, Sato J, Shimura H, Shindo H, Suzuki S, Nagano H, Furuya F, Makita N, Matsumoto F, Manaka K, Mitsutake N, Miyakawa M, Yokoya S, Sugitani I. Position paper from the Japan Thyroid Association task force on the management of low-risk papillary thyroid microcarcinoma (T1aN0M0) in adults. Endocr J. 2021 Jul 28;68(7):763-780.

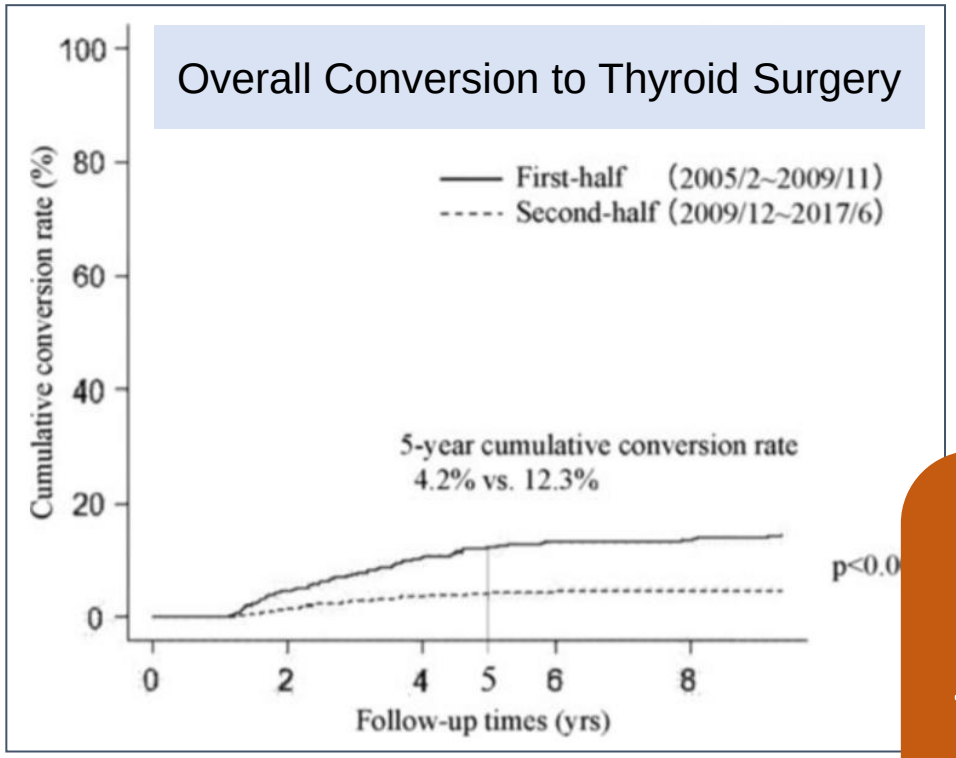
# Decreasing Rate of Conversion to Surgery During Active Surveillance of PTC in Japan

- Subjects: Low-risk thyroid cancer at Kuma Hospital, Japan from 2005-2017
- Active surveillance conversion to surgery analyzed **before** & **after** November 2011 (midpoint)



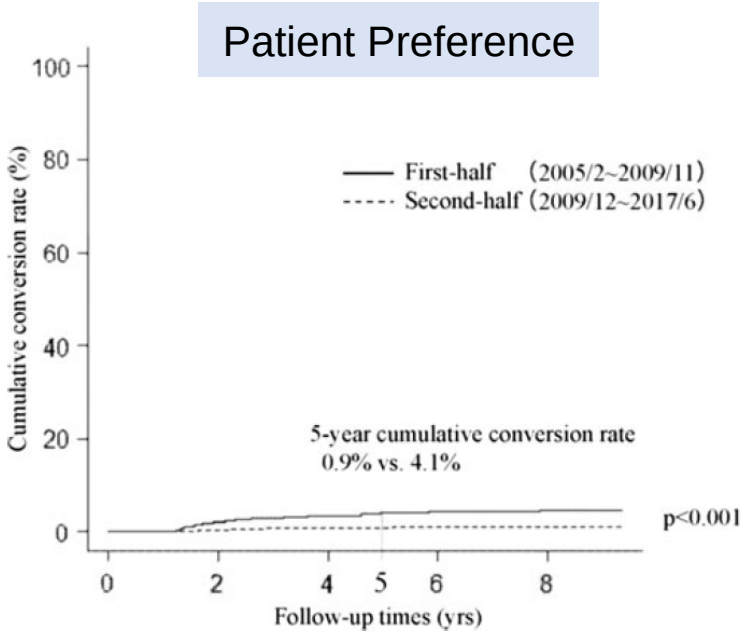

Sasaki T, Miyauchi A, Ito Y, Kudo T, Kanemura N, Sano T, Kawano S, Yamamoto M, Fujishima M, Masuoka H, Higashiyama T, Kihara M, Miya A. Marked Decrease Over Time in Conversion Surgery After Active Surveillance of Low-Risk Papillary Thyroid Microcarcinoma. Thyroid. 2021 Feb;31(2):217-223.

## Overall Conversion to Thyroid Surgery

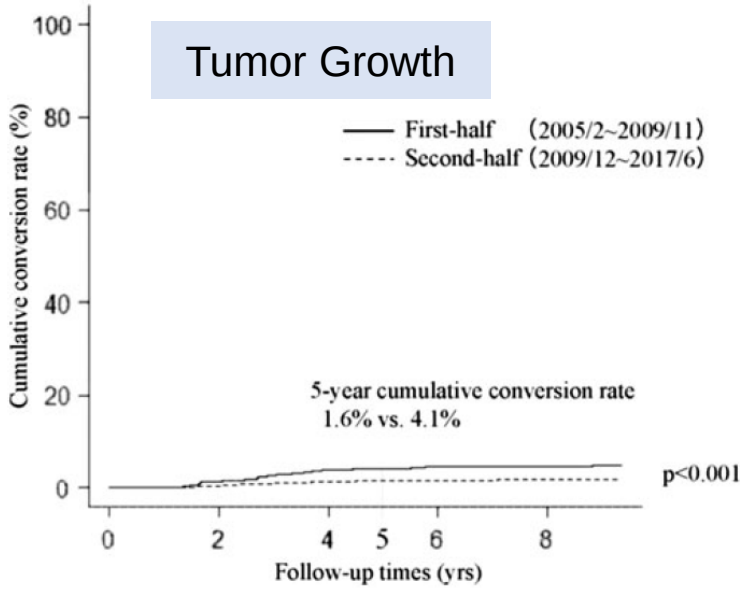



During AS of low-risk PTCs, there has been **less conversion to thyroid surgery after 2011 (**compared to before 2011)

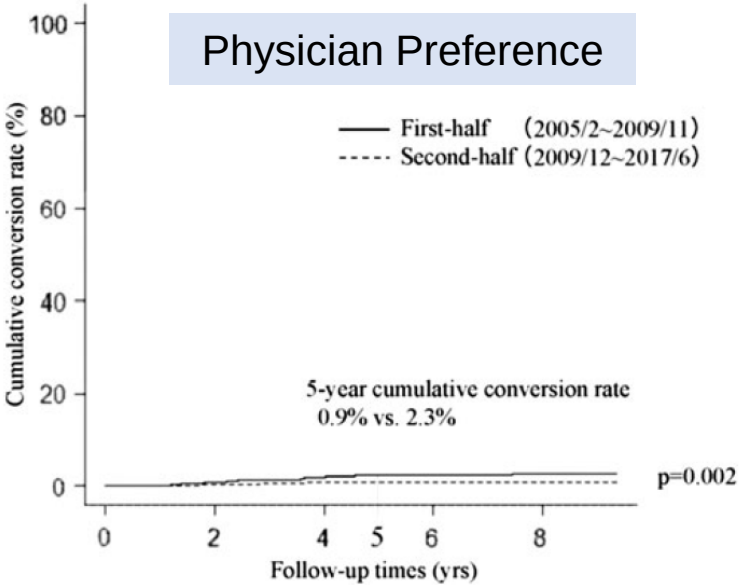
## Patient Preference




## Tumor Growth




## Physician Preference



# Active Surveillance vs Thyroid Surgery for DTC: A Systematic Review

## Included Studies

- 7 active surveillance vs. immediate surgery: 5 cohort studies (N=5432), 2 cross-sectional studies (N=538)
- 7 uncontrolled treatment series of active surveillance (N=1219)

## Results

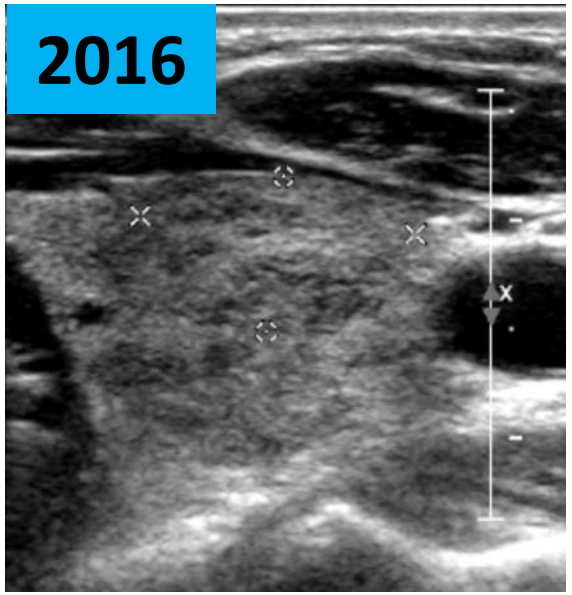
- Active surveillance and immediate surgery had similar outcomes.
  - Low risk of all-cause or cancer-specific mortality, distant metastasis, and postop recurrence
- Zero mortality in the uncontrolled treatment series.
- Low rates of tumor growth with active surveillance.
- Subsequent surgery primarily due to patient preference than tumor progression.
- Four cohort studies (N=88,654) showed surgery had improved all-cause or thyroid cancer mortality, but likely were highly influenced by confounders.

Chou R, Dana T, Haymart M, Leung AM, Tufano RP, Sosa JA, Ringel MD. Active Surveillance Versus Thyroid Surgery for Differentiated Thyroid Cancer: A Systematic Review. Thyroid. 2022 Apr;32(4):351-367.

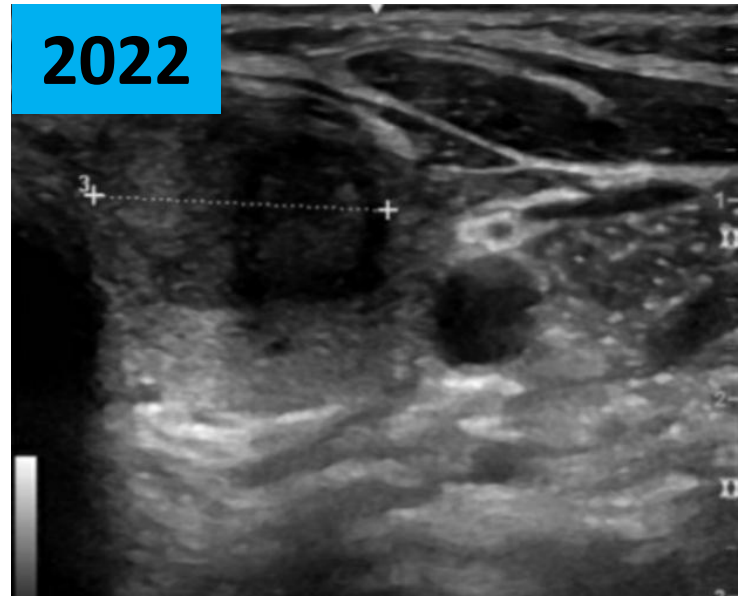
# Back to the Case

- 6 years of follow-up thus far, now age 69 years
- Ultrasounds every 6-12 months
- She has been extremely hesitant about surgery
- Considering resection soon

**1.0 cm left thyroid nodule**



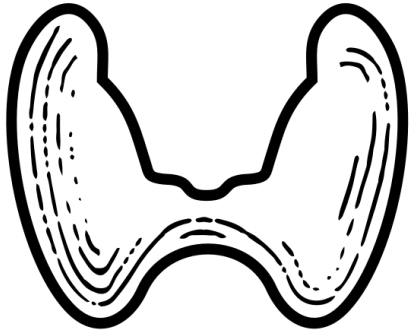

**1.6 cm left thyroid nodule**



# Key Takeaway Points

## Active Surveillance of Low-Risk PTCs (usually <1 cm)

- There are nearly 3,000 patients worldwide followed by active surveillance using established protocols
  - There are likely many more, as part of increasingly standard of care for low-risk thyroid cancers
- Active surveillance and immediate surgery appear to have similar mortality, risk of recurrence, and other longterm outcomes.
- During active surveillance, the decision to pursue surgery likely to result from patient preference, rather than disease progression.
- The recommendation to pursue active surveillance should consider both patient and health system characteristics.
- More research is needed for the active surveillance of PTCs >1cm, non-papillary thyroid cancers, and in older patients.



Created by Angelica
from the Noun Project

# Case 3

- 36 year-old woman diagnosed with **Graves' disease** -- started on methimazole
- Age 37: Two thyroid nodules (each 1.5 cm) found on routine ultrasound, during monitoring of her Graves' disease
  - FNA Biopsies: PTC in both
- Age 38: Total thyroidectomy with central neck dissection

# Surgical Pathology

**January 2018, TOTAL THYROIDECTOMY WITH BILATERAL CENTRAL NECK DISSECTION**

A. NECK MASS, LEFT (EXCISION)

- Parathyroid tissue, fibrous tissue and nerve
- Negative for malignancy

B. THYROID GLAND REMNANT, RIGHT SUPERIOR:

- Thyroid tissue and skeletal muscle; negative for malignancy
- KI-67 immunohistochemistry stain shows very low proliferative activity in the thyroid tissue

C. THYROID GLAND (TOTAL THYROIDECTOMY):

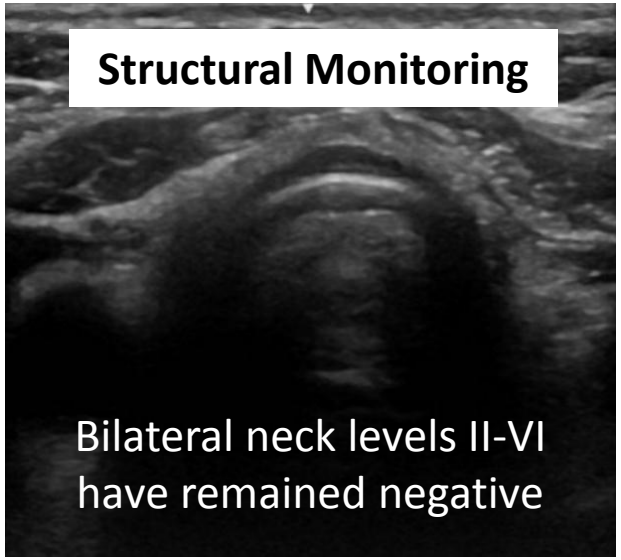
- **Papillary thyroid carcinoma, classic type, multifocal (involving right lobe)**
- Size of largest nodule: **1.4 cm, right lobe**
- Extrathyroidal extension not present
- Perineural and lymphovascular invasion not present
- Surgical margins are negative
- One perithyroidal lymph node negative for malignancy (0/1)
- Pathologic TNM Classification (AJCC 8th ed.): **pT1b (m) N0**
- Background thyroid gland with diffuse hyperplasia and patchy chronic lymphocytic thyroiditis; consistent with treated Graves' disease
- No parathyroid tissue present

D. LYMPH NODES, CENTRAL NECK (NECK DISSECTION)

- Three lymph nodes negative for malignancy (0/3)
- Normocellular parathyroid tissue

# Longterm Postoperative Monitoring

- She was recommended to not receive postoperative RAI ablation, given her low-risk disease
- **2022**: Now age 42, six years later
  - Monitoring has been performed every 6-12 months since her initial therapy




**Laboratory Monitoring (2016-2022):**

- Serum Tg Ab negative
- Serum Tg, **range 0.5-2.0 ng/mL** (three different Tg assays used)
- Serum TSH, range <0.02 to 1.62 mIU/L

Most recently (Aug 3, 2022): Serum TSH 0.25, Tg 1.9

# Monitoring Postoperative Serum Tg Levels without RAI: A Systematic Review

## Included Studies (N=37)

- 4 studies (N=561), partial thyroidectomy
- 5 studies (N=751), total/near-total thyroidectomy without RAI
- 28 studies (N=7,618), total or near-total thyroidectomy before RAI administration

## Results

- After partial thyroidectomy: Tg measurement was not accurate for diagnosing recurrence or metastasis.
- After total/near-total thyroidectomy without RAI, Tg levels were usually stable and low.
- After total/near-total thyroidectomy before RAI, there was variable diagnostic accuracy.
  - Sensitivity high (but specificity low), at a **Tg cutoffs ranging from 1.0 to 2.5 ng/mL**.

## Additional Considerations

- Uncertain applicability for patients who do not receive RAI (since patients selected for RAI likely a higher risk group)
- Very low quality for all scenarios, due to methodological limitations and variable Tg thresholds evaluated.

Chou R, Dana T, Brent GA, Goldner W, Haymart M, Leung AM, Ringel MD, Sosa JA. Serum Thyroglobulin Measurement Following Surgery Without Radioactive Iodine for Differentiated Thyroid Cancer: A Systematic Review. Thyroid. 2022 Jun;32(6):613-639.

# Recommendations:
## Monitoring Postoperative Serum Tg Levels without History of RAI Use

- Very limited evidence and available literature
- **Following partial thyroidectomy,** Tg levels for identifying recurrent/metastatic disease **has low utility**.
- **Following total/near-total thyroidectomy**, Tg levels **greater than 1.0-2.5 ng/mL** might identify low-risk patients with persistent or metastatic disease.
- Additional research needed
  - When are Tg measurements most validated?
  - What is the optimal Tg level in those who did not receive RAI?
  - What are the appropriate Tg testing intervals?

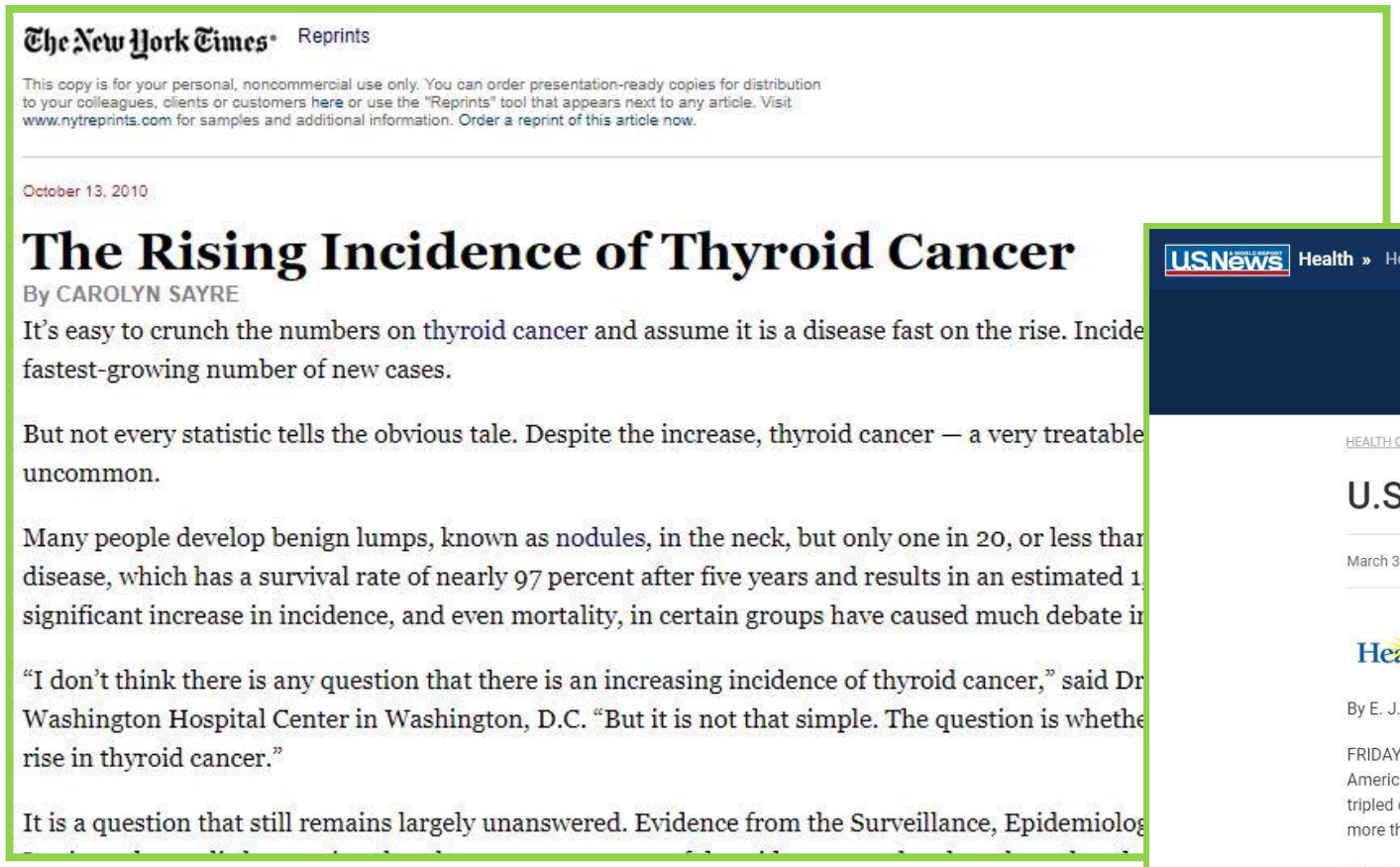
Chou R, Dana T, Brent GA, Goldner W, Haymart M, Leung AM, Ringel MD, Sosa JA. Serum Thyroglobulin Measurement Following Surgery Without Radioactive Iodine for Differentiated Thyroid Cancer: A Systematic Review. Thyroid. 2022 Jun;32(6):613-639.

# Back to the Case

- **August 2022**:  Four years of follow-up thus far, now age 42 years
- Receiving neck surveillance ultrasound and laboratory monitoring every 6-12 months
  - Serum Tg remains between 0.5-2.0 ng/mL
  - We are attempting to monitor Tg levels with the same assay
- Adjusting her levothyroxine dose as needed, aiming for a goal TSH 0.5-2.0 mIU/L
- We have not pursued any whole body imaging for now

# Optional Discussion Case 4

A 38 year old man comes to see you in consultation for a new diagnosis of papillary thyroid cancer. He asks "**How did I get this thyroid cancer**?"



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October 13, 2010

## The Rising Incidence of Thyroid Cancer

By CAROLYN SAYRE

It's easy to crunch the numbers on thyroid cancer and assume it is a disease fast on the rise. Incide fastest-growing number of new cases.

But not every statistic tells the obvious tale. Despite the increase, thyroid cancer — a very treatable uncommon.

Many people develop benign lumps, known as nodules, in the neck, but only one in 20, or less thar disease, which has a survival rate of nearly 97 percent after five years and results in an estimated 1 significant increase in incidence, and even mortality, in certain groups have caused much debate ir

"I don't think there is any question that there is an increasing incidence of thyroid cancer," said Dr Washington Hospital Center in Washington, D.C. "But it is not that simple. The question is whethe rise in thyroid cancer."

It is a question that still remains largely unanswered. Evidence from the Surveillance, Epidemiolog

U.S.News Health » Hospitals Doctors Senior Care Wellness & Diets Health Insurance Conditions



HEALTH CARE

## U.S. Thyroid Cancer Cases Continue to Rise

March 31, 2017, at 4:00 p.m.

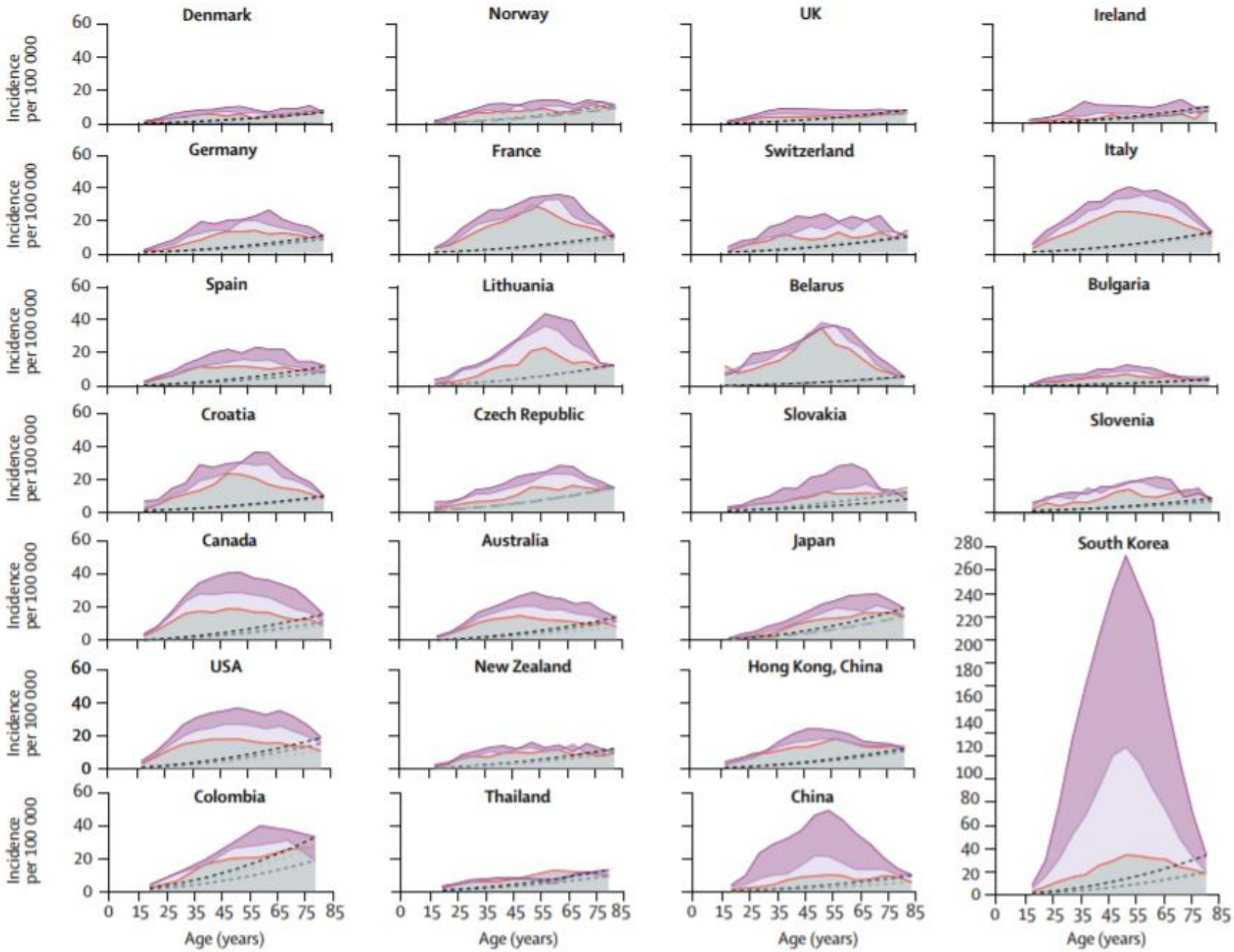
HealthDay

By E. J. Mundell, *HealthDay Reporter*

FRIDAY, March 31, 2017 (HealthDay News) -- The rate of Americans diagnosed with thyroid cancer has more than tripled over the past four decades, and continues to rise more than 3 percent a year, new research shows.

The rise can't be completely attributed to better detection or "overdiagnosis," said a team led by Cari Kitahara of the U.S.

# Global Trends in Thyroid Cancer, 1998-2012




Li M, Dal Maso L, Vaccarella S. Global trends in thyroid cancer incidence and the impact of overdiagnosis. Lancet Diabetes Endocrinol. 2020 Jun;8(6):468-470.

# Rising Incidence of Thyroid Cancer

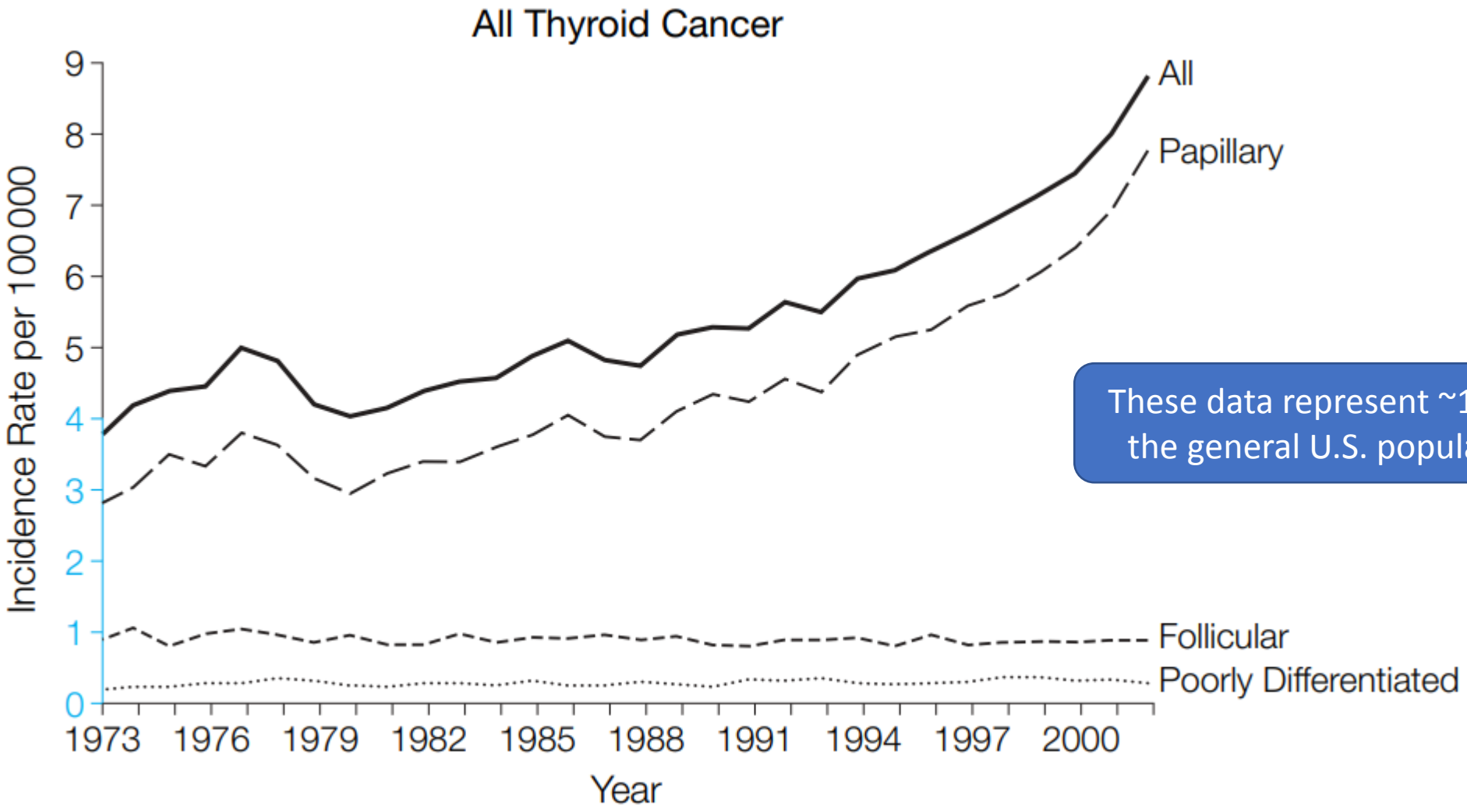
- Possible reasons:
  (1) Overdiagnosis / overdetection of thyroid cancer
  (2) Biological etiologies: Environmental exposures, autoimmunity, nutrition, obesity, other factors

- It is unclear if increased cancer incidence is associated with trends in thyroid cancer-related mortality.

# Thyroid Cancer Incidence and Mortality

| | Incidence Data from SEER-9 | Mortality Data from National Center of Health Statistics | Incidence | Mortality |
|---|---|---|---|---|
| Davies, Welch. JAMA 2006 | 1973-2002 | 1973-2002 | **2.4-fold increase between 1973-2002** (P<0.001 for trend) | **0.5/100,000 in both 1973 & 2002** (p>0.2 for trend) |

# Thyroid Cancer Incidence, U.S. (1973-2002)




These data represent ~10% of the general U.S. population

Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA. 2006 May 10;295(18):2164-7.

# Thyroid Cancer Incidence and Mortality

| | Incidence Data from SEER-9 | Mortality Data from National Center of Health Statistics | Incidence | Mortality |
|---|---|---|---|---|
| Davies, Welch. JAMA 2006 | 1973-2002 | 1973-2002 | **2.4-fold increase between 1973-2002** (P<0.001 for trend) | **0.5/100,000 in both 1973 & 2002** (p>0.2 for trend) |
| Lim et al. JAMA 2017 | 1974-2013 | 1994-2013 | **Annual percentage change 3.6%** | **Annual incidence-based mortality change 1.1%** |

# Thyroid Cancer Incidence in California, 2000-2017

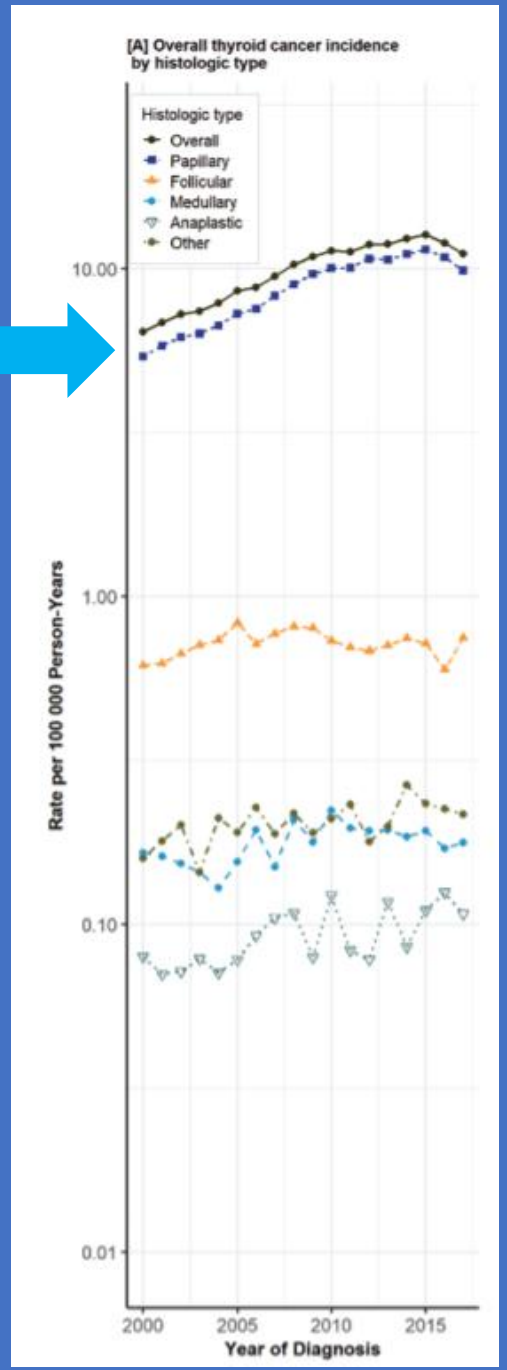
Median age: 50 years
(range, 38-61 years)

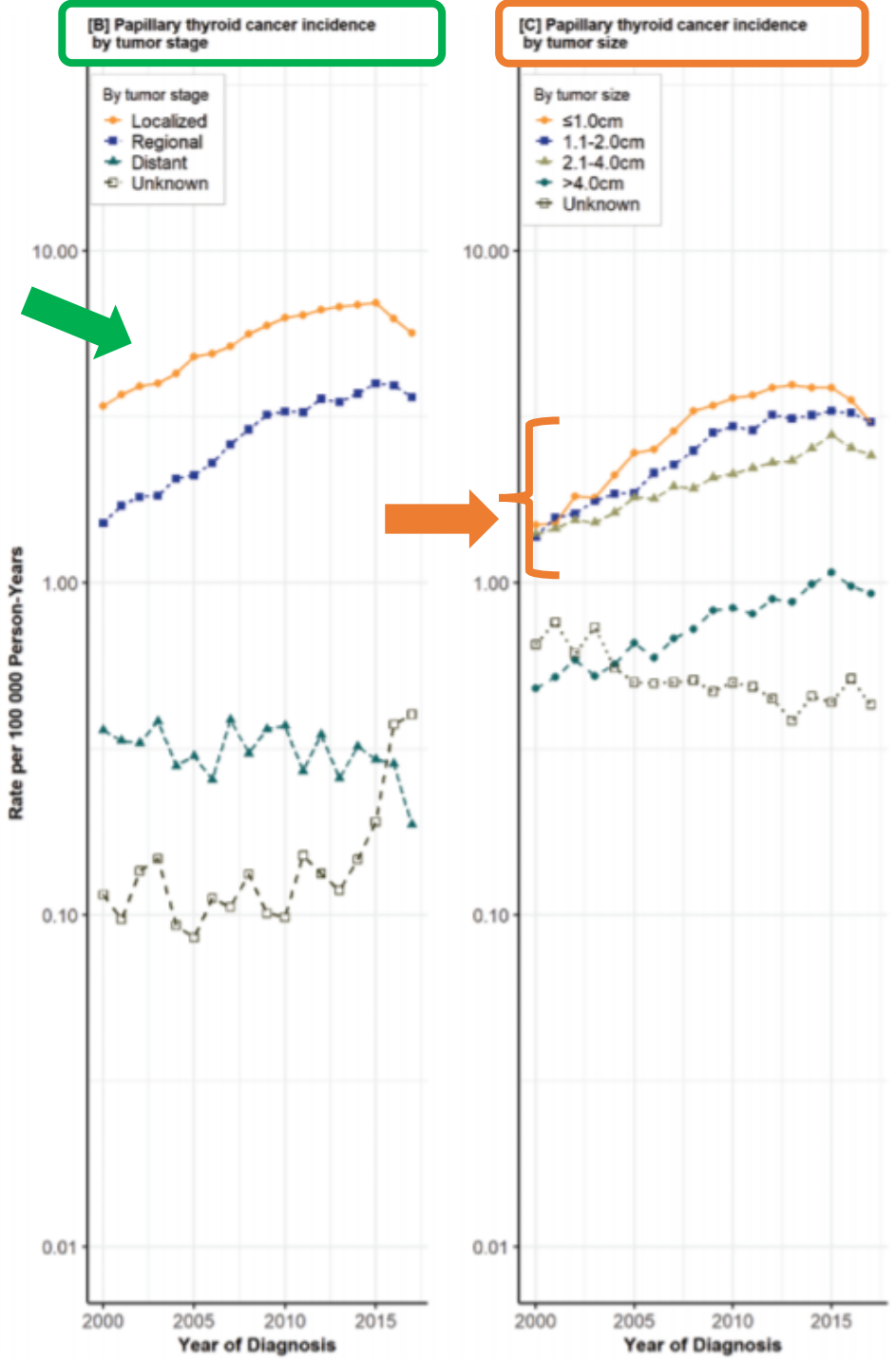
| | Cases, No (%) | Rate[a] (95%CI) |
|---|---|---|
| **Overall** | 69684 (100) | 10.06 (9.99-10.14) |
| **Sex** | | |
| Male | 16546 (23.7) | 4.68 (4.61-4.75) |
| Female | 53138 (76.3) | 15.42 (15.29-15.55) |
| **Race** | | |
| White | 54506 (78.2) | 10.55 (10.46-10.63) |
| Black | 2694 (3.9) | 5.5 (5.29-5.71) |
| Asian | 11276 (16.2) | 11.65 (11.43-11.87) |
| Other[b] | 1208 (1.7) | 3.75 (3.54-3.97) |
| **Ethnicity** | | |
| Hispanic | 18843 (27) | 7.12 (7.02-7.23) |
| Non-Hispanic | 50841 (73) | 11.55 (11.45-11.65) |
| **Age at Diagnosis, year** | | |
| <20 | 1433 (2.1) | 0.77 (0.73-0.81) |
| 20–39 | 18061 (25.9) | 9.32 (9.18-9.45) |
| 40–59 | 30504 (43.8) | 17.5 (17.3-1 7.69) |
| 60–79 | 17210 (24.7) | 20.06 (19.76-20.36) |
| 80+ | 2476 (3.6) | 11.89 (11.43-12.36) |
| **Thyroid Cancer Characteristics At Diagnosis** | | |
| **Histological subtype** | | |
| Papillary | 61203 (87.8) | 8.86 (8.79-8.94) |
| Follicular | 5044 (7.2) | 0.72 (0.7-0.74) |
| Medullary | 1250 (1.8) | 0.18 (0.17-0.19) |
| Anaplastic | 705 (1.0) | 0.09 (0.09-0.1) |
| Other[d] | 1482 (2.1) | 0.2 (0.19-0.22) |
| **Papillary Thyroid Cancer, SEER Historic Stage A** | | |
| Localized | 43478 (62.4) | 6.26 (6.21-6.32) |
| Regional | 20940 (30.0) | 3.06 (3.02-3.1) |
| Distant | 3671 (5.3) | 0.51 (0.49-0.52) |
| Unknown[e] | 1595 (2.3) | 0.23 (0.22-0.24) |
| **Papillary Thyroid Cancer, Tumor size, cm** | | |
| ≤1 | 21530 (30.9) | 3.09 (3.05-3.13) |
| >1 to ≤2 | 18638 (26.7) | 2.71 (2.67-2.75) |
| >2 to ≤4 | 16630 (23.9) | 2.42 (2.39-2.46) |
| >4 | 7894 (11.3) | 1.13 (1.1-1.15) |
| Unknown[e] | 4992 (7.2) | 0.71 (0.69-0.73) |

[a] Rates were calculated as number of cases or deaths per 100,000 person- years and age-adjusted to the 2000 California standard population.

Yan KL, Li S, Tseng CH, Kim J, Nguyen DT, Dawood NB, Livhits MJ, Yeh MW, Leung AM. Rising Incidence and Incidence-Based Mortality of Thyroid Cancer in California, 2000-2017. J Clin Endocrinol Metab. 2020 Jun 1;105(6):dgaa121.

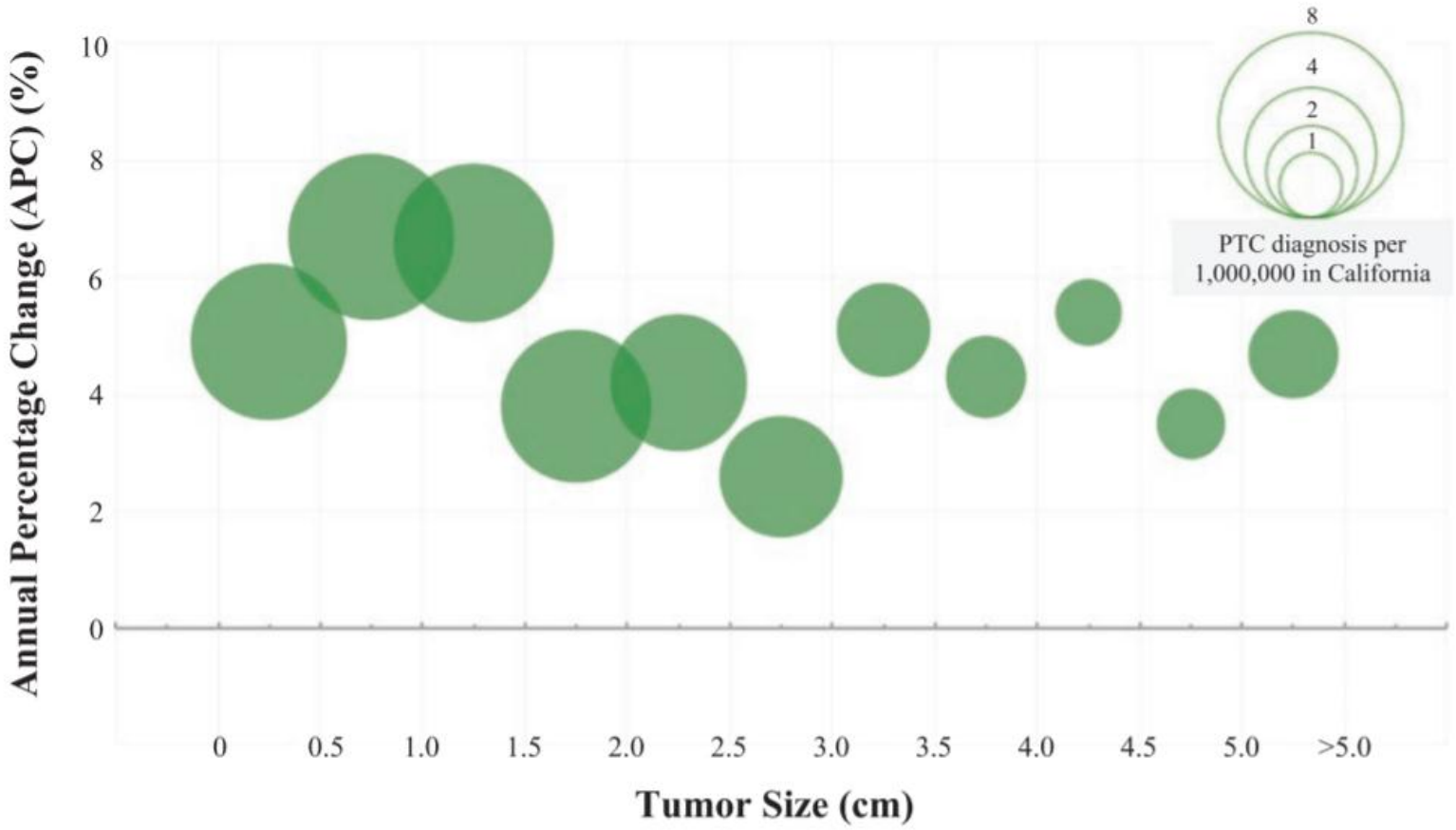
# Thyroid Cancer Incidence in California, 2000-2017




Yan KL, Li S, Tseng CH, Kim J, Nguyen DT, Dawood NB, Livhits MJ, Yeh MW, Leung AM. Rising Incidence and Incidence-Based Mortality of Thyroid Cancer in California, 2000-2017. J Clin Endocrinol Metab. 2020 Jun 1;105(6):dgaa121.

# Annual Percent Change (APC) of Papillary Thyroid Cancer Incidence by Tumor Size




- APC = Change in PTC incidence rates
- Each bubble represents number of PTC diagnoses per 1,000,000 in California from 2000-2017.

Yan KL, Li S, Tseng CH, Kim J, Nguyen DT, Dawood NB, Livhits MJ, Yeh MW, Leung AM. Rising Incidence and Incidence-Based Mortality of Thyroid Cancer in California, 2000-2017. J Clin Endocrinol Metab. 2020 Jun 1;105(6):dgaa121.

# Thyroid Cancer Incidence-Based Mortality in California, 2000-2017

| | Deaths, No (%) | Rate[a] (95% CI) |
|---|---|---|
| Overall | 2562 (100) | 0.34 (0.33-0.36) |
| Sex | | |
| Male | 1039 (40.6) | 0.27 (0.26-0.29) |
| Female | 1523 (59.4) | 0.41 (0.39-0.43) |
| Race | | |
| White | 1981 (77.3) | 0.36 (0.34-0.37) |
| Black | 127 (5.0) | 0.24 (0.2-0.29) |
| Asian | 449 (17.5) | 0.39 (0.35-0.43) |
| Other[b] | NR[c] | NR[c] |
| Ethnicity | | |
| Hispanic | 642 (25.1) | 0.21 (0.19-0.23) |
| Non-Hispanic | 1920 (74.9) | 0.4 (0.38-0.42) |
| Age at Diagnosis, year | | |
| <20 | NR[c] | NR[c] |
| 20–39 | 73 (2.8) | 0.01 (0.01-0.01) |
| 40–59 | 563 (22) | 0.08 (0.07-0.09) |
| 60–79 | 1316 (51.4) | 0.17 (0.16-0.18) |
| 80+ | 607 (23.7) | 0.08 (0.07-0.09) |
| Thyroid Cancer Charact | | |
| Histological subtype | | |
| Papillary | 1157 (45.2) | 0.16 (0.15-0.16) |
| Follicular | 282 (11.0) | 0.04 (0.03-0.04) |
| Medullary | 172 (6.7) | 0.02 (0.02-0.03) |
| Anaplastic | 554 (21.6) | 0.07 (0.07-0.08) |
| Other[d] | 397 (15.5) | 0.05 (0.05-0.06) |
| Papillary Thyroid Cance | | |
| Localized | 243 (9.5) | 0.03 (0.03-0.04) |
| Regional | 683 (26.7) | 0.09 (0.08-0.1) |
| Distant | 1443 (56.3) | 0.19 (0.18-0.2) |
| Unknown[e] | 193 (7.5) | 0.03 (0.02-0.03) |
| Papillary Thyroid Cance | | |
| ≤1 | 104 (4.1) | 0.01 (0.01-0.02) |
| >1 to ≤2 | 180 (7.0) | 0.02 (0.02-0.03) |
| >2 to ≤4 | 560 (21.9) | 0.07 (0.07-0.08) |
| >4 | 1089 (42.5) | 0.15 (0.14-0.15) |
| Unknown[e] | 629 (24.6) | 0.08 (0.08-0.09) |

[a] Rates were calculated as number of cases or deaths per 100,000 person- years and age-adjusted to the 2000 California standard population.

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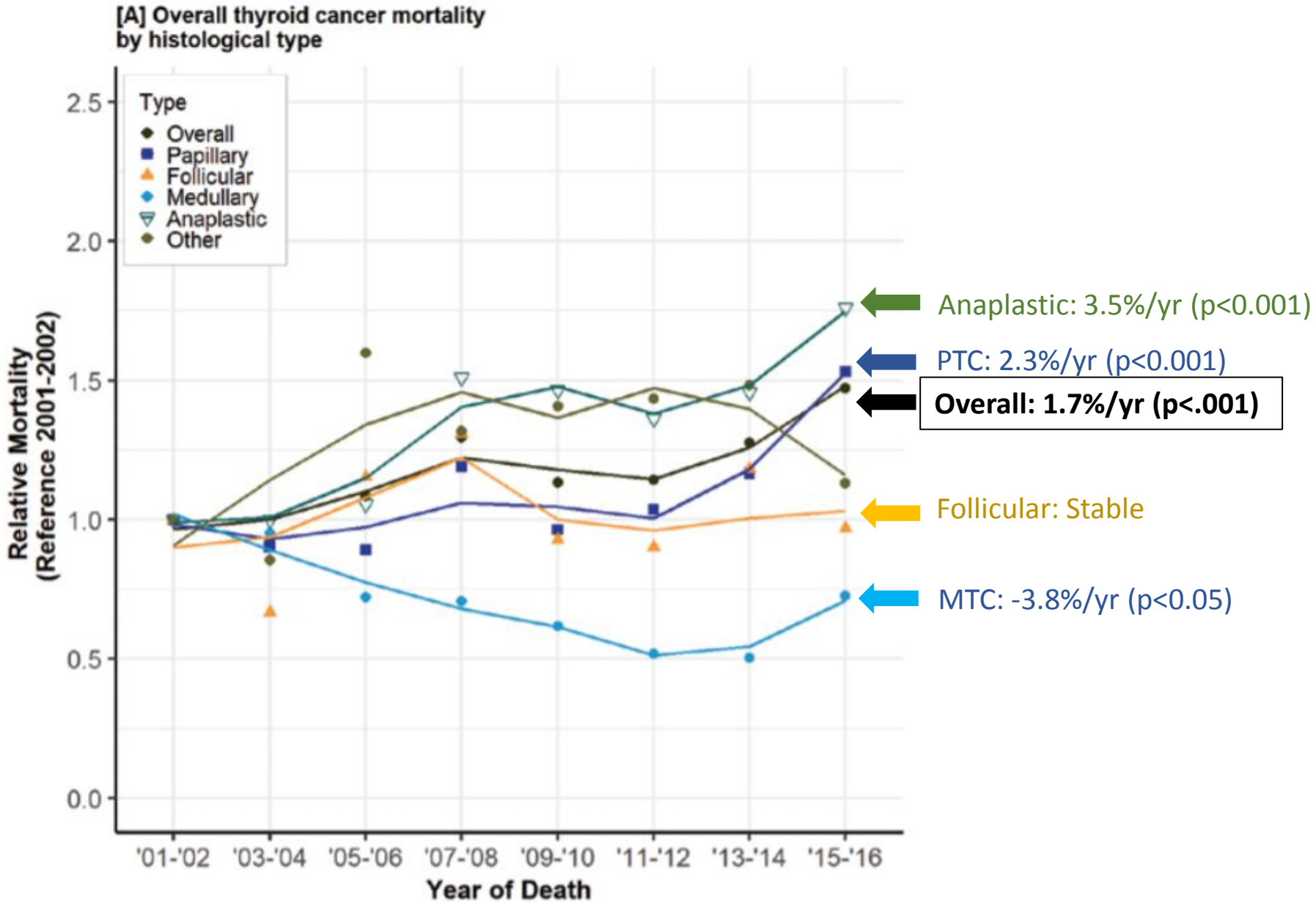


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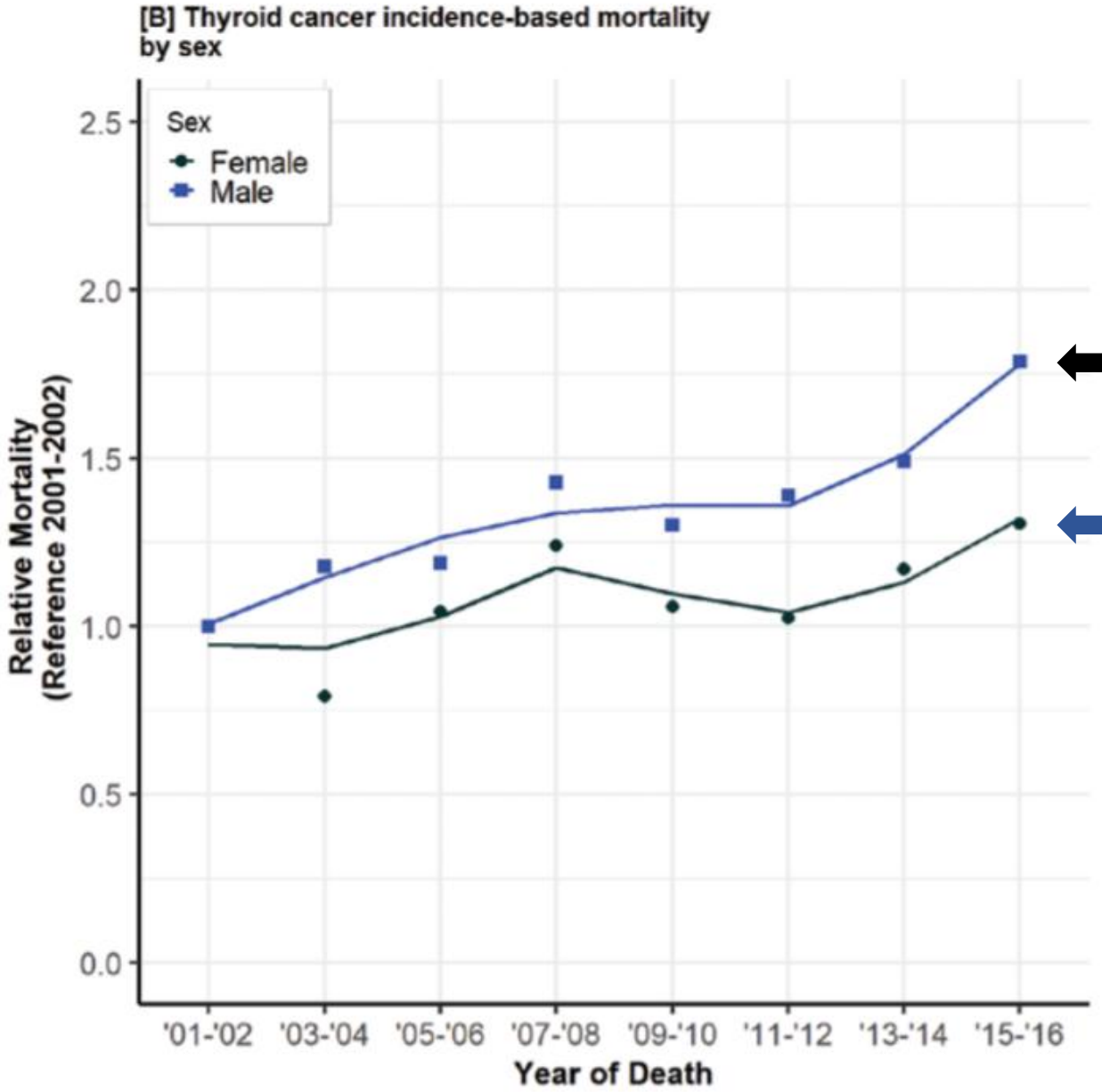
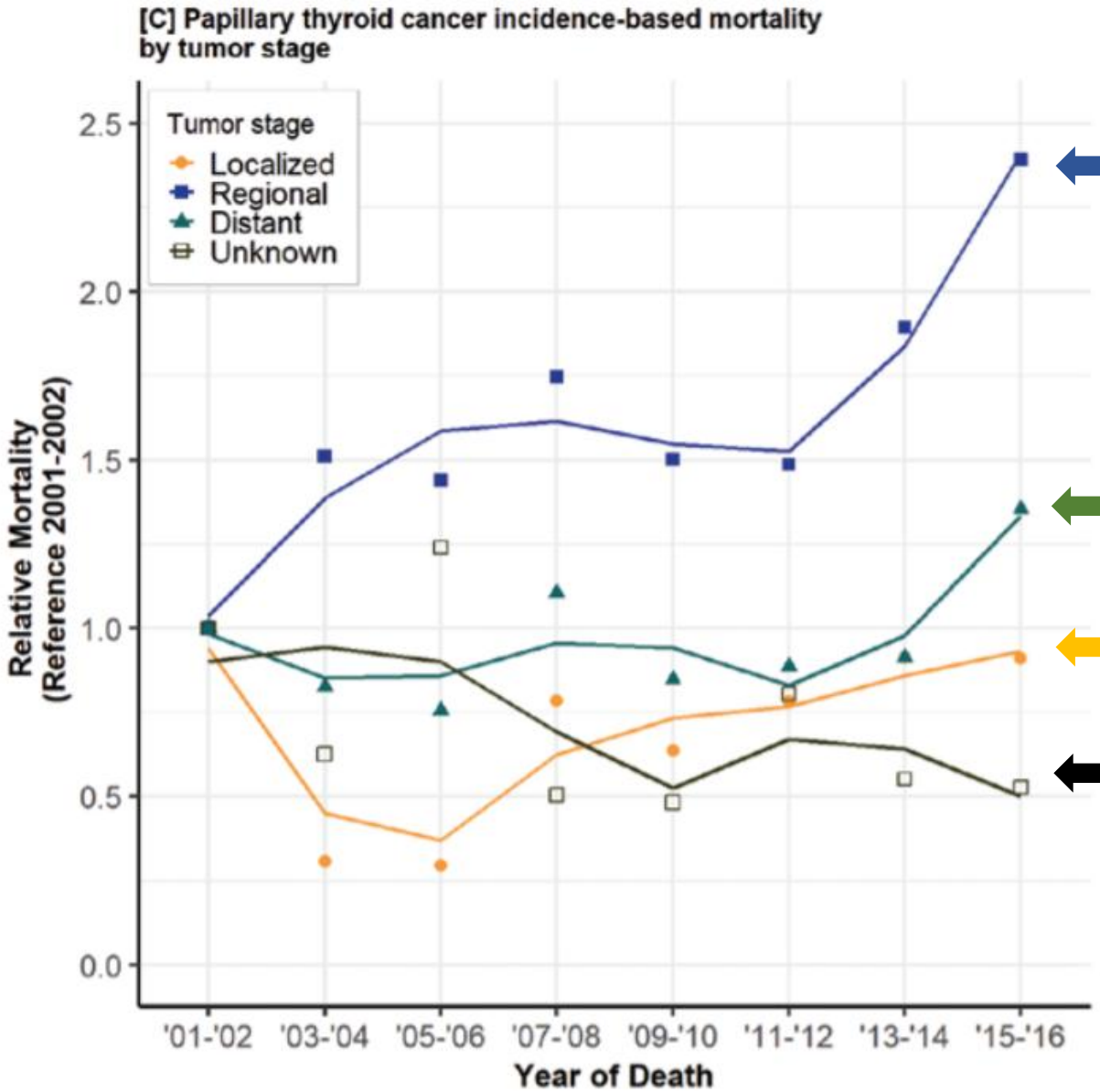



Males: 2.7%/yr (p<0.001)

Females: 1.0%/yr (p=0.07)

Yan KL, Li S, Tseng CH, Kim J, Nguyen DT, Dawood NB, Livhits MJ, Yeh MW, Leung AM. Rising Incidence and Incidence-Based Mortality of Thyroid Cancer in California, 2000-2017. J Clin Endocrinol Metab. 2020 Jun 1;105(6):dgaa121.



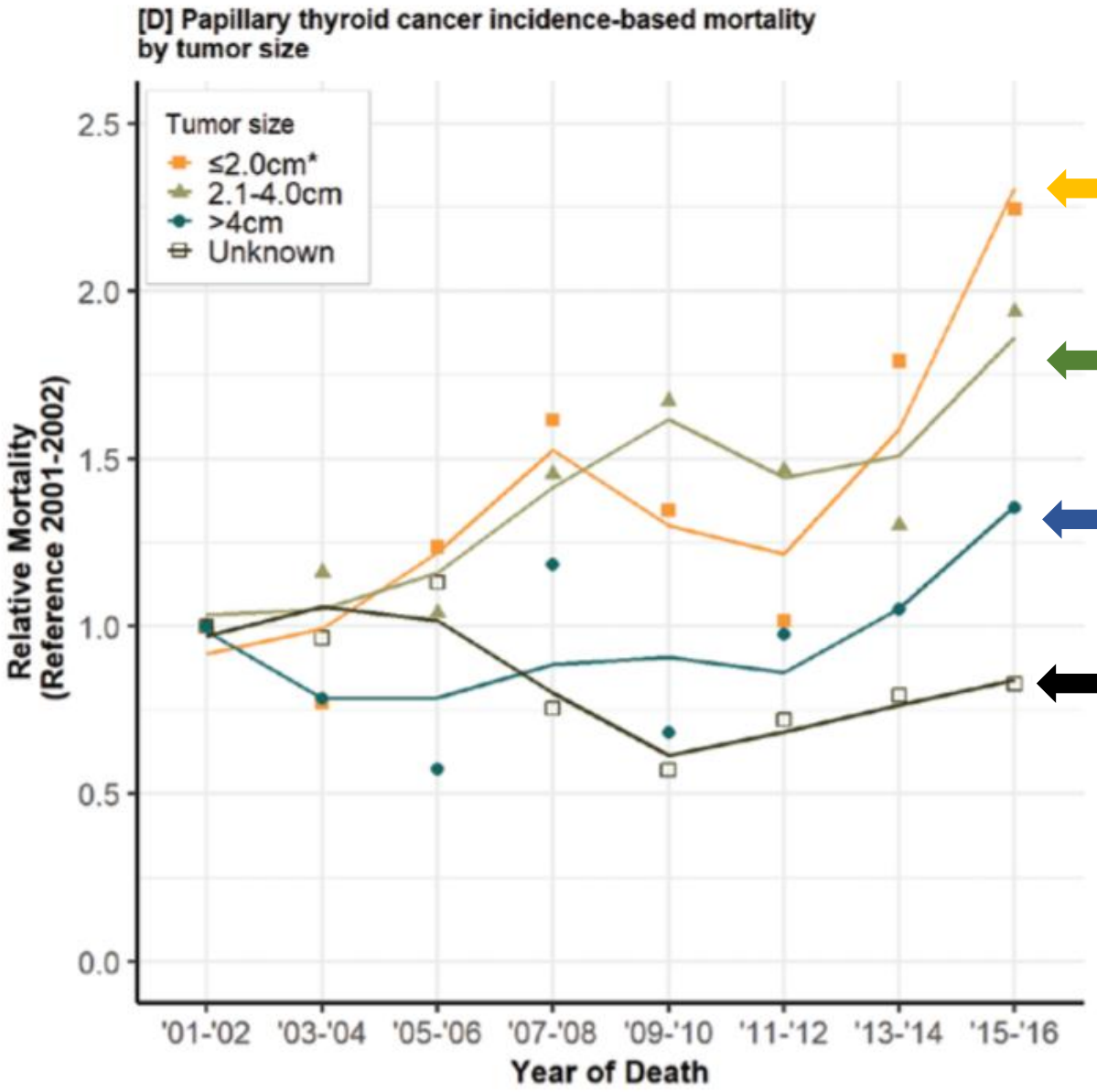

Regional: 6.0%/yr (p=0.02)

Distant: -1.7%/yr (p=0.08)

Localized: 4.1%/yr (p=0.06)

Not represented (insufficient data for analysis)

Yan KL, Li S, Tseng CH, Kim J, Nguyen DT, Dawood NB, Livhits MJ, Yeh MW, Leung AM. Rising Incidence and Incidence-Based Mortality of Thyroid Cancer in California, 2000-2017. J Clin Endocrinol Metab. 2020 Jun 1;105(6):dgaa121.




PTC 1-2 cm : 5.1%/yr (p=0.02)

PTC 2-4 cm: 3.4%/yr (p=0.01)

PTC >4 cm: 2.6%/yr (p=0.03)

Unknown: -3.4% (p=0.02)

Yan KL, Li S, Tseng CH, Kim J, Nguyen DT, Dawood NB, Livhits MJ, Yeh MW, Leung AM. Rising Incidence and Incidence-Based Mortality of Thyroid Cancer in California, 2000-2017. J Clin Endocrinol Metab. 2020 Jun 1;105(6):dgaa121.

# Thyroid Cancer in California 2000-2017

- Average overall APC of thyroid cancer incidence: **4%**
  - Irrespective of sex, ethnicity, tumor size, stage (excluding distant cancers) and histological subtype (excluding follicular tumors)
  - Importantly also captures the more rare subtypes: anaplastic cancers and cancers >4 cm
- Average overall APC of thyroid cancer incidence: **1.7%**
  - More pronounced for males with PTC (APC 2.7%/yr)
  - More pronounced for those with advanced stage PTC
  - More pronounced in older patients (APC 1.8%, ages 60-79 years)

Yan KL, Li S, Tseng CH, Kim J, Nguyen DT, Dawood NB, Livhits MJ, Yeh MW, Leung AM. Rising Incidence and Incidence-Based Mortality of Thyroid Cancer in California, 2000-2017. J Clin Endocrinol Metab. 2020 Jun 1;105(6):dgaa121.

# So Why Might New Thyroid Cancer Diagnoses be Increasing?

- Increased exposure to radiation
- Changes in dietary iodine intake
- Environmental exposures like nitrates
- Agricultural industrial practices producing thousands of chemicals with unknown carcinogenicity (i.e. heavy metals)

Vigneri R et al. Is Thyroid Cancer Increasing in Incidence and Aggressiveness? *J Clin Endocrinol Metab* 2020;105(7):dgaa223.


Thank You
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