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公立大学法人福島県立医科大学放射線医学県民健康管理センター
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2023 Fukushima Medical University International Symposium on the Fukushima Health Management Survey
Secretariat of International Symposium
Office of Public Communications and International Cooperation, Radiation Medical Science Center for the Fukushima Health Management Survey, Fukushima Medical University
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5th International Symposium:
Fukushima Health Management Survey
March 4, 2023

Understanding the causes and trends in thyroid cancer incidence

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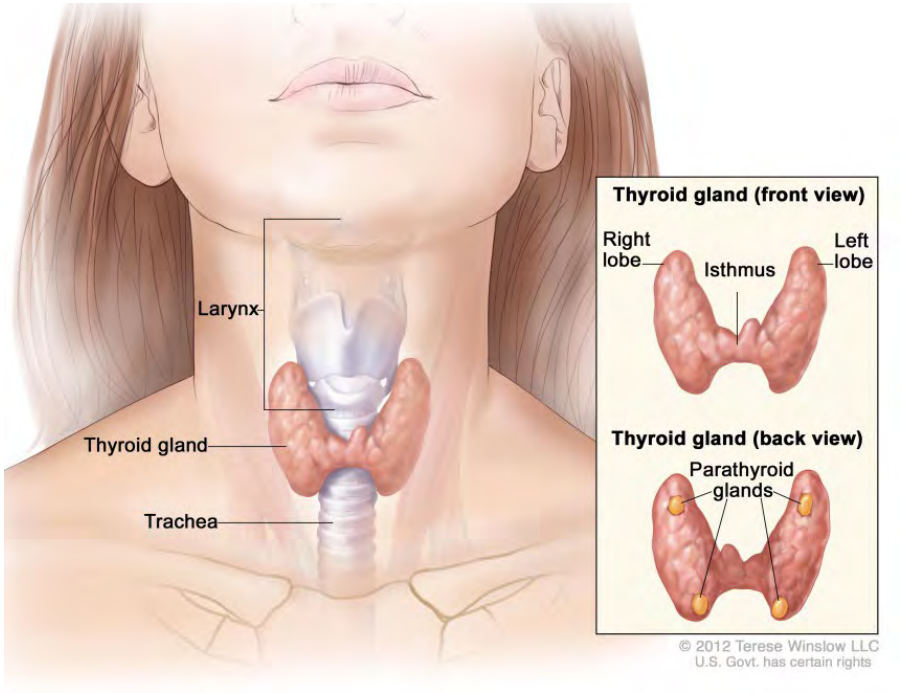
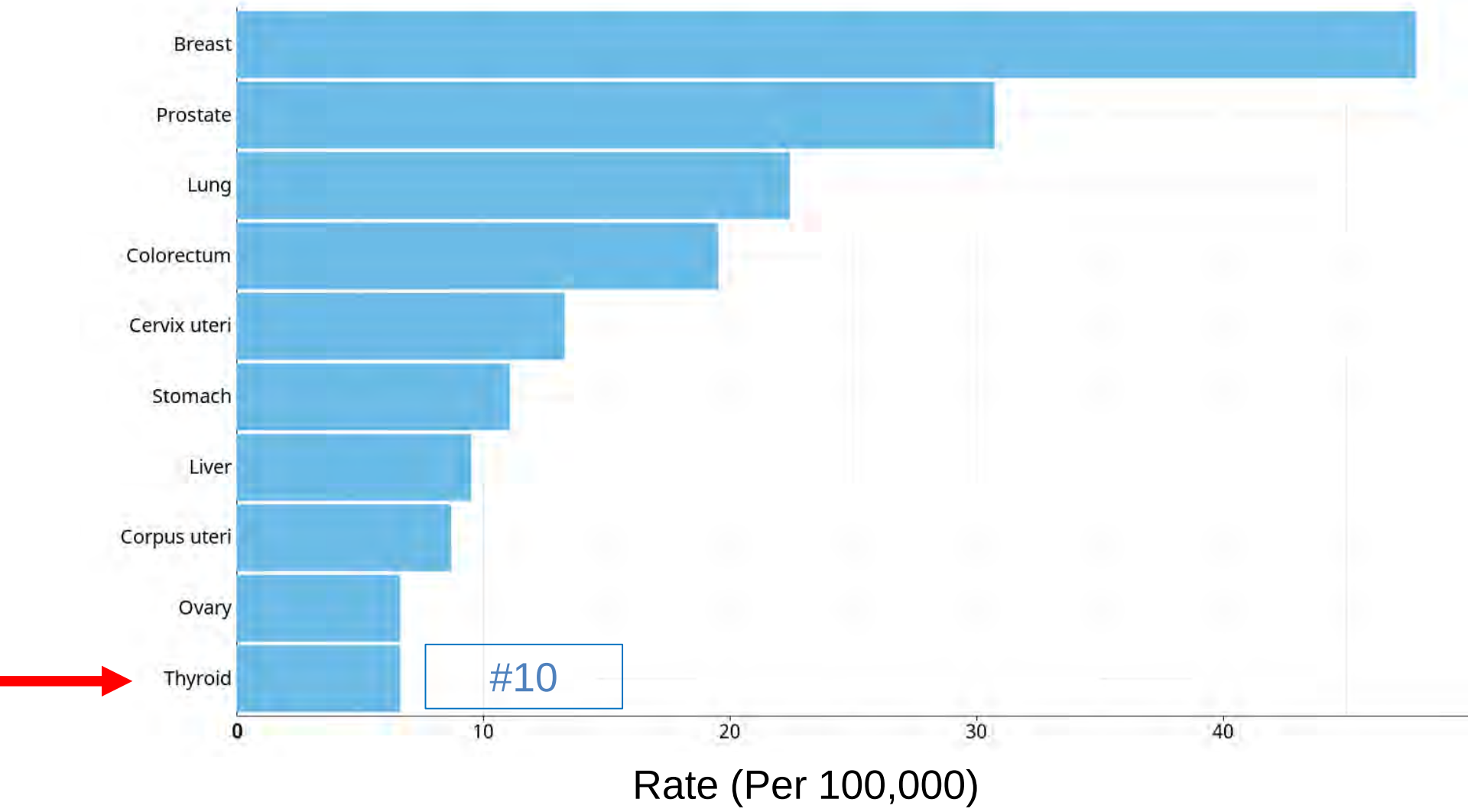
Disclosures

I have no financial disclosures or conflicts of interest.

Cancer of the thyroid gland

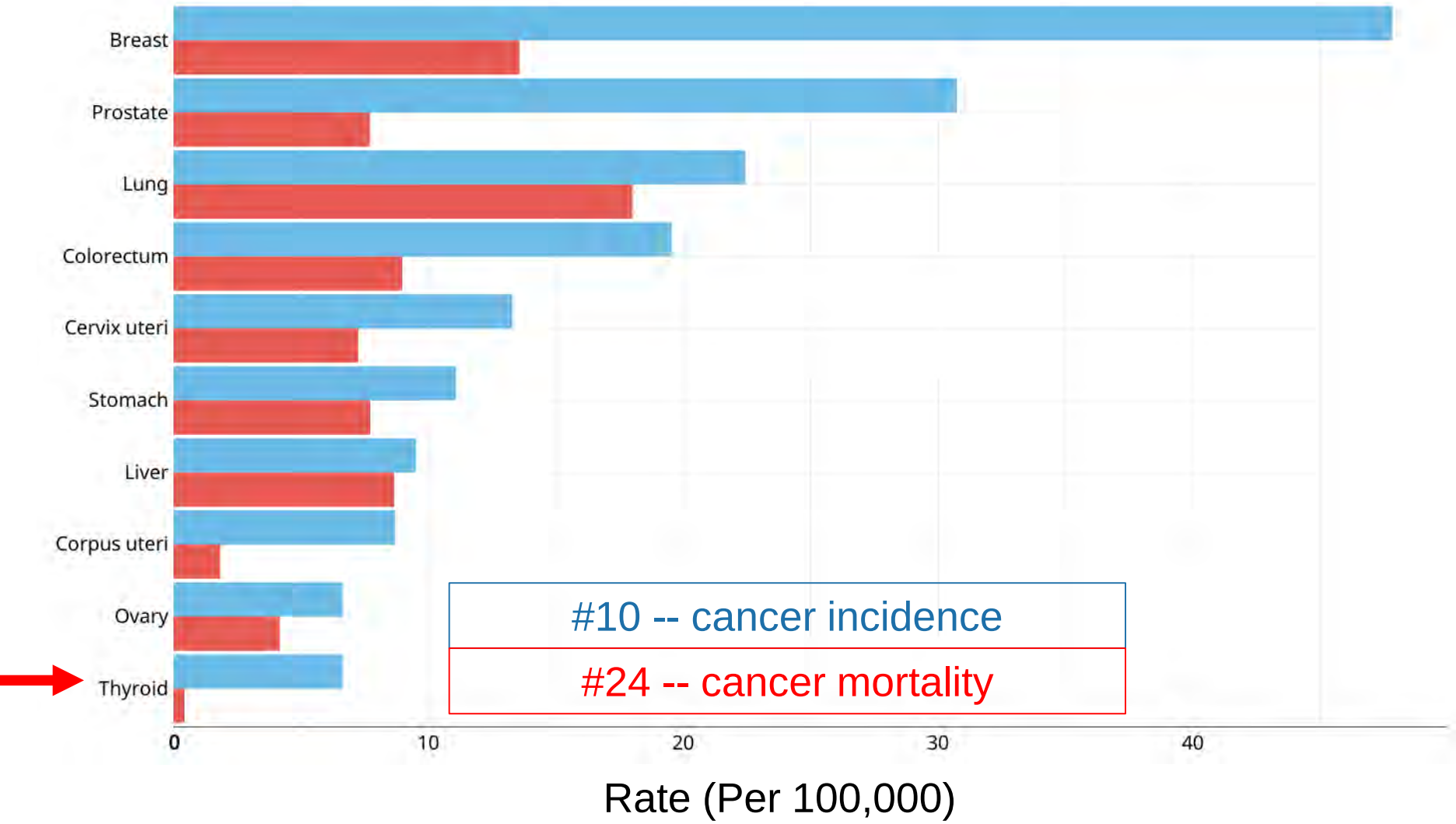


Global cancer incidence rates



Globocan 2020 (http://gco.iarc.fr)

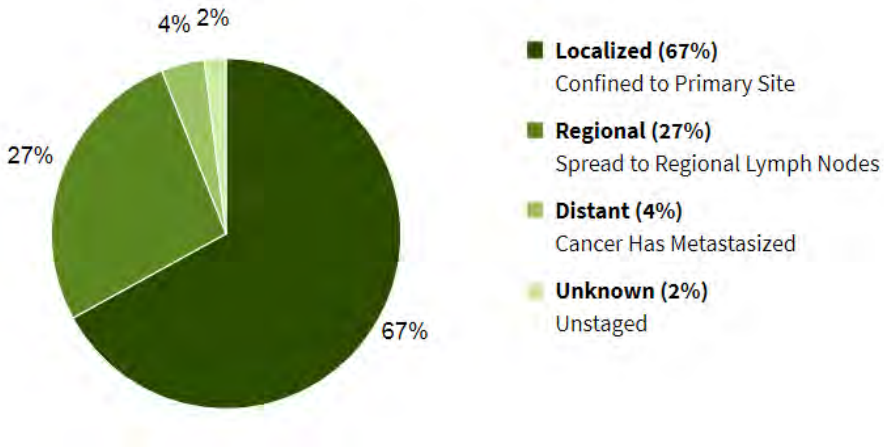
Global cancer incidence and mortality rates



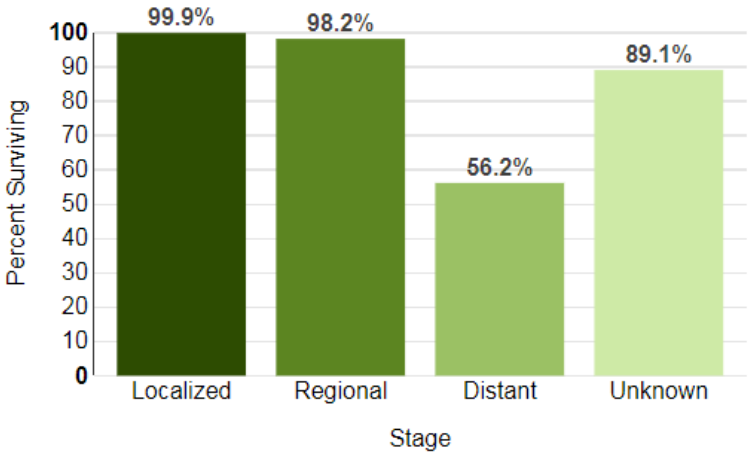
Globocan 2020 (http://gco.iarc.fr)

High survival rates after thyroid cancer diagnosis

% Cases by Stage at Diagnosis

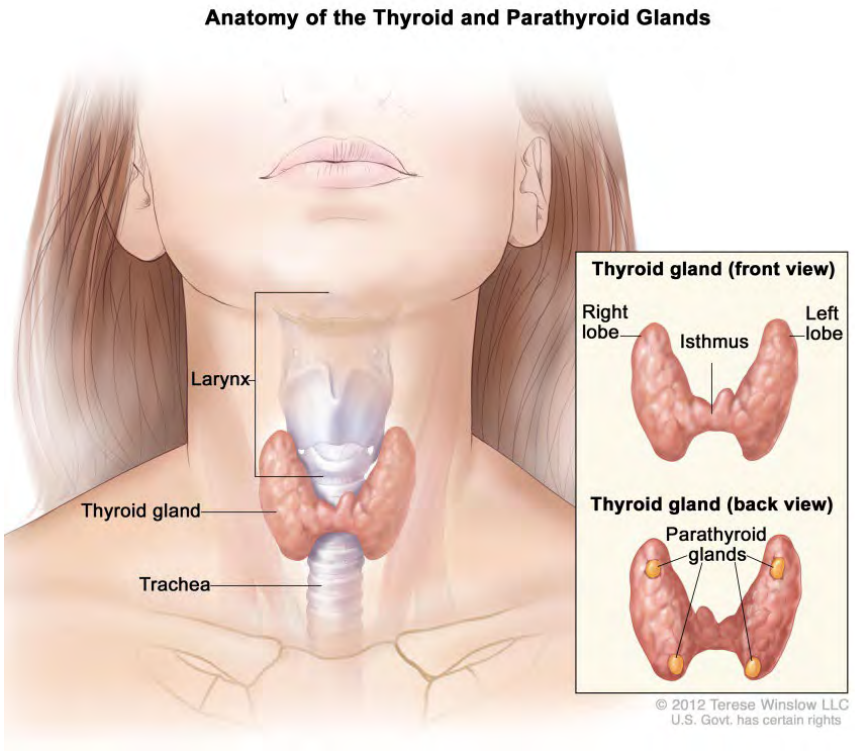


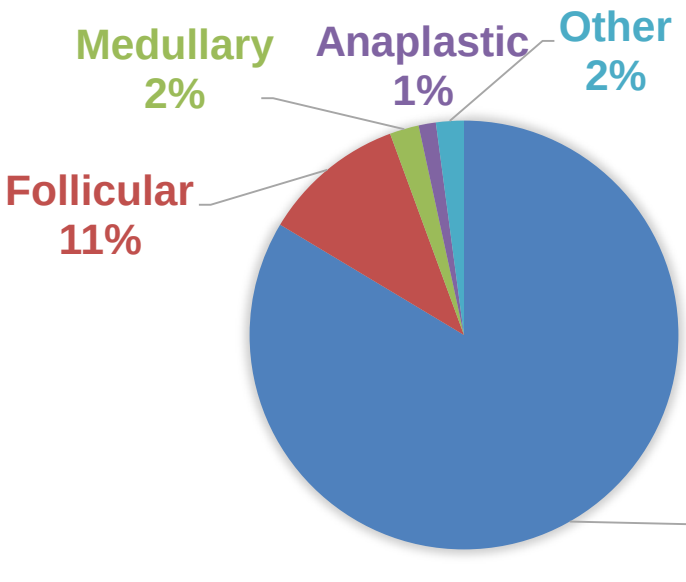
5-year relative survival



Globocan 2018; Surveillance, Epidemiology, and End Results (USA): seer.cancer.gov

Histologic types of thyroid cancer

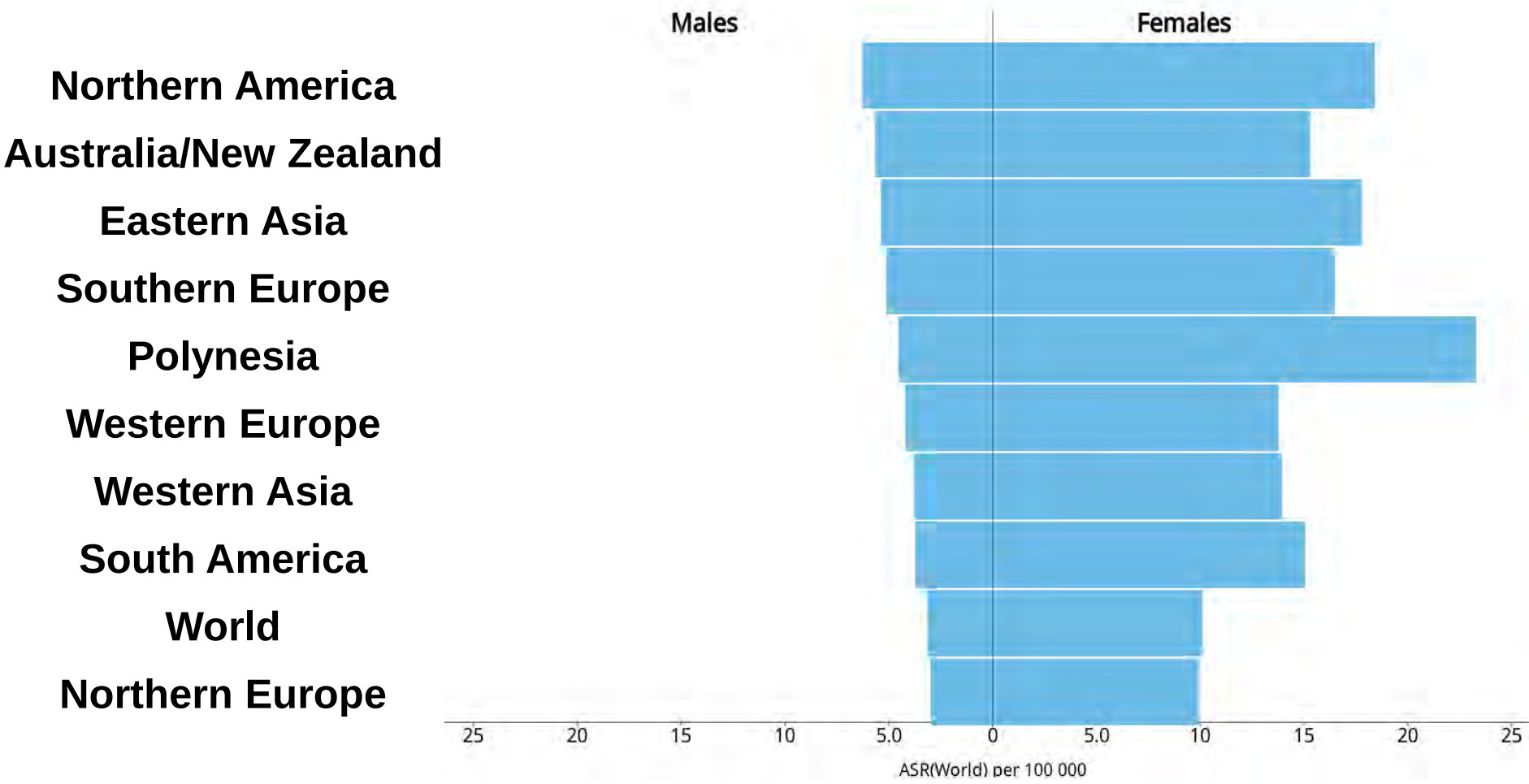




Most common type, highest survival rate

Source: National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER)-9 (1974-2013); seer.cancer.gov

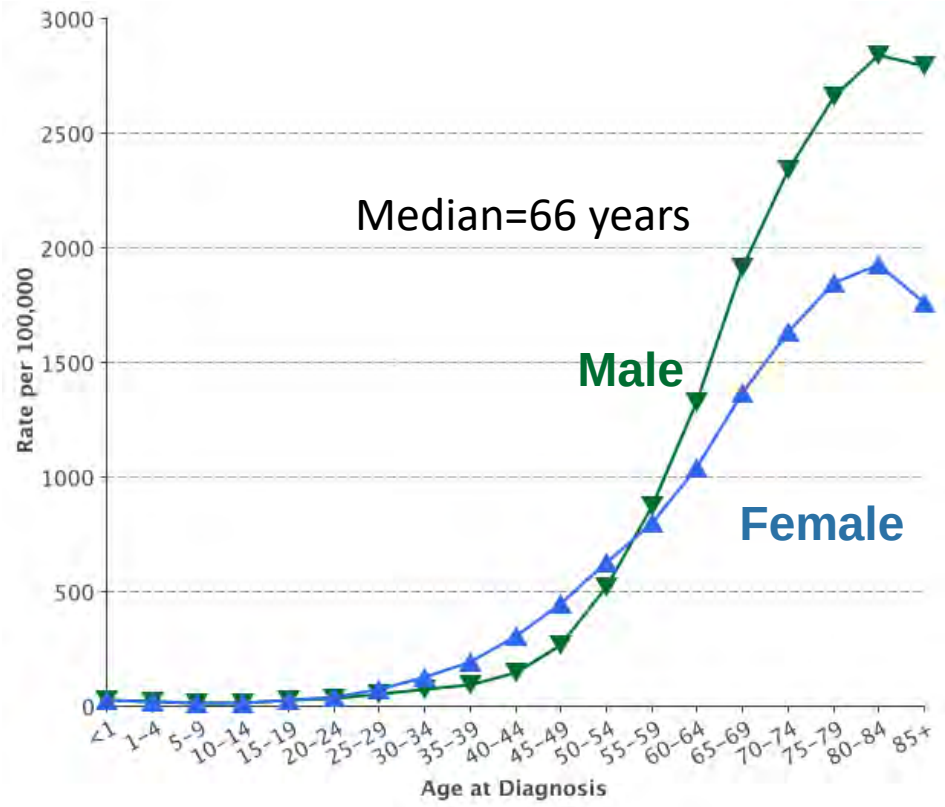
Higher thyroid cancer incidence in females than males



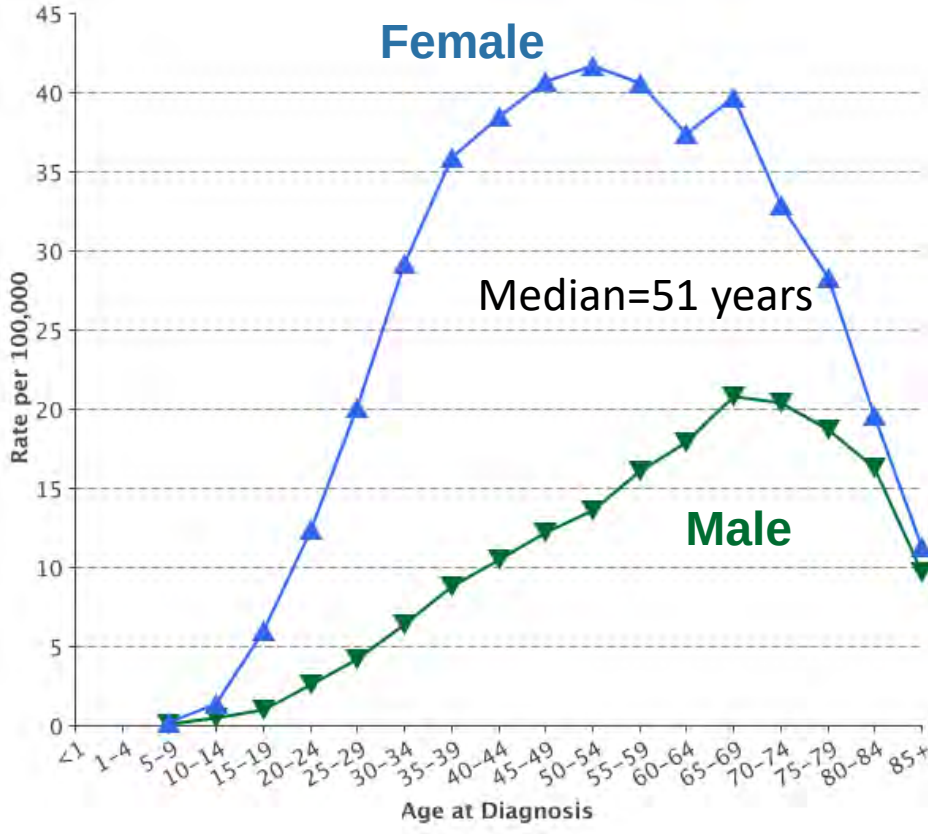
Globocan 2020 (http://gco.iarc.fr)

Cancer incidence by sex and age at diagnosis (USA)

All cancer

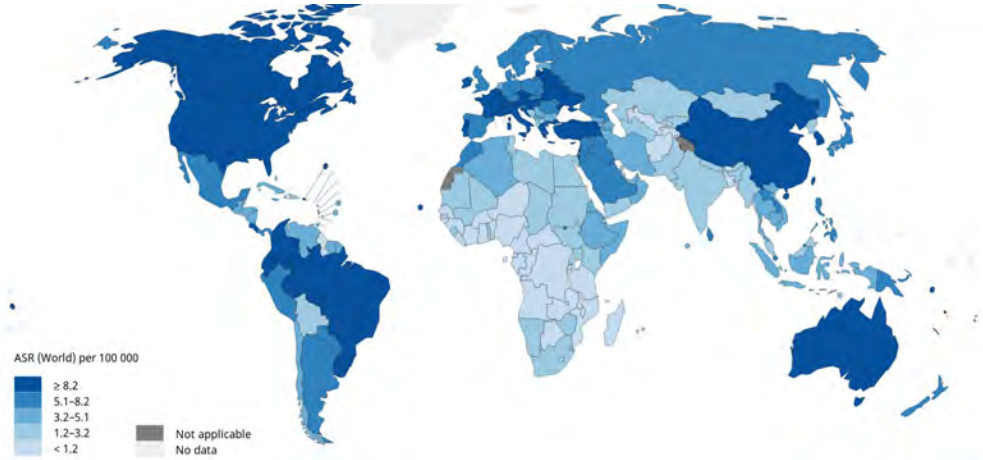


Thyroid cancer



SEER 21, 2012-2016; seer.cancer.gov

Geographic variation in thyroid cancer incidence (2020)



Population	Incidence (per 100,000)
South Korea	26.6
Canada	17.4
France	14.8
Israel	14.3
USA	11.8
Australia	11.4
China	11.3
Japan	8.0
Finland	8.2
Germany	5.3
India	1.4

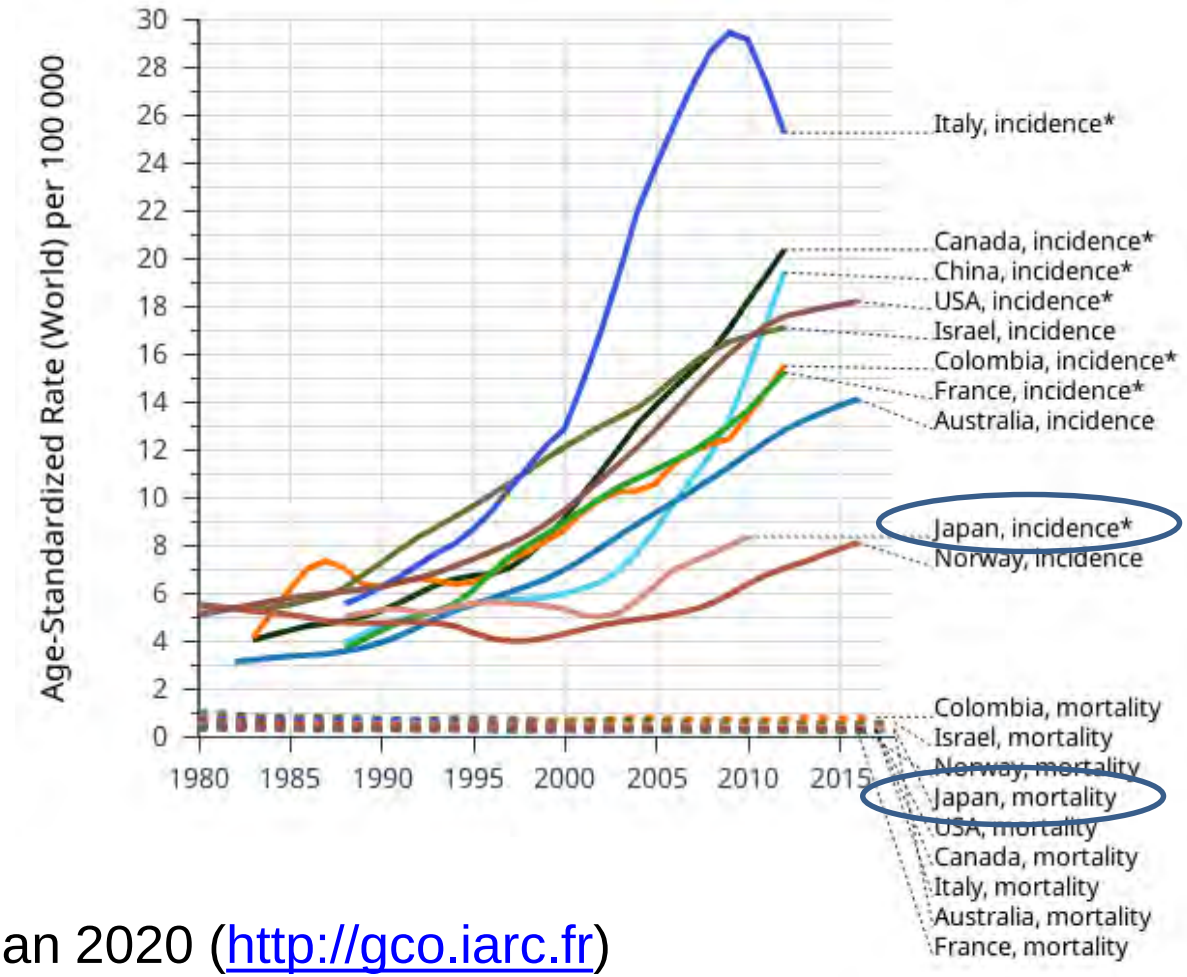
Contributing factors

- Sociodemographic factors
- Diagnosis and screening practices
- Quality of cancer registries
- Small numbers/imprecision
- Environment, lifestyle factors

Globocan 2020; https://gco.iarc.fr/

Global trends in thyroid cancer incidence and mortality

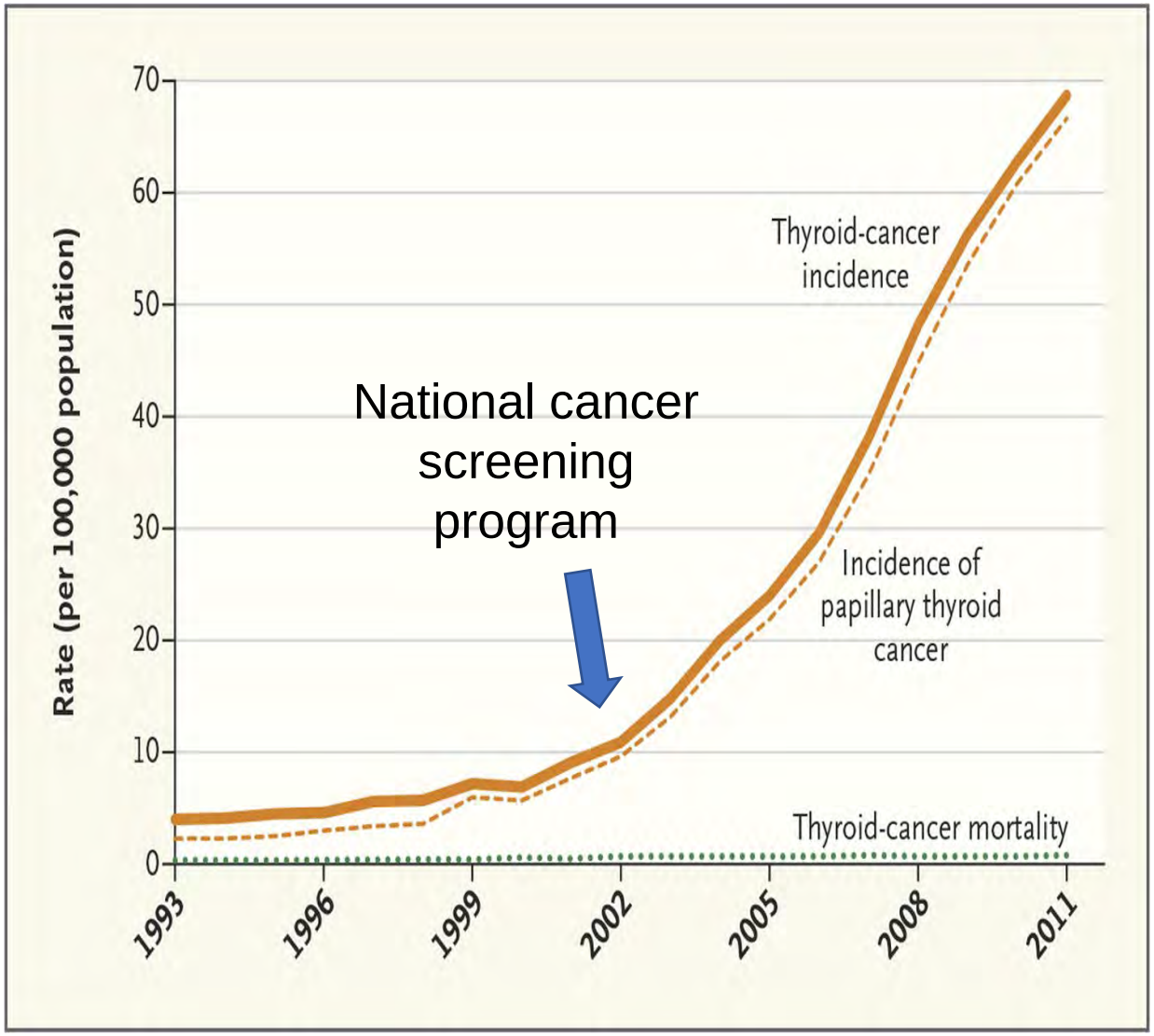
Age standardized incidence (World), **Females**



Globocan 2020 (http://gco.iarc.fr)

Thyroid cancer trends in South Korea (1993-2011)

- 15-fold increase in incidence
- Stable mortality



Ahn HS et al. N Engl J Med 2014;371:1765-1767

U.S. trends in thyroid cancer incidence (1975-2019) and mortality (1975-2020)

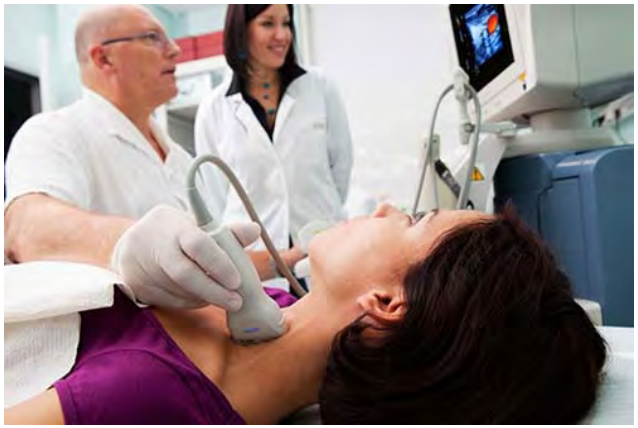
- 3-fold increase in incidence
- Stable mortality

SEER-8 and National Center for Health Statistics (seer.cancer.gov)

Epidemic of overdiagnosis?

- Rapid rise in incidence, driven by papillary carcinomas
- Increasing % of small vs large tumors over time
- Stable mortality rates
- Increasingly sensitive imaging and diagnostic tools
- High prevalence of asymptomatic, indolent disease

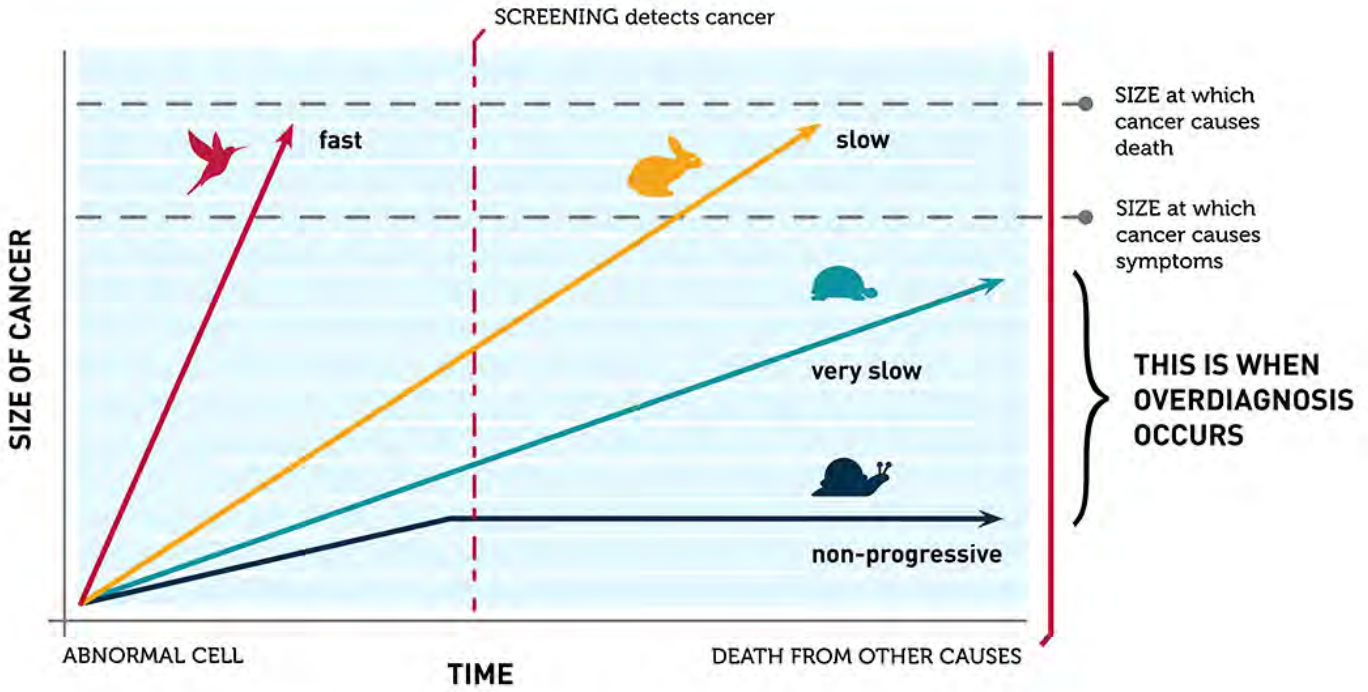
"We believe increased <u>diagnostic scrutiny</u> is the most likely explanation for the apparent increase in incidence."



Davies & Welch. *JAMA* 2006;295:2164-7

Cancer overdiagnosis

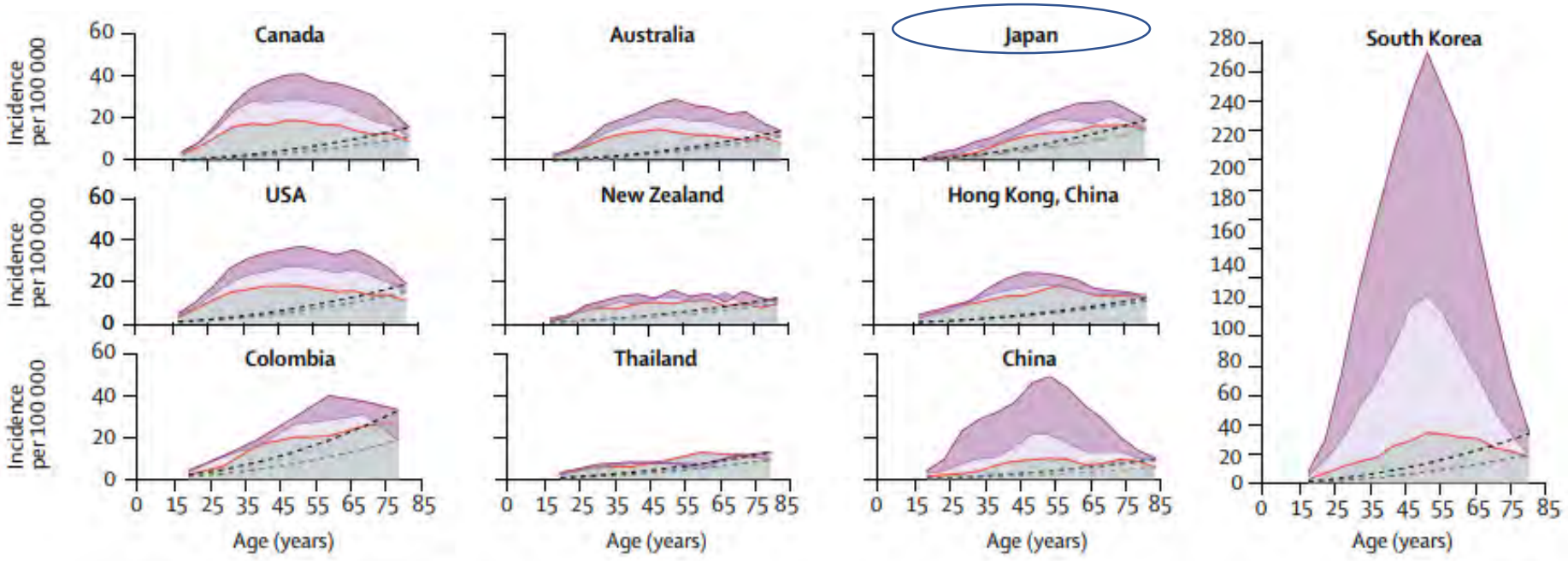
Occurs when screen-detected cancers are either non-growing or so slow-growing that they would never cause medical problems



Adapted from a figure courtesy of H. Gilbert Welch, Dartmouth Medical School

The National Cancer Institute: https://prevention.cancer.gov/news-and-events/infographics/what-cancer-overdiagnosis

Trends in thyroid cancer incidence by age at diagnosis (females)



Li et al., Lancet Diabetes Endocrinol 2020;8(6):468-470.

Proportion of thyroid cancers attributable to overdiagnosis (2008-2012)

	Females	Males
South Korea	93%	87%
Belarus	91%	82%
China	87%	81%
Italy	84%	74%
France	83%	72%
Canada	80%	67%
USA	76%	55%
Denmark	66%	68%
UK	58%	40%
Japan	**55%**	**46%**
Thailand	44%	39%

Li et al., Lancet Diabetes Endocrinol 2020;8(6):468-470.

Harms due to thyroid cancer overdiagnosis

- Psychological effects
  - Anxiety/stress
  - Fear of recurrence/growth/metastasis
- Overtreatment
  - Short-term complications
  - Late effects (2nd cancers)
- Financial burden (personal and societal)
- Overall reduced quality of life

Applewhite MK, et al. World J Surg 2016;40(3):551-61; Aschebrook-Kilfoy B, et al., CEBP 2013;22(7):1252-9; Iyer NG, et al., Cancer 2011;117(19):4439-46; Roman Br, et al. Curr Opin Endocrinol Diabetes Obes 2017;24(5):332-6.

Actions taken to minimize overdiagnosis (and overtreatment) in Japan

- Recommendations against screening for small papillary carcinomas*
- Recommendations against fine needle aspiration cytology of thyroid nodules <5 mm**
- Recommendations for active surveillance in patients with very low risk papillary carcinoma (T1N0M0)***

Shimura et al., Cancers (2021); *Japan Association of Breast and Thyroid Sonology (2012); **Japan Thyroid Association (2013); *** Japan Association of Endocrine Surgery (2010)

Thyroid Ultrasound Examination (TUE), Fukushima Health Management Survey

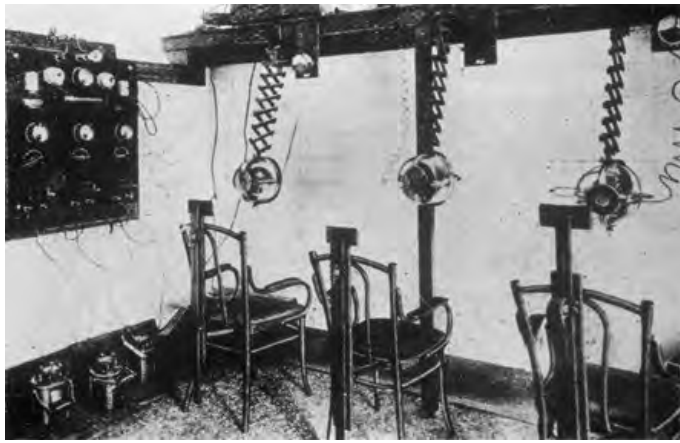
- Diagnostic procedures developed under guidance of thyroid specialists, based on revised clinical guidelines in Japan
- Informed consent after explaining advantages and disadvantages (e.g. possibility of overdiagnosis)
- Full support (including mental care support) provided to those diagnosed with thyroid cancer
- Less extensive treatments → reduced complication rates

Shimura et al., J Epidemiol 2022

What are the causes of thyroid cancer?

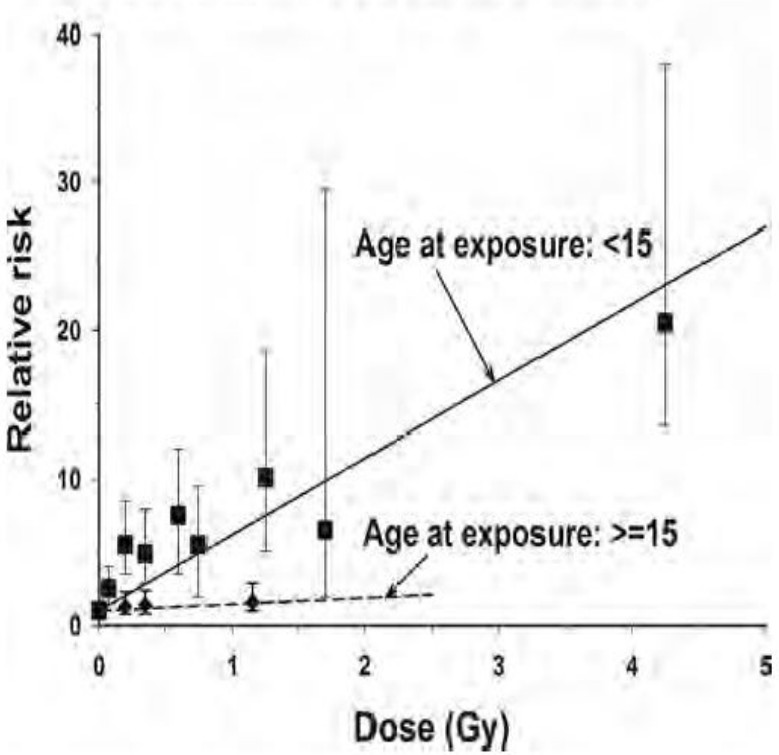
Childhood exposure to ionizing radiation

- Japanese atomic bomb survivors
- Chernobyl-area evacuees and residents
- Children receiving radiotherapy for benign conditions and cancer



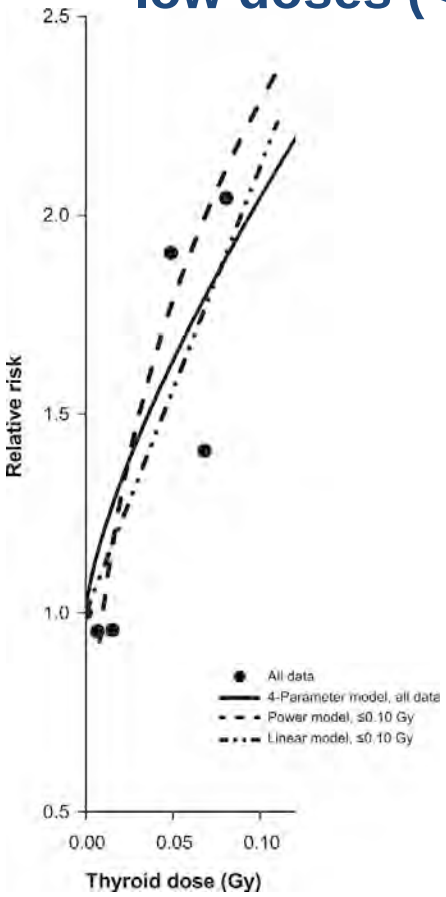
Ionizing radiation and thyroid cancer risk

Association restricted to childhood exposure



Adapted from Ron E, et al. Radiat Res 1995

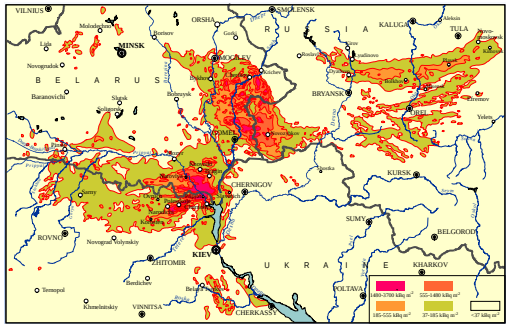
Linear association at low doses (<0.1 Gy)



Veiga LH, et al. Radiat Res 2016.185:473-84

Chernobyl nuclear accident (1986)

- Most serious nuclear power accident to date
- Radioactive material released and deposited in Ukraine, Belarus, Russia



- Iodine-131 was most significant radionuclide <2 months after accident
  - Inhaled and ingested (mainly via contaminated milk)
  - Children most vulnerable to carcinogenic effects
  - Iodine deficient population → greater thyroid uptake

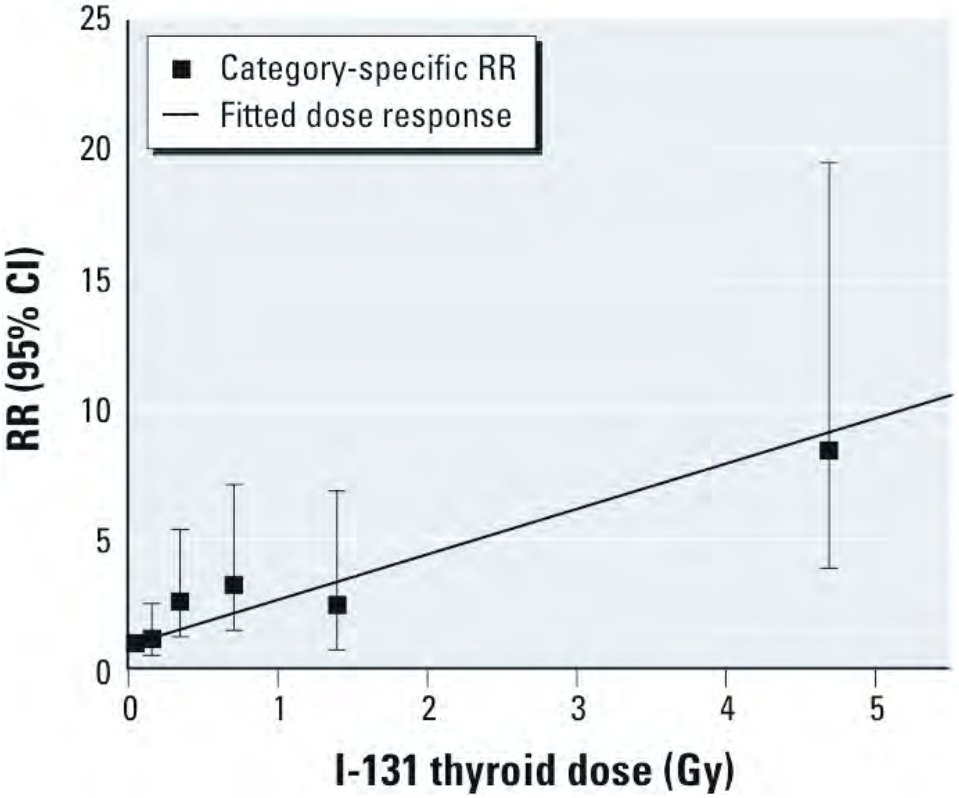
Childhood exposure to ^{131}I (Chernobyl) and thyroid cancer risk

Screening cohorts

- 12,500 in Ukraine (5 cycles, 1998-2015)
- 11,600 in Belarus (3 cycles, 1996-2008)

Mean thyroid dose ~0.5 Gy

Childhood exposure to I-131 caused ~5,000 out of 20,000 (~25%) thyroid cancer diagnoses to date



Tronko et al JNCI 2006; Brenner et al Environ Health Perspect 2011; Tronko et al Cancer Epidemiol 2017; Zablotska et al Br J Cancer 2011

Comparing radiation exposure from Chernobyl and Fukushima

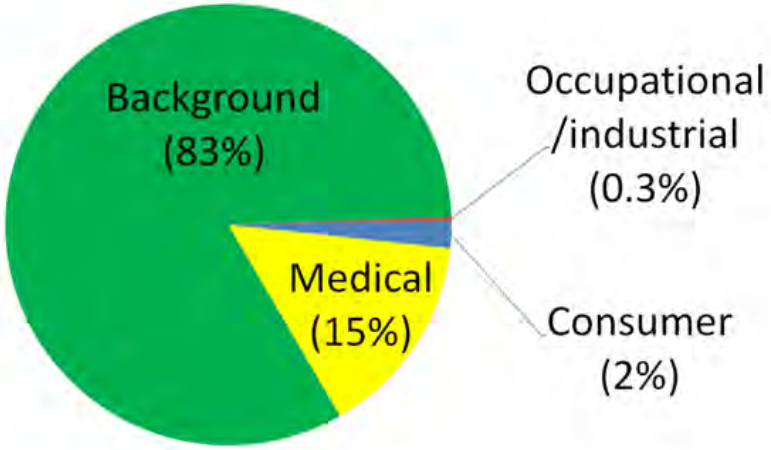
- Chernobyl accident released **10 times more** radioactivity than Fukushima
  - Quicker response by Japanese government: evacuation, iodide prophylaxis, control of food supply
- Less iodine deficiency in Japan

➢ Low doses from Fukushima not expected to cause substantial (or discernible) health effects in the general population

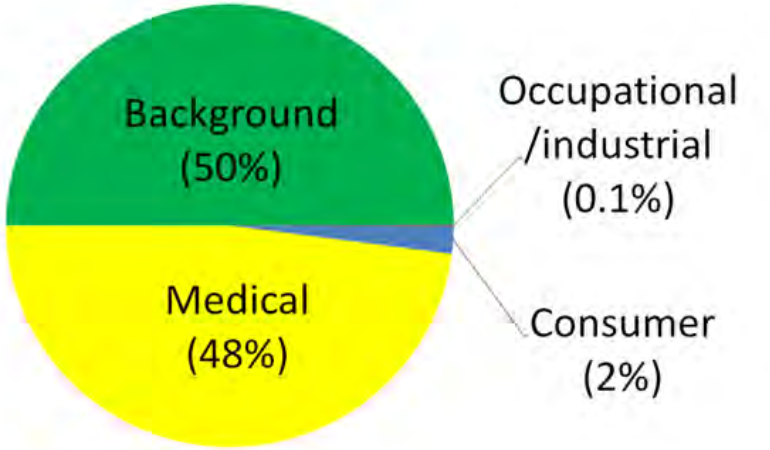
United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), Chernobyl and Fukushima White Papers, 2017, 2020

Medical sources of ionizing radiation exposure (United States)

Early 1980s
Effective dose per person: 3.6 mSv

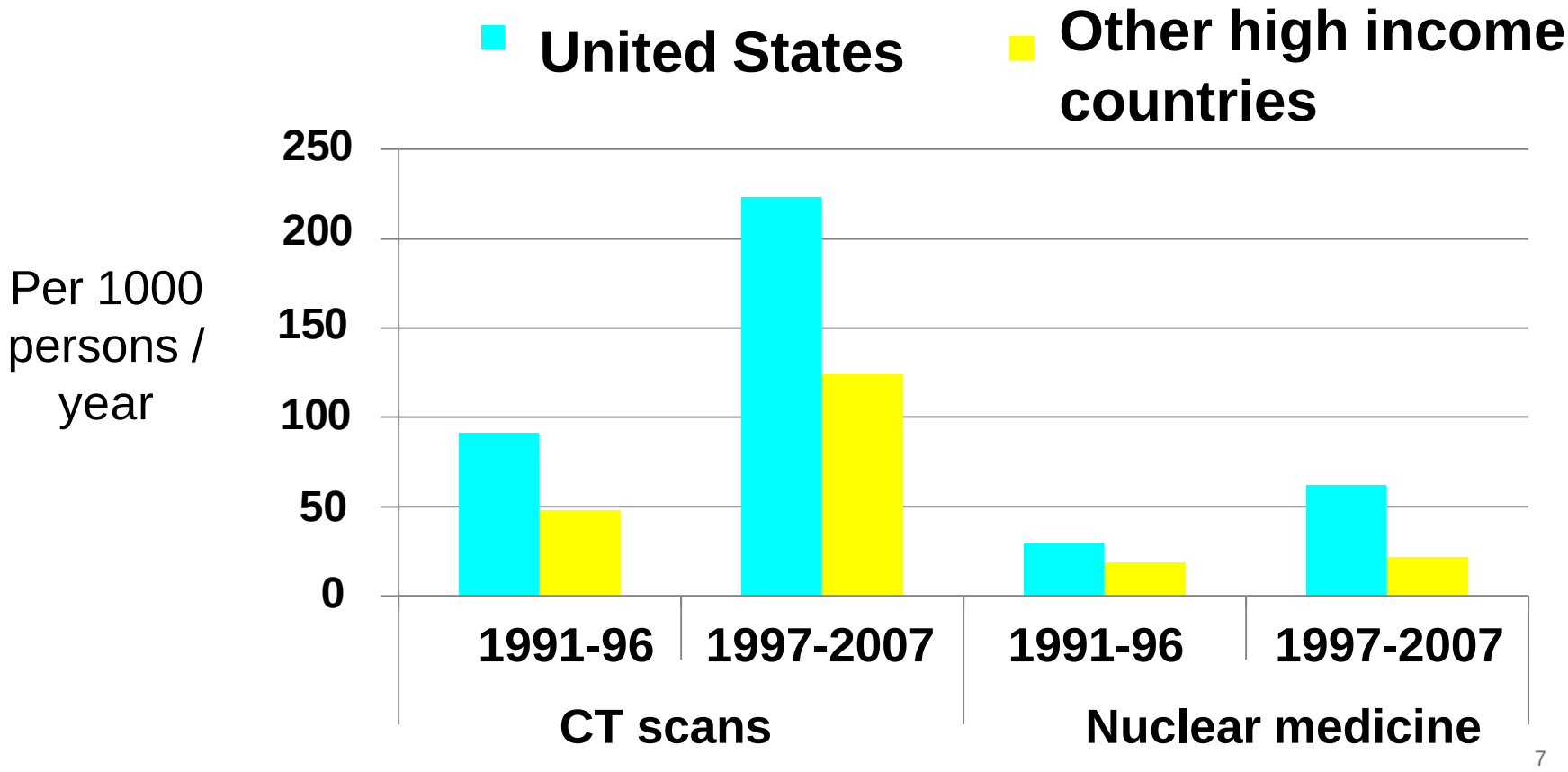


2006
Effective dose per person: 6.2 mSv



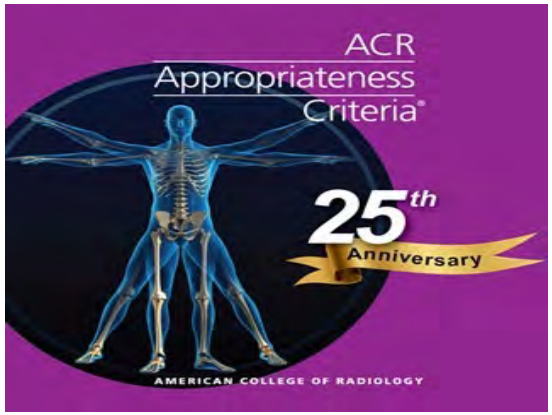
National Council on Radiation Protection and Measurements (NCRP). Ionizing radiation exposure of the population of the United States. NCRP Report No. 160. 2009.

International trends in diagnostic imaging



Mettler, et al. Radiology 2009

Campaigns to reduce unnecessary use of ionizing radiation in medicine



World Health Organization

If test is clinically justifiable, the benefits should outweigh risks

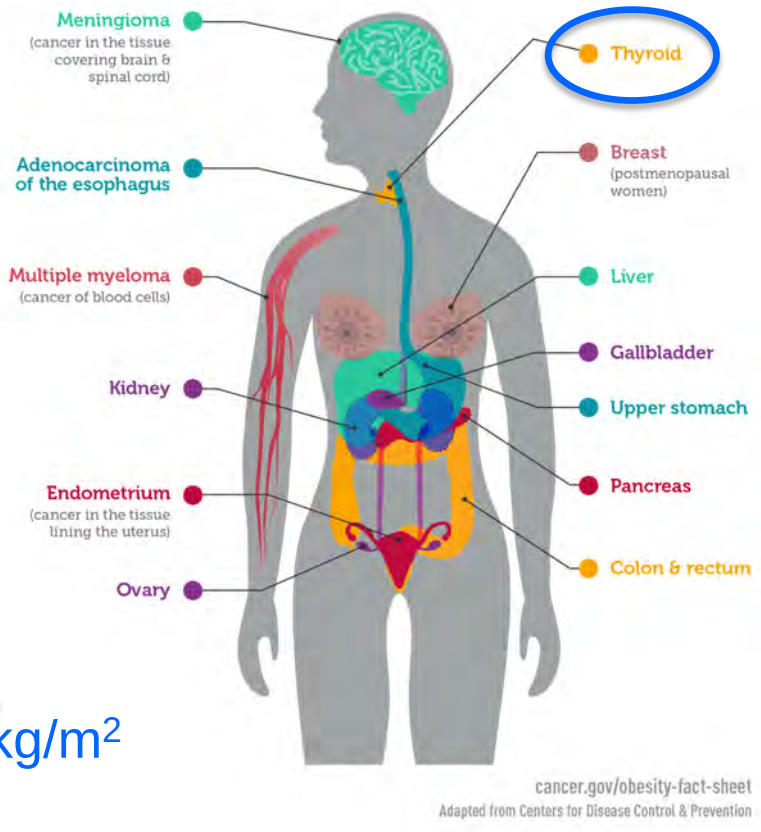
Obesity and thyroid cancer risk

Report by the International Agency for Research on Cancer, 2016

Table 2. Strength of the Evidence for a Cancer-Preventive Effect of the Absence of Excess Body Fatness, According to Cancer Site or Type.*

Cancer Site or Type	Strength of the Evidence in Humans†	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI)‡
Esophagus: adenocarcinoma	Sufficient	4.8 (3.0–7.7)
Gastric cardia	Sufficient	1.8 (1.3–2.5)
Colon and rectum	Sufficient	1.3 (1.3–1.4)
Liver	Sufficient	1.8 (1.6–2.1)
Gallbladder	Sufficient	1.3 (1.2–1.4)
Pancreas	Sufficient	1.5 (1.2–1.8)
Breast: postmenopausal	Sufficient	1.1 (1.1–1.2)§
Corpus uteri	Sufficient	7.1 (6.3–8.1)
Ovary	Sufficient	1.1 (1.1–1.2)
Kidney: renal-cell	Sufficient	1.8 (1.7–1.9)
Meningioma	Sufficient	1.5 (1.3–1.8)
Thyroid	Sufficient	1.1 (1.0–1.1)§
Multiple myeloma	Sufficient	1.5 (1.2–2.0)

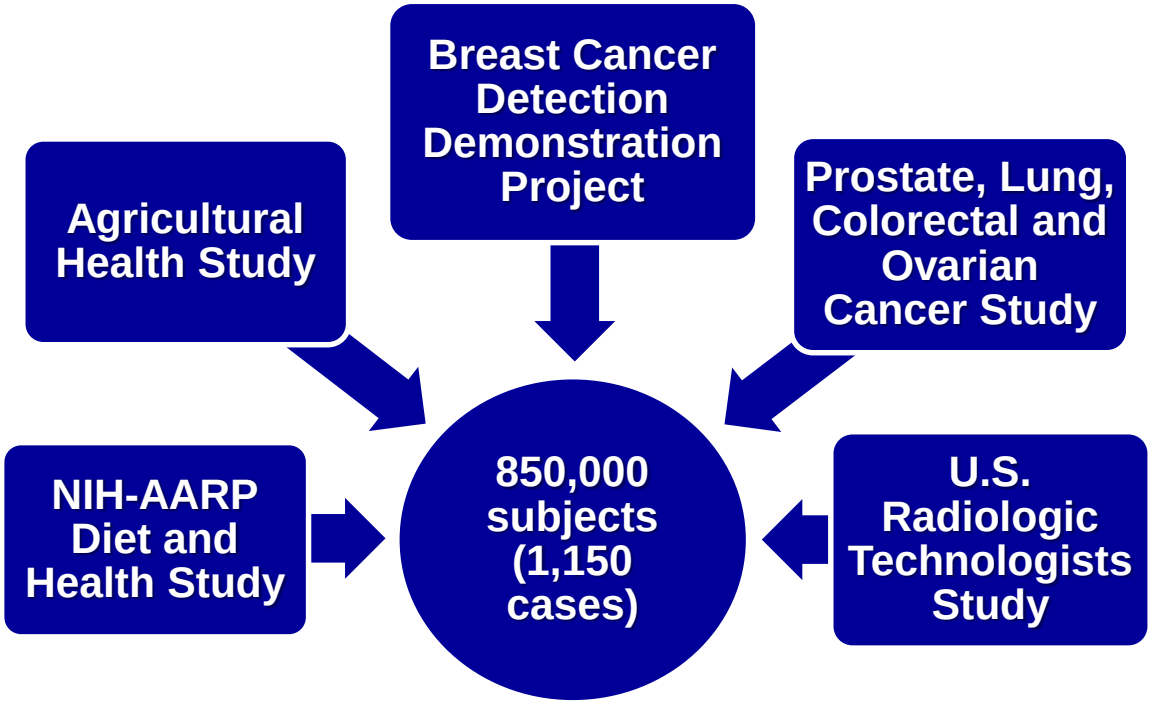
RR per 5 kg/m^2



Lauby-Secretan, et al., NEJM 2016;
cancer.gov/obesity-fact-sheet

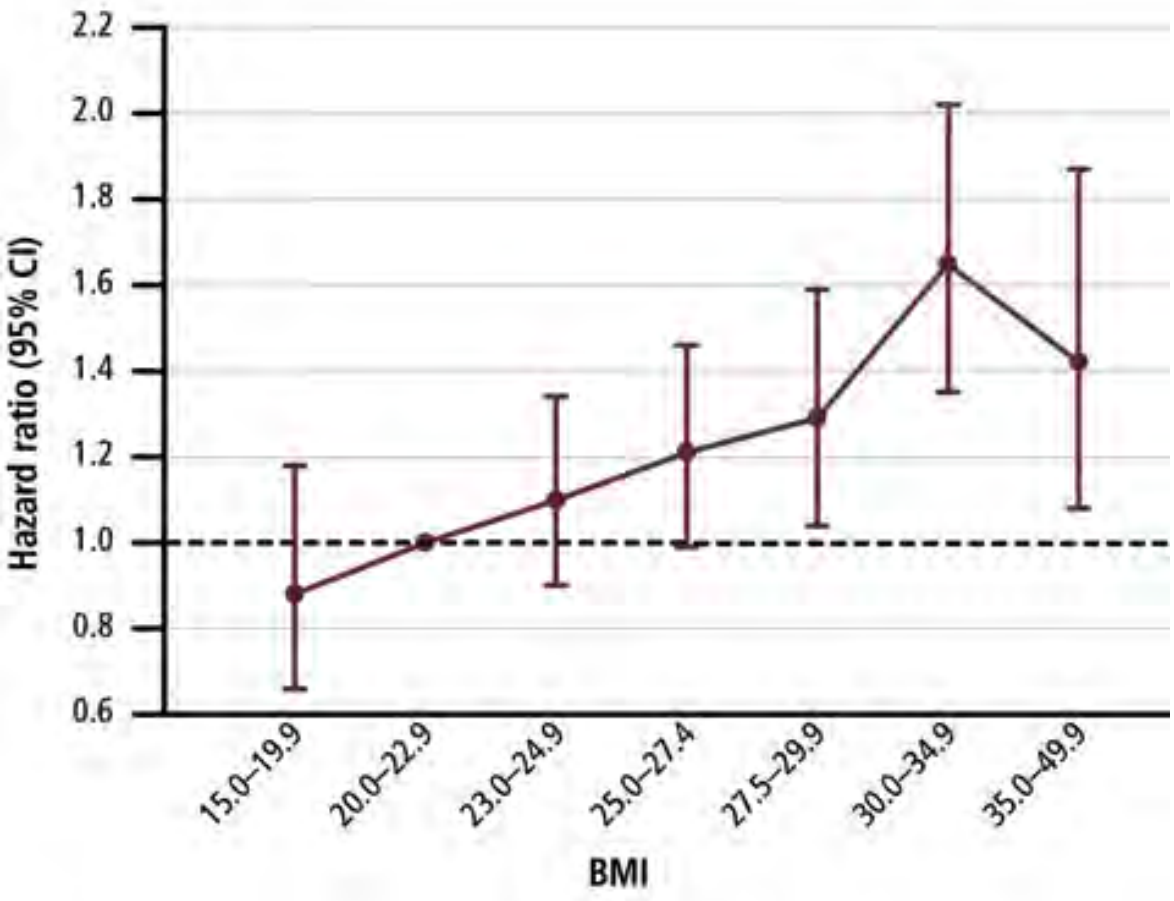
Pooled analysis of 5 prospective studies in U.S. on risk factors for thyroid cancer

- Height
- BMI
- Cigarette smoking
- Alcohol intake
- Physical activity
- History of diabetes



Kitahara CM, et al., Cancer Epidemiol Biomarkers Prev 2011
Kitahara CM, et al., Cancer Causes Control 2012a
Kitahara CM, et al., Cancer Causes Control 2012b

Pooled analysis of 5 prospective U.S. studies: results for body mass index



Per 5 kg/m^2:
HR= 1.17 (95% CI 1.11-1.24)

Adjusted for age, sex, education, race, marital status, smoking, alcohol intake, and cohort

Kitahara CM, et al., Cancer Epidemiol Biomarkers Prev 2011

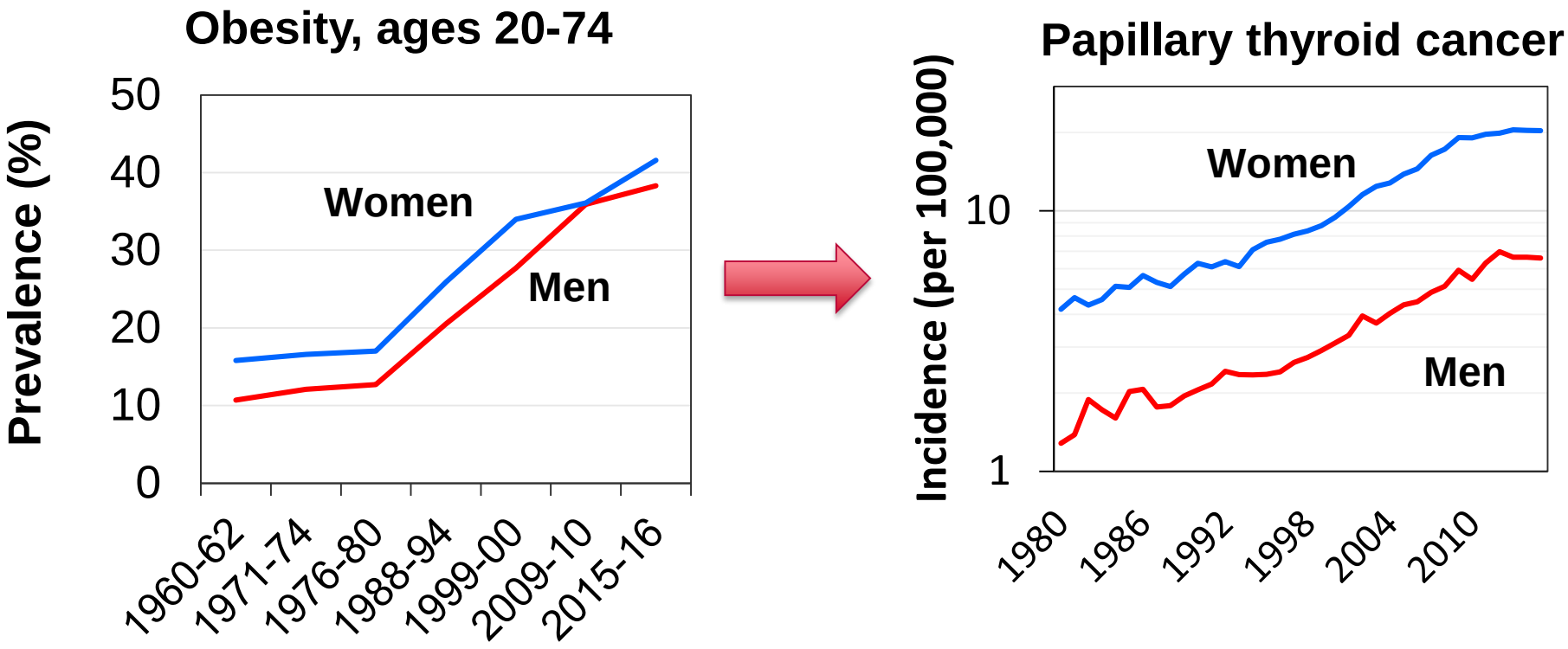
International pooled analysis of 22 prospective studies (n=2,000,000)

	Incidence			Mortality	
	Cases	HR (95% CI)[a], per 5-unit ↑		Cases	HR (95% CI)[a], per 5-unit ↑
Height	2,825	1.07 (1.04-1.10)[b]		104	1.14 (1.00-1.31)[b]
BMI	2,825	1.06 (1.02-1.10)		104	1.29 (1.07-1.55)
Waist circumference	1,397	1.03 (1.01-1.05)		45	1.22 (1.10-1.36)
Young-adult BMI	970	1.13 (1.02-1.25)		62	1.56 (1.13-2.15)
Adulthood BMI gain	970	1.07 (1.00-1.15)[c]		62	1.23 (0.94-1.60)[c]

[a] Adjusted for sex, alcohol intake, physical activity level, race, marital status, education, and smoking status and stratified by cohort
[b] Additionally adjusted for BMI
[c] Additionally adjusted for young-adult BMI

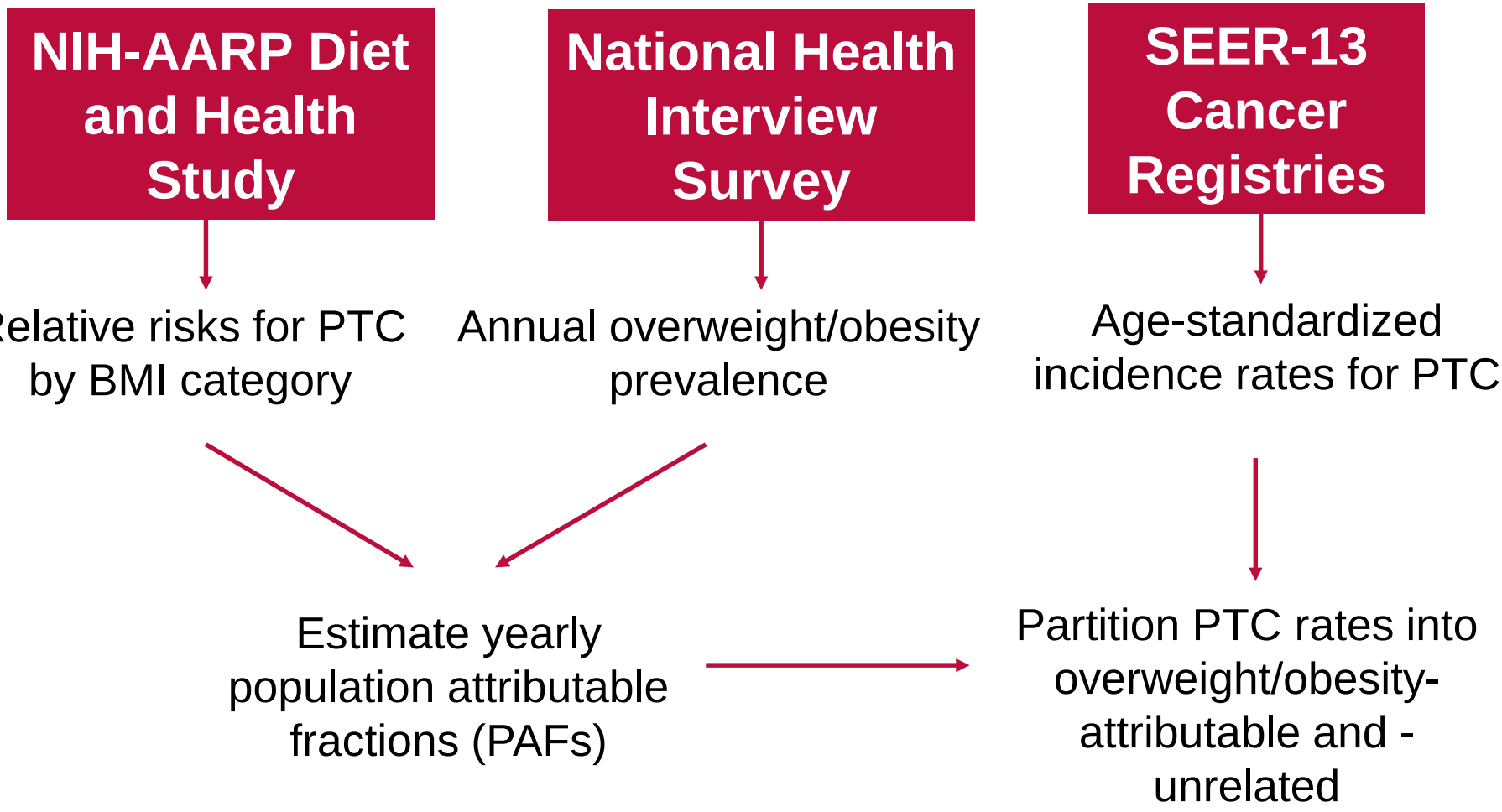
Kitahara CM, et al. Thyroid 2016

What has been the impact of obesity on U.S. papillary thyroid cancer trends?



Kitahara et al, *J Natl Cancer Inst* 2020

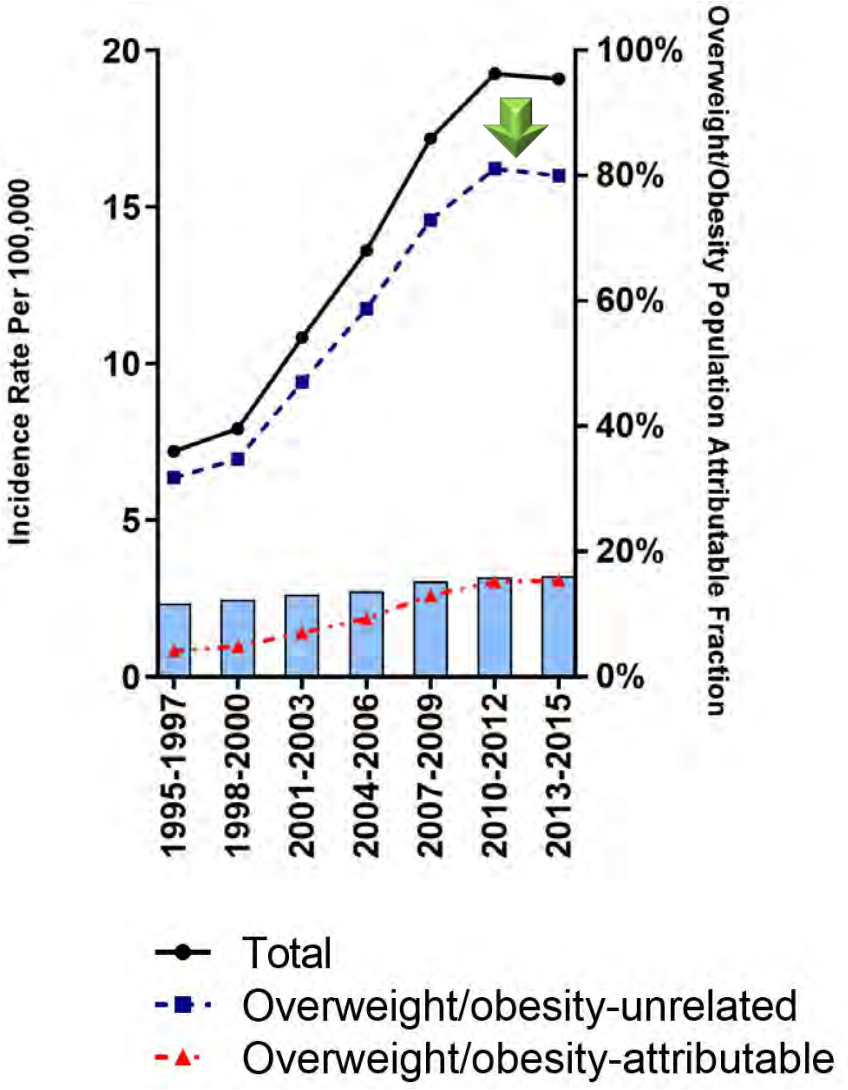
Study Design



Kitahara et al, *J Natl Cancer Inst* 2020

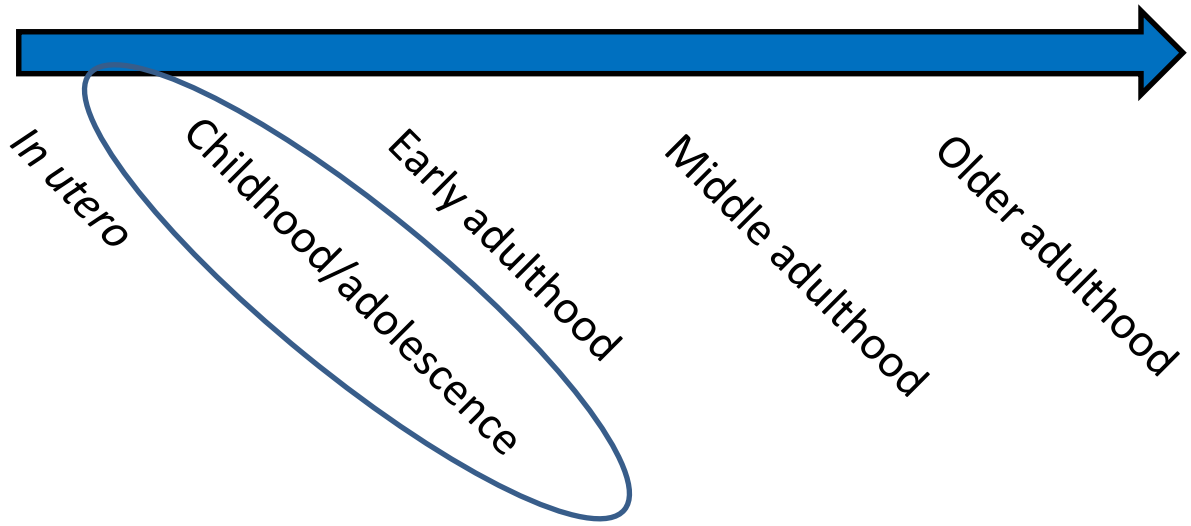
Impact of overweight/obesity on papillary thyroid cancer incidence trends (U.S.)

- Overweight/obesity responsible for ~15% of PTCs
- In the absence of overweight/obesity:
  - PTC incidence trends would have ↓ by 13%



Kitahara et al, *J Natl Cancer Inst* 2020

Could excess adiposity in <u>early life</u> influence thyroid cancer risk?



Childhood BMI and thyroid cancer risk

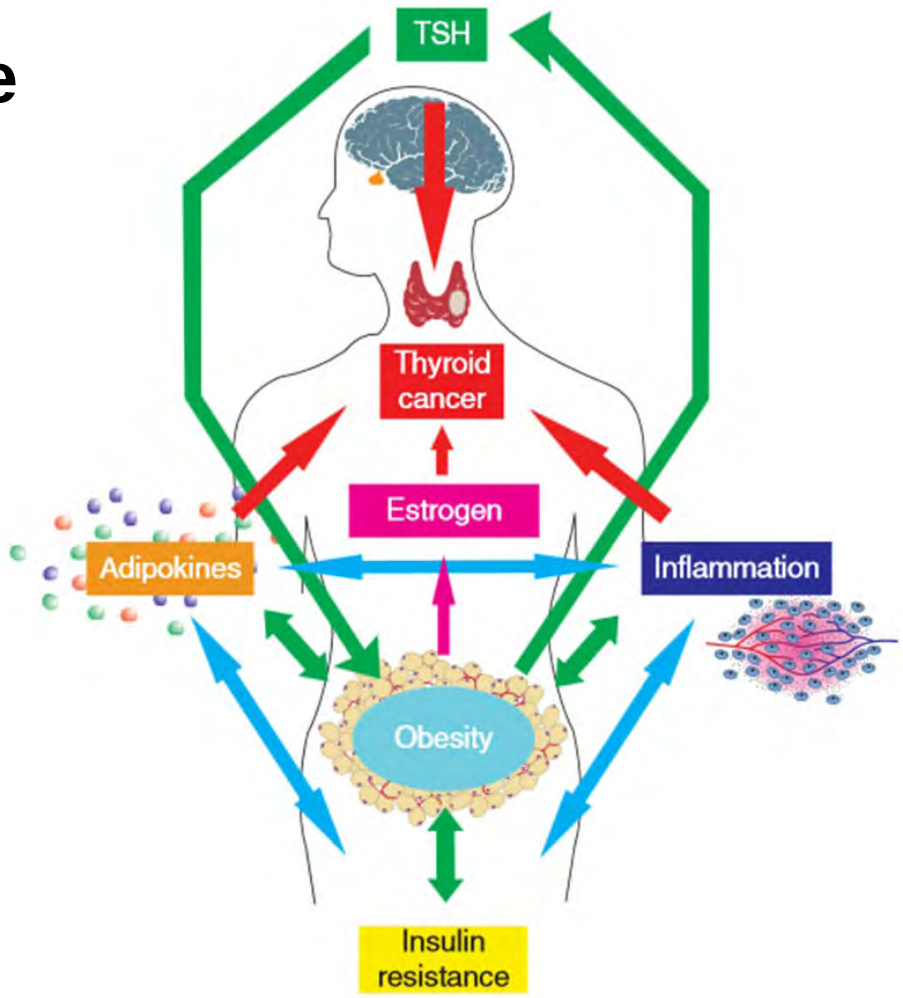
Copenhagen School Health Records Register

- 372,636 schoolchildren born 1930-89
- Annual height and weight measurements
- Linkage with Danish Cancer Registry (1968-2010) → 235 thyroid cancers

Age at measurement	HR (95% CI) per 1-SD change in BMI
7	1.15 (1.01-1.33)
8	1.15 (1.00-1.33)
9	1.19 (1.03-1.38)
10	1.15 (1.00-1.34)
11	1.14 (0.99-1.32)
12	1.13 (0.98-1.31)
13	1.16 (1.00-1.34)

Kitahara, et al. *Cancer Research.* 2014;74(1):235-42

Biological mechanisms potentially underlying the obesity-thyroid cancer association



Marcello, et al. *Endocr Relat Cancer* 2014;21(5):T255-71

Other suspected risk factors

Mixed evidence

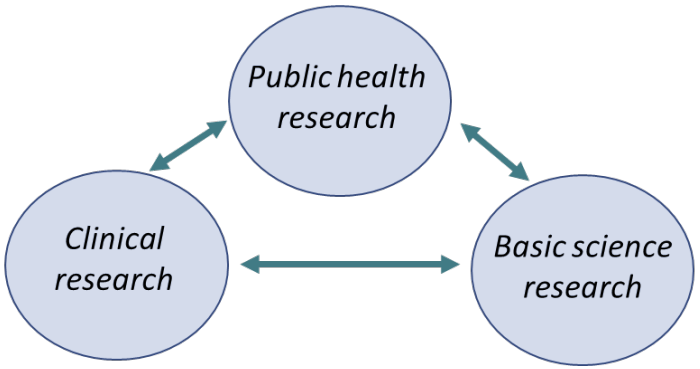
- Diet (including iodine, goitrogens)
- Reproductive/hormonal factors

Limited evidence

- Endocrine disrupting chemicals
  - Industrial chemicals (PCBs, BPA, phthalates, brominated flame retardants, perchlorates, heavy metals, pesticides)
- Ultraviolet radiation
- Sleep disturbances

How can we reduce incidence and burden of thyroid cancer?

- Minimize overdiagnosis
- Primary prevention
  - Ionizing radiation exposure in children
  - Obesity
  - Other risk factors yet to be discovered



Thank you for your attention

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