Cancer Overdiagnosis

(A Biological Challenge and Clinical Dilemma)

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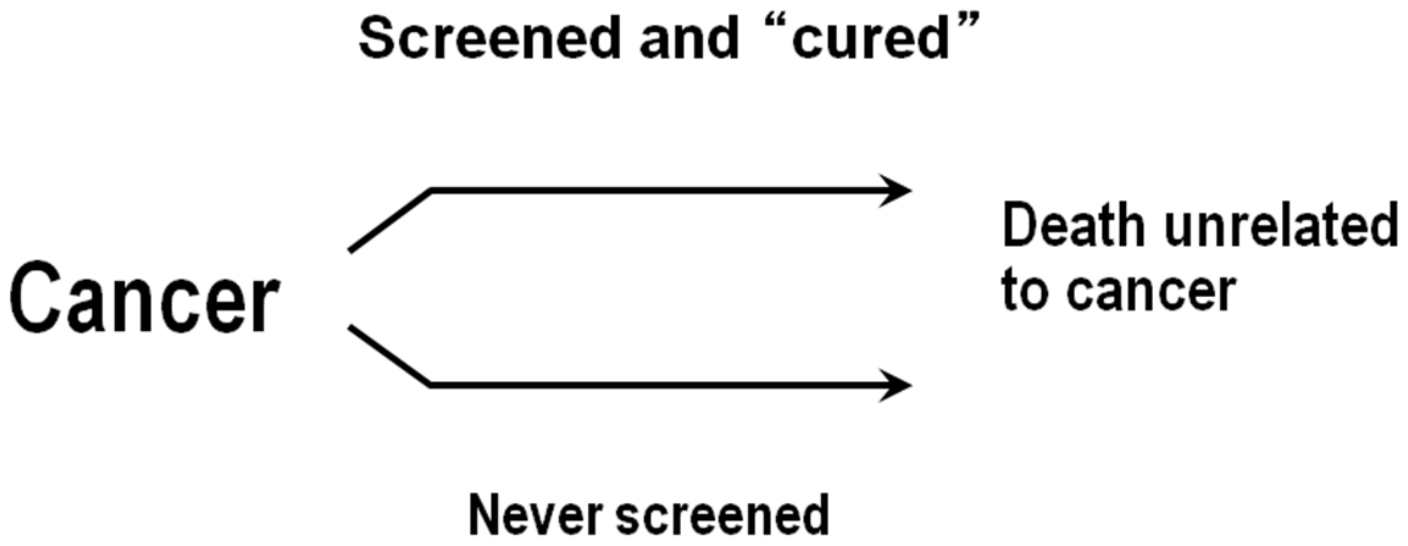
Disclosure Information

None

I am a contractor in the National Cancer Institute (NCI). Opinions are my own and should not be taken as official positions of the U.S. government or National Institutes of Health/NCI.

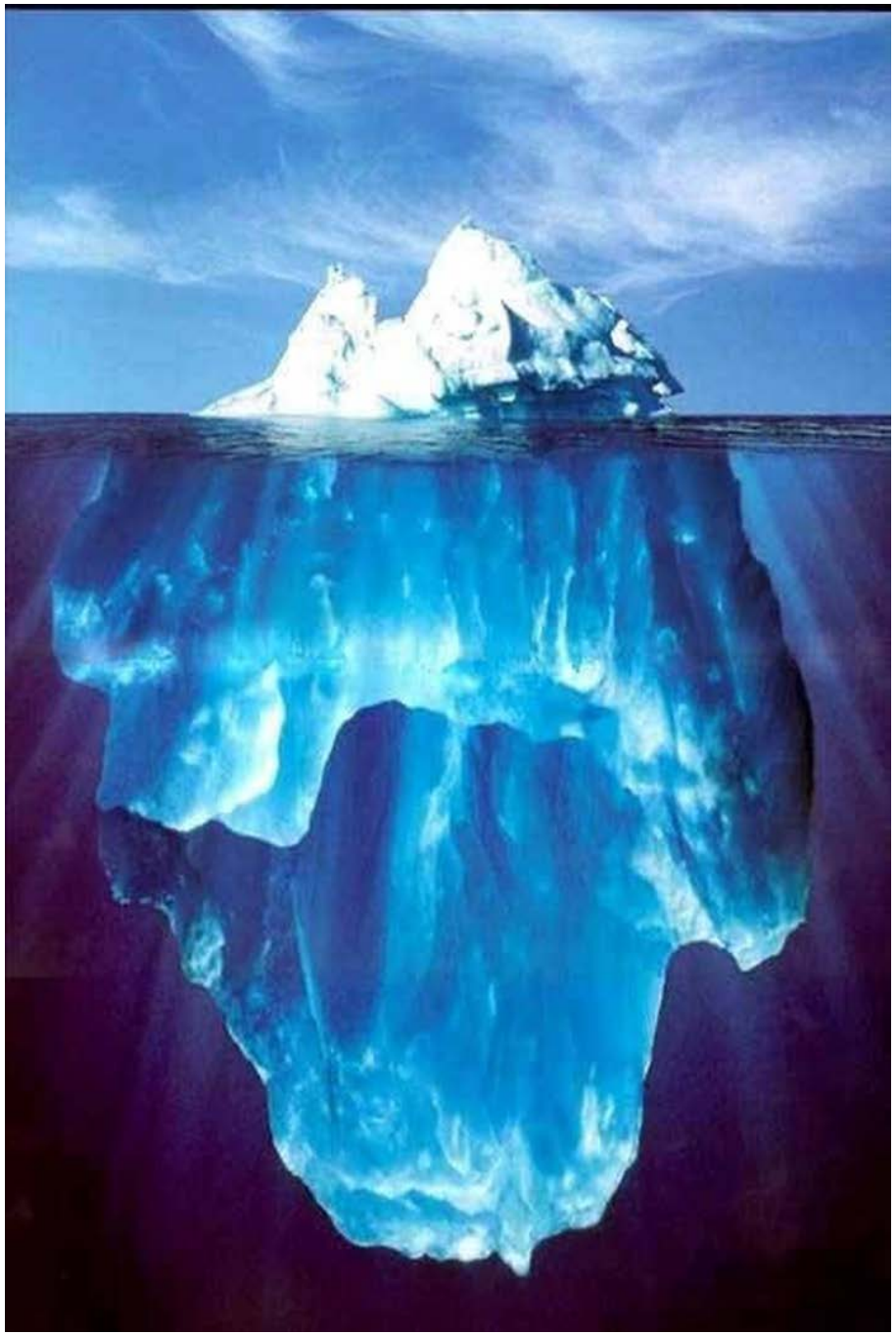
Overdiagnosis



Requirements for Overdiagnosis

- Existence of a silent disease reservoir
- Activities leading to its detection (particularly screening)

From G. Welch and W. Black, JNCI 2010



→ Symptoms

→ No Symptoms

Research Emphasis: Increased Screening Sensitivity

- More detection of life threatening lesions: *possible* benefit
- More overdiagnosis → *definite* harm

- The challenge: sorting the two sources of increased sensitivity

Screening and the Transformation of Medicine

"Ancient medical history": **diagnosis & management of established disease**

- Testicular cancer, lymphomas, childhood malignancies

Screening for early, asymptomatic disease

- Cervical cancer, colorectal cancer, lung cancer

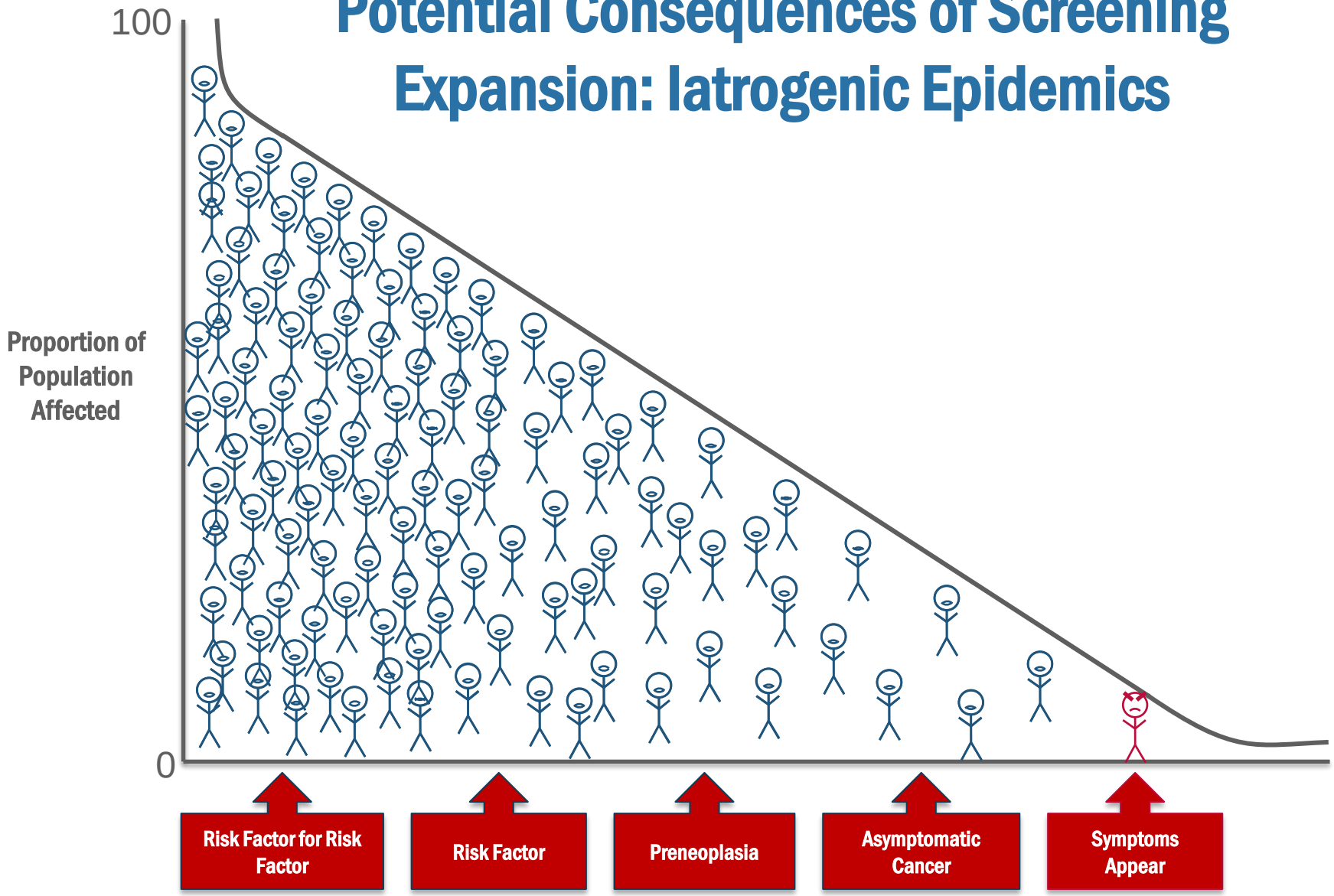
Screening for risk factors of disease

- Family history, genetics, obesity

Screening for risk factors <u>for</u> risk factors ("disease risk predisposition")

- Genetic markers for nicotine addiction, obesity, microbiomics, diabetes…
- Mammogram calcium to predict cardiac atherosclerosis

Potential Consequences of Screening Expansion: Iatrogenic Epidemics



Sources of Cancer Overdiagnosis

1. Patient biology/survival
2. Tumor biology

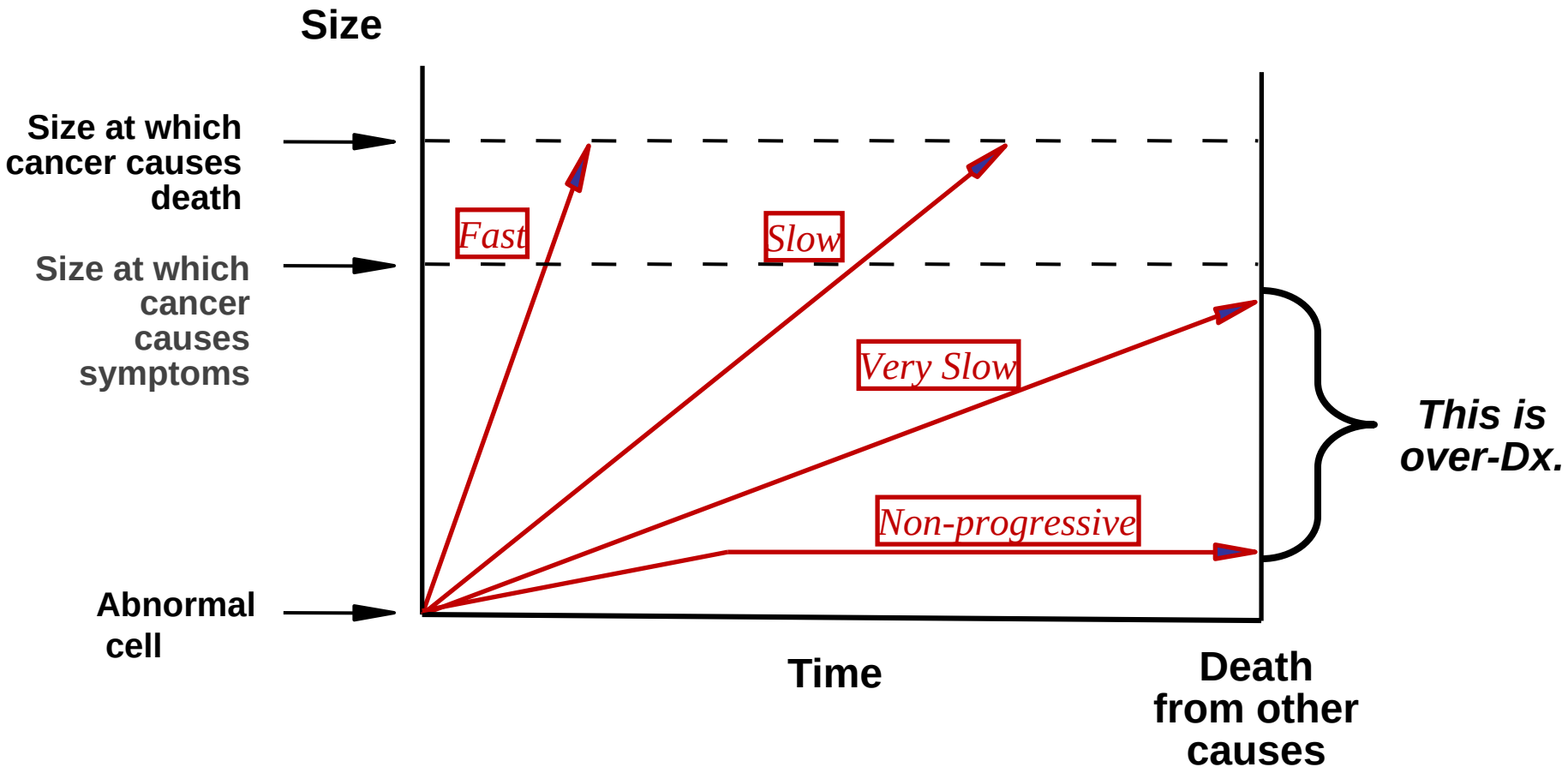
Screening Prevalence in U.S. Adults Aged ≥ 85 (2015)

(National Health Interview Survey)

Mammography (past 2 years)	34%
Pap test (past 3 years)	18%
Stool (1 yr); Sigmoidoscopy (5 yrs); Colonoscopy (10 yrs)	52%
Males	60%
Females	47%
PSA test (past 1 year)	29%

(CE DeSantis et al.: CA Journal for Clinicians, 2019)

The Heterogeneity of Cancer Progression

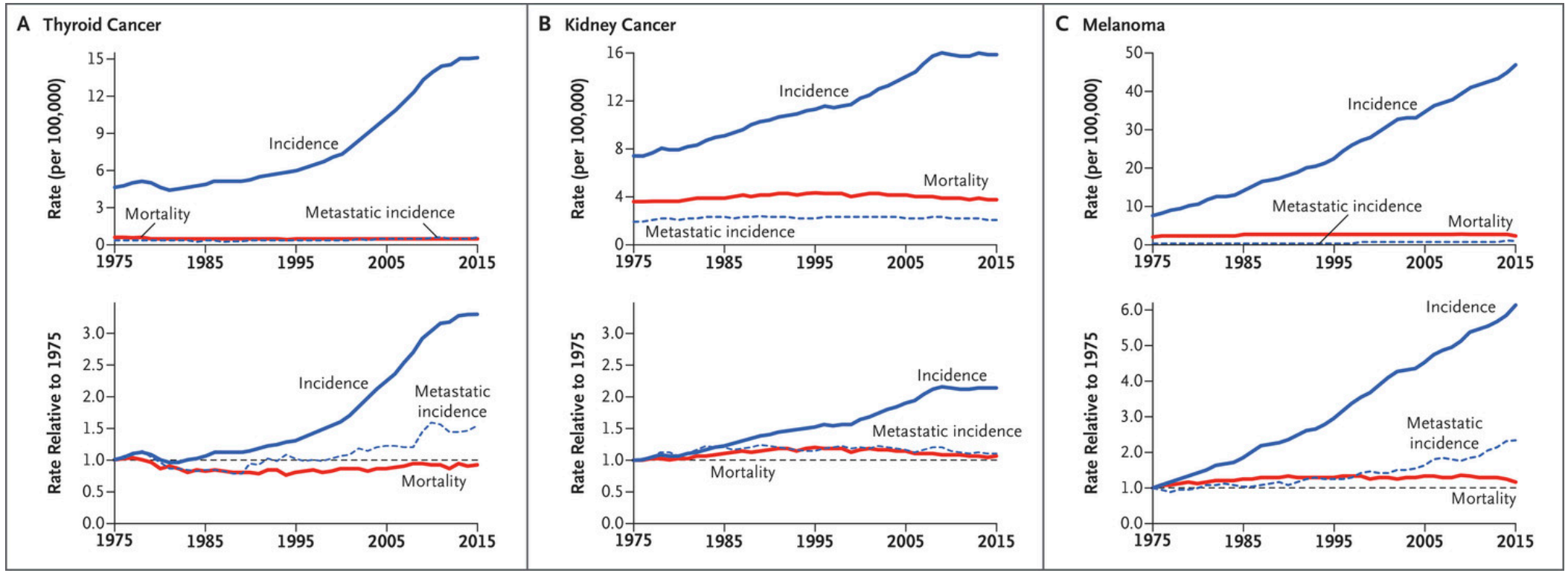


(*Courtesy of H. Gilbert Welch, Dartmouth)*

Indicators of Overdiagnosis vs. Increased True Occurrence of Cancer

	Expected Change In Incidence		
	Early Stage	**Late Stage**	**Expected Change in Mortality**
Increased True Incidence	↑	↑	↑
Overdiagnosis	↑	No Change	No Change

Overdiagnosis with Stable True Cancer Occurrence



HG Welch, BS Kramer, WC Black. N Engl J Med 2019;381:1378-1386

The Clinical Dilemma of Overdiagnosis

- Population trends may provide evidence of overdiagnosis.
  - Big problem?
  - No problem?
- But precise estimation of overdiagnosis from population trends is a challenge.
- And clinicians treat individuals.

- That’s why we need clinical trials.

Seeking Truth without Clinical Trials: Can We Get a Free Lunch?

- Does clinical experience provide reliable truth?
- Can “real world” observational evidence replace randomized trial evidence?

What the Physician and Patient See with Overdiagnosis

- "Cures" people that did not need to be cured
  - Artificially raises the "cure" and survival rates
  - Vicious cycle: reinforcement of perceived benefit → diminished equipoise

Does "Real World" Observational Evidence Provide a Free Lunch?

A Comparison of Population-Based Observational Studies with Randomized Trials in Oncology

- MEDLINE search (2000-2016) → 350 observational studies, 121 matching randomized trials
- No significant correlation between HR estimates (correlation coefficient 0.083, 95% CI –0.068 to +0.230)
- No agreement beyond chance (Kappa statistic = 0.037)
- Only 38% of observational HRs fell within the 95% Cis of the matched RCT (more likely to show better survival than RCT)
- No improvement with adjustment for study quality, co-variates, propensity weighting, instrumental variables

Payal Soni et al.: J Clin Oncol 37(14): 1209-1216 [2019]

What Can We Do about Cancer Overdiagnosis?

1. **Education about its existence**
   - Public and Media (the honest brokers of information)
   - Health professionals
2. **Change the terminology**
   - Language corrupts thought (and action)
   - Example: Indolent Lesions of Epithelial Origin (IdLE)
3. **Prevention/Deimplementation research**
4. **Research targeting the underlying biology (both tumor & microenvironment)**

Strategies to Investigate Overdiagnosis (1)

- Annotate collected specimens with method of diagnosis
  - Molecular patterns of screen-detected cases are enriched with overdiagnosed cases
  - Molecular patterns of true interval cases are enriched with aggressive cases that we need to prevent (and target pathways for prevention)
- Collect normal organ as well as the tumor
  - Study cancer as a tissue-level, not simply a cell-based, disease
  - Examples: prostate, breast, esophageal, melanoma

Strategies to Investigate Overdiagnosis (2)

- Use clinical opportunities to study natural history of indolent lesions
  - Prostate cancer: active surveillance
  - Barrett's esophagus: serial endoscopy/biopsy
  - DCIS
  - Small renal tumors
- Better animal models of progression of very early lesions

Thank You