4.40: H Gilbert Welch - Melanoma Screening; Blood Based Cancer testing; Lung CA screening

Season	4
Type	Plenary Session

We Discuss:

- Introduction [0:00]
- NEJM Paper [2:41]
- Pathology [4:49]
- Diagnosis [8:54]
- Covid-19 [11:00]
- Melanoma [13:35]
- Liquid Biopsy [25:26]
- All-cause mortality as the primary endpoint for the GRAIL/National Health Service England multi-cancer screening trial [37:00]
- What is cancer? [43:48]
- Congress [45:50]
- Expansions in screening [52:00]

Plenary Session 4.40 Show Notes

Overview

Conversation with Dr. Gilbert Welch

- **YouTube**
    - Watch this conversation on YouTube

Introduction [0:00]

- Dr. Welch completed his undergraduate degree at Harvard
    - He earned his M.D. from the University of Cincinnati and MPH from the University of Washington
        - He served a professor of medicine at Dartmouth
- Dr. Welch completed his internal medicine residency at the University of Utah
    - He also completed a Rotating Internship at the Conemaugh Valley Memorial Hospital in Johnstown, PA
- Dr. Welch completed public health service by serving as a General Medical Officer in Bethel, AK for 2 years
    - He then ended up in Seattle as a Robert Wood Johnson Clinical Scholar at the University of Washington where he learned how to do research
- He is now a general internist and senior investigator in the Center for Surgery and Public Health at Brigham and Women's Hospital in Boston

NEJM Paper [2:41]

- **The Rapid Rise in Cutaneous Melanoma Diagnoses**
    - Paper by Welch et al.
- **Background**

> *"Once a rare tumor, the incidence of melanoma has increased rapidly — it is now 6 times as high as it was 40 years ago (for context, thyroid cancer is 3 times as high and breast cancer 1.5 times as high). Although this dramatic rise has been referred to as an epidemic,3 considerable disagreement surrounds the issue of whether this increased incidence represents an epidemic in the true occurrence of disease or an "epidemic of diagnosis." - Welch et al.*

- What can explain the 6-fold increase?
  - A popular answer is that people are sunbathing and self-tanning too much
    - The researchers take into account a variable of the worst case scenario of sun exposure in a population, but even this assumption only explains 1/3rd of the cases of metastatic melanoma
- Cigarette smoking thought experiment

> *"Cigarette smoking is strongly related to lung cancer, with a relative risk of approximately 20. Under the assumption that all other factors are held constant, the incidence of lung cancer would remain stable if the proportion of the population smoking cigarettes remained stable. On the other hand, if no one smoked initially and everyone subsequently adopted the habit, then the incidence would be expected to rise by a factor of approximately 20, albeit after a delay of multiple decades." - Welch et al.*

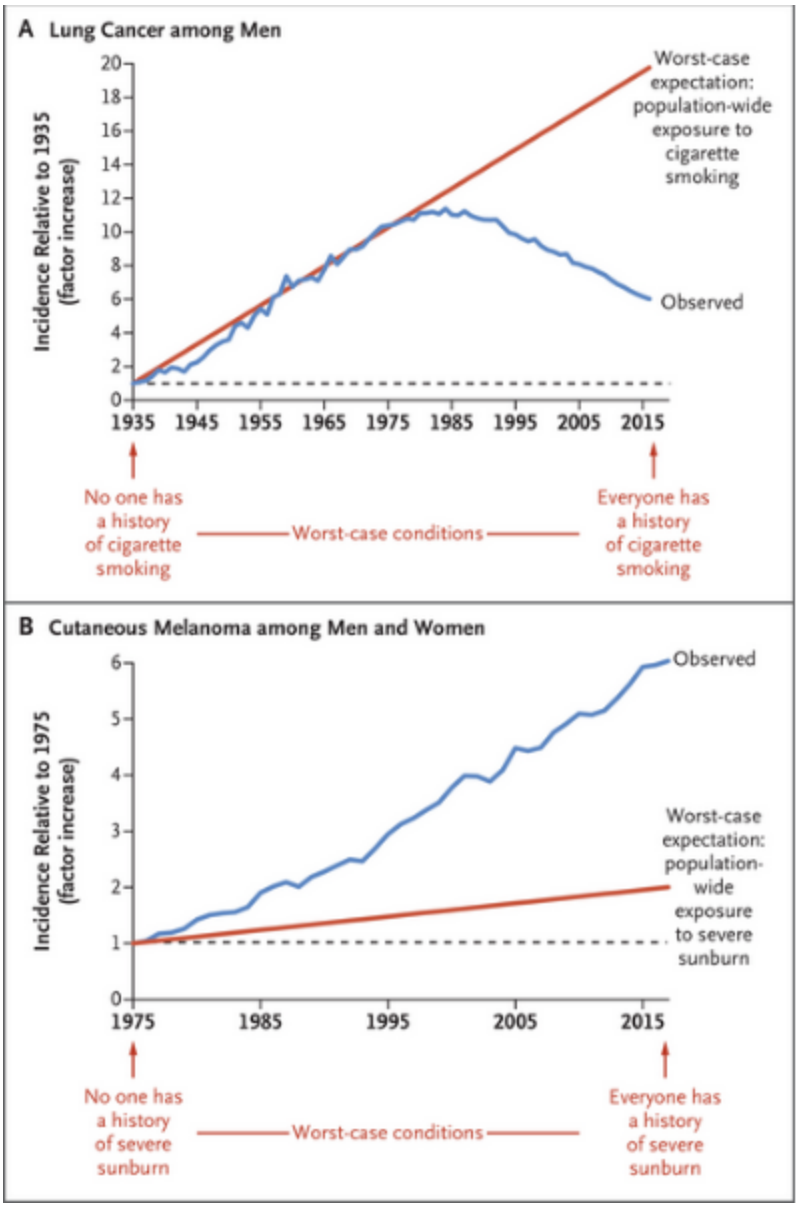


Figure 2. Expected Change in the Incidence of Cancer after Population-wide Exposure to a Known Risk Factor, as Compared with Observed Incidence. Welch et al.

- The researchers then conclude the cause of the increased incidence must be something that is *not* exogenous

- There is a massive disconnect between incidence and mortality

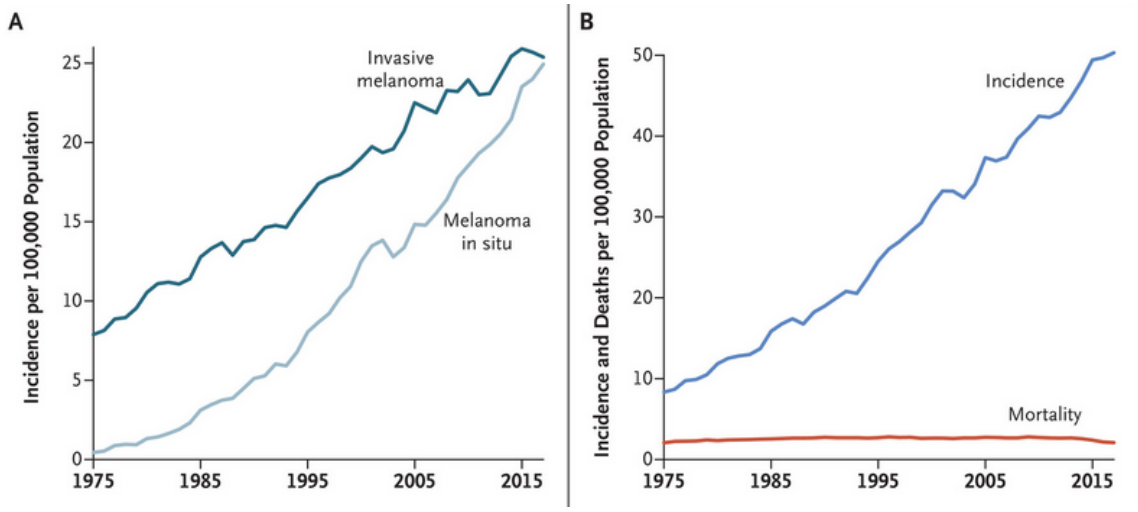


Figure 4. Summary Trends in Cutaneous Melanoma in the United States from 1975 through 2017. Welch et al.

- When there is rising incidence and flat mortality–this may serve as a pathognomic for overdiagnosis

- **Pathology [4:49]**
  - The key here is that we're discussing gray zone lesions, we're discussing the most challenging pathologic diagnoses to make
    - The distinction between dysplastic naevi and melanoma in situ to or early invasive melanoma is unclear
  - As we start sending pathologists smaller and smaller lesions, we've discovered a number of problems that arise
    - The lesions may have abnormality in cellular architecture or in the individual cells, but that may not have any bearing on the actual dynamics of the process of growth

> "I think the reality is that they [pathologists] can't tell us what clinicians want to know – *is this a cancer that's gonna matter to someone?*" - Dr. Welch

  - 50 years ago, the entity we cared about was clinical (i.e., the patient died of metastatic melanoma)

- **Diagnosis [8:54]**

- What makes researching screening rather than treatments is that there is incidental detection occuring
    - In other words, the intervention (screening) is dealing with asymptomatic people, and you're looking hard to see if there's something wrong with them
        - This distinction is very important

Covid-19 [11:00]

- Covid testing
    - What does cancer screening tell you about COVID?
        - Dr. Welch emphasizes the distinction between the two - on the one hand, you're dealing with an infectious disease, while on the other, you're dealing with a chronic disease.
            - When dealing with infectious disease, you're in a kind of a different world and a different set of conditions
                - This is a whole other environment with a unique set of circumstances, but one thing they have in common is, “if you look for more, you’ll find more”

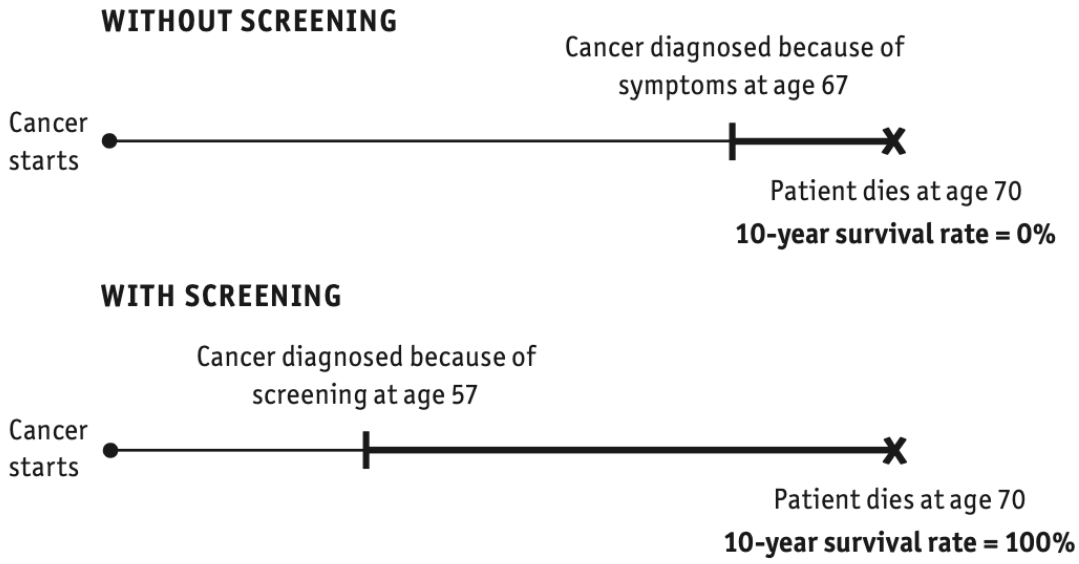
Melanoma [13:35]

- **Melanoma Epidemic: More Apparent Than Real**
    - A talk given by Robert Swerlick at the Mayo Clinic of Dermatology on April 21, 1995 on melanoma over diagnosis
- **Lawrence Livermore National Laboratory**

> *“Lawrence Livermore National Laboratory has a mission of **strengthening the United States' security through development and application of world-class science and technology** to: Enhance the nation's defense. Reduce the global threat from terrorism and weapons of mass destruction.” - Source*

- **Pushback**

    - The misleading feedback from early detection is unbelievably powerful at every level
        - While there are undoubtedly terrible instances of cancer, a positive feedback loop arises when indolent or early illness is eliminated and the physician feels they have averted another severe case of cancer by their aggressive screening method
            - This may be true, but randomized studies would assist in determining if our intensive screening measures are net beneficial
- **5 year survival**
    - Survival statistics cannot tell you whether fewer people are dying from cancer
        - In comparison, cancer specific mortality rates (e.g., death from melanoma) may provide insight into what is really occurring.



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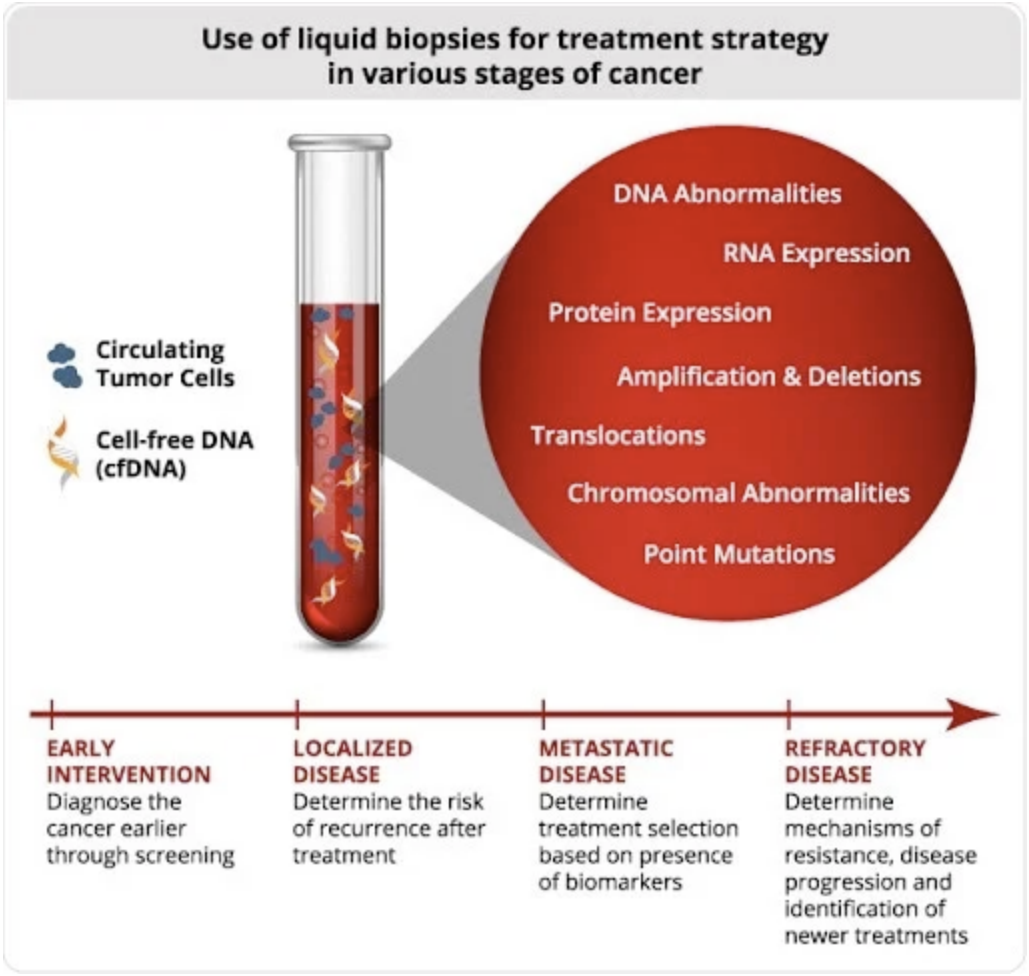
Liquid Biopsy [25:26]

- **The intervention**



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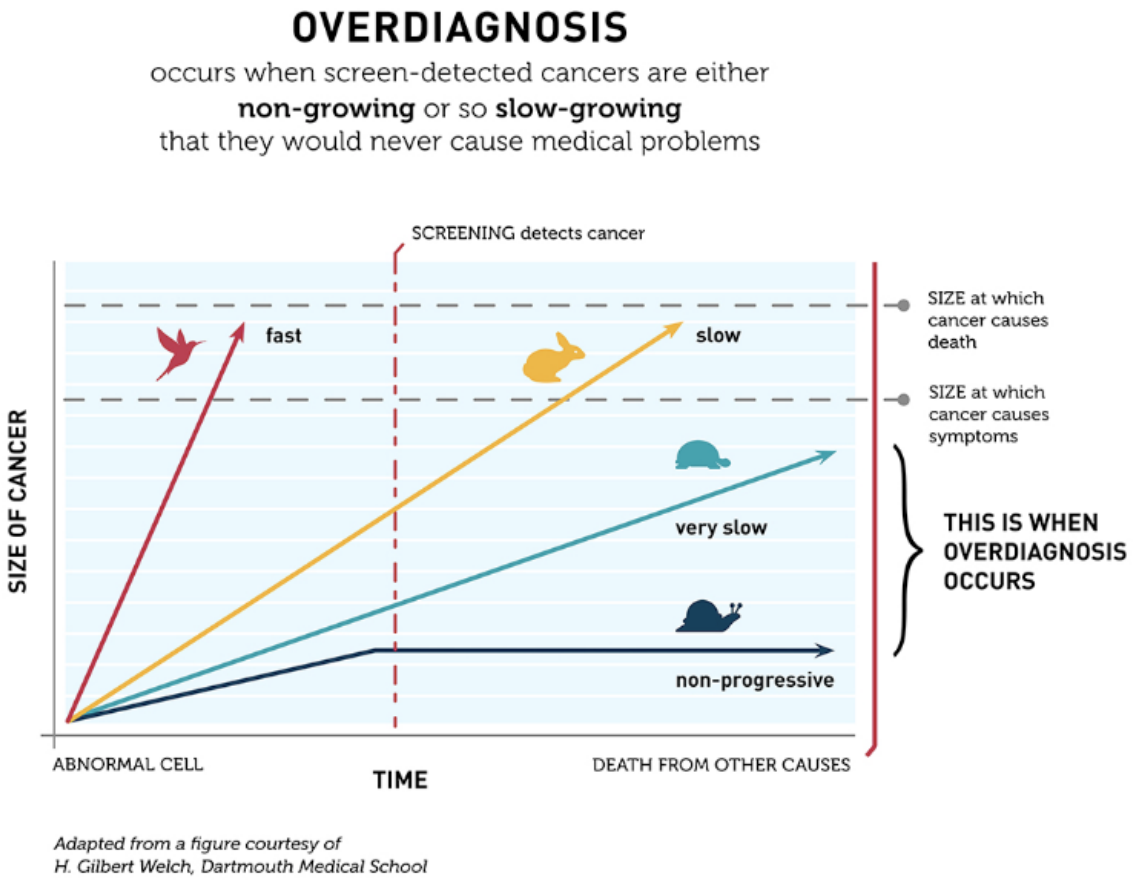
- **Turtles, rabbits, and birds**



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> "That's the challenge. It's not just finding bad cancers earlier, you got to find bad cancers earlier AND earlier treatment has to confer an advantage over later treatment" - Dr. Welch

- **All-cause mortality as the primary endpoint for the GRAIL/National Health Service England multi-cancer screening trial [37:00]**
    - Carr et al., *Journal of Medical Screening*

> *“A randomized trial of the GRAIL GalleriTM multi-cancer screening test is being planned for the National Health Service in England, and will have 140,000 healthy participants aged 50-79: 70,000 exposed to screening and 70,000 unexposed. The test reportedly detects 50 different cancers and is expected to reduce all-cancer mortality by approximately 25%. Given this effect size-and that cancer deaths constitute a large fraction of all deaths-the trial is sufficiently large to test the effect on all-cause mortality. Because most patients believe cancer screening "saves lives", the GRAIL/National Health Service collaboration could set the evaluation standard for multi-cancer screening.“* -
> Source

- Off target deaths
  - One of the problems with screening is that you may be able to reduce one cause but unwittingly increase another

> “To me, it's an important question, particularly if we're going to sell these things [screening] as saving lives.” - Dr. Welch

What is cancer? [43:48]

- **The patient definition**
  1. Growth of slightly abnormal cells
  2. It's a condition that makes you feel bad or kills you
  3. There are many undefined areas
     a. e.g., In the setting of immune dysregulation

Congress [45:50]

- **The crazy confluence of Congress, liquid biopsies, Medicare, and health inequities**
  - Welch & Kramer, *STAT*

> *"The Medicare Multi-Cancer Early Detection Screening Coverage Act of 2021 is a bipartisan effort that currently has 144 cosponsors in the House of Representatives and 30 cosponsors in the Senate. It would require Medicare to cover annual genomic sequencing of blood for the purpose of 'early detection of cancer across many cancer types.'" - Source*

- Health disparities
  - If public health officials truly care about health disparities, then the focus should shift from medical care to more basic social determinants of health
    - There is no way that as a society, we can biopsy our way out of health disparities
      - Our efforts should be concentrated on children and the poor.

Expansions in screening [52:00]

- **Association of Computed Tomographic Screening Promotion With Lung Cancer Overdiagnosis Among Asian Women**
  - Gao et al., *JAMA Internal Medicine*

Figure 2. Self-reported Smoking Prevalence Among Taiwanese Adults by Sex, 1980-2018

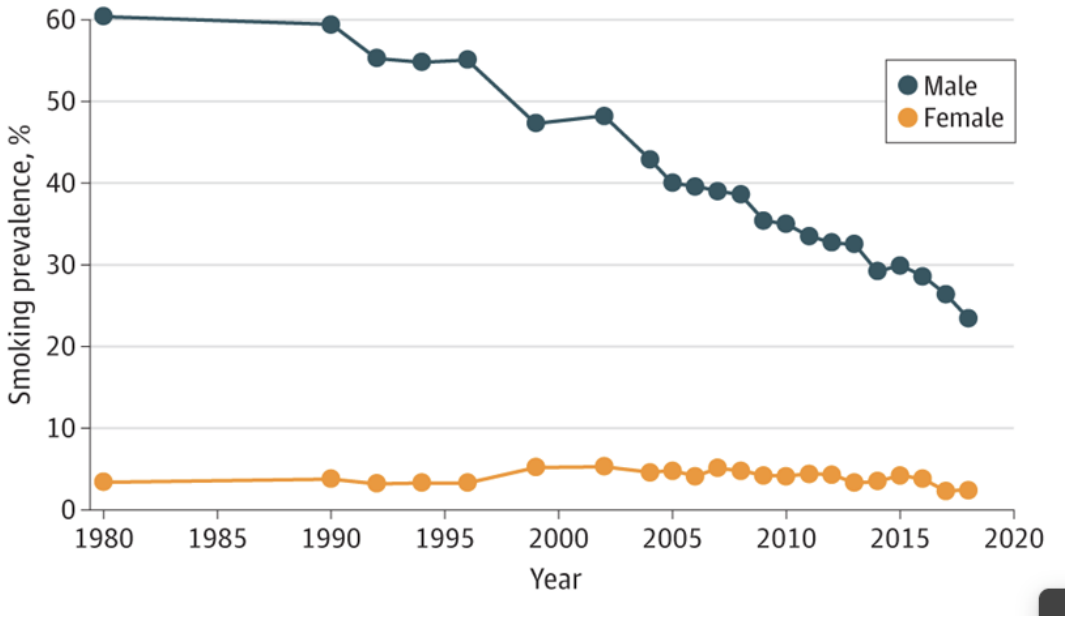


Figure 3. Lung Cancer Incidence and Mortality in Taiwanese Women, 1998-2018

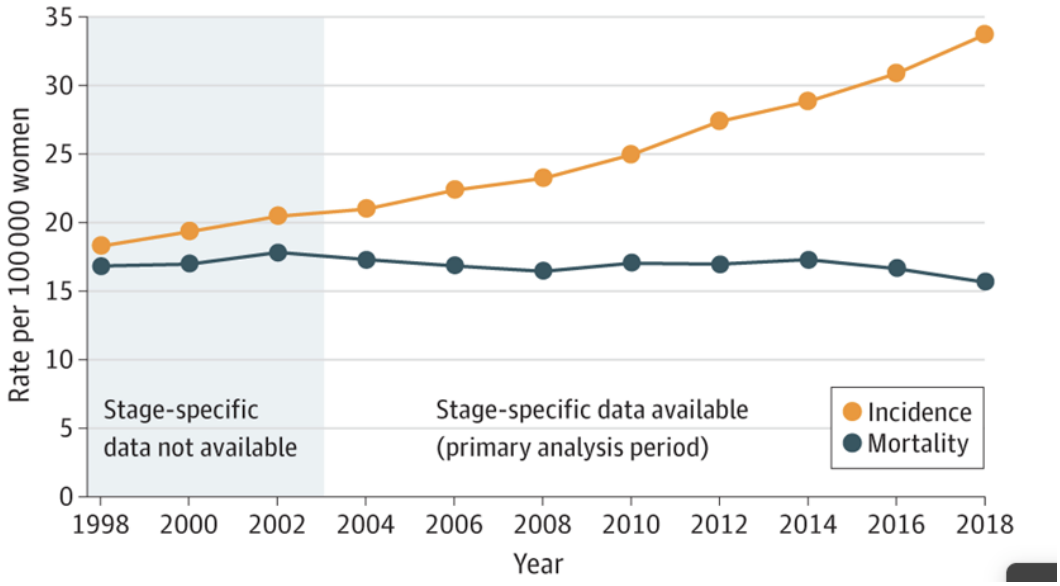
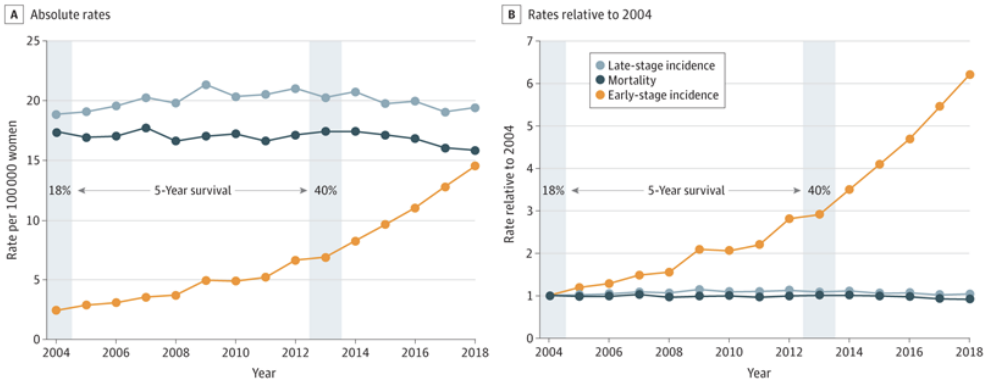


Figure 4. Stage-Specific Lung Cancer Incidence and Mortality in Taiwanese Women, 2004-2018



Early stage indicates stages 0 to I; late stage, stages II to IV. Absolute rates are age adjusted to the 2000 world standard population; in rates relative to 2004, 1 denotes no change. Gray shading indicates lung cancer 5-year survival for all women diagnosed with lung cancer in 2004 and 2013, the most recent year with 5 years of follow-up.

Source

- **Other literature mentioned:**
  - The Minnesota Colon Cancer Control Study
  - Editor's note: This opinion piece is now outdated
    - Carr & Welch, *STAT*
  - Liquid biopsy: misplaced faith in early cancer detection?

- Welch, *STAT*

Plenary Session is a podcast on medicine, oncology, & health policy.

Host: Vinay Prasad, MD MPH from University of California, San Francisco.

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Written By: Kerrington L. Powell B.S.