Opportunities to Reach a 50% Reduction in Cancer Mortality Rates by 2047

Meredith Shiels

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NIH NATIONAL CANCER INSTITUTE

Today's Talk

- Presents an overview of a manuscript recently published in *Cancer Discovery*

- Represents a collaboration between principal investigators in the Center for Cancer Research and the Division of Cancer Epidemiology and Genetics, NCI

- Project grew from a request by Dr. Doug Lowy to examine the feasibility of President Biden's Cancer Moonshot goal

- Launched under the leadership of then Vice President Joe Biden in 2016 to speed progress from cancer prevention to survivorship
- 2016 21st Century Cures Act devoted $1.8 billion dollars over 7 years to Cancer Moonshot-driven research at the National Cancer Institute focused on
  - Accelerating scientific discovery
  - Fostering greater collaboration
  - Improving data sharing

- On February 2, 2022, President Biden and First Lady Dr. Biden reignited the Cancer Moonshot
- New goals:
  - To reduce age-standardized cancer mortality rates by at least 50% over the next 25 years
  - To improve the experience of people and their families living with and surviving cancer, ending “cancer as we know it”

Goal: To reduce age-standardized cancer mortality rates by at least 50% over the next 25 years

- Specifically, we focused on:
  - Estimating cancer death rates in 2047 if current trends continue
  - Focusing on the leading 6 causes of cancer death as these cause >50% of cancer deaths
  - Identifying some of the most promising, and realistic, opportunities to further reduce cancer death rates over the next 25 years

Shiels et al., Cancer Disc 2023

- This effort focuses on specific opportunities to achieve one of the new Cancer Moonshot goals

- Less common cancers, including pediatric cancers, and exposures are important and should be studied
- Not recommendations for DCEG or NCI priorities

Accompanying commentary by NCI Director

SCIENCE IN SOCIETY

Achieving the Goals of the Cancer Moonshot Requires Progress against All Cancers

Monica M. Bertagnolli[1], Danielle Carnival[2], and Elizabeth M. Jaffee[3]

- Highlights the importance of making progress against mortality from all cancer types, including the less common sites

Amy Berrington, ICR

Neal Freedman, DCCPS

Mark Schiffman, DCEG

John Schiller, CCR

Stanley Lipkowitz, CCR

Nicole Campos, Harvard

Leading causes of cancer death, 2019

Cancer type	N	% of cancer deaths
Lung and Bronchus	139,601	23.3%
Colon and Rectum	51,896	8.7%
Pancreas	45,885	7.7%
Female Breast	42,280	7.1%
Prostate	31,636	5.3%
Liver and Intrahepatic Bile Duct	27,958	4.7%
Leukemia	23,337	3.9%
Non-Hodgkin Lymphoma	20,270	3.4%
Brain and Other Nervous System	17,232	2.9%
Urinary Bladder	16,796	2.8%
Esophagus	15,961	2.7%
Kidney and Renal Pelvis	14,021	2.3%
Ovary	13,445	2.2%
Myeloma	12,455	2.1%
Uterine corpus	11,556	1.9%
Unknown primary	28,481	4.8%

Leading causes of cancer death, 2019

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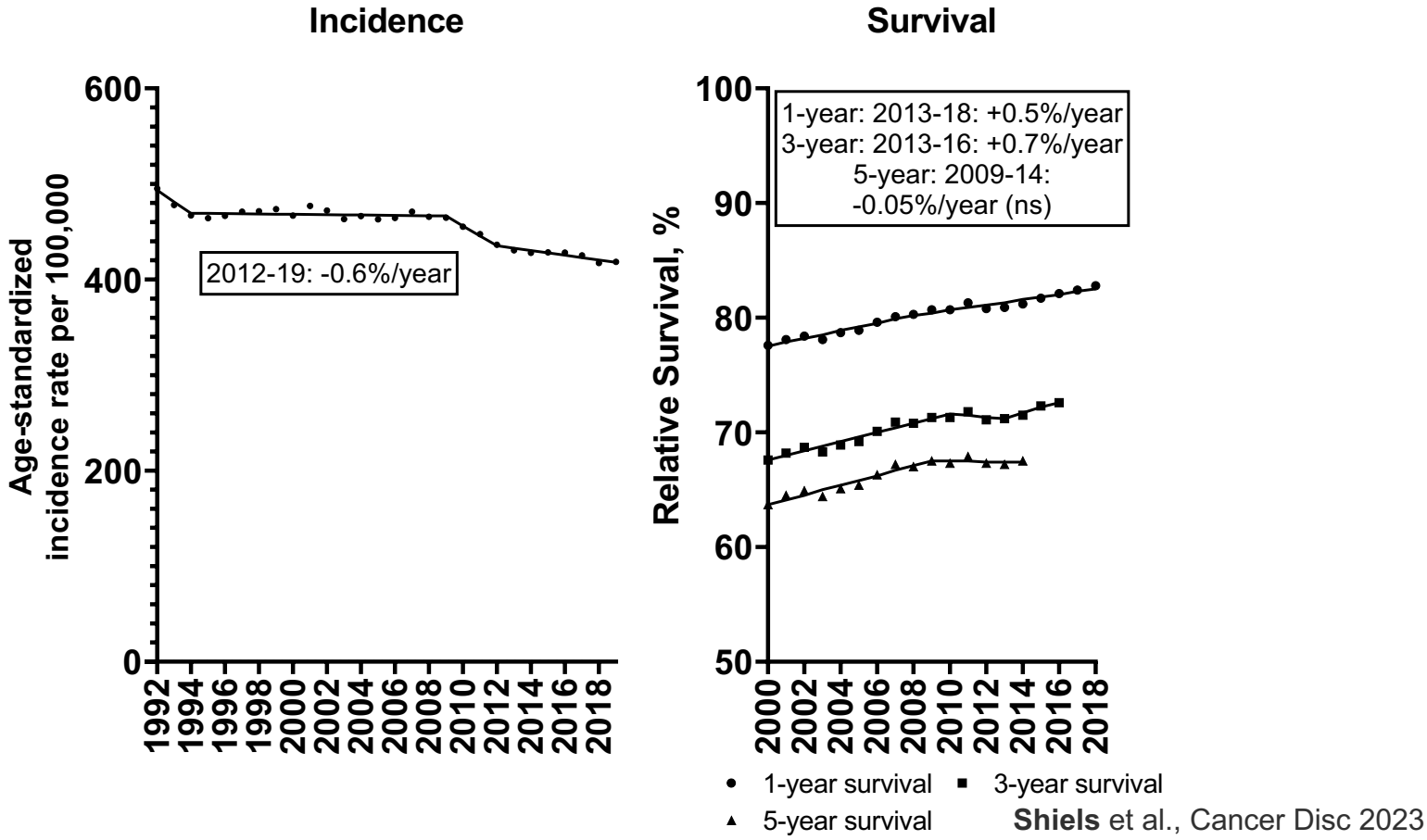
- 56% cancer deaths in men and 57% in women
- Progress against these cancers is required to reach the 50% goal

Approach

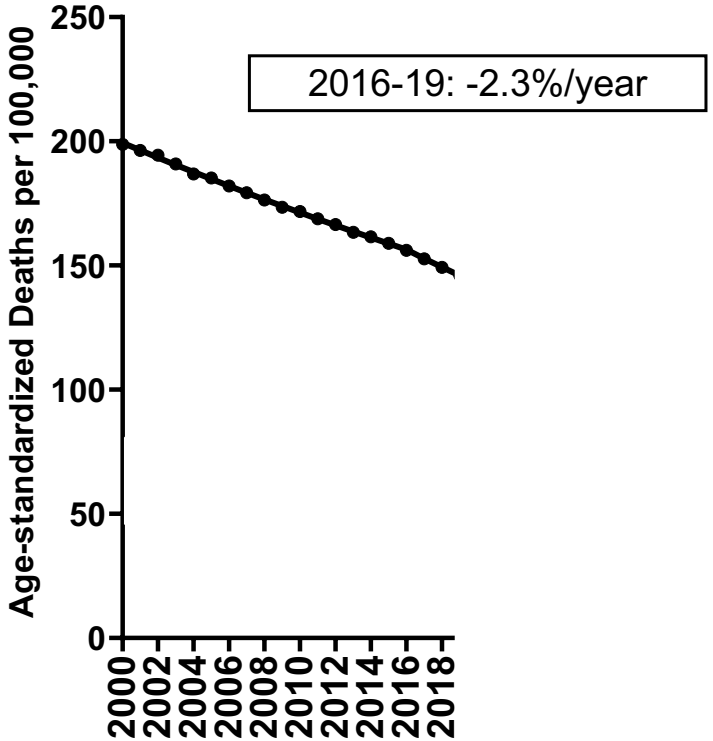
- Cancer incidence, relative survival and mortality
  - Data from SEER and NCHS death certificate data
- Mortality rate projections from 2022-2047
  - Most recent trend in cancer mortality rates identified
  - Projections assume most recent trend will continue from 2022-2047
  - Provides overall picture of whether we are on or off track to meet the Moonshot goal

Total Cancer



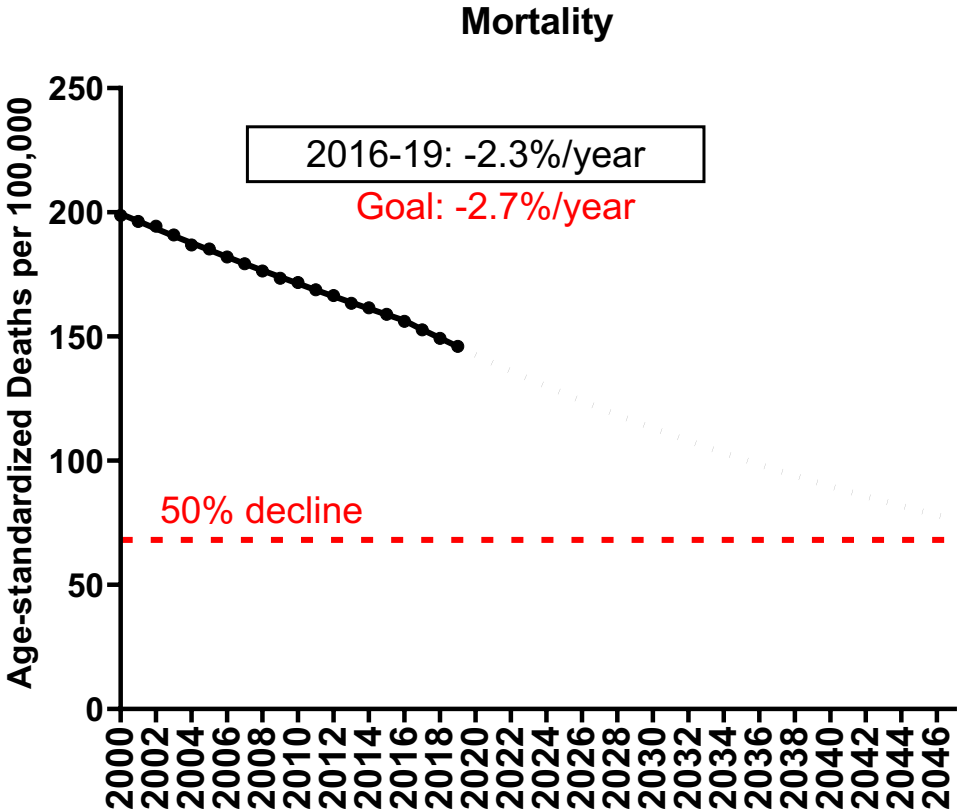
Shiels et al., Cancer Disc 2023

Total Cancer



Shiels et al., Cancer Disc 2023

Total Cancer



Shiels et al., Cancer Disc 2023

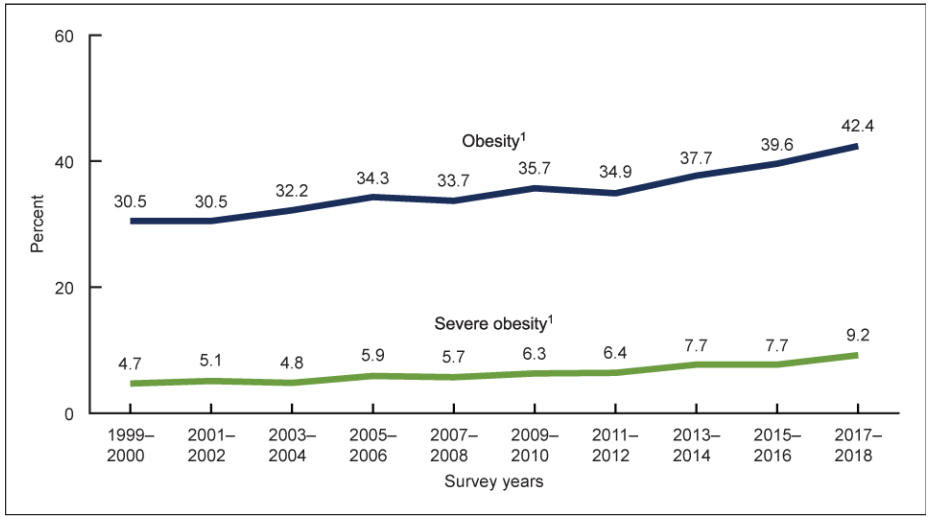
Opportunities to accelerate progress

- Approaches should be cancer type specific, as etiology, prevention, and treatment differ by site
- Highlight established interventions with the greatest promise of reducing cancer deaths over a 25-year period
- This does not discount the importance of discovery and continued efforts to develop new approaches to prevent, discover, and treat cancer

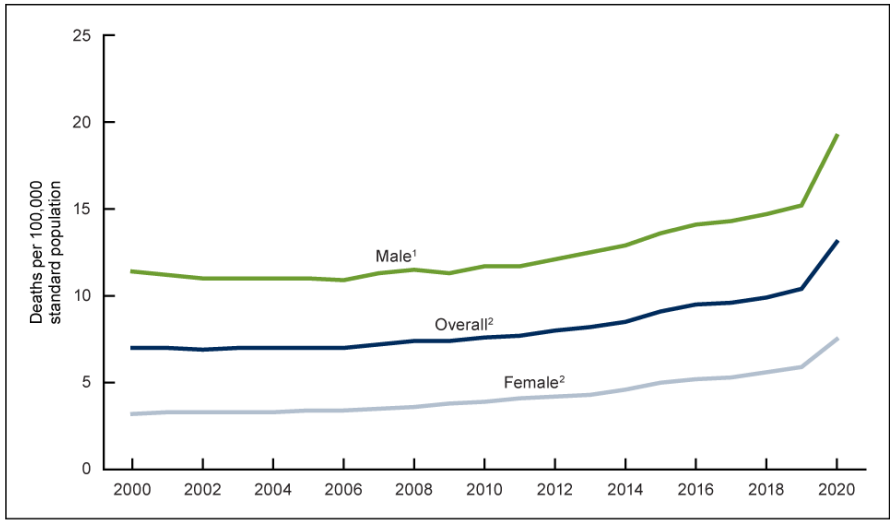
Modifiable risk factors

- Cigarette smoking, obesity, physical inactivity and alcohol intake contribute to mortality from many cancer types as well as other chronic diseases
- Progress against these risk factors is critically important
- Population-level interventions to reduce these risk factors are challenging (except for cigarette smoking)

U.S. Obesity Prevalence, 1999-2018



Alcohol-induced Death Rates, 2000-2020



Data from NCHS

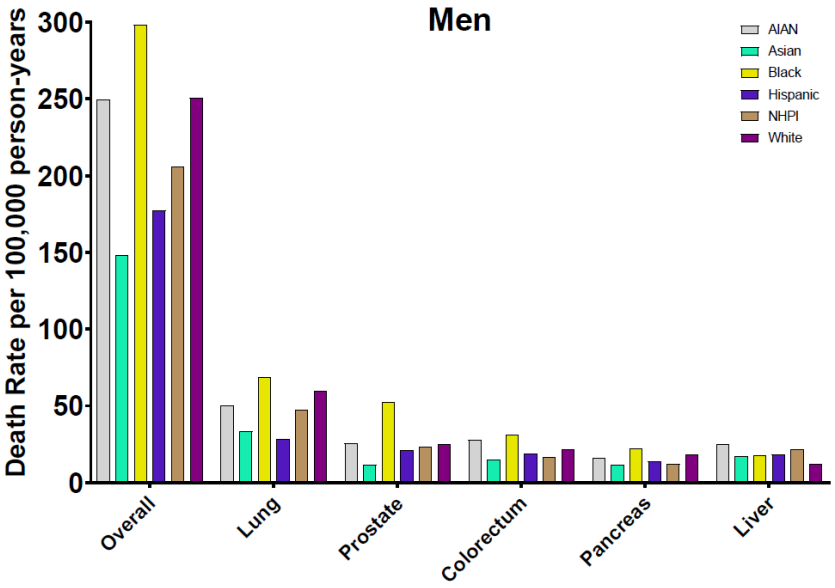
Modifiable risk factors

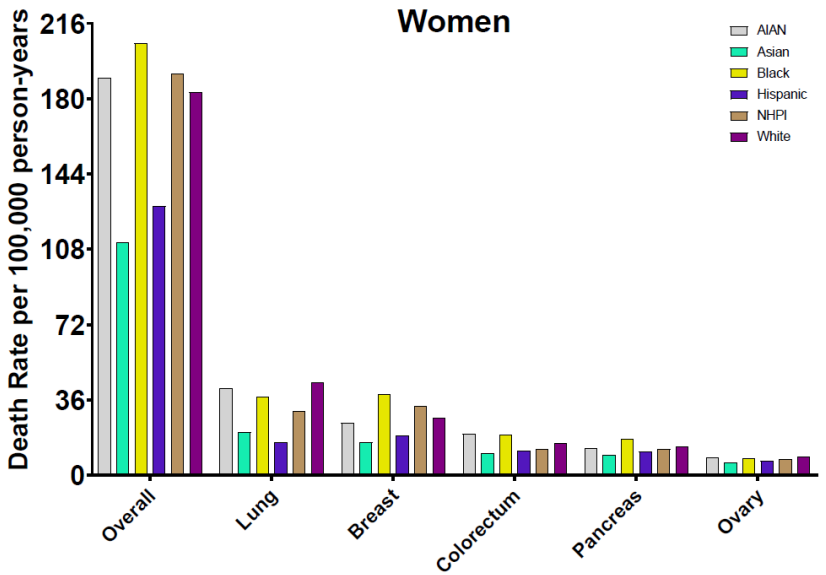
- Successful population-level efforts to increase physical activity, decrease obesity and alcohol consumption would lower deaths from cancer and other chronic diseases
- It is likely to take longer than the 25-year time frame to reverse the current trends and observe an impact at the population-level

Cancer treatment

- Focus on treatments with large survival benefits for a substantial fraction of cancer patients
- Treatments with limited survival benefits are tremendously important for individual patients, but are unlikely to have an impact at the population level

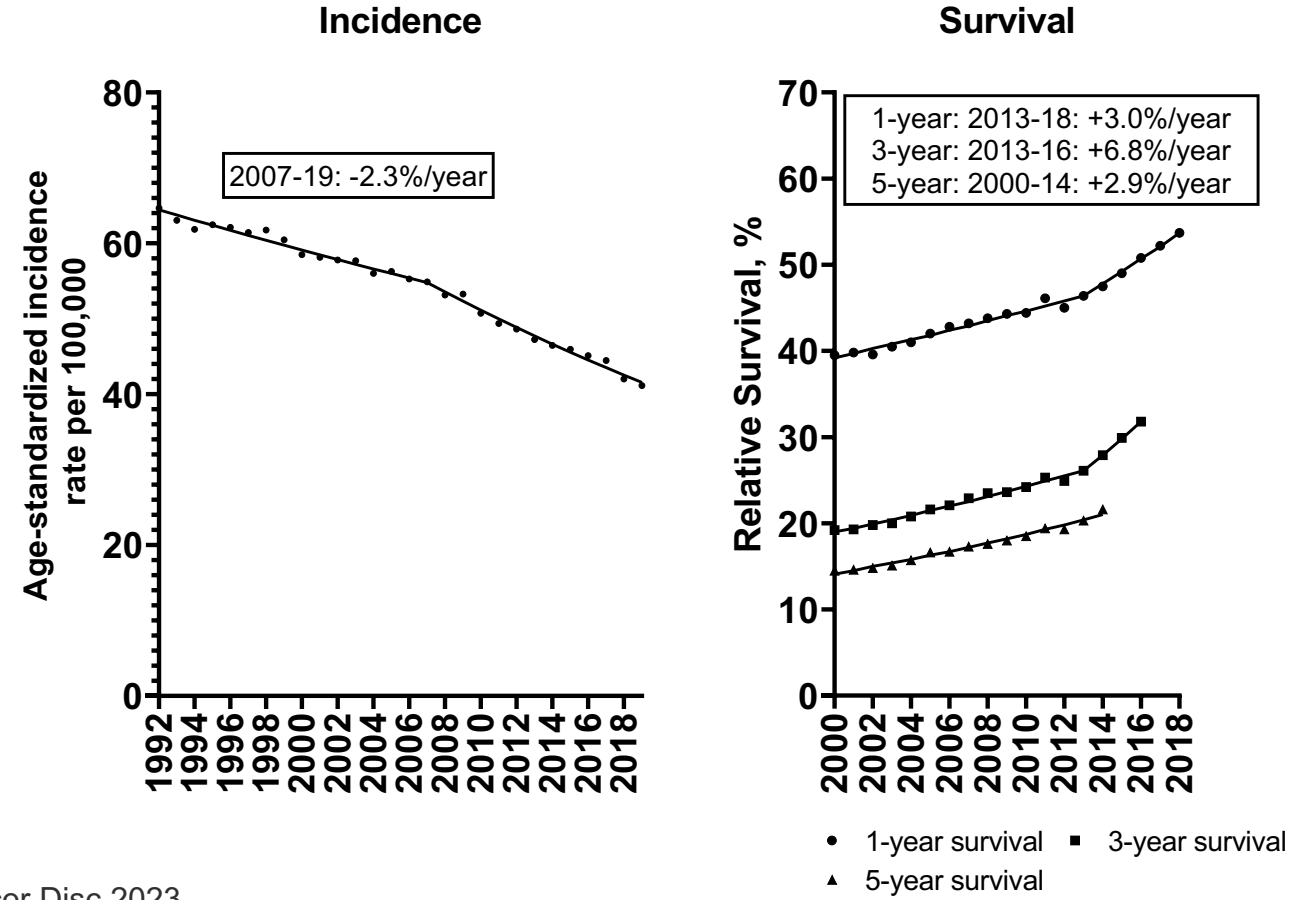
Addressing disparities in cancer prevention, early detection and treatment is a critical component of many of the opportunities outlined





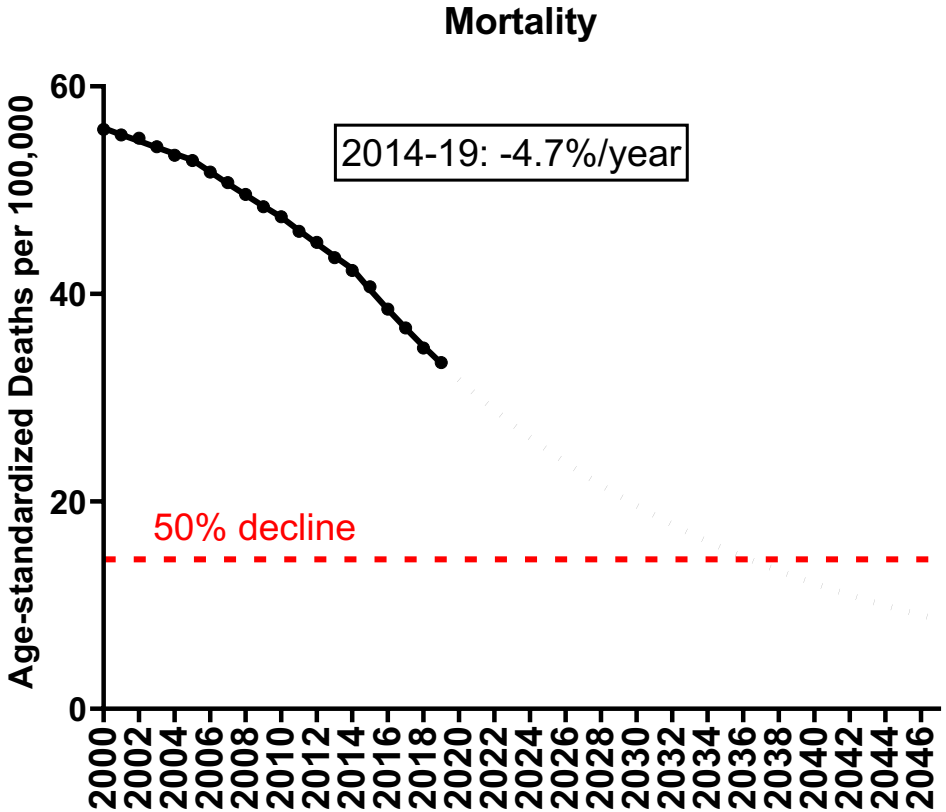
Haque et al., JNCI in press

Lung Cancer



Shiels et al., Cancer Disc 2023

Lung Cancer

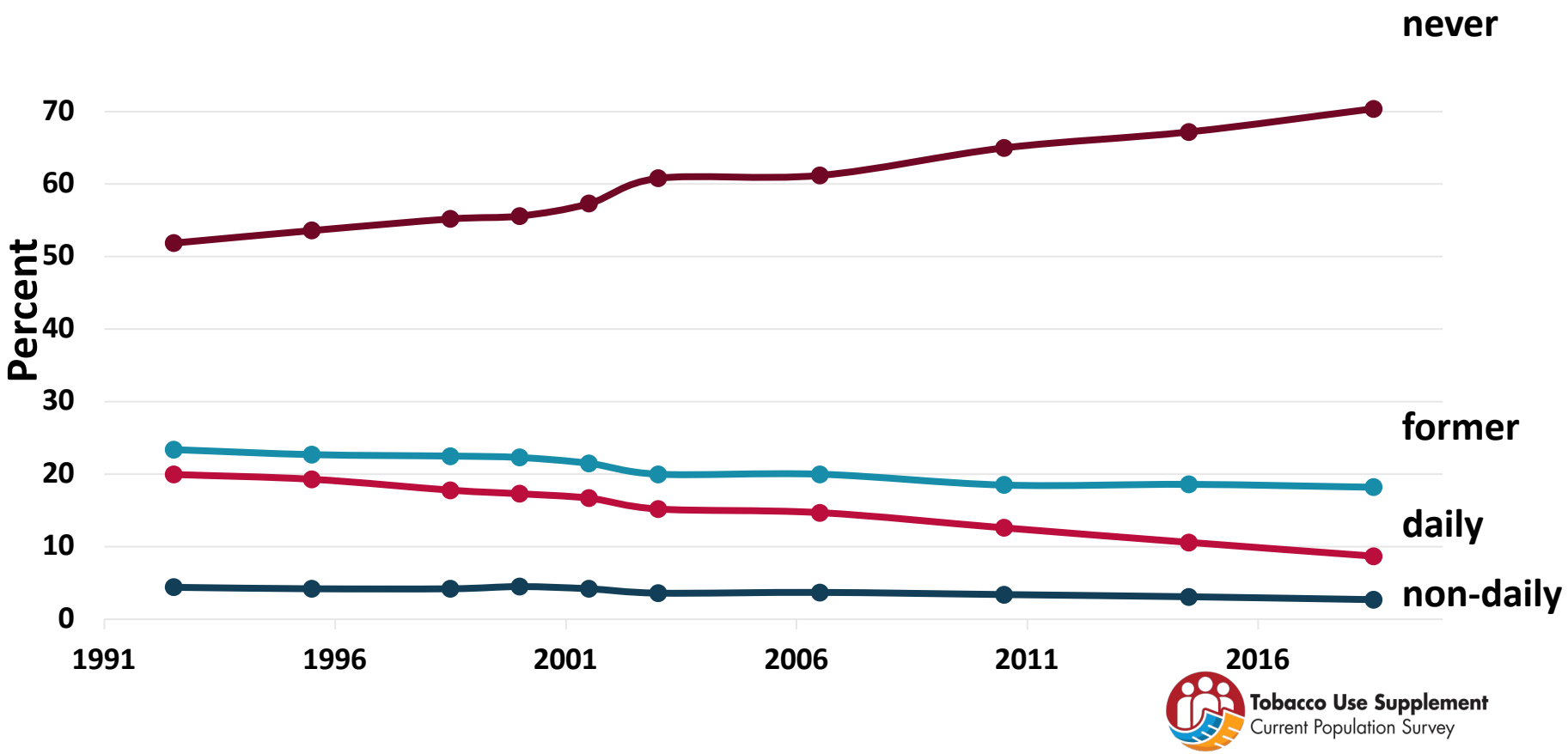


Shiels et al., Cancer Disc 2023

Lung Cancer

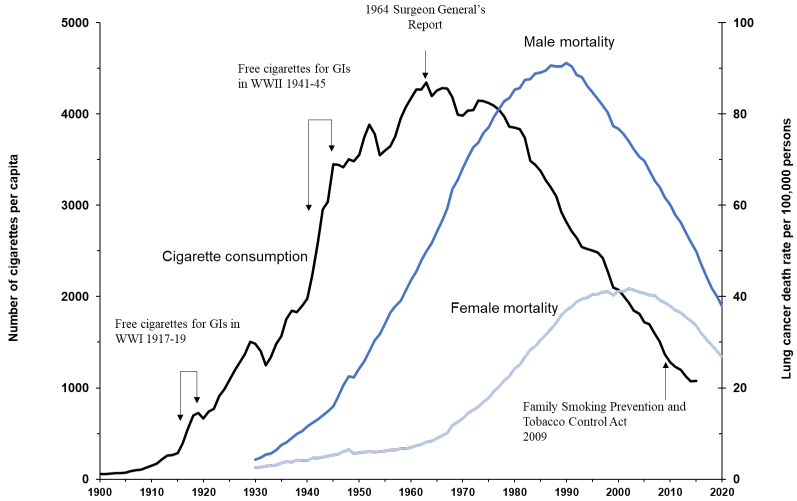
Outcome	Potential intervention type	Opportunity?
Incidence	Risk factors	Increase smoking cessation; prevent initiation

Smoking prevalence in the U.S.



Continued declines in lung cancer expected

- Progress in smoking declines from recent years has not yet impacted lung cancer death rates
- 2% of high school students reported smoking in 2022
- FDA has proposed new tobacco product standards
  - Prohibiting menthol
  - Reducing nicotine

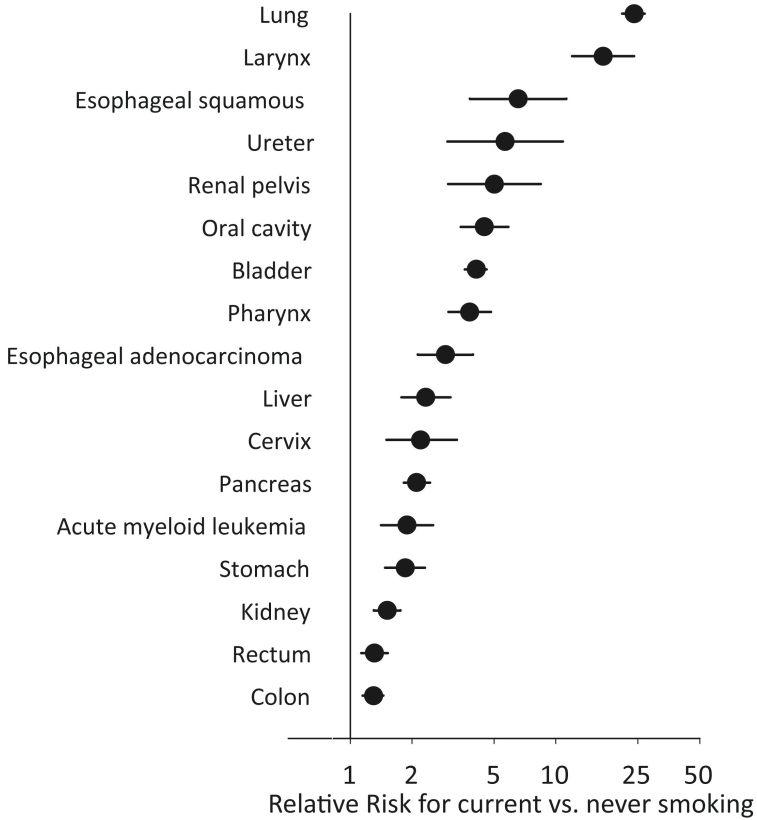


Disparities in cigarette smoking remain

Prevalence of cigarette smoking by Education in adults, 2020 (NHIS)	
0-12 years (no diploma)	21.5%
GED	32.0%
High School diploma	17.6%
Associate Degree	12.7%
Bachelor’s degree	5.6%
Graduate degree	3.5%

Cornelius et al, MMWR, 2022

Smoking causes many cancer types



Freedman et al, IJE, 2016

Lung Cancer

Outcome	Potential intervention type	Opportunity?
Incidence	Risk factors	Increase smoking cessation; prevent initiation
Mortality	Screening (Early detection)	Increase low-dose CT uptake and reduce disparities in use

Centers for Disease Control and Prevention

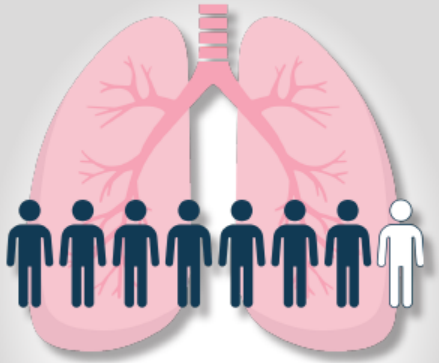
MMWR

LUNG CANCER SCREENING SAVES LIVES

Lung Cancer is #1 Cause of Cancer Deaths

Screening with low dose CT* can detect lung cancer early and save lives

More Screening is Needed



7 of **8** adults who met **screening criteria** did not report recommended screening

Healthcare Providers: Discuss Screening

With Adults

- Age 55–80
- Heavy smoking history**
- Smoke now or quit within the past 15 years

*Low-dose computed tomography (CT) is the only test recommended by the US Preventive Services Task Force.

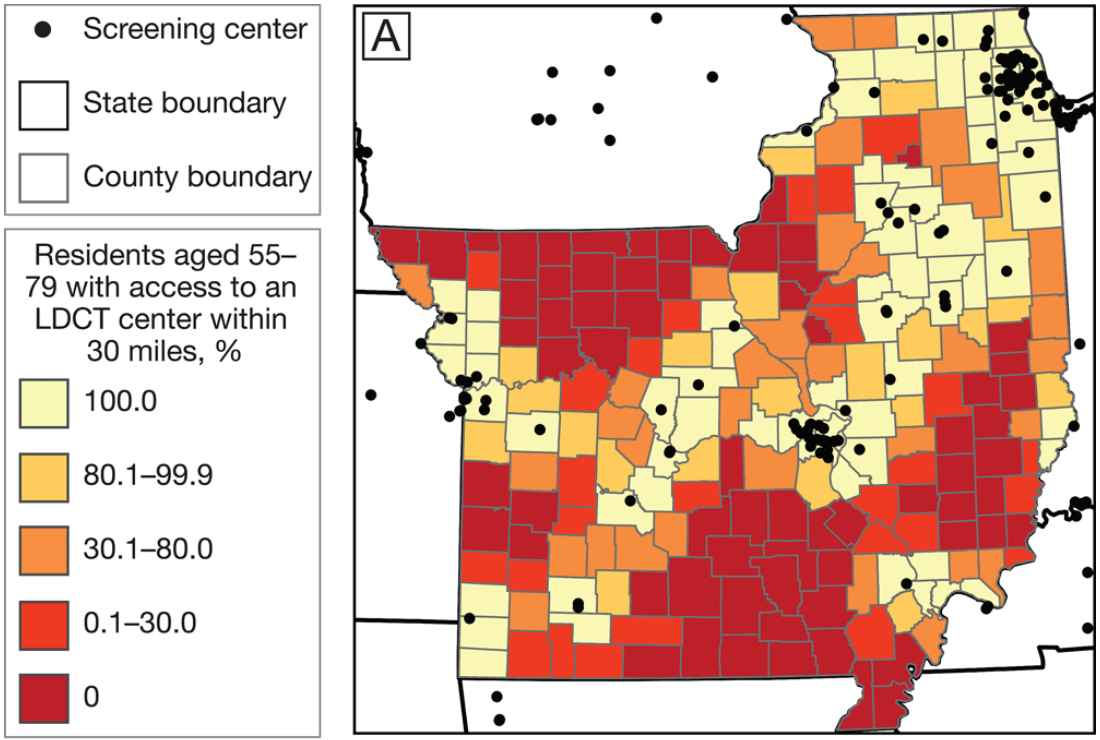
**Heavy smoking is a smoking history of 30 pack-years or more. A pack-year is smoking an average of one pack of cigarettes per day for one year.

Data from BRFSS, 10 states in 2017, as reported in Richards et al, *MMWR* 2020 Read the full report: bit.ly/CDCVA34

WWW.CDC.GOV

CS 14820-B

Rural/urban disparities in access to LDCT screening in Missouri and Illinois



Rohatgi et al., 2020

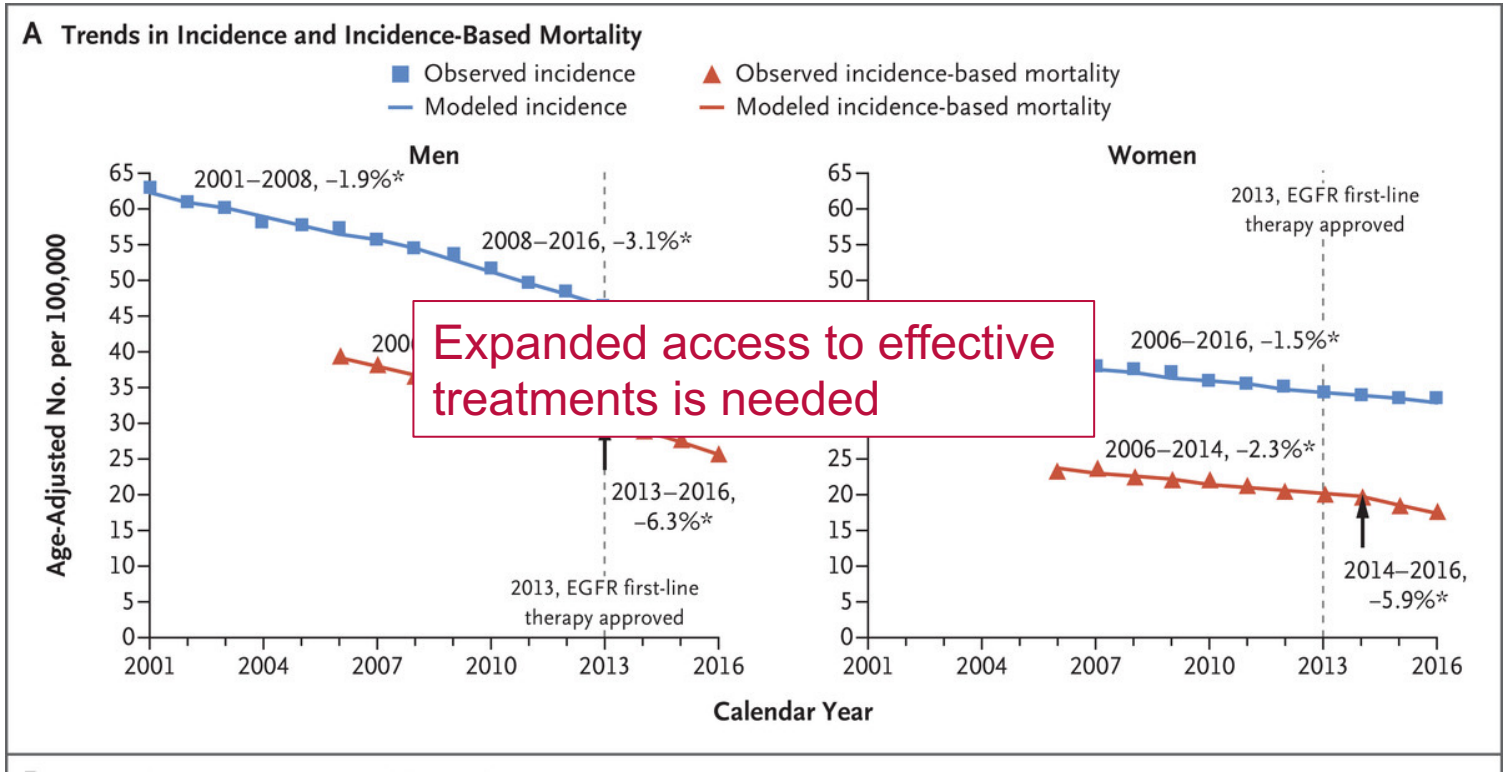
Lung Cancer

Outcome	Potential intervention type	Opportunity?
Incidence	Risk factors	Increase smoking cessation; prevent initiation
Mortality	Screening (Early detection)	Increase low-dose CT uptake and reduce disparities in use
	Treatment	Reduce disparities in access to more effective treatments (targeted and immune-based therapies for NSCLC)

Non-small cell lung cancer (NSCLC) treatments improved survival

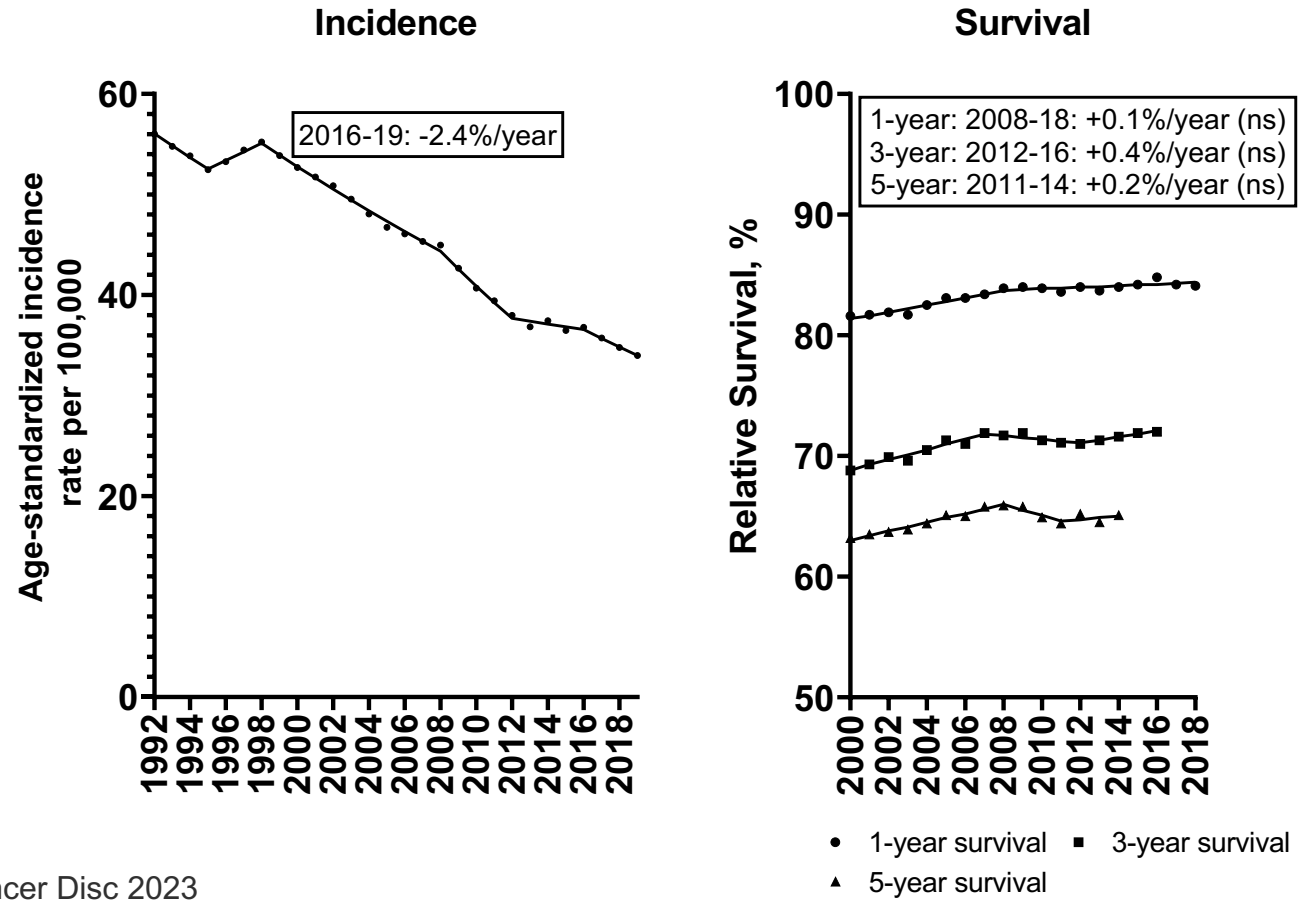
- ¾ of lung cancer cases in the U.S.
- Targeted therapies against oncogenic driver mutations and immune-based therapies have resulted in population-level declines in lung cancer mortality

NSCLC treatments improved survival



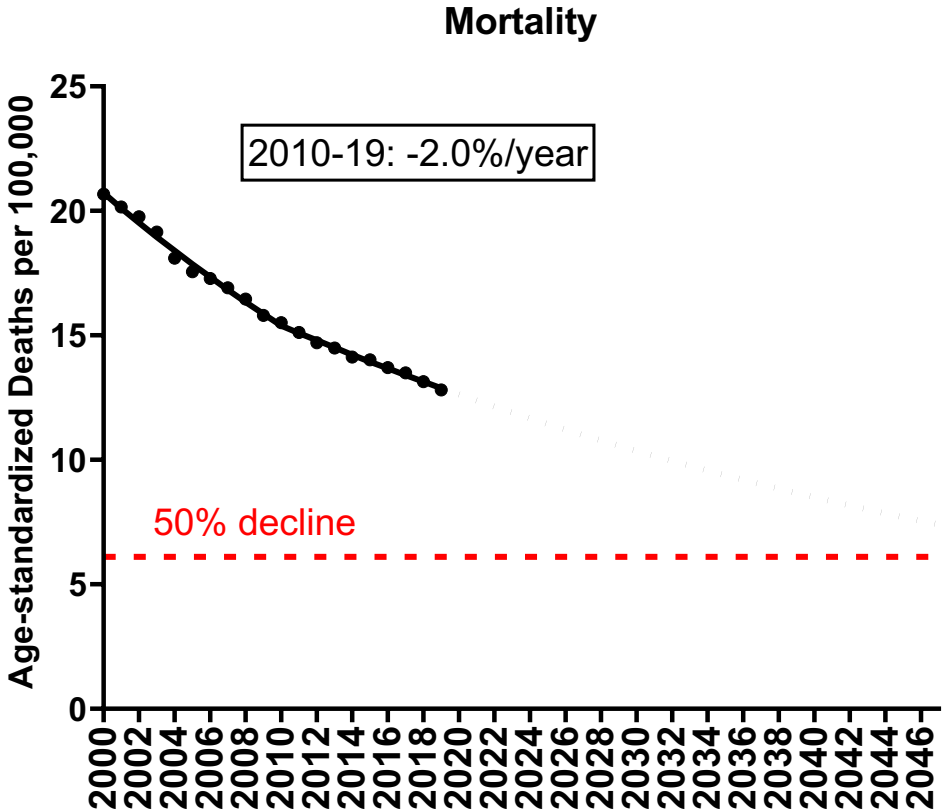
Howlader et al. 2020

Colorectal Cancer



Shiels et al., Cancer Disc 2023

Colorectal Cancer



Shiels et al., Cancer Disc 2023

Colorectal Cancer

Outcome	Potential intervention type	Opportunity?
Incidence	Screening (Prevention)	Increase uptake of colonoscopy, flexible sigmoidoscopy, and FIT/FIT-DNA for hard-to-reach populations
	Preventive treatment	Increase adherence to diagnostic follow-up and polyp removal
Mortality	Screening (Early detection)	Increase uptake of colonoscopy, flexible sigmoidoscopy; gFOBT and FIT with diagnostic follow-up

USPSTF guidelines for colorectal cancer screening

Screen all adults aged 45 to 75 years for colorectal cancer. Several recommended screening tests are available. Clinicians and patients may consider a variety of factors in deciding which test may be best for each person. For example, the tests require different frequencies of screening, location of screening (home or office), methods of screening (stool-based or direct visualization), preprocedure bowel preparation, anesthesia or sedation during the test, and follow-up procedures for abnormal findings.

Recommended screening strategies include

- High-sensitivity guaiac fecal occult blood test (HSgFOBT) or fecal immunochemical test (FIT) every year
- Stool DNA-FIT every 1 to 3 years
- Computed tomography colonography every 5 years
- Flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 10 years + annual FIT
- Colonoscopy screening every 10 years

Selectively screen adults aged 76 to 85 years for colorectal cancer.

- Discuss together with patients the decision to screen, taking into consideration the patient's overall health status (life expectancy, comorbid conditions), prior screening history, and preferences.

Source: US Preventive Services Task Force *JAMA* 2021.

Mortality reductions by screening test

- Non-invasive:
  - Guaiac fecal occult blood test (gFOBT) and fecal immunochemical test (FIT) ↓9-22%
- Direct visualization (permit polyp removal)
  - Colonoscopy ↓ 68% mortality reduction with one round
  - Flexible sigmoidoscopy ↓ 26% reduction with screening every 3-5 years

Lin et al., JAMA 2020

CRC screening uptake (NHIS 2018): room for improvement

Table 1. Percentage of adults aged 50–75 up-to-date with colorectal cancer screening, by test type, sex, and age, NHIS, 2018.

	N	Any CRC screening test[a] % (95% CI)	*P*	Colonoscopy within 10 years % (95% CI)	*P*	FOBT/FIT[b] within 1 year % (95% CI)	*P*	FIT-DNA within 3 years % (95% CI)	*P*	Sigmoidoscopy within 5 years % (95% CI)	*P*	CT colonography within 5 years % (95% CI)	*P*
Total	10,595	66.9 (65.8–68.1)		61.1 (59.9–62.3)		8.8 (8.1–9.5)		2.7 (2.4–3.2)		2.4 (2.1–2.8)		1.0 (0.8–1.3)	
Sex			0.43		0.61		0.04		0.19		0.09		0.11
Male	4,846	67.4 (65.8–69.0)		61.4 (59.8–63.1)		9.5 (8.5–10.6)		2.5 (2.0–3.1)		2.7 (2.2–3.4)		1.2 (0.9–1.7)	
Female	5,749	66.5 (64.9–68.1)		60.8 (59.1–62.5)		8.1 (7.3–9.1)		3.0 (2.5–3.5)		2.1 (1.6–2.6)		0.8 (0.6–1.2)	
Age (years)			<0.001		<0.001		<0.001		<0.001		0.01		0.17
50–64	6,294	61.8 (60.2–63.3)		55.9 (54.3–57.5)		7.9 (7.0–8.8)		2.2 (1.8–2.8)		2.1 (1.7–2.5)		0.9 (0.7–1.2)	
65–75	4,301	76.9 (75.4–78.4)		71.1 (69.5–72.8)		10.5 (9.4–11.7)		3.7 (3.1–4.5)		3.0 (2.4–3.7)		1.2 (0.9–1.7)	

Abbreviation: CRC, colorectal cancer.

[a]Any colorectal cancer screening test within the recommended time period (up-to-date with CRC screening), defined as either colonoscopy within the past 10 years, CT colonography or sigmoidoscopy within the past 5 years, FOBT or FIT within the past year, or FIT-DNA within the past 3 years.

[b]Use of FOBT/FIT does not include a FIT that the respondent reported was conducted as part of a FIT-DNA test.

Shapiro CEBP 2021

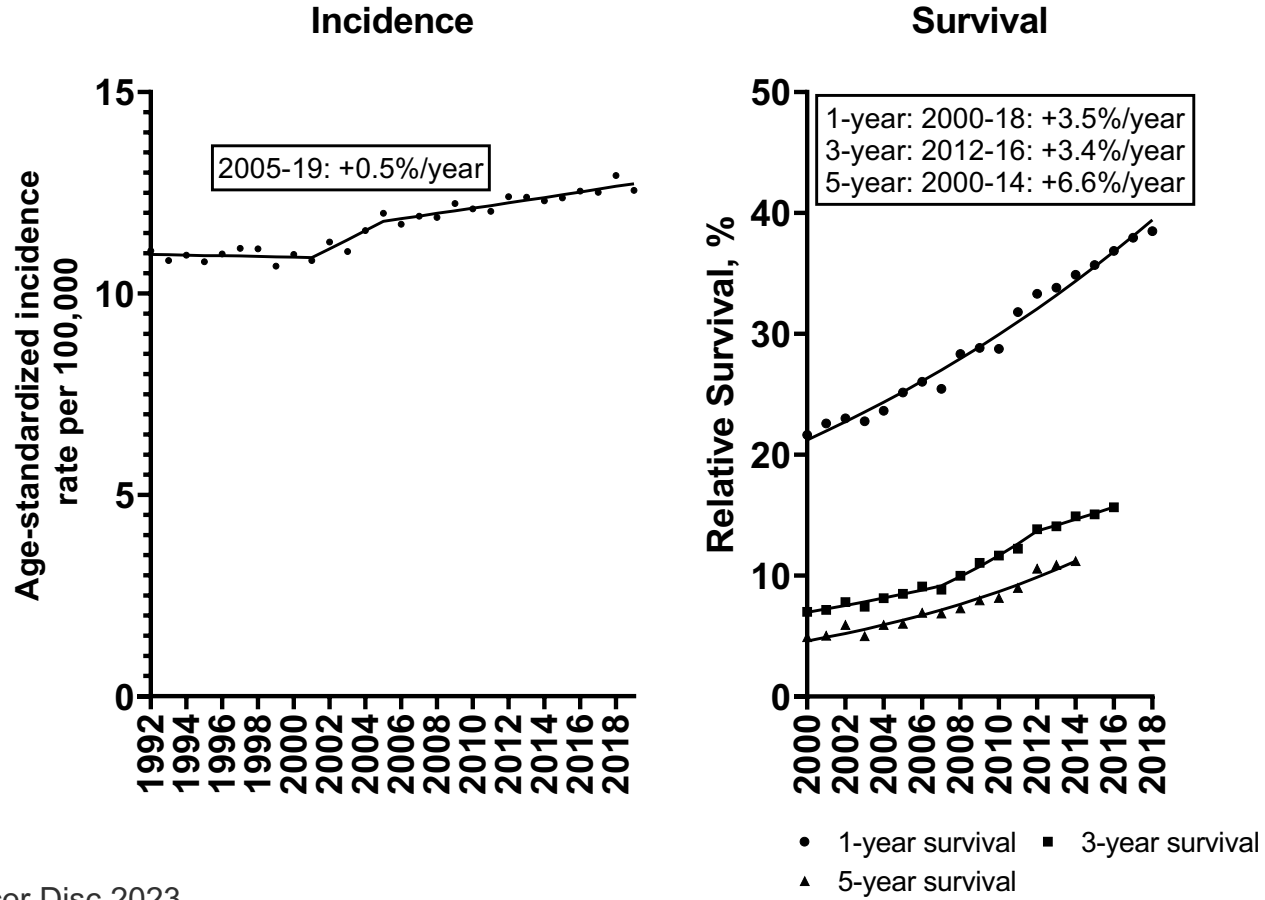
Diagnostic follow-up (PROSPR): low adherence among FOBT-positive or FIT-positive

PROSPR site	Colorectal Age 50-75			
	E	F	G	H
Percent tested	31.4	45.5	37.5	22.2
Percent screened	27.2	43.3	34.6	20.6
Percent testing up-to-date	69.1	78.5	79.3	44.4
Percent screening abnormal	5.7	4.0	4.8	6.9
Percent with diagnostic evaluation	63.9	81.4	73.3	45.6
Cancer / 1,000 screens	1.95	1.15	1.79	1.48
Cancers / 1,000 women in the population	0.70	0.82	0.83	0.63

Incomplete follow-up after screening positive

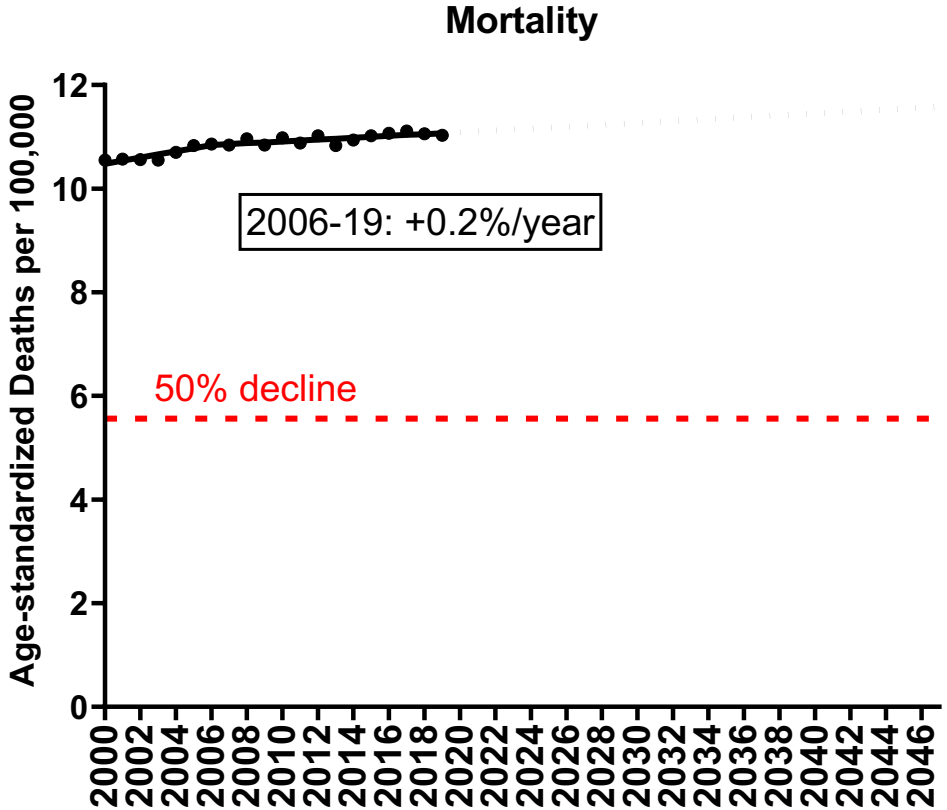
Barlow JNCI 2020

Pancreas Cancer



Shiels et al., Cancer Disc 2023

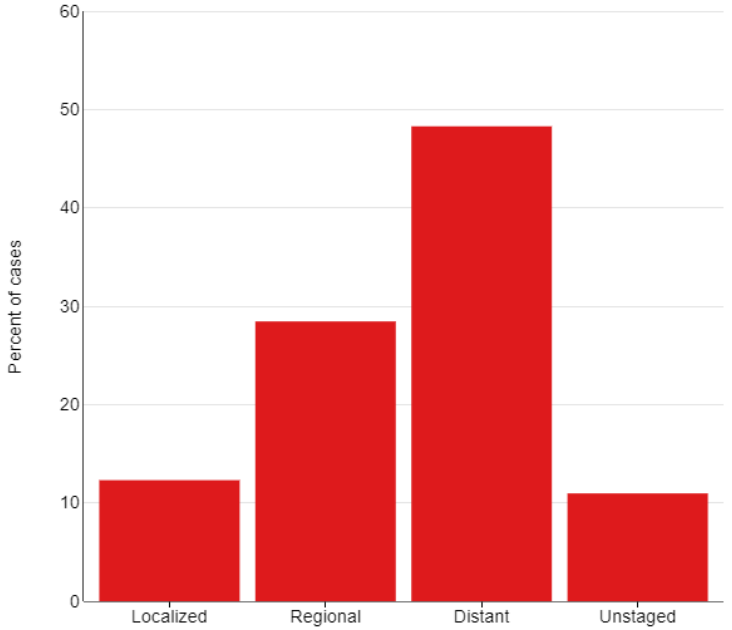
Pancreas Cancer



Shiels et al., Cancer Disc 2023

Pancreatic cancer prevention and early detection is challenging

- Modifiable risk factors cause only about 25% of cases
- Difficult to detect at an early stage
- Surgery of early-stage pancreatic cancer is the only curative treatment
  - 10-20% of patients eligible



Islami et al., CA 2018

Pancreas Cancer

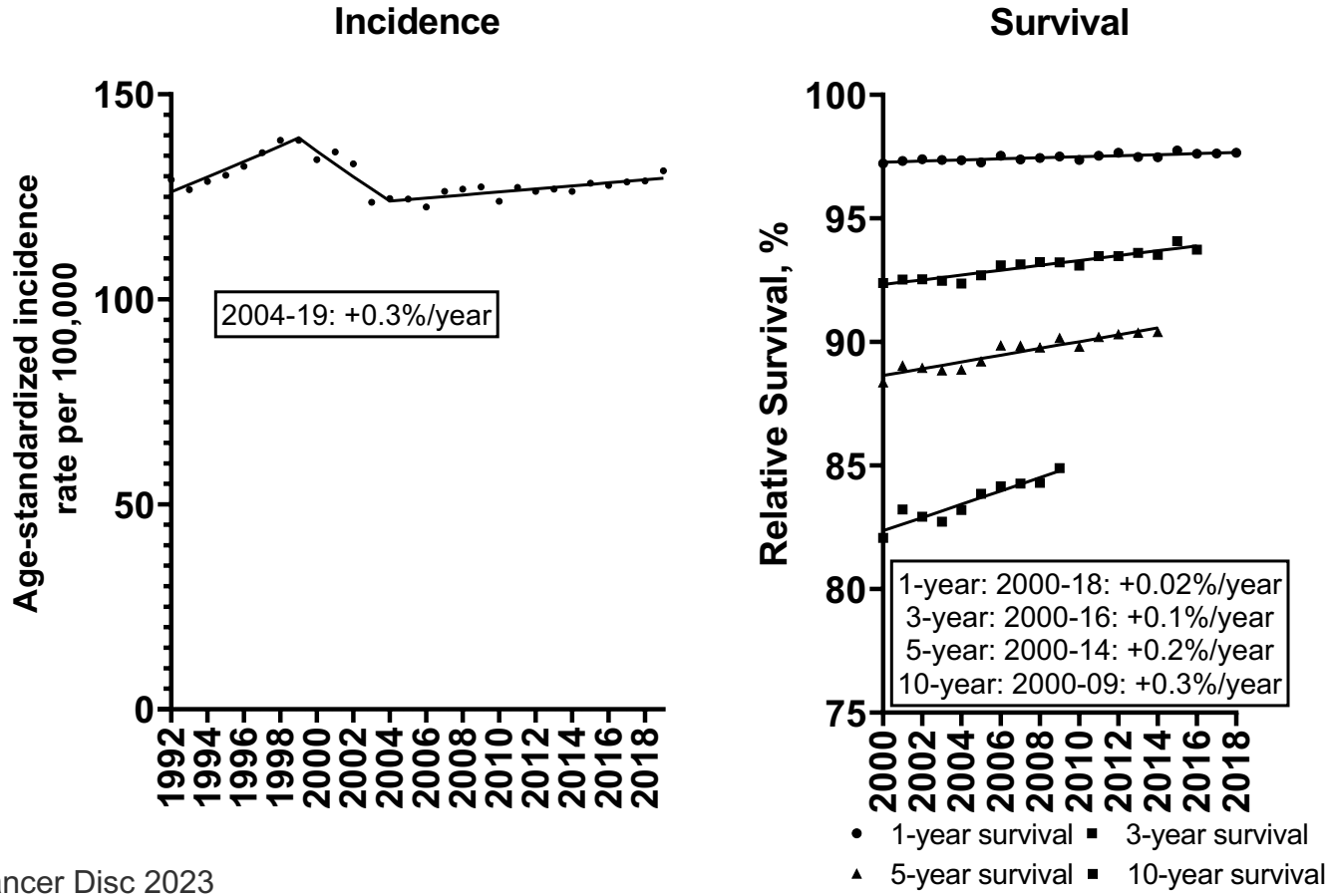
Outcome	Potential intervention type	Opportunity?
Mortality	Treatment	Develop and evaluate new mutant KRAS inhibitors

KRAS inhibitors may improve survival

- Mutant KRAS is a driver mutation in 90% of pancreatic cancers
- Inhibitors for these KRAS mutants are under active development
- Perhaps hold the greatest promise for increasing survival of a substantial fraction of pancreatic cancer patients in the future

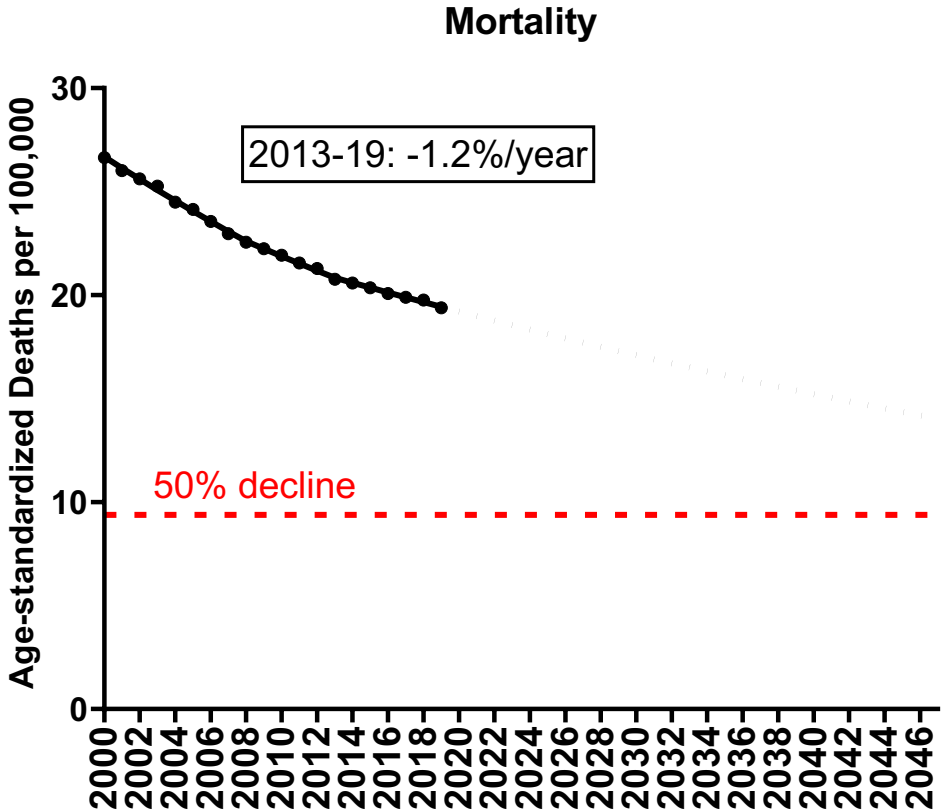
Wang et al., J Med Chem 2022; Kemp et al., Can Discovery 2023

Breast Cancer



Shiels et al., Cancer Disc 2023

Breast Cancer



Shiels et al., Cancer Disc 2023

Breast Cancer

Outcome	Potential intervention type	Opportunity?
Incidence	Preventive treatment	Evaluate efficacy of low-dose hormone therapies & improve risk-stratification

Hormone therapy reduces breast cancer risk in high-risk women

	Deaths (2010-2019)	
	No.	%
All	79,023	100
Estrogen Receptor Status		
ER Positive	46,399	58.7
ER Negative	25,714	32.5
ER Unknown	6,910	8.7

- Hormonal therapies in high-risk women: reduced ER+ breast cancer incidence by 50-65%
- ~10 million eligible, <10% receive
- Medications with fewer side effects and risk stratification may improve the risk-benefit

Fisher, JNCI 1998 and 2005; Goss NEJM 2011; Ropka JCO 2010

Breast Cancer

Outcome	Potential intervention type	Opportunity?
Incidence	Preventive treatment	Evaluate efficacy of low-dose hormone therapies & improve risk-stratification
Mortality	Risk factors post-diagnosis	Evaluate strategies for increasing physical activity and decreasing obesity in survivors

Breast Cancer

Outcome	Potential intervention type	Opportunity?
Incidence	Preventive treatment	Evaluate efficacy of low-dose hormone therapies & improve risk-stratification
Mortality	Risk factors post-diagnosis	Evaluate strategies for increasing physical activity and decreasing obesity in survivors
	Screening (Early detection)	Increase mammography uptake amongst under-served populations

Disparities in mammography in U.S., 2018

- Mammography reduces breast cancer mortality by 10-30%, but there are disparities in access

	Breast cancer screening*	
	No.	%§ (95% CI)
Insurance¶,***		
Private	3,305	77.2 (75.5–78.9)
Military	167	78.2 (70.2–85.0)
Public only	1,521	67.2 (64.2–70.2)
Uninsured	304	39.5 (32.8–46.5)
P-value††	<0.001	
Education		
Less than high school	597	63.0 (57.7–68.1)
High school/GED	1,311	68.6 (65.5–71.5)
Some college	1,686	71.6 (68.9–74.2)
College degree	1,694	80.4 (78.1–82.7)
P-value††	<0.001	
Federal poverty threshold, %		
≤138	1,060	58.6 (54.5–62.6)
>138–250	980	66.7 (62.6–70.6)
>250–400	1,030	72.1 (68.5–75.5)
>400	2,240	79.5 (77.3–81.6)
P-value††	<0.001	

Sabatino, MMWR 2021

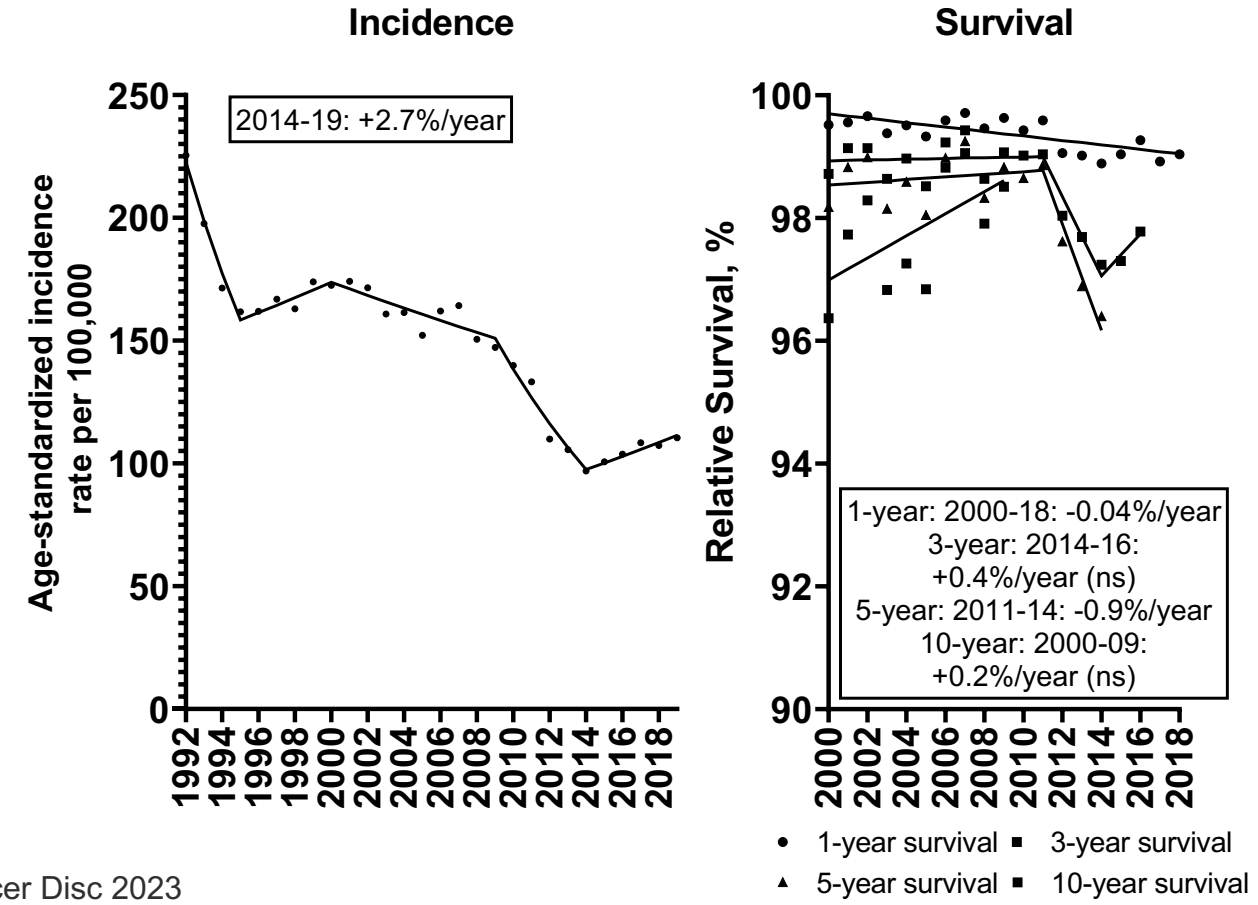
Breast Cancer

Outcome	Potential intervention type	Opportunity?
Incidence	Preventive treatment	Evaluate efficacy of low-dose hormone therapies & improve risk-stratification
Mortality	Risk factors post-diagnosis	Evaluate strategies for increasing physical activity and decreasing obesity in survivors
	Screening (Early detection)	Increase mammography uptake amongst under-served populations
	Treatment	Increase uptake/adherence to hormone therapy and chemotherapy especially in under-served populations

Increased treatment could further reduce breast cancer mortality rates

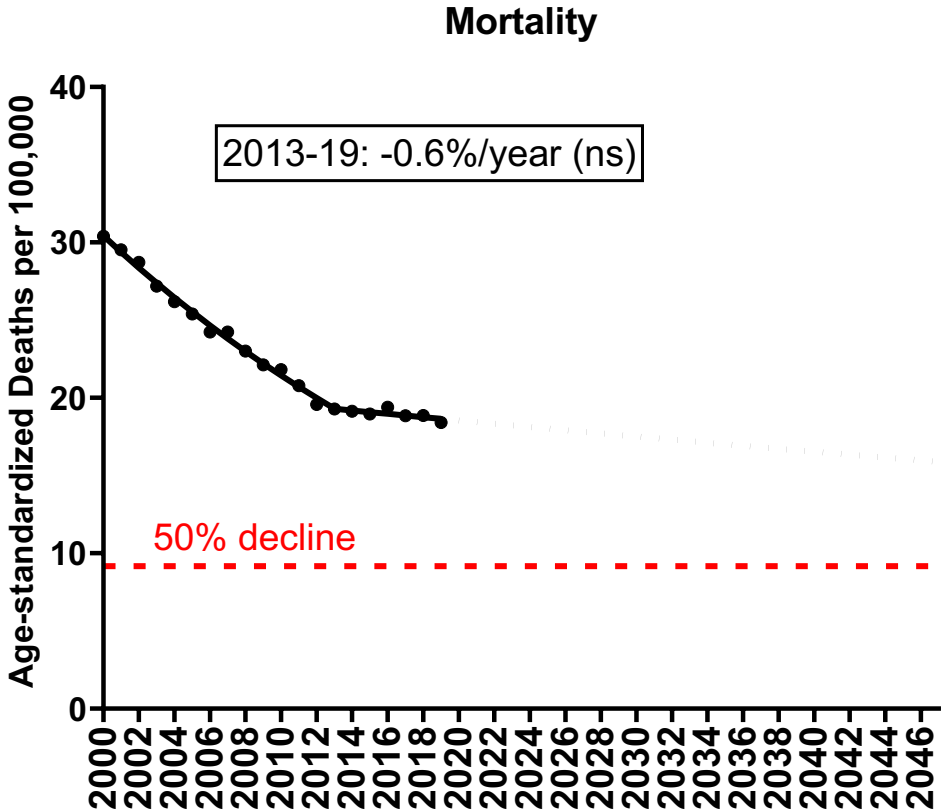
- In early stage breast cancer, endocrine therapy, chemotherapy and targeted therapies have steadily decreased recurrences and improved overall survival
- Disparities in access and timeliness of treatment
- Efforts to increase uptake and adherence should further decrease breast cancer mortality

Prostate Cancer



Shiels et al., Cancer Disc 2023

Prostate Cancer



Shiels et al., Cancer Disc 2023

USPSTF guidelines for PSA testing

- 2012: recommended against screening
- 2018: shared decision making
- Increase in metastatic prostate cancer diagnoses since 2012, and also in localized and regional disease since 2014 – cause unclear
- Risk stratification and more sensitive and specific tests for high-risk disease could improve risk: benefit for PSA testing

Butler, Cancer 2020; Jeong, Prostate Int 2021; Bryant JAMA Oncol 2022, Cook, Eur Url 2021

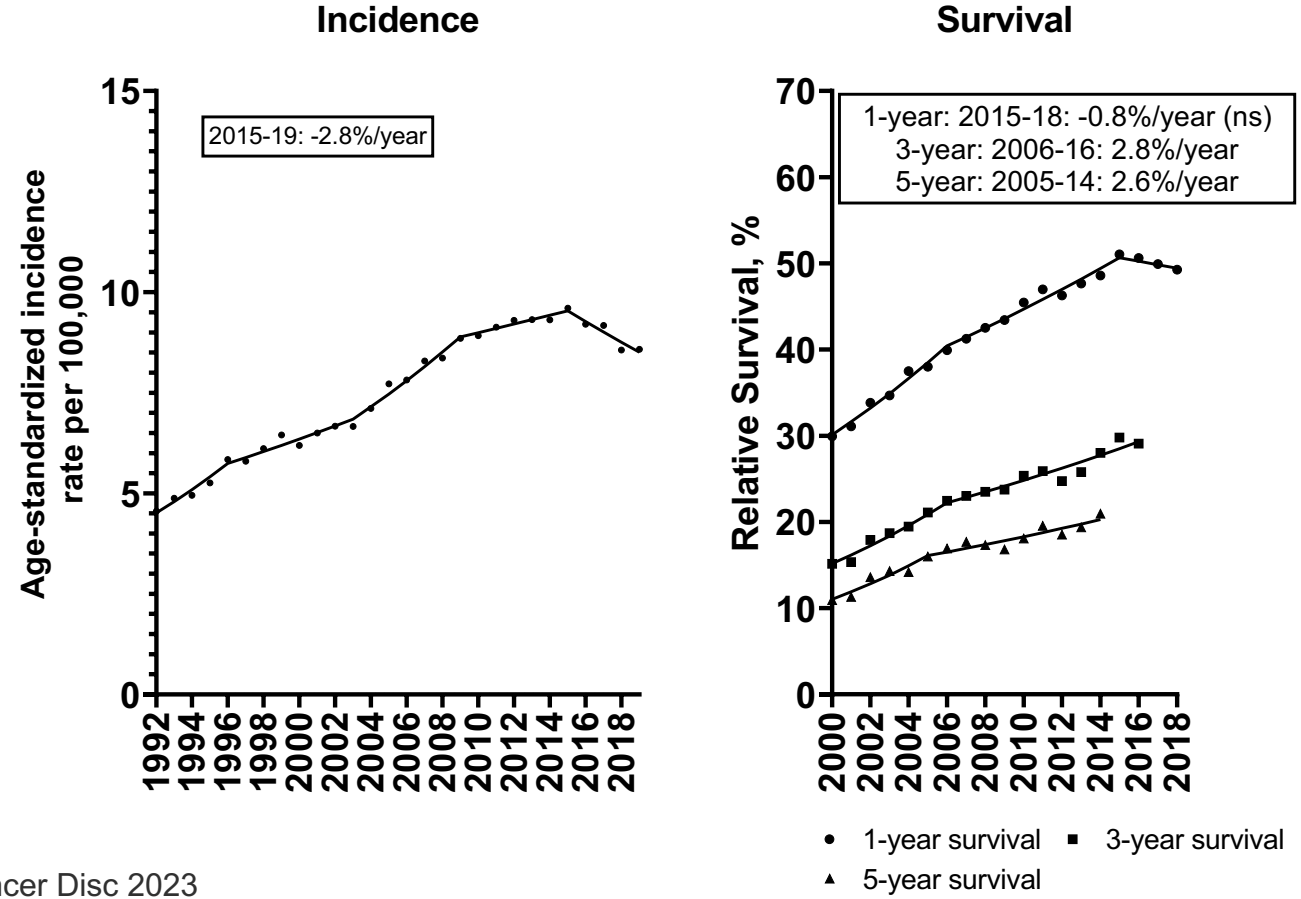
Prostate Cancer

Outcome	Potential intervention type	Opportunity?
Mortality	Screening (Early detection)	Evaluate risk-stratified PSA screening & improved diagnostic testing

Prostate Cancer

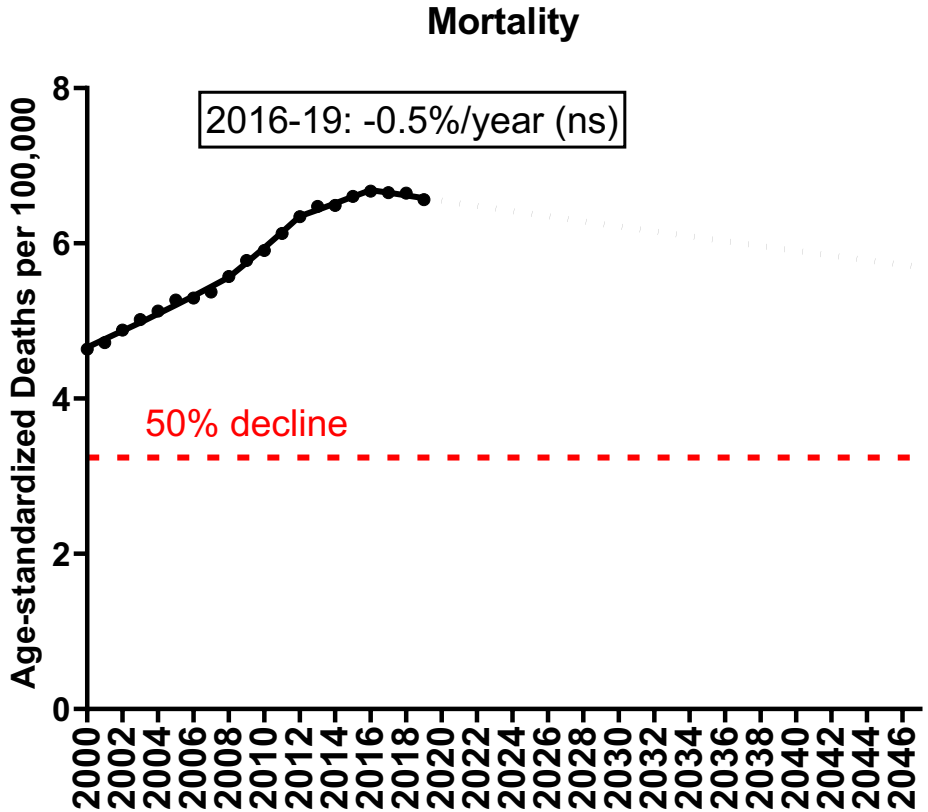
Outcome	Potential intervention type	Opportunity?
Mortality	Screening (Early detection)	Evaluate risk-stratified PSA screening & improved diagnostic testing
	Treatment	Evaluate strategies to further reduce over treatment and reduce disparities

Liver/Intrahepatic Bile Duct Cancer



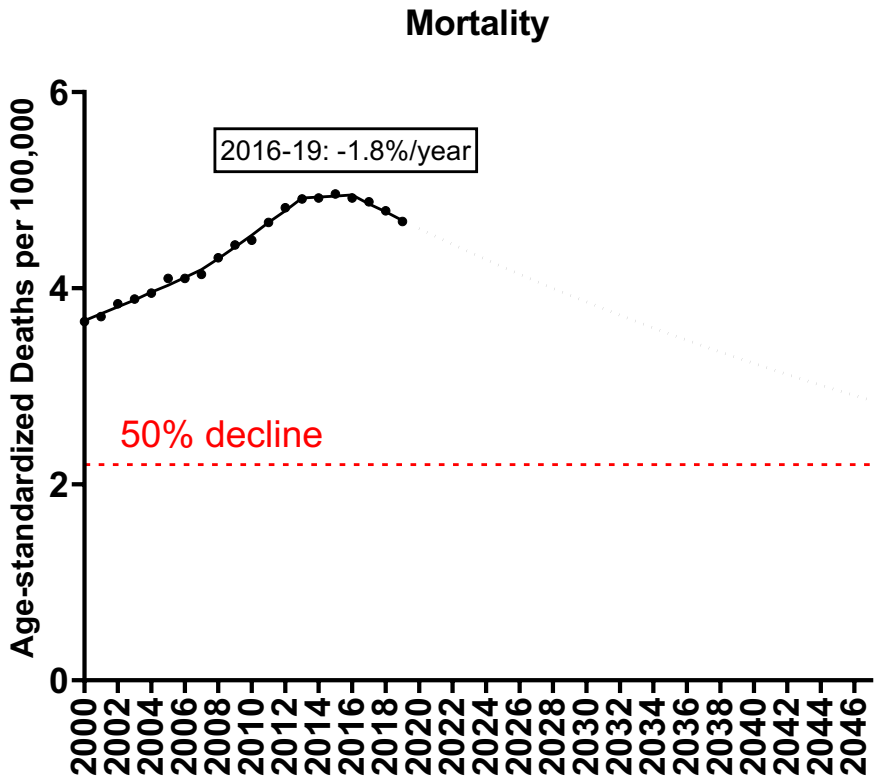
Shiels et al., Cancer Disc 2023

Liver/Intrahepatic Bile Duct Cancer



Shiels et al., Cancer Disc 2023

Liver Cancer Mortality (no IHBD)



Shiels et al., Cancer Disc 2023

Liver Cancer

Outcome	Potential intervention type	Opportunity?
Incidence	Risk factors	Increase uptake of HBV and HCV treatments, decrease smoking prevalence

Modifiable risk factors and liver cancer deaths

- Excess body weight: 33%
- Alcohol intake: 20%
- Smoking: 22%
- Hepatitis B virus: 7% → 1.5-2.4 million people
- Hepatitis C virus: 21% → 2.5-4.7 million people

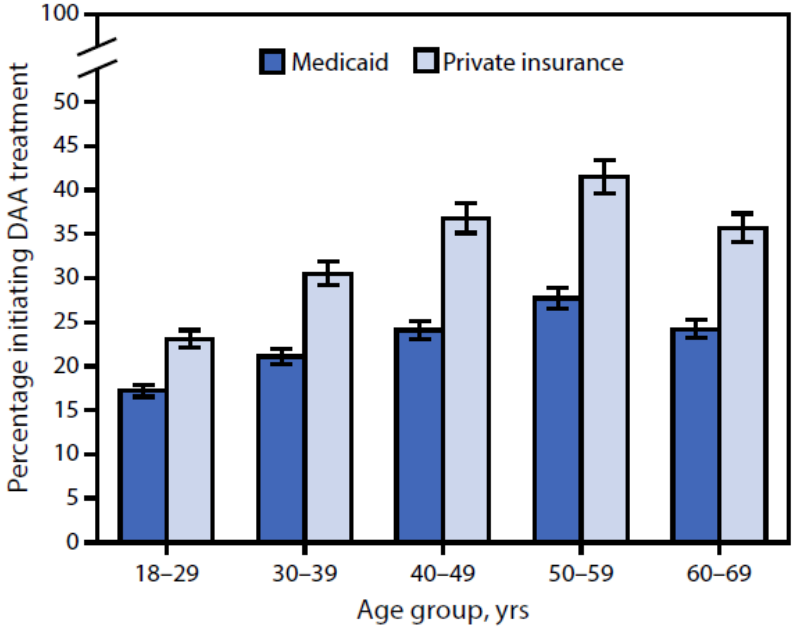
Progress is critically important

Islami, CA 2018 ;Wong, Hepatology 2021; Edlin Hepatology 2015

HBV and HCV treatment can reduce liver cancer risk

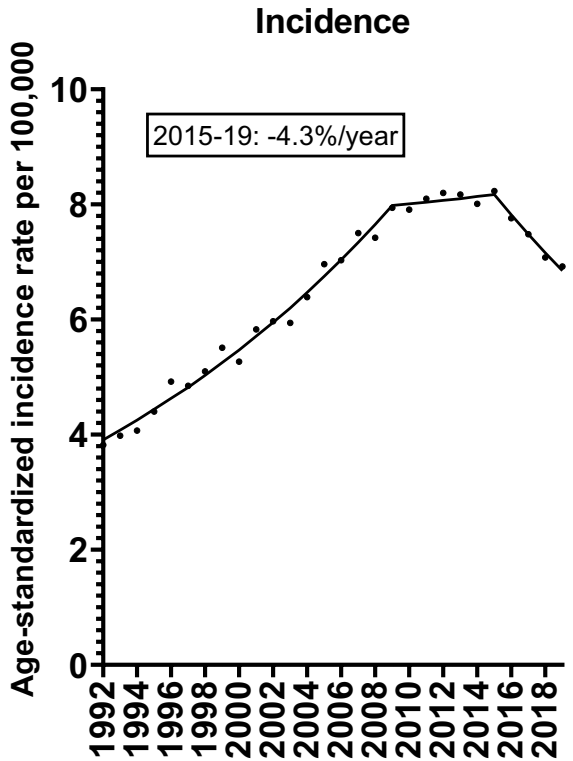
- HBV
  - Infant vaccination started in 1991
  - Treatments for chronic HBV can reduce liver cancer risk
- HCV
  - No HCV vaccination
  - Direct acting antiviral agents introduced in 2014 and are curative
- Increased HBV and HCV testing and treatment are needed

DAA treatment among those with chronic HCV



Thompson, MMWR 2022

Liver cancer rates have begun to decline, consistent with hepatitis treatment



Shiels et al., Cancer Disc 2023

Liver Cancer

Outcome	Potential intervention type	Opportunity?
Incidence	Risk factors	Increase uptake of HBV and HCV treatments, decrease smoking prevalence
Mortality	Screening (Early detection)	Increase cirrhosis diagnosis and screening uptake

Screening of people with cirrhosis

- No general population screening programs for liver cancer
- Surveillance of people with cirrhosis using ultrasound with or without alpha-fetoprotein measurements is recommended, and is associated with increased odds of having a transplant-eligible tumor
  - Cirrhosis precedes 80% of cases
  - 69% of individuals in the U.S. with cirrhosis are unaware of their diagnosis

Kim, Viral Hepat, 2019; Schillie MMWR 2020; Marrero, Hepatology 2018; Khalili, Can J Gastro Hep 2015

Next 9 leading causes of cancer death

	Most Recent Trend	
	Years	APC, 95% CI
Leukemia	2013-19	-2.28 (-2.70, -1.86)
Non-H	2005-19	-2.23 (-2.29, -2.17)
Brain		)
Urina		0)
Esophagus	2005-19	-1.10 (-1.25, -0.96)
Kidney	2015-19	-2.50 (-3.30, -1.70)
Ovary	2017-19	-4.33 (-7.28, -1.29)
Myeloma	2014-19	-2.08 (-2.85, -1.31)
Uterine Corpus	2008-19	1.85 (1.57, 2.14)

Progress in the prevention, early detection and treatment of these and less common cancers is critically important.

Limitations

- Projections rely on the assumption that recent changes will continue at the same rate without factoring in the relative importance of exposures, prevention, and treatment
- May be too optimistic if, for example, the prevalence of overweight and obesity accelerates in the coming years
- 50% decline in age-adjusted mortality rates does not correspond to a similar decline in the number of cancer deaths due to aging US population
  - 50% decline: 608,000 → 573,000 cancer deaths
  - No decline: 608,000 → 907,000 cancer deaths

Summary

- Accelerated progress will be needed to reach the Moonshot goal of a 50% reduction in cancer mortality rates by 2047
- In addition to continued innovation, substantial progress towards this goal could be accomplished by increasing use of what is already known to prevent, detect, and treat common cancers.
- Addressing underutilization of, and disparities in, access to prevention, screening, and treatment must play a central role

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