The potential benefits and harms of cancer screening: perspectives from the US Preventive Services Task Force

Mark H. Ebell MD, MS
Professor, University of Georgia,
Athens, Georgia, USA
2019 Fulbright Scholar at the HRB Primary Care Research Centre, RCSI, Dublin 2, Ireland

BIOSKETCH

- Family physician (GP) and Professor, University of Georgia (“UGA”), Athens, GA, USA
- Member US Preventive Services Task Force, 2012-2015
- Fulbright Scholar at HRB Centre for Primary Care Research, RCSI, 2019
- Editor-in-Chief, *Essential Evidence Plus*
- Research interests: clinical decision-making and decision support, meta-analysis, clinical prediction rules, cancer screening

UGA X and Hairy Dawg

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TODAY'S GOALS

- Comparing cancer screening in Ireland and the US
- A brief overview of how USPSTF recommendations are created
- Potential benefits and harms of cancer screening
- The importance of "overdiagnosis" and how to mitigate it

Lake Michigan, 2018

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“All screening programs do harm… some do good as well.”

- Sir Muir Gray

CANCER SCREENING: INTERNATIONAL COMPARISONS

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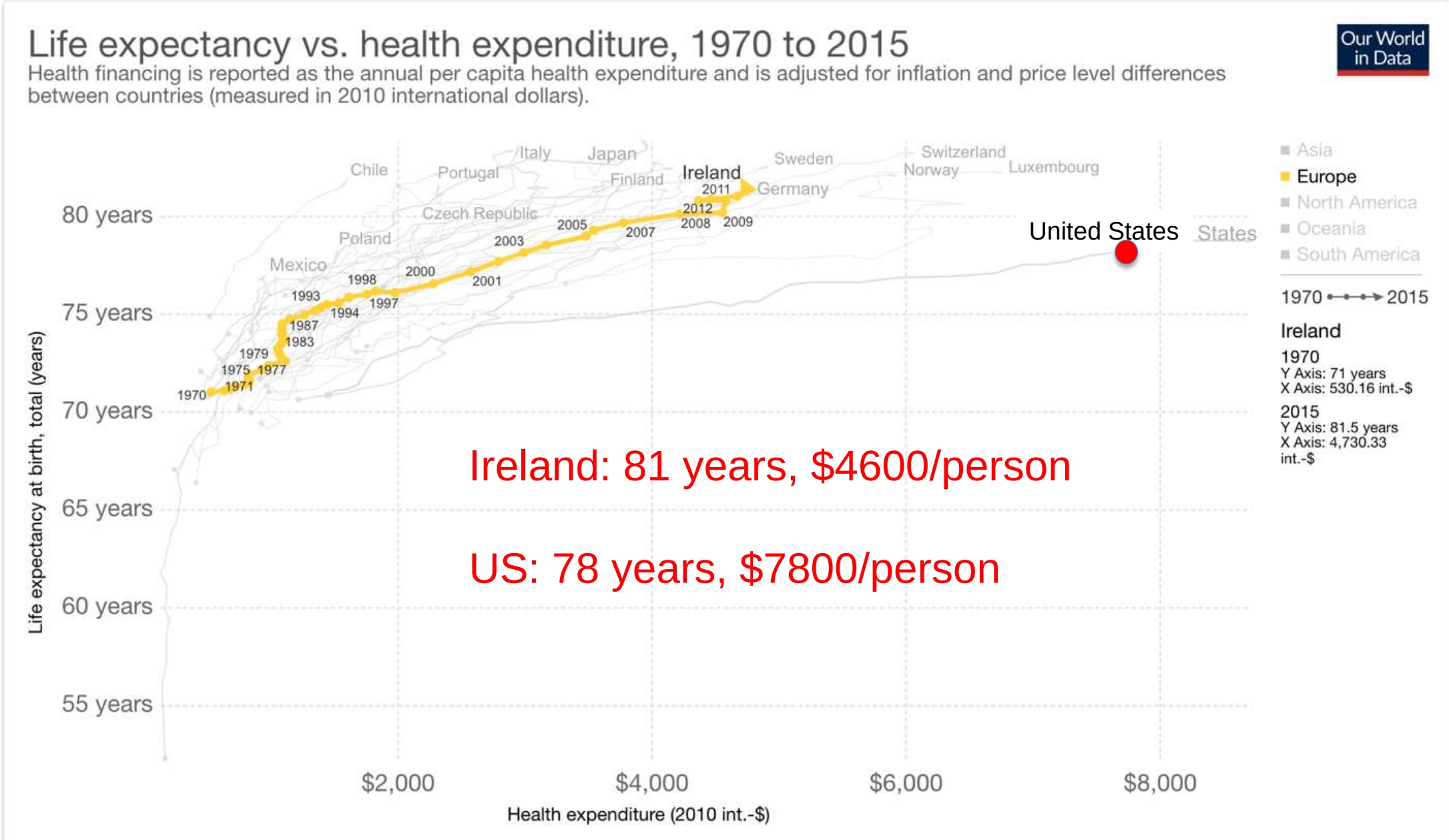
THE US AND IRISH HEALTH SYSTEMS COMPARED



SCREENING PROGRAMMES IN IRELAND AND US

Screening Program	Ireland	US
Breast cancer	50 - 69: mammography q 2 yrs	40 - 49: shared decision making 50 - 75: mammography q 2 yrs
Cervical cancer	25 - 44: cytology q 3 yrs 45 to 60: cytology q 5 yrs Reflex HPV testing if abnormal	21 - 29: cytology q 3 yrs 30 - 65: cytology + HPV or HPV alone q 5 yrs
Bowel cancer	60 - 69: stool based FIT q 2 yrs	50 - 75: any of 7 strategies, most opt for colonoscopy q 10 yrs
Prostate cancer	No national program	55 - 69: shared decision making
Lung cancer	No national program	50 - 80: annual low dose CT if 30+ pack years smoking

COMPARISON WITH OTHER DEVELOPED ECONOMIES: BREAST

Country	Organization (Type)	Year	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+
United States	US Preventive Services Task Force (A)	2016								
United States	American Cancer Society (B)	2015								*
United States[1]	American College of Obstetrics & Gynecology (C)	2017								*
United States	American College of Radiology (C)	2016								
Luxembourg	Ministry of Health (A)	NA								
Switzerland[2]	League Against Cancer (B)	2016								
Norway	Cancer Registry of Norway (B)	2010								
Netherlands[3]	NIPHE (A)	2017								
Germany	Federal Joint Committee (A)	2015								
Sweden[4]	National Board of Health and Welfare (A)	2013								
Ireland	National Screening Service (A)	NA								
Austria	Austrian Cancer Aid Society (B)	2014								
Denmark	National Board of Health (A)	2014								
Belgium	Foundation Against Cancer (B)	2017								
Canada[5]	CTFPHC (A)	2011								
Australia	Australian Government Department of Health (A)	2015								
France[6]	National Cancer Institute (A)	2015								
Japan[7]	National Cancer Center (A)	2016								
Iceland	Icelandic Cancer Society (B)	NA								
UK	UK National Screening Committee (A)	2012								
Finland	Cancer Society of Finland (B)	2010								
New Zealand	Ministry of Health (B)	2014								
Italy	National Screening Observatory (A)	2015								
Spain	Cancer Strategy of National Health System (A)	2009								

US

Ireland

Recommend:		Recommend selectively:		Do not recommend		Insufficient evidence:	
Every 3 years:		Every 2 years:		Every 1 year:			

Source: Ebell, et al. Public Health Rev. 2018 Mar 2;39:7. doi: 10.1186/s40985-018-0080-0.

KEY DIFFERENCES BETWEEN US AND IRELAND

Topic	United States	Ireland
General	Opportunistic, often not adherent to guidelines, overscreening common	Centrally organized, good adherence, little overscreening
General	11% of women 18-65 have no insurance	Free
General	More aggressive in terms of start and stop ages, interval	Later start and/or earlier stop
Colorectal	Colonoscopy every 10 years is dominant	Fecal immunochemical test
Lung cancer	Recommend low dose CT annually for persons 55-80 with 30+ pack years	Do not recommend
Prostate cancer	Shared decision-making for prostate CA screening age 55 - 69	Do not recommend

USPSTF AND ITS METHODS

THE US PREVENTIVE SERVICES TASK FORCE

- Established 1984 by US government and supported by HHS
- 16 primary care physicians (mostly) with expertise in screening, prevention, evidence based practice, guideline development
- Members have no financial conflict of interest
- Make recommendations regarding screening and primary prevention
- 70+ topics reviewed every 5-7 years

Sample Topics:

- Cancer screening
- Aspirin and statin use
- Lifestyle recommendations for prevention
- Behavioral health screening and counseling
- Cardiovascular screening and prevention
- Obstetrical care
- Infectious disease screening and prevention

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Step 1: Analytic framework → key questions

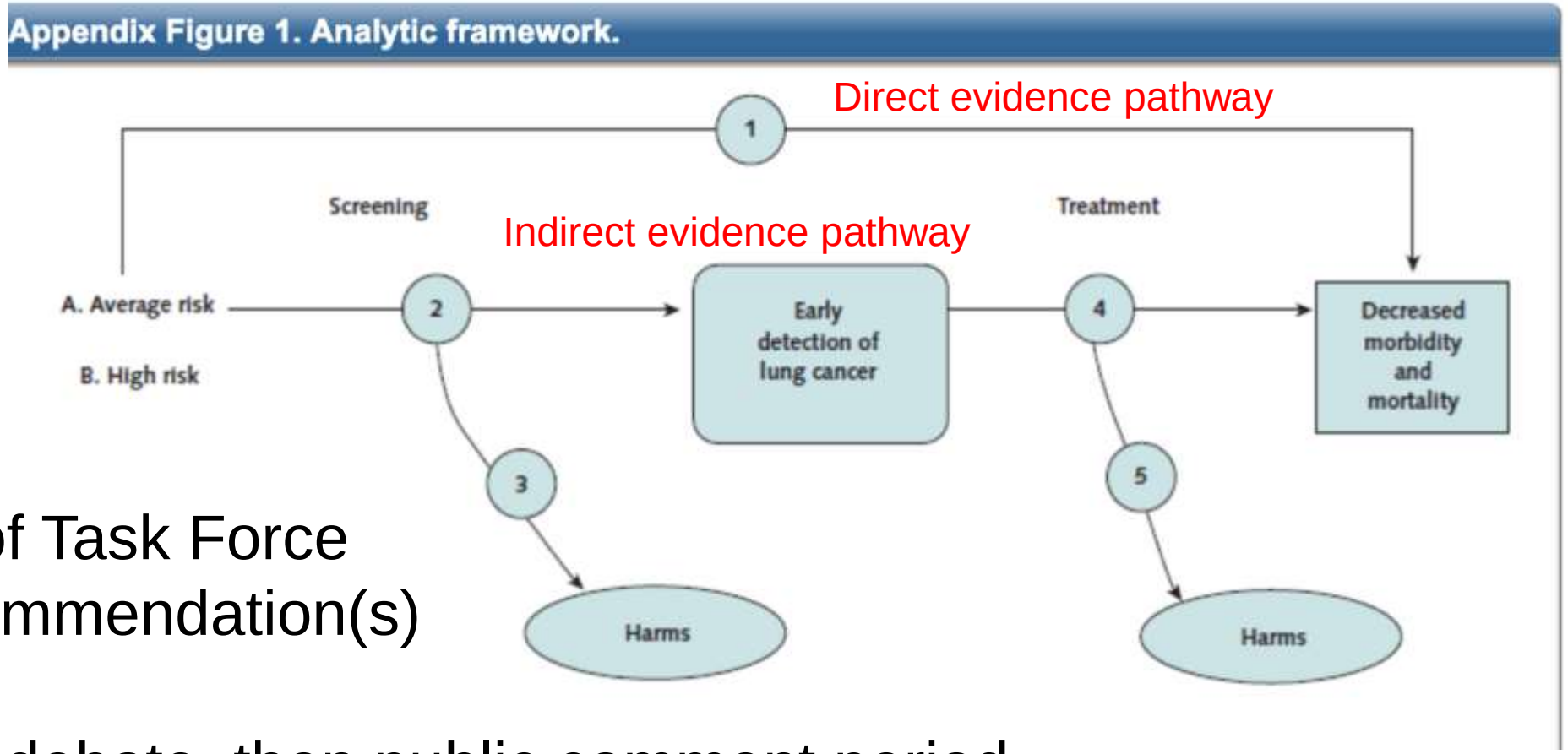
Step 2: Systematic reviews answer each key question

Step 3: Subgroup of Task Force develops draft recommendation(s)

Step 4: Task Force debate, then public comment period

Step 5: Final recommendation(s) published and disseminated

Sample Analytic Framework: Lung Cancer Screening



GRADE IS ASSIGNED TO EACH RECOMMENDATION

	Degree of Certainty	Net Benefit (benefit minus harm)	Suggestion for Practice
A	High certainty	Substantial	Offer or provide service
B	Moderate to high certainty	Moderate to substantial	Offer or provide service
C	Moderate certainty	Small or variable	Shared decision-making
D	Moderate to high certainty	None or net harm	Do not offer or provide
I	Low certainty	Unknown	Variable

Population	Recommendation	Grade (What's This?)
Women aged 21 to 65 years	The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women aged 21 to 29 years. For women aged 30 to 65 years, the USPSTF recommends screening every 3 years with cervical cytology alone, every 5 years with high-risk human papillomavirus (hrHPV) testing alone, or every 5 years with hrHPV testing in combination with cytology (cotesting). See the Clinical Considerations section for the relative benefits and harms of alternative screening strategies for women 21 years or older.	A
Women older than 65 years	The USPSTF recommends against screening for cervical cancer in women older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. See the Clinical Considerations section for discussion of adequate prior screening and risk factors that support screening after age 65 years.	D
Women younger than 21 years	The USPSTF recommends against screening for cervical cancer in women younger than 21 years.	D
Women who have had a hysterectomy	The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (ie, cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer.	D

EXAMPLE: CERVICAL CANCER SCREENING

From Affordable Care Act ("ObamaCare"):

"…a health insurance issuer …shall provide coverage for and shall not impose any cost sharing requirements for evidence-based items or services that have a rating of A or B in the current recommendations of the USPSTF".

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WEIGHING POTENTIAL BENEFITS AND HARMS

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POTENTIAL BENEFITS AND HARMS OF SCREENING

Key point: we are doing something to a perfectly healthy, happy person. We have to be very certain that on average, the **potential benefits clearly outweigh the potential harms**.

Potential benefits

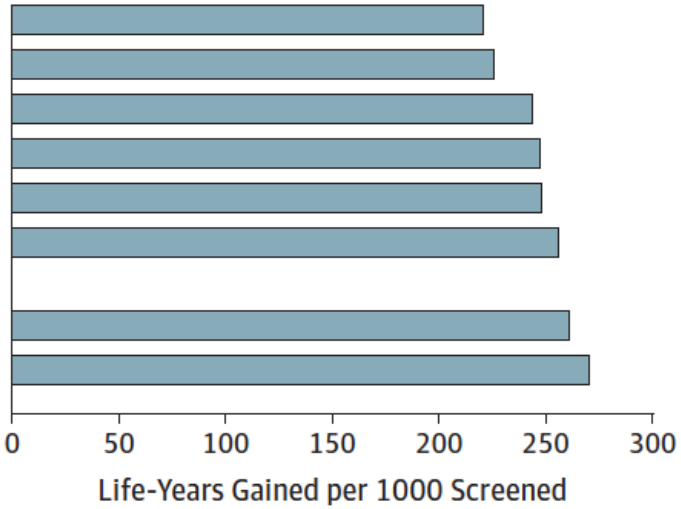
- Reduced disease-specific mortality
- Reduced all-cause mortality
- Reduced morbidity (treatment of early disease may have less harm than treatment of late disease)

Potential harms

- Direct harm (e.g. pain, radiation)
- Harm of downstream tests (e.g. biopsies)
- Worry (false positives → “cancer scares”)
- Cost
- Unintended behavior change (i.e. lung CA screening and smoking)
- Overdiagnosis (more on that later…)

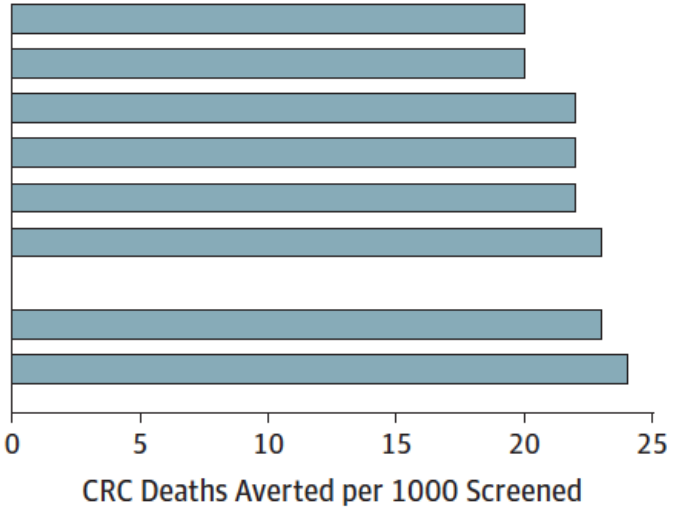
A Benefit: Life-years gained per 1000 individuals screened

Screening Method and Frequency	Model Estimates, Life-Years Gained per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	221	181	227
FIT-DNA every 3 y	226	215	250
FIT every year[a]	244	231	260
HSgFOBT every year	247	232	261
CT colonography every 5 y[b]	248	226	265
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	256	246	270
FIT-DNA every year	261	246	271
Colonoscopy every 10 y[a]	270	248	275



B Benefit: Colorectal cancer deaths averted per 1000 individuals screened

Screening Method and Frequency	Model Estimates, CRC Deaths Averted per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	20	17	21
FIT-DNA every 3 y	20	19	22
FIT every year[a]	22	20	23
HSgFOBT every year	22	20	23
CT colonography every 5 y[b]	22	20	24
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	23	22	24
FIT-DNA every year	23	22	24
Colonoscopy every 10 y[a]	24	22	24



BOWEL SCREENING POTENTIAL BENEFITS:

221 TO 270 LIFE-YEARS GAINED, AND 20 TO 24 DEATHS AVERTED, PER 1000 PERSONS SCREENED.

OR

~ 2 DEATHS PER 100 SCREENED AVERTED, ADDING 11 YEARS OF LIFE PER PERSON

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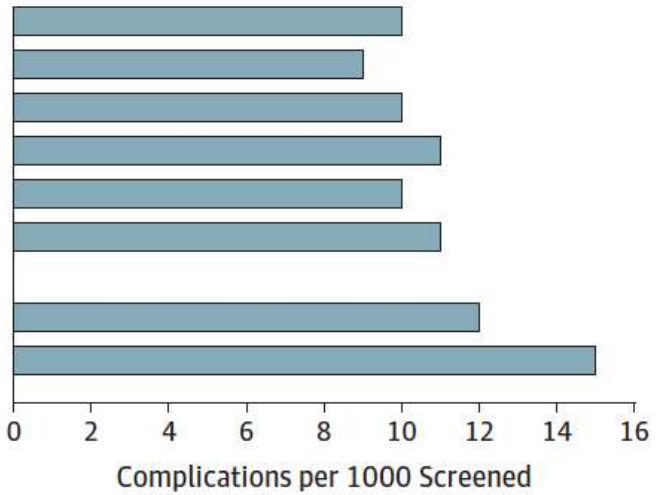
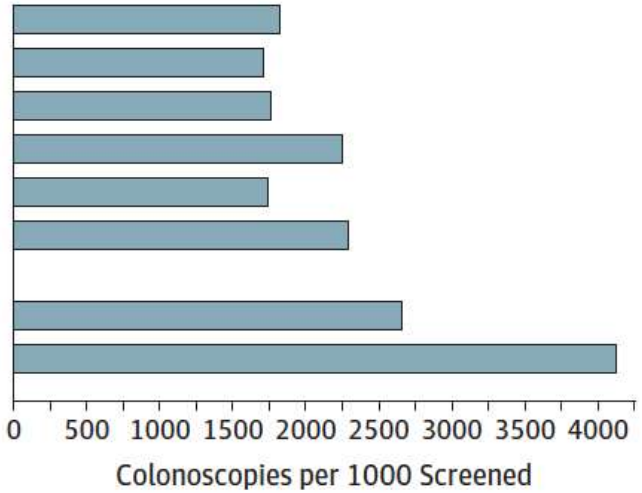
C Harms: Complications (gastrointestinal and cardiovascular events) of colorectal cancer screening and follow-up testing per 1000 individuals screened[c]

Screening Method and Frequency	Model Estimates, Complications per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	10	9	12
FIT-DNA every 3 y	9	9	10
FIT every year[a]	10	10	11
HSgFOBT every year	11	11	11
CT colonography every 5 y[b]	10	10	11
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	11	11	12
FIT-DNA every year	12	12	13
Colonoscopy every 10 y[a]	15	14	15



D Burden: Lifetime No. of colonoscopies per 1000 individuals screened

Screening Method and Frequency	Model Estimates, Lifetime Colonoscopies per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	1820	1493	2287
FIT-DNA every 3 y	1714	1701	1827
FIT every year[a]	1757	1739	1899
HSgFOBT every year	2253	2230	2287
CT colonography every 5 y[b]	1743	1654	1927
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	2289	2248	2490
FIT-DNA every year	2662	2601	2729
Colonoscopy every 10 y[a]	4049	4007	4101



Bowel Screening Potential harms:

Range of 1.7 to 4.1 colonoscopies/person and 0.9 – 1.5 serious complication/100 persons screened

Most harms with colonoscopy based strategies

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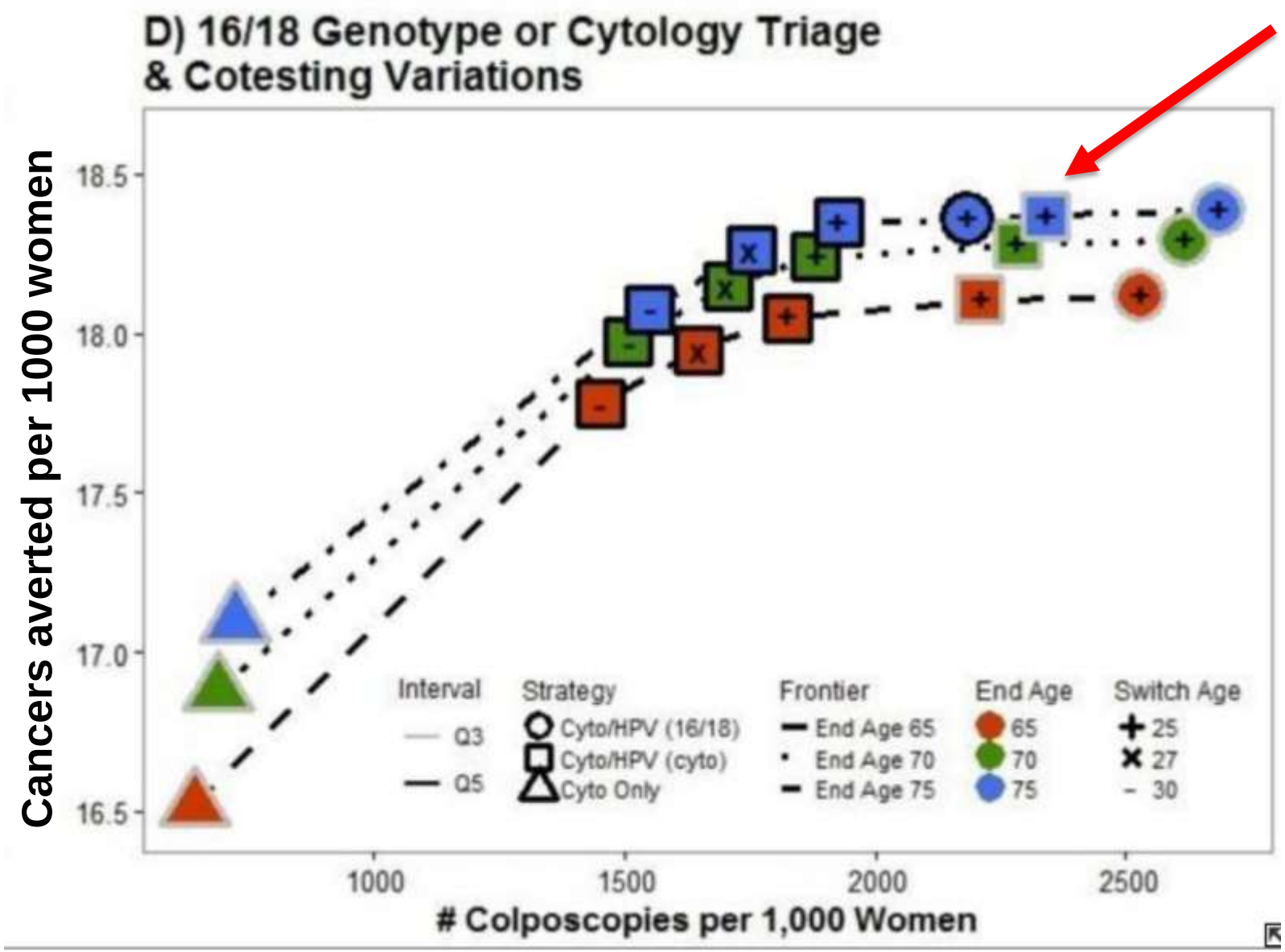
BALANCING BENEFITS AND HARMS: CERVICAL CANCER



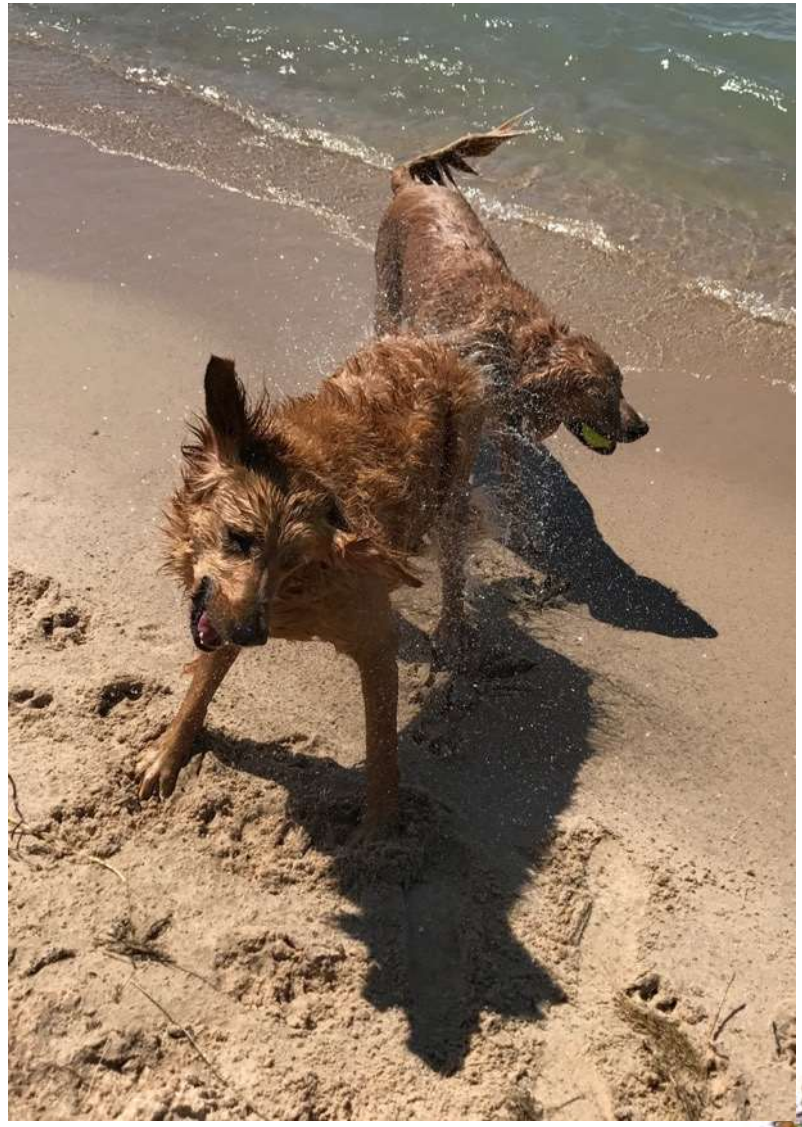
”Flat of the curve” medicine: q3 rather than q5 year interval increases burden and cost with no increase in benefit

Important point: more screening is not always a net good, with diminishing returns and increasing harms as it intensifies

Source: Kim JJ, et al. Evidence Syntheses, No. 158s. Rockville, MD: Agency for Healthcare Research and Quality (US); 2018 Aug.

HOW DO WE MEASURE BENEFIT?

- Survival from time of diagnosis, i.e.
  5 year survival?
- All-cause mortality, i.e.
  Deaths/100,000/year?
- Disease specific mortality, i.e.
  Cervical cancer deaths/100,000/year?



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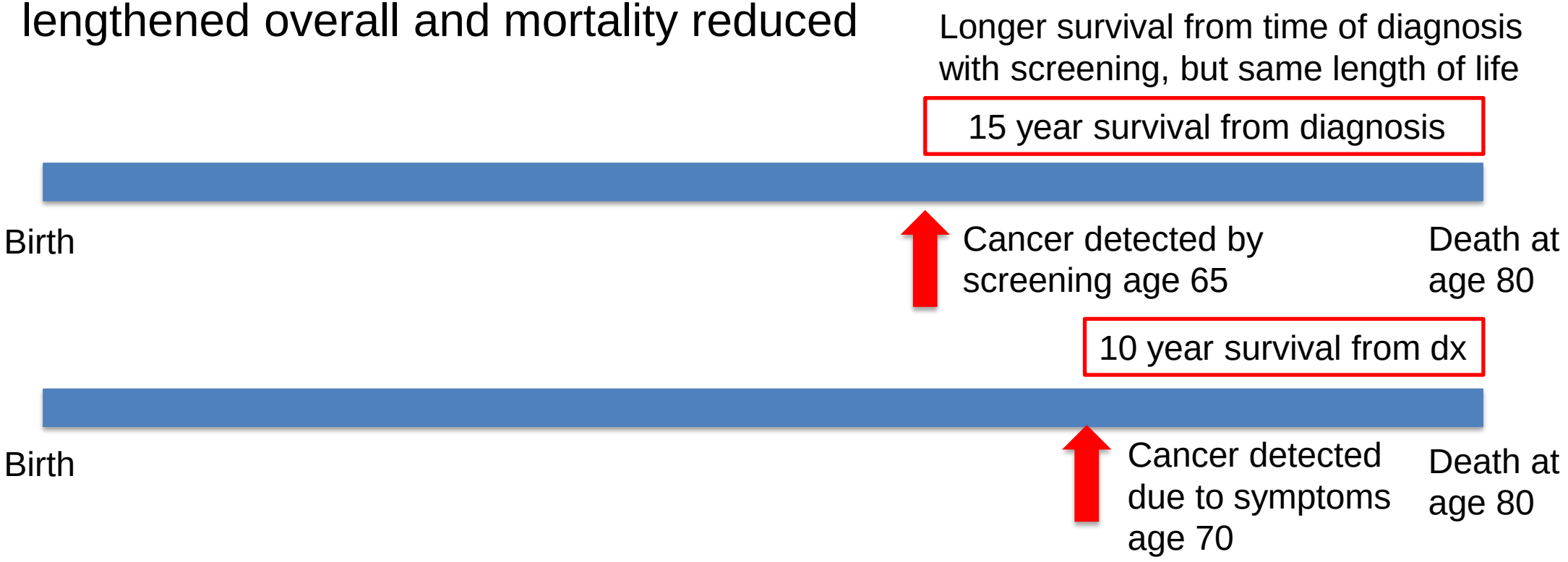
AN ILLUSORY BENEFIT: LONGER SURVIVAL FROM DIAGNOSIS

- Screening almost always increases survival from the time of diagnosis
- But that is due to earlier detection, and is not a benefit unless life is lengthened overall and mortality reduced



Lesson: measure benefit of a screening program using mortality reduction, not increase in survival from diagnosis (i.e. 5 year survival) or shift to earlier stage

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SHOULD WE INSIST THAT SCREENING PROGRAMS REDUCE ALL-CAUSE MORTALITY?

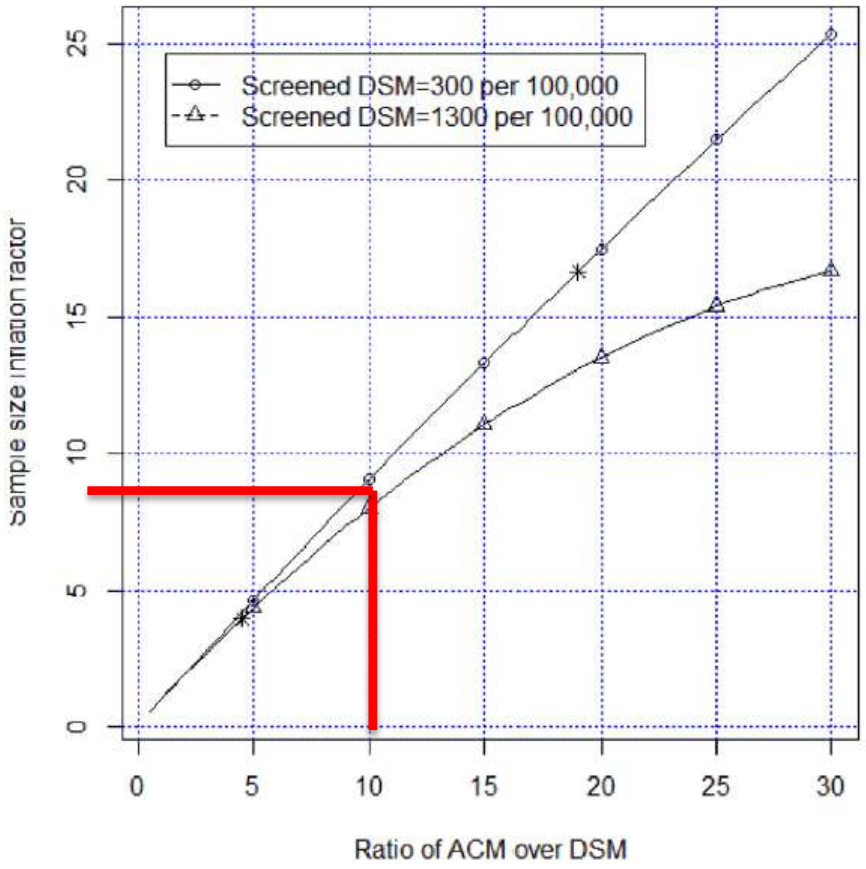

Figure 1. Sample-size inflation factors based on 90% power to detect a difference at the 0.05 level.[a]

- If 10 year all-cause mortality for a population of 65 year old women is 15%, but breast cancer mortality is only 1.5%, then the ratio of all cause to disease specific mortality is 10
- From our graph, one would need about 8 times as large a study to prove lower all-cause mortality, compared to what you would need to prove lower breast cancer specific mortality
- Larger relative risk reduction with disease-specific mortality is easier to prove

Dobbin K, Ebell M. Should we expect all-cause mortality reductions in large screening studies? Br J Gen Pract 2018

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SHOULD WE INSIST THAT SCREENING PROGRAMS REDUCE ALL-CAUSE MORTALITY?

Screening program	Mortality reduction	Fewer deaths/ 100,000 screened	Confidence interval
Breast cancer (AGE study)	Disease	47	(-14 to 108)
	All-cause	92	(-110 to 294)
Lung cancer (NLST study)	Disease	312	(106 to 518)
	All-cause	456	(18 to 896)
Ovarian cancer (UKCTOCS)	Disease	50	(-9 to 109)
	All-cause	-98	(-353 to 167)

In the absence of such gigantic studies, we should at least be sure the direction of mortality is the same for all cause and disease specific.

Ovarian CA mortality down, all-cause up (worrisome)

Source: Dobbin K, Ebell M. Should we expect all-cause mortality reductions in large screening studies? Br J Gen Pract 2018

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HOW DO WE MEASURE BENEFIT?

- ~~Survival from time of diagnosis, i.e. 5 year survival~~

  No!

- All-cause mortality, i.e. deaths/100,000/year

  Ideal, often not possible, should at least be in same direction

- Disease specific mortality, i.e. Cervical cancer deaths/100,000/year

  Usually the best option

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A NEWLY RECOGNIZED HARM: OVERDIAGNOSIS

OVERDIAGNOSIS: AN IMPORTANT SOURCE OF HARM

Study of trauma victims in Detroit, 1996, showing rates of small foci of prostate cancer by age and race:

Age	African-American	Caucasian
20-29	8%	8%
30-39	31%	31%
40-49	43%	37%
50-59	46%	44%
60-69	70%	65%
70-79	81%	83%

Source: Sakr WA, et al. Age and racial distribution of prostatic intraepithelial neoplasia. Eur Urol. 1996; 30(2):138-44.

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Old thinking: precancerous lesion → symptomatic cancer → death

Only paths where screening is beneficial

New thinking: several possible paths

1. Cancer progresses very rapidly (*melanoma, pancreatic*) or may metastasize early (*ovarian*)
2. Cancer progresses more slowly, and cancers detected by screening have a more favorable outcomes than cancers detected later due to symptoms (*many breast, lung cancers*)
3. Cancer progresses more slowly and would be amenable to better outcomes with earlier treatment (like #2), but something else causes death (*lung cancer patient dies of other smoking complications*)
4. Cancer progresses very slowly, is detected by screening, but would never have caused symptoms (*overdiagnosed prostate, lung, or breast cancer*)
5. Precancerous lesion's removal prevents cancer (*cervical, colorectal*)
6. Precancerous or early stage lesions regress without therapy (*cervical, neuroblastoma*)

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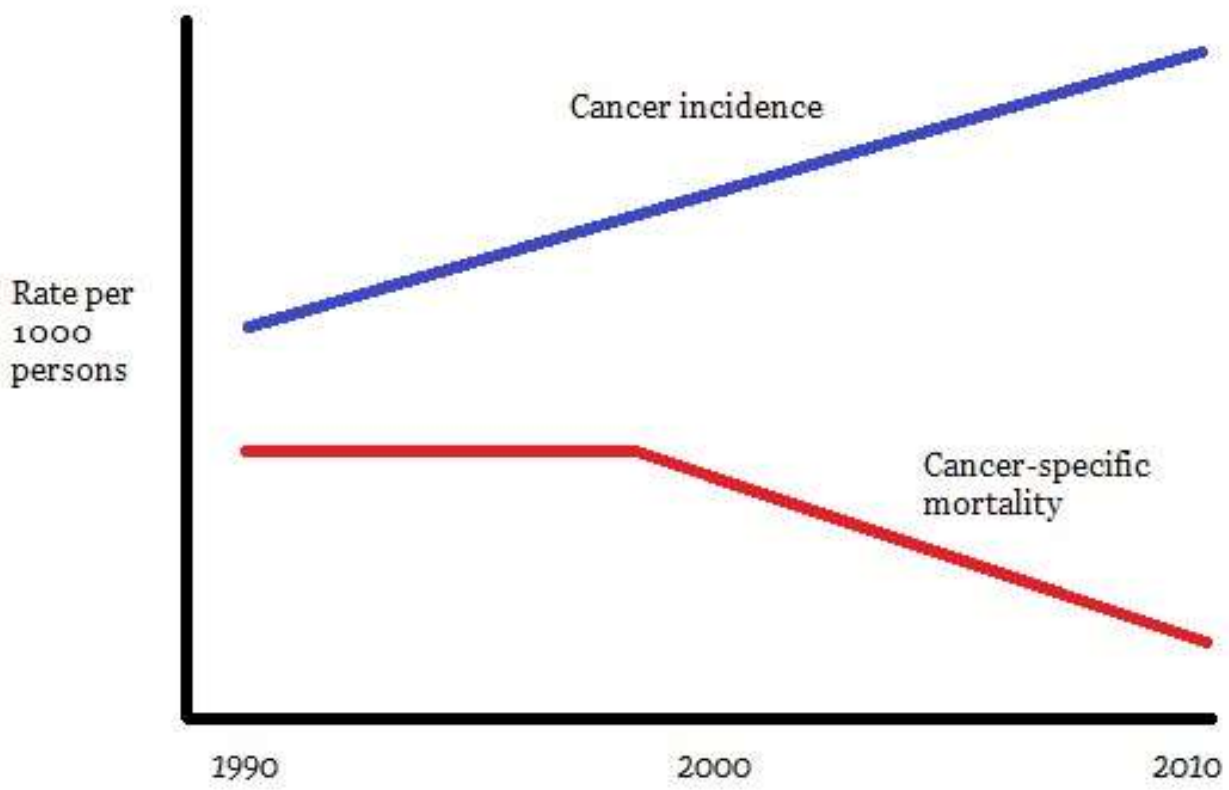
DETECTING OVERDIAGNOSIS: EFFECTIVE PROGRAM



- We begin a cancer screening program in 1990.
- We detect more cancer than before (increased incidence)
- After a few years, mortality due to that cancer begins to decline.

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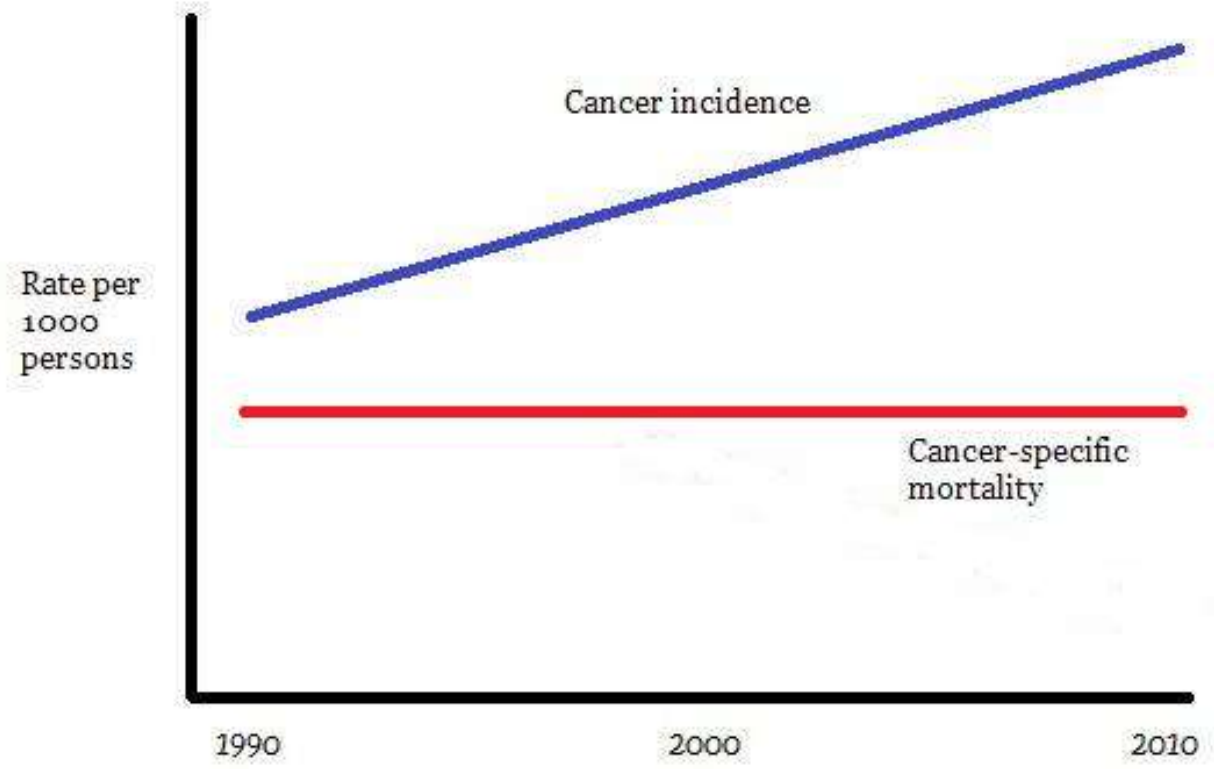
DETECTING OVERDIAGNOSIS: INEFFECTIVE PROGRAM



- We begin a cancer screening program in 1990.
- We detect more cancer than before (increased incidence)
- However, mortality remains unchanged

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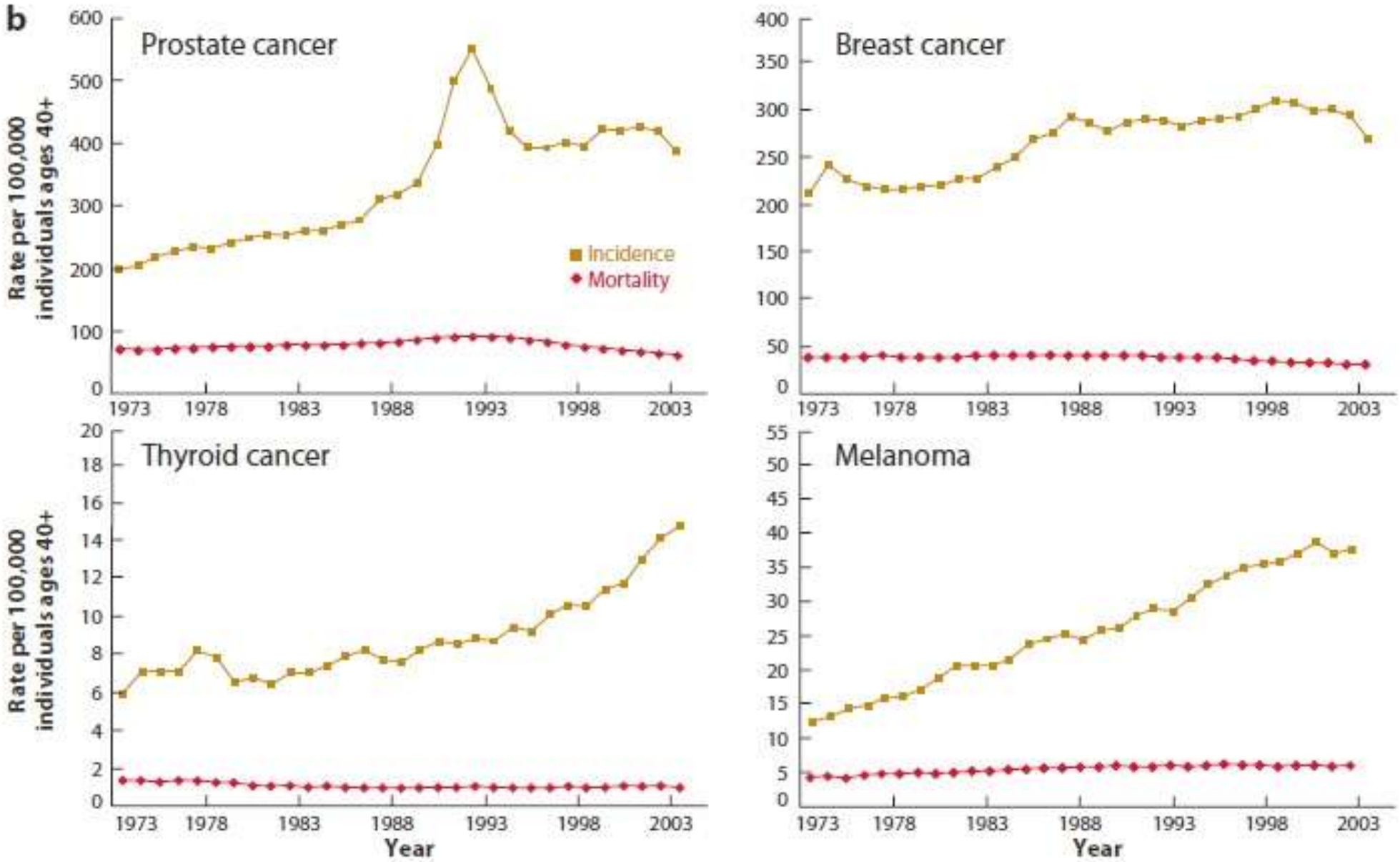

Source: Kramer BS, Croswell JM. Cancer Screening: The clash of science and intuition. Annu. Rev. Med. 2009. 60:125–37

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INCIDENCE AND MORTALITY

Example 1: mix of indolent and aggressive cancer; increasing incidence

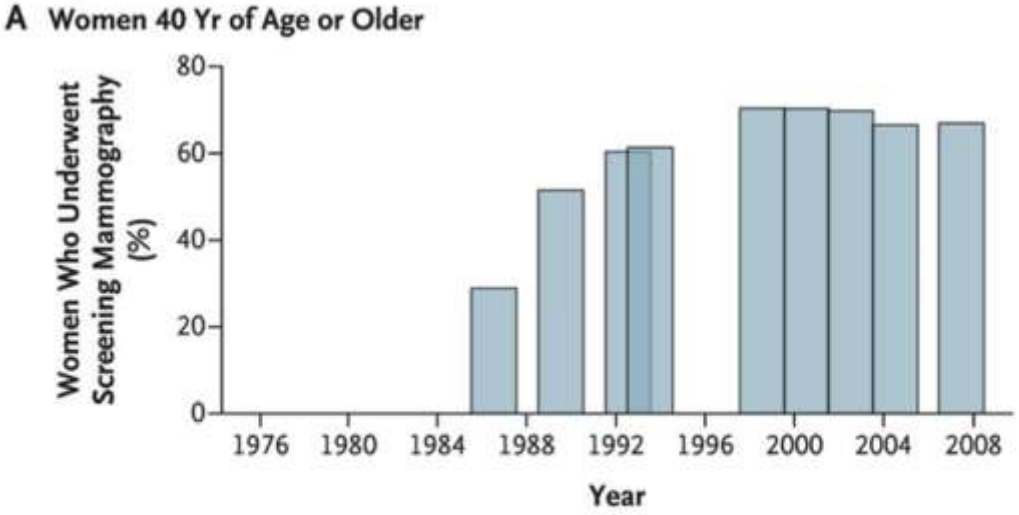
Example 2: removal of pre-cancerous lesions leading to decreased incidence and mortality

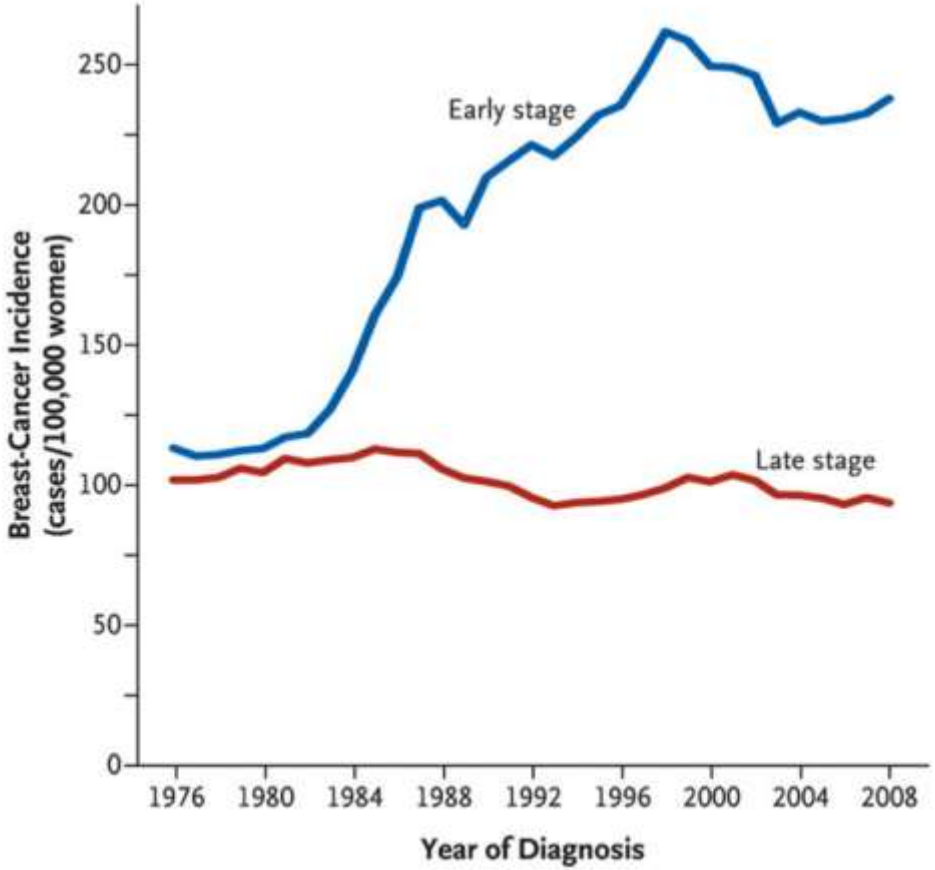
Example 3: rampant overdiagnosis with large increase in incidence and no effect on mortality

Source: Esserman L, et al. Overdiagnosis and Overtreatment in Cancer An Opportunity for Improvement. JAMA 2013; 310(8):797-798

Table. Change in Incidence and Mortality of Cancers Over Time From 1975 to 2010 as Reported in Surveillance, Epidemiology and End Results[1]

	Incidence			Mortality		
	Per 100 000		%	Per 100 000		%
Change[a]	1975	2010[b]	Change	1975	2010[b]	Change
Example 1						
Breast[c]	105.07	126.02	20	31.45	21.92	−30
Prostate	94	145.12	54	30.97	21.81	−30
Lung and bronchus[d]	52.26	56.68	8	42.56	47.42	11
Example 2						
Colon	41.35	28.72	−31	28.09	15.51	−45
Cervical	14.79	6.71	−55	5.55	2.26	−59
Example 3						
Thyroid	4.85	13.83	185	0.55	0.51	−7
Melanoma	7.89	23.57	199	2.07	2.74	32





Overdiagnosis in Breast Cancer Screening?
Data from large US cancer registry (CDC)

Top graph: widespread mammography for women in 40's began in mid 1980's

Bottom graph: Large jump in incidence of early stage cancer: from 112 to 234 cases/100,000/year (blue line)

But by now, we should have seen similar decline in late stage cancer. But, we have not: late stage only decreased from 102 to 94 cases/ 100,000/year (red line)

Source: Bleyer and Welch, N Engl J Med 2013; 367: 1998

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HOW MUCH OVERDIAGNOSIS?

- Rates of overdiagnosis for different screening programs
  - Breast cancer: 20% to 30%
  - Prostate cancer: 30% to 50%
  - Lung cancer: 20%
  - Colorectal and cervical cancer: ??
- Overdiagnosis is more common:
  - In older patients, who have more competing causes of mortality, and less time for cancer to progress and cause harm
  - With shorter intervals between tests, earlier start age, later stop age (more aggressive screening)

Source: Overdiagnosis in Prostate Cancer Screening Decision Models: A Contextual Review for the U.S. Preventive Services Task Force. AHRQ Publication No. 17-05229-EF-3 April 2017

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STRATEGIES TO REDUCE OVERDIAGNOSIS

1. Do not screen asymptomatic persons in the absence of RCT evidence of reduced mortality and acceptable harms
2. Do not screen too often (i.e. annual mammogram) or too long (i.e. 80 years old)
3. Re-name words like carcinoma and neoplasia to something less scary:
   - Ductal carcinoma in situ or high-grade prostatic intraepithelial neoplasia or precursor pancreatic lesion → IDLE (indolent lesion of epithelial origin)
4. Develop better protocols and standards for evaluating incidentalomas (i.e. TI-RADS for thyroid lesions)
5. Develop better biomarkers and prognostic models to separate truly aggressive cancers from indolent cancers

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STRATEGIES TO REDUCE OVERDIAGNOSIS

6. Consider active surveillance rather than immediate aggressive therapy
   - Standard of care for many prostate cancers, but variable uptake
   - Trials underway for active surveillance of DCIS, thyroid lesions

Low-Risk Cancers for Which Active Surveillance Is or Could Be a Treatment Option.

Type of Cancer	Median Age at Diagnosis (yr)	Sex of Affected Patients	Intensive Treatment Option	Risks Associated with Intensive Treatment	Active Surveillance Option	Physician in Charge	Stage of Adoption
Prostate	66	100% male	Radical prostatectomy or radiation	Impotence and incontinence	Prostate exam; prostate-specific antigen testing; biopsy	Urologist	In practice
Thyroid	51	75% female, 25% male	Total thyroidectomy, with or without lymph-node resection and radioactive iodine	Permanent change in voice and permanent low calcium levels	Neck ultrasound and testing of serum thyroglobulin	Endocrinologist	In trials
Breast (DCIS)	62	Nearly 100% female	Mastectomy or lumpectomy with radiation	Surgical complications and lymphedema	Mammography	Unclear	In discussion

Source: Haymart, et al. Active Surveillance for Low-Risk Cancers — A Viable Solution to Overtreatment? N Engl J Med 2017; 377:203-206

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LESSONS LEARNED

- An evidence-based, transparent, public process free of conflict of interest helps create guidelines you can trust.
- Health systems should determine optimal screening strategies based on a balance of benefits, harms, and available resources
- Randomized trials measuring mortality provide the best evidence regarding the benefit of screening programs
- Overdiagnosis is an most important harm, but is poorly understand by physicians and patients
- Strategies (and more research) are needed to mitigate the harms of overdiagnosis

Inisheer, October 2018

THANK YOU! QUESTIONS?

Inisheer, October 2018

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CANCER SCREENING PROGRAMMES IN IRELAND

Cancer Services

BreastCheck: mammography every 2 years for women 50 to 64 years, increasing to 69 by 2021

CervicalCheck: Pap smear every 3 years for women age 25 to 44, every 5 years age 45 to 60 years, with reflex to HPV testing if abnormal

BowelScreen: men and women age 60 to 69 years with a fecal immunochemical test (FIT) done at home every two years

Source: https://www.hse.ie/eng/services/list/5/cancer/patient/screen/screening.html

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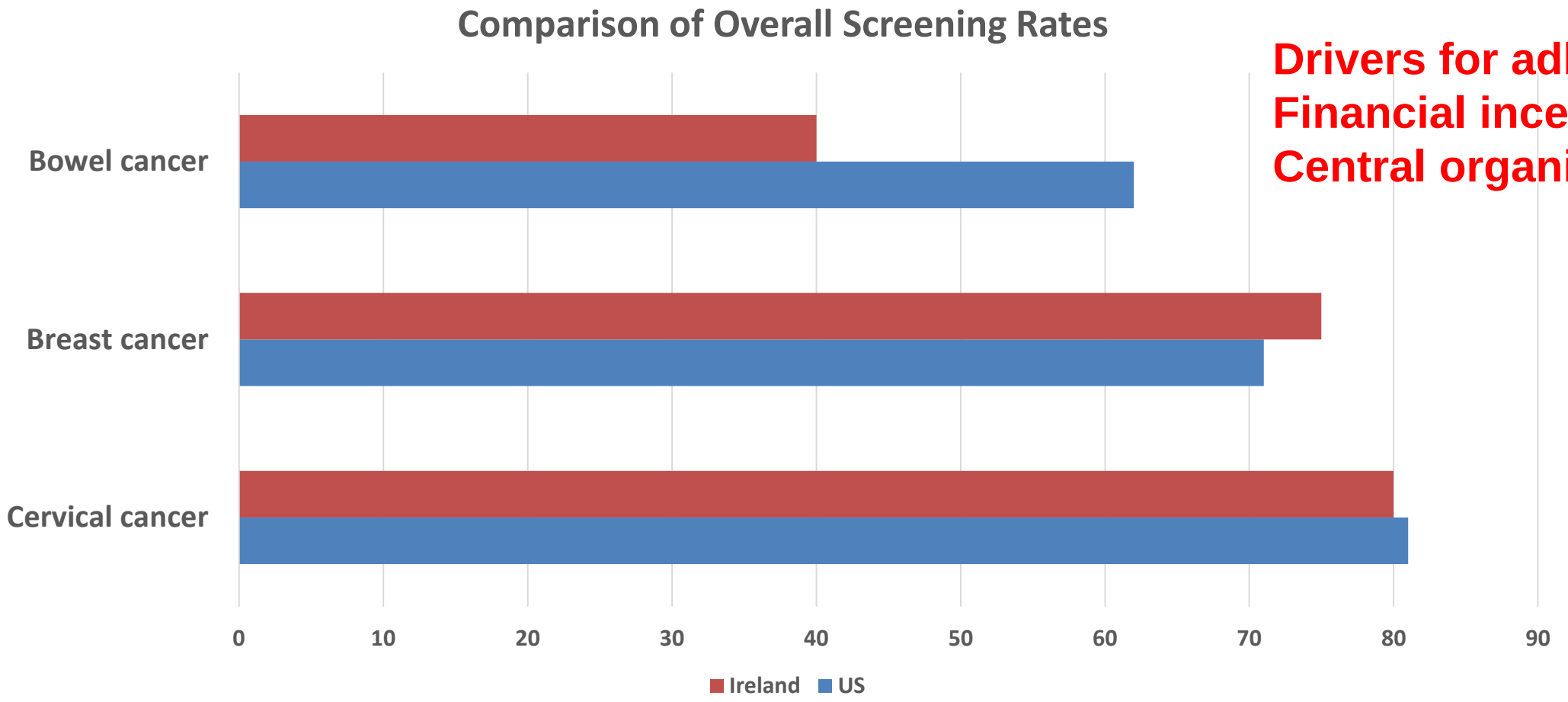
ADHERENCE TO CANCER SCREENING IN US VS IRELAND



Drivers for adherence:
Financial incentives vs.
Central organization

Source: 2015/2016 Annual Reports of BreastCheck, CervicalCheck and BowelScreen Programs; CDC, Patterns and Trends in Cancer Screening in the US, https://www.cdc.gov/pcd/issues/2018/17_0465.htm

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Country	Organization (Type)	Year	Test	10-19	20-29	30-39	40-49	50-59	60-69	70-79
United States[1]	US Preventive Services Task Force (A)	2012	Cyt							
United States[1]	US Preventive Services Task Force (A)	2012	Cyt+HPV							
United States[1]	US Preventive Services Task Force draft (A)	2017	Cyt							
United States[1]	US Preventive Services Task Force draft (A)	2017	HPV							
Switzerland[2]	League Against Cancer (B)	2010	Cyt							
Norway[3]	Cancer Registry of Norway (B)	2010	Cyt							
Norway[3]	Cancer Registry of Norway (B)	2010	HPV							
Netherlands[4]	NIPHE (A)	2015	Cyt							
Germany[5]	Federal Joint Committee (A)	2015	Cyt							
Sweden[6]	National Board of Health and Welfare (A)	2014	Cyt							
Sweden[6]	National Board of Health and Welfare (A)	2014	HPV							
Ireland[7]	National Screening Service (A)	2009	Cyt							
Austria[8]	Austrian Cancer Aid Society (B)	NR	Cyt							
Denmark[9]	National Board of Health (A)	2014	Cyt							
Denmark[9]	National Board of Health (A)	2014	HPV							
Belgium[10]	Foundation Against Cancer (B)	2017	Cyt							
Canada	CTFPHC (A)	2013	Cyt							
Australia[11]	Australian Government Department of Health (A)	2017	Cyt							
Australia[11]	Australian Government Department of Health (A)	2017	HPV							
France[12]	National Cancer Institute (A)	2017	Cyt							
Japan[13]	National Cancer Center (A)	2010	Cyt							
Japan[13]	National Cancer Center (A)	2010	HPV							
Japan[13]	National Cancer Center (A)	2010	Cyt+HPV							
Japan[13]	National Cancer Center (A)	2010	HPV with cyt triage							
Iceland[14]	Icelandic Cancer Society (B)	NR	Cyt							
UK[15]	UKK National Screening Committee (A)	2016	HPV							
Finland[16]	Cancer Society of Finland (B)	2010	Cyt or HPV							
New Zealand[17]	Ministry of Health (B)	2014	Cyt							
Italy[18]	National Screening Observatory (A)	2015	Cyt							
Spain[19]	Cancer Strategy of National Health System (A)	2009	Cyt							

Recommend:		Recommend selectively:		Do not recommend	Insufficient evidence:
Every 7 years:		Every 5 years:		Every 3 years:	
Every 2 years:		Every year:		No interval specified:	

US

Ireland

CERVICAL SCREENING PROGRAMMES

Source: Ebell, et al. Public Health Rev. 2018 Mar 2;39:7. doi: 10.1186/s40985-018-0080-0.

COMPARISON WITH OTHER DEVELOPED ECONOMIES: BOWEL

Country	Organization (Type)	Year*	Type of Test	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+
United States	USPSTF (A)	2016	FIT[a]								
United States	USPSTF (A)	2016	Colonoscopy[a]								
United States	American Cancer Society (B)	2017	Colonoscopy[a]								
United States	ACG (C)	2017	Colonoscopy								
Luxembourg	Ministry of Health (A)	2016	FIT								
Switzerland	League Against Cancer (B)	2013	FIT or gFOBT[b]								
Norway	Cancer Registry of Norway (B)	2012	FIT[c]								
Netherlands	NIPHE (A)	2014	FIT								
Germany	Federal Joint Committee (A)	2017	FIT[d]								
Sweden	NBHW (A)	2014	gFOBT								
Ireland	National Screening Service (A)	2012	FIT								
Austria	Austrian Cancer Care (B)	N/A	FIT[e]								
Denmark	National Board of Health (A)	2014	FIT								
Belgium	Foundation Against Cancer (B)	2016	FIT								
Canada	CTFPHC (A)	2016	FIT or gFOBT[f]								
Australia	AGDH (A)	2016	FIT or gFOBT								
France	Institut National Du Cancer (A)	2015	FIT								
Japan	National Cancer Center (A)	2016	FIT								
Iceland	Icelandic Cancer Society (B)	2015	FIT								
United Kingdom	UK National Screening Committee (A)	2016	FIT								
Finland	Cancer Society of Finland (B)	2010	gFOBT								
New Zealand	Ministry of Health (A)	2017	FIT								
Italy	National Screening Observatory (A)	2015	FIT[g]								
Spain	CSNHS (A)	2009	FIT								

Source: Ebell, et al. Public Health Rev. 2018 Mar 2;39:7. doi: 10.1186/s40985-018-0080-0.