

Updates in Cancer Screening (and pharmacologic prevention) 2020

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**...and I have no
disclosures**



The daunting screening agenda

First list:

Hypertension
Hypercholesterolemia
Colon cancer
Cervical cancer
Breast cancer
Prostate cancer
Lung cancer
Hep C
Diabetes
HIV
STDs
Skin cancer

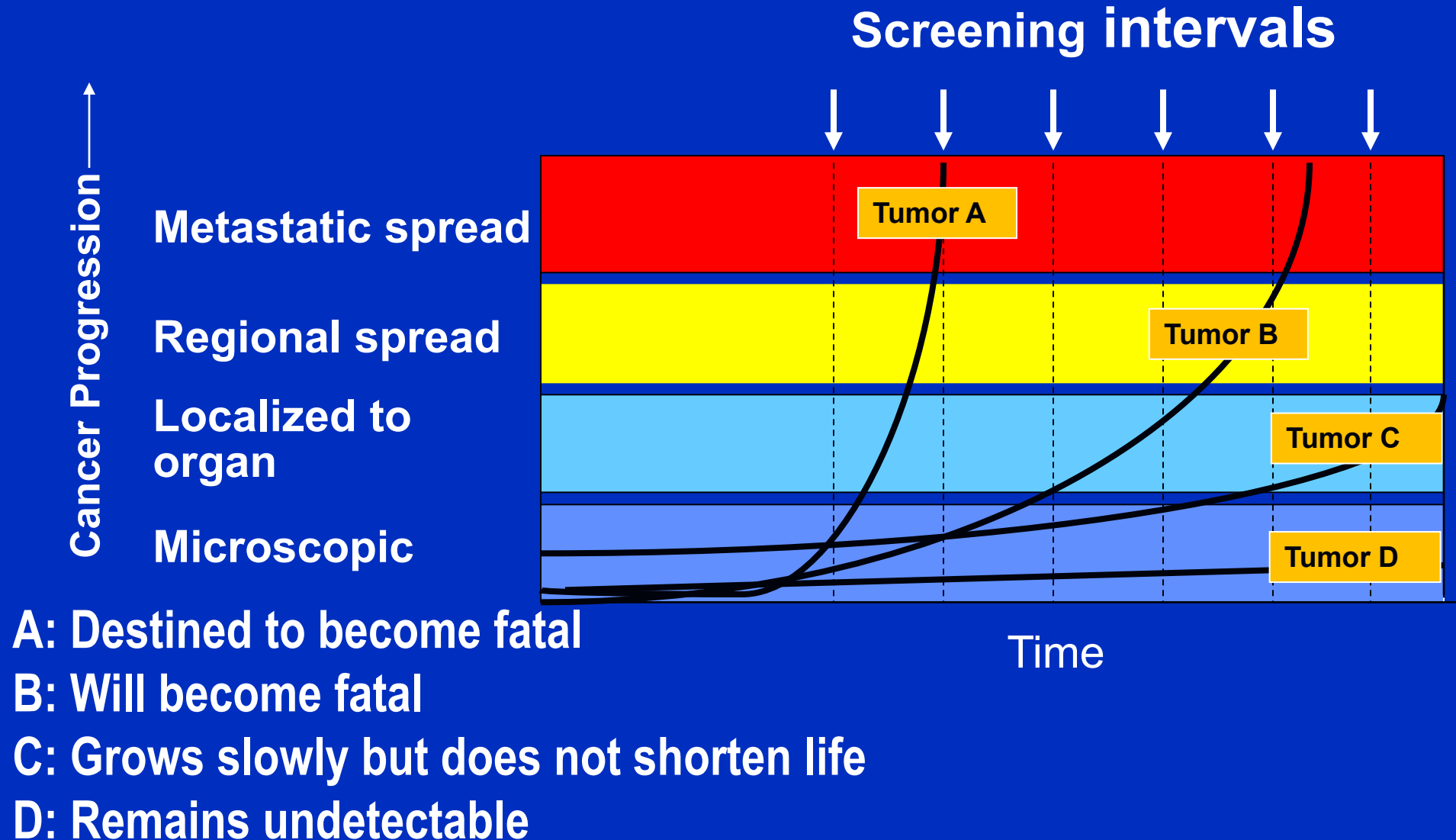
Second list:

Alcohol abuse
Obesity
Visual impairment
Hearing impairment
Balance
Injury
Opioids
Hypothyroidism
Osteoporosis
Depression
Abdominal Aortic Aneurism
for men at risk

Cancer screening: Key challenges

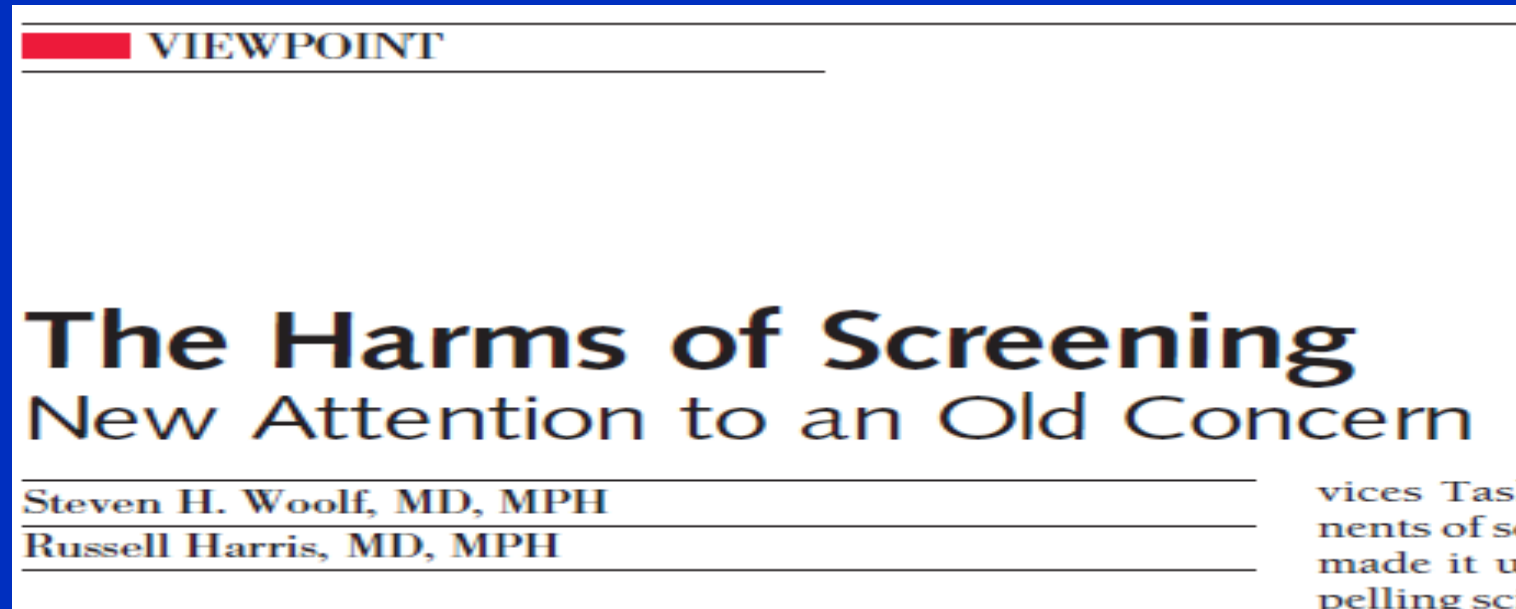
1. Tumor biology confounds screening.
2. The value of screening has been actively questioned.
3. Long term follow-up has only shown the promised benefits with colon CA
4. Is there a role for pharmacologic prevention?

Screening detection capability based on tumor biology and growth rates



Screening doctrine challenged: 2012-2020

JAMA 2012



Annals of Internal Medicine

ORIGINAL RESEARCH

Overdiagnosis of Invasive Breast Cancer Due to Mammography Screening: Results From the Norwegian Screening Program

Mette Kalager, MD; Hans-Olov Adami, MD, PhD; Michael Bretthauer, MD, PhD; and Rulla M. Tamimi, ScD

**Ann Intern Med
2012**

Benefits vs. burdens of cancer screening, US and Europe (2009 Meta-analysis)

Deaths
Screened Years/Visits Cancers Prevented

Breast CA (> 50 yrs.)

US

838

6/5866

18 Invasive
6 DCIS

1

Europe

838

6/3352

15 Invasive
5 DCIS

1

Prostate CA

Europe

1410

9/2397

48

1

The oncology community pushes back...

IDEAS AND OPINIONS

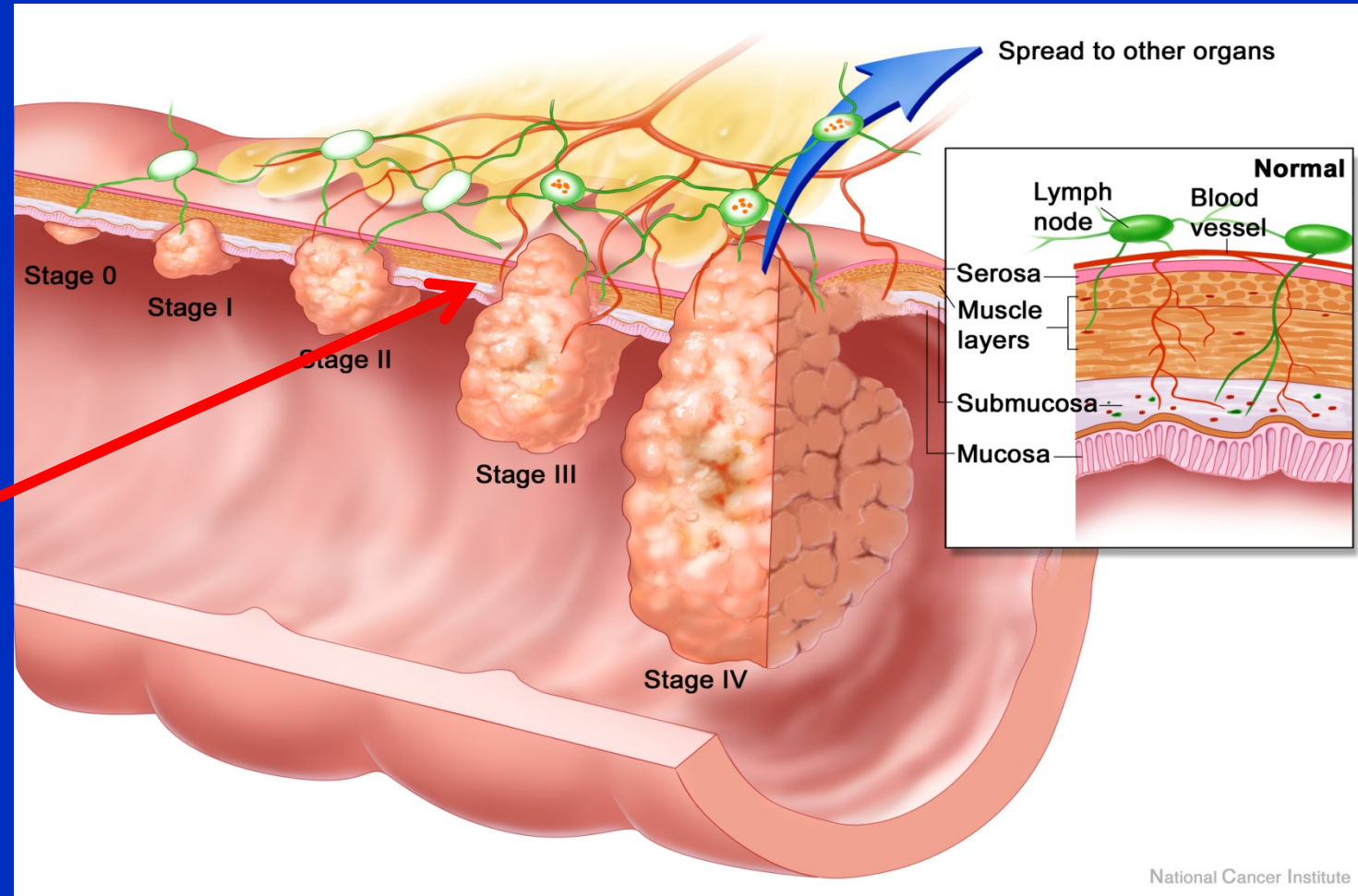
Annals of Internal Medicine

The Breast Cancer Overdiagnosis Conundrum: An Oncologist's Viewpoint

Henry G. Kaplan, MD, and Judith A. Malmgren, PhD

“..If we don't continue to find and do research on cases of early breast cancer, we will never learn how to tell which cases have a good prognosis...”

Colon cancer: The best case for screening



**Surgical
cure**

Stage 0

Stage II

Stage IV
3-5 years

Colorectal Cancer

Recommendations (USPSTF, 2016):

Screening at age 50 up to age 75,
situational age 76-85, stop over 85.

Recommendations (ACP):

Screening at age 50, age 40 if high risk or
10 years younger than the age youngest
relative diagnosed with colon CA. Stop
age 75 if under 10 years of life expectancy

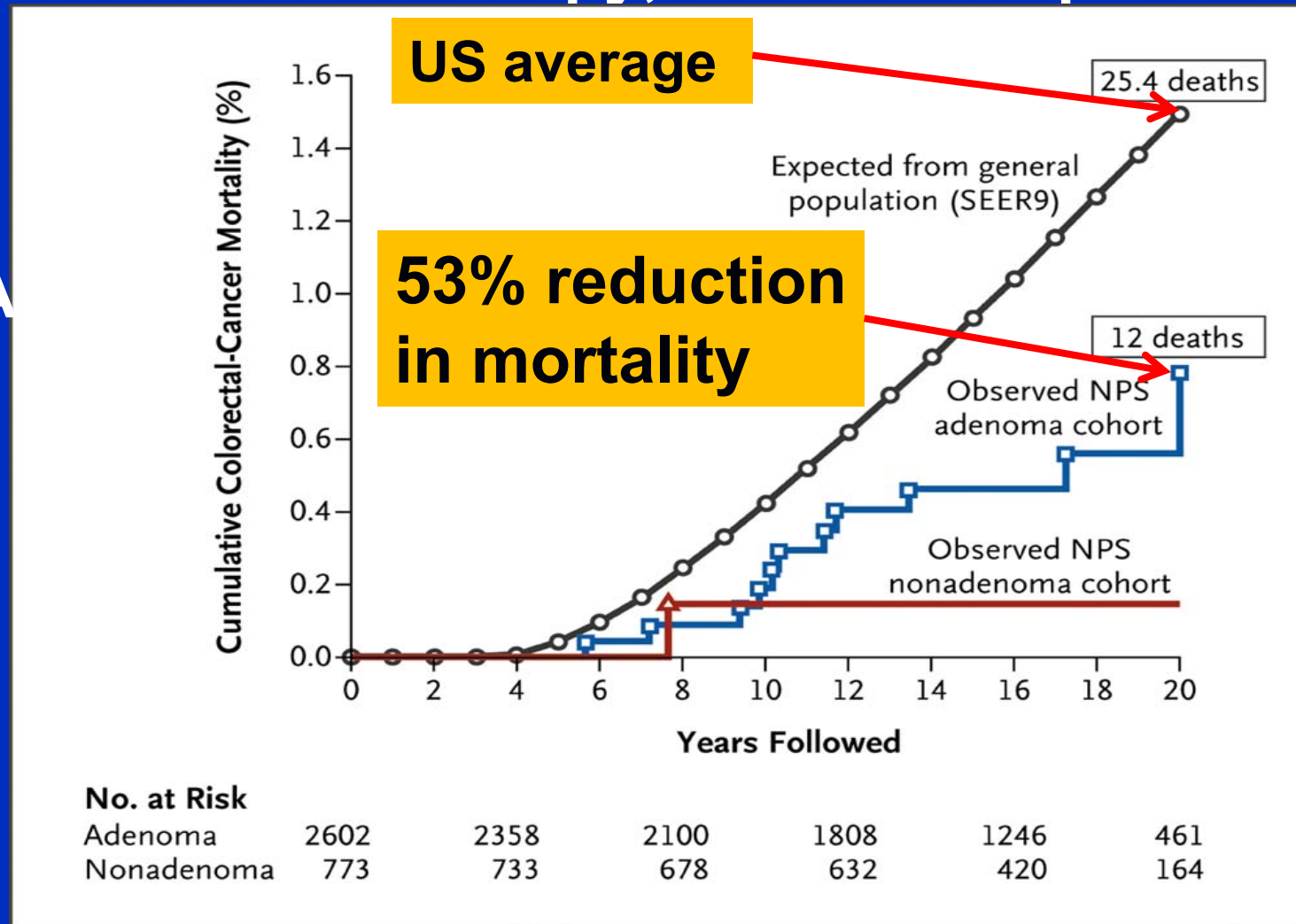
American Cancer Society (2018): Start age 45

US Colonoscopy study, 2012:

N = 2602, 1980-90, 23 yrs. follow up.

Study patients: Colonoscopy; Control: Expected incidence

Colon CA
mortality



US pop

After TA
removal

No TAs

Standard colonography screening does not detect small polyps

Size of adenoma or CA

	5mm	6mm	7mm	8mm	9mm	10mm
Sensitivity of CT colonography	0.31	0.48	0.45	0.75	0.60	0.84

What do you tell patients?

Characteristics of colonic adenomas predict risk
(Polyp follow up trial, 15 935 patients, 1993-2013, 12.9 yrs. FU)

Colorectal cancer risk
at 15 years, per 10 000 patient years

Risk Status:

Advanced adenomas	20.0
(≥ 1.0 cm, high grade dysplasia, tubulovillous adenoma)	
Non-advanced adenoma	9.1*
(< 1 cm.)	
No adenoma	8.9*

* NS

5 year risk after a hyperplastic polyp is low

(Indiana 2008, 1256/2436 patients
rescreened at 5 yrs)

Advanced adenoma

Baseline

5 years

Hyperplastic polyps

2%

No polyps

1.1%

P=N.S.; No different risk of CA

Screening thresholds over 75 years based on co-morbidities: Cost benefit analysis (including complications)

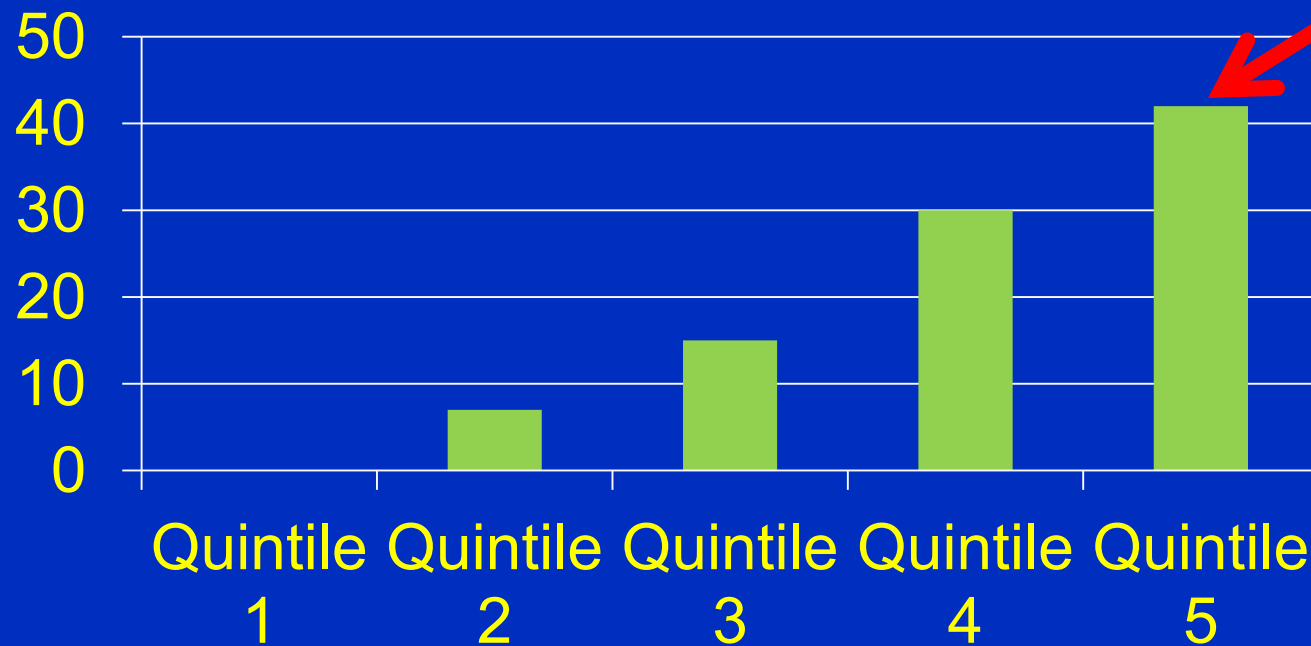
Years of age

	76y	77y	78y	79y	80y	81y	82y	83y	84y	85y	86y
None	COL	COL	COL	COL	COL	COL	COL	COL	SIG	SIG	FIT
Mod	COL	COL	COL	COL	COL	SIG	FIT	FIT			
Severe	COL	COL	SIG	FIT	FIT						

Consider colonoscopy screening up to age 83 in
those with no co-morbidities, any screening up through age 86

Skill of colonoscopist may be related to mortality: Kaiser experience 1998-2010

Percent reduction in cancer risk per year of follow-up based on adenoma detection rates by quintile



Over 40% lower CA mortality for colonoscopists with highest detection

■ Reduction in cancer risk per year of followup

Mayo colonoscopy follow-up intervals based on pathologic findings

Baseline colonoscopy findings	Surveillance interval
No findings	10 yrs
Small (< 10 mm) hyperplastic polyps in rectum or sigmoid	10 yrs
1-2 small (<10 mm) tubular adenomas	5-10 yrs
1-10 tubular adenomas	3 yrs
> 10 adenomas	< 3 yrs
Any adenoma > 10 mm	3 yrs
Any adenoma with villous elements or high grade dysplasia	3 yrs

Alternative strategies

Flexible sig: Lower death rate from distal cancers.

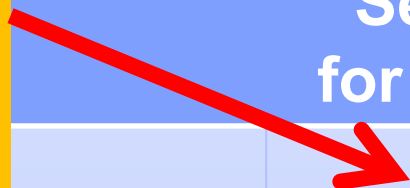
Fecal occult blood: 9% lower death rate with 20 years of screening.

Fecal Immunochemical Testing (FIT), with and without stool DNA (Immunochemical testing for blood with and without testing for DNA fragments): Widely variable performance (sensitivities 73-86%).

How good is the FIT?

(UK cohort study. N = 5938, ages 60-72, at
“intermediate risk” = 3-4 small TAs or 1 TA > 10mm)

**72.4% of
Colon CAs
not detected at
high threshold**



		Sensitivity for Colon CA	Specificity for Colon CA
High heme threshold, harder to reach		27.6%	94.1%
	Years 1+2	62.5%	89.8%
	Years 1-3	77.3%	85.8%
Low heme threshold, easier to reach	Year 1	51.7%	86.2%
	Years 1+2	76.9%	77.6%
	Years 1-3	87.5%	70%

Should the age of screening shift to 45 yrs.?

The increase in colon cancer presenting under < 50

US National Cancer Data Base, 2015 vs. 2004

	2004	2015	
% of all colon CA presenting < 50 years of age	10.0%	12.2%*	P < 0.001
Young adults presenting with Stage III/IV disease	40.0%	51.6%	

***Increase primarily upper income non Hispanic males**

Cervical cancer

Recommendations (USPSTF 2018):

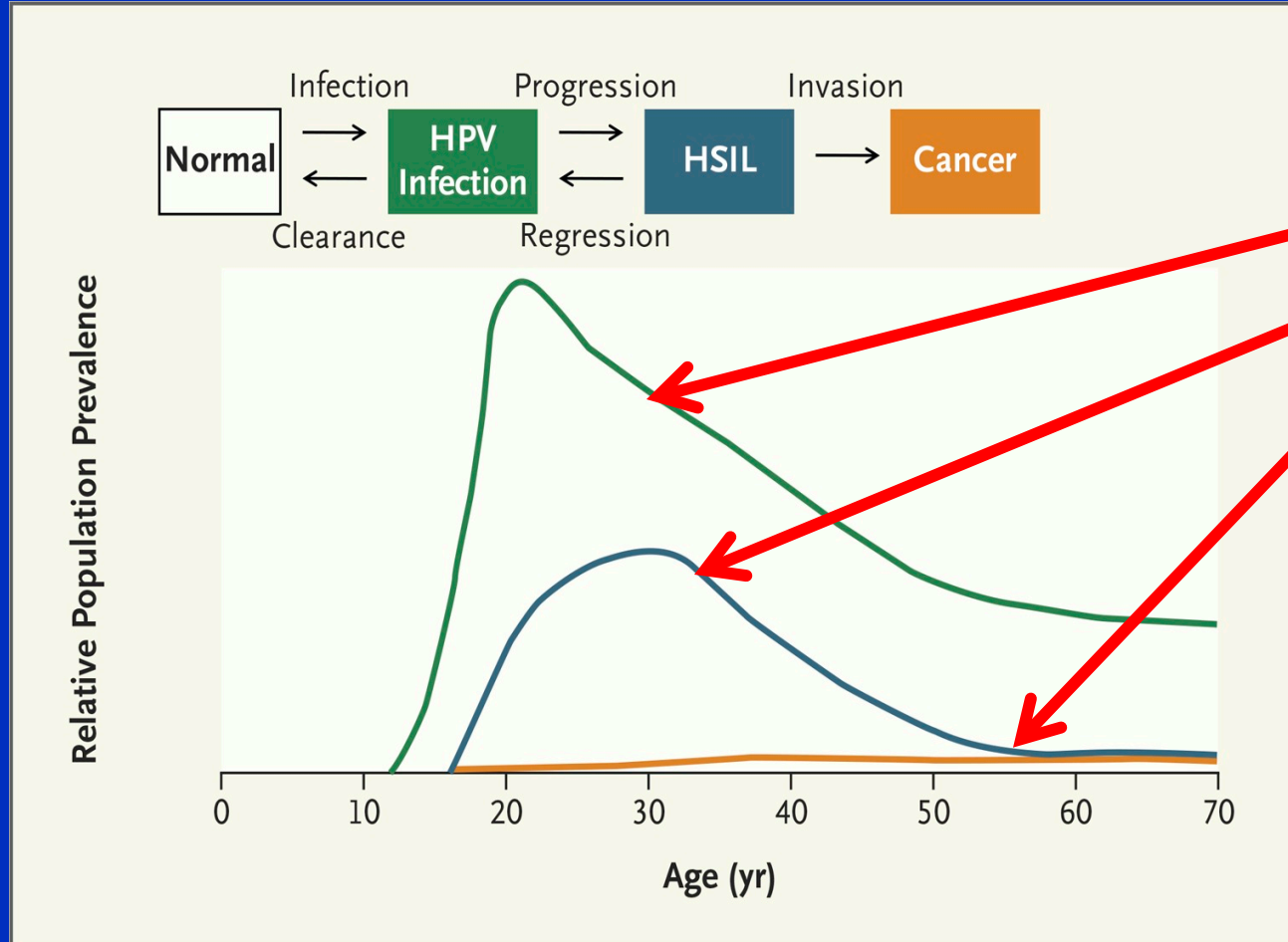
Age <21: No screening

Age 21-29: PAP every 3 years

Age 30-65: HPV +/- PAP every 5 years; PAP every 3 years without HPV

PAP testing not necessary after total abdominal hysterectomy unrelated to cervical or vaginal cancer.

The progression of HPV and the incidence of cervical cancer



HPV infection
HSIL
Cervical CA

Pap vs. HPV testing

RCT, N =19 009, 224 Canadian practices, 4 yrs.

	Number of new cases of premalignant findings per 1000 women after negative baseline testing			
Premalignant findings at 4 year follow-up	<u>Baseline negative HPV</u>	<u>Baseline negative PAP</u>	Cases missed by PAP	Percentage cases missed by PAP
Cervical intraepithelial neoplasia 3	1.4	5.4	4.03	75%
Cervical intraepithelial neoplasia 2	3.6	10	6.38	54%

Breast cancer (without RFs)

Recommendations (USPSTF, 2016):

Biennial mammogram age 50-74

Biennial after age 40-49, “for women who place higher value on potential benefits...”

Recommendation (ACS, 2015):

Annual mammograms age 45-55

Biennial age 55 to age 75 with > 10 years life expectancy

Breast cancer 5 year absolute risk:

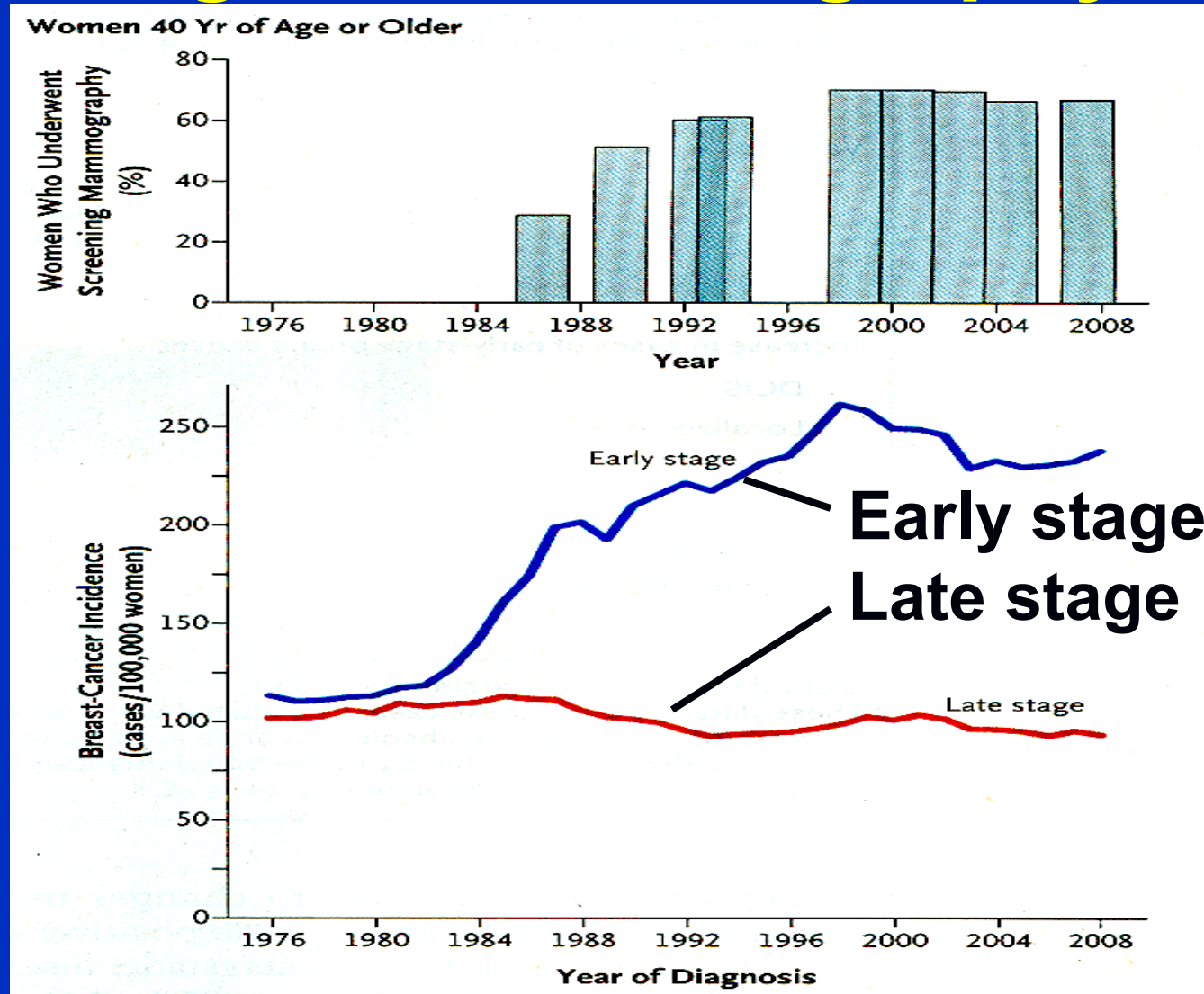
The older the higher the risk!

Age, yrs	5 yr absolute breast cancer risk	Breast cancer incidence/100, 000
1-34	0.2	5.3
35-39	0.3	59.5
40-44	0.6	122.5
45-49	0.9	188.6
50-54	1.1	224.0
55-59	1.3	266.4
60-64	1.6	346.7
65-69	2.0	420.2
70-74	2.1	433.8
79-79	2.0	443.3
80-84	1.9	420.6
≥85	2.5	354.4

More breast early breast CA found in the age of mammography

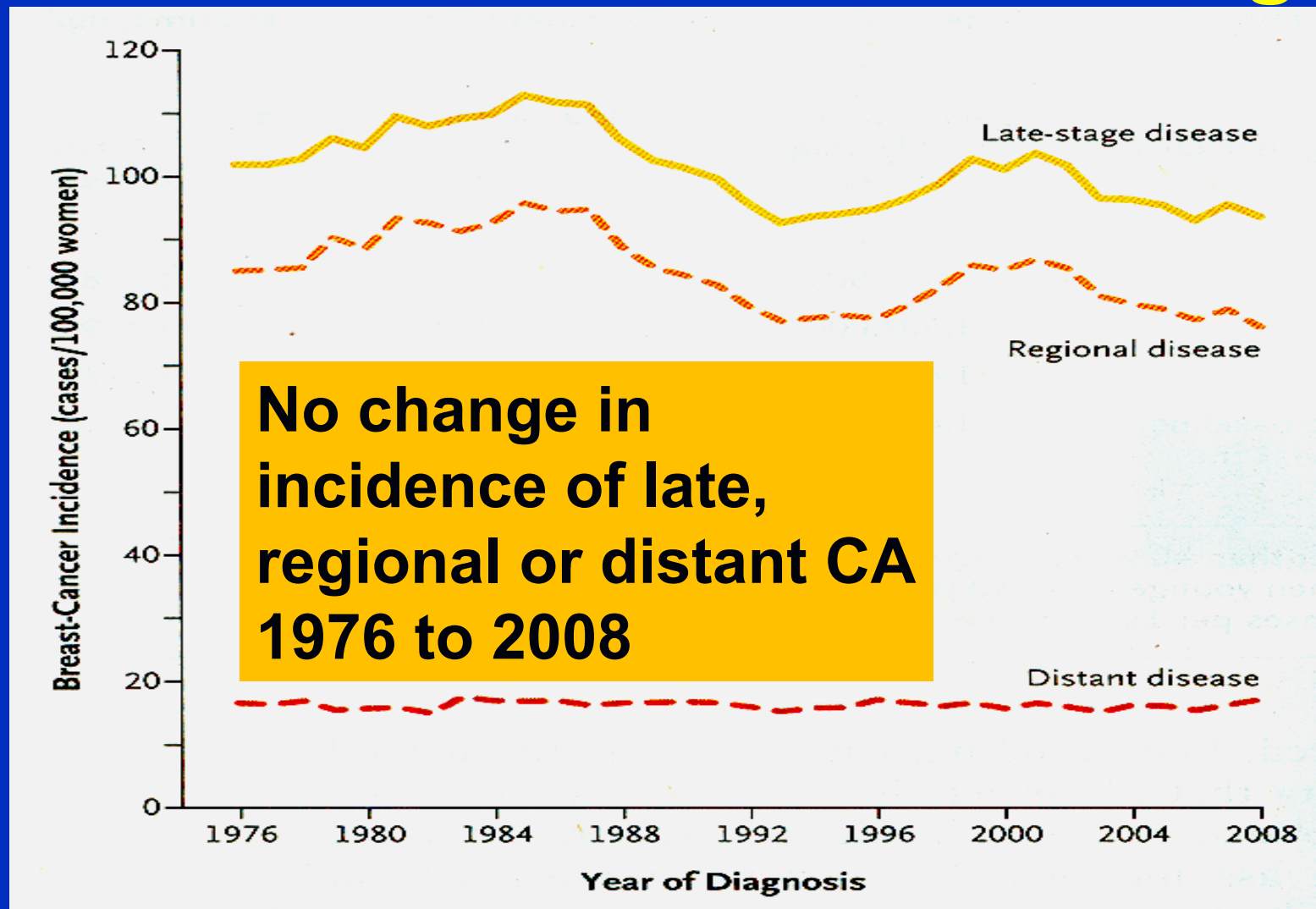
% US Women with mammo

Breast CA incidence

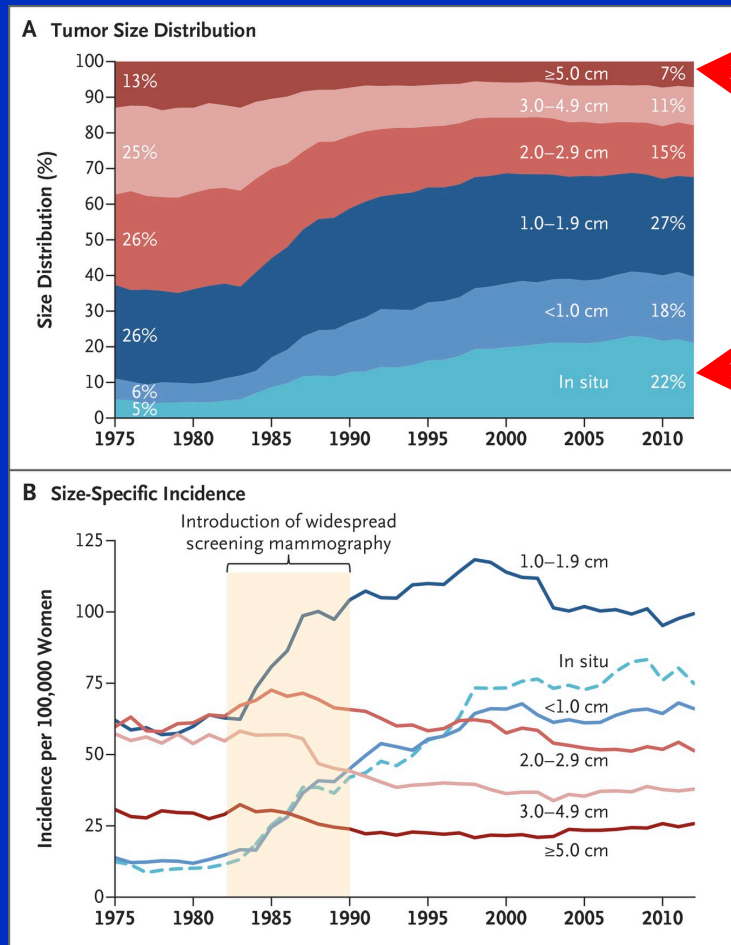


The incidence of regional, late stage and distant disease has not changed

**Breast CA
Per
100,000**



Mammography associated with increased numbers of small and in-situ breast tumors (1975-2010)



Large breast cancers

In situ breast cancers

Benefits from screening mammograms are costly

Deaths prevented for 10,000 women over 10 years (100,000 mammograms)		
	Deaths prevented	Mammograms per death prevented
39-49 years	2.9	34,482
50-59 years	7.7	12,977
60-69 years	21.3	4,694
70-74 years	12.5	8,000

Annual vs. Biennial Mammograms

USPSTF 2016

Harms vs. benefits per 1000 women screened		
	Ages 50-74 yrs Annual	Ages 50-74 yrs, Biennial
Fewer breast CA deaths	9 (5-10)	7 (4-9)
Life-years gained	145 (104-180)	122 (75-154)
False-positive	1798 (1706-2445)	953 (830-1325)
“Unnecessary” Biopsies	228 (219-317)	146 (121-205)
“Over-diagnosed” tumors	25 (12-68)	19 (11-34)

What do others say?

	Clinical exam	Age	Age to stop	Interval
ACOG, 2017	Yes	40 offer 50 start	≥ 75	Annual or biennial
ACR, 2017	Neutral	40	None	Annual
ACS, 2015	No	45	> 10 yrs. life expectancy	Annual 45-54 Biennial ≥ 55
CTFPHC, 2018	No	50	Neutral	2-3 yrs.
NCCN, 2018	Yes	40	None	Annual
USPFTF, 2016	Neutral	40-49 consider 50	75	Biennial
WHO, 2016	Yes	50	75	Biennial

Breast imaging reporting and data system assessment categories used

Category	Assessment	Likelihood ratio for breast cancer diagnosis ⁺
1	Negative	0.1
2	Benign finding	0.1
3	Probably benign finding; short-interval follow-up suggested	1.2
0	Need additional imaging evaluation	7.0
4	Suspicious abnormality – biopsy should be considered	125
5	Highly suggestive of malignancy	2200

⁺Likelihood ratios for risk of breast cancer diagnosis at first screening mammography

“Tipping the balance” for age 40-49

2012: Risk modeling using best screening technology (digital) showed that women age 40-49 have same benefit as older women if at 2.0 fold increased risk

Two fold risk = **First degree FH**

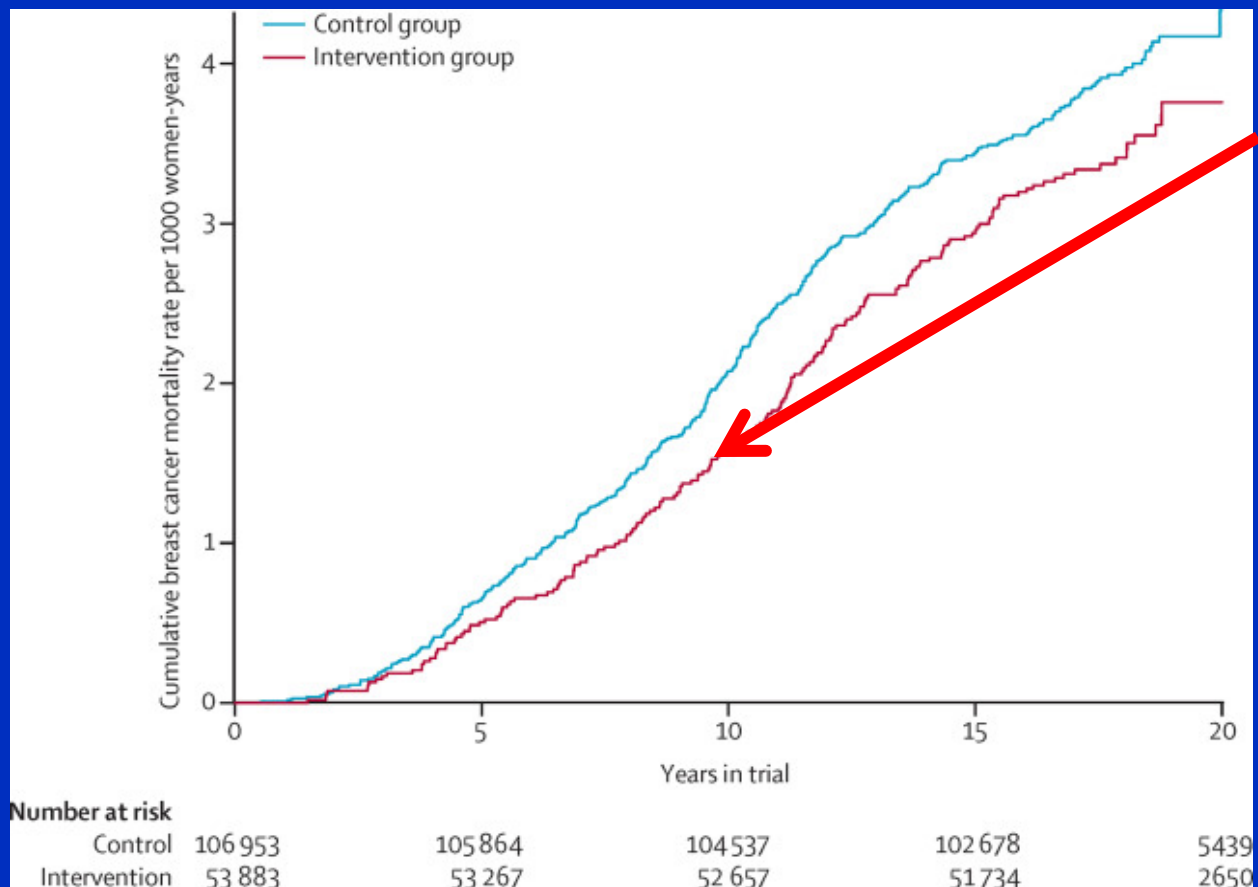
Dense breasts? Probably not

BUT the debate continues

UK RCT, invitation to mammogram

Age 40-48, 1990-97, N = 160,921

17 year follow up (2015)



51 % mortality risk reduction per year for the first 10 years (not thereafter)

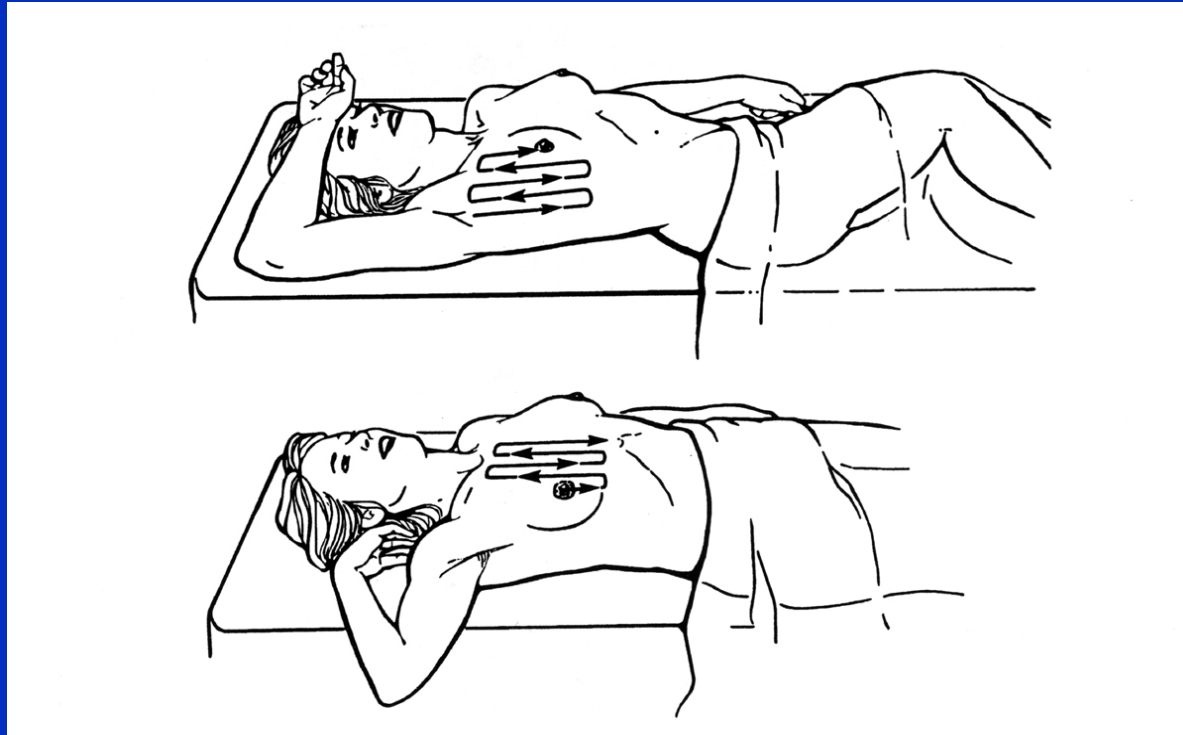
**0.156/1000 patient yrs
vs.
0.207/1000 patient yrs**

Should you examine breasts?
USPSTF neutral, ACS “qualified” no
If not mammograms, then what?

“Potential harms of screening mammograms include overdiagnosis (i.e. finding a breast cancer that would not have clinically surfaced in the absence of screening) as well as the pain and anxiety associated with false-positive biopsies.” JAMA 2014; 311:1340

**What does “clinically surfaced” mean if not by
Clinical Breast Exam (CBE)?**

Palpation techniques for CBE: Finger tips and hand relaxation



Prostate Cancer

Recommendations of USPSTF 2018:

Age 55-69: Individualized. “Screening offers a small potential benefit...”

Age ≥ 70 : No screening

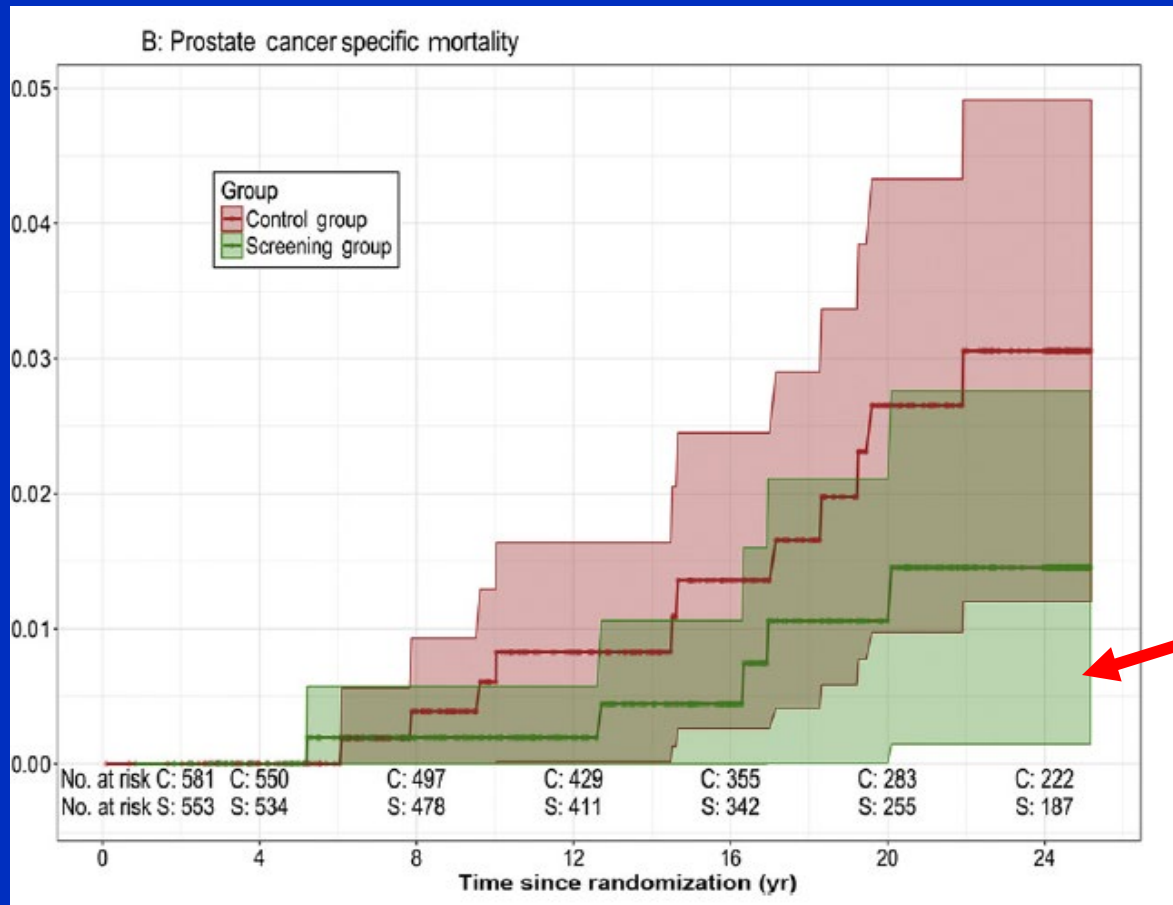
Recommendations of ACS 2016:

Age ≥ 50 or ≥ 10 years life expectancy: Men should have “a chance to make an informed decision...”

Age > 45 if first degree relative with prostate CA, African American

Newer data questions orthodoxy: Rotterdam screening trial (2018)

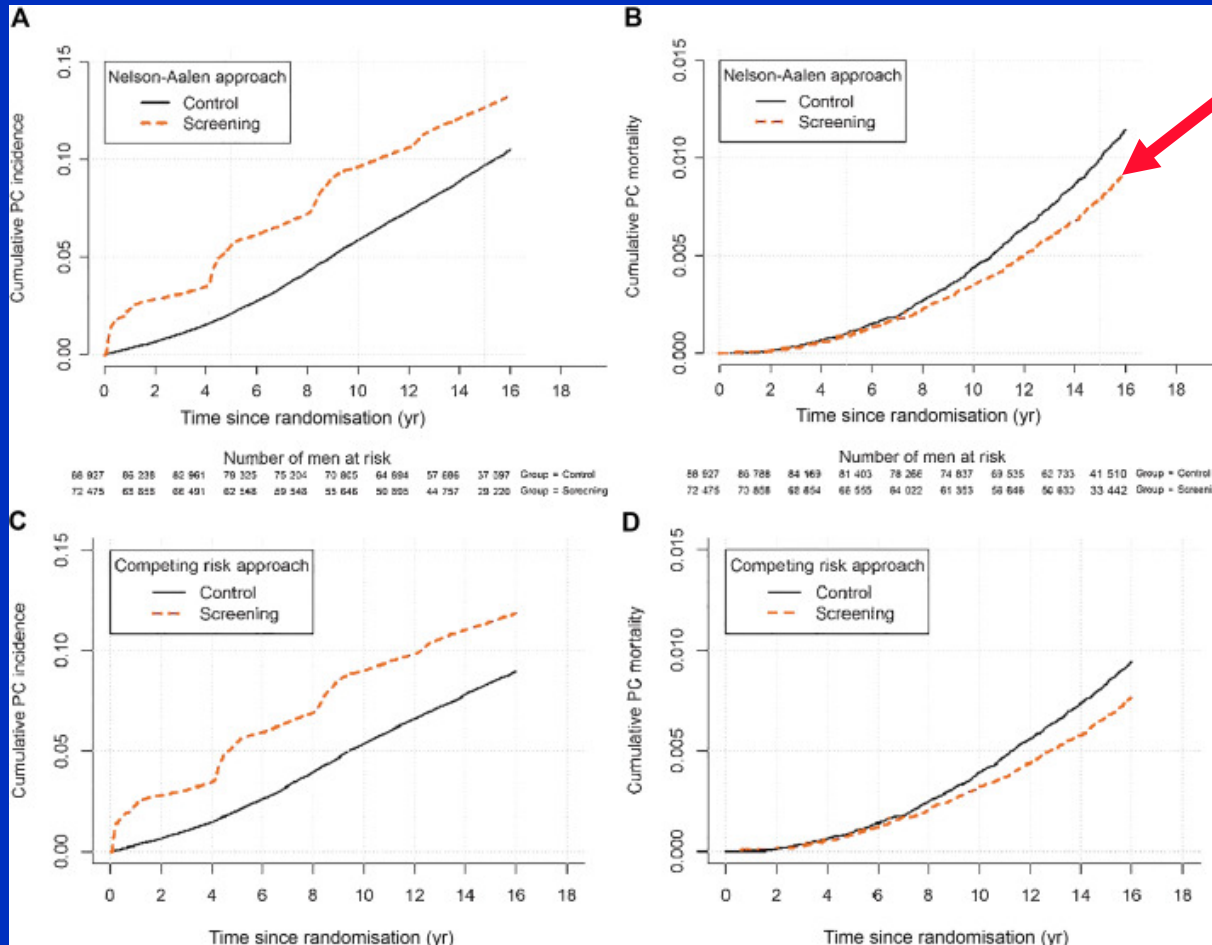
RCT: 1186 men, 1991-94, average age 64 yrs. PSA/DRE/TRUS screen (4yr. Interval) vs. No screen 19 yr. follow-up. Baseline PSAs 1.2, 1.1



52% reduction in prostate CA mortality among screened patients

16 year follow-up of the European RCT of prostate cancer screening (2-4 y) showed ongoing benefit

(2019: N = 182,160, age 55-69 at entry, 16 yrs. follow-up)

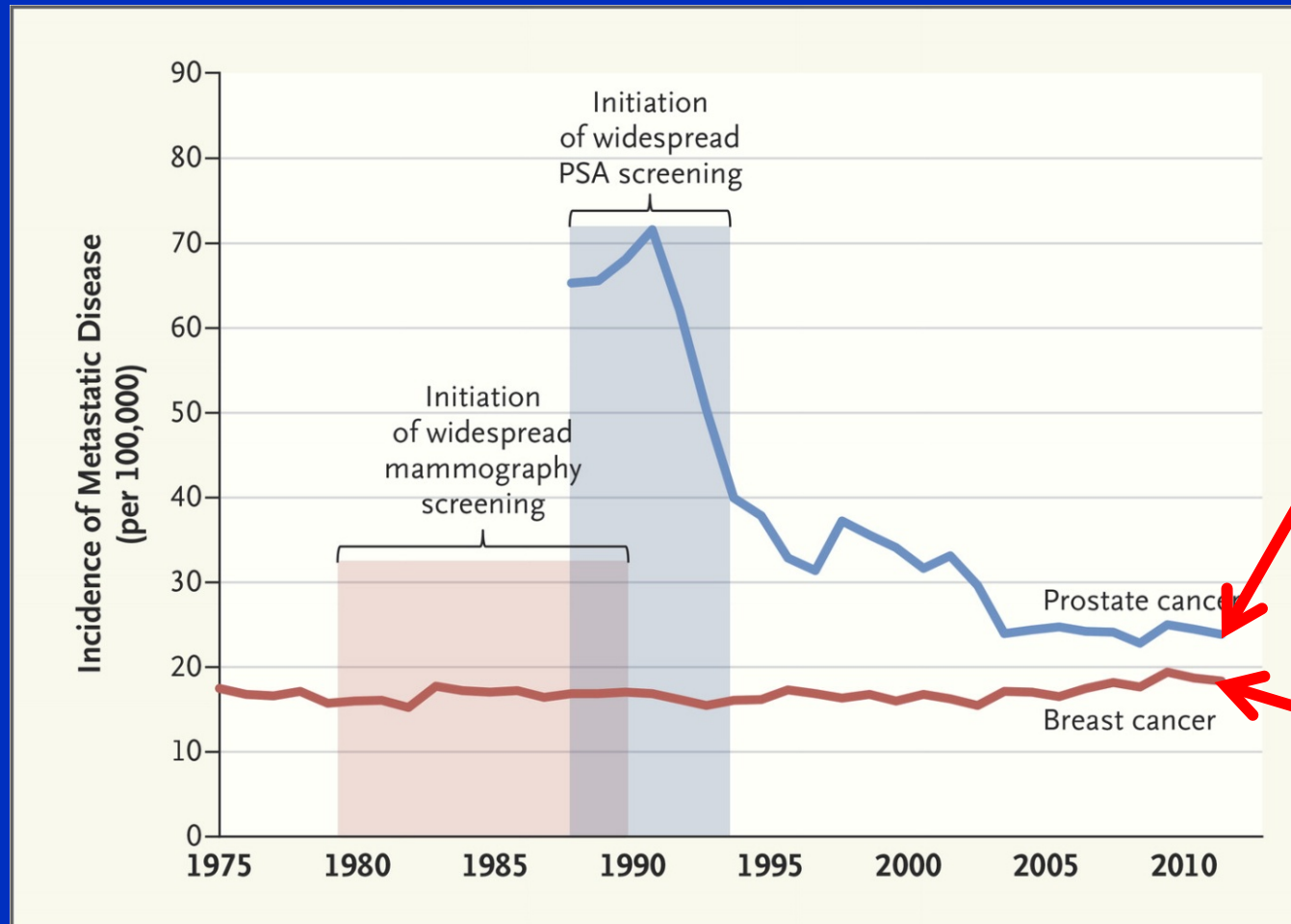


20% reduction of prostate cancer mortality at 16 yrs.

Number “invited” to prevent one cancer death = 570 (1947 at 9 yrs., 742 at 13 yrs.)

Number needed to diagnose at 13 yrs., = 18 (48 at 9 yrs.)

Prostate cancer screening reduced the incidence of metastatic disease vs. no change in breast metastatic disease

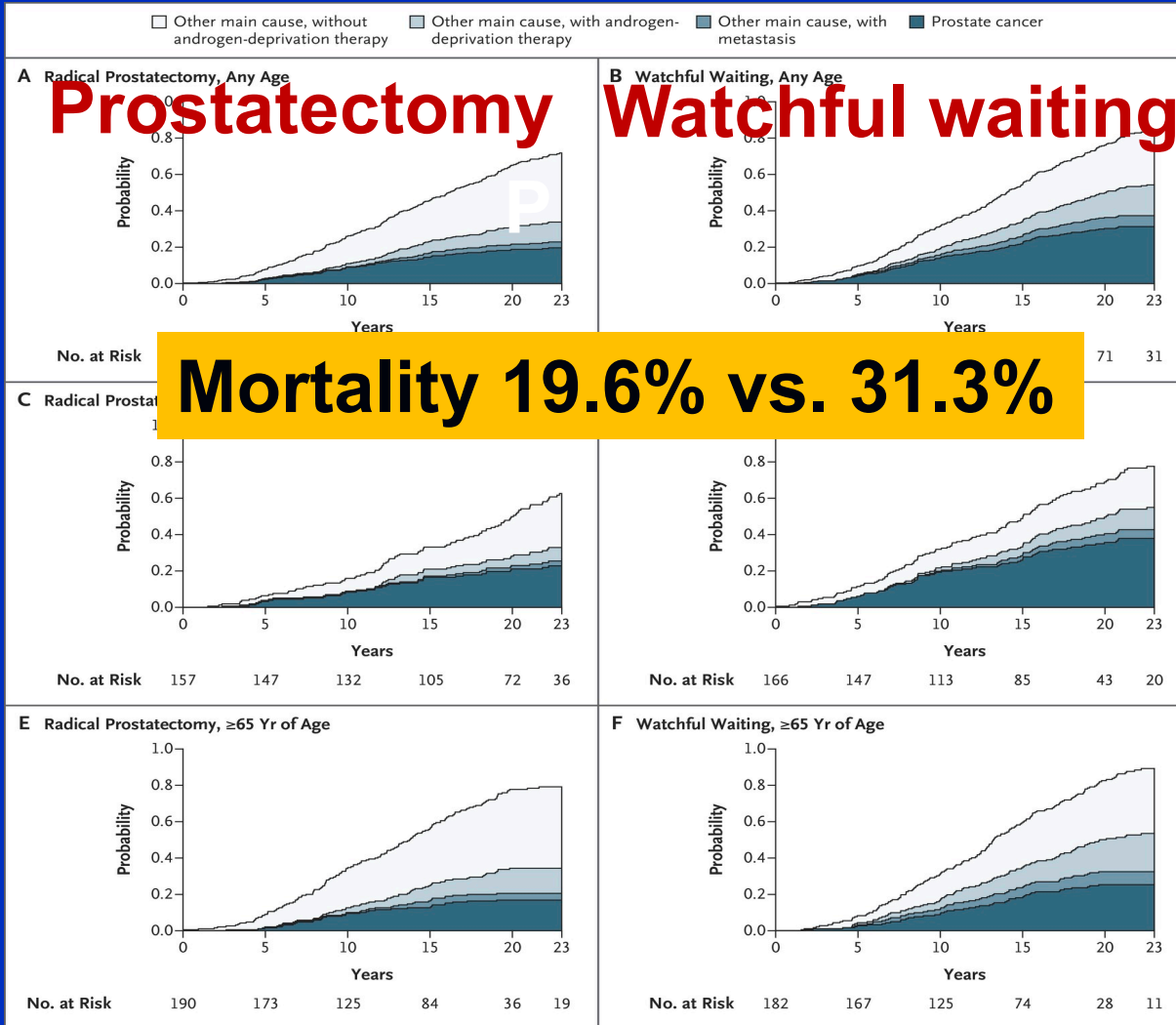


**Decline in
metastatic
prostate cancer**

**No change in
metastatic
breast cancer**

RCT of prostate cancer treatment (2018)

RCT: 14 Scandinavian centers, men < 75 years, localized prostate CA. Prostatectomy vs. Watchful waiting; 29 yrs. FU



45 % reduction of prostate cancer deaths

NNT to prevent one prostate cancer death = 8.4

2.9 years of added life from radical prostatectomy

What are the consequences of Prostate CA treatment?

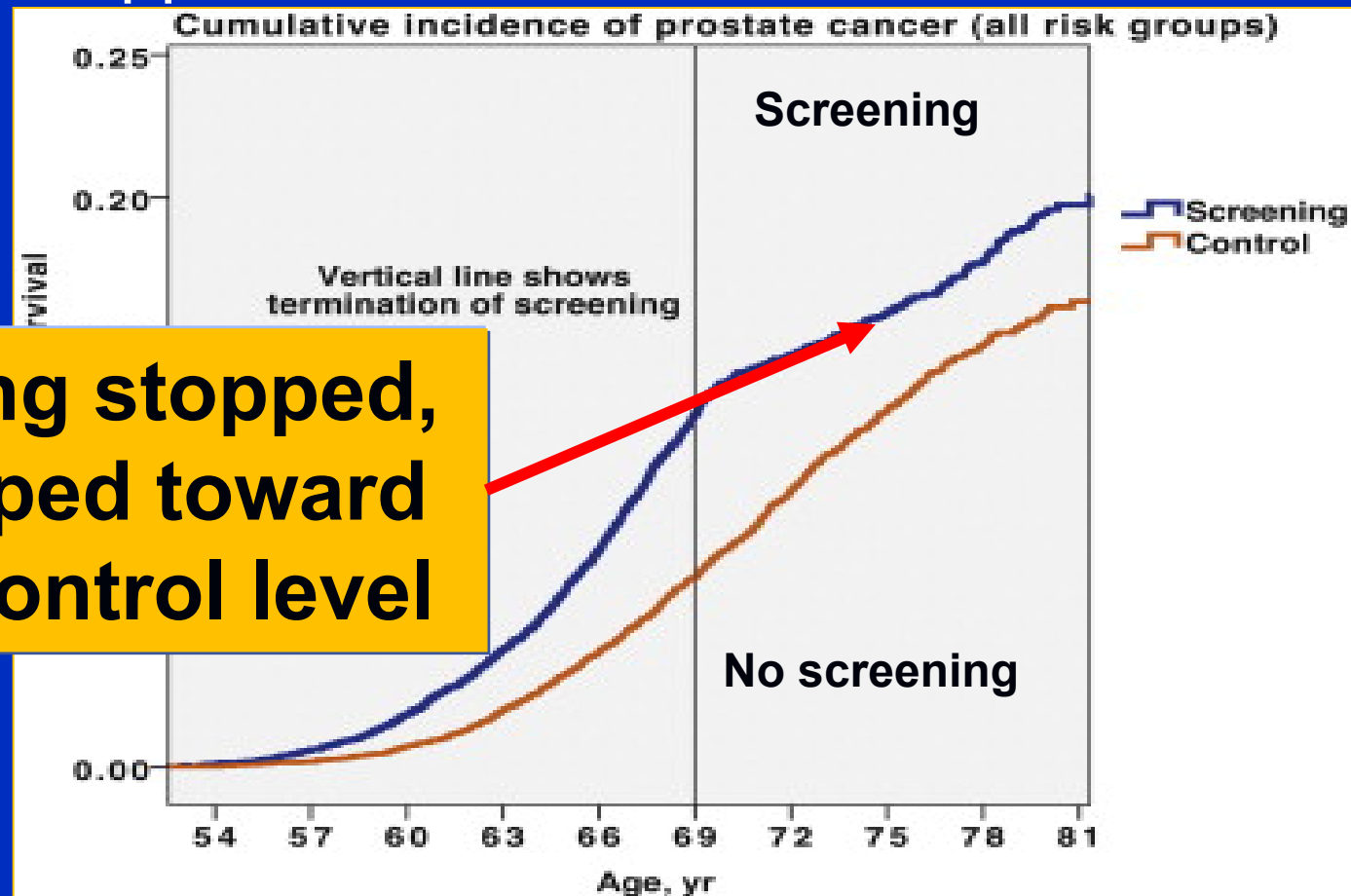
USPSTF Meta-analysis N = 1,904,950 63 studies

	Increased risk of urinary incontinence	Increased risk of erectile dysfunction
Prostatectomy	2.75	1.49
Radiation	NS	1.31

Screening for Prostate Cancer... the debate continues

Swedish study of men 9 years after screening
stopped showed a DECLINE in survival

Survival

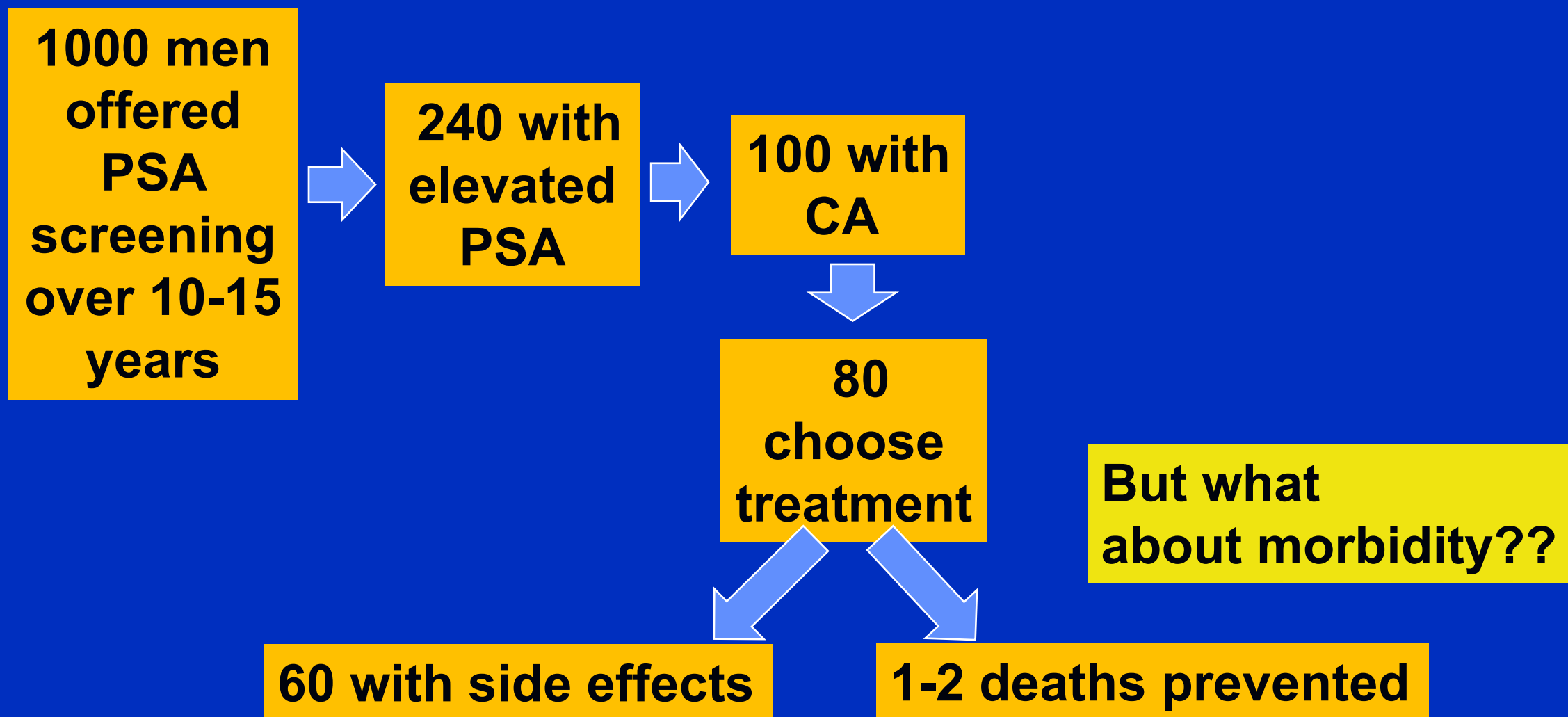


**When screening stopped,
survival dropped toward
unscreened control level**

What do other organizations recommend?

Organization	Recommendation	Year
USPSTF	Shared decision making, age 55-69	2018
Canadian Task Force	Against	2014
American College of Preventive Medicine	Against	2016
AAFP	Against	2012
American Urologic Association	Shared decision making, age 55–69	2015
ACP	Shared decision-making, age 50–69	2015
National Comprehensive Cancer Network	Shared decision making, age 45–75	2016

USPSTF estimates



RCT of prostate cancer treatment

	Radical Prostatectomy	Watchful Waiting	RR
Death, %			
All	71.9	83.8	0.74
< 65	62.6	77.6	0.62
≥ 65	79.2	89.3	NS
Death from prostate CA			
All	19.6	31.3	0.55
< 65	22.8	37.9	0.50
≥ 65	16.9	25.3	0.63
Distant metastasis			
All	26.6	43.3	0.54
< 65	30.8	49.4	0.49
≥ 65	23.2	37.7	0.59

Enter “active surveillance:” Broadly defined

	Toronto	UCSF	Hopkins	Goteborg	ProtecT
Number	993	810	1298	474	545
Follow up, yrs.	6.4	5	5	8	10
Monitoring	PSA Bx q 3-4 yrs.	PSA, US, Bx q 1-2 yrs.	PSA. DRE Bx q 1 yr.	PSA Bx q 2-3 yrs.	PSA
Threshold	PSA double ≤ 3 yrs.	Bx or “anxiety”	Bx	Bx	PSA > 50%
Definitive tx	27%	43%	36%	43%	53%
Mets	2.8%	0.12 %	0.4%	1.48%	6.06%
Prostate CA death	1.51%	0	0.15%	1.27%	1.47%

Multi-parametric MRI: A screening

(UK N=576 “at risk” for prostate CA
mpMRI vs. TRUS guided bx. vs. template prostate
mapping bx. 40% found to have Gleason ≥ 7 CA)

	Sensitivity	Specificity	Positive predictive power	Negative predictive power
TRUS Bx	48%	96%	90%	74%
mpMRI	93%	41%	51%	89%

17/158 with a negative mpMRI had a Gleason ≥ 7 CA

Prostate Cancer

Where do we stand?

- Screening finds prostate cancer
- Prostate cancer is multi-centric, sampling can be misleading
- Low level prostate cancer (Gleason 6) is relatively indolent and can be watched with active surveillance
- Emerging technologies are targeted toward non invasive staging (mpMRI) and better screening tools
- Is it better to know and follow than not to know?

Lung cancer

Recommendation (USPSTF, 2015):

Annual screening for lung cancer with low-dose computed tomography (LDCT)

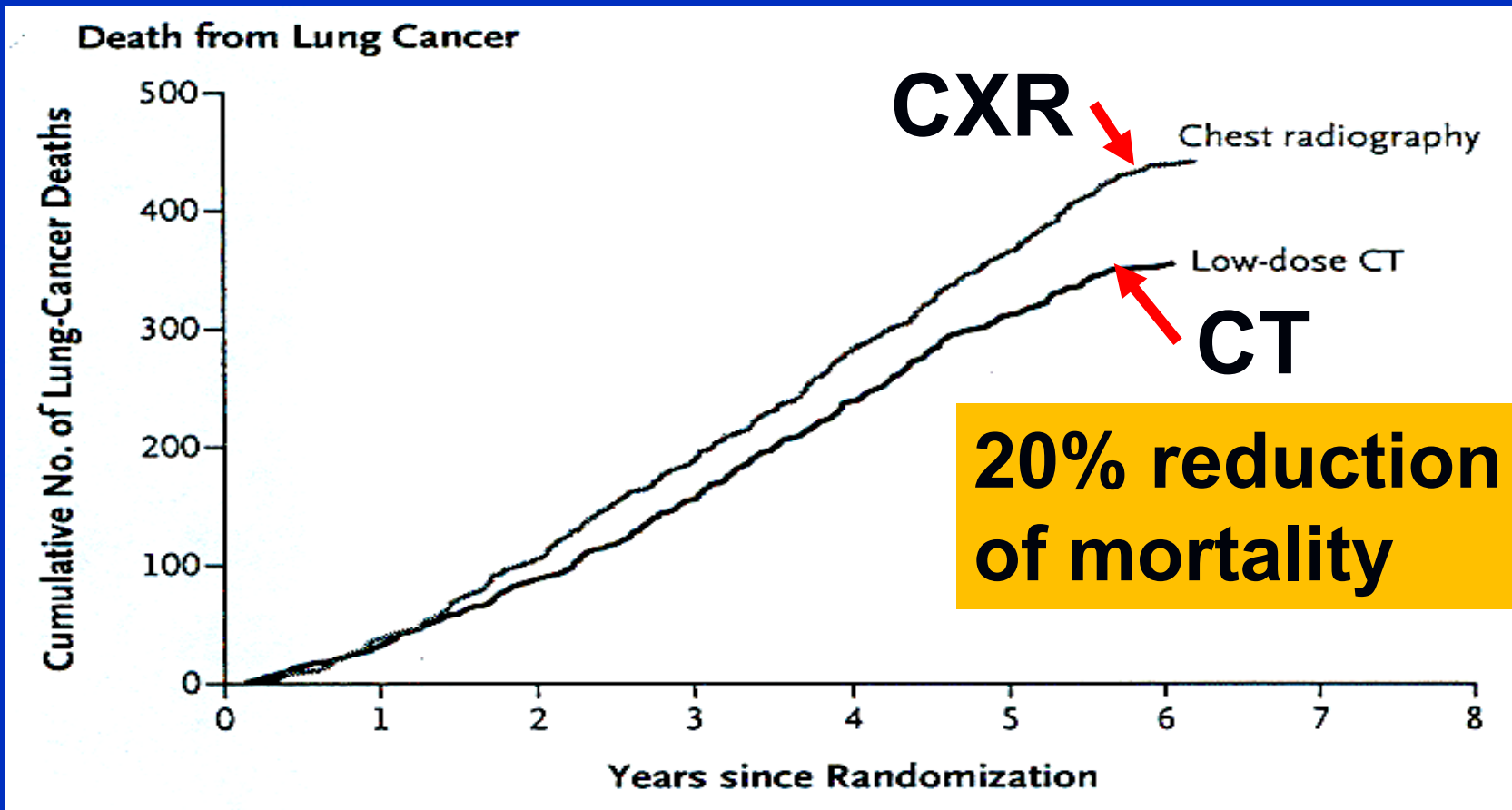
- Ages 55 to 80 years who have a 30 pack-years
- Currently smoke
- Quit within the past 15 years.

Screening should be discontinued

- Once a person has not smoked for 15 years
- Develops a health problem that substantially limits life expectancy or the ability/willingness to have curative lung surgery.

Screening with annual low dose CT for high risk smokers confers benefit

(RCT, N=53454, “high risk” of ≥ 30 py, within 15 yrs., 5 yr. follow-up)



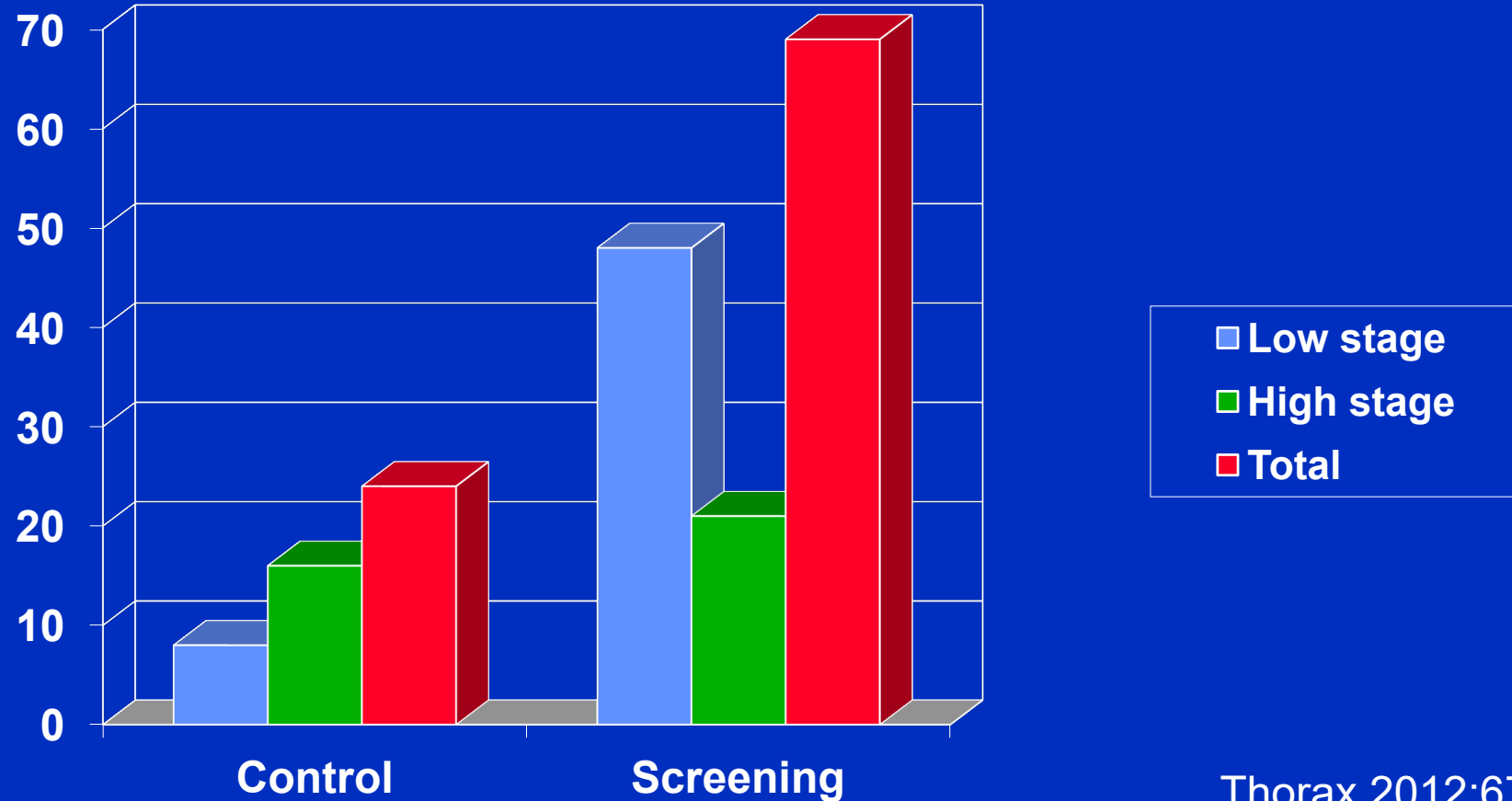
Lung-RADS classification, National Lung Screening Trial

(N = 26,455, 3 year follow up)

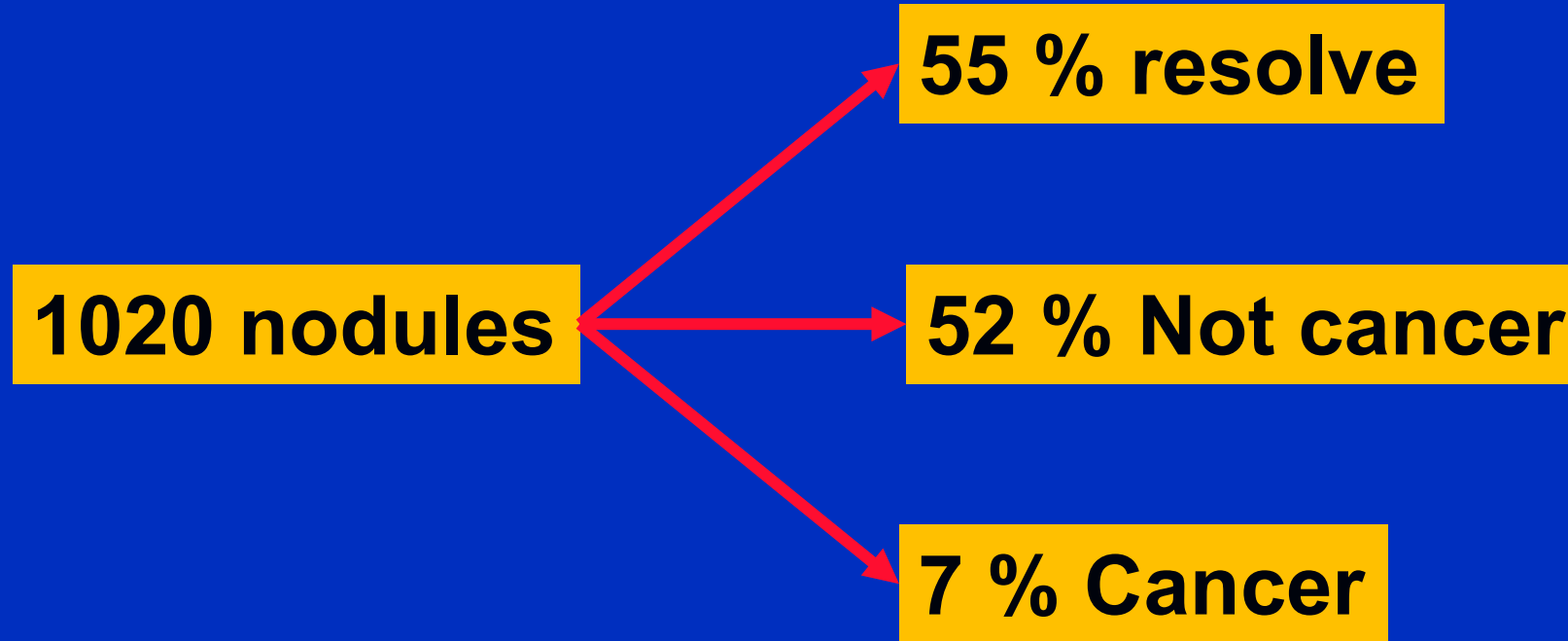
Lung-RADS Classification	Cancer present, %
1: No nodules, nodules with calcification	0.05
2: Nodules, solid or partially solid, < 6 mm	0.40
3: Nodules, solid, $\geq$ 6 mm to <8 mm	1.70
4A: Nodule, solid $\geq$ 8 mm to <15 mm	4.60
4B: Nodule, solid $\geq$ 15 mm	23.50
ALL	0.80

But...screening with annual low dose CT for High risk smokers leads to a “stage shift”

(Danish RCT, N = 4104, men and women, annual CTs for 5 years)



Follow-up of new low risk nodules (under 15 mm) and low density (Netherlands cohort N = 1020 nodules)



Do we know what we are doing yet?

JAMA Internal Medicine | [Original Investigation](#)

Analysis of Computed Tomography Radiation Doses Used for Lung Cancer Screening Scans

Joshua Demb, PhD, MPH; Philip Chu, MS; Sophronia Yu, MPH; Robin Whitebird, PhD; Leif Solberg, PhD; Diana L. Miglioretti, PhD; Rebecca Smith-Bindman, MD

65% of screening CT scans exceeded recommended radiation doses

What about cancer prevention?

Vaccine prevention

Hepatitis B for Liver Cancer

HPV for Cervical Cancer

Pharmacologic prevention

Colon Cancer: ASA

Prostate Cancer: Finasteride

Breast Cancer: SERMs and aromatase inhibitors



Aspirin and Colon CA prevention



Original Investigation | Public Health

Association of Aspirin Use With Mortality Risk Among Older Adult Participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Holli A. Loomans-Kropp, PhD, MPH; Paul Pinsky, PhD; Yin Cao, ScD, MPH; Andrew T. Chan, MD, MPH; Asad Umar, PhD, DVM

PLCO (Prostate, Lung, Colorectal, Ovarian) Cancer Screening Trial

N = 146,152, 10 US sites, enrolled 1993-2001

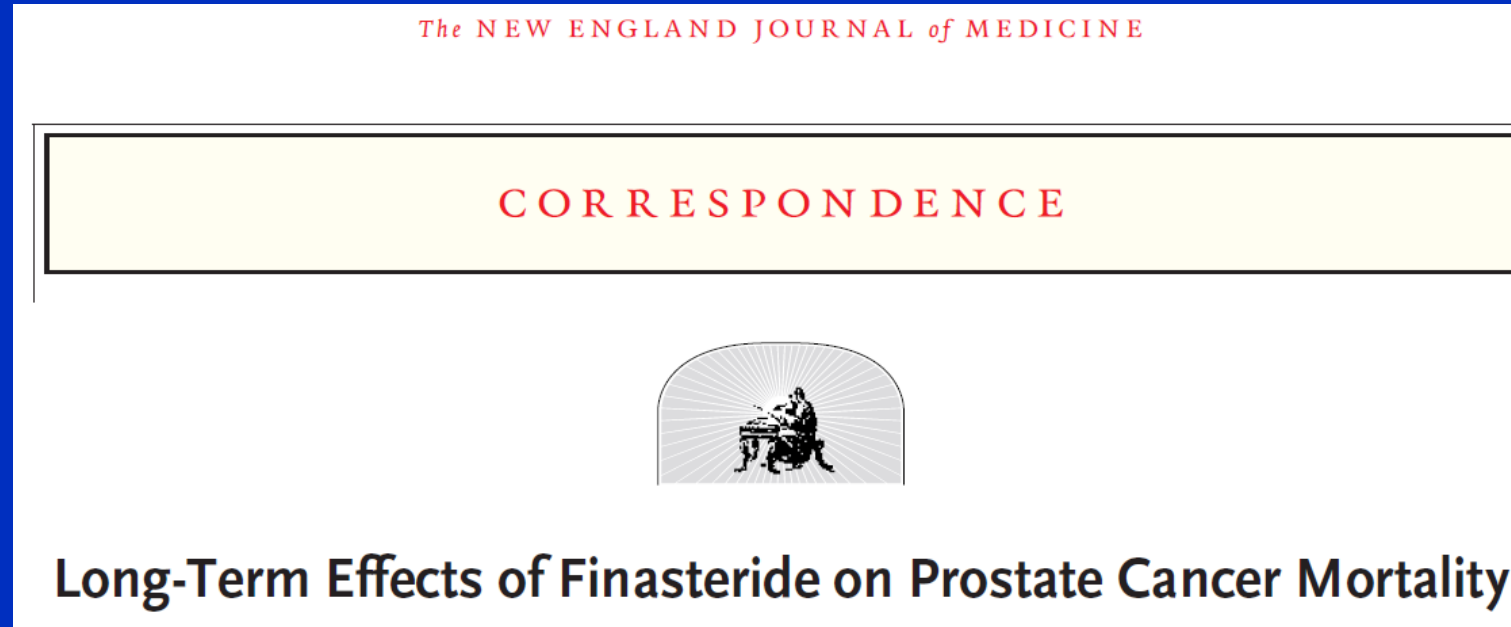
Average age = 66.3 yrs.

Average follow-up = 12.5 years

Modest aspirin use lowered Colon CA mortality for BMIs 25-29.9

BMI	Colon CA reduction, ASA use ≥ 3 times per week vs. no use	P value
≤ 20	42%	.16
20-24.9	24%	.08
25-29.9	34%	.001
≥ 30	23%	.08

Finasteride and prostate cancer prevention



Prostate Cancer Prevention Trial (PCPT): Finasteride vs. placebo

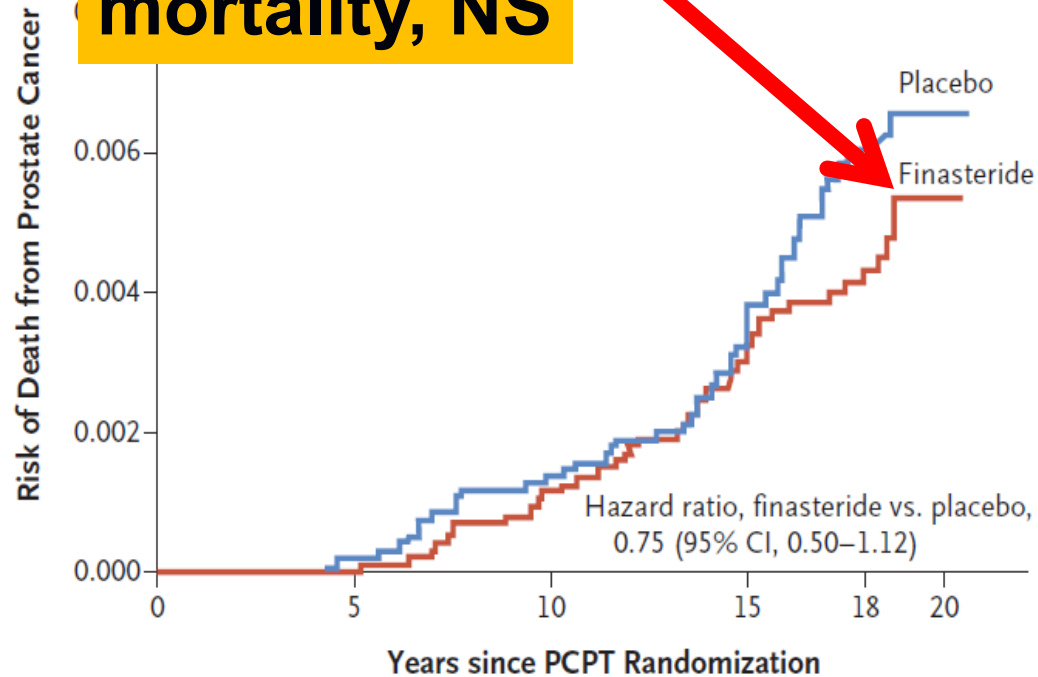
N = 9423, US multicenter study, 1994-1997

Average age = 63.2 years

Average follow up = 18.4 years

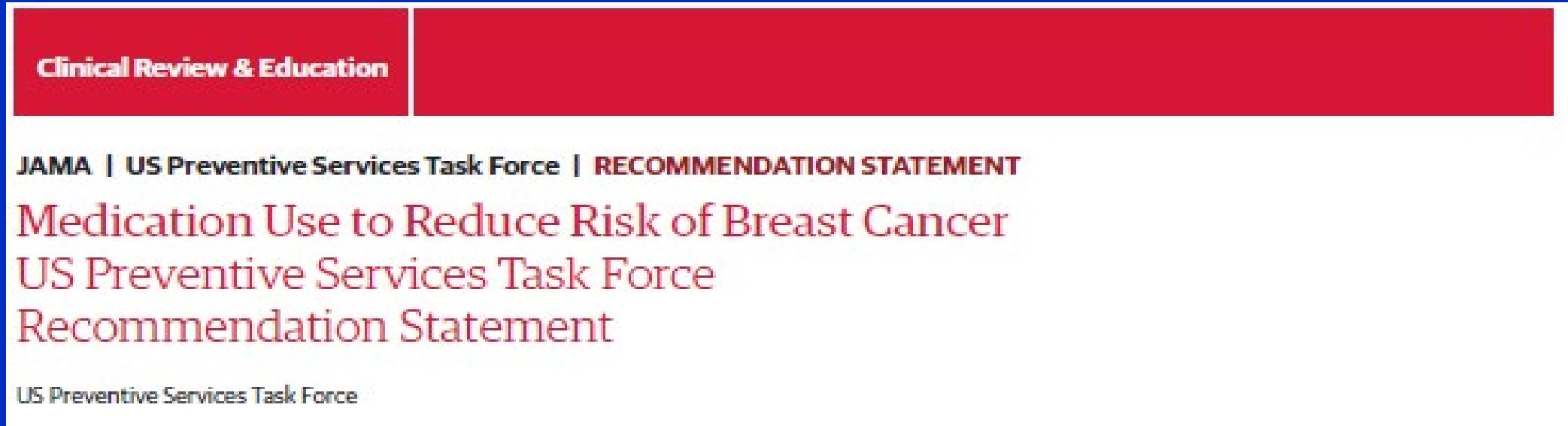
Finasteride reduced prostate cancer incidence

**25% lower
Prostate CA
mortality, NS**



	Placebo	Finasteride
N	9457	9427
FU yrs.	18.4	18.4
Prostate CA death	56	42
Gleason at Dx		
< 6	16	7
7	9	5
8-10	11	13
Unknown	20	17

Breast CA prevention



USPST: Tamoxifen, raloxifene, or aromatase inhibitor for women at increased risk for breast CA and low risk for medication SEs.**

*****Women > 35 years with benign breast lesions (atypical ductal hyperplasia or lobular hyperplasia and lobular CA in situ but NOT previous CA or DCIS)***

Breast CA prevention: Benefits* vs. risks

	Events for 1000 women over 5 years (95% CIs)		
	Tamoxifen	Raloxifene	Aromatase Inhib.
Prevented			
Invasive Breast CA	4-12	3-9	8-24
Vertebral Fx	NS	5-9	NS
Non-vertebral Fx	0.2-5	NS	NS
Caused			
Venous thrombotic event	2-9	0.3-17	NS
Endometrial CA	1-8	NS	NS
Cataracts	5-50	NS	NS

***5 years of use**

JAMA 2019; 322:857-867

Vaccine for cancer prevention: Yes

Pharmacologic cancer prevention: Maybe

Vaccine prevention

Hepatitis B for Liver Cancer: For those at risk

HPV for Cervical Cancer: Boys and girls, women

Pharmacologic prevention

Colon Cancer: Consider low dose ASA for patients with polyps

Prostate Cancer: Consider using finasteride for BPH

Breast Cancer: Very mixed results for SERMs and aromatase inhibitors

Screening is shared work

Primary care:

Education

Tracking

Specialty care:

Active support

Our messaging:

Consistency and repetition are essential

There is always a possibility of ambiguity

In summary

- **Colon cancer:** Yes, 50-85, 40-49 if RFs.
Colonoscopy remains the gold standard
- **Cervical cancer:** Yes, 30-65 (?60). Will HPV alone be sufficient?
- **Breast cancer:** Yes, 50-75, 40-49 with RFs.

In summary

- **Prostate cancer:**

Should we be more proactive for men
ages 45-70?

MRI supplements active surveillance

- **Lung cancer:** Yes, 55-80, if over 30 PYs
and current smoker or stopped
 ≤ 15 yrs.

In summary

- **Cancer prevention**
 - **Hepatitis B for those at risk**
 - **HPV for boys and girls, women to age 45**
- **Aspirin for patients with polyps**
- **Finasteride risk has been overstated**
- **SERMs and aromatase inhibitor use requires shared decision making**

Thank you

Questions?