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Principles of Screening

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Principles of Screening

Finding disease is not a measure of success in screening.

Increased survival is not a legitimate measure of success outside of a randomized clinical trial.

Reduction of mortality rate in a randomized trial is the only true proof of effective screening.



Principles of Screening

- There are several examples of cancer screening tests that have:
 - found localized disease,
 - increased the amount of disease found,
 - increased the proportion surviving five years.
- Some without changing the risk of death:
 - urine vanillylmandelic acid (VMA) screening for neuroblastoma.
 - Wood et al, NEJM, 2002
 - chest x-ray screening for lung cancer.
 - Marcus et al, JNCI, 2006



Cancer Screening

- Can be beneficial! Can be harmful!
- Often both and only a good randomized clinical trial can disclose the net benefit to the population (risk/benefit ratio).
- Need to follow good science.



Cancer Screening

- Screening is doing a test to determine if cancer might be present in an asymptomatic individual.
- Most distinguish mass screening versus screening within physician-patient relationship.
- Diagnostic tests are used when there are symptoms to cause a clinical suspicion of disease.



Cancer Screening

The aims of screening are:

- Reduction in mortality and
- Secondarily: a reduction in morbidity.

Screening can cause harm, therefore the benefit/harm ratio of a screening test is always important.

Continuous assessment of quality is important.



Prostate Cancer Screening

- There are positive and negative trials, all with significant biases tainting their results.
- It is likely that screening saves a few lives but causes significant harm.
- The harms are better proven than the benefits.

Brawley OW, Annals of Internal Medicine, 2012

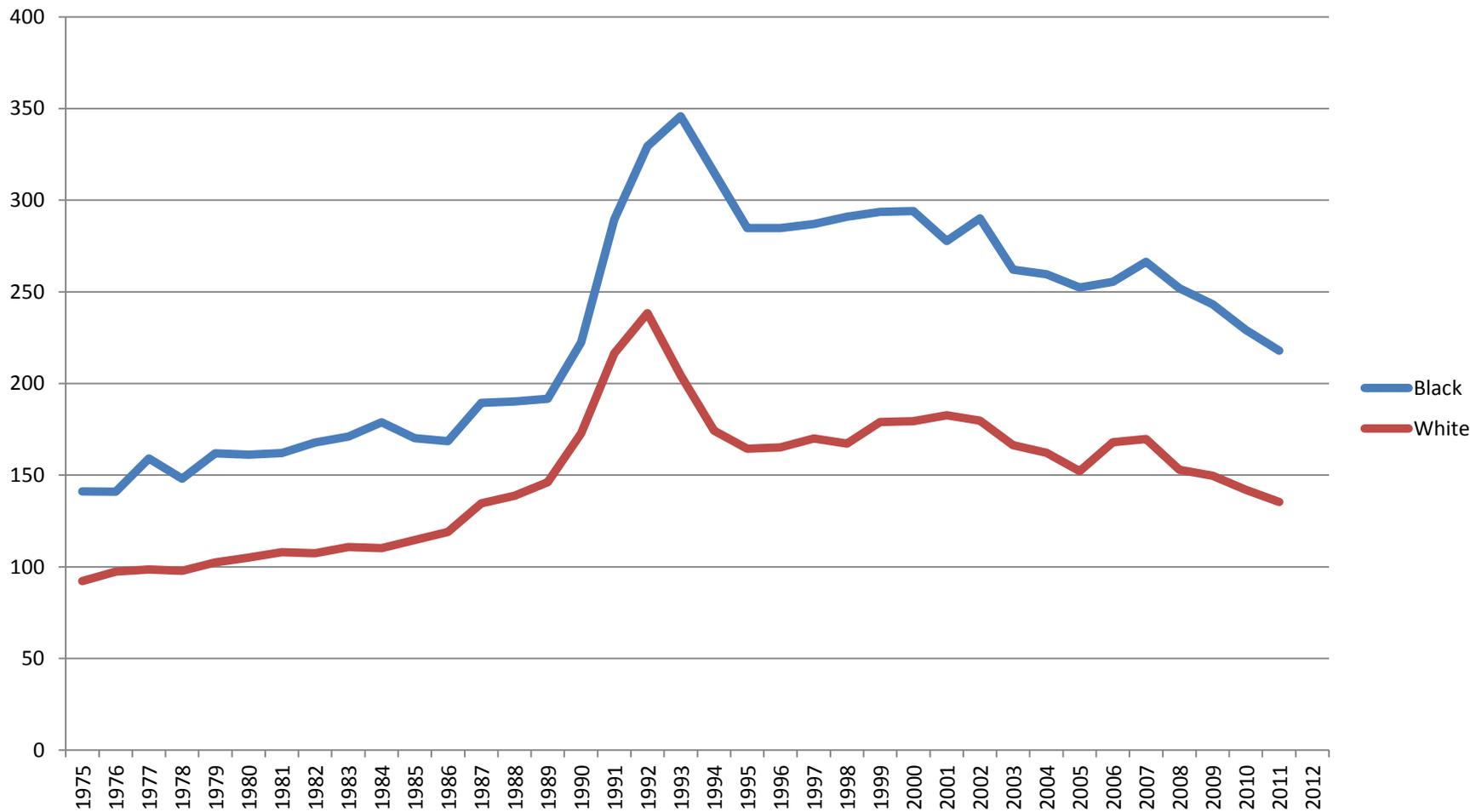
Prostate Cancer

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U.S. Prostate Cancer Incidence 1975-2012

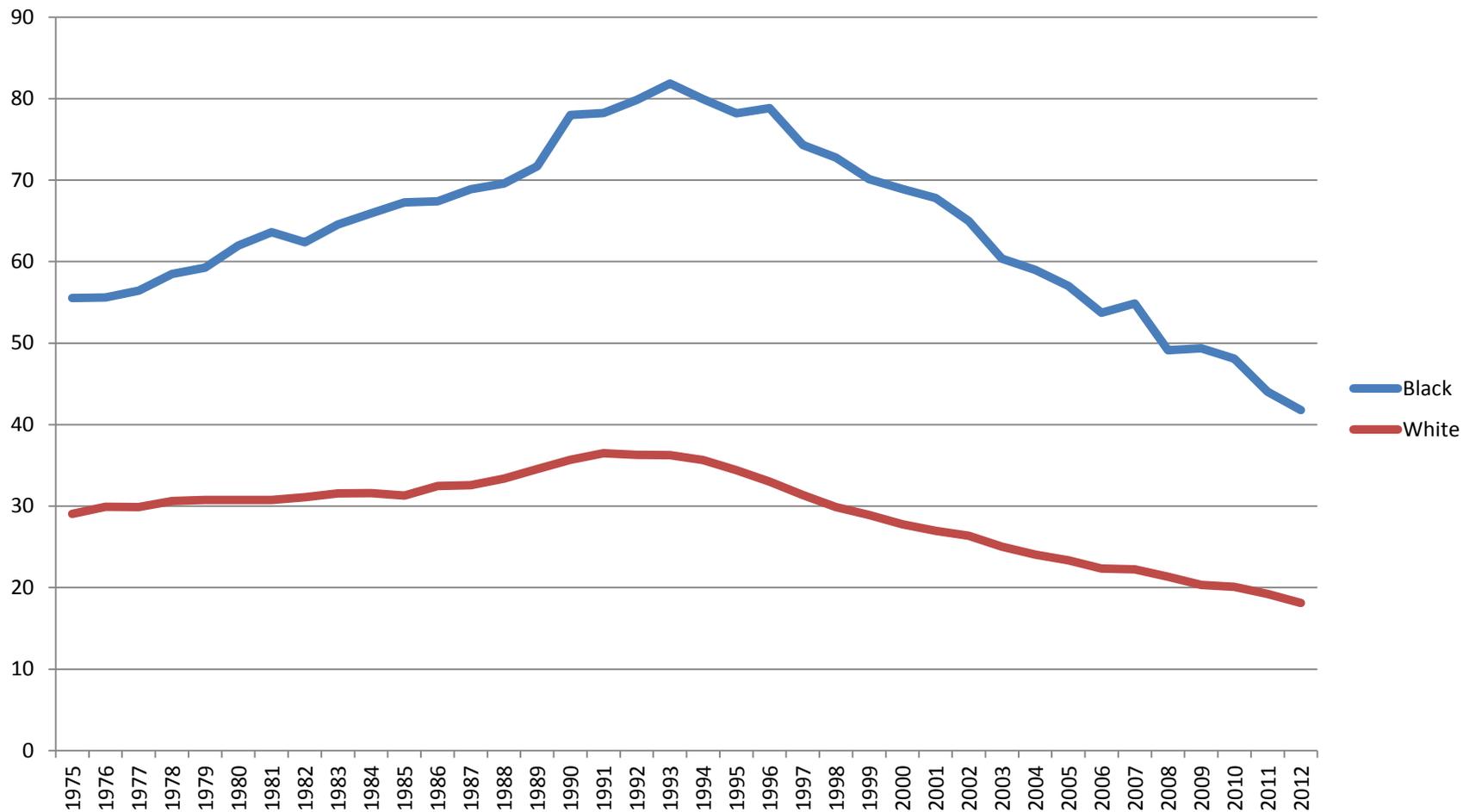
Rate per 100,000



Age Adjusted to 2000 US Standard

U.S. Prostate Cancer Mortality 1975-2012

Rate per 100,000



Age Adjusted to 2000 US Standard



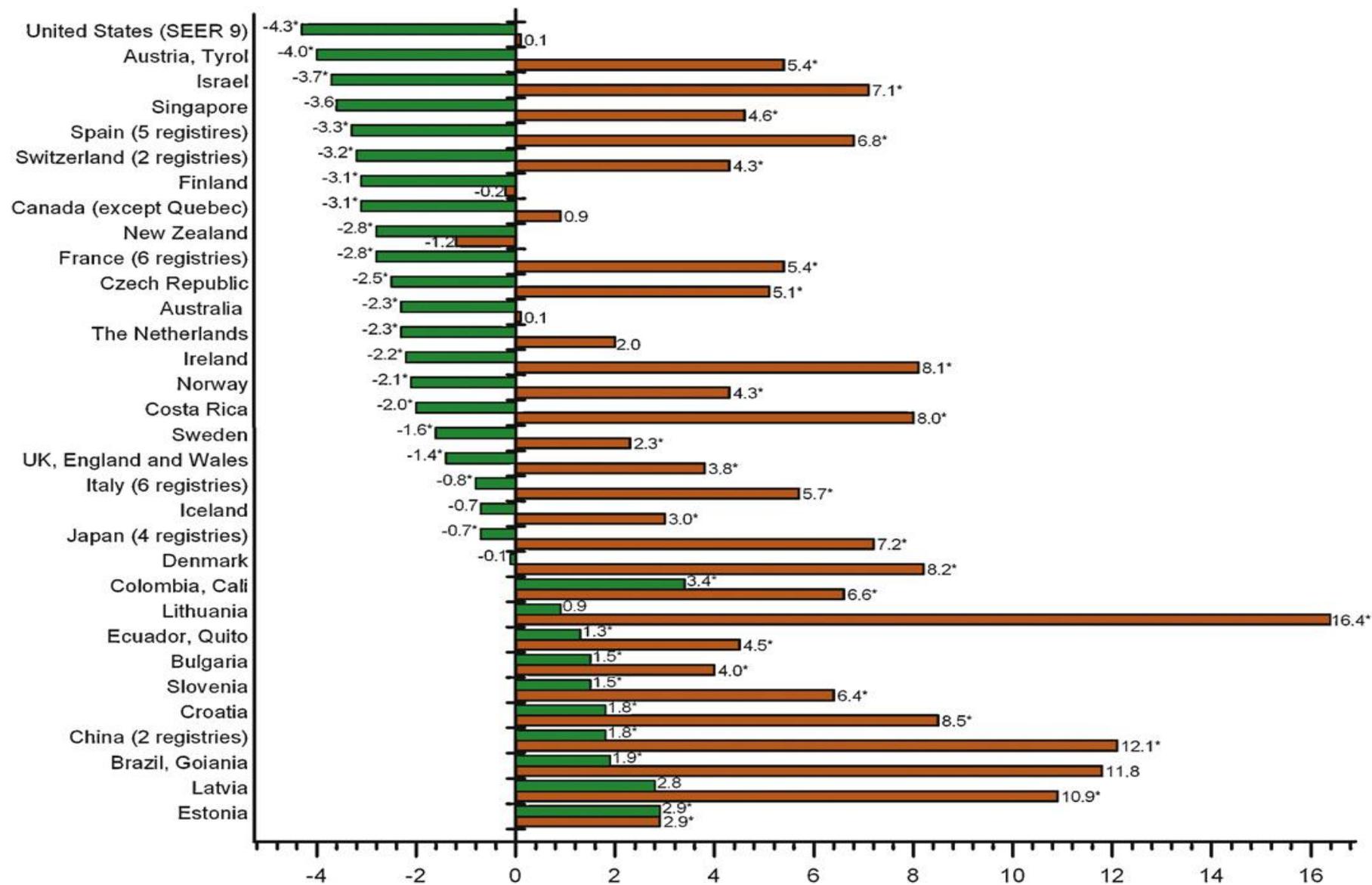
Prostate Cancer Mortality

Screening is not the only reason for the decline, if it is a reason.

- US Prostate Cancer Mortality began declining in 1988 after peaking in 1987
- PSA screening became common in the US in 1990
- PCa Mortality is declining in 21 countries, most do not screen for Pca.

International Variation in Prostate Cancer Incidence and Mortality

Average Annual Percent Change Using Last Ten Years of Data



*AAPC is statistically different from zero

Mortality Incidence



Possible Reasons for Decline in Prostate Cancer Mortality

- Screening with PSA and local treatment saves lives
- Changes in WHO algorithm for cause of death in 1988 (a shift that favored more deaths attributed to infection)
- Treatment of metastatic disease prolongs life such that competing causes of death overcomes prostate cancer.
- Hormonal therapy increases cardiovascular death and prevents prostate cancer death.
 - Boyle P, BJU, 2003
 - Haines I, JNCI, 2013



Treatment of disease, even regional and metastatic disease, has advanced tremendously.

“Does screening and aggressive treatment of localized disease save lives?” is a legitimate question.



Prostate Cancer Screening

- There are positive and negative trials, all with significant biases tainting their results.
- It is likely that screening saves a few lives but causes significant harm.
- The harms are better proven than the benefits.

Brawley OW, Annals of Internal Medicine, 2012



Recommending Against Routine Prostate Cancer Screening

- U.S. Preventive Services Taskforce
- Canadian Taskforce on the Periodic Health Examination
- American College of Preventive Medicine
- American College of Physicians
- American Academy of Family Physicians



Recommending for Informed Decision Making

- American Cancer Society
- National Comprehensive Cancer Network
- American Society for Clinical Oncology
- European Urology Association
- American Urology Association

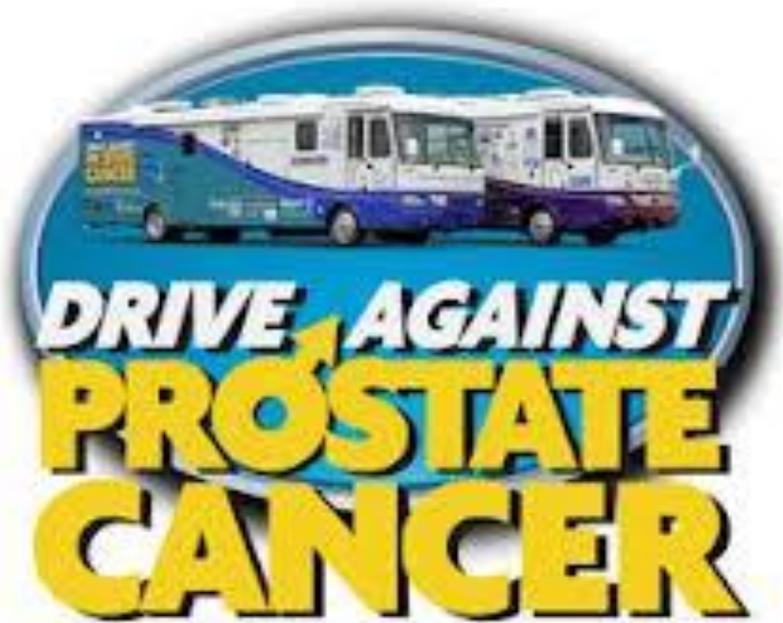
Prostate Cancer Screening Recommendations of Respected Organizations

Recommending for Informed or Shared Decision Making within the
Physician-Patient Relationship

American Cancer Society
National Comprehensive Cancer Network
American Society for Clinical Oncology
European Urology Association
American Urology Association

Recommending Against **Routine** Prostate Cancer Screening

U.S. Preventive Services Taskforce
Canadian Taskforce on the Periodic Health
Examination
American College of Preventive Medicine
American College of Physicians
American Academy of Family Physicians





The American Cancer Society 2010 Prostate Cancer Screening Guideline

“Men should have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer, after receiving information about the uncertainties, risks, and potential benefits associated with prostate cancer screening.”



American Urological Association*

Given the uncertainty that PSA testing results in more benefit than harm, a thoughtful and broad approach to PSA is critical.

Patients need to be informed of the risks and benefits of testing before it is undertaken. The risks of over detection and overtreatment should be included in this discussion.

AUA PSA Best Practice Statement 2009 and 2013



Prostate Cancer Screening

- The quandary of prostate cancer screening
 - There are cancers that do not need to be cured but can be cured.
 - There are cancers that need to be cured but cannot be cured. (Our patients and friends who die).
 - We do not know if we cure any disease that needs to be cured. (“Do we save lives?” is an open question).

Gleason Score 6 Adenocarcinoma: Should It Be Labeled As Cancer?

H. Ballentine Carter, Alan W. Partin, Patrick C. Walsh, Bruce J. Trock, Robert W. Veltri, William G. Nelson, and Donald S. Coffey, *The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD*
Eric A. Singer, *National Cancer Institute, National Institutes of Health, Bethesda, MD*
Jonathan I. Epstein, *The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD*

JCO Vol 30, Dec 10, 2012, p 4294-6



Prostate Cancer Screening Trials

The Prostate, Lung, Colorectal, Ovarian Cancer (PLCO)

- The American study (PLCO) randomized 77,000 men aged 55 to 74 to annual DRE and PSA. It failed to show screening was effective. Designed to look at a highly screened vs not highly screened population.
- PLCO also had weaknesses:
 - Approximately half had been screened prior to the study.
 - Approximately half of control arm received at least one PSA screen during the study.
 - Screened group did have 12% more prostate cancer compared to control.

Andriole et al., JNCI, 2012



Prostate Cancer Screening Trials

The European Study of Prostate Cancer

The European study (ERSPC) seven trials enrolled and randomized 182,000 men aged 50 to 74.

It was a negative study (RR 0.85 95% CI, 0.73 to 1.0).

The analysis of the seven pooled trials failed to demonstrate that PSA screening was associated with a decline in prostate cancer mortality.



Prostate Cancer Screening Trials

The European Study of Prostate Cancer

The European study (ERSPC) subset analysis of men aged 55 to 69 suggests that screening may save lives (it has some design weaknesses)

- It was a planned subset analysis
- There were country by country variations
 - In the randomization scheme
 - The screening schedule
 - outcomes
- The screened and control arms had differences in availability of treatment.
- It suggests that 37 men needed to be treated to save one life at ten years of follow-up.

Schroder et al, NEJM 2012



Applying ERSPC to the Population fourteen years of follow-up

- Of 200 men aged 55 to 69 diagnosed with localized PCa by PSA Screening
 - 8 lives saved through treatment (radical prostatectomy)
 - 1 life lost due to treatment
 - 191 suffer side effects without a change in PCa destiny



Prostate Cancer Screening Trials

The European Study of Prostate Cancer

Screening was net beneficial in:

- The Netherlands and
- Sweden

Screening did not save lives in:

- Finland,
- Belgium,
- Switzerland,
- Spain and
- Italy



Prostate Cancer and Chemoprevention

Pretend you are a 55 year old male and a preventive pill exists:

- If you take the pill it will definitely double your risk of prostate cancer diagnosis from 10% lifetime to 20% lifetime.
 - If you take it, it may decrease your lifetime risk of prostate cancer death by 20% from 3% to 2.4%.
- Would you take this pill?



Prostate Cancer Screening

- 11 of 11 prospective randomized trials have shown the harms of prostate cancer screening
 - Considerable overdiagnosis.
 - Overtreatment.
 - Harms of treatment:
 - Fever and sepsis associated with diagnostic biopsies.
 - Mental anguish.
 - Poor quality of life after diagnosis and treatment.
- 2 of 11 prospective randomized trials have claimed a small mortality reduction.
- All 11 trials have flaws.



Prostate Cancer Screening

The quandary of prostate cancer screening

- In the US Prostate Cancer Prevention Trial 28 percent of men age 55 and above were diagnosed with prostate cancer yet less than three percent of men die of prostate cancer.
- A lot of prostate cancer can be diagnosed in a screened population and we cure a lot of men who do not need to be cured.



Overdiagnosis Due to PSA Screening

Estimated 40 to 60 percent of men
(black men > white men)

-Draisma et al, JNCI, 2009

An excess of more than 1 million U.S.
men between 1986-2008

-Welch and Albertsen, JNCI, 2009



Prostate Cancer Screening

- Prostate Specific Antigen testing is widely done in the U.S. despite questions regarding its efficacy.
 - It clearly leads to increased numbers diagnosed.
 - It also clearly misses as much cancer as it finds.
 - It is unclear that it finds most of the disease that is life threatening but treatable.



Prostate Cancer Screening

- Most screening experts believe that benefits of prostate cancer screening are questionable.
- No organization recommends mass screening! Some advocate informed choice within the the physician-patient relationship.
- It is very resource intensive.

Breast Cancer

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Breast Cancer Screening Guidelines for Average Risk Women: ACS (2003); USPSTF (2009)

Recommendation	ACS	USPSTF
Breast Self Exam (BSE)	Not recommended	Against clinicians teaching BSE (D)
Clinical Breast Exam (CBE)	Ages 20-39: Every 3 yrs. Ages 40+: Annual	Insufficient evidence (I).
Mammography	Ages 40+: Annual End screening when curative therapy would not be offered due to life-limiting co-morbidity	Against routine screening in women ages 40-49 (C) Ages 50-74: Biennial (B) Ages 75+ : Routine screening not recommended (C) Ages 85+ Not recommended (D)

The ACS Guideline Development Process Was Updated in December 2011

- Last previous update in the process – 1998
- Greater scrutiny in guidelines processes
- Need for greater rigor in systematic reviews
- Growing concerns about specialty conflicts of interest
- *New process influenced by two Institute of Medicine Reports*

SPECIAL COMMUNICATION

New American Cancer Society Process for Creating Trustworthy Cancer Screening Guidelines

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Richard Wender, MD

American Cancer Society (ACS) cancer screening guidelines have high credibility in the United States among the general population and health care professionals and have been cited by policy makers as legal mandates for health insurance companies in many states.¹⁻⁴ The organization is therefore in an important position to educate these groups about the benefits, limitations, and harms of cancer screening tests. However, there are many other cancer screening guidelines. The National Guidelines Clearinghouse includes a collection of nearly 3000 clinical practice guidelines, with more than 180 guidelines for early detection of cancer.⁵ Many cancer screening guidelines differ, even when purported to have been based on the same set of evidence.⁶ Those differences can cast doubt on the credibility of both the recommendations and the organizations that produced them.

Guidelines for cancer screening written by different organizations often differ, even when they are based on the same evidence. Those dissimilarities can create confusion among health care professionals, the general public, and policy makers. The Institute of Medicine (IOM) recently released 2 reports to establish new standards for developing more trustworthy clinical practice guidelines and conducting systematic evidence reviews that serve as their basis. Because the American Cancer Society (ACS) is an important source of guidance about cancer screening for both health care practitioners and the general public, it has revised its methods to create a more transparent, consistent, and rigorous process for developing and communicating guidelines. The new ACS methods align with the IOM principles for trustworthy clinical guideline development by creating a single generalist group for writing the guidelines, commissioning independent systematic evidence reviews, and clearly articulating the benefits, limitations, and harms associated with a screening test. This new process should ensure that ACS cancer screening guidelines will continue to be a trustworthy source of information for both health care practitioners and the general public to guide clinical practice, personal choice, and public policy about cancer screening.

JAMA. 2011;306(22):2495-2499

www.jama.com

In March 2011, the Institute of Medicine (IOM) released 2 reports on standards for creating trustworthy clinical practice guidelines, one providing recommendations for how clinical practice guidelines should be created⁷ and the other providing recommendations for how systematic evidence reviews should be conducted.⁸ The primary goals of the reports were to motivate guideline developers to use good processes and provide the users of guidelines with metrics to judge their trustworthi-

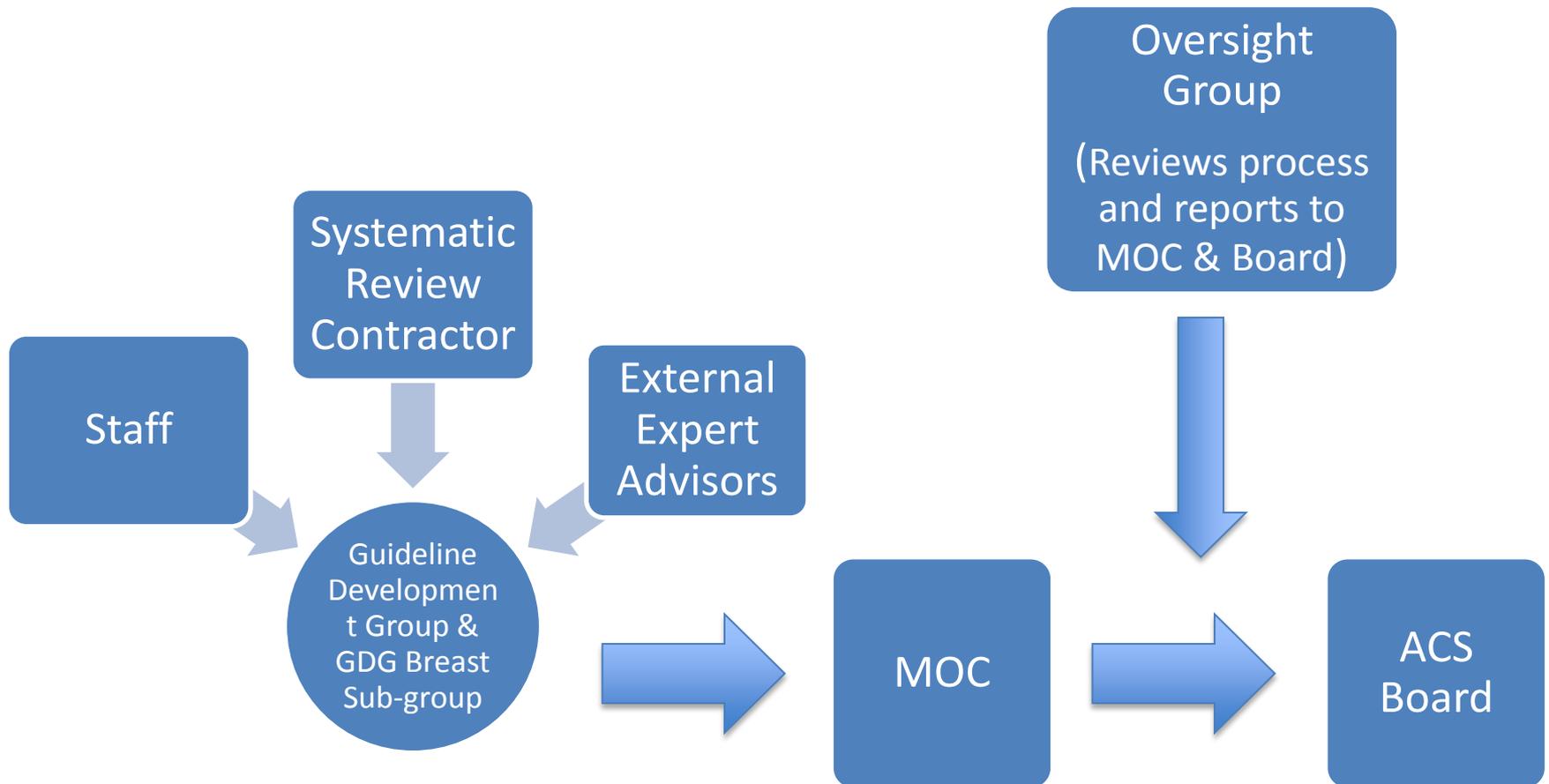
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Current ACS Guideline Development Process



2015 ACS Breast Cancer Screening Guideline – Preface Statement

- These recommendations represent guidance from the American Cancer Society (ACS) for women with an average risk of breast cancer - an individual may reach a decision about breast cancer screening that is different from this guidance. The ACS recommends that all women should become familiar with the known benefits, limitations, and potential harms associated with breast cancer screening.

Preface Statement, cont.

- We considered average-risk women as those without a personal history of breast cancer, a genetic mutation known to increase risk of breast cancer (e.g., BRCA), or a history of previous radiotherapy to the chest at a young age.

The Risk within Average Risk Varies

- 80% to 90% of women will fall into the average risk category
- Risk is not equal within this group:
 - Family history
 - Age of childbearing
 - African American women may be at slightly higher risk

2015 ACS Breast Cancer Screening Guideline

- Recommendations:
 1. Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years. **(Strong Recommendation)**
 - 1a: Women who are ages 45 to 54 years should be screened annually. **(Qualified Recommendation)**
 - 1b: Women who are 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. **(Qualified Recommendation)**
 - 1c: Women should have the opportunity to begin annual screening between the ages of 40 and 44 years. **(Qualified Recommendation)**

2015 ACS Breast Cancer Screening Guideline, cont.

2. Women should continue screening as long as their overall health is good and they have a life expectancy of 10 years or longer. (Qualified Recommendation)

3. The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age. (Qualified Recommendation)

2003 vs. 2015 ACS Guidelines for Average Risk Women

Recommendation	2003	2015
BSE	Not recommended	Not recommended
CBE	Ages 20-39: Every 3 yrs. Ages 40+: Annual	Not recommended
Mammography	Annual screening beginning at age 40 End screening when curative therapy would not be offered due to life-limiting co-morbidity	<p>Women 40-44 should have the opportunity to begin annual screening before age 45</p> <p>Women aged 45 to 54: annual</p> <p>Women 55+ should transition to biennial screening, but should have the opportunity to continue screening annually</p> <p>Women should continue screening as long as their overall health is good and they have a life expectancy of 10 years or more</p>

Current Breast Cancer Screening Guidelines for Average Risk Women: ACS (2015); Draft USPSTF (2015)

Recommendation	ACS	USPSTF (Draft)
Breast Self Exam (BSE)	Not recommended	Against clinicians teaching BSE (D)
Clinical Breast Exam (CBE)	Not recommended	Insufficient evidence (I).
<p>Mammography USPSTF GRADES (A & B, C, D, I)</p> <p>ACS S = Strong Q = Qualified</p>	<p>40-44: Opportunity for informed decision (Q), Annual (Q)</p> <p>45-54 (S): Annual (Q)</p> <p>55+ Biennial (Q), with option to continue annual screening (Q)</p> <p>75+ Continue screening as long as health is good and life expectancy 10+ yrs (Q)</p>	<p>40-49: Individual decision (C)/Biennial</p> <p>Ages 50-74: Biennial (B)</p> <p>Ages 75+ : Insufficient evidence (I)</p>

Clinical Breast Exam (CBE)

- Important to not place too much emphasis on CBE screening.
- While CBE will detect some tumors, it will not detect the majority of breast cancers.

Breast Cancer Detection Among Women 20-44	
Self	71.2%
CBE	9.3%
Mammography	19.6%

A Note About Women 50 to 75

- 35 to 40 percent do not get routine mammography
- Incidence of breast cancer and death from breast cancer is far higher than aged less than 44.
- The number of lives to be saved in this age group is huge!!!

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