Prostate Cancer Screening

18th February 2016

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BC Cancer Agency
CARE + RESEARCH
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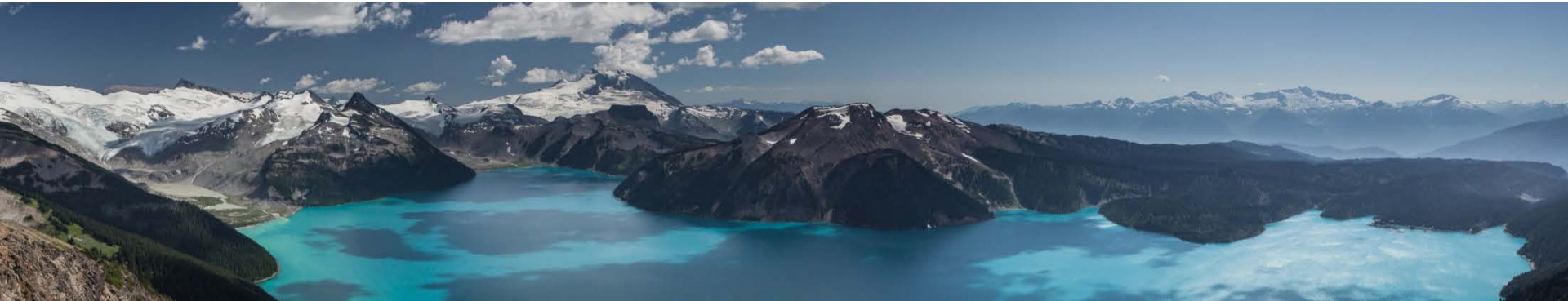
UBC



CONFLICT OF INTEREST

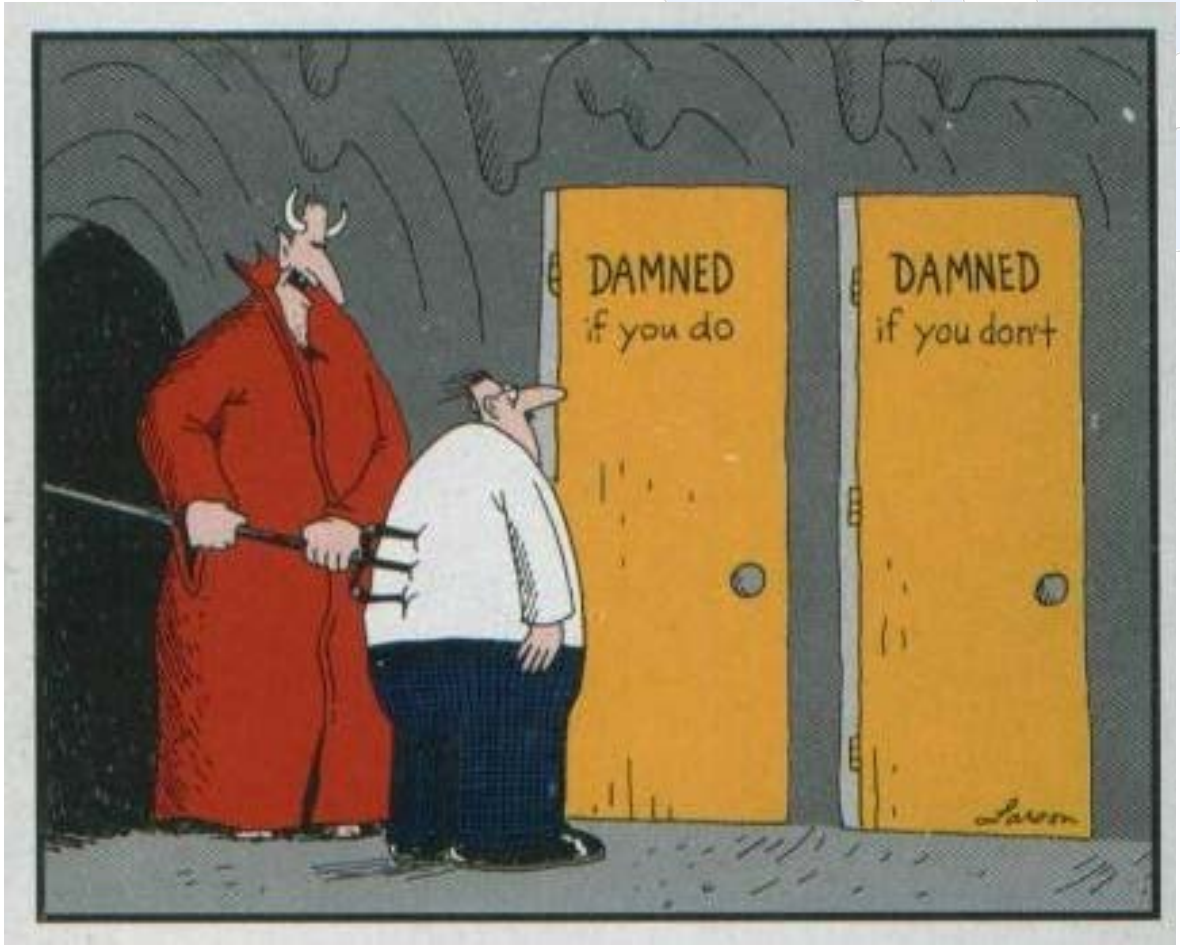
NONE

Have you had your PSA screening test yet?

If not, should you?

If yes, was that a good idea?

PSA screening – summary?



Gary Larson – Far Side

Prostate Cancer Demographics

- In Canada in 2015
  - 24,000 new cases (#1 overall)
  - 4,100 deaths (#3 in men)
- In B.C. in 2013
  - 3,800 new cases (#1 overall)
  - 600 deaths (#3 in men)

There is a disparity between the high prevalence and low risk of death
Life time risk of diagnoses is 16% and risk of death 3%

10-15% of men with Pca die of the disease
85% die form other causes

5 y OS with organ confined disease is ~ 98% and with metastatic disease is 30%

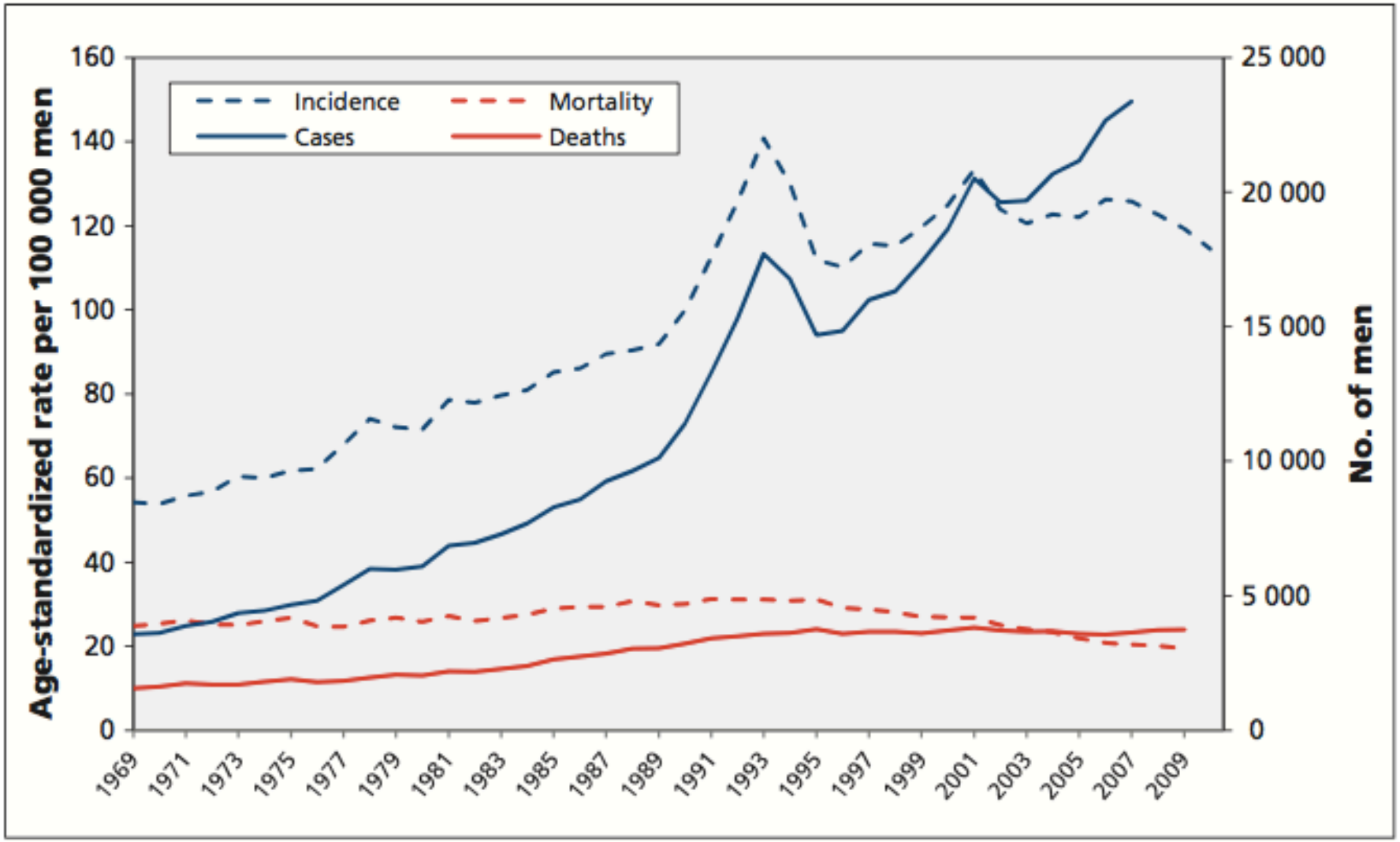


Figure 1: Cases of and deaths from prostate cancer, with associated age-standardized incidence and mortality (per 100 000 men), among Canadian men aged 45 years and older. Age was standardized to the 1991 Canadian population. Incidence data were not available for Quebec from 2008 to 2010; therefore, the population denominator for age-standardized incidence was adjusted and case counts for 2008–2010 were omitted. Mortality data were available only to 2009.

Outline

1. Background – screening concepts

   Properties of Screening Tests, Bias

2. Challenges with PSA screening

3. Screening Recommendations

   Canadian Task Force, BCCA

4. **Smart screening**

1. BACKGROUND

SCREENING CONCEPTS

PROPERTIES OF SCREENING TESTS

Potential **benefits** of screening

Screening is the use of tests or procedures in “healthy people” (no symptoms) to detect disease early

General benefits may include:

1. **Reduced likelihood of death**
2. **Less invasive treatment:**
   - Screen detected cancers are generally lower stage and treatment is frequently less complex

3. Reduced likelihood of cancer development:
   - Some screening tests identify pre-cancerous disease which may be successfully treated, colon, lung cervix.

Potential **harms** of screening

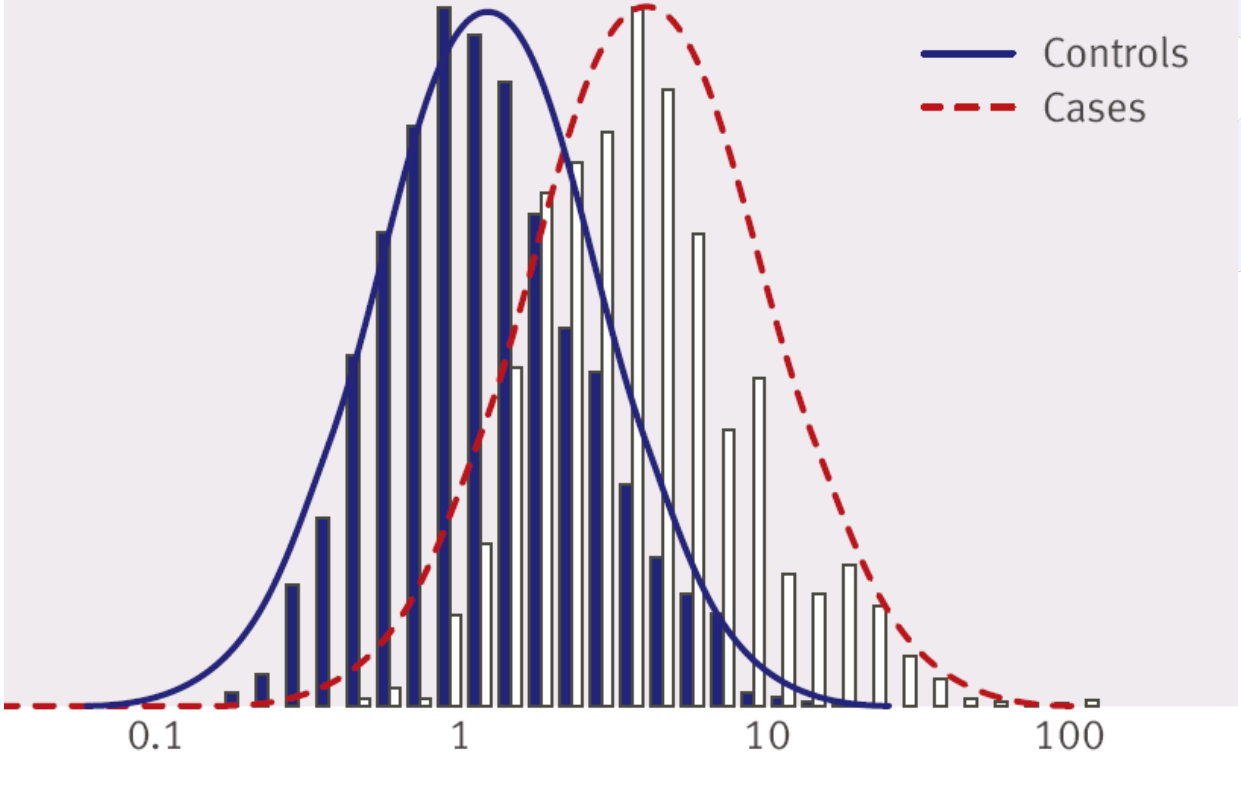
1. False-positive results
   - cause morbidity, anxiety, waste money and waste time.
2. Labeling:
   - Patients live longer with the knowledge of cancer, Life insurance etc., can be affected.
3. Over-diagnosis:
   - Some cancer would never have been diagnosed, or caused symptoms if patients hadn't been screened.
4. Overtreatment - harm form the treatment, investigations

PSA AS A SCREENING TEST?

PSA

- Protein made by prostate tissue
- Half life 2.2 days
    - ~10x more from malignant tissue
- Benign causes of elevation (small)
  - BPH
  - Prostatitis/inflamation
  - Day to day & lab variation
  - Local trauma
  - Biopsy TURP - elevation persist for 4-6 weeks
  - urinary obstruction
  - Ejaculation
  - DRE
- Prostate cancer

Population PSA* levels



No safe level

PSA ≤ 4 = 25% of pCa and < 5% of high grade ca

* Prostate specific antigen

Holmström,BMJ 2009;339:

What can improve sensitivity and specificity with PSA testing?

- Age-adjusted reference ranges
- PSA velocity (rate of change over time)
- Free/total PSA ratio
  - Ratio of free-total-PSA is reduced in men with Pca
  - Helpful at extreme ration values – increase PPV form 25-50% for PSA 4-10.
- PSA density (PSA level relative to gland volume)
- PCA3 Pca antigen 3 gene

None very good!

Assessment of Screening Test Results

- **Sensitivity**
  - Probability that a person **with** the disease is correctly identified by the test
- **Specificity**
  - Probability that a person **without** the disease is correctly identified by the test

Assessment of Screening Test Results

- **PPV - Positive Predictive Value**
  - Proportion of those who have positive test and who have the disease
    - PSA PSA >4 =30%
    - PSA 4-10 =25%
    - PSA >10 = 40-60%
- **NPV Negative Predictive Value**
  - Proportion with a negative test who do not have the disease
    - PSA<4 -85%

DRE?

- Many question the utility of DRE in screening
  - PPV ~10-30%
  - If PSA normal – PPV for abnormal DRE is only 10%
  - IF DRE is normal and PSA is 4-10 PPV 25%

- **Combination of PSA and DRE slightly better**

PSA AS A SCREENING TEST?

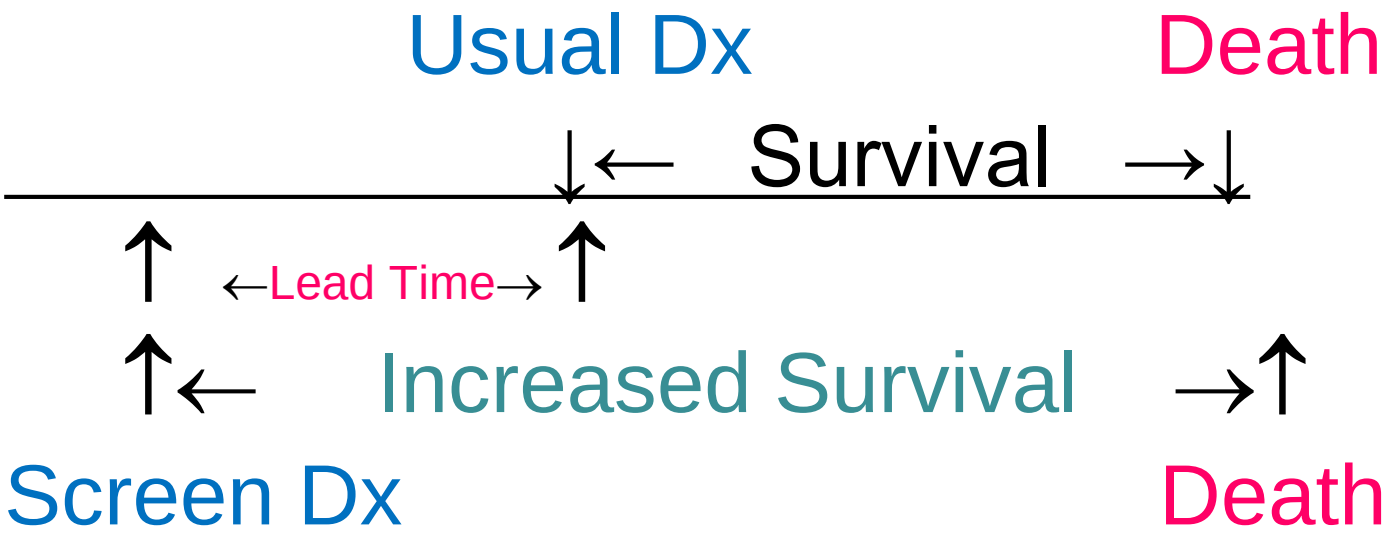
PSA is not a very good screening test!

BIAS IN SCREENING

Lead Time Bias – survival analysis

Lead time bias:

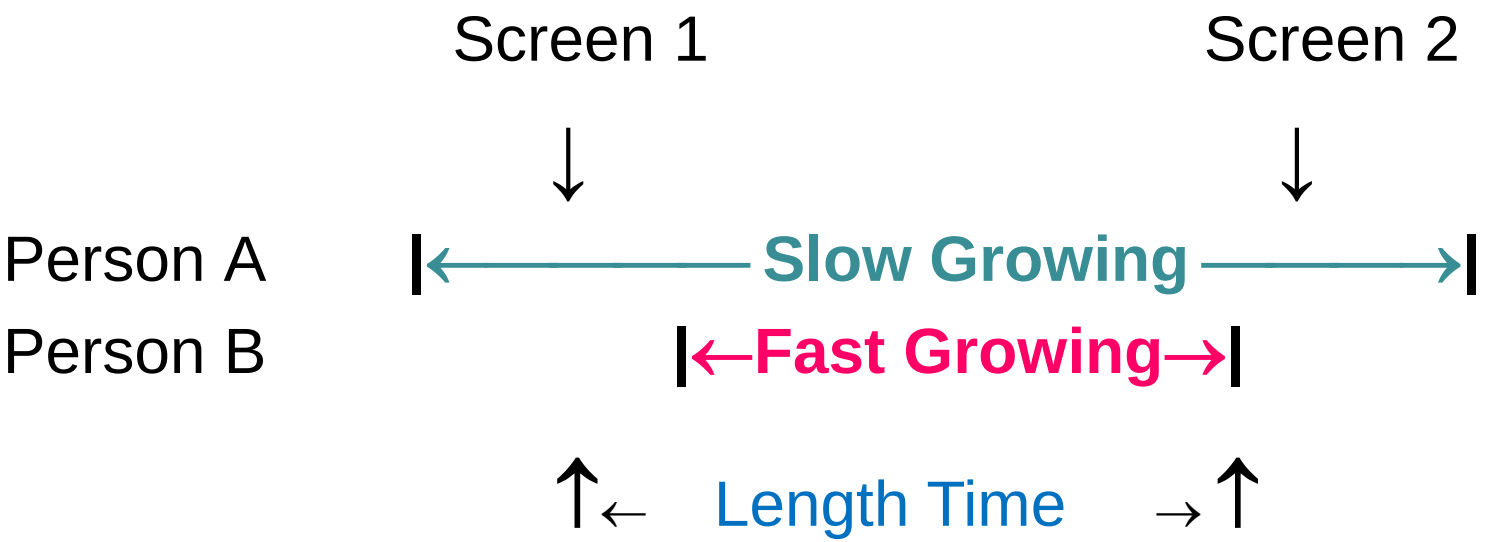
increased survival is achieved by virtue of having and earlier diagnosis, in fact no impact on survival



Length Bias – in survival analysis

Length time bias :

slower growing cancers are more likely to be detected at screening – aggressive ca missed by screening



Men die form aggressive prostate cancer, even when disease is detected by screening

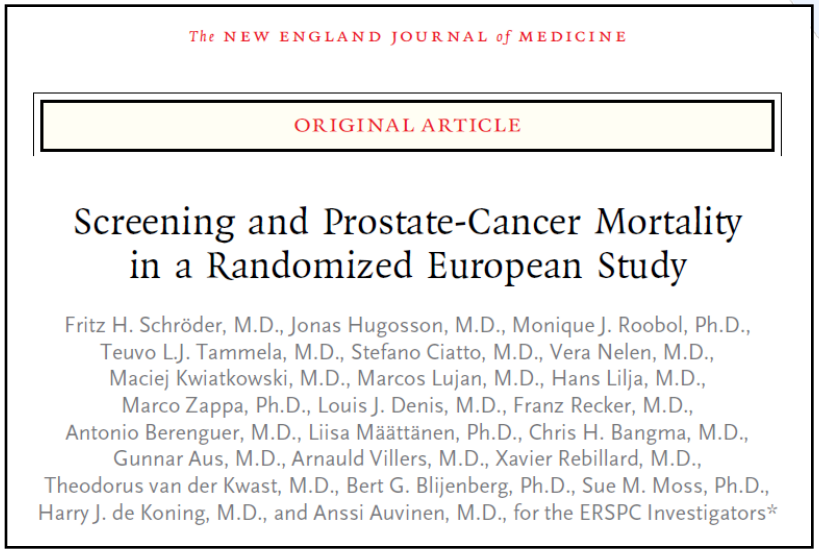
Bias in screening of Prostate Cancer?

Bias is a significant issue PSA screening

PSA screening

detects significant portion of indolent cancers
aggressive cancers remain lethal or are missed altogether

The two main PSA screening trials

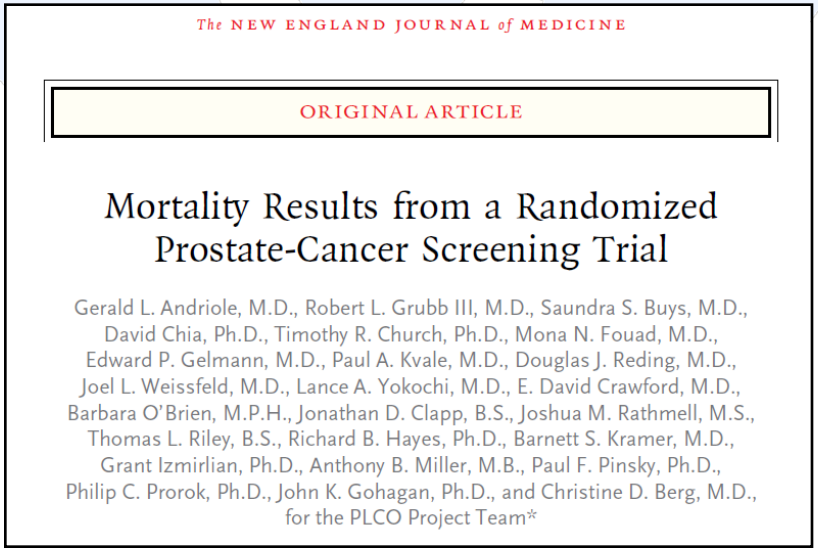


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., Robert L. Grubb III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D., Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D., Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D., E. David Crawford, M.D., Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S., Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D., Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D., Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., and Christine D. Berg, M.D., for the PLCO Project Team*

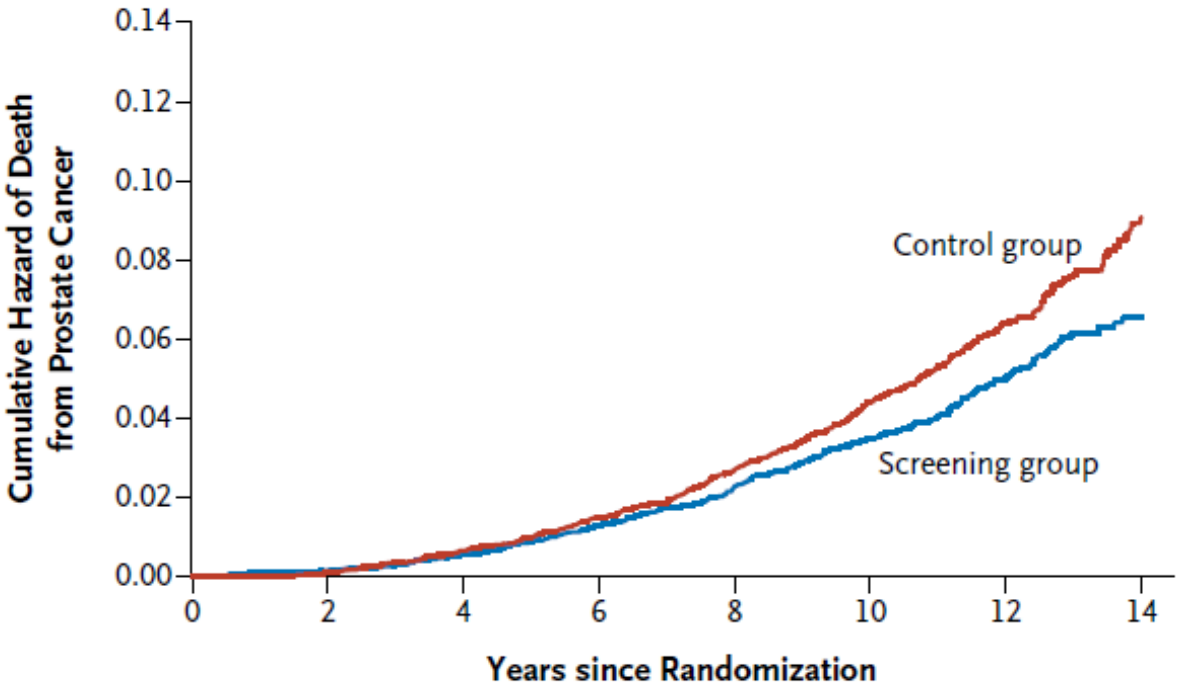
Europe - ERSPC

USA - PLCO

NEJM March 2009

European ERSPC trial

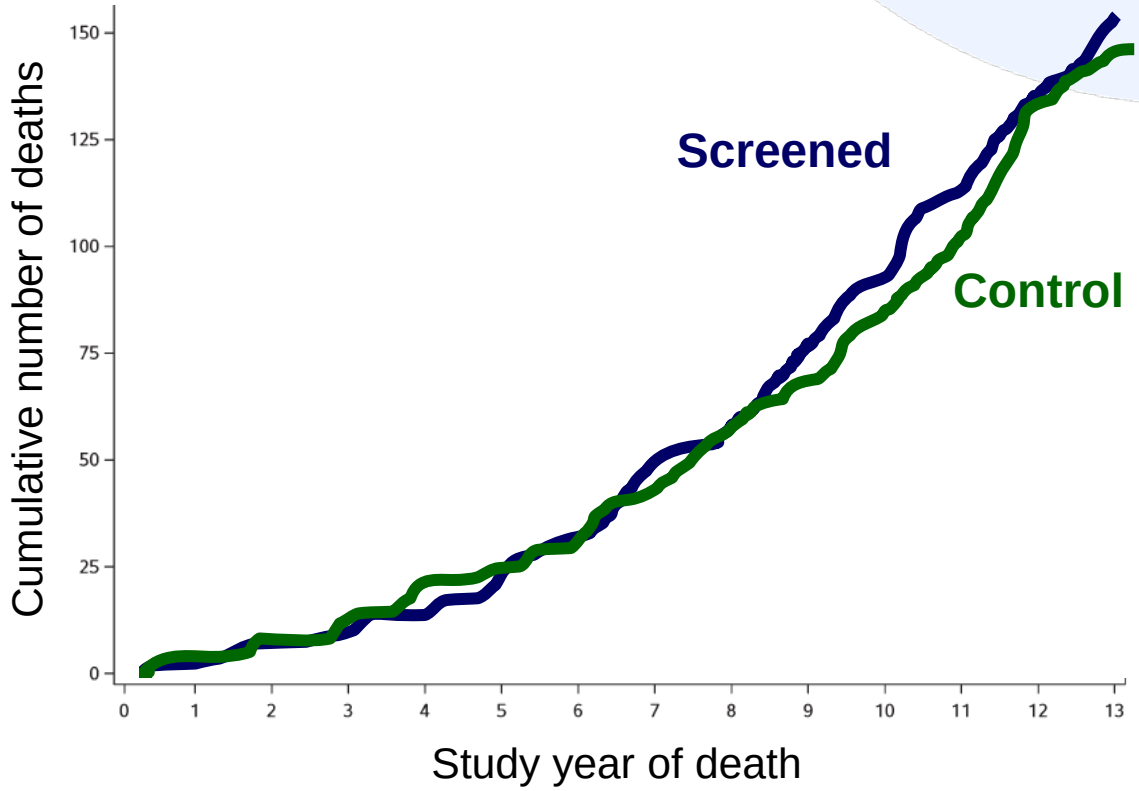
- **20% mortality reduction**



Schroder: NEJM March 15, 2012

US PLCO trial

No mortality reduction



Redrawn from Andriole JNCI On line 2012

Contradiction in 2 RTC

- **USA study**
- Smaller study
- FU 7 years
- Older men
- 44% screened in control arm

- **No mortality reduction**

- **EUROPEAN study**
- Bigger study
- Fu 9 years
- Younger men
- 10% screened if control arm

- **20% mortality reduction**

So it was a trial of *more* screening versus *~50%* screening

Reanalysis of USA trial – based on comorbidities at baseline

Men stratified by co-morbidities

Testing the hypothesis that men in good health would benefit more from screening

- Minimal co-morbidity was seen in only 35% men

50% mortality reduction at 10 years

E. D Crawford at al JCO Feb 2011

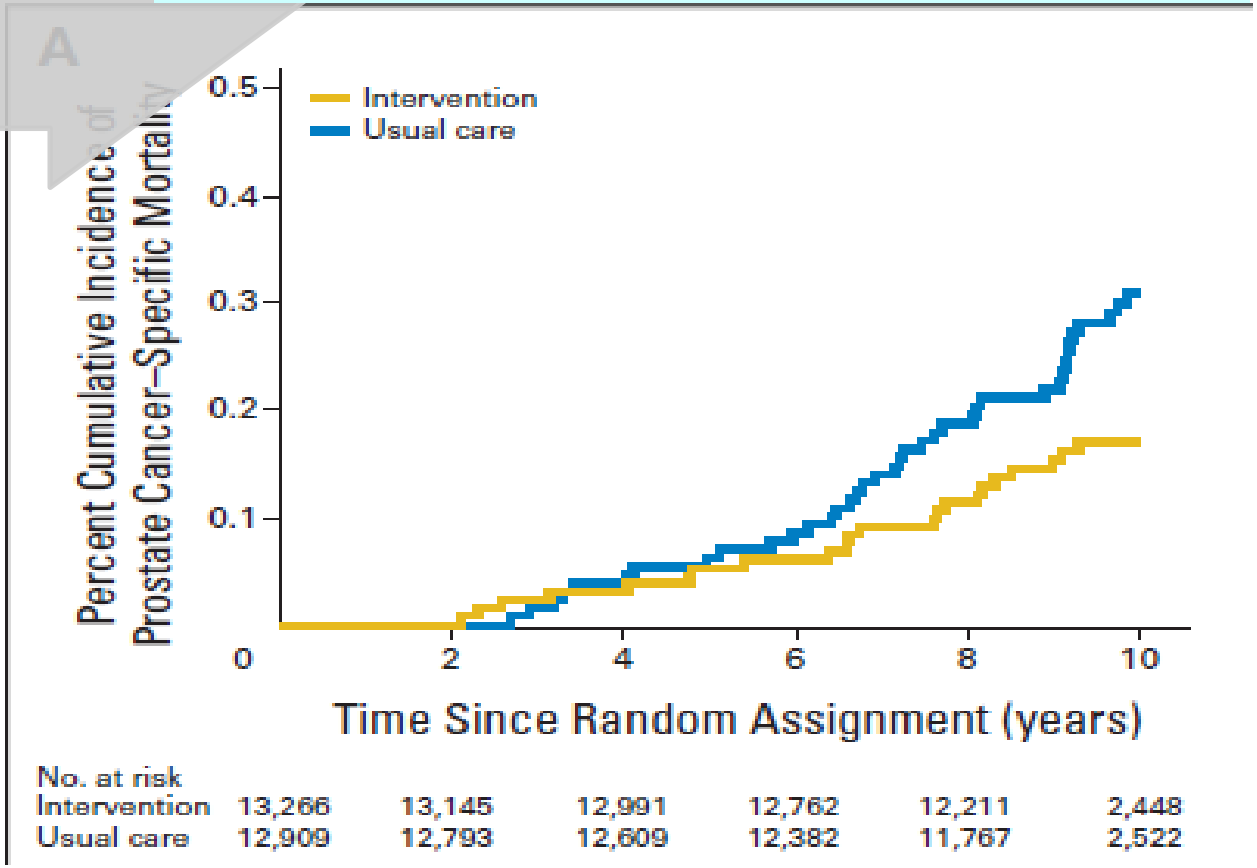
NNS – number need to screen to prevent one death

PC specific mortality Reduction by 50%

NNS 723

NNT 5

Results changed form NO mortality Reduction to 50% mortality reduction



E. D Crawford at al JCO Feb 2011

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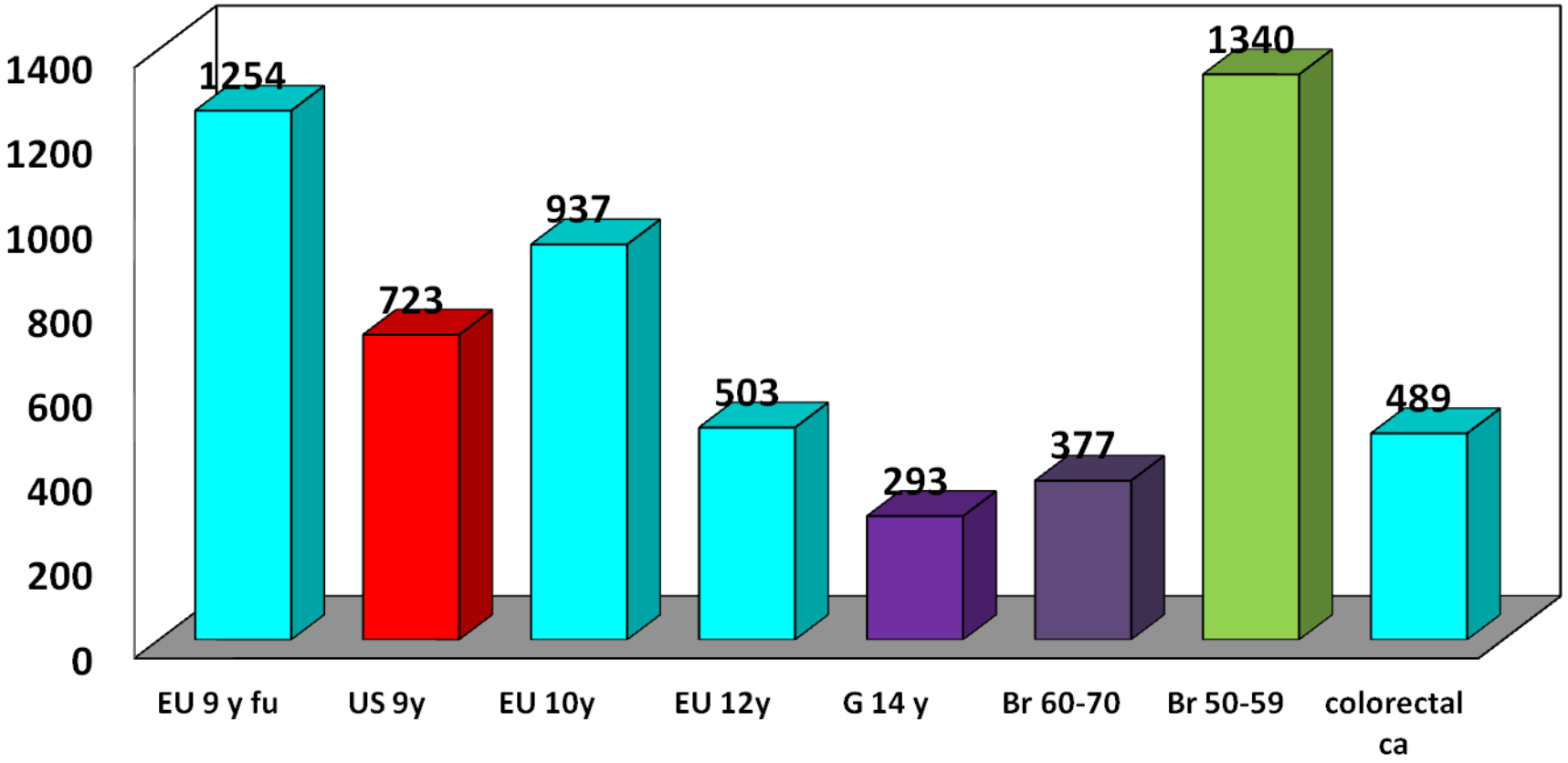

Length of follow up is critical

Loeb at al JCO 2011

Hugosson at al. Lancet Oncology 2010

PSA SCREENING RECOMMENDATIONS

Confusion in the lay press, and no just lay press…..

New data fuels debate over **prostate cancer** screening
Fox News
Updated results from a long-term study concludes that regular **prostate cancer** screening cuts the risk of death from **prostate cancer**. But there was no overall difference in death rates between men who got screened and those who didn't.
See all stories on this topic »

Updated Study Underscores **Prostate Cancer** Screening Saves Lives
MarketWatch (press release)
TALLAHASSEE, Fla., March 15, 2012 /PRNewswire via COMTEX/ -- In a comprehensive study published today in the New England Journal of Medicine, PSA screening was shown to reduce the mortality rate of **prostate cancer** by 29 percent.
See all stories on this topic »

Prostate Screening Isn't Saving Lives, Study Finds
Huffington Post
By MARILYNN MARCHIONE 03/14/12 05:25 PM ET -- A big study of men in Europe gives mixed results about **prostate cancer** screening that may do little to change minds about its value. The study finds that PSA blood tests every four years seem to cut the **...**
See all stories on this topic »

AUCNY Supports New Study Confirming the Need for **Prostate Cancer** Screening and **...**
MarketWatch (press release)
New information, a follow-up of the European Randomized Study of Screening for **Prostate Cancer** (ERSPC), was published today in the New England Journal of Medicine by Dr. Fritz Schröder, the lead author of the ERSPC trial.
See all stories on this topic »

Google alert March 2012

Screening recommendations Form various organizations

Table 3: Summary of recommendations for PSA screening for prostate cancer from Canada and elsewhere

Organization	Age at initiation of PSA screening	Screening interval	Age at discontinuation of PSA screening
Canadian Task Force on Preventive Health Care (current)	Routine PSA screening not recommended		
Canadian Task Force on the Periodic Health Examination (1994)[11]	Routine PSA screening not recommended as part of periodic health examination		
US Preventive Services Task Force (2012)[8]	PSA screening not recommended; applies to men of all ages		
Canadian Urological Association (2011)[54]	• Average risk: offer at age 50 yr to men with life expectancy ≥ 10 yr • Increased risk (e.g., family history of prostate cancer, African descent): offer at 40 yr • Offer baseline PSA test at age 40–49 yr to establish future risk of prostate cancer	Not specified	75 yr
Canadian Cancer Society (2014)[55]	Men aged > 50 yr should talk with their doctor about whether they should be tested for prostate cancer	Not specified	Not specified
American Cancer Society (2012)[56]	Average risk: discussion at age 50 yr Increased risk: discussion at age 40 or 45 yr, depending on extent of risk	PSA < 2.5 ng/mL: 2 yr PSA ≥ 2.5 ng/mL: annual	Life expectancy < 10 yr
National Cancer Institute (2012)[22]	Insufficient evidence to determine whether screening with PSA or digital rectal examination reduces prostate cancer mortality		
National Health Service (2013)[57]	No organized screening program; informed-choice program = men concerned about the risk of prostate cancer receive clear and balanced information about the advantages and disadvantages of PSA testing and cancer treatment		
Prostate Cancer Canada (2013)[58]	• Offer baseline PSA test at age 40–49 yr • Men aged > 40 yr should talk with their doctor about early detection • Men at high risk should talk with their primary care provider before age 40 yr about prostate cancer	Not specified	≥ 70 yr; decision should be based on individual factors (not specified)
American Urological Association (2013)[59]	• Routine screening not recommended for men aged 40–54 yr at average risk • Shared decision-making recommended for men aged 55–69 yr; decision to proceed based on patient's values and preferences	≥ 2 yr	≥ 70 yr or life expectancy < 10–15 yr
American College of Physicians (2013)[60]	Men aged 50–69 yr: clinicians should discuss the limited benefits and substantial harms of screening for prostate cancer; they should not screen for prostate cancer with the PSA test in patients who do not express a clear preference for screening	Not specified	≥ 70 yr or life expectancy < 10–15 yr
Cancer Council Australia, Australian Health Ministers' Advisory Council (2010)[61]	PSA test not suitable for population screening		

Note: PSA = prostate-specific antigen.

PSA screening confusion

- **US and Canadian Task Force recommended against screening – highly influential**
- Most other organization recommend that informed decision be made by the patients after the discussion
- **Many decision aids**
  - Conflicting numbers
  - Difficult to understand
  - Too much or too little information – Goldilocks
  - Detailed discussion about benefits and harms of screening- how do you do that?? In 5 min??
  - What is the knowledge of the primary providers??

Committees which provide recommendations on clinical preventive strategies are

Canada: Canadian Task Force on Preventive Health Care http://www.canadiantaskforce.ca/

US: US Preventive Services Task Force

http://www.ahrq.gov/clinic/uspstfix.htm

BC: The BC Cancer Agency

provides recommendations and operates cancer screening programs

Canadian Task Force 2014 PSA screening

Canadian Task Force on Preventive Health Care*

See related commentary on page 1201 and at www.cmaj.ca/lookup/doi/10.1503/cmaj.141252

- For men aged less than 55 years, we recommend **not screening** for prostate cancer with the PSA test.
  - ***Strong recommendation**; low quality evidence*
- For men aged 55–69 years, we recommend **not screening** for prostate cancer with the PSA test.
  - ***Weak recommendation**; moderate quality evidence*
- For men 70 years of age and older, we recommend **not screening** for prostate cancer with the PSA test.
  - ***Strong recommendation**; low quality evidence*

http://canadiantaskforce.ca/ctfphc-guidelines/2014-prostate-cancer/

10 y benefits of screening a1000 men age 5-65 every 1-4 years

Die (pCa) no Screening	5/1000
Die with screening	4-5/1000
Did not die because of screening	0-1/1000
Complications of bx	100-120/1000
Men asymptomatic form cancer for the entitle life	110/1000

D recommendation against prostate cancer screening

Level D is the strongest category of recommendation against an intervention.

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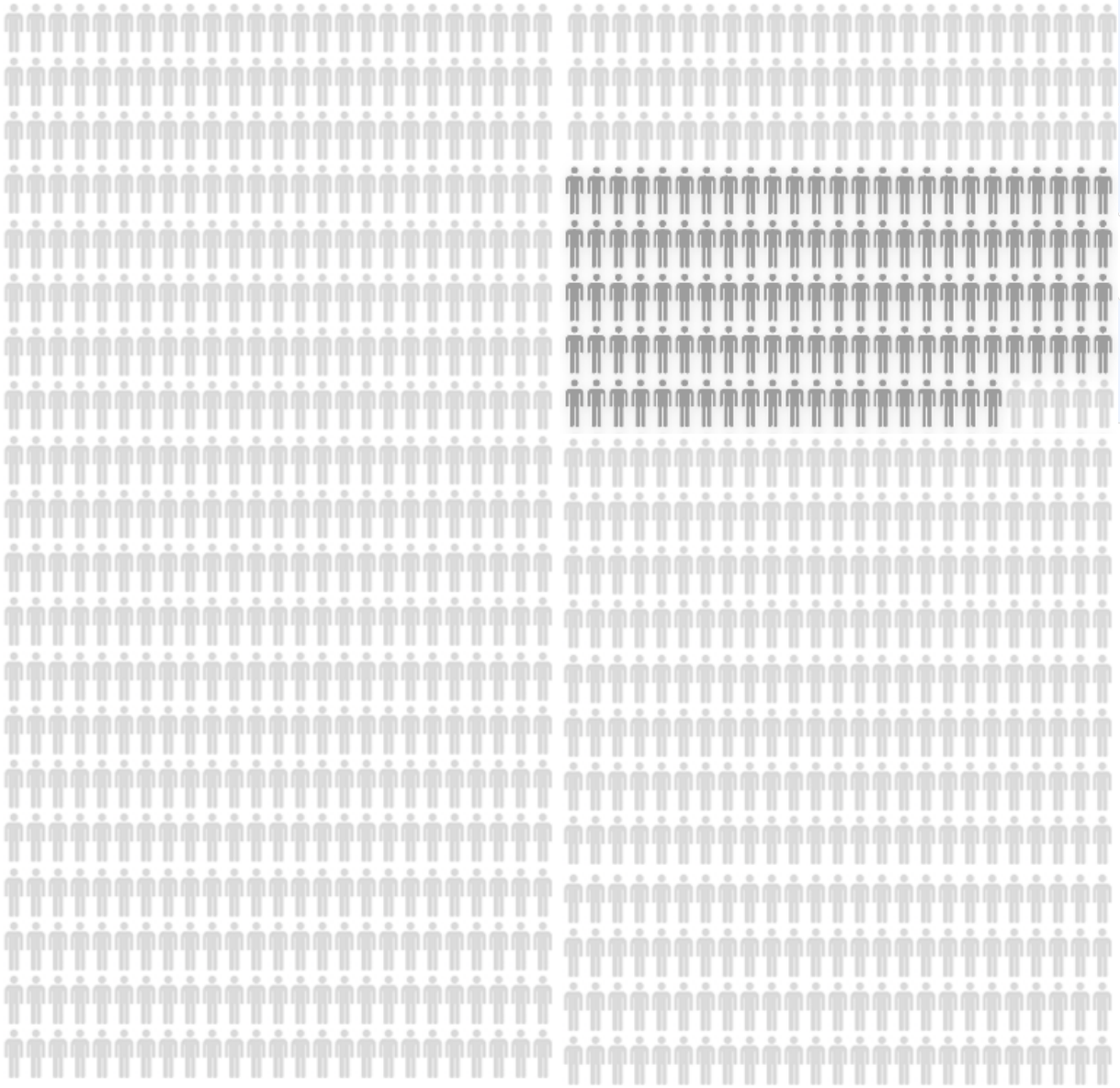
US Services Taskforce infographic http://www.cancer.gov/ncicancerbulletin/112712/page12



1,000 men screened.

Of these:

100-120

get false-positive results that may cause anxiety and lead to biopsy

(Possible side effects of biopsies include serious infections, pain, and bleeding)

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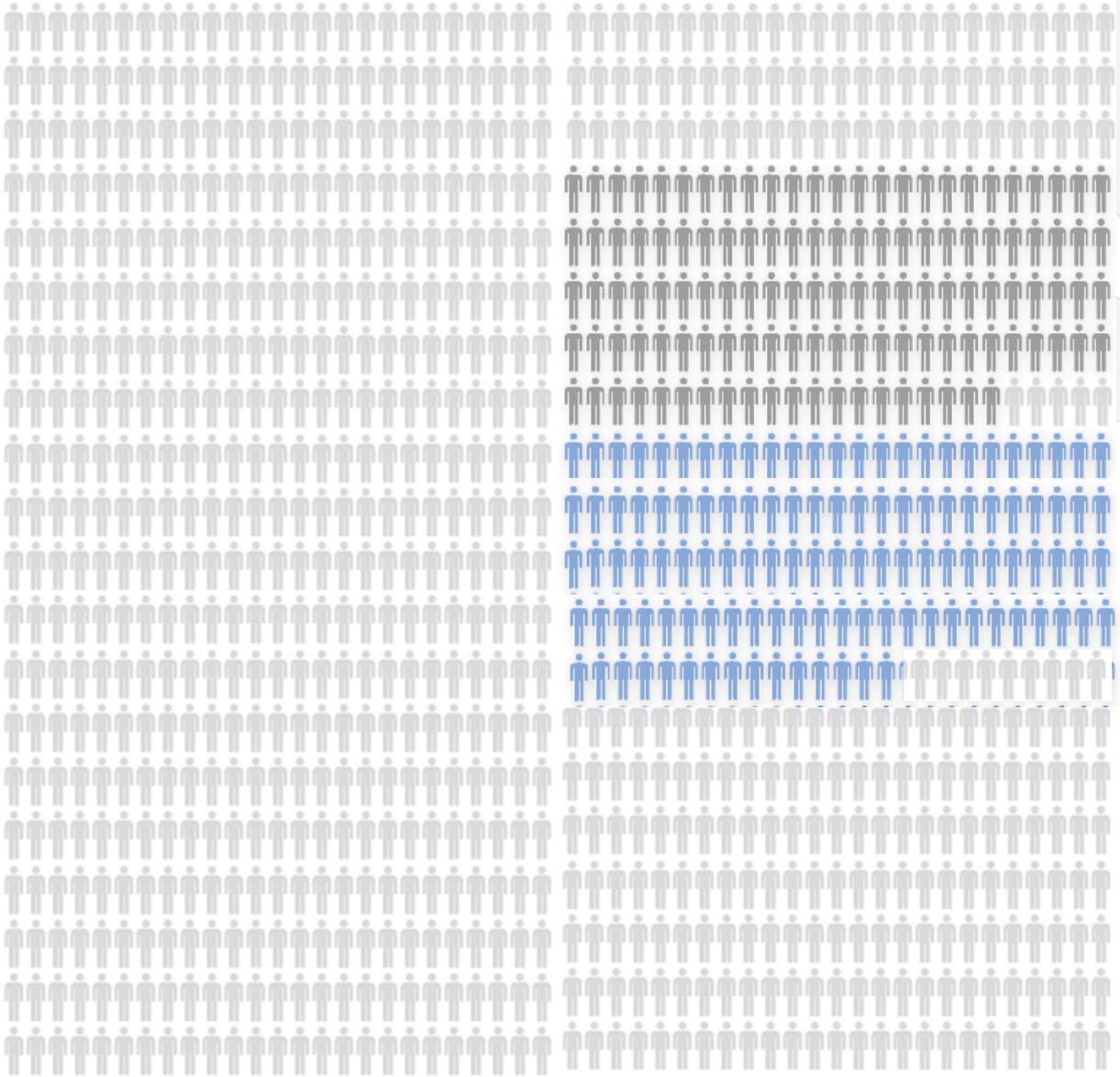

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110

get a prostate cancer diagnosis, and of these men:

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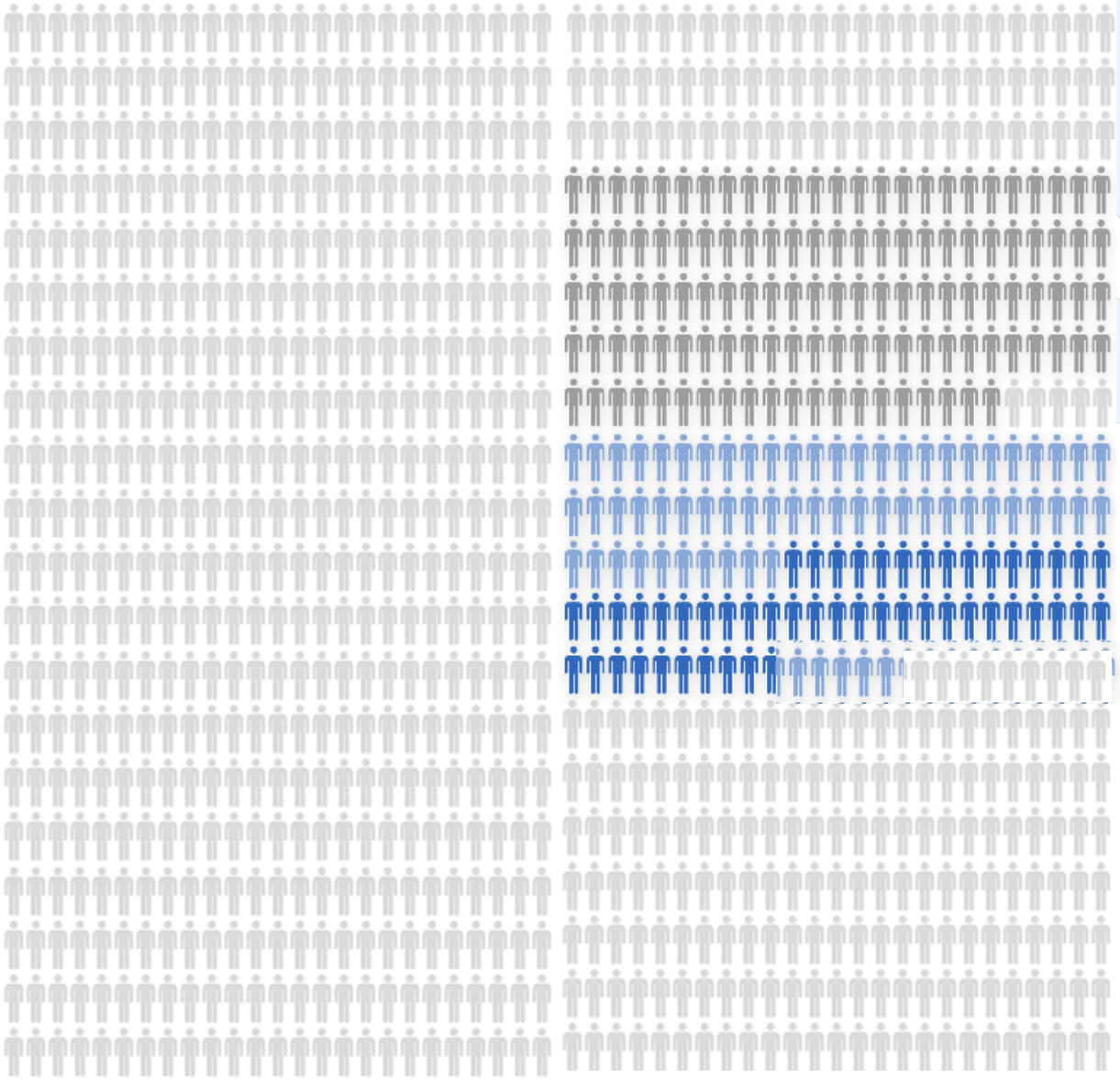

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110

get a prostate cancer diagnosis, and of these men:

- **at least 50**

  will have treatment complications, such as infections, sexual dysfunction,or bladder or bowel control problems

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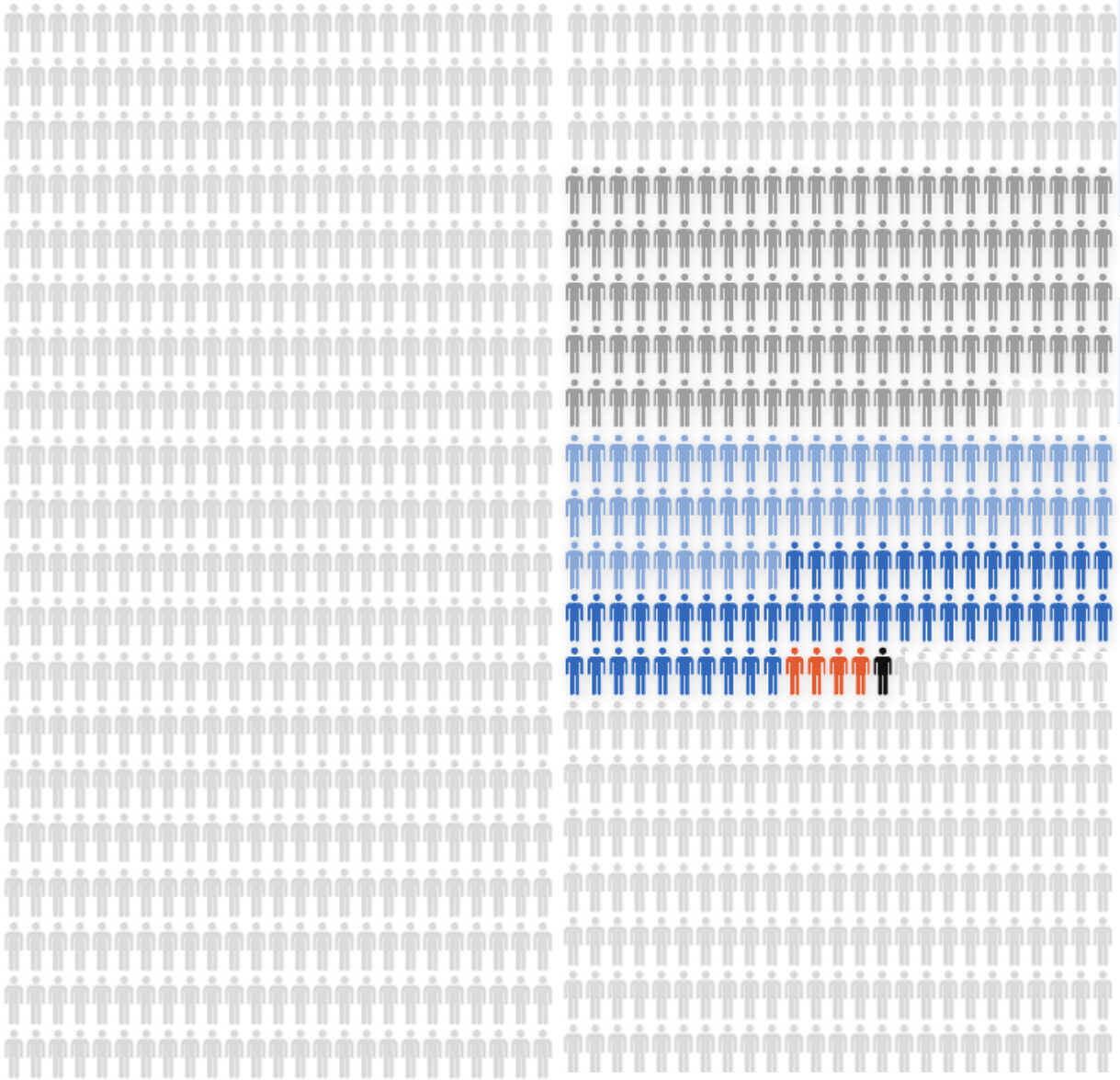

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Of these:

100-120

get false-positive results that may cause anxiety and lead to biopsy

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110

get a prostate cancer diagnosis, and of these men:

- **at least 50** will have treatment complications, such as infections, sexual dysfunction,or bladder or bowel control problems
- **4-5** die from prostate cancer (5 die among men who do not get screened)
- **0-1** death from prostate cancer is avoided

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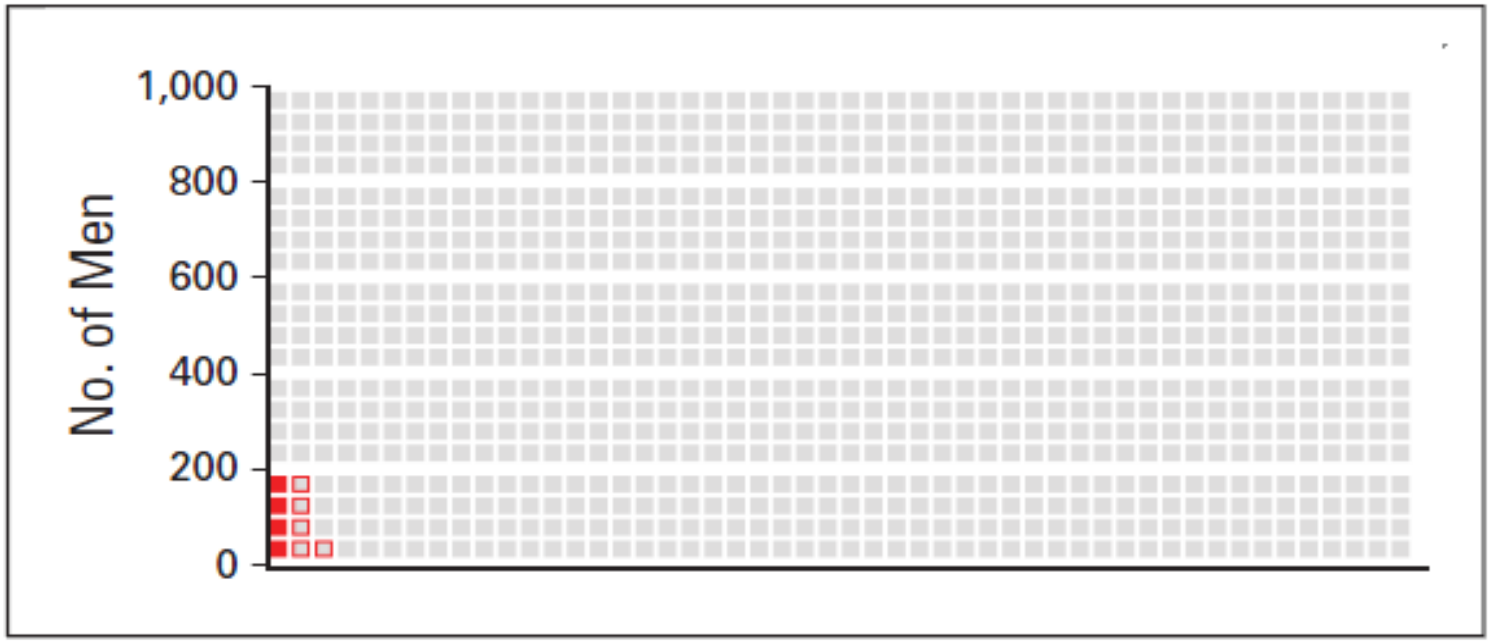
US Services Taskforce infographic http://www.cancer.gov/ncicancerbulletin/112712/page12

Absolute reduction in PC mortality Goteborg trial – 14 y Follow up



Goteborg trial – 1000 men and 14 y follow up
due to PSA screening would reduce mortality form 9 to 4 man . Gray boxes are men who would not die of prostate cancer, regardless of screening.

P Carroll JCO 2011

Reviews

BJUI
BJU International

The Melbourne Consensus Statement on the early detection of prostate cancer

Declan G. Murphy[1,2,3], Thomas Ahlering[4], William J. Catalona[5], Helen Crowe[2,3], Jane Crowe[3], Noel Clarke[10], Matthew Cooperberg[6], David Gillatt[11], Martin Gleave[12], Stacy Loeb[7], Monique Roobol[14], Oliver Sartor[8], Tom Pickles[13], Addie Wootten[3], Patrick C. Walsh[9] and Anthony J. Costello[2,3]

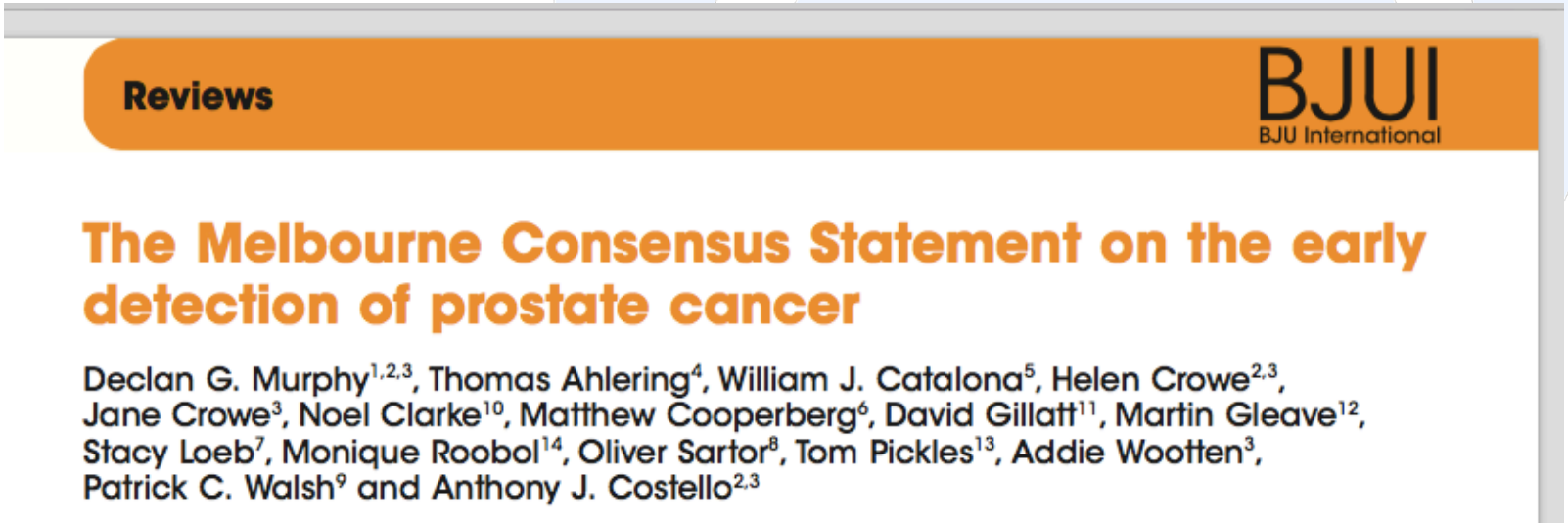
PSA screening reduce met pCa and increase cause specific survival (age 50-69)

Pca diagnosis must be uncoupled with decision to treat

PSA screening should not be considered on it own (or standalone test)

PSA is not good stand alone test

- Ethnicity, family history medical history
- DRE, PSA ,prostate volume
- PSA3
  - to reduce over diagnosis



Baseline PSA testing age 40-50

Older men in good health with life expectancy >10 should not be denied PSA test

BCCA recommendations

- Early detection *(not PSA screening!)* of prostate cancer should be offered to asymptomatic men 50 y or older
- How often? (2-4 years)
- Stop when life expectancy <10 y
- Only if they wish to be tested and are well informed of harms and benefits
- Men with higher risk for prostate cancer:
  - screening at age 40 to 45 (African American origin, family history of prostate cancer, BRCA1 or BRCA2 mutation carrier).

- **Abnormal results should trigger referral to a urologist**.

- **Who should be referred to Urology?**
  - **PSA of >3.0 µg/L**
  - PSA > 2.0 and by more than 0.75-1.0 /year
  - **DRE abnormal**

- **Who to biopsy?**
  - consideration of life expectancy, co-morbidities, prostate co-conditions (e.g. large BPH, prostatitis), PSA velocity, DRE findings, and patient risk factors and preference.

PSA screening confusion

- **US and Canadian Task Force recommended against screening – highly influential**
- Most other organization recommend that informed decision be made by the patients after the discussion
- **Many decision aids**
  - Conflicting numbers
  - Difficult to understand
  - Too much or too little information – Goldilocks
  - **Detailed discussion about benefits and harms of screening- how do you do that?? In 5 min??**
  - **What is the knowledge of the primary providers??**

What is GP to do??

- ¼ GPs are confident in their knowledge about PSA screening
- Low correlation between confidence and knowledge
- Less than a half of primary care physicians are compliant with the recommendations of PSA screening - discuss: pros and cons

- Fear of missing cancer
  - Screen all or none

Tasian GE at al Urol Onoclogy: 2012 30(2)

Annals of Internal Medicine | IDEAS AND OPINIONS

A Simple Schema for Informed Decision Making About Prostate Cancer Screening

Andrew J. Vickers, PhD; Kelly Edwards, PhD; Matthew R. Cooperberg, MD, MPH; and Alvin I. Mushlin, MD, ScM

2014 Volume 61

1. Information must be based on evidence, and be beyond dispute

1. Patient should be presented with a clear framework for a decision

   Decision aids provide a large number of estimates and ask the pt to somehow integrate this into the choice

2. The schema must be appropriate for the primary care and should not assume that the provider has a detailed knowledge of the subject

Table. Decision Tool for Prostate Cancer Screening

Key facts about prostate cancer and screening

- Prostate cancer is common; most men will develop it if they live long enough.
- Although only a small proportion of men with prostate cancer die of the disease, the best evidence shows that screening reduces the risk for prostate cancer death.
- Screening detects many low-risk or "indolent" cancer cases.
- In the United States, most low-risk cancer is treated and the treatment itself can lead to complications, such as incontinence, erectile dysfunction, and bowel problems.

Key take-home messages

- The goal of screening is to find aggressive prostate cancer early and cure it before it spreads beyond the prostate.
- Most cancer cases found by screening do not need to be treated and can be safely managed by a program of careful monitoring known as "active surveillance."
- If you choose to be screened, there is a good chance that you will be diagnosed with low-risk cancer and you may face pressure from your physicians or family to treat it.

Discrete decision

- If you are concerned that you would be uncomfortable knowing that you have cancer and not treating it, screening may not be for you.
- If you are confident that you would only accept treatment for aggressive cancer and would not be unduly worried about living with a diagnosis of low-risk disease, you are probably a good candidate for screening.

FACTS

- Pca is very common
- Most men will not die form pca
- PSA screening reduce the risk of dying form pca
- Most pCa found by screening are indolent and may not need treatment

Key take home messages

- Goal of PSA screening is to find aggressive Pca
- Most cancers found by PSA screening are indolent and may not need any treatment
- If you have PSA test, you may be diagnosed with indolent pCa, and may experience pressure to treat it

Decision

- If you are confident that you would only accept treatment for aggressive pca , than PSA screening is for you

SMART SCREENING?

PSA at age <50 – Malmö study

- 1974 to 1986, > 21,277 men age 50 in Malmö, Sweden, enrolled onto a cardiovascular study
    - 18 y later, 498 were later diagnosed with pCa
- A single PSA test at age 44 to 50 years predicts subsequent clinically diagnosed prostate cancer.

- **This raises the possibility of risk stratification for prostate cancer screening**

Hans Lilja JCO 2007

PSA at age <50 –Malmö study

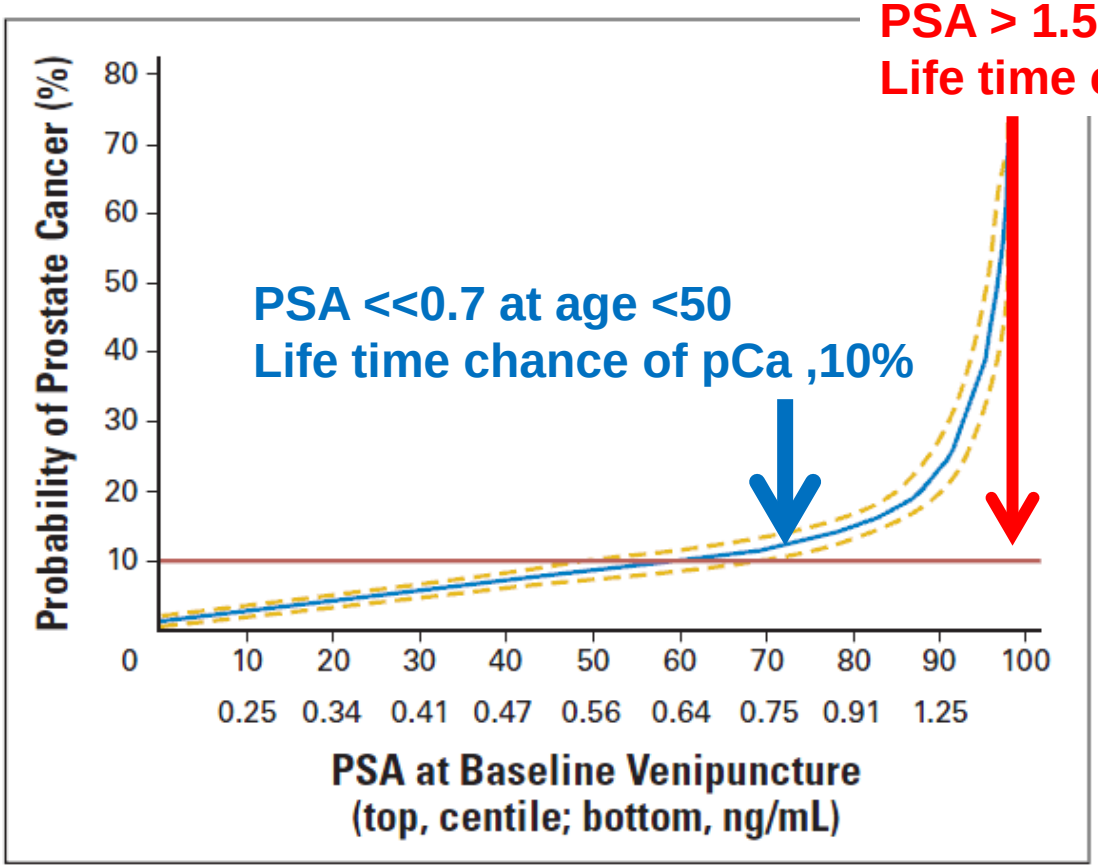


Fig 2. Predicted probability of a prostate cancer diagnosis before age 75 years by population-based centiles of prostate-specific antigen (PSA) measured at age 44 to 50 years, with 95% CIs.

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Hans Lilja JCO 2007

PSA age specific medial values
This can help in your practice!!!

Age (years)	Age-specific median value
40-50 yrs	0.7ng/ml
50-60	0.9ng/ml
60-70	1.2ng/ml
>70	1.5ng/ml

Smart PSA Screening

- **Age ~45 – 50 repeat in 1 year**
  - If PSA <1 -Then every 4 yearly
  - If PSA >1 - test q 2 years
- Monitor PSA doubling time
  - Look for change in underlying trend
  - DRE
  - Stop when life expectancy <10yrs
  - Incorporate active surveillance

Conclusion

- **...**selective use of PSA screening for men in good health appears to reduce the risk of PC mortality with minimal overtreatment....(when active surveillance incorporated into screening programs)

- It is still unclear whether prostate cancer screening results in more benefit than harm, and thus a thoughtful and balanced approach to PSA testing is critical.

Crawford et al JCO 2011

Conflict of interest

- NONE
- I am a Radiation Oncologist
  - Pca is a complex disease and treatment decisions are complex
  - Require multidisciplinary input
- Message form Provincial GU Radiation Oncology
  - All patients with localized prostate cancer should be seen by both Urology and Radiation Oncology **prior** to making decision regarding the treatment

Prostate Cancer Screening

18th February 2016

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Thank You

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