Clara Oromendia

Screening for Prostate Cancer

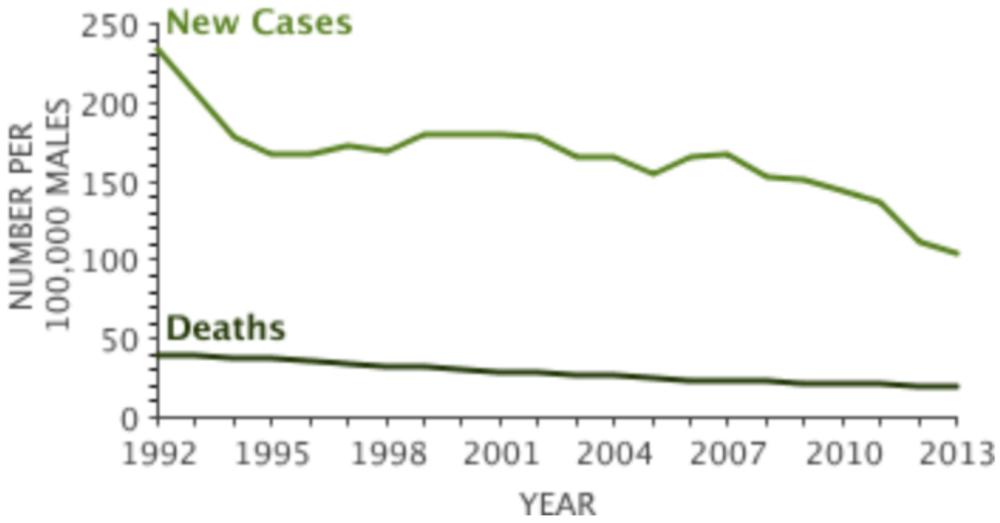
A statistician's view

Department Seminar, April 11 2017

Prostate cancer

At a Glance

Estimated New Cases in 2016	180,890
% of All New Cancer Cases	10.7%
Estimated Deaths in 2016	26,120
% of All Cancer Deaths	4.4%



Percent Surviving 5 Years

98.9%

2006-2012

Number of New Cases and Deaths per 100,000: The number of new cases of prostate cancer was 129.4 per 100,000 men per year. The number of deaths was 20.7 per 100,000 men per year. These rates are age-adjusted and based on 2009-2013 cases and deaths.

Lifetime Risk of Developing Cancer: Approximately 12.9 percent of men will be diagnosed with prostate cancer at some point during their lifetime, based on 2011-2013 data.

Prevalence of This Cancer: In 2013, there were an estimated 2,850,139 men living with prostate cancer in the United States.

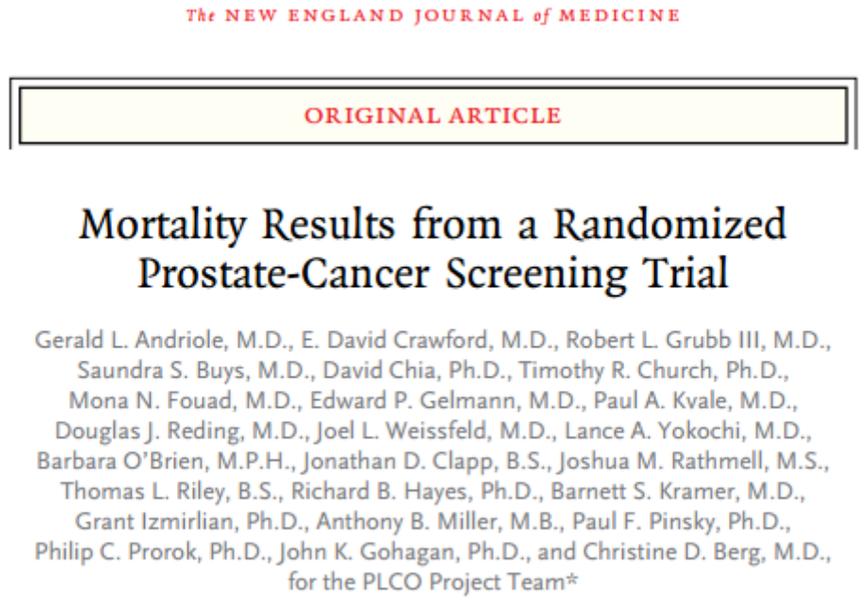
SEER Cancer Stat Facts: Prostate Cancer. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/prost.html

Screening Tests

- Prostate specific antigen (PSA)
  - Blood test for protein level
  - Also elevated for benign reasons
- Digital rectal exam (DRE)
  - Quick exam often done by PCP
  - Role in screening mostly ignored in literature

PLCO Screening Trial

- Year: 1993 - 2001
- Schema:76,693 men
  - 38,850 control
  - 38,343 screening
    - Annual PSA years 1-6
    - Annual DRE years 1-4
  - Biopsy decision left to patient and physician



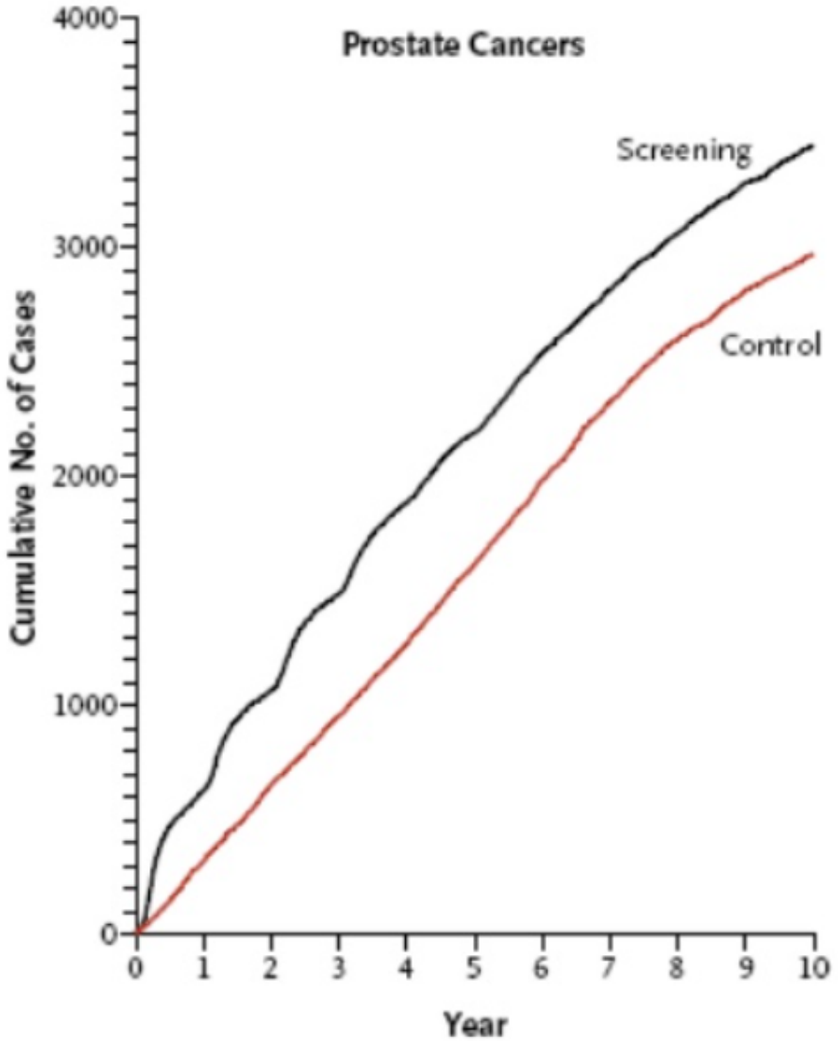
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

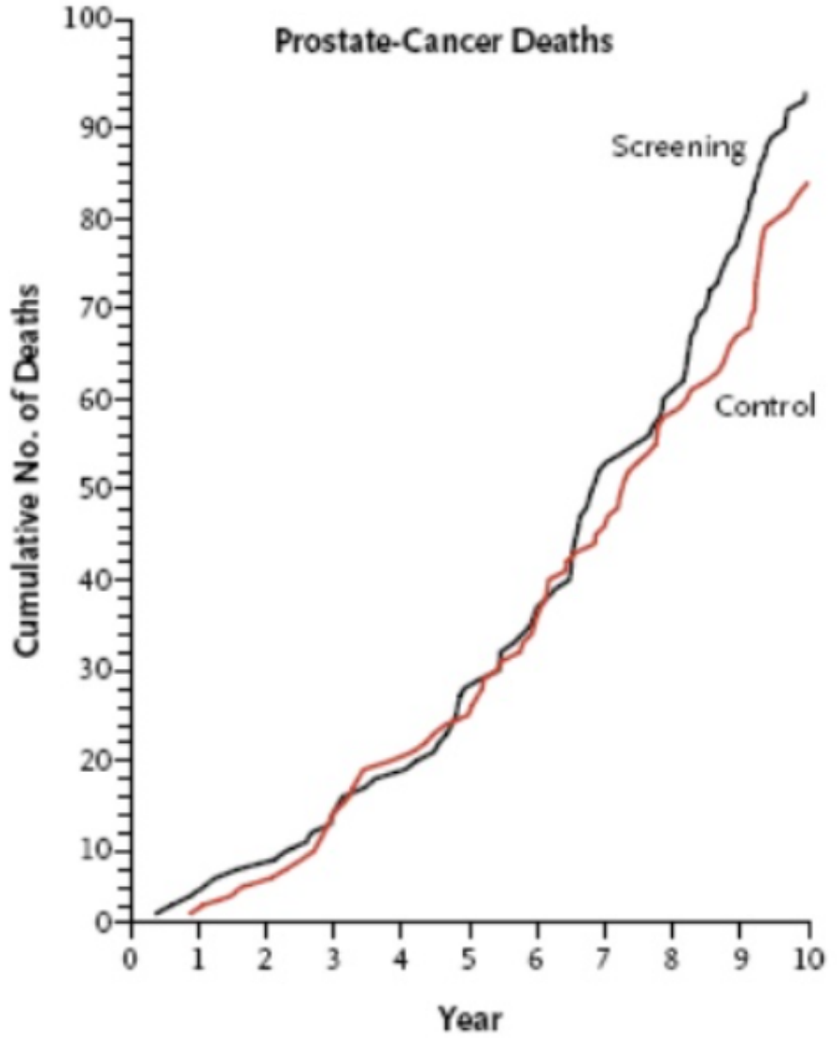
Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, 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., 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*

PLCO Screening Trial



Incidence 12% higher



Mortality the same

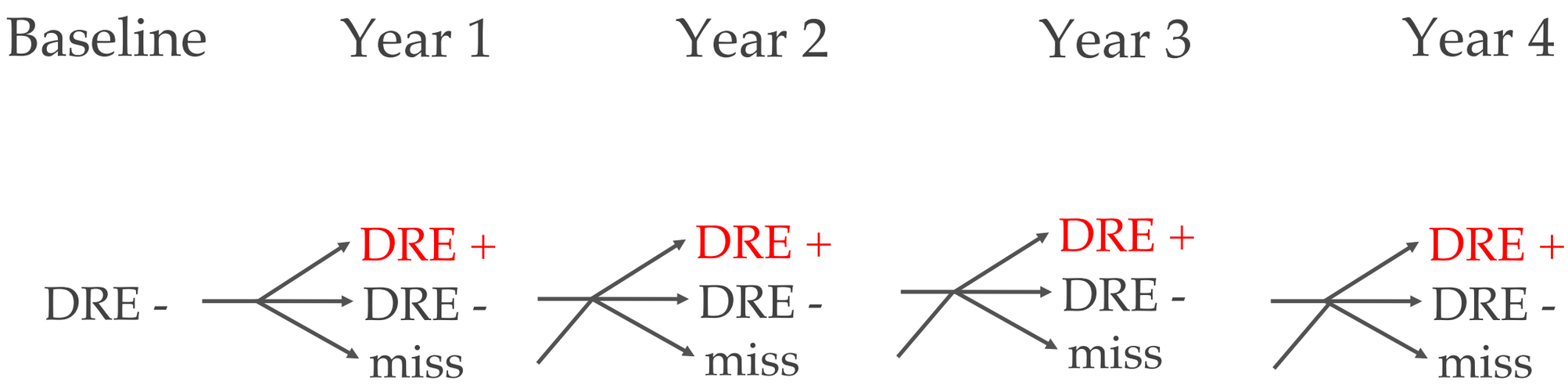
Andriole GL, Crawford ED, Grubb RL III, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360:1310-1319

Question

- Scientifically:
  - Are people with abnormal DRE at higher risk for prostate cancer?

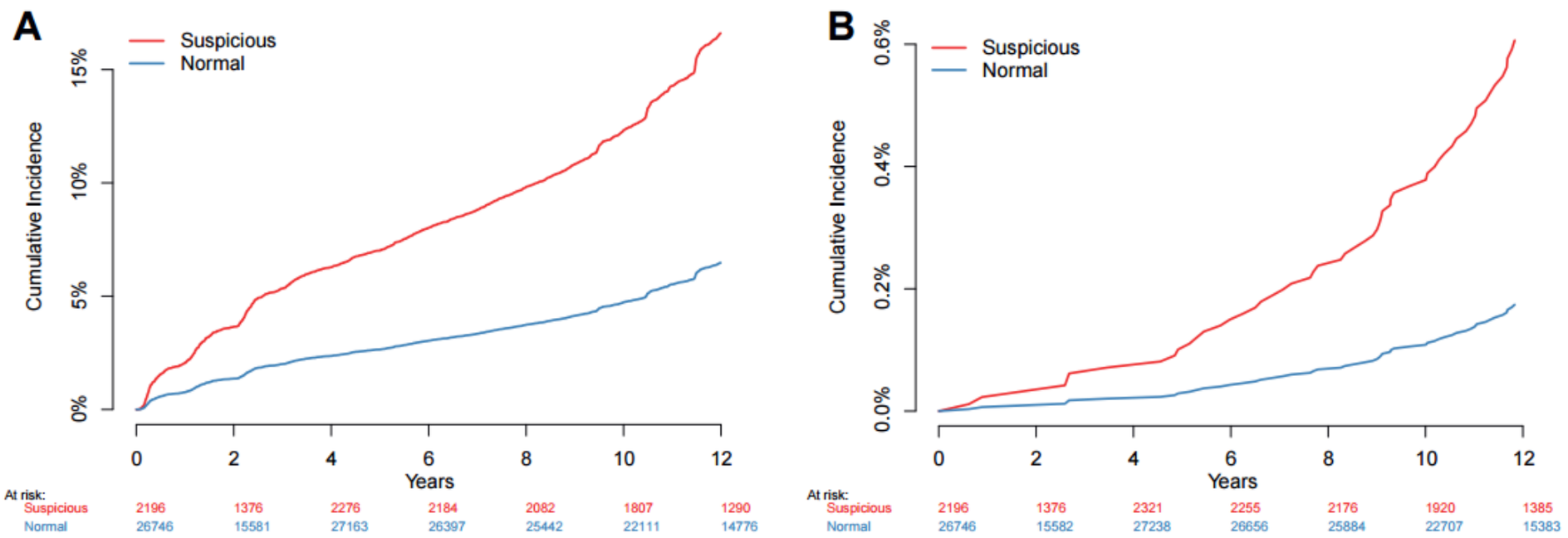
- Statistically:
  - Sample: Screening Arm
  - Outcome: Time to Prostate Cancer Death
  - Method: Competing Risks Regression (Fine and Grey)
  - Predictor: Abnormal DRE

Question



- Predictor: Ever abnormal DRE
  - Time varying
  - Missing until up to date on screening schedule

Answer



Cumulative incidence of clinically significant prostate cancer (*A*) and PCSM (*B*) by DRE screening status

The Journal of Urology

Volume 197, Issue 2, February 2017, Pages 363–368

Adult Urology

Prognostic Significance of Digital Rectal Examination and Prostate Specific Antigen in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Arm

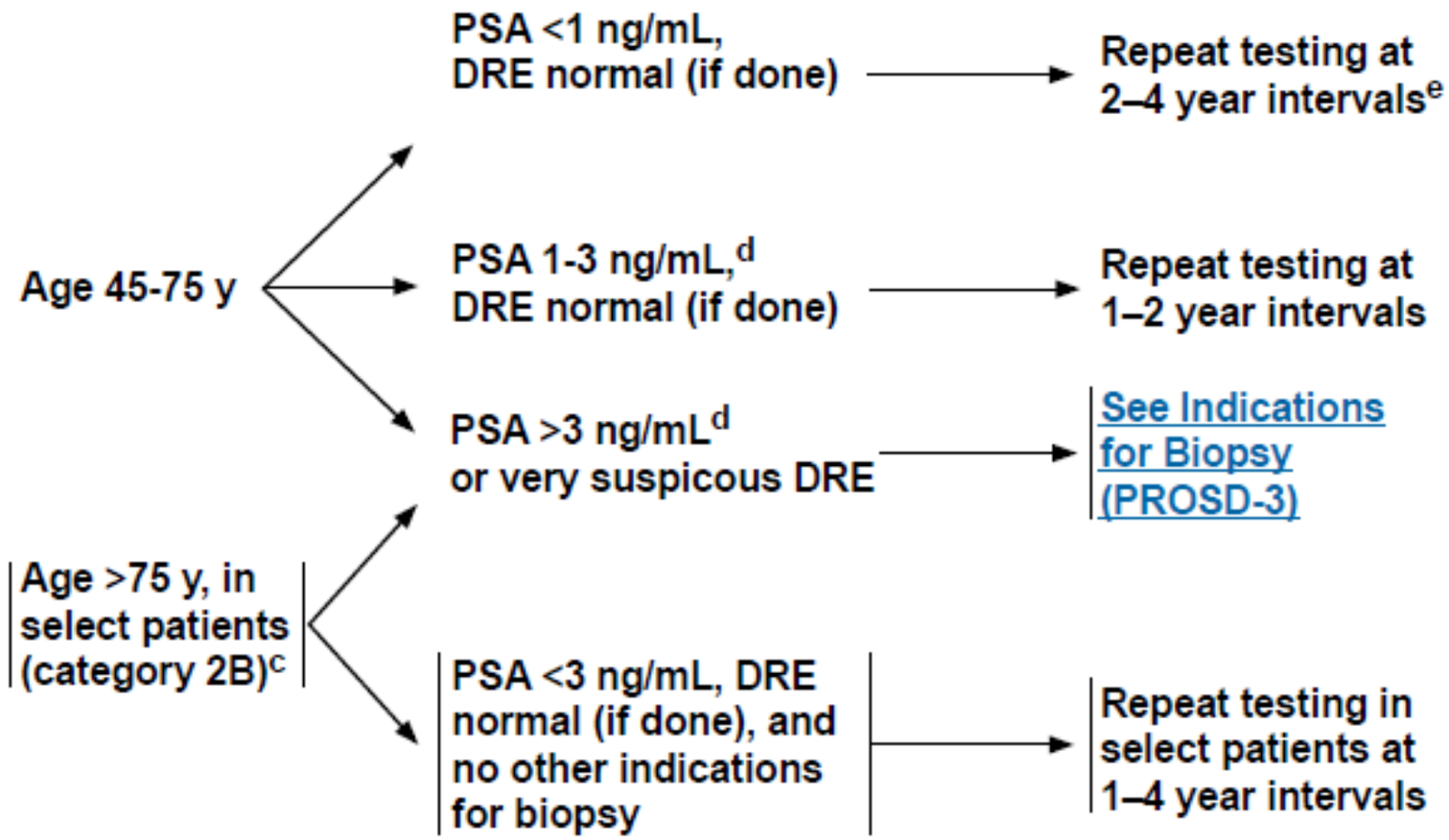
Joshua A. Halpern[a], Jonathan E. Shoag[a], Sameer Mittal[a], Clara Oromendia[b], Karla V. Ballman[b], Dawn L. Hershman[c], Jason D. Wright[c], Ya-Chen Tina Shih[d], Paul L. Nguyen[e, *], Jim C. Hu[a, ‡]

What about PSA?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Prostate Cancer Early Detection

EARLY DETECTION EVALUATION

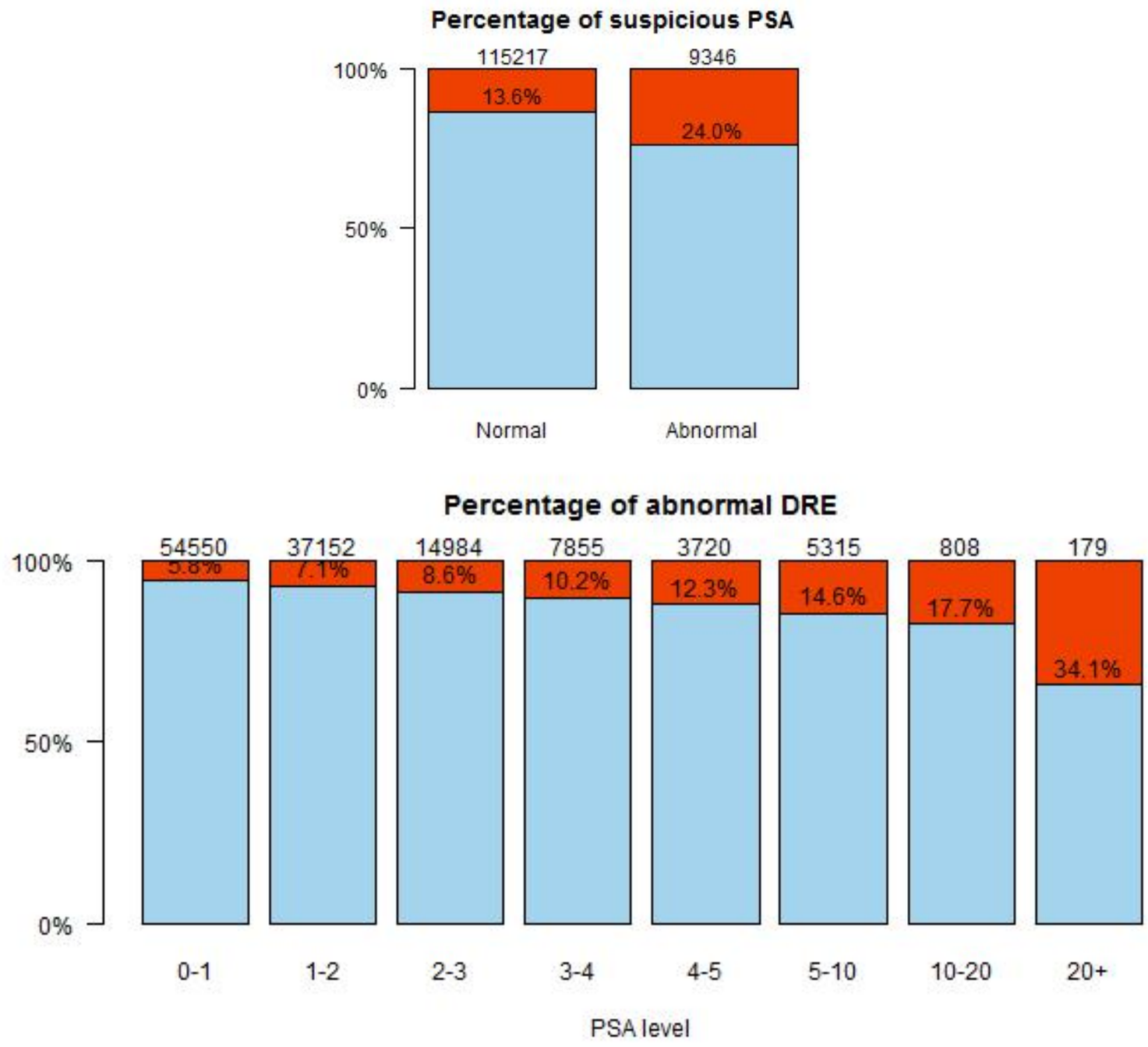


Question 2

- Scientifically
  1. How are DRE and PSA related?
  2. Is DRE useful beyond PSA?
  3. Is DRE useful for everyone?

- Statistically
  1. Agreement at each screening
  2. Account for PSA in regression
  3. Interaction effects with stratified analyses

DRE vs PSA


Percentage of suspicious PSA
115217
9346
100%
50%
0%
13.6%
24.0%
Normal
Abnormal
Percentage of abnormal DRE
54550
37152
14984
7855
3720
5315
808
179
5.8%
7.1%
8.6%
10.2%
12.3%
14.6%
17.7%
34.1%
0-1
1-2
2-3
3-4
4-5
5-10
10-20
20+
PSA level

Interactions

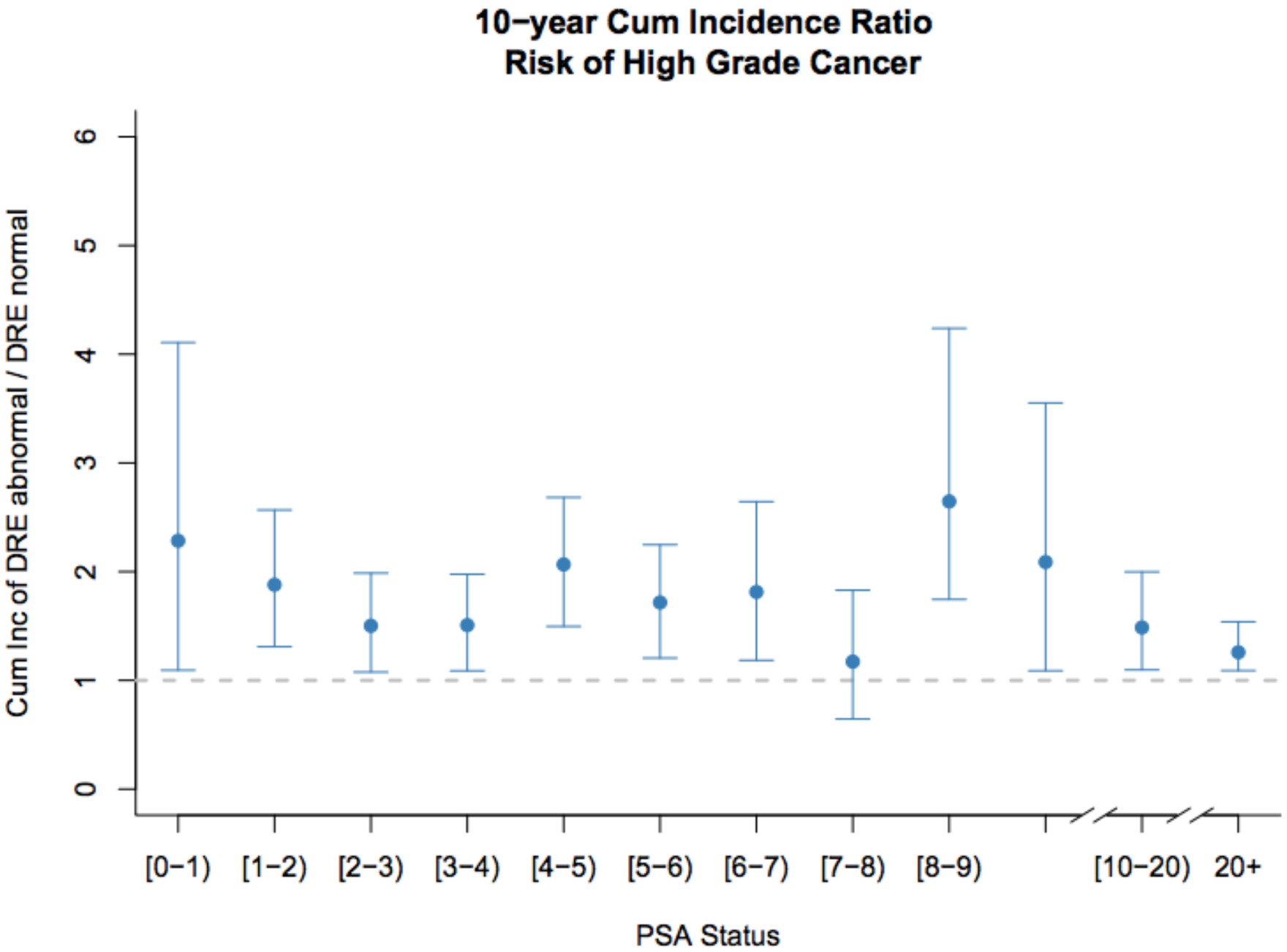
Fine and Gray Competing Risks Model:

Variable	Estimate	P-value
DRE abnorm	2.71 (2.46,2.46)	<0.01
PSArslt	1.02 (1.01,1.01)	<0.01
DRE abnorm & PSArslt	0.99 (0.99,0.99)	<0.01
age	1.01 (1.00,1.00)	0.06

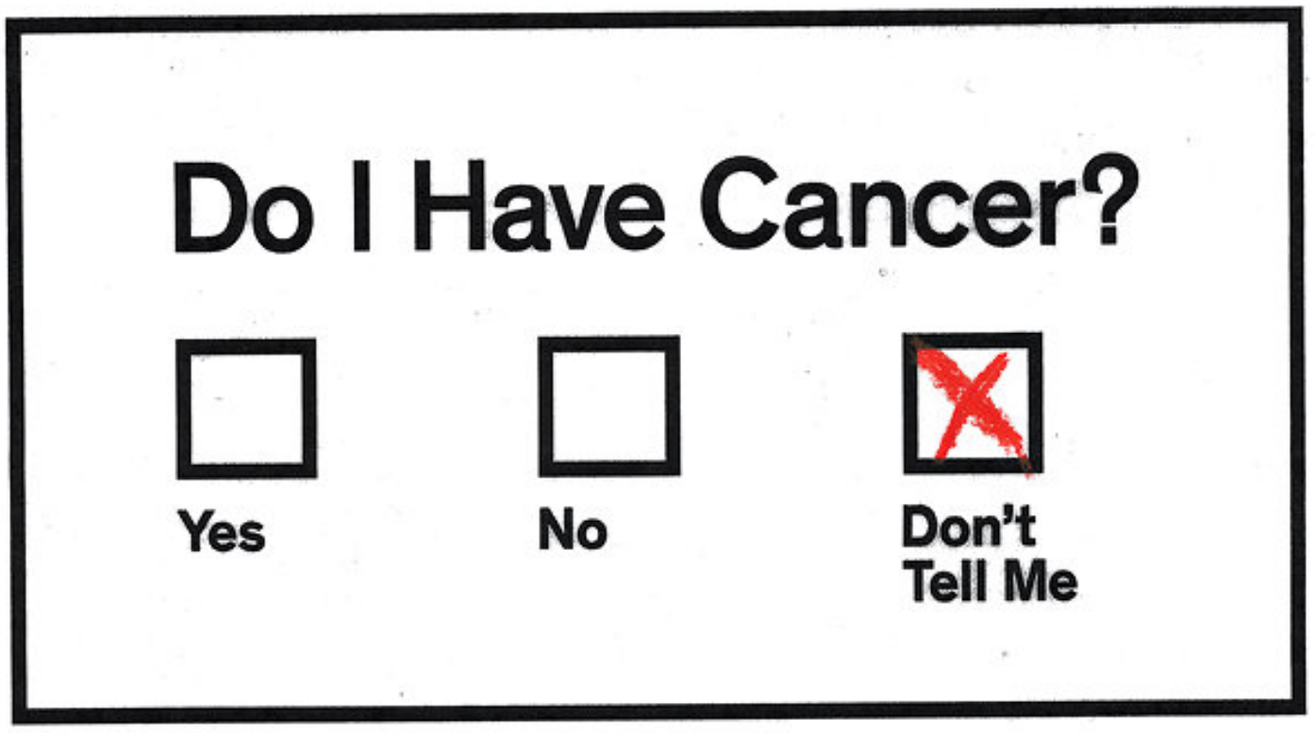
Conclusion: DRE is less important with increasing PSA

→If anything, we should be sure to perform a DRE in those with low PSA.

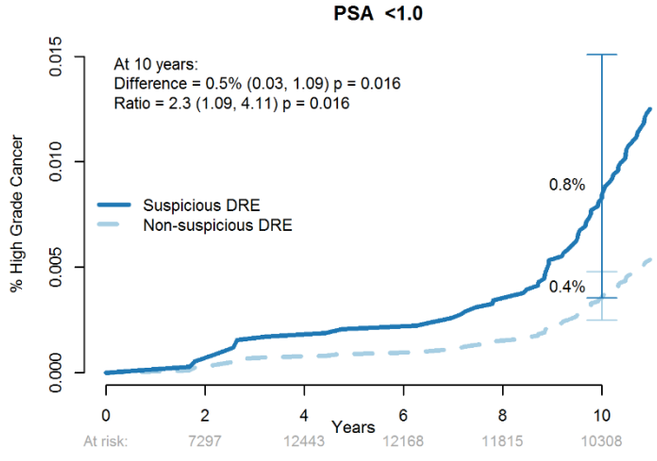
Interactions

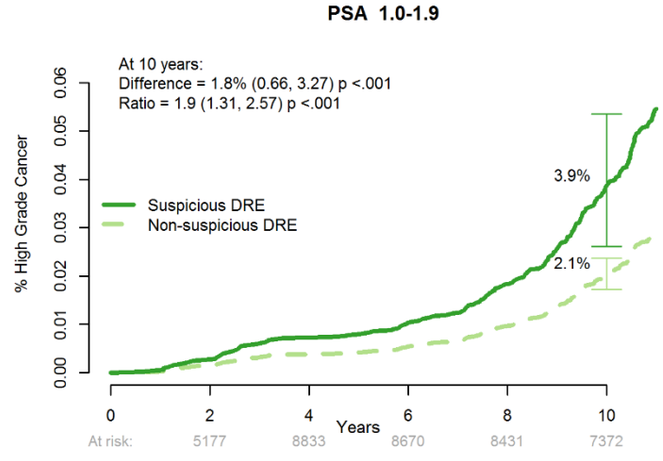


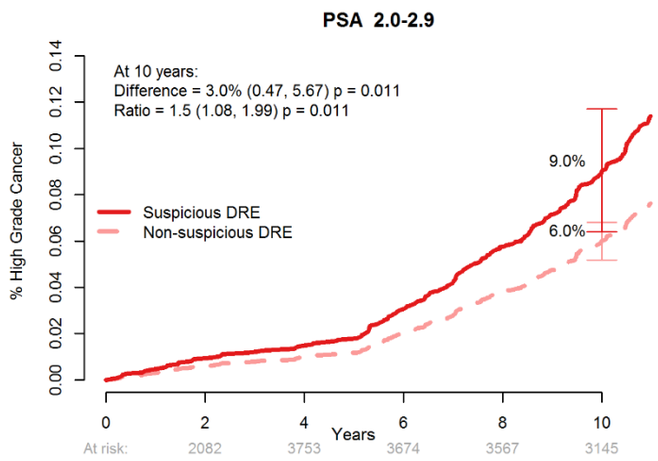
Real Question

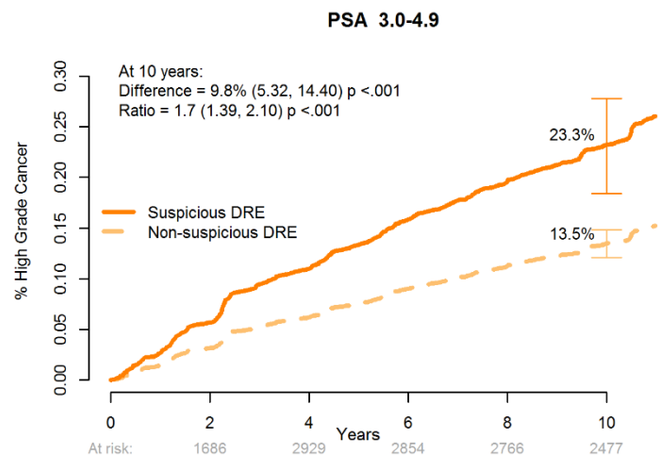


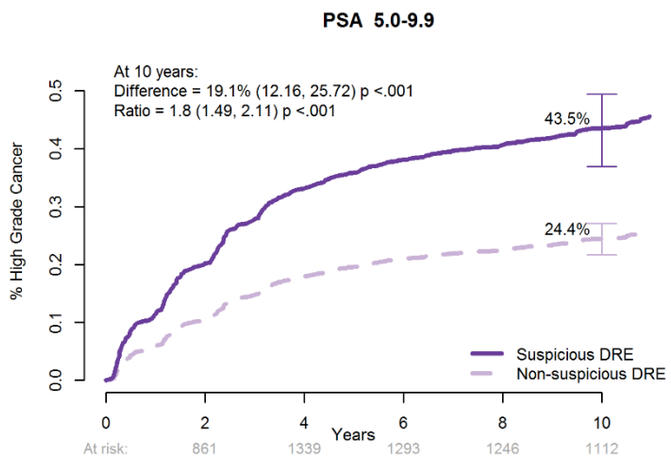
Cumulative Incidence

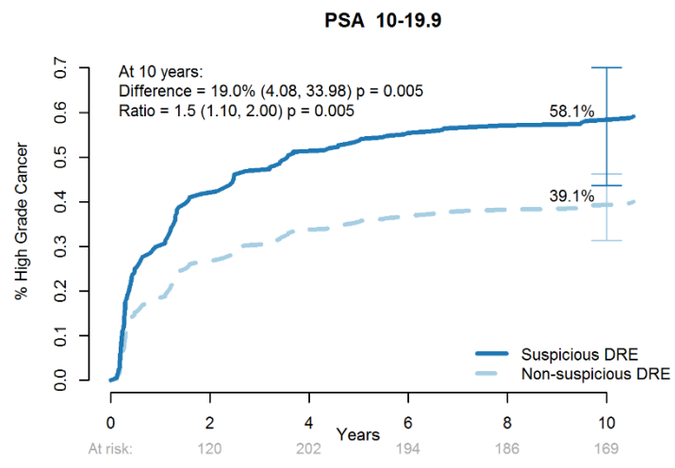






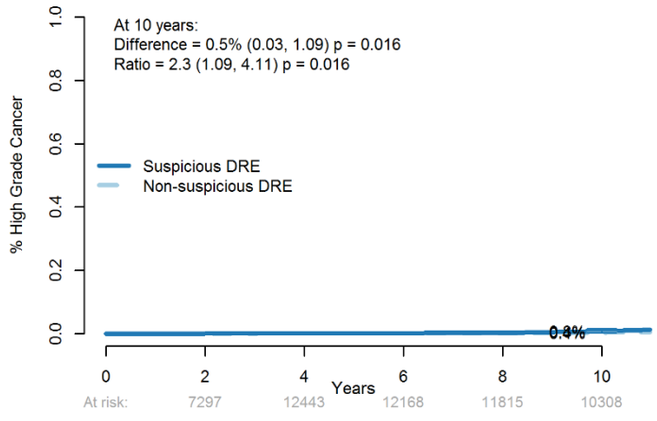




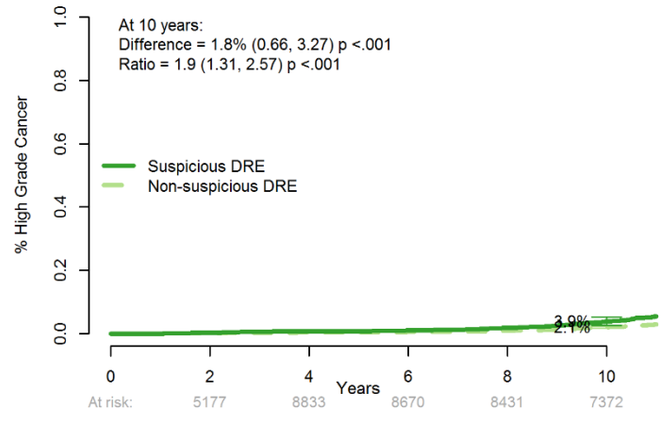


Cumulative Incidence

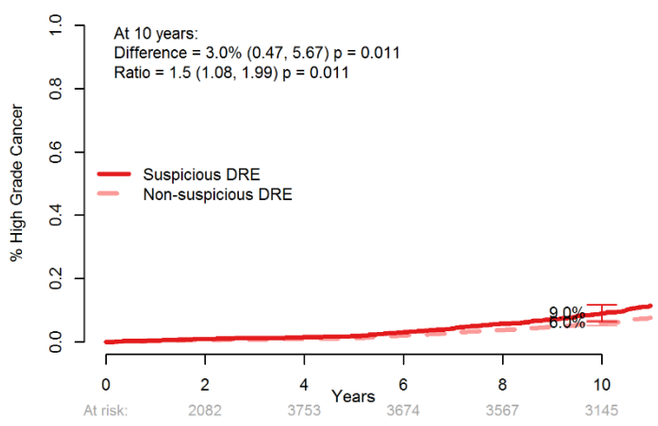
PSA <1.0



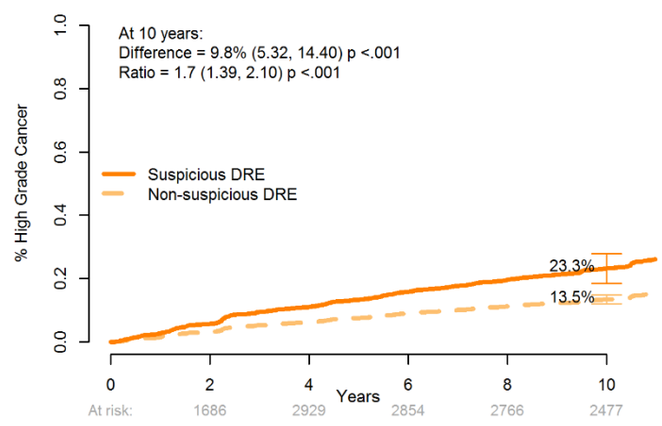
PSA 1.0-1.9



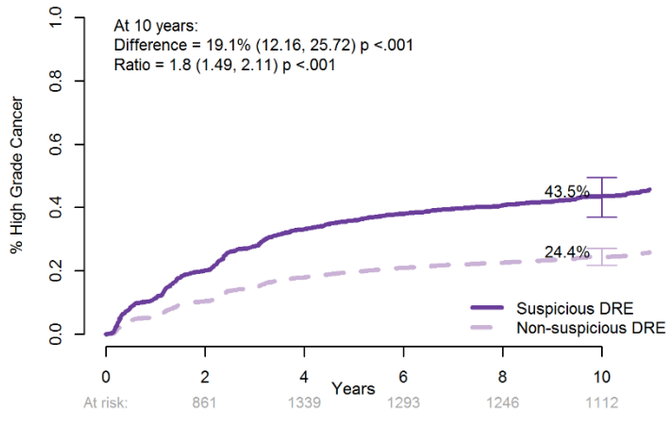
PSA 2.0-2.9



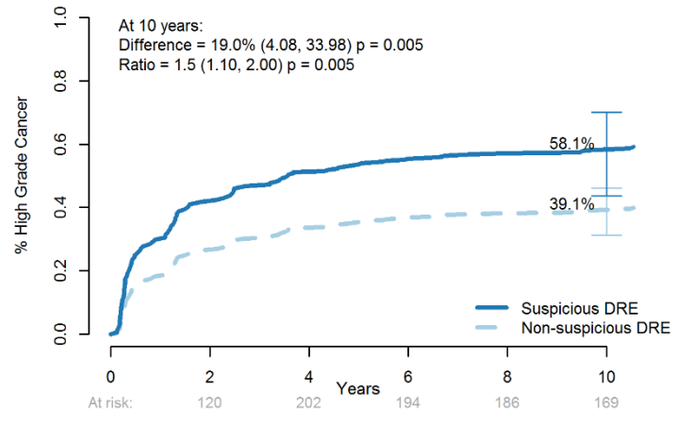
PSA 3.0-4.9



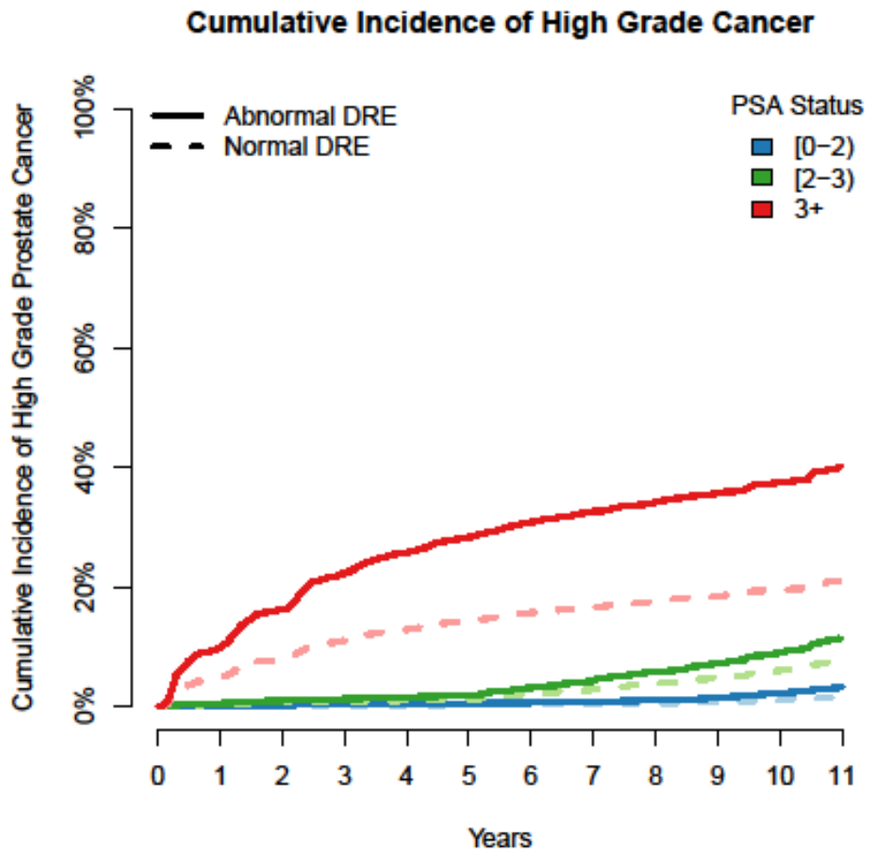
PSA 5.0-9.9



PSA 10-19.9



Statistical Conclusion



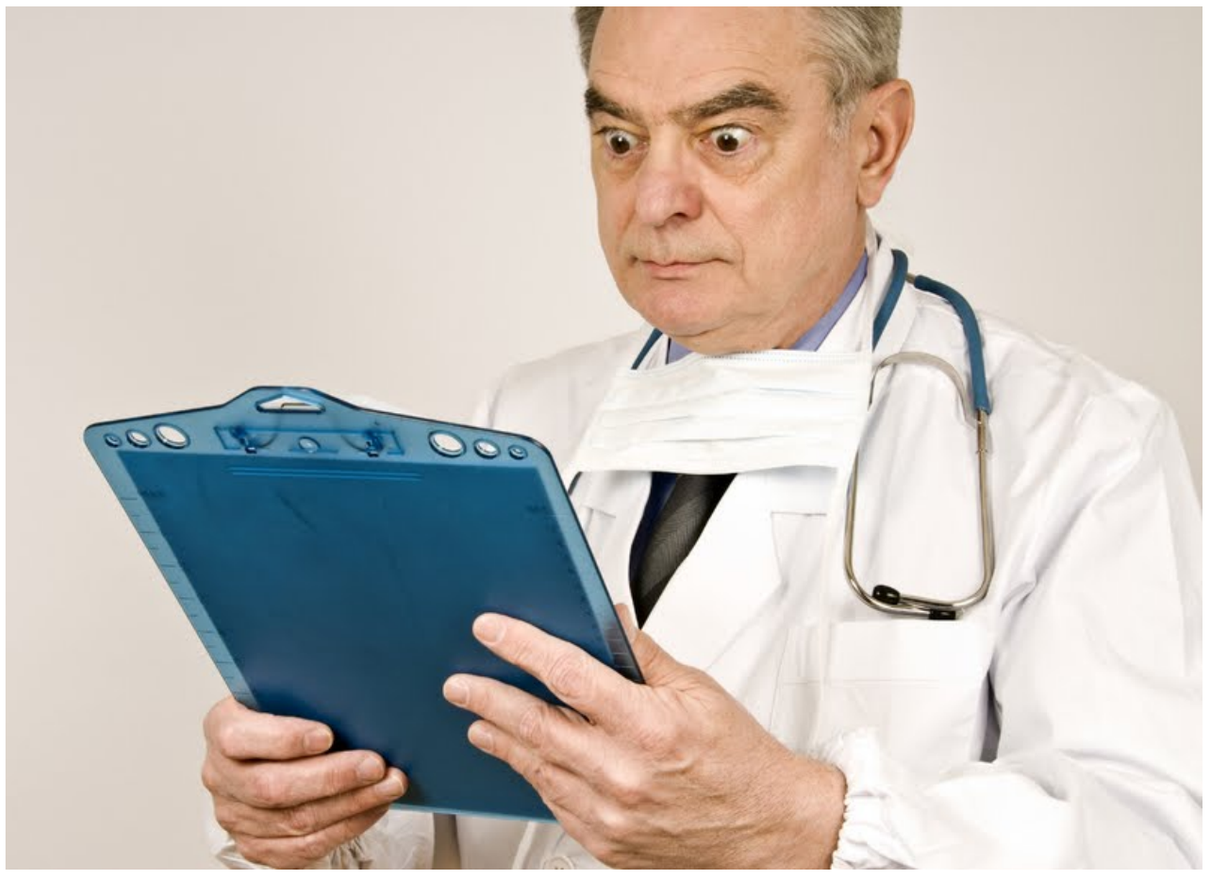
PSA 0-2 → no need for DRE

PSA 2-3 → maybe need DRE, more research needed

PSA 3+ → no need for DRE, directly to biopsy since even normal DRE has incidence of 20% at 10 years, no need to waste it.

Statistical Conclusion

If PSA is high enough that you are surely going to biopsy, it is useless to do a DRE.



Scientific Conclusion

- DRE is also used for disease staging
  - T1: Tumor cannot be felt on DRE, not seen on imaging
  - T2: Tumor can be felt on DRE

→ Doc would never do a biopsy without first doing a DRE

Acknowledgements

- Karla Ballman
- Josh Halpern
- Jim C Hu
- Andrew Vickers
- Jonathan Shoag
- Sameer Mittal
- Dawn Hershman
- Jason Wright
- C2 Stats Mafia

This morning

Experts reverse themselves on prostate cancer screenings

By **Michael Nedelman, CNN**
Updated 9:14 AM ET, Tue April 11, 2017

Top stories

npr

TREATMENTS

Federal Task Force Softens Opposition To Routine Prostate Cancer Screening

April 11, 2017 · 6:01 AM ET
Heard on Morning Edition

The New York Times

HEALTH

Prostate Cancer Tests Are Now OK With US Panel, With Caveats

By THE ASSOCIATED PRESS APRIL 11, 2017, 6:15 A.M. E.D.T.

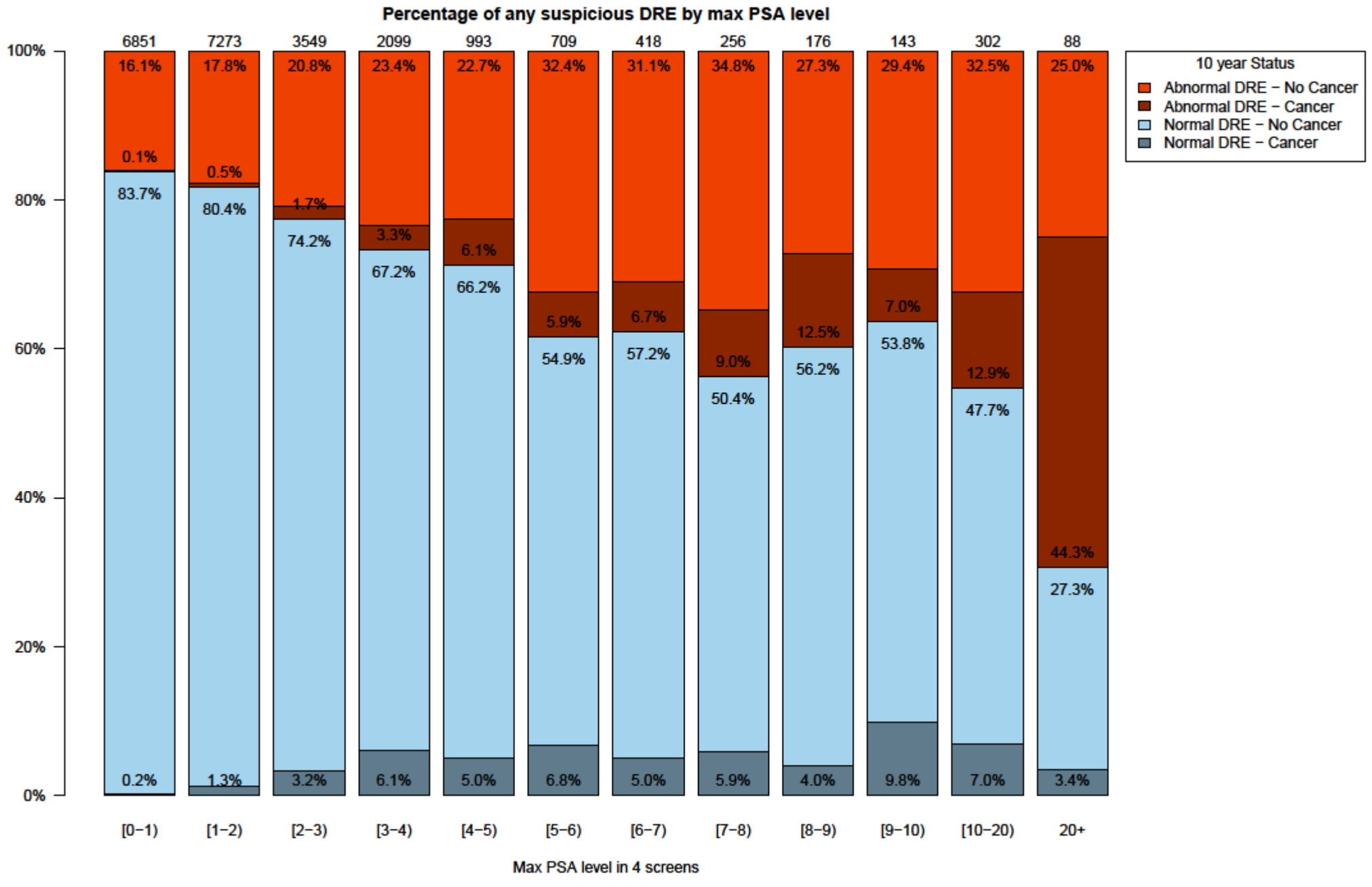
Discussion

- Prostate Cancer Screening
  - Ideas for analysis?

- Consulting
  - Karl Broman: **Thoughts on statistical consulting**

- Stat Methods
  - Time varying covariates & survival bias
  - Absolute vs relative effects
  - Competing risks regression
  - Bootstrapped confidence intervals

DRE vs PSA


Percentage of any suspicious DRE by max PSA level
6851
7273
3549
2099
993
709
418
256
176
143
302
88
16.1%
17.8%
20.8%
23.4%
22.7%
32.4%
31.1%
34.8%
27.3%
29.4%
32.5%
25.0%
0.1%
0.5%
1.7%
3.3%
6.1%
5.9%
6.7%
9.0%
12.5%
7.0%
12.9%
44.3%
83.7%
80.4%
74.2%
67.2%
66.2%
54.9%
57.2%
50.4%
56.2%
53.8%
47.7%
27.3%
0.2%
1.3%
3.2%
6.1%
5.0%
6.8%
5.0%
5.9%
4.0%
9.8%
7.0%
3.4%
100%
80%
60%
40%
20%
0%
[0−1)
[1−2)
[2−3)
[3−4)
[4−5)
[5−6)
[6−7)
[7−8)
[8−9)
[9−10)
[10−20)
20+
Max PSA level in 4 screens
10 year Status
Abnormal DRE − No Cancer
Abnormal DRE − Cancer
Normal DRE − No Cancer
Normal DRE − Cancer