Long-term prostate cancer risk in the Prostate Cancer Prevention Trial

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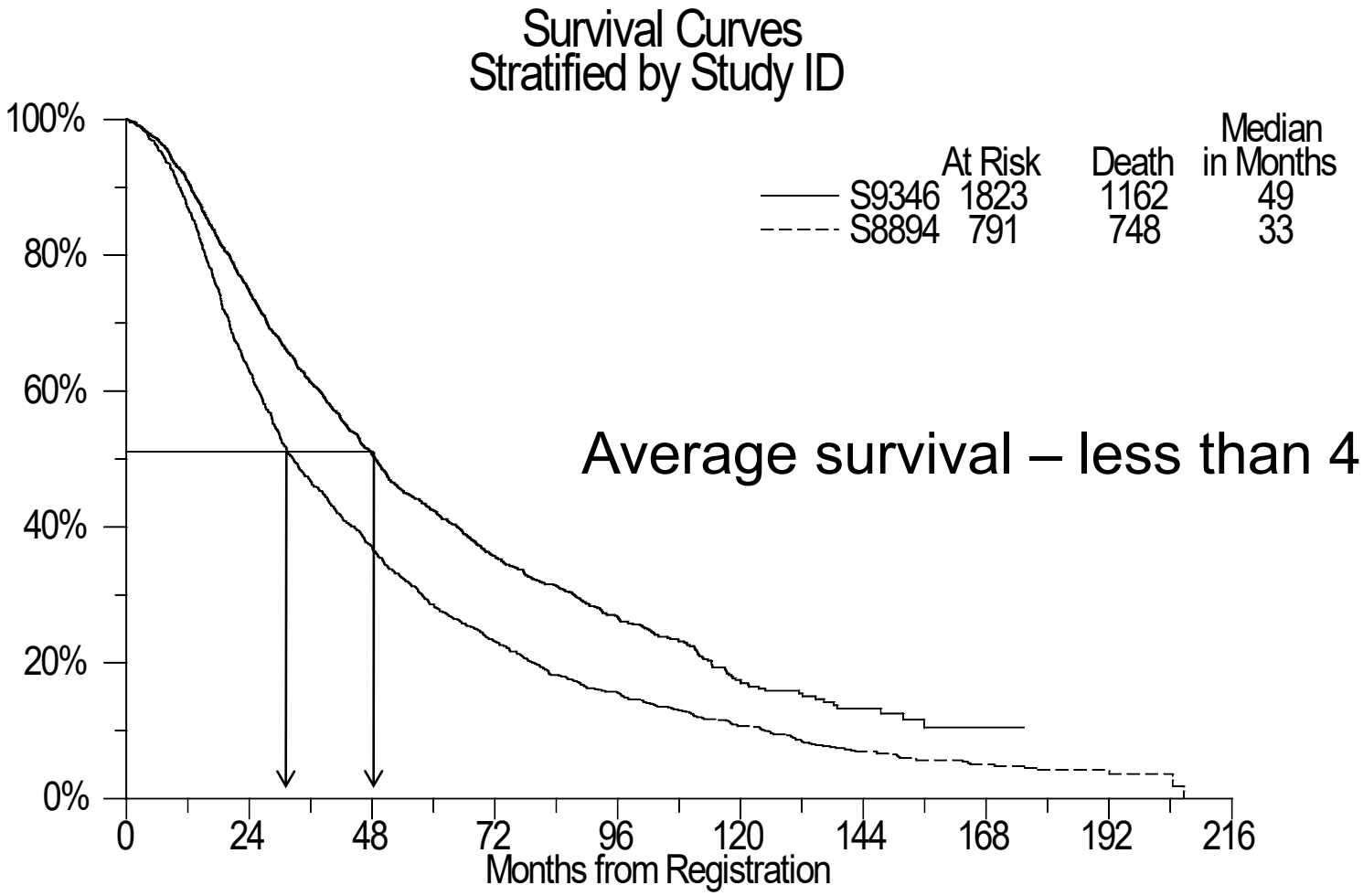
The challenges of prostate cancer

- About 75% of men will have it during their lifetime
- We can detect many of these tumors
  - Significant risk of ‘overdetection’
  - Treatment has many toxicities
    - Erectile dysfunction, incontinence, GI toxicities, secondary malignancies

The challenges of prostate cancer

- Nonetheless, 3-6% of men, depending on race/ethnicity, will die from prostate cancer
- If diagnosed when symptomatic, most patients have metastases
  - Most with metastases will die from cancer
  - Treatments are morbid and expensive
- Screening with PSA detects disease early
  - Modest reduction in PCA mortality

What happens if we wait for symptoms? SWOG studies from 1980's and 1990's



Average survival – less than 4 years

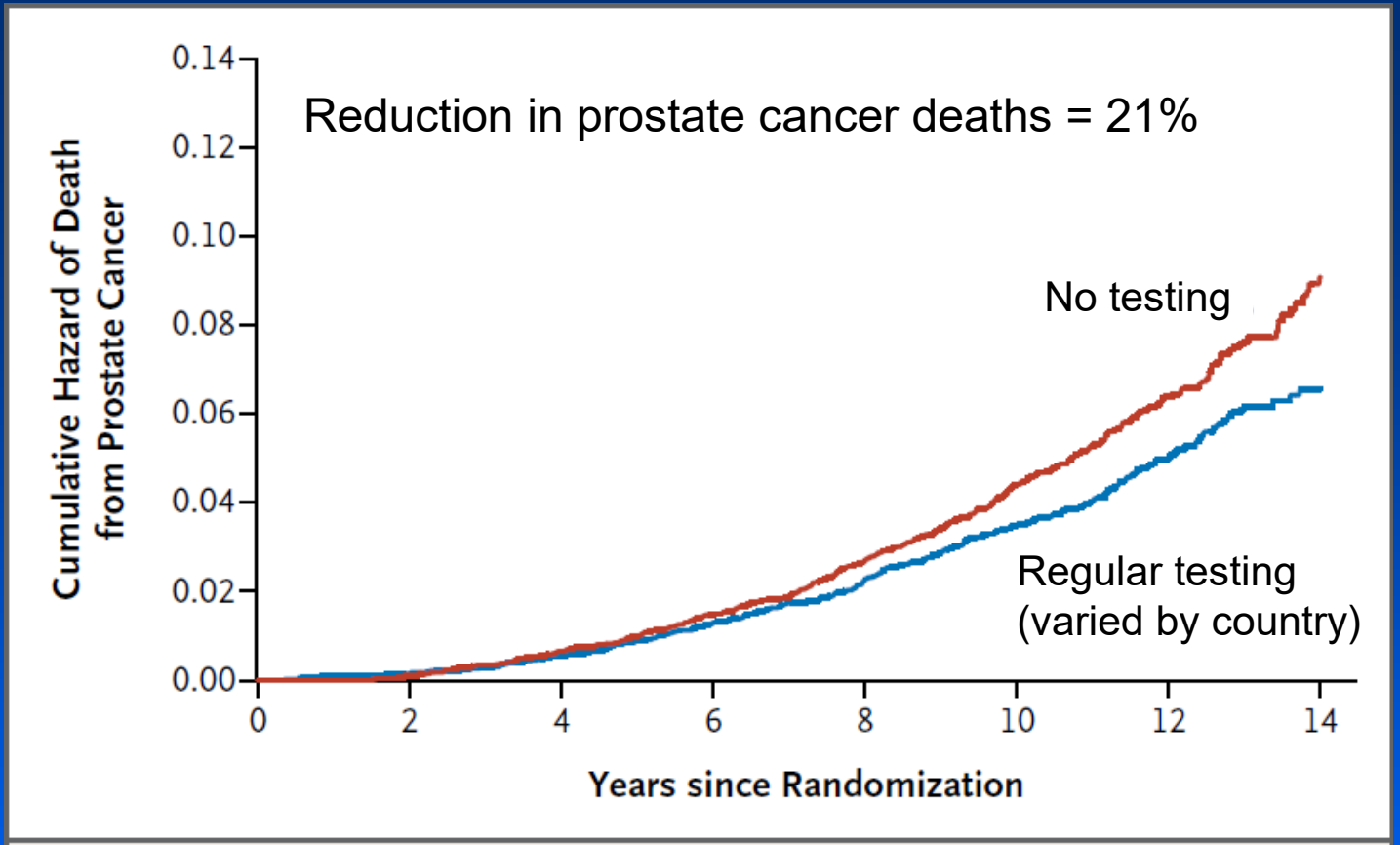


Figure 2. Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.

Values are not included for centers in France because of the short follow-up period (median, 4.6 years). The Nelson–Aalen method was used to calculate the cumulative hazard of death from prostate cancer.

Schröder FH, et al. N Engl J Med 2012;366:981-90.

Options for Prostate Cancer Control

- Cure symptomatic disease
  - Death from cancer eventual outcome
- Screen for the disease
  - Risk of overtreatment, side effects, cost
- Prevention

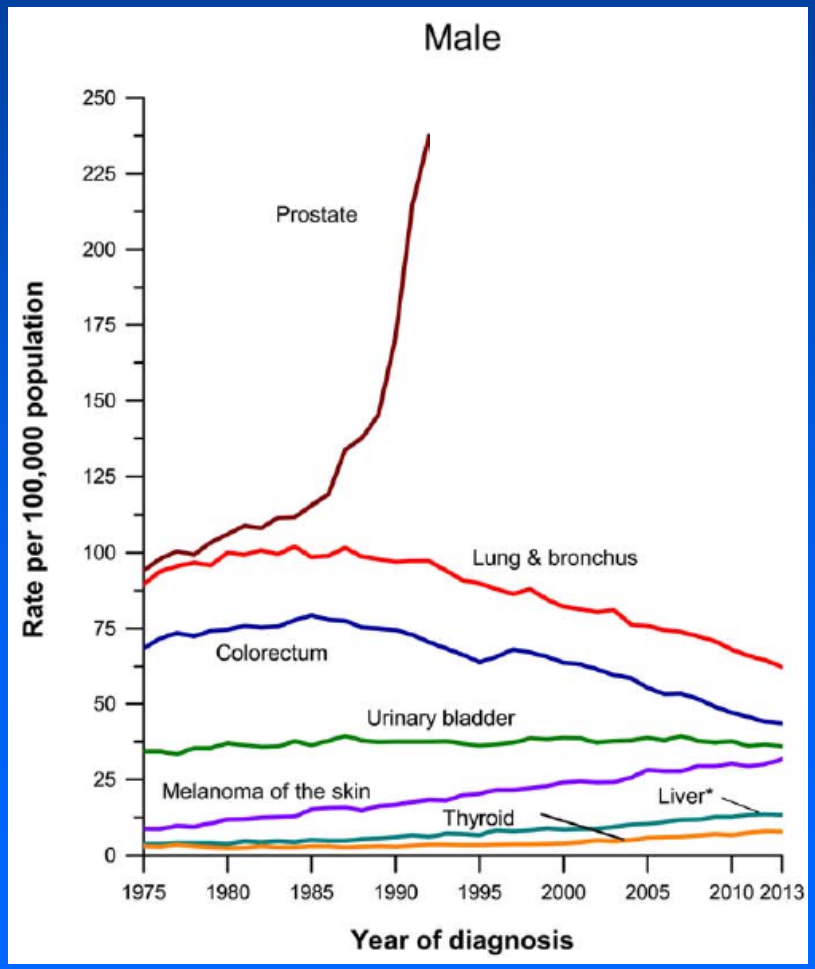
Attractive features of prostate cancer prevention

Median age of death = 80. Average life years lost from prostate cancer = 9.

May not need to prevent it; delay will reduce mortality

Confluence of events in 1990

1991-1992 – Significant spike in prostate cancer diagnoses



1234 THE NEW ENGLAND JOURNAL OF MEDICINE Oct. 22, 1992

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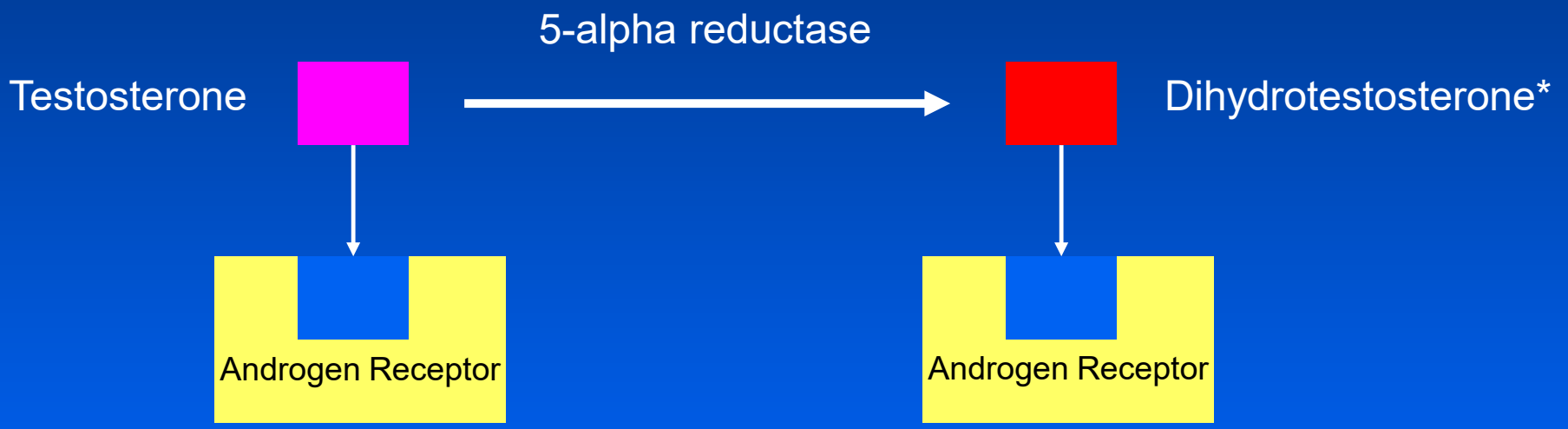
IS THE PROSTATE PILL FINALLY HERE?

After fulfilling its reproductive role, the prostate mostly causes trouble by virtue of its propensity for benign or malignant cellular proliferation in aging men. Benign prostatic hypertrophy causes symptoms of bladder-outlet obstruction in 50 percent of men 60 years of age or older, and 25 to 30 percent ultimately need surgery. Prostatectomy, mostly by transurethral

FDA Registration of finasteride

First 5AR inhibitor



*8-fold greater affinity for AR than testosterone

Development of 5ARI's

Males with a *SRD5A2* mutation don't develop BPH or prostate cancer

For four decades, androgen deprivation therapy used for treatment of prostate cancer

Clinical studies of finasteride: well tolerated (later, approved for male-pattern baldness)

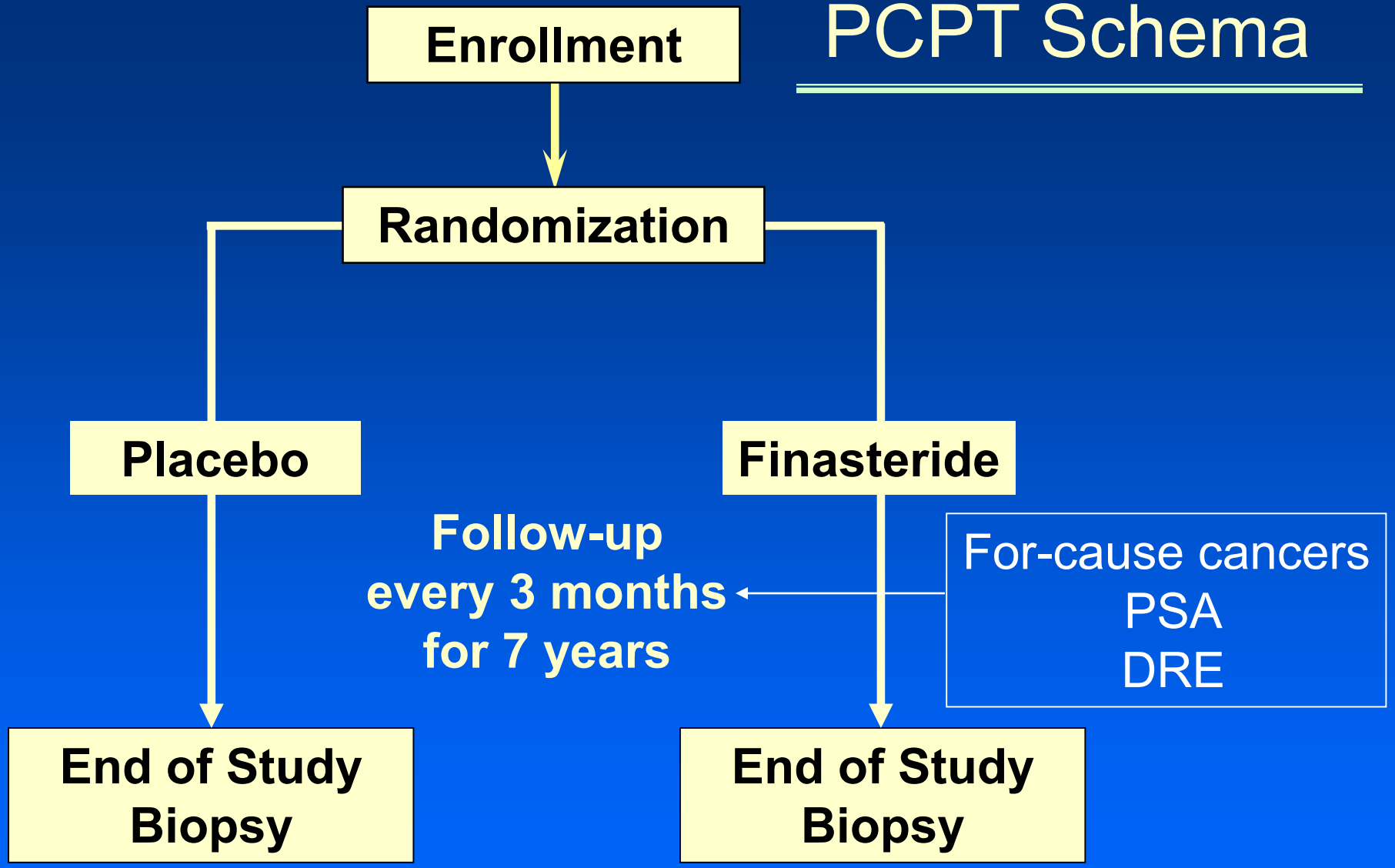
A confluence of events 1991

- Board of Scientific Counselors of Division of Cancer Prevention recommends study of finasteride for prostate cancer prevention
- SWOG leadership invited to NCI to design trial

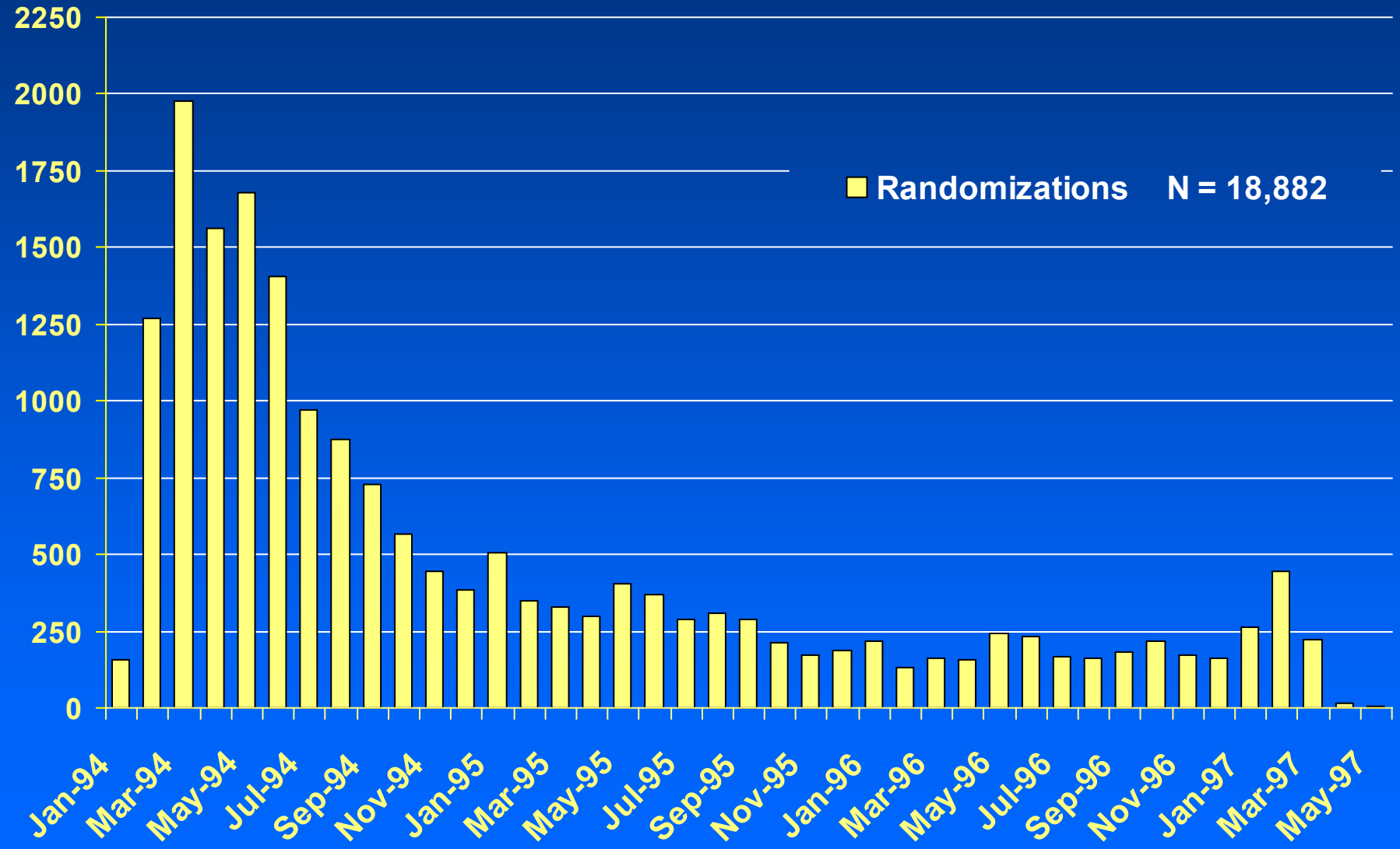
Major design challenge

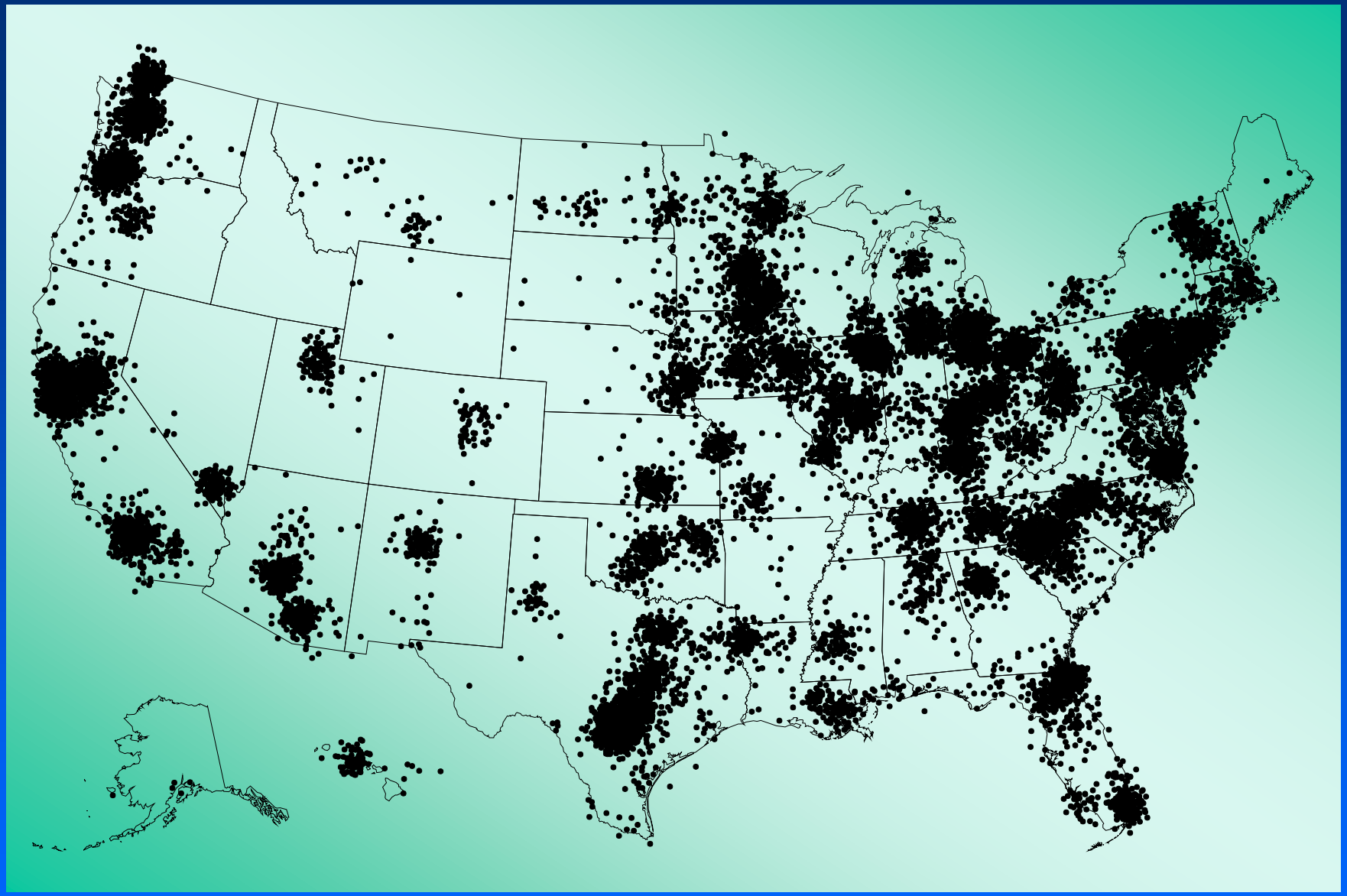
- Primary method of prostate cancer diagnosis – PSA
- Finasteride reduces PSA by about 50%
- *If study is simply finasteride vs placebo*
  - How would you adjust for PSA?
  - Does PSA drop the same in patients with CA?
- Only one answer – biopsy all men

PCPT Schema


Enrollment
Randomization
Placebo
Finasteride
Follow-up
every 3 months
for 7 years
For-cause cancers
PSA
DRE
End of Study
Biopsy
End of Study
Biopsy

PCPT Accrual
January 1994 - May 1997

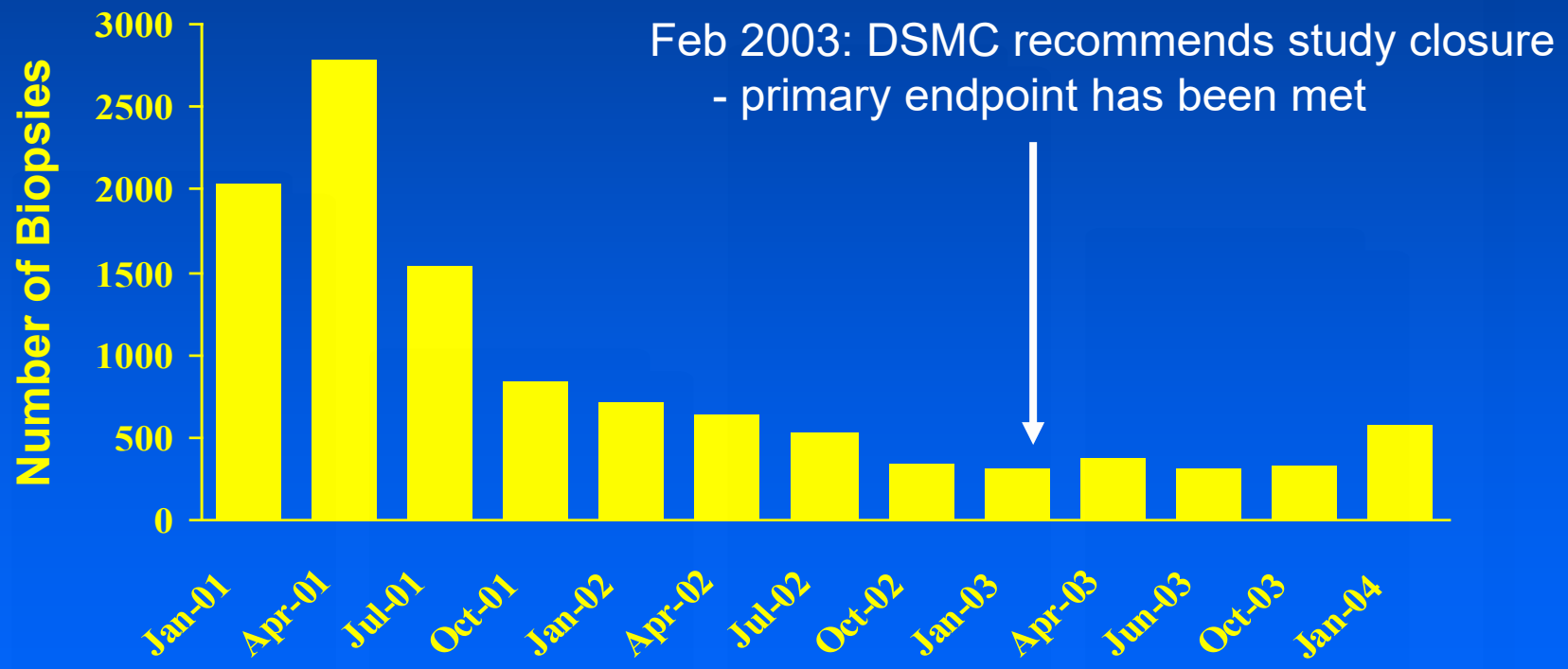




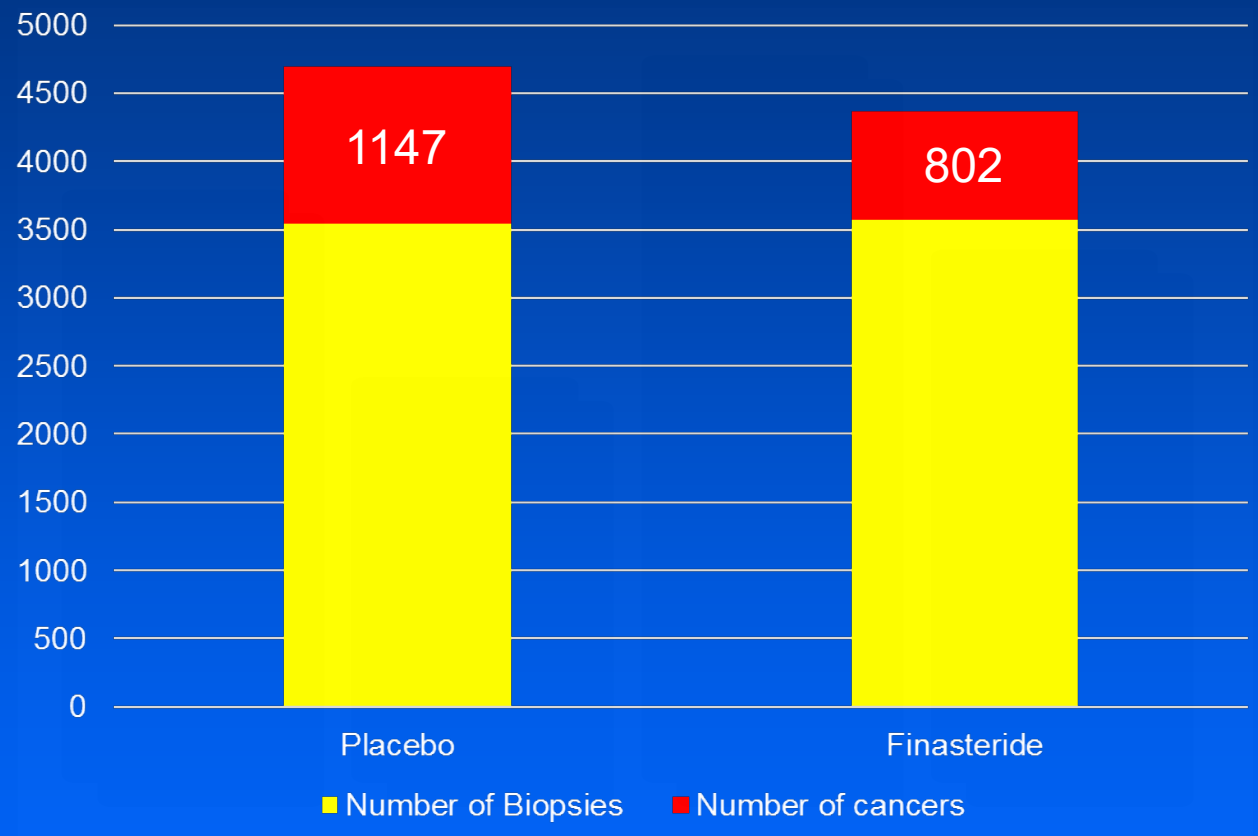
PCPT Randomizations

18,882 participants randomized at 219 Study Centers and Sites

Prostate Cancer Prevention Trial Projected Biopsy Rate



What was the impact on cancer risk?



Cancer Risk:

Placebo – 24%

Finasteride – 18%

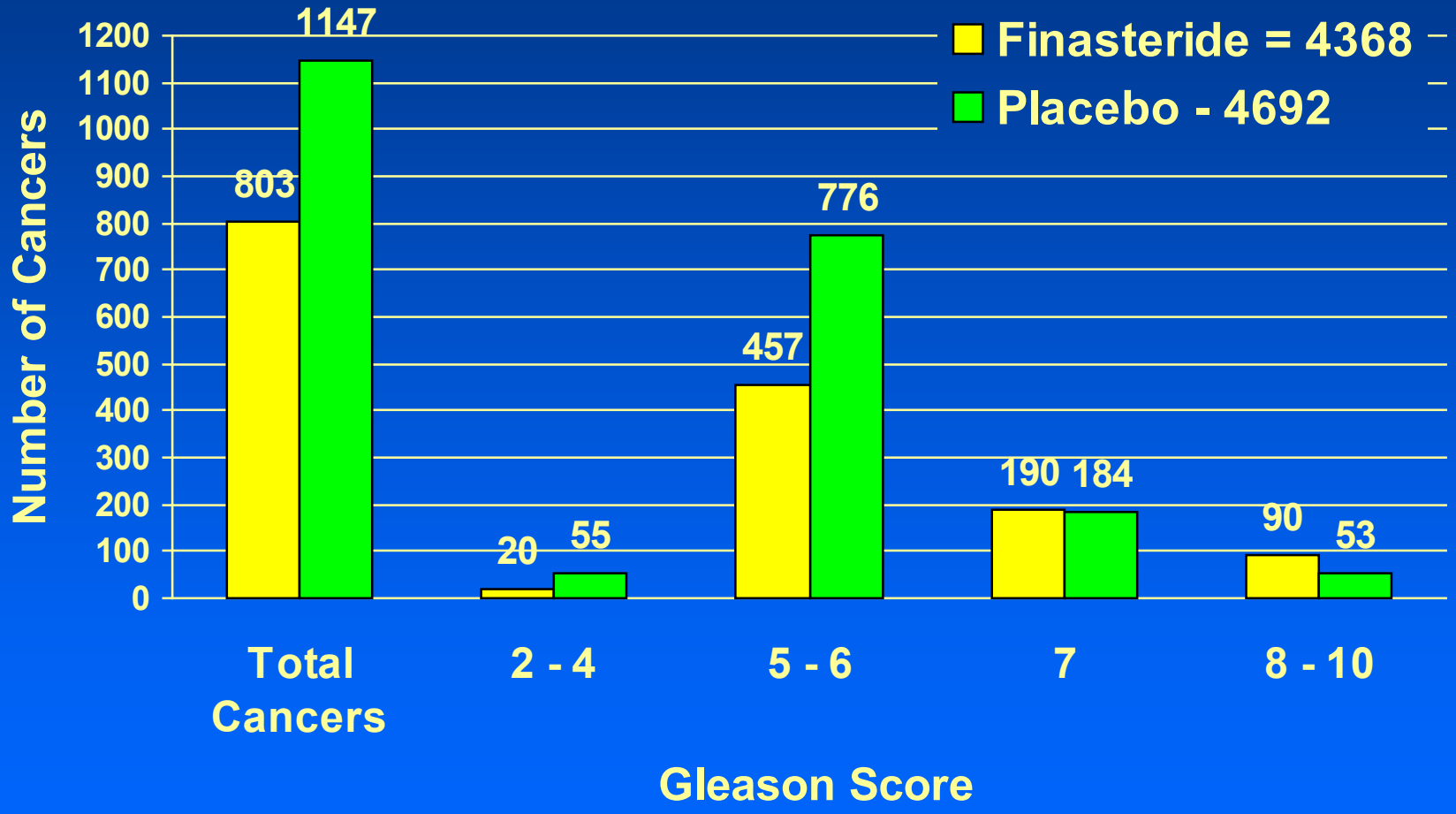
Relative Risk Reduction - 24.8%

Finasteride Reduces Risk of Cancer

	Finasteride	Placebo	p-value
Number of biopsies	4368	4692	
Prostate cancer	803 (18%)	1147 (24%)	p<0.001
Abnormal PSA or DRE	435 (10%)	571 (12%)	p<0.001
Normal PSA/DRE (EOS)	368 (8%)	576 (12%)	p<0.001
Number randomized	9423	9459	

Relative Risk Reduction - 24.8%

Impact of Finasteride on Tumor grade: Gleason Scores



Effect:	345 fewer	35 fewer	319 fewer	6 more	37 more	cancers

February 2003

- DSMC releases data to SWOG.
- Recommends ending study due to futility
- Study leadership focus:
  - Stopping drug, ending end-of-study biopsies
  - Peer review publication of results for study participants and public

- Answering the paradox would have to wait

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 17, 2003 VOL. 349 NO. 3

The Influence of Finasteride on the Development of Prostate Cancer

Ian M. Thompson, M.D., Phyllis J. Goodman, M.S., Catherine M. Tangen, Dr.P.H., M. Scott Lucia, M.D., Gary J. Miller, M.D., Ph.D., Leslie G. Ford, M.D., Michael M. Lieber, M.D., R. Duane Cespedes, M.D., James N. Atkins, M.D., Scott M. Lippman, M.D., Susie M. Carlin, B.A., Anne Ryan, R.N., Connie M. Szczepanek, R.N., B.S.N., John J. Crowley, Ph.D., and Charles A. Coltman, Jr., M.D.

N ENGL J MED 349;3 WWW.NEJM.ORG JULY 17, 2003

EDITORIALS

The Prevention of Prostate Cancer — The Dilemma Continues

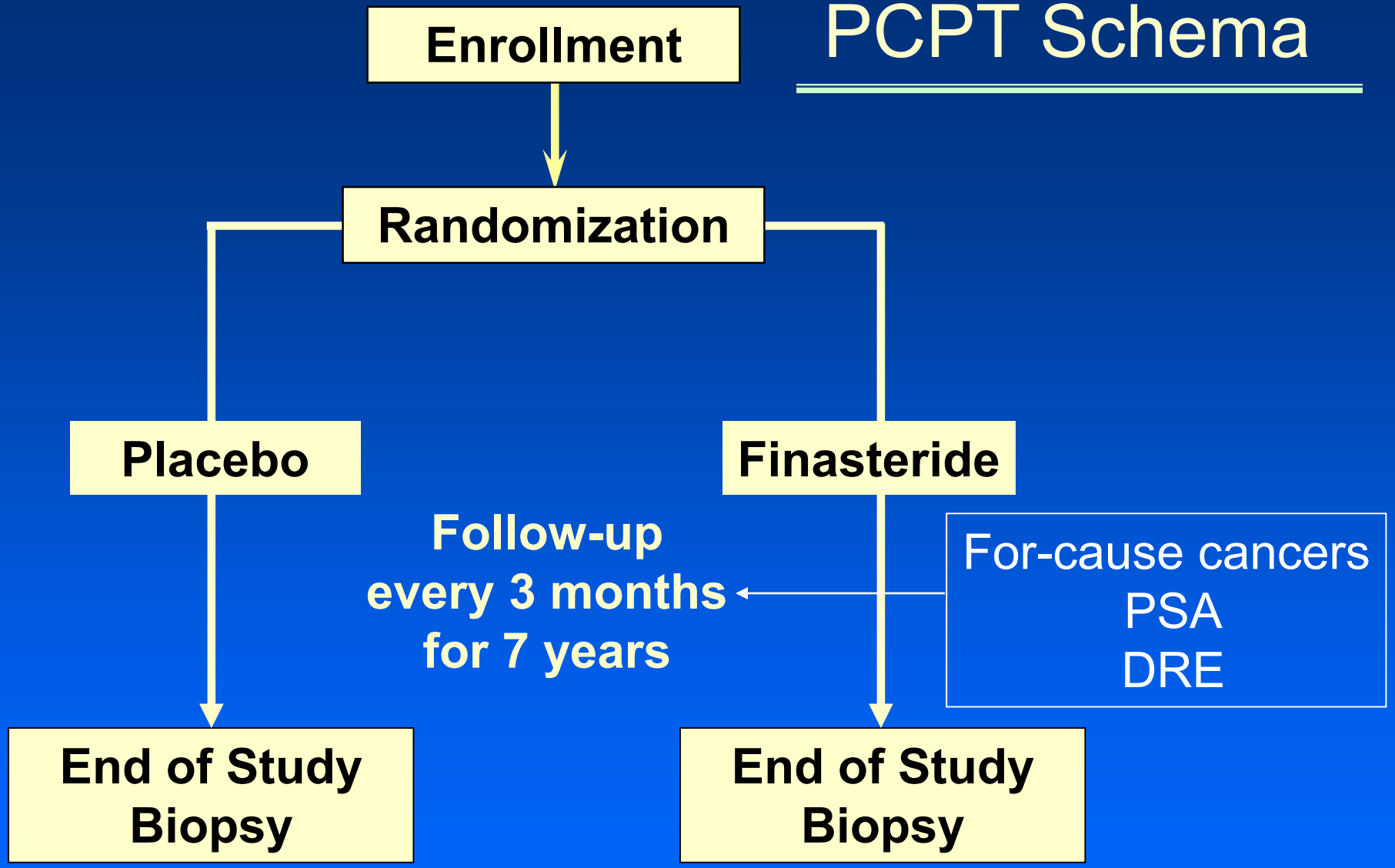
Peter T. Scardino, M.D.

Contrary to the expectations of many experts, there was a substantial effect of finasteride on the rate of detection of cancer.

Should finasteride now be recommended to men in order to lower their risk of prostate cancer? Several disturbing findings in the report argue that it should not.

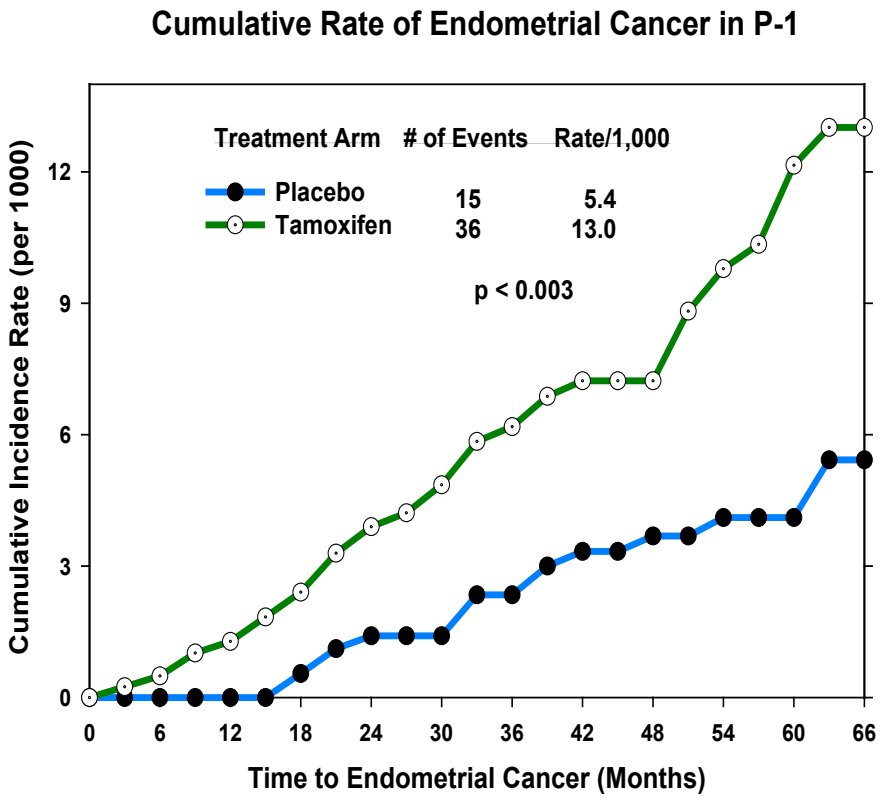
To understand the malignant potential of the large number of cancers detected in this trial, it will be important to document the type of treatment these men receive, their long-term survival, and which cancers progress.

PCPT Schema

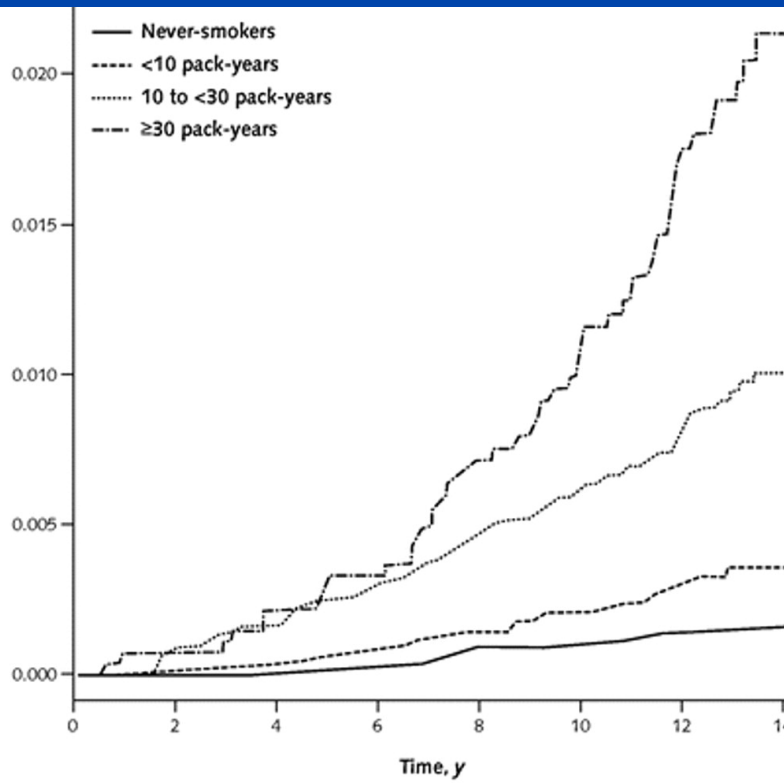

Enrollment
Randomization
Placebo
Finasteride
Follow-up
every 3 months
for 7 years
For-cause cancers
PSA
DRE
End of Study
Biopsy
End of Study
Biopsy

Exposure and risk of cancer

Over time, risk curves diverge.

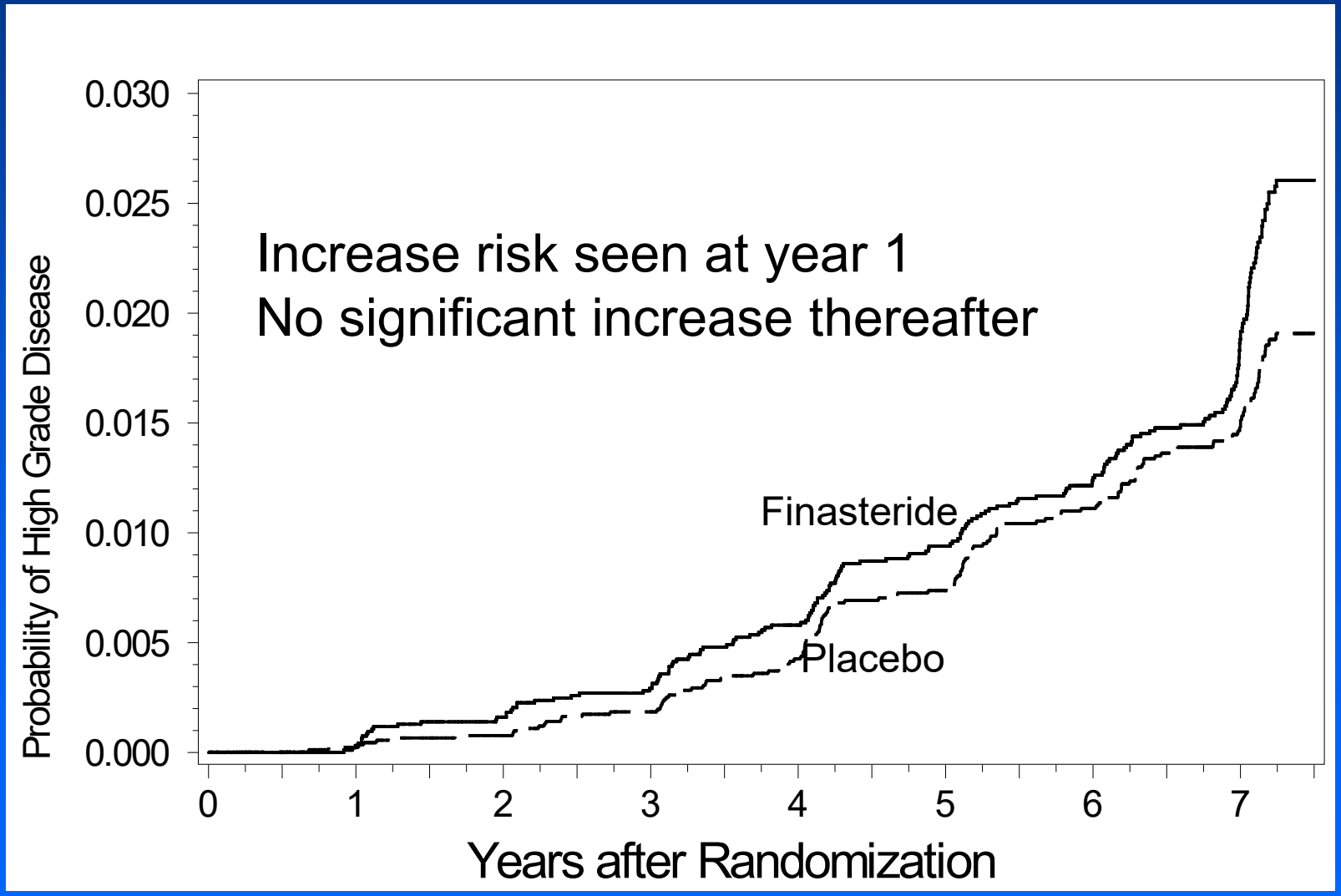


BCPT – P1



Ann Int Med 2011;154:719-26.

Risk of high grade disease in PCPT



To Determine if Prostate Cancer is present

Two things are necessary:

You must first *suspect* cancer.
(i.e., PSA or DRE must be Positive)

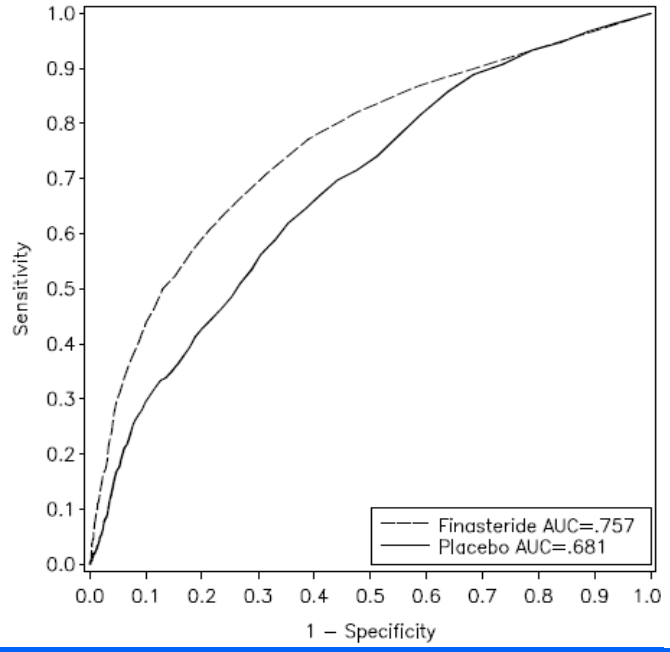
You must then *pathologically diagnose* cancer.
(i.e., your needle must *strike the tumor.*)

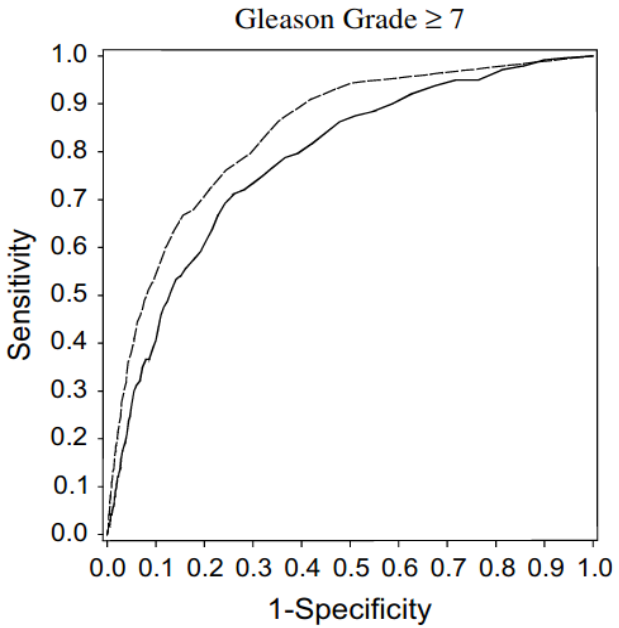
What we didn't know about finasteride

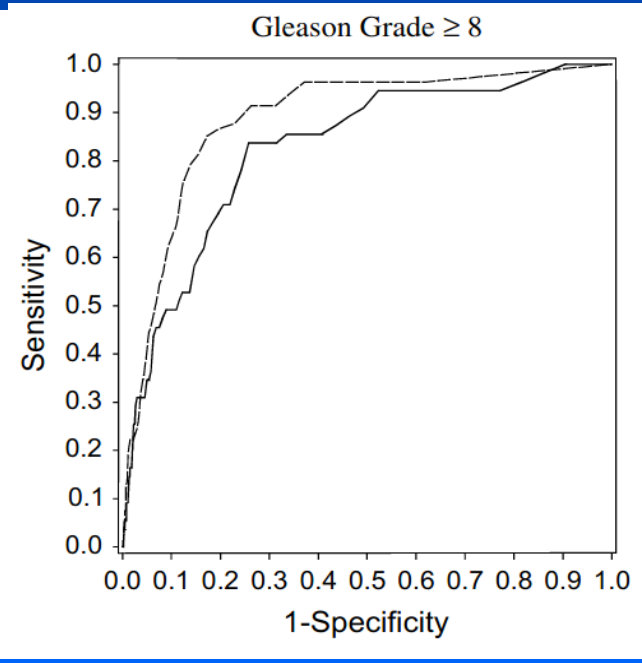
Finasteride

- Increases sensitivity of PSA for cancer
- Increases sensitivity of DRE for cancer
- Improves sensitivity of prostate biopsy

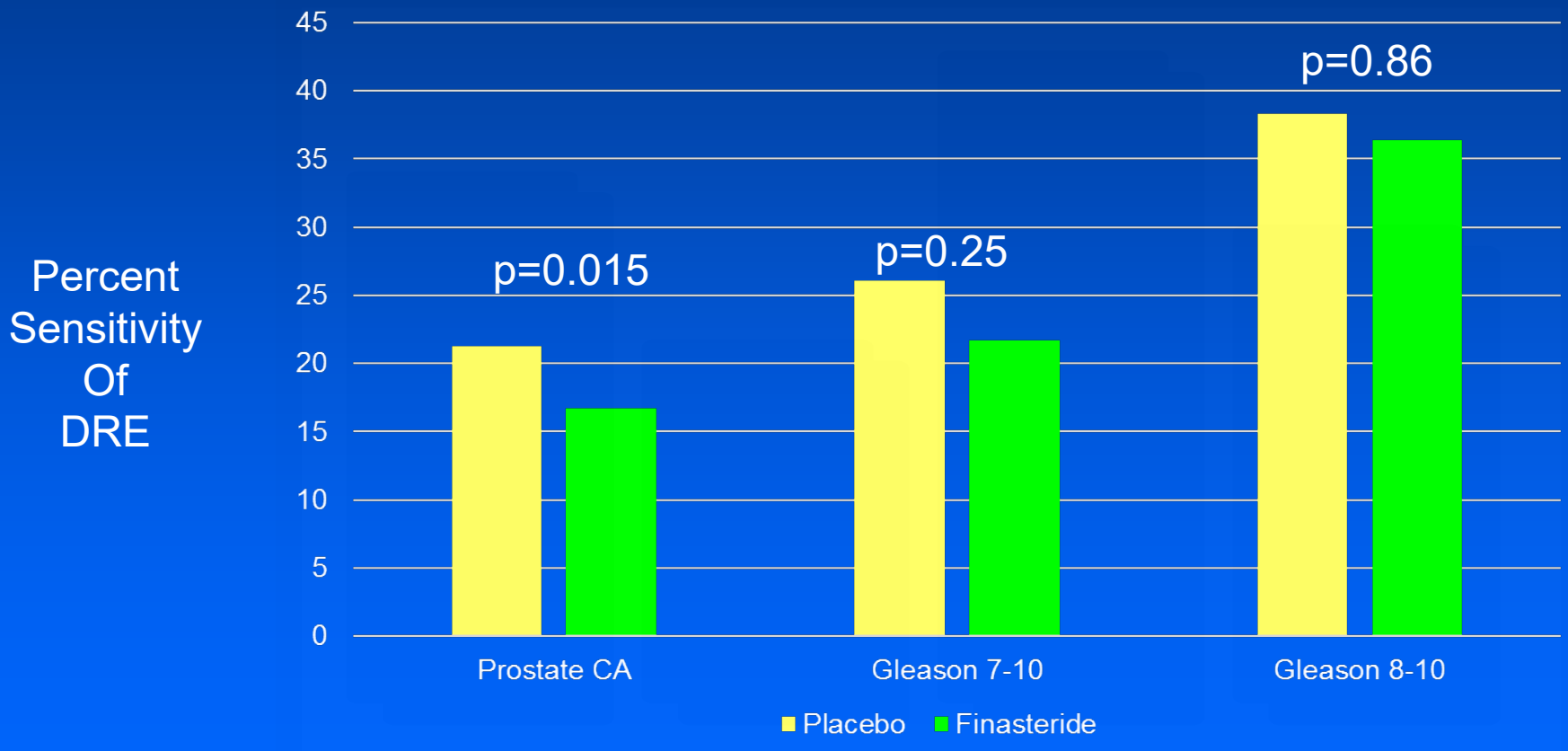
Finasteride improves sensitivity of PSA







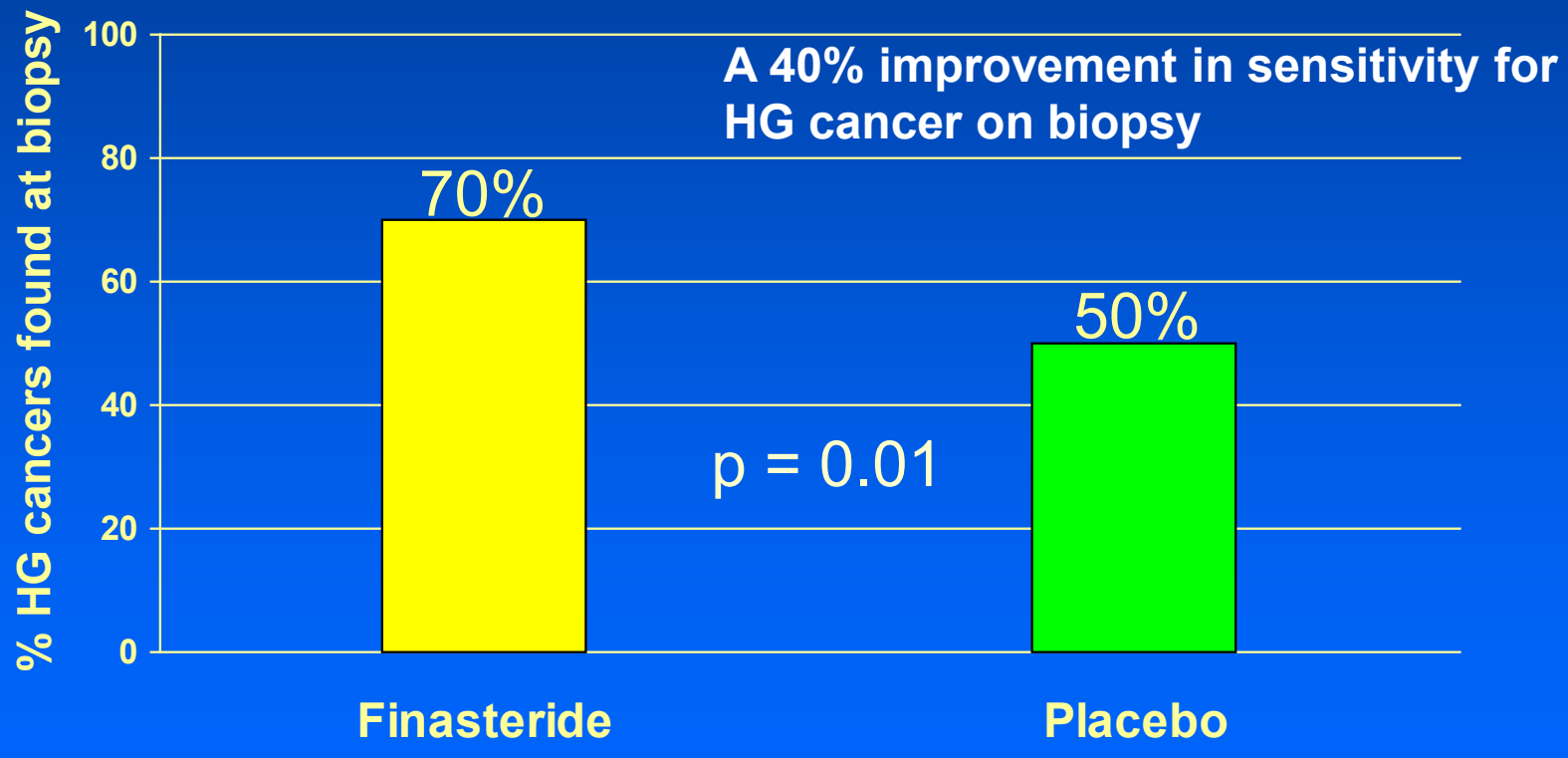
Finasteride Improves Sensitivity of DRE



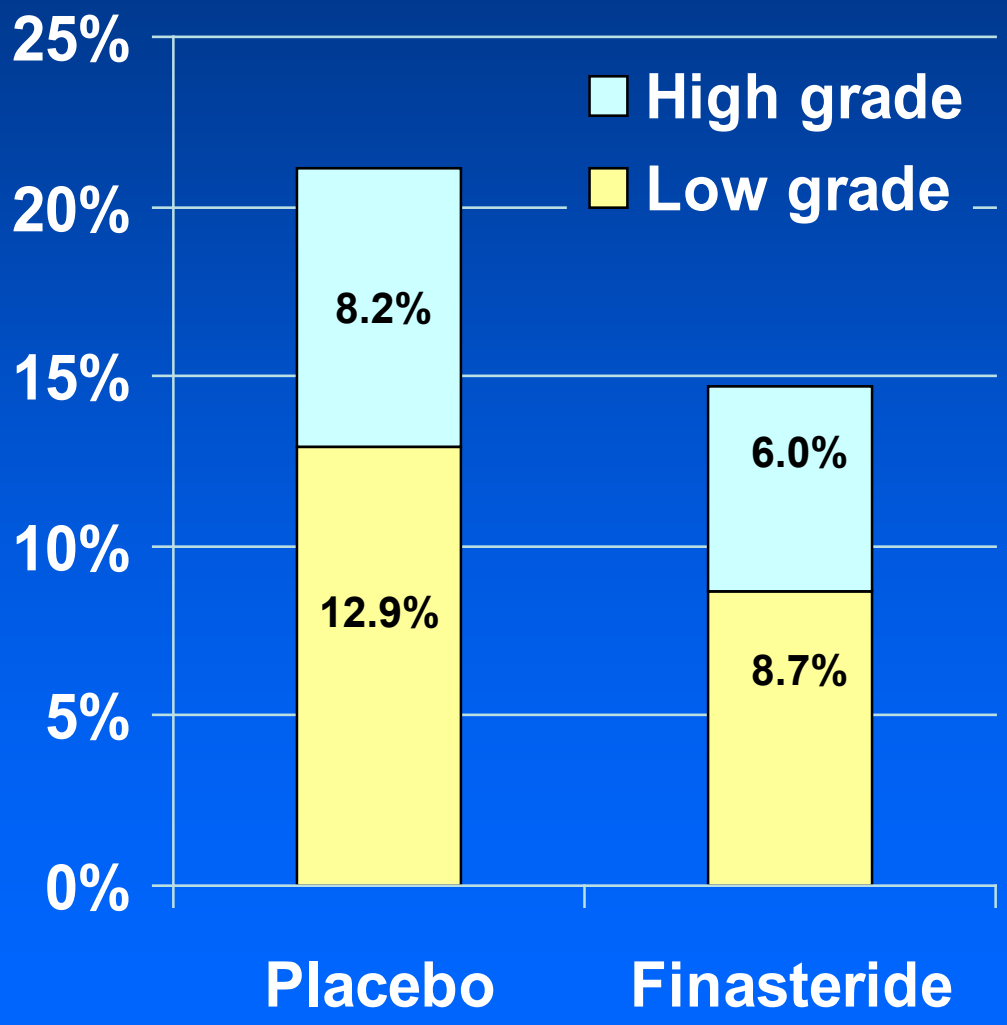
THE JOURNAL OF UROLOGY®

Vol. 177, 1749-1752, May 2007

Men with Gleason 7-10 at RP. What % were diagnosed at biopsy?



Overall Impact of Finasteride



Cancer

30% reduced risk (24-36%) p < .0001

Gleason ≤ 6

32% reduced risk (18-43%) p < .0001

Gleason ≥ 7

28% reduced risk (6-45%) p < .02

Redman M, et al.

Lingering Questions

While bias seemed to explain excess high-grade tumors, *we were not certain*

- How did survival differ between the arms?
- What happened when men stopped study drug….did the difference disappear?
- Most importantly, how did finasteride impact on prostate cancer mortality (understanding the study was *underpowered* for this endpoint)

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ESTABLISHED IN 1812 AUGUST 15, 2013 VOL. 369 NO. 7

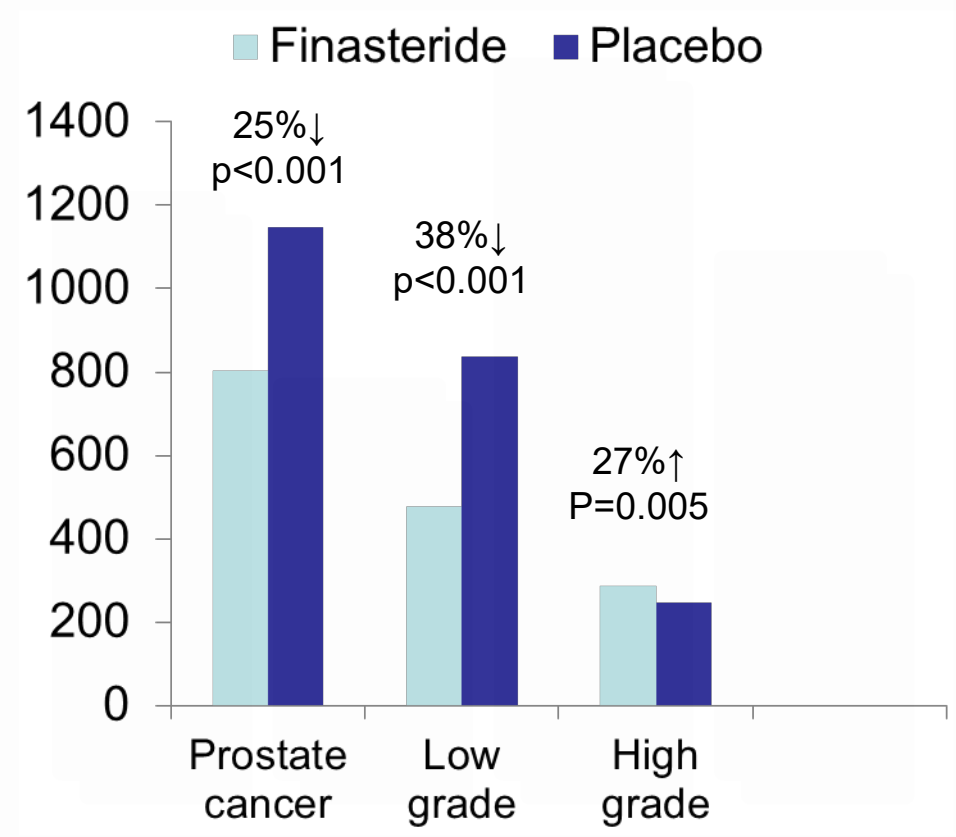
Long-Term Survival of Participants in the Prostate Cancer Prevention Trial

Ian M. Thompson, Jr., M.D., Phyllis J. Goodman, M.S., Catherine M. Tangen, Dr.P.H., Howard L. Parnes, M.D., Lori M. Minasian, M.D., Paul A. Godley, M.D., Ph.D., M. Scott Lucia, M.D., and Leslie G. Ford, M.D.

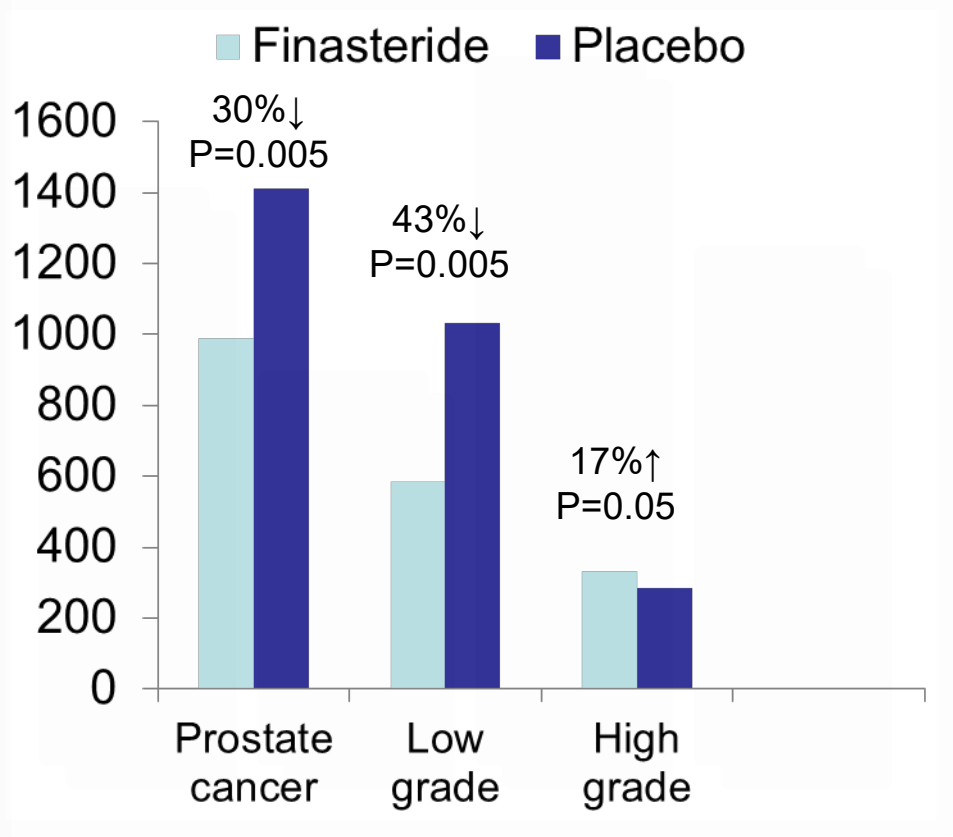
ABSTRACT

Incorporating patients with prostate cancer diagnosed after the NEJM data freeze (until October 31, 2003). *There may be operational biases.*

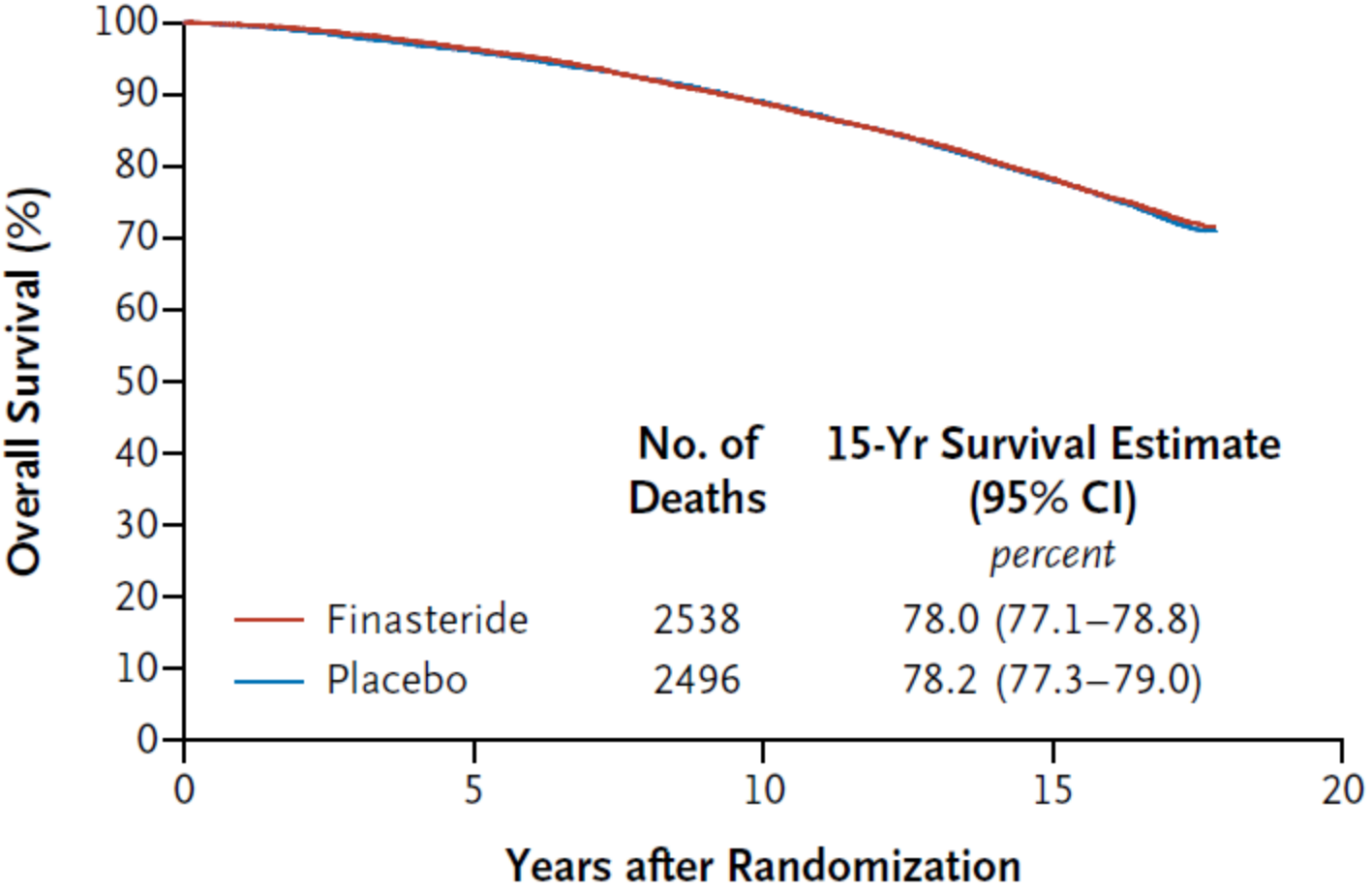
2004 Initial Report



2013 Updated Report



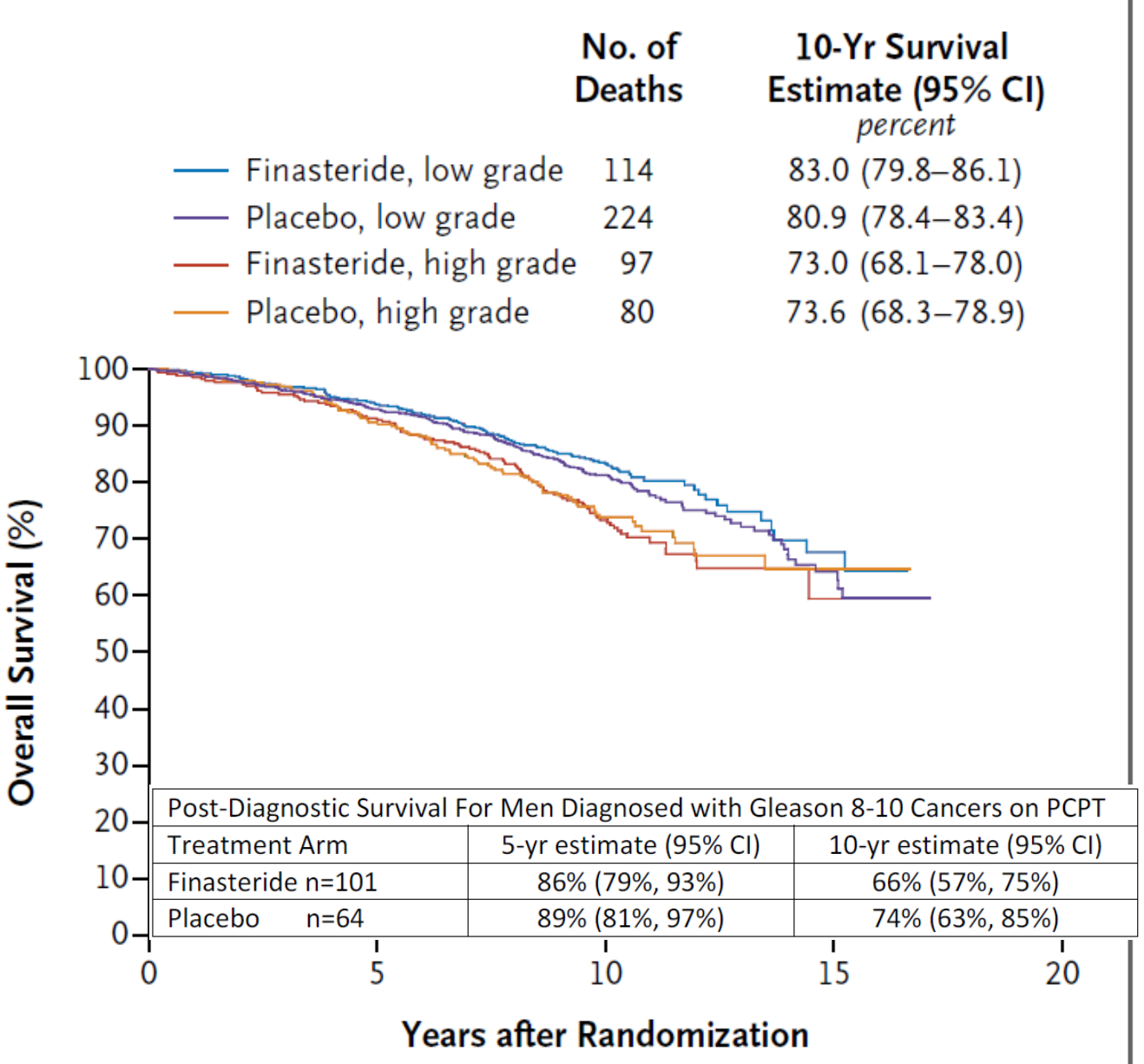
Longer-term relative risk reduction = 30%



No. at Risk

Finasteride	9423	9043	8358	6793
Placebo	9457	9106	8354	6788

Figure 2. Kaplan–Meier Curves for Overall Survival.



Post-Diagnostic Survival For Men Diagnosed with Gleason 8-10 Cancers on PCPT		
Treatment Arm	5-yr estimate (95% CI)	10-yr estimate (95% CI)
Finasteride n=101	86% (79%, 93%)	66% (57%, 75%)
Placebo n=64	89% (81%, 97%)	74% (63%, 85%)

Figure 3. Overall Survival of Men with Prostate Cancer, According to Cancer Grade.

Definition of Big Data

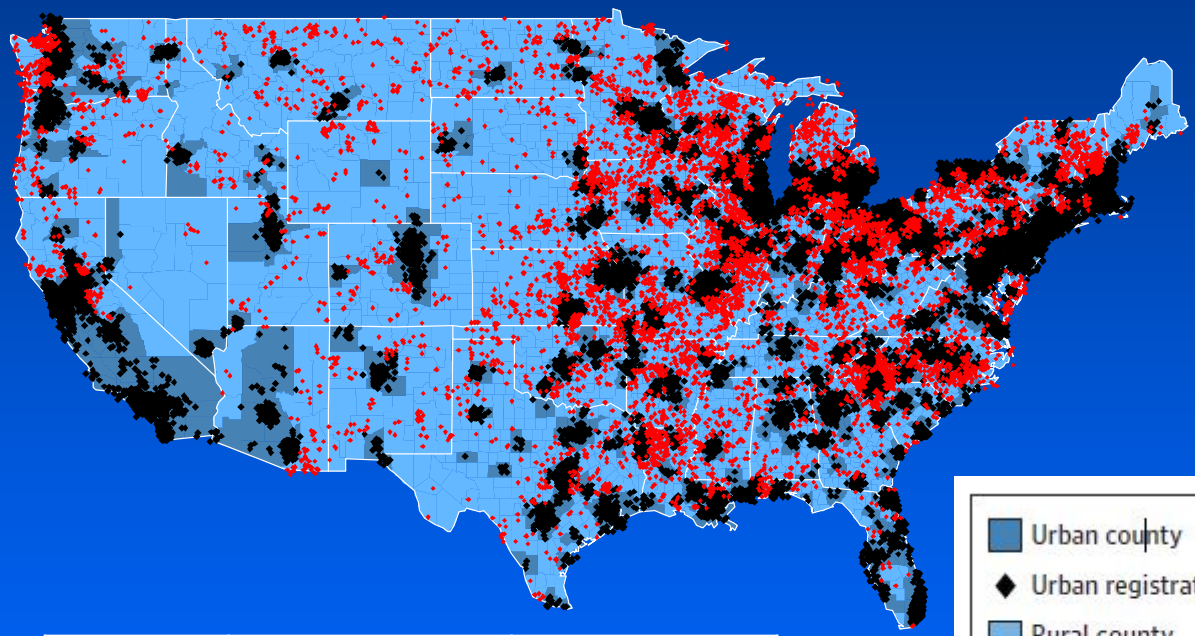
- Big data characterized as pertaining to the **Volume, Velocity, and Variety** of data (Laney, 2001; De Mauro, 2016)

Big Data Strategies in SWOG

- Emphasis on both **variety** and **volume**
- Using data from a large, NCI network group national clinical trials database, in combination with…
  - Registry (SEER)
  - Life-table
  - Census
  - Geospatial data
  - Publication
  - Citation
  - Medicare claims

Rural/Urban Disparities

SWOG Enrollments from 1986-2012 by Rural vs Urban County of Origin (n=36,995)



	% of Total		% Rural	
	SWOG	US	SWOG	US
West	23%	23%	13%	11%
Midwest	39%	21%	23%	22%
South	24%	37%	23%	24%
Northeast	14%	18%	14%	16%

"Geographic Distribution and Survival Outcomes for Rural Patients With Cancer Treated in Clinical Trials"*

- Combined SWOG treatment trial data with geospatial mapping data
- Examined 36,995 patients from 44 phase III treatment trials from all 50 states
- Rural patients had worse survival in only 1/17 cancer cohorts
- Best approach to improve outcomes for rural cancer patients may be to provide access to the kind of quality, guideline-based care available in trials

** Unger et al, JAMA Network Open, 2018*

Prostate Cancer Prevention Trial: Lingering Questions

- Unclear if the trial duration was sufficient to determine the maximum benefit of finasteride
- Concern that the reduced risk of PC seen in subjects receiving finasteride might not be maintained after discontinuation

Limitations of Using Clinical Trial Data Alone

- Limited long term follow-up (7 years)
- No adverse events after treatment stops
- Limited utilization data (beyond protocol specified therapy)

Program Objectives

- Link PCPT trial records to Medicare claims
- Examine late effects, long term prostate cancer incidence, treatment utilization, and complications

The PCPT-Medicare Linked Database

- Clinical trials: baseline demographics; clinical risk factors; intervention duration; during-study prostate cancer diagnosis
- Medicare claims data (based on ICD-9, HCPCS, and CPT codes): long-term follow-up for other illnesses, new cancer diagnoses, and treatment utilization
- Advantage of random assignment for treatment comparisons (limits confounding)

What are the patterns of long-term prostate cancer diagnoses in the Prostate Cancer Prevention Trial?

Methods

- PCPT study records linked to Medicare claims to augment the detection of prostate cancer diagnoses
- Defined a (Medicare) claims-based prostate cancer diagnosis algorithm
  - Diagnosis and procedure codes
- All men were included in this analysis
  - Including those without a linkage to Medicare
- PCPT enrolled patients from 1993-1997; Medicare claims available from 1999-2011

Medicare Claims-Based Algorithm for Prostate Cancer Diagnosis

- Examined multiple claims-based algorithms
- Considered diagnosis of prostate cancer in PCPT as “gold standard”
- Compared PCPT to Medicare diagnoses among men with concurrent coverage in both databases
- This overlap region is especially useful for validating claims-based approaches to event identification

Medicare-Based Algorithm for PC Diagnosis

"Best" algorithm identified as…

- **Diagnosis** code 185 for PC
  - Any hospital claim, or
  - ≥2 physician or outpatient claims >30 days apart* but not more than 6 months apart
- **Procedure** code for radical prostatectomy
  - Based on ICD9 or HCPCS codes
- **Sensitivity, 83.3%; specificity, 96.3%**

** Smith et al., JCO, 2005*

Statistical Methods

- Cumulative incidence at 5, 10, and 15 yrs
- Cox regression to test intervention effect
- Due to required 7 year biopsy, examined intervention effect within intervals:
  - 0-6.5 years vs. 6.5-7.5 years vs. after 7.5 years
  - Change point analysis*

** Liang et al., Biometrics, 1990*

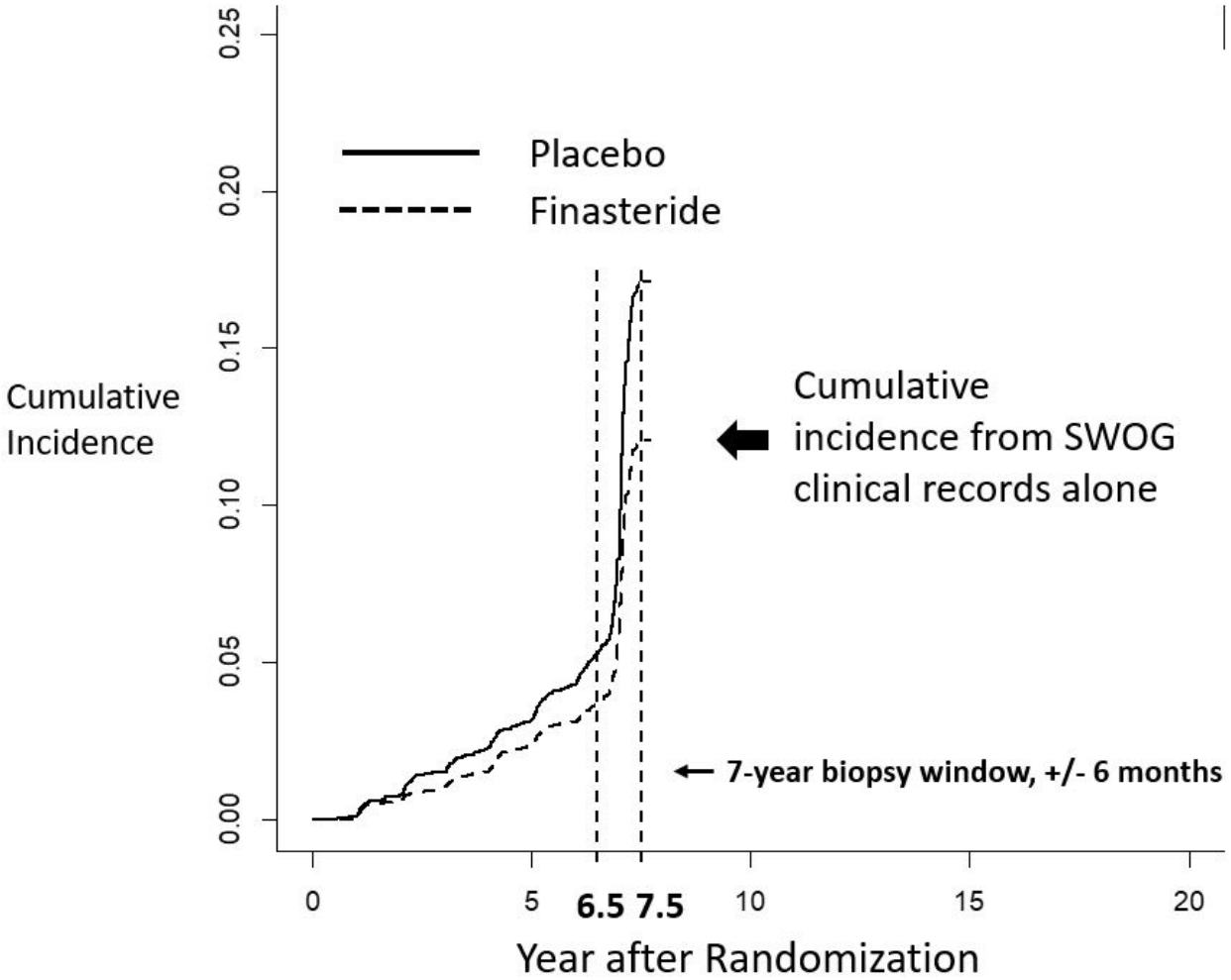
Participant Characteristics

- N=14,176 participants (75.1%) had a Medicare linkage (placebo, 7107; finasteride, 7069)
- Subject characteristics by arm well balanced
- Median time from PCPT randomization = **16.0** years for each arm
  - Increase from 7 years using PCPT clinical records alone

Prostate Cancer Diagnoses

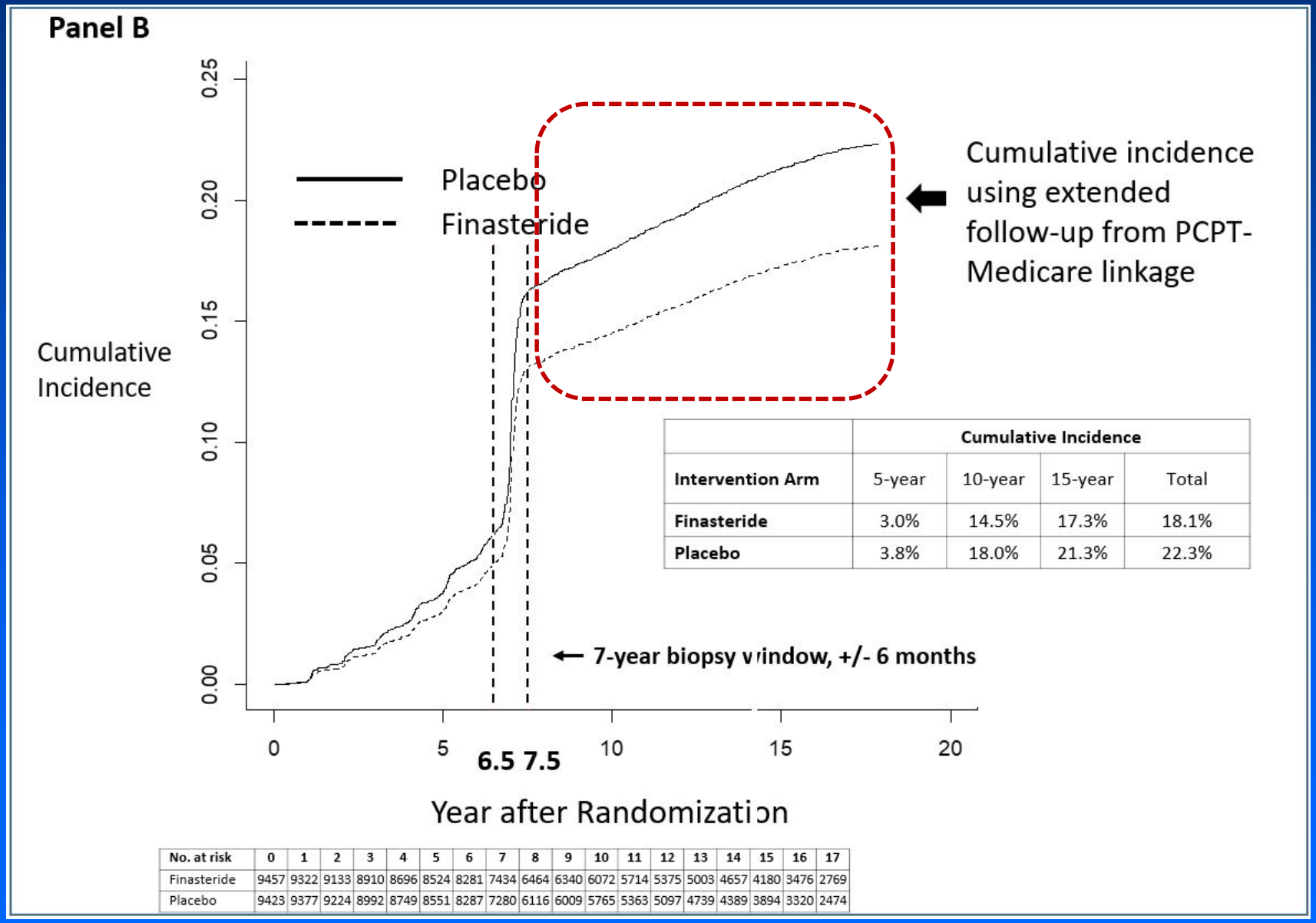
Diagnosed with prostate cancer by…	Overall	Placebo	Finasteride
PCPT records alone	895	528	367
Medicare alone	959	455	504
PCPT and Medicare	1390	822	568
Total	**3244**	**1805**	**1439**

Cumulative Incidence of Prostate Cancer



No. at Risk	0	1	2	3	4	5	6	7
Finasteride	9457	9322	9130	8895	8654	8393	8091	6591
Placebo	9423	9377	9223	8987	8725	8440	8133	6504

Cumulative Incidence of Prostate Cancer

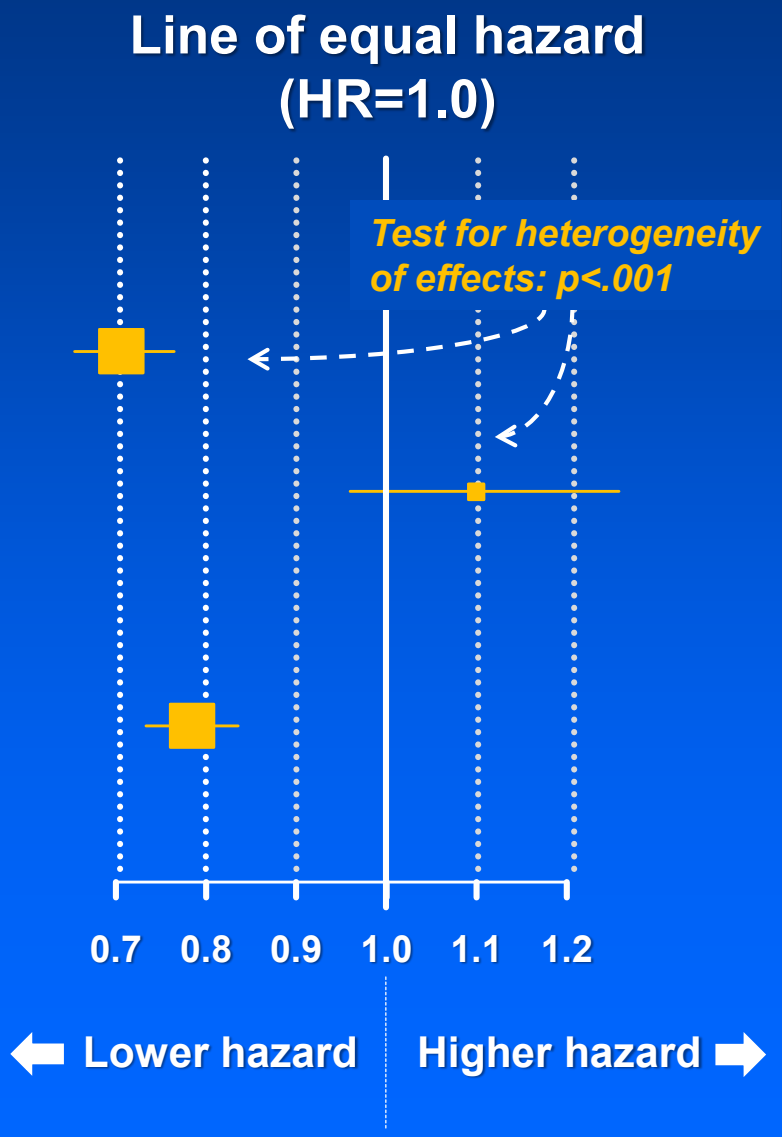


	Cumulative Incidence			
Intervention Arm	5-year	10-year	15-year	Total
Finasteride	3.0%	14.5%	17.3%	18.1%
Placebo	3.8%	18.0%	21.3%	22.3%

No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Finasteride	9457	9322	9133	8910	8696	8524	8281	7434	6464	6340	6072	5714	5375	5003	4657	4180	3476	2769
Placebo	9423	9377	9224	8992	8749	8551	8287	7280	6116	6009	5765	5363	5097	4739	4389	3894	3320	2474

Forest plot of HR of time to prostate cancer (finasteride vs placebo)

Period	Hazard Ratio	95% Confidence Interval	p-value
0 to 7.5 years	0.71	0.66 - 0.77	<.001
After 7.5 years	1.10	0.96 - 1.26	.18
Overall	0.79	0.74 - 0.84	<.001



Bias Assessment

- No differences in utilization patterns for finasteride vs. placebo:

Utilization type	Finasteride	Placebo
Prostate cancer screening claims	13,228	12,457
Hospital inpatient or physician outpatient visits	3204	3277
Overall claims	302,183	308,279

- No evidence of bias in diagnosis dates
- No evidence of differences in baseline demographic and clinical risk factors

Summary

- No evidence that 7 years of finasteride continued to prevent new PC diagnoses after finasteride was discontinued
- Also, no evidence that finasteride had more PCs after completing finasteride use
- Finasteride provides a substantial reduction (21%) in risk of PC through a median of 16 years of follow-up

Using Secondary Data for Clinical Trial Follow Up

- Cancer prevention trials involve following a large number of participants for many years
- Costs of conducting such studies are very high
- Use of secondary data sources augments detection of long term outcomes at much reduced cost

CONCLUSION

- Big data strategies can be used to both **extend and enrich** valuable NCTN and NCORP clinical trial data either…
  - Extending follow-up or data collection for individual trials
  - Through their inclusion in secondary data analyses
- Approach is especially advantageous in disease settings with rare or long term events including prevention or adjuvant treatment (i.e. early stage breast or prostate)

Prostate cancer mortality

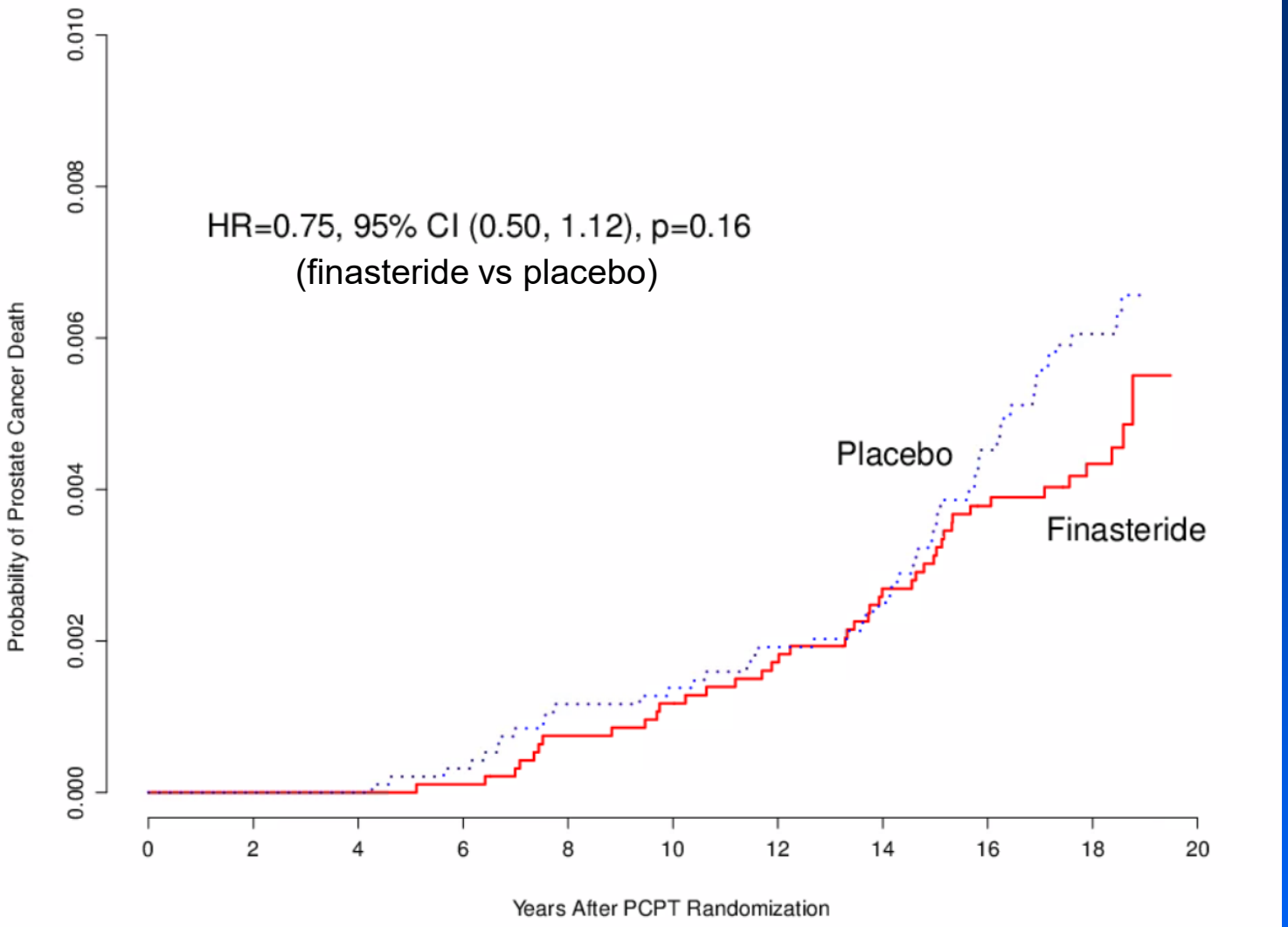
- If high-grade disease is more common (and not an artifact), risk of a higher prostate cancer death rate.
- Given high prevalence and low mortality, prostate cancer mortality is the most important outcome.

Brief Methods

- Using linkage analyses including SSN, PCPT participants were matched with the U.S. National Death Index.
- Studied for outcomes:
  - Death
  - Death due to prostate cancer
  - Assessment made based on death certificate

	Placebo	Finasteride
Total eligible randomized	9457	9423
Deaths (total)	2979	3048
Prostate cancer death	56	42
PCA diagnosis on PCPT	40	27
Later PCA diagnosis	16	15
Follow-up for patients still alive (years)		
Median (IQ range)	18.4	18.4
Inter-Quartile range	17.4, 18.7	17.3, 18.7
Total person-years of follow-up	148,895	147,947
PCA = prostate cancer; IQ=Inter-quartile range		

	Placebo		Finasteride		
	PCA/Not PCA Death[1]	PCA death	PCA/Not PCA Death[1]	PCA Death	
Total	1372	56	962	42	
Gleason Score					p-value[2]
≤ 6	1021 (98.5%)	16 (1.5%)	582 (98.8%)	7 (1.2%)	< .0001
7	213 (96.0%)	9 (4.1%)	228 (97.9%)	5 (2.2%)	
8 - 10	55 (83.3%)	11 (16.7%)	88 (87.1%)	13 (12.9%)	
Unknown	83	20	64	17	
Age at diagnosis (years)					
55 - 64	300 (97.7%)	7 (2.3%)	190 (96.0%)	8 (4.0%)	0.25
65 - 69	392 (97.5%)	10 (2.5%)	291 (97.0%)	9 (3.0%)	
70 - 74	410 (97.4%)	11 (2.6%)	285 (99.0%)	3 (1.0%)	
≥ 75	270 (95.7%)	12 (4.3%)	196 (96.6%)	7 (3.5%)	
Unknown	0	16	0	15	
PSA at diagnosis[3]					
0.3 – 2.0	633 (97.8%)	14 (2.2%)	441 (98.4%)	7 (1.6%)	0.0003
2.1 – 4.0	423 (96.6%)	15 (3.4%)	270 (97.5%)	7 (2.5%)	
4.1 – 6.0	243 (97.6%)	6 (2.4%)	157 (98.1%)	3 (1.9%)	
> 6.0	72 (93.5%)	5 (6.5%)	94 (90.4%)	10 (9.6%)	
Unknown	1	16	1	15	
DRE at diagnosis					
Normal	1175 (97.4%)	31 (3.6%)	818 (97.5%)	21 (2.5%)	0.08
Suspicious	197 (95.6%)	9 (4.4%)	144 (96.0%)	6 (4.0%)	
Unknown		16		15	
PCPT Biopsy prompt					
Other[4]	550 (95.7%)	25 (4.4%)	419 (95.4%)	20 (4.6%)	0.41
EOS	822 (96.4%)	31 (3.6%)	543 (96.1%)	22 (3.9%)	



	10 years	15 years	18 years
Number at risk			
Placebo	8229	7094	4060
Finasteride	8198	7026	4012
Incidence (95%CI)			
Placebo	0.14% (0.07,0.23)	0.35% (0.02, 0.49)	0.60% (0.45, 0.78)
Finasteride	0.12% (0.06,0.21)	0.31% (0.21,0.44)	0.43% (0.31, 0.59)

Cost of finasteride in 2018

- Good Rx (CVS) - $8.65
- Walmart (with free discount) - $4.00
- Kroger (with free coupon) - $8.57
- Costco (free coupon) - $8.78
- Albertsons (free coupon) - $9.23
- Health Warehouse (online) - $7.50

- About 25¢ a day

Chemoprevention of Prostate Cancer with Finasteride

- After 20 years, 7 years of finasteride treatment reduces risk of prostate PCA by 25-30%
- This risk reduction is in the face of improved prostate cancer detection
- Reduction in risk is durable
- Most tumors prevented are Gleason 3+3
- Risk of prostate cancer death is 25% less with finasteride (not statistically significant)

Pros/cons of chemoprevention

Pros:

- 25-30% reduction in risk of diagnosis

  Likely translates into less surgery, radiation, treatment complications
- No excess risk of prostate cancer death (25% reduction in risk of prostate cancer death [not statistically significant])
- Significant improvement in current urinary symptoms and reduced complications from BPH (retention, TURP)
- Inexpensive (compared to other interventions)

Pros/cons of chemoprevention

Cons:

- Small but increased risk of sexual side effects
- Gynecomastia: placebo-2.8%. Finasteride-4.5%

Commentary

Some will posit that tumors prevented are inconsequential

Response:

- Diagnosis of low-grade cancer is an adverse event
  - 30-50% risk of eventual treatment (with side effects)
- Repeated MD visits, PSA anxiety
- Repeated biopsies (expensive, sepsis)
- Cost of surveillance is as expensive as surgery
- 38% of prostate cancer deaths in PCPT were due to Gleason 3+3 tumors.
- Almost 50% of prostate cancer deaths were in patients with normal PSA/DRE

The final chapter awaits

- Dr Unger and colleagues will examine the impact of finasteride chemoprevention on risk of other outcomes.

- If you aren't diagnosed with prostate cancer, you won't be treated for prostate cancer and you therefore *cannot suffer side effects of treatment*.

Initial analysis plans (*precis*)

Diagnoses

- Radiation proctitis
- Radiation cystitis
- Urinary incontinence
- Sexual Dysfunction
- Urinary retention
- Urosepsis
- Prostatitis

Procedures

- Placement of AUS
- Placement of IPP
- Incision of stricture

Who deserves the credit for this body of work?

- Far too many people for us to acknowledge at this time.
- Hundreds of investigators at >200 sites
- Even more research associates

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Michael LeBlanc
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Most of all, thanks to 18,882 remarkable men