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## **Prostate Cancer 2006**

*Are We Being Too Aggressive or  
Not Aggressive Enough?*

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## **Support**

- Funding for the CaPSURE™ national disease registry is provided by a grant from TAP Pharmaceutical Products Inc to the Urology Outcomes Research Group, Department of Urology, UCSF
- NCI - UCSF Prostate Cancer SPORE, R01
- Department of Defense

CaPSURE: Cancer of the Prostate Strategic Research Endeavor

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## **PROSTATE CANCER**

- Most Common Cancer in American Men, Second Leading Cause of Cancer Death
- No Consensus on the Benefits of Early Detection and Treatment
- No Consensus on What Constitutes the Best Form of Treatment for Any Stage of Disease

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## **Historical Paradigm (Then)**

- Prostate cancer treated by monotherapy
- Risk assessment was imprecise and often wrong
- Sensitive biomarker not available and used until mid to late 1980's
- In high - risk patients, androgen deprivation not advised until symptomatic, metastatic disease noted
- Chemotherapy and secondary androgen deprivation felt to be morbid and ineffective

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## Now

- Sensitive biomarker widely used
- Natural history and risk assessment more precise
- Combination therapy proven to be effective in select patient populations
- Early rather than delayed androgen deprivation in high risk patients supported
- Secondary androgen deprivation and chemotherapy shown to be effective
- Novel therapy a high priority

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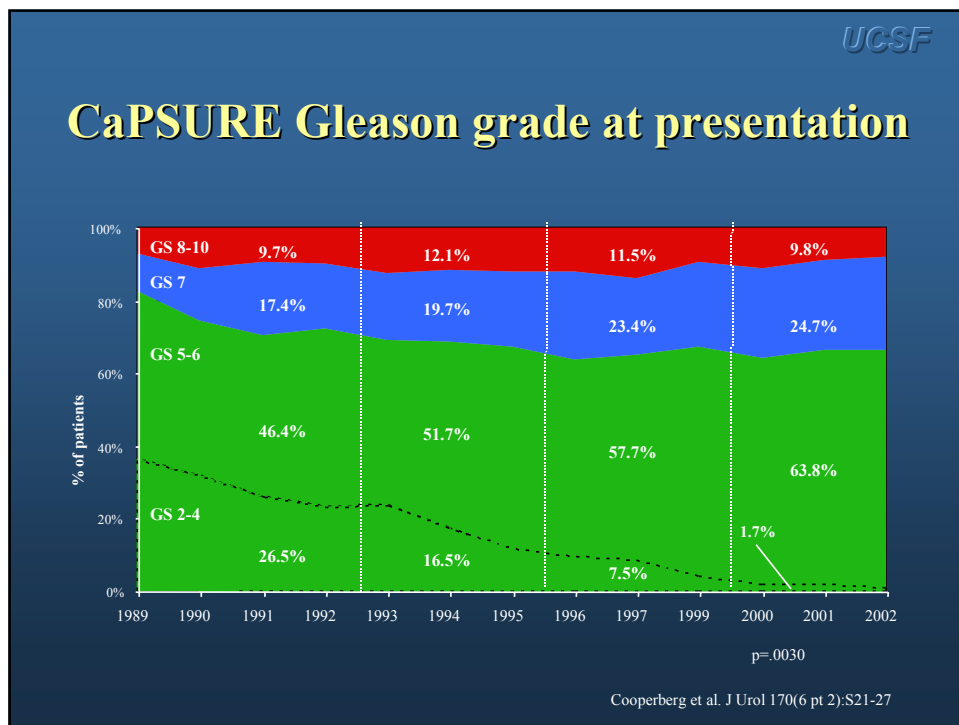
## Prostate Cancer

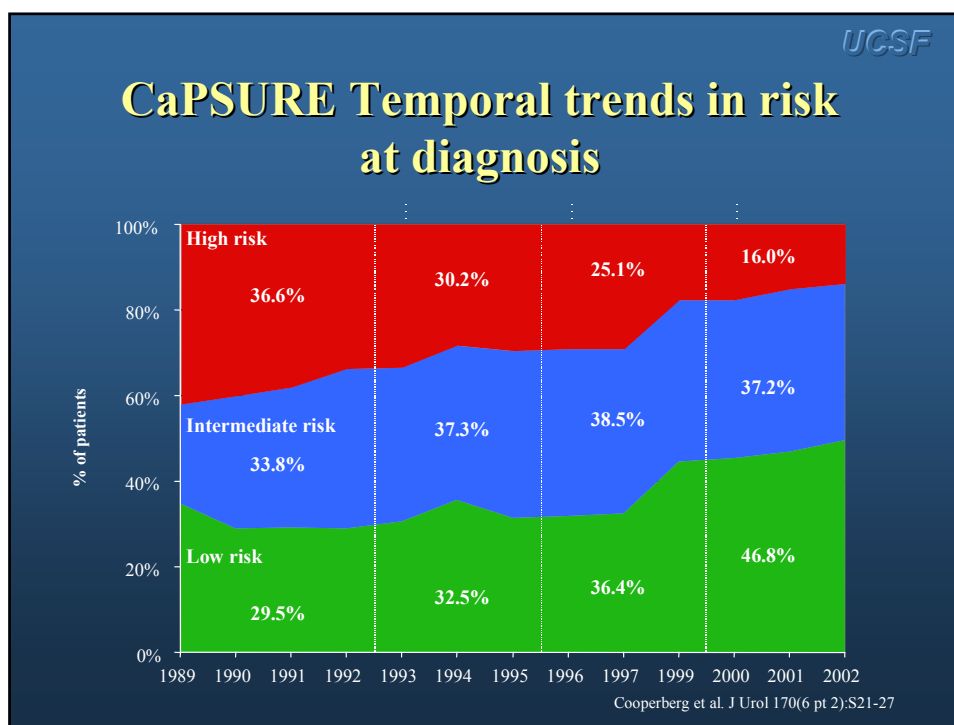
### *Early Detection*

- Younger Patients
- Lower Cut - points
- More Biopsies
- Smaller Cancers
- *Considerable Controversy!*

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## Early Detection *Where Has It Gotten Us?*



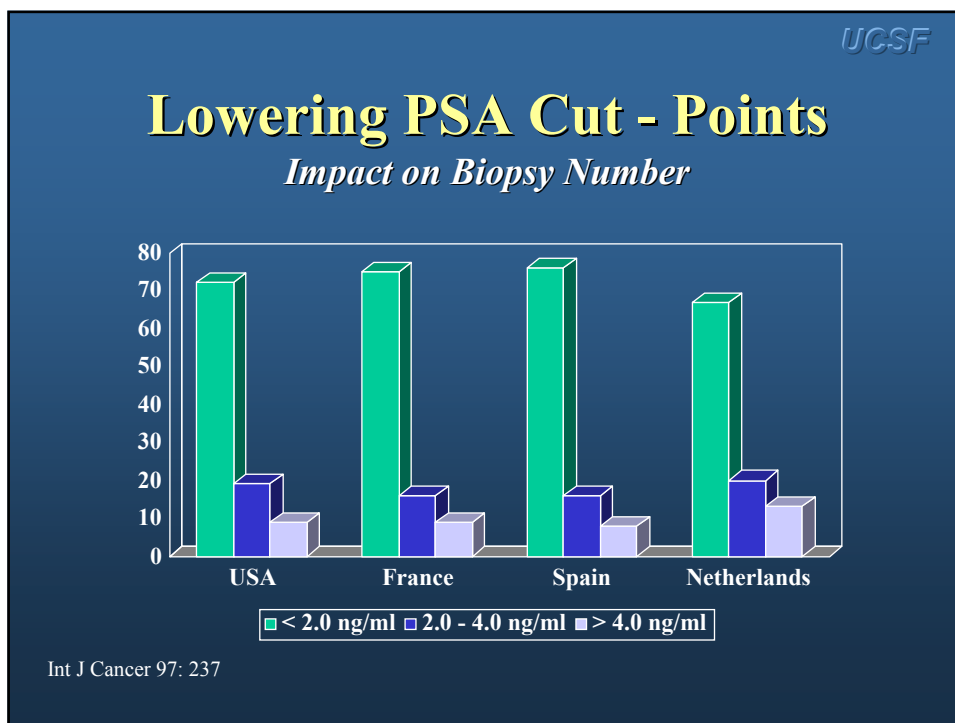


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### Results from Prostate Cancer Prevention Trial

PSA	# Positive	# Biopsied	% +ve Biopsy
≤4.0	449	2950	15.2%
≤0.5	32	486	6.6%
0.6-1	80	791	10.1%
1.1-2.0	170	998	17.0%
2.1-3.0	115	482	23.9%
3.1-4.0	52	193	26.9%

N Engl J Med. 2003 Jul 17;349(3):215-24

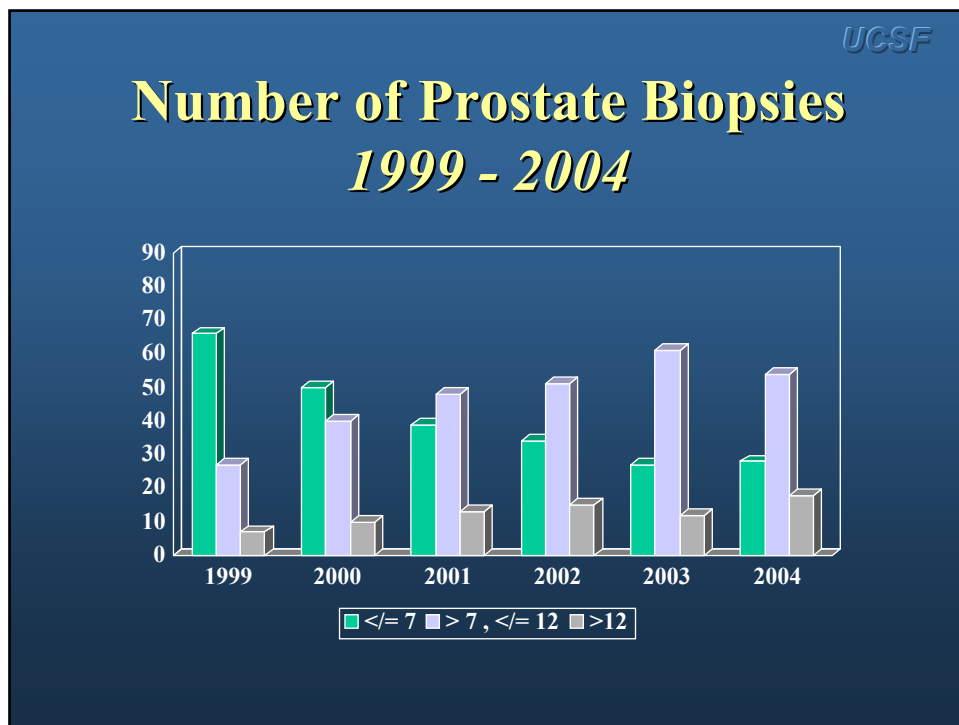
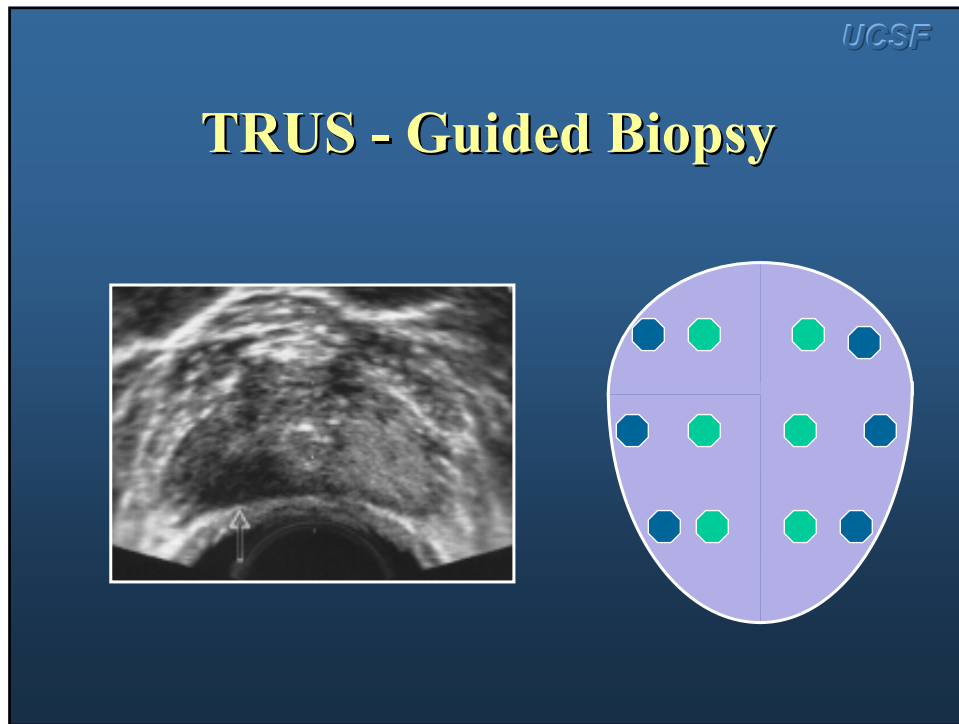


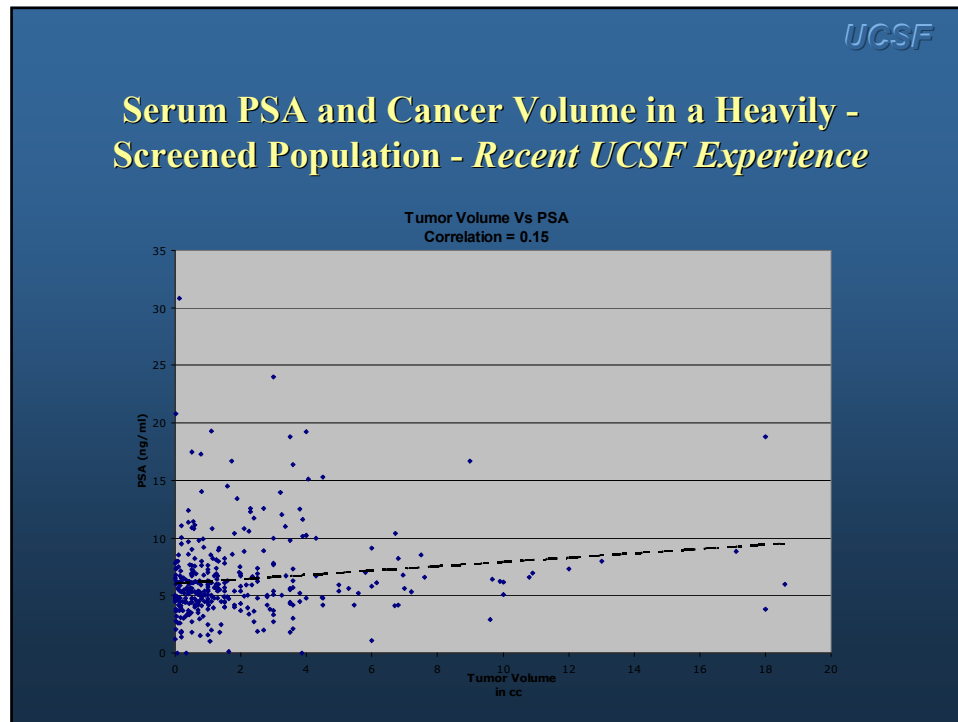
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## Natural History of Screen Detected Cancers

Grade	Lead time (years)	15 year CS mortality (%)	15 year survival benefit (%)
< 7	14.1	1	0
7	9.3	7 - 20	11
8 - 10	5.0	23 - 68	23

Assumes biennial PSA screening  
 C Parker et al 2006 ASCO Prostate Cancer Symposium





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- Is PSA Dead?**
- Race to discover new markers (i.e. proteomics)
  - Consider more intelligent use of PSA
    - *Isoforms*
    - *Velocity or doubling time*
    - *Less frequent testing*



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## Who Is The Average Prostate Cancer Patient?

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### Prostate Cancer - Defining the “Average Patient”

- Mean Age 65.2 years
- 58% with some college education
- 15% with no co - morbidities (31% with 3 or more)
- 25% of normal BMI
- With regard to HRQOL - good performance *except in sexual health* (mean 50)

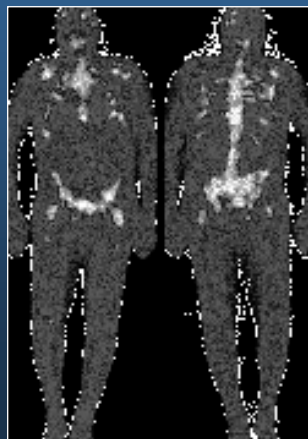
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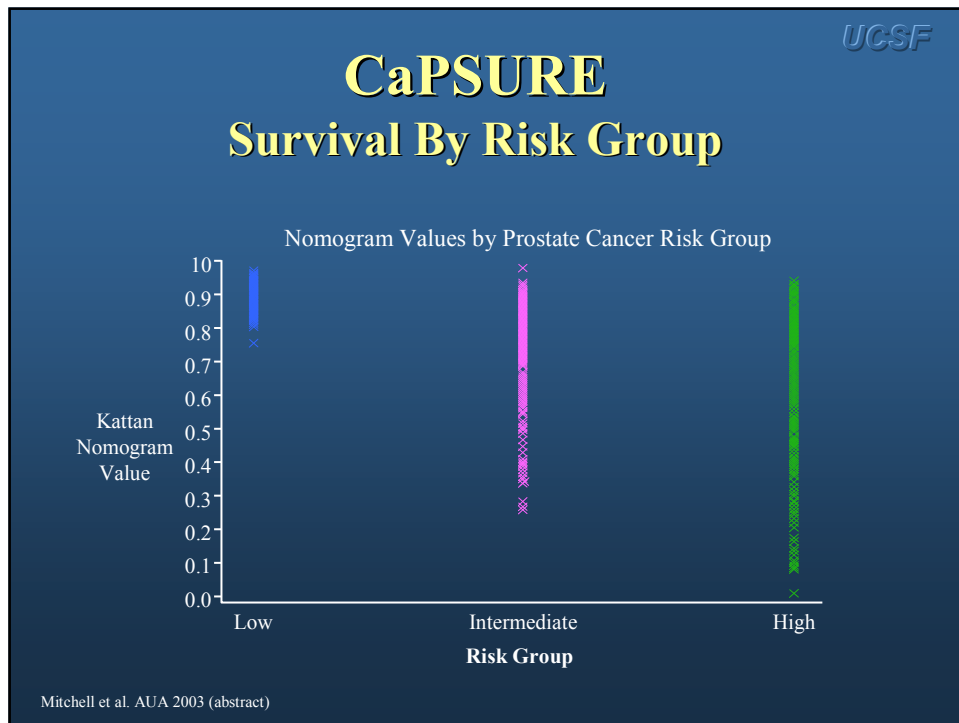
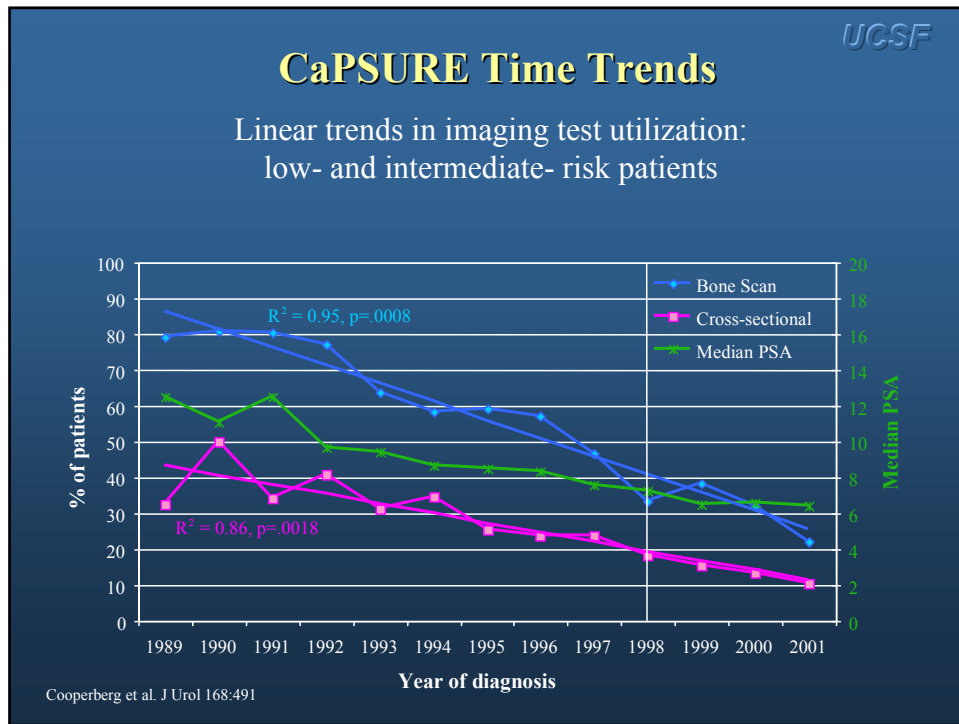
## How Good Are We At Risk Assessment?

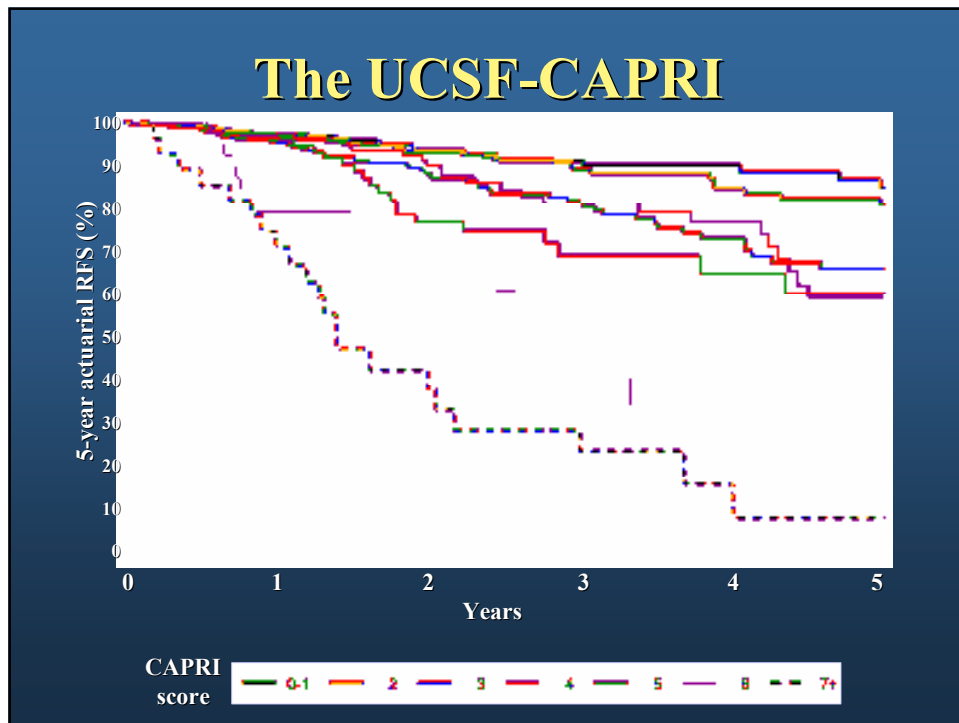
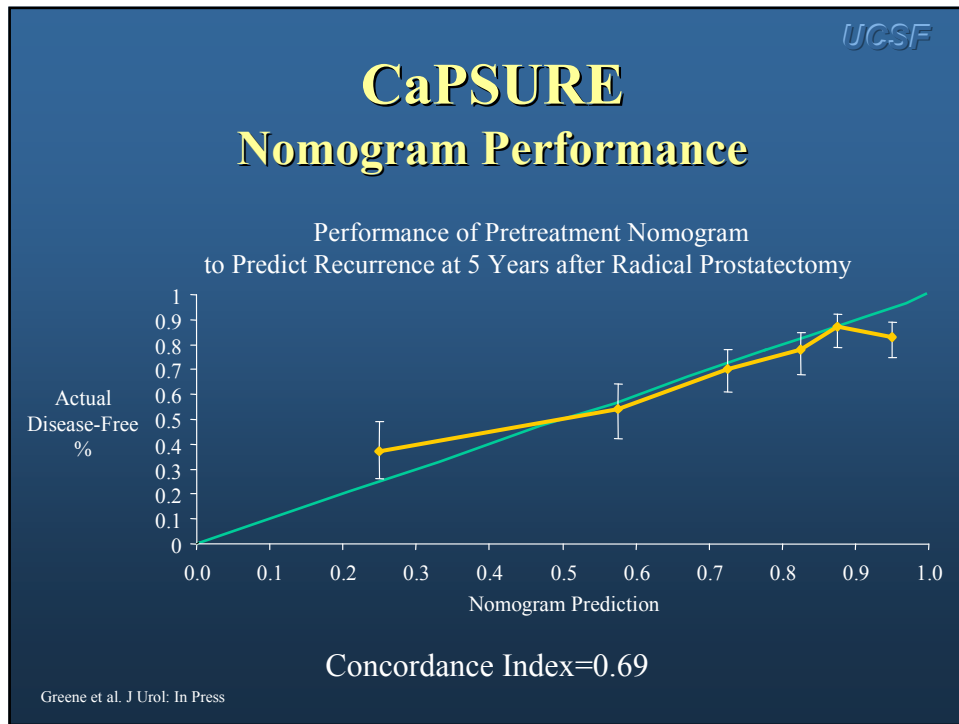
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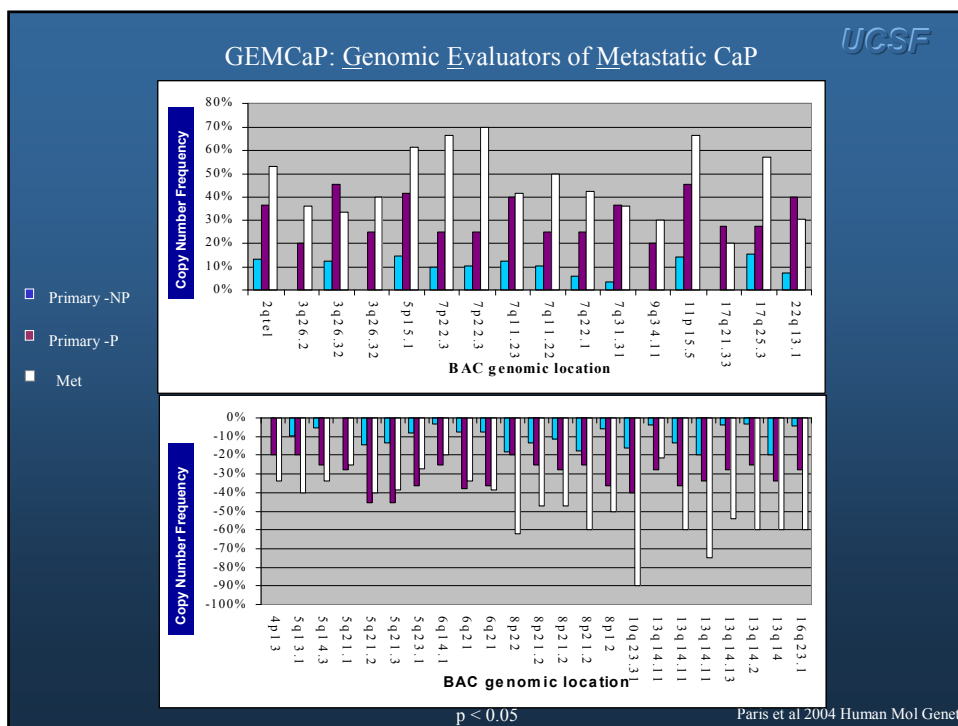
## PROSTATE CANCER

*A Spectrum of Disease*



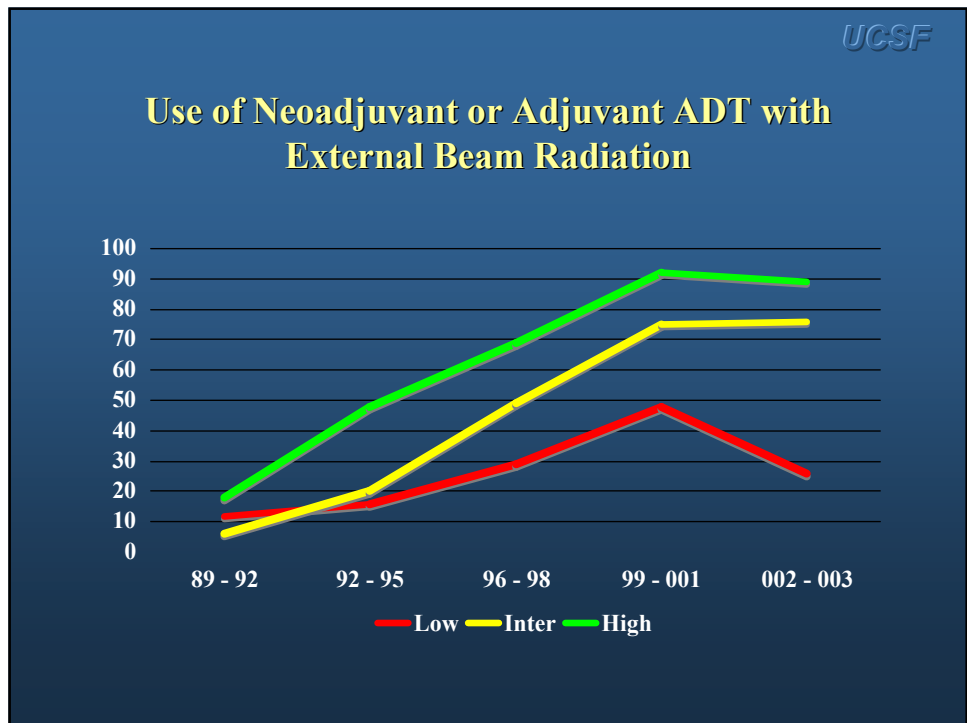
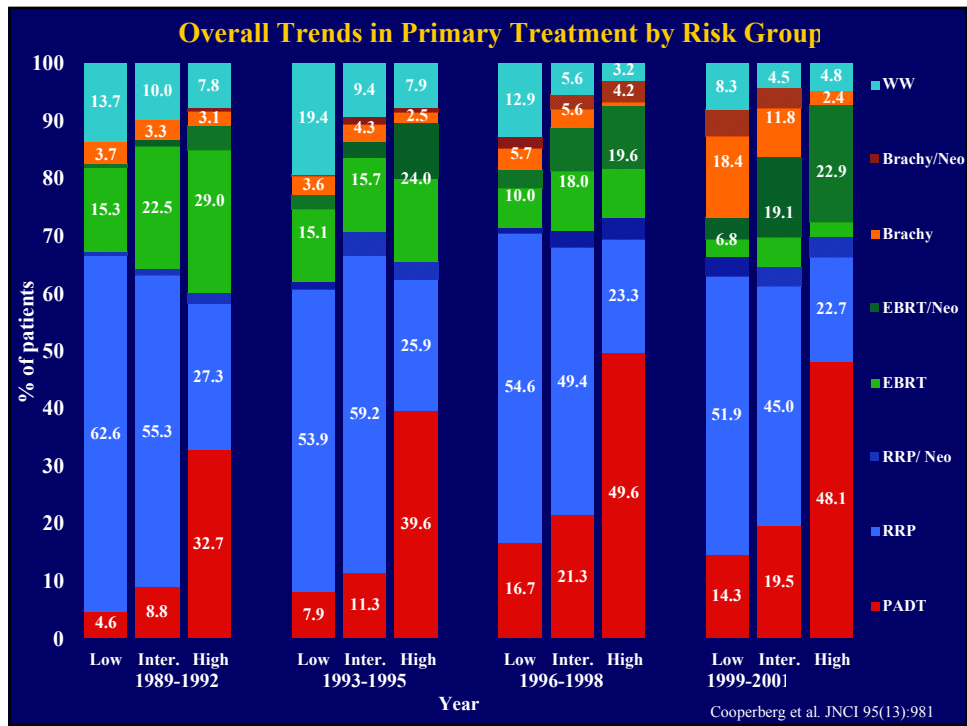






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## Is Prostate Cancer Care Changing?



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## **Are We Being Too Aggressive?**

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### **Prostate Cancer *Surveillance - Rationale***

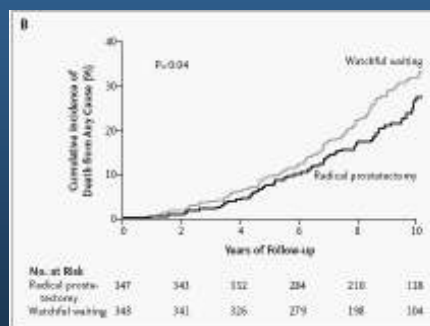
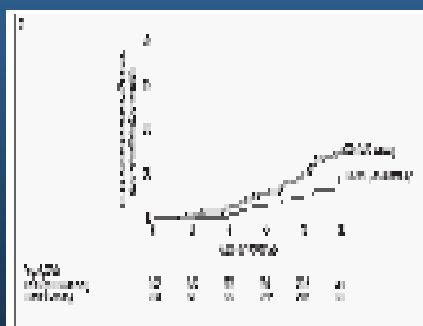
- Considerable stage migration to lower stage/risk disease
- Better/more accurate risk assessment
- Protracted natural history for most low risk patients
- Surveillance regimens support initial surveillance followed by selective therapy

## Caution!

	Initial (to 15 years)	Late (21% Alive)
PF Survival	45	36
MetF Survival	76.9	51.2
CS Survival	78.7	54.4
Mort. Rate*	15	44

•Per 1000 patient years  
 •JAMA 2004 Jun 9;291(22):2713-9

## Radical Prostatectomy vs. Watchful Waiting



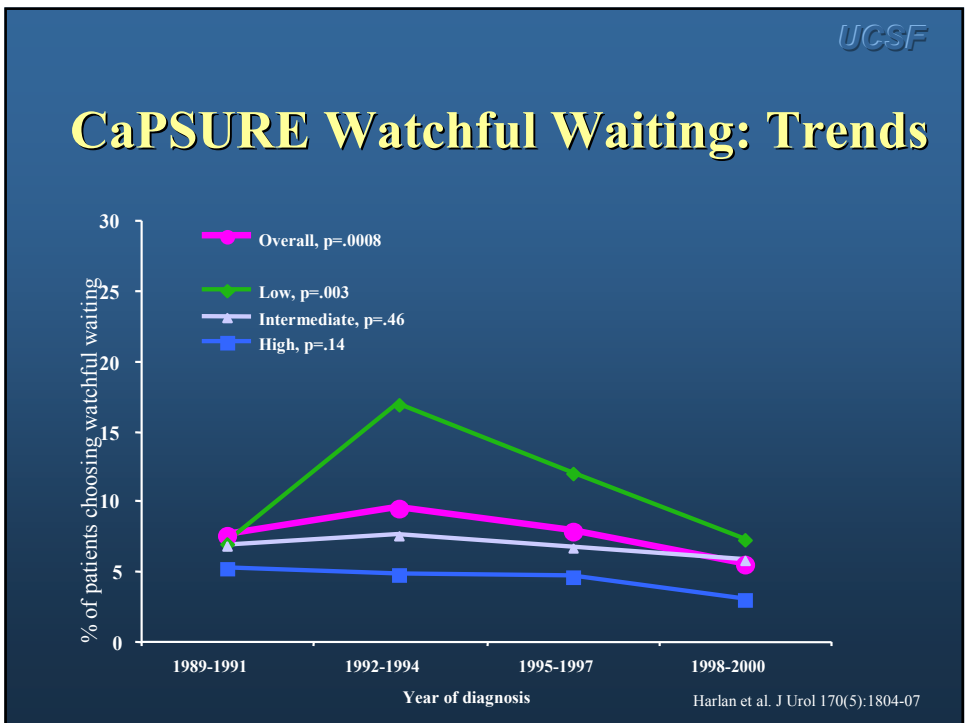
CaP specific mortality in WW group <65 yrs highest at – 19.2%

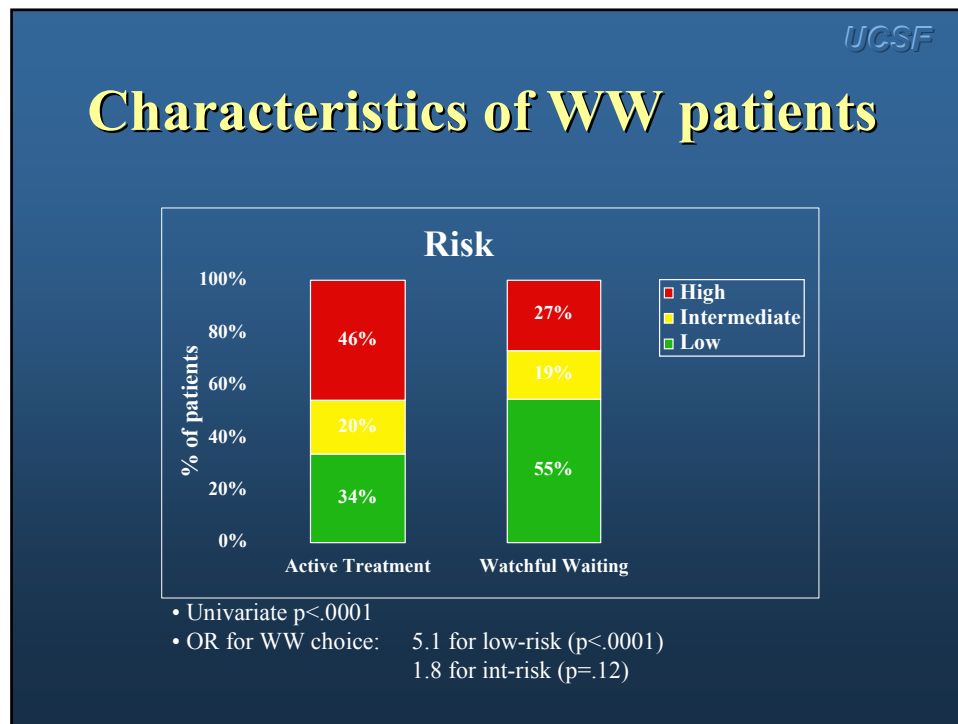


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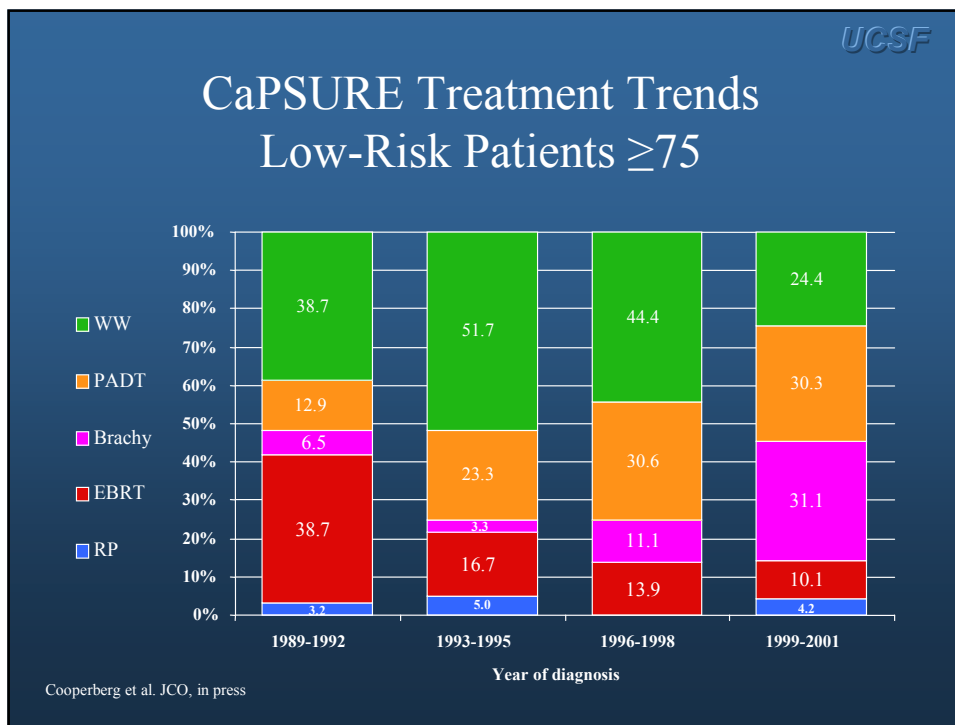
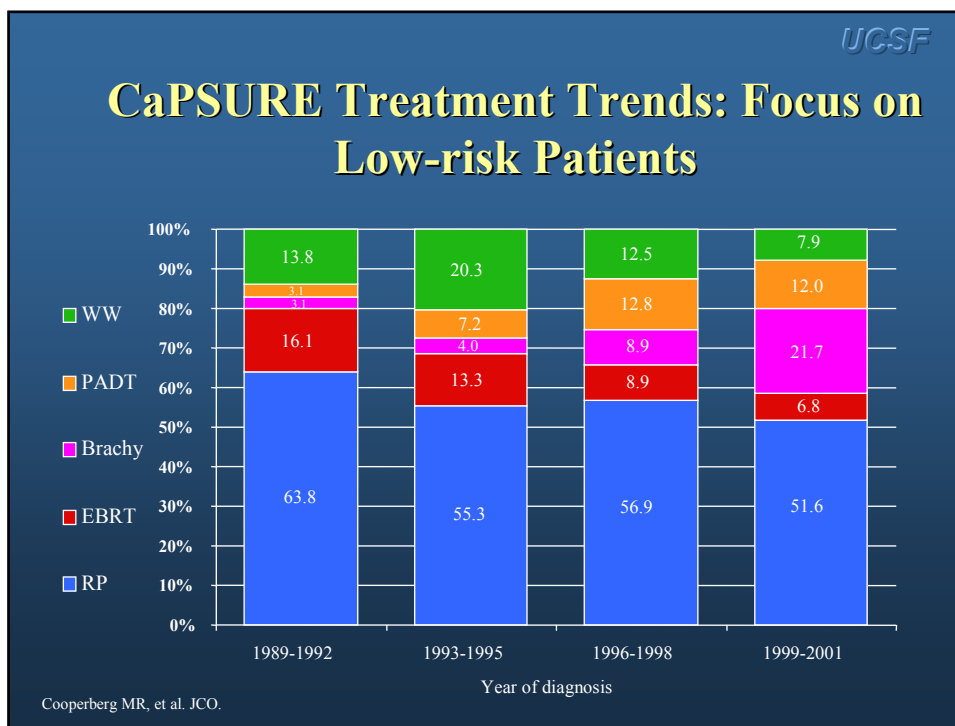
## Evolution of Watchful Waiting

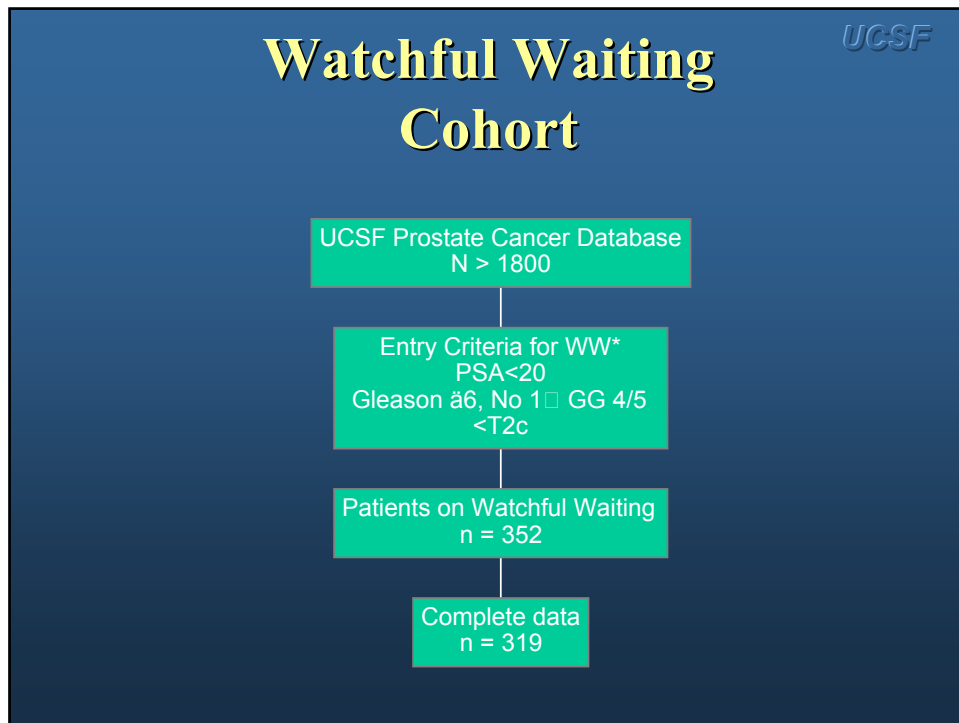
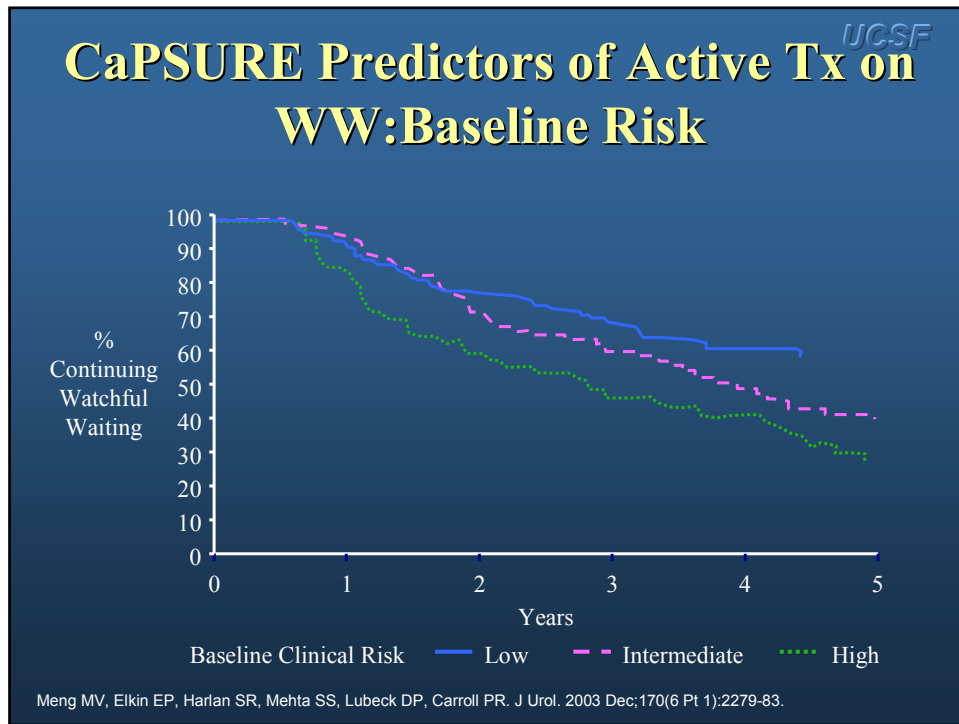
- Old
  - Less well assessed
  - Usually more advanced
  - Monitoring not rigid/planned
  - Treatment delayed until clinically significant, symptomatic disease noted
  - Managed with androgen deprivation
- New
  - Patients well assessed
  - Early stage disease
  - Monitored closely
  - Treatment at first sign of progression
  - Treated based on risk; local therapy





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- ## What Predicts for Watchful Waiting?
- Age
  - Insurance Status
  - Co - morbidity
  - Cancer risk group
  - Not education, ethnicity or income





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## UCSF Active Surveillance cohort

- Selection criteria:
  - PSA <10ng/ml
  - Gleason <7 with no component 4/5
  - < 33% of biopsy cores involved
  - < 50% of any core involved
  - cT2a or lower

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## Cohort demographics

- Total number on active surveillance n= 352
- Data available n= 319
- Did not meet criteria n=114
- Met one or more criteria n=205
- Median age 65 years
- Median PSA 5.7
- Median Gleason on biopsy 6
- Median % positive cores 14%

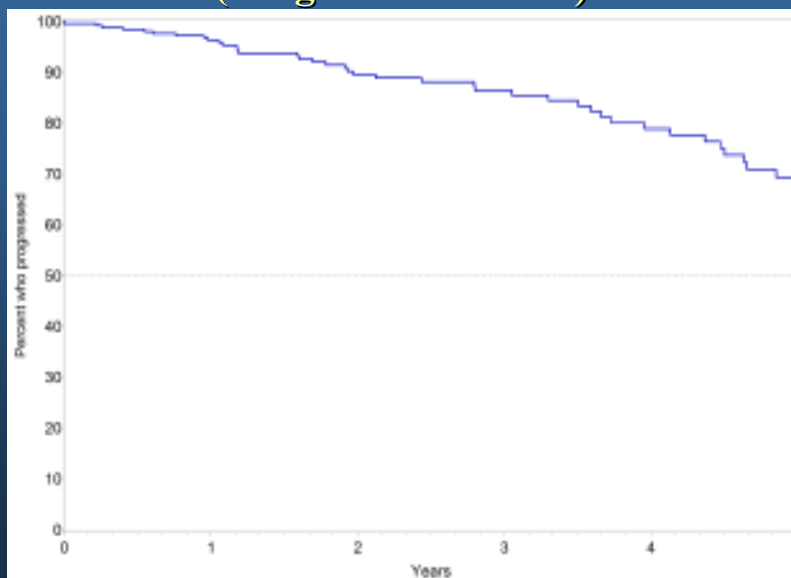
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## Progression

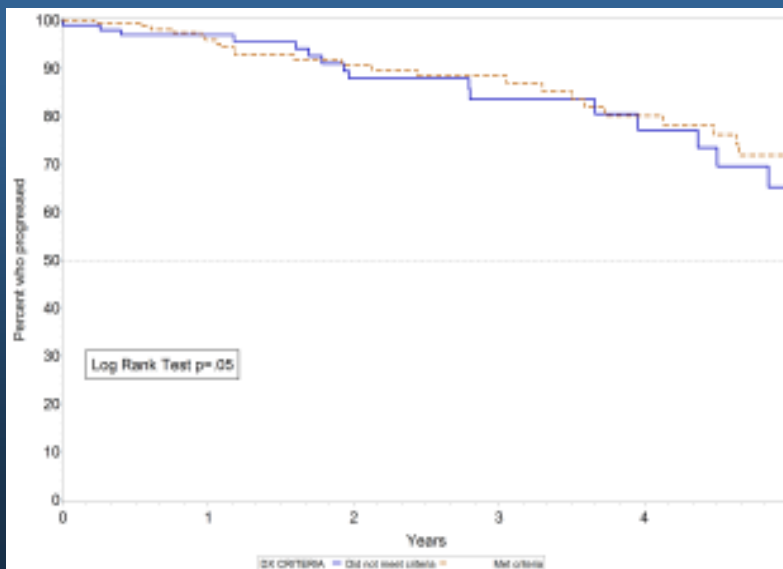
- Median follow-up 2.89 years
- Follow-up of non-progressors 2.66 years
- Follow-up of progressors 3.72 years
- Progression defined as:
  - Change in Gleason grade to  $\geq 7$
  - PSA velocity  $> 0.75 \text{ ng/ml/year}$
  - Increase in TRUS detected lesion number

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## Time to progression (Progressors = 22%)



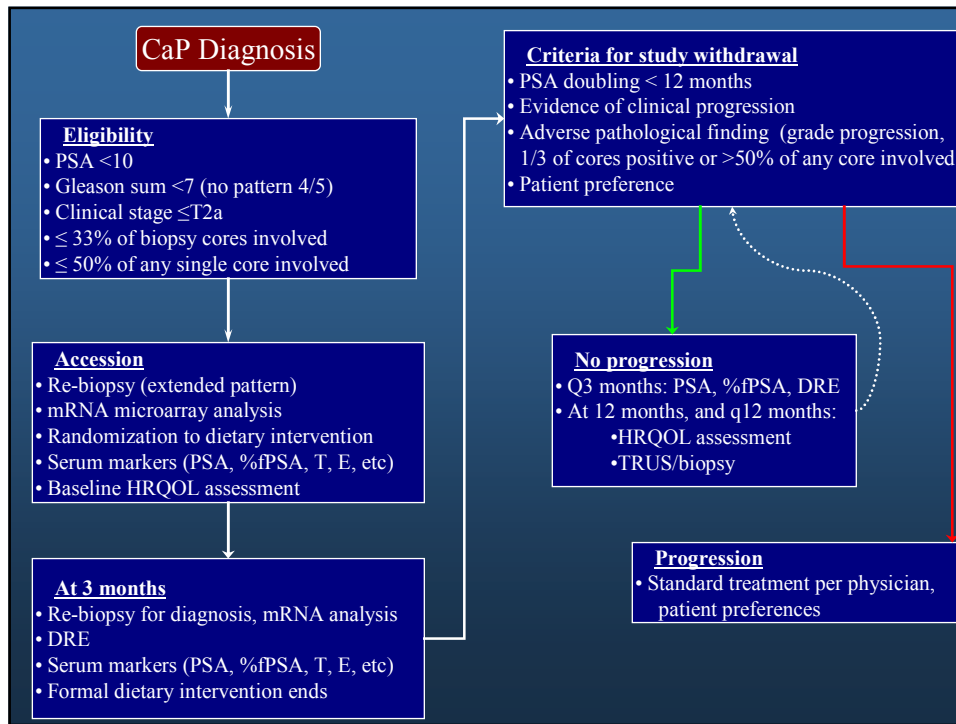
## Difference in progression based on meeting selection criteria



## Active Surveillance

### *Best Candidates*

- Based on Extended - Pattern Biopsy
  - Low grade (no pattern 4 or 5)
  - Low volume (< 33% of core); < 33% of total cores
  - Non - palpable (T1C)
- Serum PSA < 10 ng/ml; Stable, Free - Fraction Elevated, PSAD < 0.15
- Older Age and/or Significant Co - Morbidity
- Available for Follow - up



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## Clinical Trials

- Genomic Effects in Men by Interventions of Nutrition and Lifestyle (GEMINAL), Pilot study, Completed
  - Low fat diet
  - Supplements
  - Stress reduction
  - Exercise
- Molecular Effects of Nutritional Supplements (MENS), NCI-funded, OPEN @ UCSF
  - Lycopene
  - Omega - 3 - fatty acids
  - Combination
  - Placebo

Group	PSA	LNCaP Growth	Treatment
Control	6	9	8.1
Lifestyle	4	70	0



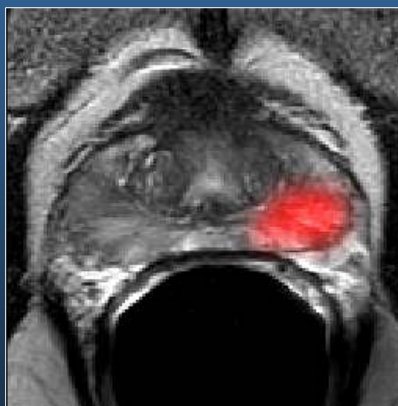
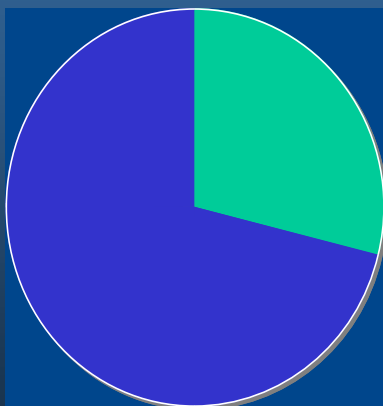
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## Nutritional, Lifestyle Intervention

- Genomic Effects in Men by Interventions of Nutrition and Lifestyle (GEMINAL), Pilot study (Completed)
- Molecular Effects of Nutritional Supplements (MENS), NCI-funded, Open

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## Prostate Cancer Treatment *Evolution or Revolution?*



■ Unifocal ■ Multifocal

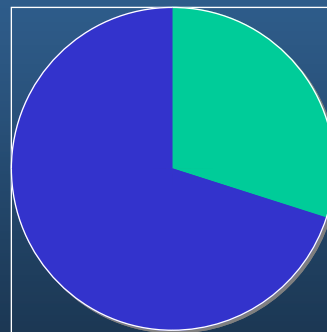
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## ARE WE BEING AGGRESSIVE ENOUGH?

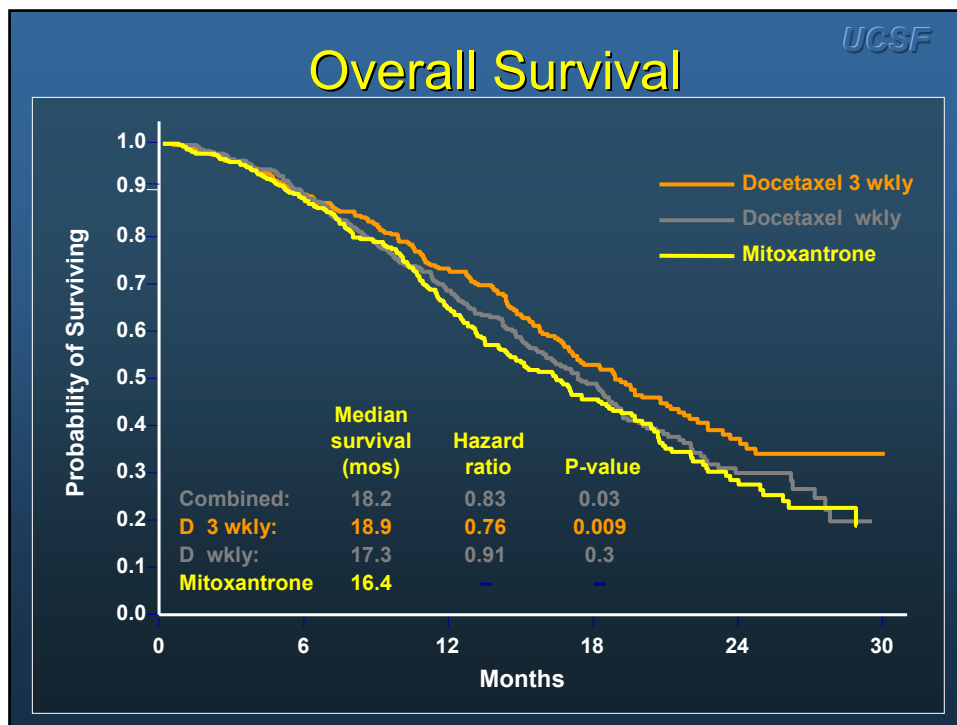
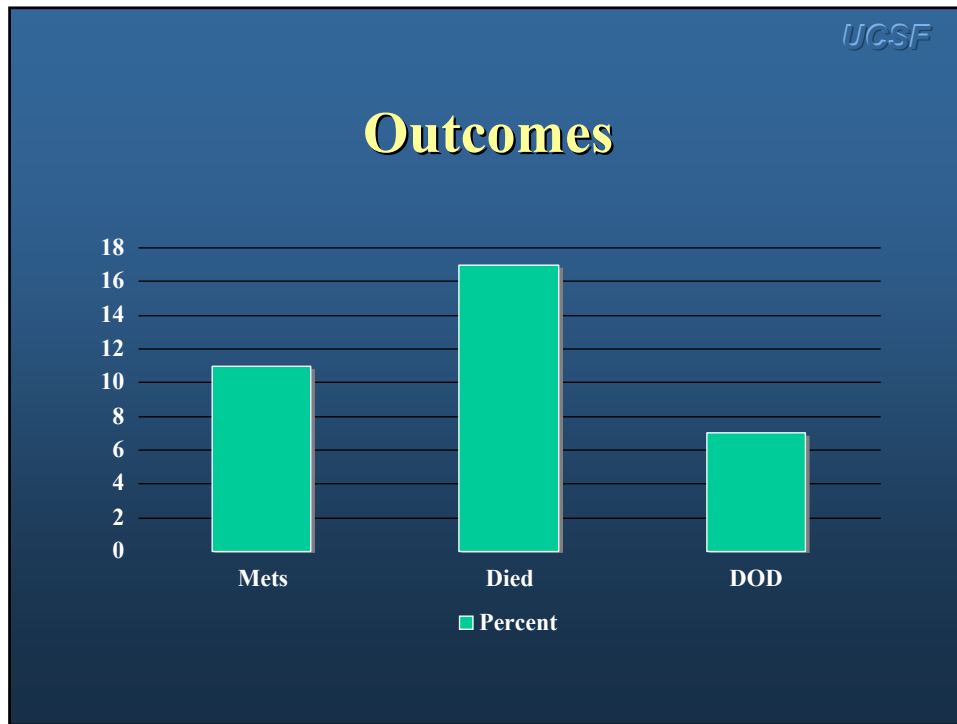
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### Risk of Relapse

- 5,277 Patients
- Mean time between treatment and relapse, 34 and 38 months
- Related to risk category (17%, 39% and 44% for low, inter., and high risk)



■ yes ■ no



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## Are We Being Aggressive Enough?

Fact	Reality
The use of adjuvant radiation is of value in those with biochemical recurrence after surgery	Of the 303 patients with biochemical failure 102 (33.7%) received second treatment a mean of 12 months after failure was documented
Chemotherapy and secondary androgen deprivation effective in those with late stage disease	Less than 17% of such men getting such therapy

J Urol. 2004 Jan;171(1):215-9

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**Table 1: Phase III National Trials**

Group/Number	Trial Therapy	Disease stage	Accrual goals	Primary endpoints
RTOG 0232	RT + brachytherapy vs. brachytherapy	Local therapy for intermediate-risk disease	1520	OS
CALGB 90203	Neoadjuvant docetaxel (S 8 cycles) + RP versus RP alone	High risk newly diagnosed prostate cancer	610	5-year DFS
VA CSP 553	Adjuvant docetaxel	High risk disease post prostatectomy	636	
SWOG 9921	Adjuvant CAB (2 years goserelin/bicalutamide) +/- chemotherapy (6 cycles mitoxantrone 12mg/m <sup>2</sup> + prednisone)	High-risk disease post prostatectomy	1360	OS, DFS
TAX 3501	Adjuvant AA (18 mos leuprolide 1-month depot) +/- docetaxel* versus observation	High risk disease post prostatectomy	1600	
RTOG 0521	AA (2 years LHRH + initial antiandrogen) + RT +/- post-radiation docetaxel/prednisone	Localized, high-risk prostate cancer; no prior treatment	600	OS
CALGB 9593	CAB +/- pelvic irradiation	Locally advanced prostate cancer	1200	OS, TTP
TAX 3502	AA (leuprolide 24 mos) +/- docetaxel	Rising PSA following definitive local therapy, PSA doubling time <9 months, minimum PSA 2		
PARADIGM (E1805)	PROSTVAC-VF/GM-CSF vs GM-CSF	Non-metastatic HRPC	700 (not yet open)	TTP
DAHRT (S0421)	Docetaxel/prednisone + placebo versus docetaxel/prednisone + atrasentan	HRPC	706 (not yet open)	TTP
VITAL-1.	Randomized open-label: GVAX versus docetaxel	Asymptomatic metastatic HRPC; no prior chemotherapy	600	OS
VITAL-2	Randomized open label docetaxel +/- GVAX	Symptomatic metastatic HRP; no prior chemotherapy	600	OS
ASCENT II	Docetaxel +/- calcitriol (45 mcg day)	Metastatic HRPC; no prior	900	

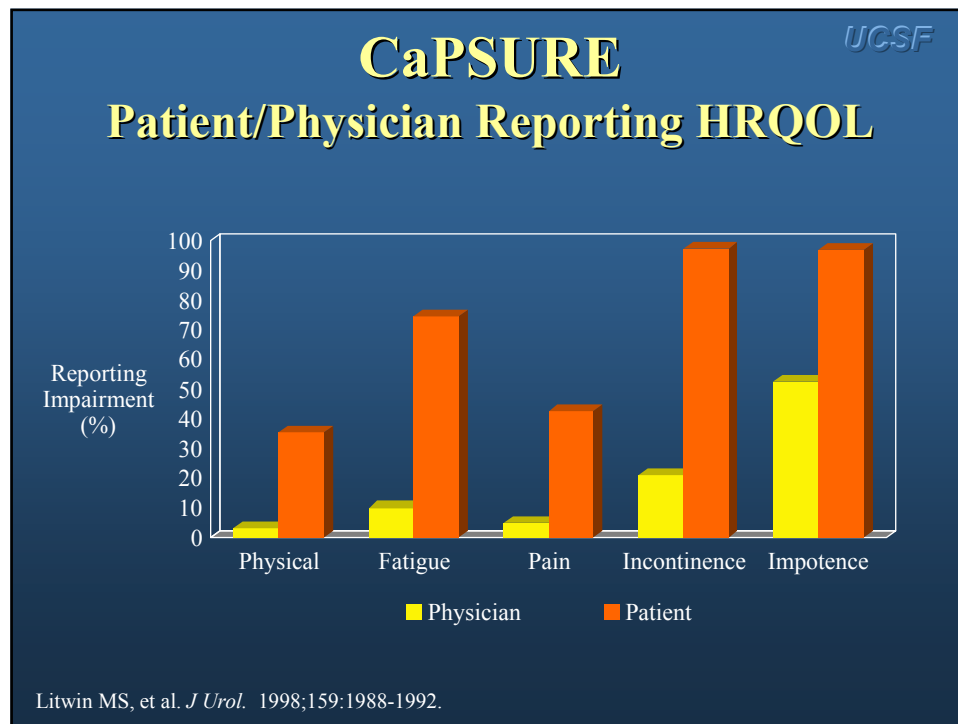
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## Are New Outcomes Being Assessed?

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### CaPSURE HRQOL—Instruments

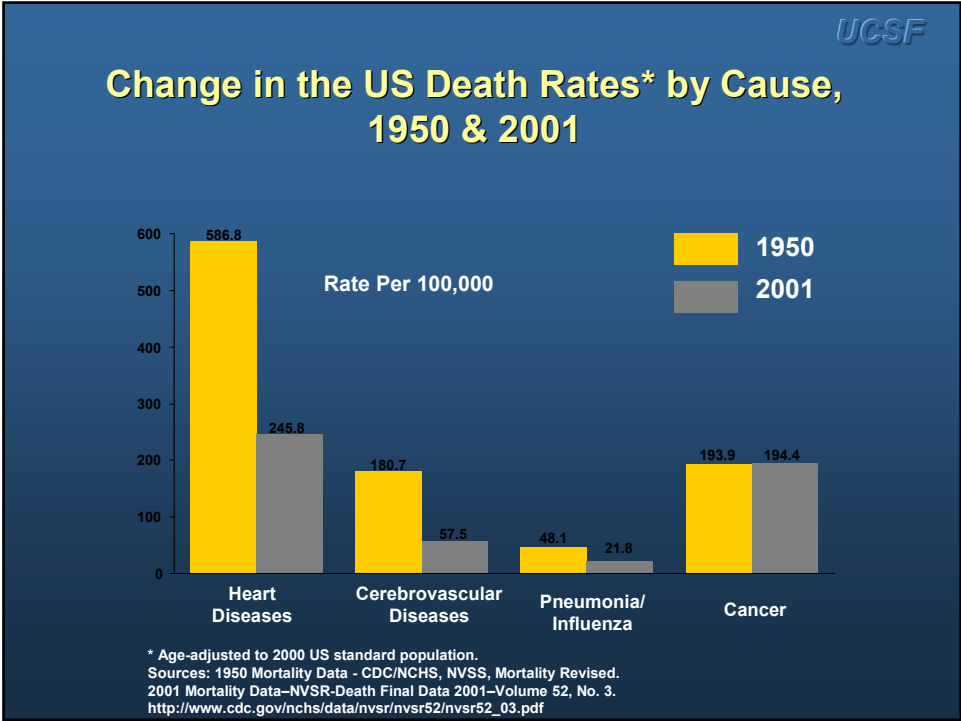
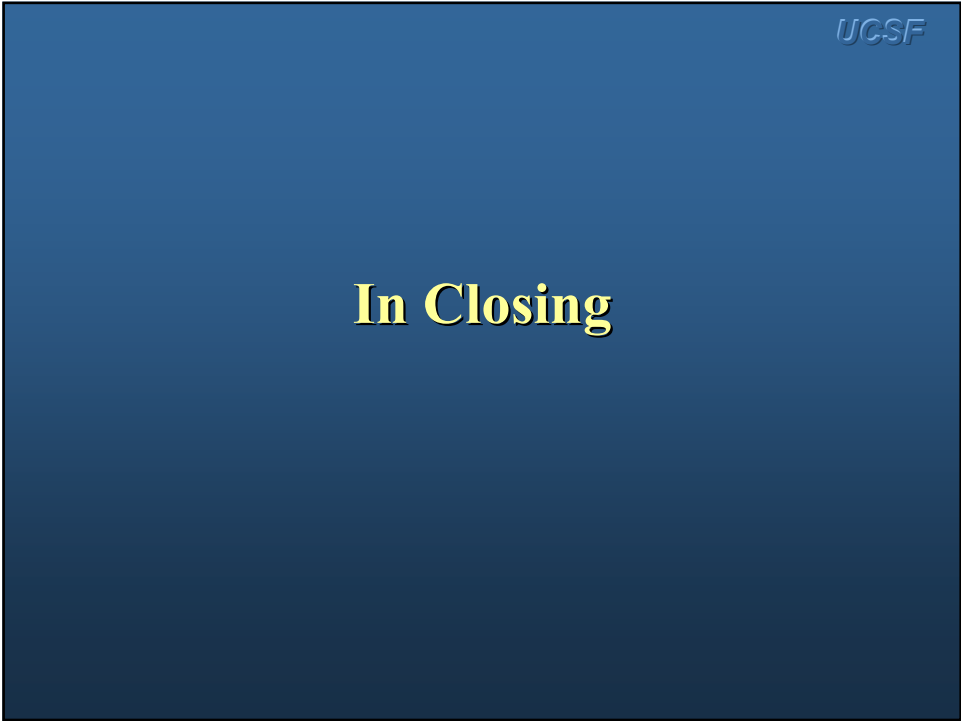
- Patients complete questionnaires every 6 months
- Rand 36-item health survey (8 domains covering physical and emotional function) and 2 summary scores
- UCLA prostate cancer index function and bother
  - Urinary
  - Bowel
  - Sexual

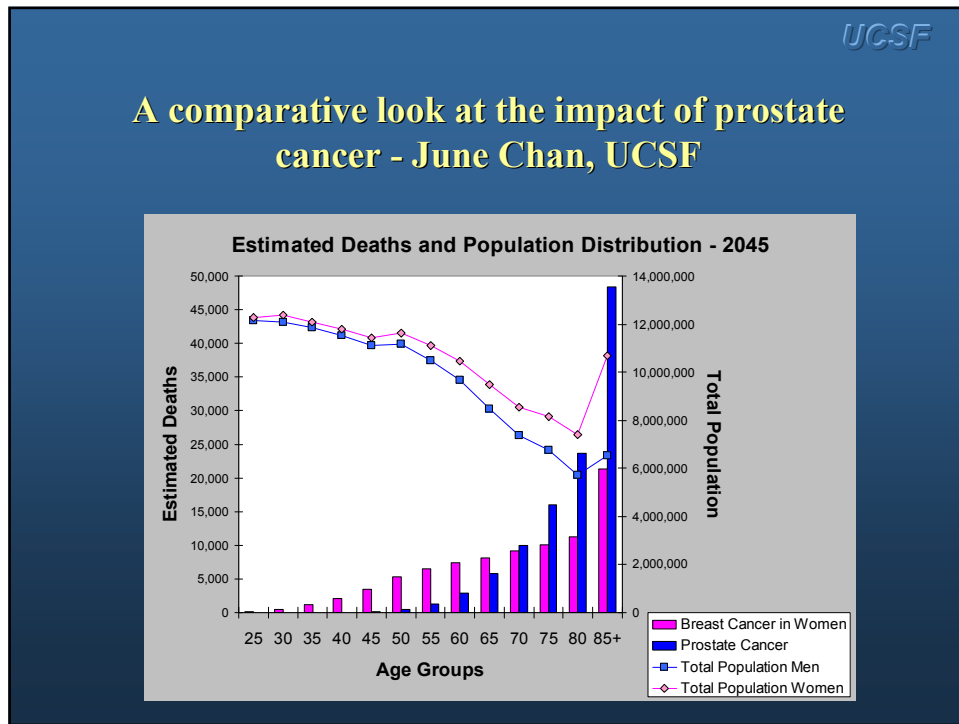


## EMPHASIS

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- Discussion of all options openly and honestly
- Full characterization of risk
- Multidisciplinary care
- Continuum of care
- Clinical trials
- Further investment in basic and clinical research (translational research a priority)





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## The Future

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**THE END*****Thank You***

- Urologic Oncology
  - Chris Kane, MD
  - Max Meng, MD
  - Katusto Shinohara, MD
- Imaging
  - Fergus Coakley, MD
  - John Kuhanowicz, PhD
- Medical Oncology
  - Eric Small, MD
  - Chuck Ryan, MD
  - Brian Rini, MD
  - Jonathan Rosenberg, MD
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- Radiation Oncology
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  - Joyce Speight, MD
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  - June Chan, PhD
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