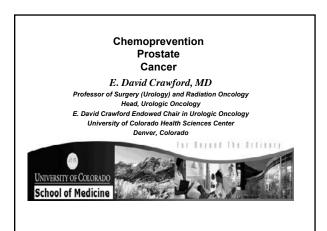
Point-Counterpoint:

Why Every Man Should Be Offered Chemoprevention for Prostate Cancer ~ E. David Crawford, MD

Chemoprevention Is Not for Every Man ~ Mark A. Moyad, MD, MPH





The Clinical and Economic Burden of Prostate Cancer

Expenditures

- Prostate- 8 billion 11.2%
- Lung- 9.6 billion 13.3%
- Breast 8.1 billion 11.2&

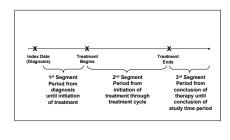
Presentation Outline

- Study Design
- · Research Objectives
- Results
- · Next Steps

Selection Criteria

- · Inclusion Criteria
 - Men ≥ 40 years of age
 - Index date occurs during the enrollment period
 - Continuously eligible for at least 18 months (6-month pre-period and a minimum 12-month post-period)
- · Exclusion Criteria
 - Members with ICD-9 claims for any other cancer

Measurement Segments



Data Sources

- PharMetrics
 - Data from over 85 health plans and 45 million lives
 - Mostly a commercial population (80%)
 - Timeframe of the dataset is 1995 to present (approximately a 6-month lag)



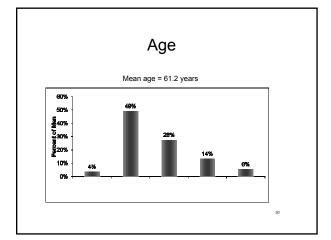
Patient Selection

Men with Prostate Cancer Diagnosis N = 109,029

Exclusion Criteria	Men Excluded
Men less than 40 years of age	587
Index date not within enrollment period	33,628
Not continuously eligible for 6 months pre- and 12 months post-PCa diagnosis	89,033
ICD-9 for any other cancer	20,941

An excluded patient may have met >1 exclusion criterion

Final Study Population N = 23.278



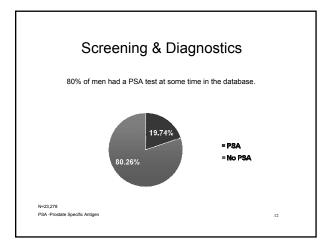
Screening & Diagnostics

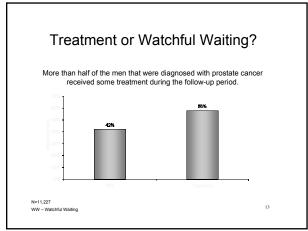
80% of men had screening/diagnostic exam(s) in the 6-month pre-period through the cancer index date. Men had PSA most often.

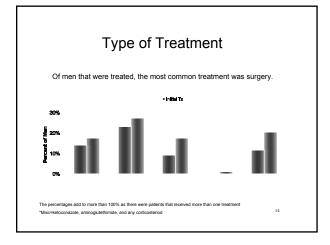


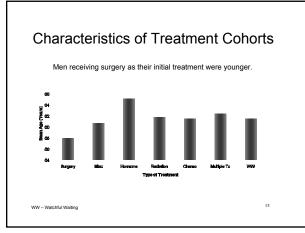
*35% had 1, 16% had 2, and 30% had ≥3 screening or diagnostic exams

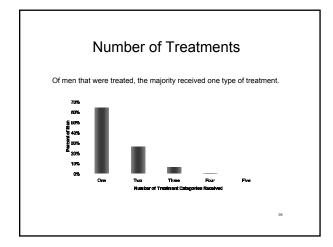
DRE - Digital Rectal Exam, PSA -Prostate Specific Antigen, SPE - Surgical Pathological Exam, TRUS - Transrectal Ultrasound, LNB - Lymph Node Biopsy

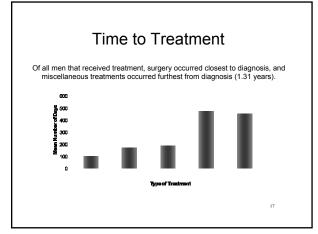


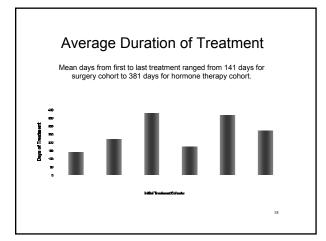


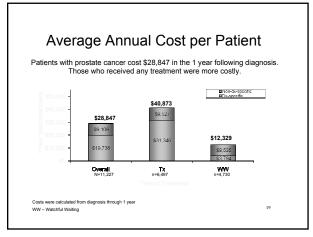


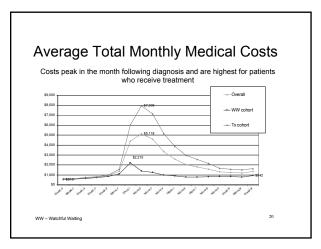


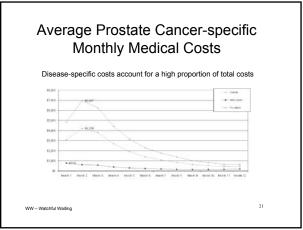


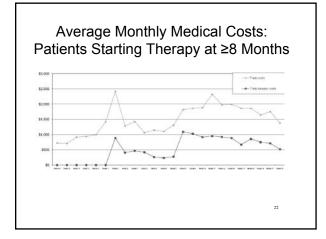




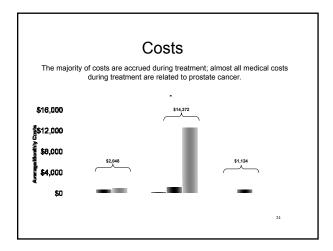


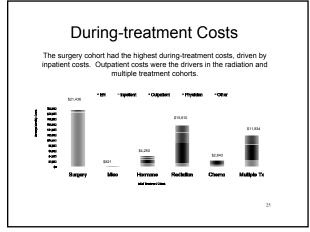


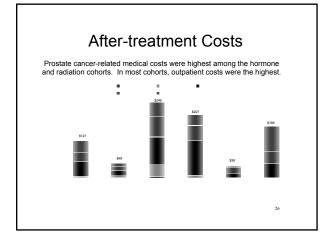


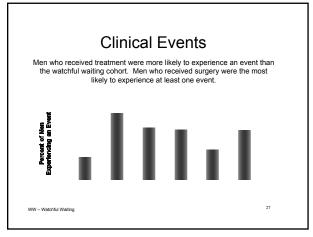


Measurement Segments Treatment Begins Treatment Begins Treatment Begins Treatment Begins Treatment Begins Treatment Begins Treatment Bends Treatment Bends Treatment Bends Treatment Bends Treatment Period from Initiation of Initi









Summary

- · The majority of men receive one type of treatment.
- Surgery was the most common treatment. It was received by the youngest men and resulted in the highest costs and most clinical events.
- Annual costs, regardless of treatment pattern, were \$30K per patient in the year following diagnosis.
- · Costs peaked in the month following diagnosis.
- The watchful waiting cohort had the lowest costs and fewest clinical events.

Why Prostate Cancer Prevention?

- · Significant public health risk
 - 186,000 new cases and 26,000 deaths yearly (2008)
- · Risk factors (age, race, genes) are not modifiable
- · Benefit of screening on mortality is unproven
- · Therapy is associated with morbidity

Diet & Exercise Risk Factors

- May <u>Increase</u> Risk
 - · Fat / Red Meat
 - Dairy/Calcium
 - Smoking
 - Total Calories, Body size

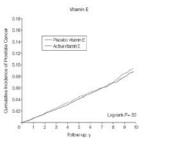




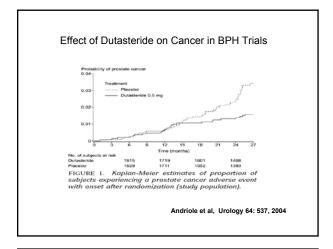


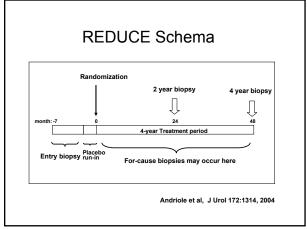
Courtesy J. Chan, UCSF

Physicians Health Study II



N = 14,641





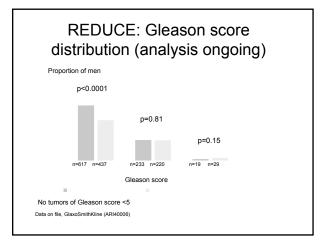
REDUCE and PCPT Study Design

Differences				
Parameter	REDUCE	PCPT		
Study drug	AVODART 0.5 mg daily	Finasteride 5 mg daily		
Study duration	4 years	7 years		
Number of patients	8,250	18,882		
Age (years)	50 to 75	≥ 55		
Baseline biopsies	Yes (1 negative biopsy)	No		
Follow up (planned) biopsies	Year 2 and Year 4 (mandatory)	Year 7 (recommended)		
PSA entry criteria	2.5 - 10 ng/mL if 50-60 years; 3 - 10 ng/mL if > 60	≤ 3 ng/mL		
Location	International	United States		

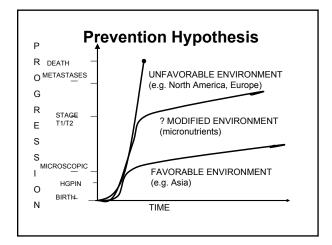
Note: Due to the differences in study design and patient population, comparisons of the results from REDUCE and PCPT cannot be made.

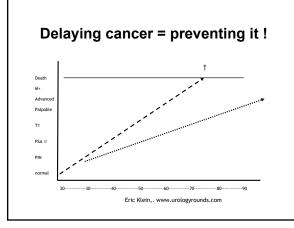
 Thompson IM et al. NEJM 2003;349(3):215-224. 2. Andriole G et al for the REDUCE Study Group. J Urol 2004;172-1314-1317. 3. Gomella LG. Curr Opin Uro 2005;15:2932. 4. Musquera M et al. Expert Reviews 2008;8(7):1073-1079.

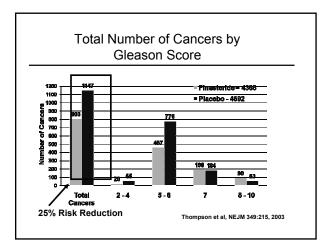
REDUCE: Primary endpoint (analysis ongoing) Dutasteride reduced the risk of prostate cancer over 4 years by 23% p<0.0001 (857 placebo vs 659 dutasteride) REDUCE trial is ongoing. Once the analysis is complete, the results will be published. Data on file, GlaxoSmithKline (ARI40006)



Consensus Meeting Panelists From left to right: Jergen Nordling, Manfred Wirth, Pierre Teillac, Per-Anders Abrahamsson, David Crawford (key note speaker on the PCPT data), Ohristopher Chapple, Adrian Joyce, Gle mert-Claude Abbou, Jean-Louis Misset, Andrea Tubaro, Eduardo Solsona, Meeting Meeting of the Chappe, United Kingdom Professor Glement Claude Abbou, Francia McChristopher Chapple, United Kingdom Mr Adrian Joyce, United Kingdom, Professor Jean-Louis Misset, France Professor Jergen Nordling, Demmark, Dr Eduardo Solsona, Spain Professor Andrea Tubaro, Italy, Professor Manfred Wirth, Germany







Statins and Prostate Cancer Risk

Risk Group	Risk Ratio
Any Px Cancer	1.09
Advanced Px Cancer Any use Use < 5 yrs Use > 5 yrs	0.51 0.60 0.26

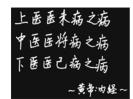
Health Professionals Follow-up Study, N = 34,989

Platz et al, JNCI 98:1819-25, 2006

Prevention: What to Tell Patients



Historical Imperative for Prevention



- Superior doctors prevent the disease.
- Mediocre doctors treat the disease before evident.
- Inferior doctors treat the full blown disease.

Nai-Ching (2600 B.C. 1st Chinese Medical Text)

Chemoprevention for prostate cancer is not for every man!

Mark A. Moyad, MD, MPH Jenkins/Pokempner Director of Preventive/Alternative Medicine University of Michigan Medical Center Dept of Urology

Ann Arbor, MI moyad@umich.edu

Hobbies: Forest over the tree & why there are no support groups for men that have...!

1. CVD= #1 cause of death in men & women in the U.S.!

- Since 1900!
- Under the age of 65=50% diagnosed CVD &
- 15-20% of CVD deaths
- Cancer>>CHD???

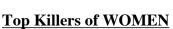
(Bonow RO. Circulation 2002;106:3140-3141)



Top Killers of Men

(CDC 2006)

Į.



((Movad MA, Sem Prev Alt Men, 2006)

1. CVD (since 1984)	483,842
2. Cancer	267,902
3. Respiratory Diseases*	65,672
4. Alzheimer's Disease	45,058
5. Diabetes*	35,748



predictor CVD/all-cause mortality!!

- 3-largest prospective investigations
- Follow-up 16-34 years

(Stamler J, et al. JAMA 2000;284:311-318)



3. CVD is #1 cause of death in largest U.S./world Rx prev. trials!!!

- P-1 tamoxifen trial
- PCPT (10 deaths vs. ____)

(Fisher B, et al. J Natl Cancer Inst 1998;90:1371-1388. & Thompson IM, et al. N Engl J Med 2003;349:215-224)



4. CVD= #1 cause of death in largest diet/supplement prev. trials!

- ATBC
- Selenium supplement trial
- SELECT (1 death vs. _____

(The ATBC Study Group. JAMA 2003;290:476-485. & Clark LC, et al. JAMA 1996;276:1957-1963.)



5. CVD= #1 cause of death in largest PSA screening trials!

- PLCO??????????????????????
- 1700 CHD vs. 174 Pca.
- 472 from "accidents"
- ERSPC? Where are they??? (appendix 8?)

(Andriole GL, Crawford D, et al. for PLCO Project team. N Engl J Med 2009;360:1310-1319.)



6. Most dietary supplements do not impact CVD? (Eidelman RS, et al. Arch Intern Med 2004;164:1552-1556)

China	ATBC	CHAO	GISSI	HOPE	PPP	HPS
(1993)	(1994)	(1996)	(1999)	(2000)	(2001)	(2002)
5 yrs	6.1 yrs	1.5 yrs	3.5 yrs	4.5 yrs	3.6 yrs	5 yrs
-29500	-29133	-2002	-11324	-9541	-4495	-20536
30 mg	50 mg	800 to	300	400	300	600
		400	mg	mg (n)	mg	mg
		mg (n)				

Ι¥Ι

Zinc & Cancer

- HDL, LDL, Bisphosphonates...
- HPFS (N=47,974 US men-14 yr follow-up)
- 2901 New cancers (434 advanced)
- >100 mg/d=RR=2.29
- 10 or more yrs=RR=2.37

Bottom Line=Why?

Leitzmann MF, et al. JNCI 95:1004-1007, 2003.



7. Some dietary supplements attenuate CVD agents?

- N=160, 3-yr randomized trial
- 800 IU vitamin E +
- 100 mcg selenium +
- 1000 mg vitamin C +
- 25 mg beta-carotene

Brown BG et al: N Engl J Med 345:1583-1592, 2001.



8. PSA Screening=lipid disorders?

- Over 1000 men= 3 cities
- 8% abnormal PSA/DRE...
- 52% w/dyslipidemia!

Moyad MA, et al. ASCO 2005.



9. Majority of diet/lifestyle changes for prostate cancer=heart healthy?

- Exercise
- · Fat in the diet
- · Flaxseed, Fruits & veggies
- · Lycopene-diet & CVD
- Soy
- Weight Control...

(Moyad MA. Urol Oncol 2004;22:466-471)



10. CVD=#1 cause of death in men post-dx & treatment!

- 14,000 men (307,931 records)
- 66% die from non-prostate causes!

Bottom Line=Heart healthy=Prostate Healthy!

Sun L, et al. AACR 43:page 932, abstract 4616, 2002



Klotz-Canada WW

- "Most men with favorable risk prostate cancer will die of unrelated causes."
- PSA<10, Gleason=6 or less, T2a or less
- N=299, mean age >70 yrs
- 8 yrs=overall survival=85%,
- Disease Specific Survival=99%...

Klotz L. J Urol 2004;172(5,pt 2 of 2):S48-S51.



11. Mechanisms increase risk of CVD=increase p.ca risk-MSR-1...

- Prospective study (Austria)=862 patients
- Group 1=P.cancer (n=291)
- Group 2=2 biopsies (no cancer) (n=340)
- Group 3=no prostate cancer (n=231)

Bottom Line=Signif. elevated cholesterol/HDL

Sonnleithner M, et al. AUA Annual Meeting J Urol 169: page 76-abstract #294, 2003.



12. Statins & laboratory data

- Cholesterol increased in solid tumors.
- Prostate synthesizes cholesterol at a rate=liver.
- Inhibits all cell lines=PC-3, LNCaP...
- Add LDL=increase tumor growth...
- SCID mice=increase cholesterol=HRPC

(Moyad MA. Urol Oncol 23:49-55, 2005)



13. Pleiotropic effects & secondary benefits?

- · Alzheimer's disease
- Mac. Degen.
- E.D./F.S.D.
- M.S.
- · Osteoporosis
- R.A..

Moyad MA. Urol Oncol 2004;22:466-471, 472-477.



Biologic Properties of Statins-Apart from Cholesterol Reduction?

- Inhibit thrombotic process
- Inhibit tumor cell proliferation
- · Inhibit angiogenesis
- Modulate immune responses
- Reduce inflammation
- Improve vascular endothelium function
- Stimulate bone growth/prevent bone loss
- Reduce oxidative stress
- Modulate smooth muscle cell proliferation
- · Stabilize plaques
- · Enhance fibrinolysis

Stamm JA, Ornstein DL. Oncology 19(6):739-754, May, 2005.



14. P Ca. Effects (aka forest over the tree)?

Jacobs (2007)	N=55,454	Followed=	-40% Adv/
	(317 adv)	6-years	Fatal P Ca.
Flick (2007)	69,047 (131)	14 years	-43%
Murtola (2007)	49,446 (3680)	8 years	-25% (CC)
Platz (2006)	34,989 (316)	13 years	-50%
Marcella (2009)	380 cases	10 years	-63% DEATHS!!

Adjusting for PSA testing...=More Robust!!! Murtola TJ, et al. Nat Clin Prac Uro 2008;5(7):376-387.

Atorvastatin=Lipitor® ? Fluvastatin=Lescol® ? Lovastatin=Mevacor® Patent lost Pravastatin=Pravachol® Patent lost-06 Rosuvastatin=Crestor® ? (once a week?!) Simvastatin=Zocor® Patent lost-June 06 Moyad once a week solution????

death/clinical endpoints) Evidence Exists?

LDL	hs-CRP	WHAT
"bad cholesterol"		HAPPENED?
≥70	≥1 mg/L	-9% Reduction
≥70	≤1 mg/L	-35% Reduction
<70	≥1 mg/L	-50% Reduction
<70	≤1 mg/L	-79% Reduction!!!

Ridker PM, et al. Lancet 373:1175-1182, April 4, 2009. Justification for the Use of Statins in Property -DVT?

NUMBER 17=I am tired! Other promising agents?

- COX-II inhibitors
- Finasteride
- Toremifene
- Vitamin E
- Selenium

Moyad MA. Urol Oncol 2004;22:466-471, 472-477.