# 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

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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 $\geq 40$ 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


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Screening \& Diagnostics

$\cdot 35 \%$ had $1,16 \%$ had 2 , and $30 \%$ had 23 screening or diagnostic exams
DRE- Digital Rectal Exam, PSA-Prostate Specific Antigen, SPE - Surgical Pathological Exam,
DRE - Dipital Rectal Exam, PSA - Prostate Specific Antigen,
TRUS - Transsectal Utrasound, LNB - Lymph Node Biopsy


# Why Every Man Should Be Offered Chemoprevention for Prostate Cancer 



Type of Treatment

Of men that were treated, the most common treatment was surgery.
= Intilia Tx
30\%
The percentages add to more than 100\% as there were patients that received more than one treatment
-Misc-ketoconazole, aminogutethimide, and any corticosteriod


Why Every Man Should Be Offered Chemoprevention for Prostate Cancer



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## Average Annual Cost per Patient

Patients with prostate cancer cost $\$ 28,847$ in the 1 year following diagnosis.
$\qquad$ Those who received any treatment were more costly.


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Costs were calculated from diagnosis through 1 yea
ww - Watchfu Wating
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## Why Every Man Should Be Offered Chemoprevention for Prostate Cancer



Average Prostate Cancer-specific Monthly Medical Costs

## Disease-specific costs account for a high proportion of total costs <br> 

Average Monthly Medical Costs: Patients Starting Therapy at $\geq 8$ Months



Why Every Man Should Be Offered Chemoprevention for Prostate Cancer

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## Clinical Events

Men who received treatment were more likely to experience an event than
$\qquad$ the watchful waiting cohort. Men who received surgery were the most likely to experience at least one event.

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# Why Every Man Should Be Offered Chemoprevention for Prostate Cancer 

## 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
- That Leaves Prevention


## Prostate Cancer

Diet \& Exercise Risk Factors


Vitamin E and Prostate Cancer Physicians Health Study II $\qquad$


Why Every Man Should Be Offered Chemoprevention for Prostate Cancer

Effect of Dutasteride on Cancer in BPH Trials


Andriole et al, Urology 64: 537, 2004


REDUCE and PCPT Study Design

| 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 | $\geq 55$ |
| Baseline biopsies | Yes (1 negative biopsy) | No |
| Follow up (planned) biopsies | Year 2 and Year 4 (mandatory) | Year 7 (recommended) |
| PSA entry criteria | $2.5-10 \mathrm{ng} / \mathrm{mL}$ if $50-60$ years; <br> $3-10 \mathrm{ng} / \mathrm{mL}$ if $>60$ | $\leq 3 \mathrm{ng} / \mathrm{mL}$ |
| 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.



## Why Every Man Should Be Offered Chemoprevention for Prostate Cancer



Consensus Meeting Panelists


From left to right: Jorgen Nordling, Manfred Wirth, Pierre Teillac, Per-Anders Abrahamsson,
Christopher Chapple, Adrian Joyce, Cle'ment-Claude Abbou, Jean-Louis Misset,
Andrea Tubaro, Eduardo Solsona.
Professor Pierre Teillac, France Professor Per-Anders Abrahamsson, Sweden
Professor Clement Claude Abbou, France.Mr Christopher Chapple, United Kingdom
Professor Jorgen Nordling, Denmark. Dr Eduardo Solsona, Spain
Professor Andrea Tubaro, Italy. Professor Mantred Wirth, Germany



Why Every Man Should Be Offered Chemoprevention for Prostate Cancer


Statins and Prostate Cancer Risk

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

Health Professionals Follow-up Study, $\mathrm{N}=34,989$
Platz et al, JNCI 98:1819-25, 2006

Prevention: What to Tell Patients


Historical Imperative for Prevention

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[^1]
## Chemoprevention for prostate cancer is not for every man!

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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. $\mathrm{CVD}=$ \#1 cause of death in men <br> \& 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)




## 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. $\qquad$ _)
(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. $\mathrm{CVD}=$ \#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. $\mathrm{CVD}=$ \#1 cause of death in largest PSA screening trials!

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


## 6. Most dietary supplements do not 

| China <br> $(1993)$ | ATBC <br> $(1994)$ | CHAO <br> $(1996)$ | GISSI <br> $(1999)$ | HOPE <br> $(2000)$ | PPP <br> $(2001)$ | HPS <br> $(2002)$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 5 yrs <br> -29500 | 6.1 yrs <br> -29133 | 1.5 yrs <br> -2002 | 3.5 yrs <br> -11324 | 4.5 yrs <br> -9541 | .6 yrs <br> -4495 | 5 yrs <br> -20536 |
| 30 mg | 50 mg | 800 to <br> 400 <br> $\mathrm{mg}(\mathrm{n})$ | 300 <br> mg | 400 <br> $\mathrm{mg}(\mathrm{n})$ | 300 <br> mg | 600 <br> mg |

## Zinc \& Cancer

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

Bottom Line=Why?
Leitzmann MF, et al. JNCI 95:1004-1007, 2003

## 7. Some dietary supplements attenuate CVD agents?

- $\mathrm{N}=160,3$-yr randomized trial
- 800 IU vitamin E +
- 100 mcg selenium +
- 1000 mg vitamin $\mathrm{C}+$
- 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!

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. $\mathrm{CVD}=\# 1$ 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
- $\mathrm{N}=299$, 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 ( $\mathrm{n}=291$ )
- Group $2=2$ biopsies (no cancer) $(n=340)$
- Group 3=no prostate cancer $(\mathrm{n}=231)$

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

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

- Stimulate bone growth/prevent bone loss
- Reduce oxidative stress
- Modulate smooth muscle cell proliferation
- Stabilize plaques
- Enhance fibrinolysis



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

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


| 15. Cost? |  |
| :---: | :---: |
| Atorvastatin=Lipitor® | ? |
| Fluvastatin=Lescol® | ? |
| Lovastatin=Mevacor® | Patent lost |
| Pravastatin=Pravachol® | Patent lost-06 |
| Rosuvastatin=Crestor ${ }^{\circledR}$ | ? (once a week?!) |
| Simvastatin=Zocor ${ }^{\circledR}$ | Patent lost-June 06 |
| Moyad once a week solution??? |  |


| death/clinical endpoints) Evidence Exists? |  |  |
| :---: | :---: | :---: |
| LDL <br> "bad cholesterol" | hs-CRP | WHAT <br> HAPPENED? |
| $\geq 70$ | $\geq 1 \mathrm{mg} / \mathrm{L}$ | -9\% Reduction |
| $\geq 70$ | $\leq 1 \mathrm{mg} / \mathrm{L}$ | -35\% Reduction |
| $<70$ | $\geq 1 \mathrm{mg} / \mathrm{L}$ | -50\% Reduction |
| <70 | $\leq 1 \mathrm{mg} / \mathrm{L}$ | -79\% Reduction!!! |

## NUMBER 17=I am tired! <br> Other promising agents?

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

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


[^0]:    $w n$-Watchful Waiting

[^1]:    - Superior doctors prevent the disease.
    - Mediocre doctors treat the disease before evident.
    - Inferior doctors treat the full blown disease.

