Chemoprevention Strategies

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Chemoprevention Strategies for Prostate Cancer

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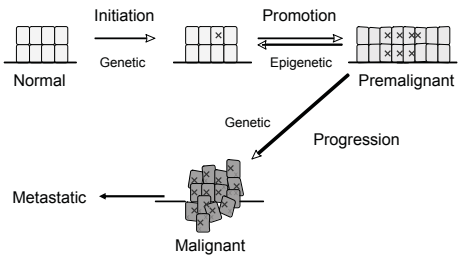
Chemoprevention

The use of specific natural or synthetic agents, dietary or pharmacological, to reverse, retard or prevent the development or progression of cancer

Sporn 1976

Multistep Carcinogenesis

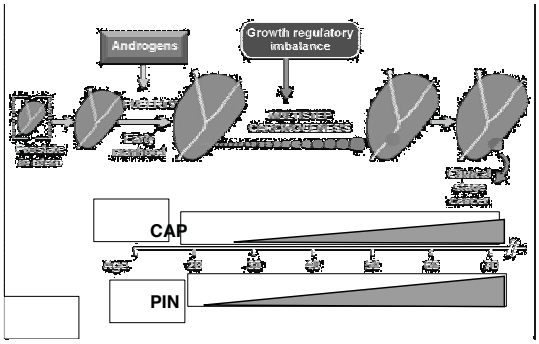


Characteristics of Prostate Cancer that support a role for chemoprevention

- Disease of aging (oxidative stress? Inflammation? epigenetic events)
- Long latency
- Putative precursor lesion
- Early dependence on androgen
- Susceptability to oxidative damage:
  - High prevalence of GSTP1 hypermethylation[1]
  - Overexpression of COX-2[2]
- Altered growth factor responsiveness

1. Lee WH, et al. Proc Natl Acad Sci U S A 1994;91:11733-7
2. Aparicio Gallego G et al. Clin Transl Oncol 2007;9:694-702

Early Events in Prostatic Carcinogenesis



Prostate Cancer – Risk Factors

- Age
- Family history
- Intact Androgen Axis
- Diet
  - High fat (oxidative stress? alteration of hormone balance? arachidonic acid?)
  - Low selenium/ antioxidants/ isoflavanoids
- Geographic locale
  - Western cultures (diet)
  - Low UV light exposure (vit D)
- Prostatitis (oxidative stress?)
- African-American ethnicity (androgens? vit D?)

Candidate Chemopreventive Agents for PCa

- Hormonal agents
  - 5α-reductase inhibitors (eg. Finasteride, Dutasteride)
  - Antiandrogens/ LHRH antagonists (eg. Flutamide, leuprolide)
  - SERM's (eg. Tamoxifen, raloxifene, toremifene, SERM-3)
- Phytoestrogens and Protein Kinase Inhibitors
  - Isoflavanoids (eg. Genestein, silibinin)
  - Angiogenesis inhibitors (eg. SU-101)
- Antiproliferative or Differentiating Agents
  - Vitamin D analogs
  - Retinoids (eg. 4-HPR, 9cis-retinoic acid)
  - Polyamine inhibitors (eg. DFMO)
- Anti-inflammatory Agents
  - COX-2 inhibitors (eg. Celecoxib, sulindac sulfone)
  - Statins
- Antioxidants
  - Vitamin E (SELECT)
  - Selenium (SELECT)
  - Carotenoids (eg. Lycopene)

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Hormonal Agents
Antiandrogens/ 5α-reductase inhibitors

<u>Rationale</u>

- Androgen major regulator of growth and differentiation
  - Basis for androgen ablation therapy
- Males castrated < 40 yrs age don't get clinical prostate cancer[1]
- Males with 5a-reductase deficiency don't get prostate cancer[2]
- Racial differences in androgen metabolism[3]

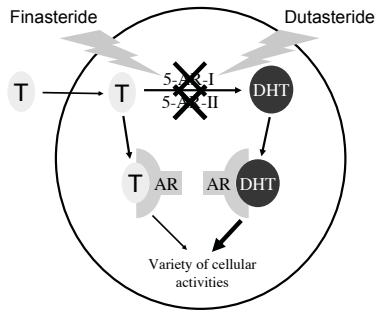
1. Moore RA. Surgery 1944.
2. Imperato-McGinley J et al. Science 1974.
3. Ross RK et al. Cancer Res 1998.

Hormonal Agents for Prostate Cancer Chemoprevention

<u>Limitations</u>

- Side effects! (hot flashes, gynecomastia, sexual dysfunction, weakness, etc.)
  - LHRH agonists
  - Androgen receptor antagonists
- Candidates for prevention generally healthy with active physical & sexual lives
  - Must maintain acceptable QOL
- 5α-reductase inhibitors (5ARI's)
  - Favorable side effect profile
  - Treatment for BPH

5ARI's: Mechanism of Action



Chemoprevention Trials for Prostate Cancer Using 5ARI's

Prostate Cancer Prevention Trial (PCPT)

Primary Endpoint: To determine if ***finasteride*** administration for a period of seven years could reduce the period prevalence of prostate cancer.

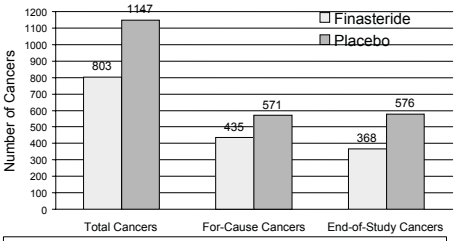
REduction by DUtasteride of prostate Cancer Events (REDUCE)

Primary Endpoint: To determine if ***dutasteride*** could reduce the likelihood of prostate cancer diagnosis on *repeat* biopsy after 2 and 4 years.

Design comparison between PCPT and REDUCE

	PCPT	REDUCE
Test agent	Finasteride (5mg/day)	Dutasteride (0.5 mg/day)
N	18,800	8200
Age at randomization	≥ 55	50-75
PSA at randomization	≤ 3 ng/ml	>2.5 and <10 ng/ml
Negative DRE	Yes	No
Negative baseline bx	No	Yes
Scheduled biopsies	At 7 yrs	At 2yrs and 4 yrs
Biopsy scheme	6 core (80%)	10 core
For-cause biopsies (↑PSA, +DRE)	Many	Few

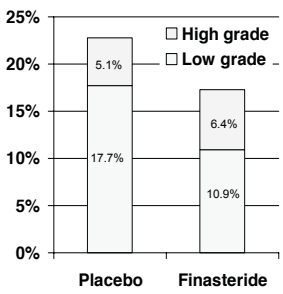
Prostate Cancer Prevention Trial



	Total Men Evaluated	Men with For-Cause Biopsy/Procedure	Men with End-of-Study Biopsy
Finasteride	4368	1639	3652
Placebo	4692	1934	3820

Thompson IM, et al. *NEJM* 2003.

Observed fractions of total subjects with low- and high-grade cancer in the PCPT

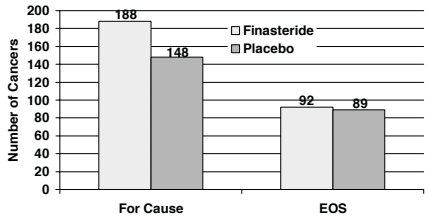


Cancer
RR=0.75 (0.60, 0.99)
p < .001

Gleason ≥ 7
RR=1.27 (1.07, 1.50)
p =0.005

Thompson IM, et al. *NEJM 2003;349:211-20*

Grade 7-10 Cancers diagnosed in PCPT



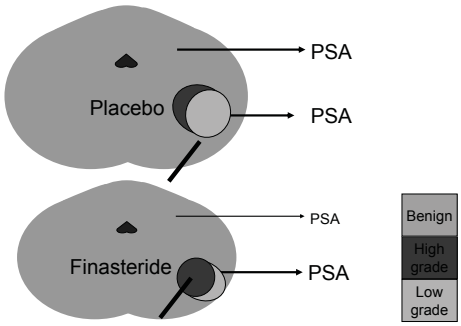
"For cause" = biopsy for ↑PSA and/or abnormal DRE
"EOS" = end-of-study biopsy

Detection bias led to increased detection of high-grade cancer in PCPT

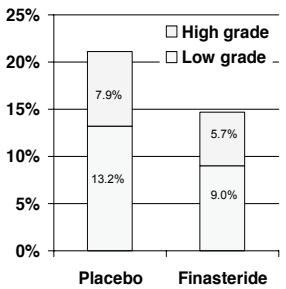
- Finasteride improved performance of PSA for cancer and high-grade cancer[1]
- Finasteride increased sensitivity of DRE[2]
- Finasteride increased sensitivity of prostate biopsy for detection of high grade cancer by reducing prostate volume[3]

1. Thompson, I. M. et al. *J Natl Cancer Inst.* 2006;98:1128-1133
2. Thompson IM, et al. *J Urol* . 2007;177:1749-52
3. Lucia MS, et al. *J Natl Cancer Inst.* 2007;99:1375-83

Effect of finasteride on cancer detection



Estimated actual fractions of total subjects with low- and high-grade cancer after adjusting for bias



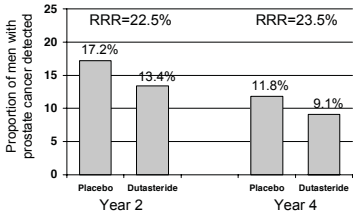
Cancer
RR=0.70 (0.64, 0.76)
p < .0001

Gleason ≥ 7
RR=0.73 (0.56, 0.96)
p < .02

Gleason ≤ 6
RR=0.68 (0.57, 0.82)
p < .0001

Redman MW, et al. *Cancer Prev Res* 2008;1:174-81

REDUCE Primary Results



Gleason 7-10: Placebo = 6.8%
Dutasteride = 6.7%

Andriole G. AUA 2009
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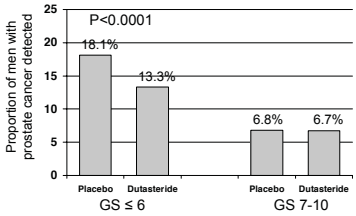
Gleason score (GS) distribution by treatment group in REDUCE



Andriole G. AUA 2009
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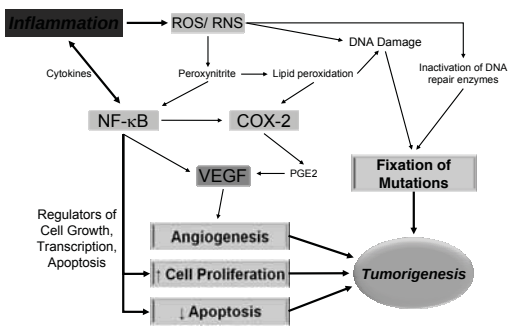
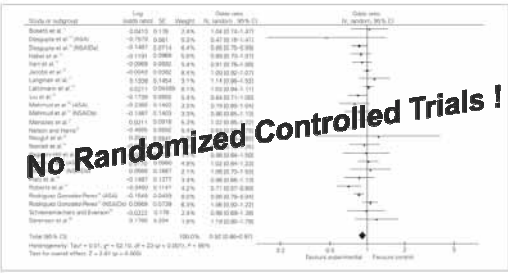
Future Directions for Prostate Cancer Chemoprevention: What next?

- Phytoestrogens (Phase II trials)
  - Inhibition of PKC, cell growth, angiogenesis
- Anti-proliferative agents (Phase II trials)
  - Vit D analogues, retinoids, DFMO
- Anti-inflammatory agents/ antioxidants
- Statins
  - Reduction of cholesterol
  - Anti-inflammatory



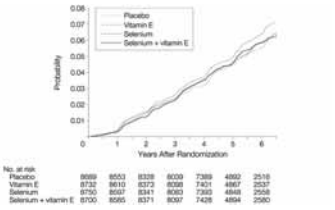
ROS=reactive oxygen species RNS=reactive nitrogen species
COX-2-cyclooxygenase-2 VEGF-vascular endothelial growth factor

Meta-analysis of effect of Non-steroidal anti-inflammatory drugs (NSAIDS) on prostate cancer risk



From: Jafari S. et al. Non-steroidal anti-inflammatory drugs and prostate cancer: A systematic review of the literature. CUAJ 2009;3:323-30.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT): Cumulative Incidence of Prostate Cancer Detected Each Year by Intervention Group



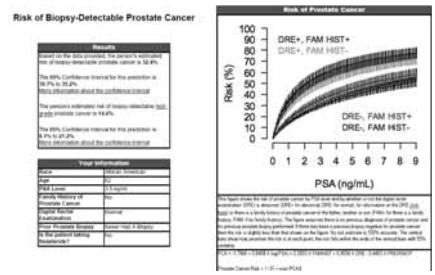
Lippman, S. M. et al. JAMA 2009;301:39-51.

JAMA

How do we identify those men who would benefit most?

- Patient desire?
- Positive family history?
- The REDUCE model?
  - Elevated PSA and negative biopsy
- Risk calculator/ nomogram?

Prostate Cancer Risk Calculator based upon data from the placebo arm of the PCPT



http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp

Chemoprevention of Prostate Cancer
Challenges

- Candidates for chemoprevention
- Optimal dosages/ combinations
- Impact on lifestyle
- Surrogate biomarkers
- Design of trials