

# Prostate Cancer **Prevention Strategies: Diet and Chemoprevention**

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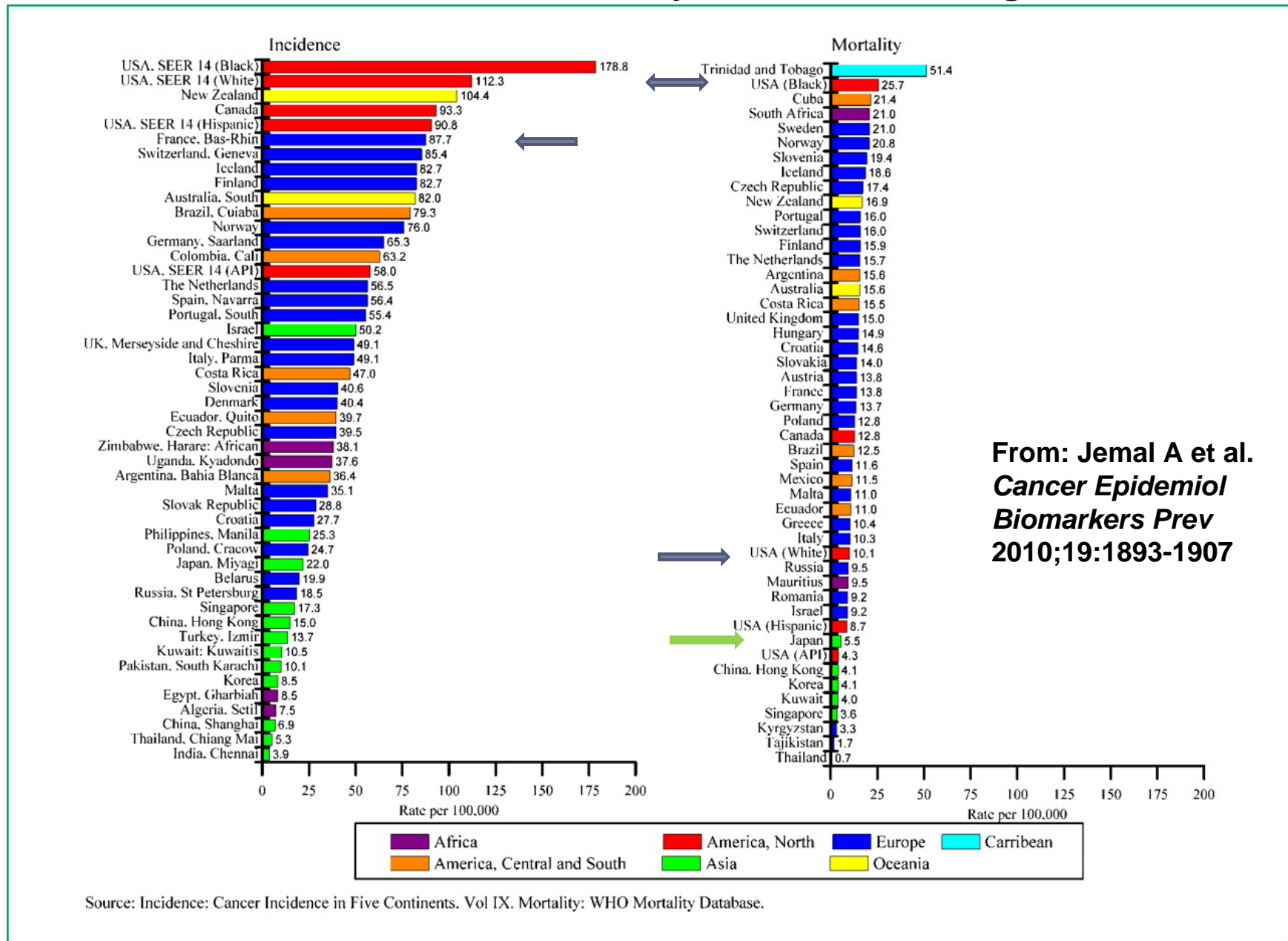
September 23, 2010

# Prostate Cancer

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- ▶ The incidence and mortality rates exhibit widespread geographic variation, and the quality of the cancer registries and national health statistics **CANNOT** account for this extent of variation.

# Prostate cancer incidence & mortality rates in select registries 1998-2002



Source: Incidence: Cancer Incidence in Five Continents, Vol IX. Mortality: WHO Mortality Database.

# What Influences Your Chance of Getting Prostate Cancer?

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## Factors You Cannot Control

- ▶ **Age** (*the older you are, the greater your risk*)
- ▶ **Racial Background** (*Blacks are at greater risk than whites*)
- ▶ **Family History** (*genetics*)

## Factors You *May Be* Able to Control

- ▶ **Weight** (*it's not known if losing weight helps, but never becoming obese is protective*)
- ▶ **Unidentified factors in diet or environment** (*risk increases for an immigrant from Asia, e.g. Japan, after arrival in US*)

# Prevention: BEWARE of false claims!

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## Regarding Prostate Cancer PREVENTION:

- ▶ Vitamin E and Selenium don't work
- ▶ Data on other dietary changes and supplements have **not** been proven
  - Low calorie diet
  - Specific diets – e.g., fruit(s), vegetables
  - Exercise
  - Weight reduction
- ▶ 5-alpha reductase inhibitors are safe and effective, and is the only intervention supported by results of Phase III controlled trials

# Prevention: BEWARE of false claims!



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## Vitamins get 'F' in cancer prevention

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Enlarge

By Tim Dillon, USA TODAY

Vitamin E capsules.

By Liz Szabo, USA TODAY

A flotilla of recent studies — including two papers published today — has sunk the notion that individual vitamin supplements prevent cancer.

With so many earlier studies suggesting that people can eat their way to longer lives, experts acknowledge that their latest findings may leave people confused and even frustrated.

**Q&A:** Which studies should we listen to?

**BETTER LIFE:** More on supplements and alternative medicine

"A lot of people are looking at this and asking, 'What happened?'" says Lori Minasian, whose study in today's *Journal of the American Medical Association* found that taking vitamin E or selenium does not ward off cancer.

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# ***Finding Out What Does Not Work:*** **The SELECT Trial**

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(**S**elenium and Vitamin **E** Cancer Prevention **T**rial)

- ▶ Largest-ever prostate cancer prevention **trial**
- ▶ Rationale: previous work suggested that selenium and vitamin E (alone or in combination) might reduce the risk of developing prostate cancer by 60 percent and 30 percent, respectively
- ▶ Why perform a trial?
- ▶ Only a large clinical trial such as SELECT can confirm or refute those suggestions

# The SELECT Trial

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**FINDINGS: Selenium and vitamin E supplements – taken either alone or together – did not prevent prostate cancer.**

- ▶ 2 observed trends were **of concern**:
  - ▶ a small but not statistically significant **increase** in the number of **prostate cancer** cases among the over 35,000 men age 50 and older in the trial **taking only vitamin E**
  - ▶ a small, but not statistically significant **increase** in the number of cases of adult onset **diabetes** in men **taking only selenium**.
- ▶ Thus, no benefit, but **possible harm!**

## Overview – Prostate Cancer Issues

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**The good news:** if you're diagnosed with prostate cancer, your odds of surviving 10 years are roughly 93 percent. And death rates have dropped since 1990. **The bad news:** researchers haven't figured out how to prevent prostate cancer. That could be because they're looking at two different versions of the disease. "With PSA screening, you find a lot of slow-growing, indolent tumors that would never bother people at all," says Walter Willett of the Harvard School of Public Health in Boston. "They'll die at 90 of a heart attack or something else." And that may lead to contradictory results. "The risk factors for these indolent cancers seem to be different than the risk factors for aggressive cancers," says Willett. "But many studies haven't sorted them out or don't have enough of the aggressive, potentially fatal tumors."

– B. Liebman, *Nutrition Action HealthLetter*, 36(7), Sept. 2009, p. 3

# *Prevention Issues – Prostate Cancer*

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- There is much **merely suggestive** evidence concerning possible dietary & lifestyle factors that may influence risk of prostate cancer.
- **But**, the history of medicine is littered with suggestive evidence for things that, when assessed with careful studies, proved **useless** or **even harmful**
- **So**, suggestive evidence is **only** useful for generating hypotheses for good studies, **not** as a basis for health recommendations.

# *Prevention Issues – Prostate Cancer*

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- **On the other hand**, some things for which the evidence related to **prostate cancer** is only suggestive may be very healthful with respect to **other diseases**, such as ***cardiovascular disease***:
- **SO**,
  - **By all means eat plenty of vegetables and fruit, eat very little saturated fat, do get some exercise,**
  - **Not** because anyone knows if those things will help to protect you against ***prostate cancer***, but because they **will** reduce your risk of ***heart attack and stroke!***

And now it's time to return to considering prostate cancer ...

# 5-alpha-reductase inhibitors

(“5ARIs” = 5 $\alpha$ -Reductase Inhibitors)

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## ▶ 5-alpha-reductase inhibitors:

- ▶ group of drugs with antiandrogenic activity, used in the treatment of benign prostatic hyperplasia (**BPH**)
- ▶ decrease the levels of available 5 $\alpha$ -reductase prior to testosterone's binding with the enzyme, thus reducing levels of dihydrotestosterone that derives from such a bond
- ▶ inhibiting the enzyme reduces excessive prostate growth

# PSA Reduction on 5ARIs

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- ▶ Within 6 months of use of a 5ARI, PSA is generally lowered:

5ARI	Mean change in PSA	Range
finasteride <sup>1</sup>	- ~50%	-81% to +20%
dutasteride <sup>2</sup>	-48% to -57%	

<sup>1</sup> HA Guess et al, *Prostate* 1993; 22:31

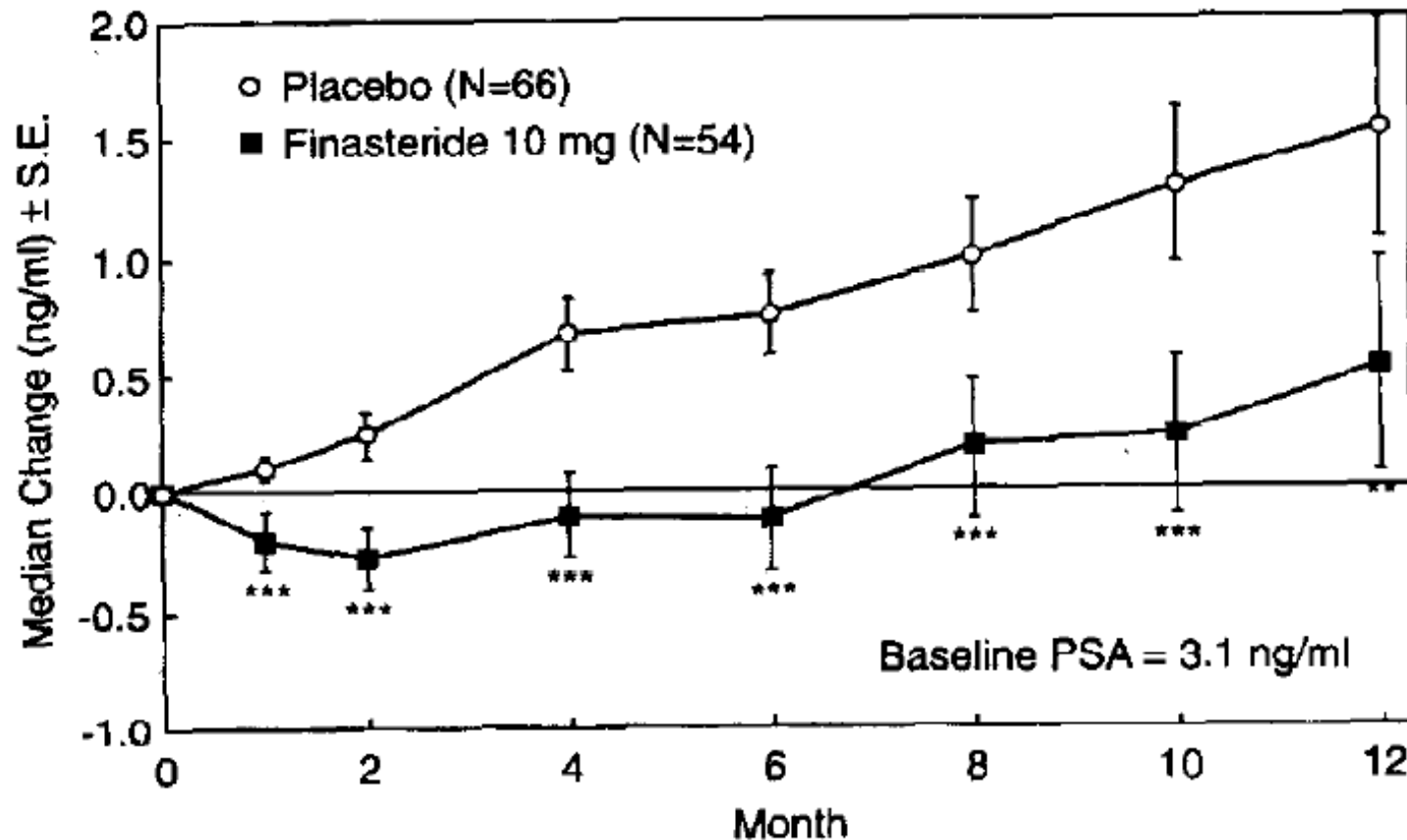
<sup>2</sup> GG Roehrbon et al. *Urology* 2004; 63:709

# 5-alpha-reductase inhibitors

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- ▶ In most men, BPH is a progressive disorder; left alone, over time the prostate grows larger, urinary flow becomes impeded, and voiding symptoms increase
- ▶ Two ARI's have been approved by the FDA to **treat BPH**:
  - ▶ finasteride (Proscar)
  - ▶ dutasteride (Avodart)
  - ▶ Efficacy does not appear related to severity of symptoms
  - ▶ Increased efficacy seen when prostate volume is large, as reflected by a PSA > 1.5 ng/ml
- ▶ Each has been examined in clinical trials to assess efficacy in prostate **cancer ...**

# Finasteride Therapy Instituted in Men with Prostate Cancer When PSA Has Risen (marking a “biochemical recurrence”)



From: Andriole et al, *Urology* 45:491, 1995

# Dutasteride Therapy for “Biochemical Recurrence”

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- ▶ The ARTS Study is examining the use of ***dutasteride*** in the setting of biochemical recurrence.

(See supplemental slides for further details.)

# 5ARI Side Effects

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- **Potential Harms:**

Reversible:

- Erectile Dysfunction – 2-4% increase
- Decreases in ejaculate volume – 1.3-2.9%
- Decreased libido – 1-4%
- Sexual dysfunction decreases over time

May not be reversible:

- Gynecomastia – 1.6-3.1% [benign breast tissue enlargement]

- **Other Effects**

- Decrease in PSA
- Decreased male pattern baldness (indeed, finasteride, marketed as Propecia, has been approved by the FDA for this indication)

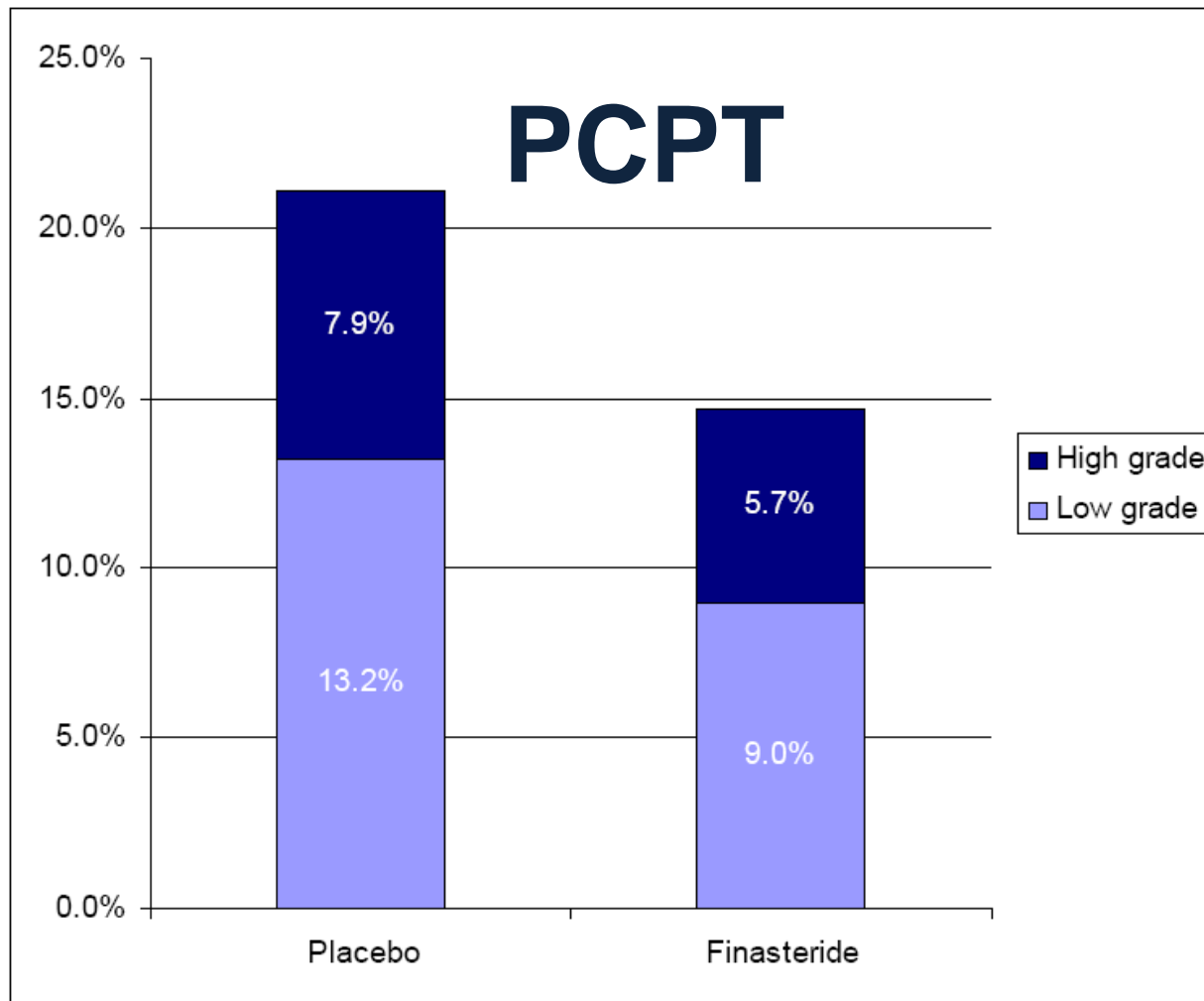
## *Finasteride:*

# Prostate Cancer Prevention Trial

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- ▶ NCI funded the Prostate Cancer Prevention Trial (PCPT)
- ▶ Prevention study using finasteride (Proscar) for 7 years
- ▶ **Initial** findings:
  - finasteride decreased the incidence of prostate cancer
  - but *might* have increased the risk of developing more aggressive tumors.

# Phase III Chemoprevention Trial



# Prostate Cancer Prevention Trial

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- ▶ Subsequent studies have shown that finasteride does **not** promote more aggressive tumors **and may actually reduce their risk:**

“Effects of finasteride on prostate volume and selective inhibition of low-grade cancer, rather than effects on tumor morphology, may have contributed to the increase in high-grade cancers with finasteride in the PCPT. Although induction of high-grade cancer cannot be excluded, the results suggest that high-grade cancer was detected earlier and was less extensive in the finasteride group than in the placebo group.”

Lucia, Epstein, Goodman *et al.*, *J Natl Cancer Inst* 2007;99:1375-83

# ***Dutasteride* May Reduce Prostate Cancer Risk**

## **The REDUCE Trial**

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- ▶ Initial data from a large, international clinical trial indicate that dutasteride (Avodart) may help prevent prostate cancer among men who are at higher risk for prostate cancer
- ▶ The trial, called REDUCE, compared dutasteride treatment against placebo among 8,200 men considered to be at high risk for the disease because of their elevated levels of PSA.
- ▶ All had received negative (clean) prostate biopsies within 6 months before joining the study.
- ▶ Treated for 4 years

# Dutasteride May Reduce Prostate Cancer Risk

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- ▶ After follow-up biopsies at 2 and 4 years, dutasteride was shown to lower the risk of prostate cancer by 23 percent compared with men taking the placebo.
- ▶ Men treated with dutasteride were also found to be at no greater risk than those on placebo for developing aggressive prostate tumors.
- ▶ Funded by GlaxoSmithKline, the manufacturer of dutasteride.

THE REDUCE STUDY:  
**Statistical Analysis 1 for Number of Participants With Biopsy-detectable Prostate Cancer at Years 2 and 4 (Restricted Crude Rate Approach)**

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	Placebo	Dutasteride 0.5 mg
<b>Number of Participants Analyzed</b>	3424	3305
Number of Participants <b>With Biopsy-detectable Prostate Cancer</b> at Years 2 and 4 (Restricted Crude Rate Approach)		
Years 1-2, n=3364, 3244	578	435
Years 3- 4, n=2359, 2451	280	224
Overall, n=3424, 3305	858	659

Groups <sup>[1]</sup>	All groups
Method <sup>[2]</sup>	Mantel-Cox
P Value <sup>[3]</sup>	<0.0001
<b>Relative Risk Reduction <sup>[4]</sup></b>	<b>22.8</b>
95% Confidence Interval	( 15.2 to 29.8 )

# SUMMARY:

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## **5-ARI's May Reduce Prostate Cancer Risk**

- ▶ The dutasteride and finasteride trial results are comparable in terms of the finding that each can reduce the occurrence of prostate cancer

# Knowledge and Use of Finasteride for the Prevention of Prostate Cancer

RJ Hamilton, LC Kahwati, and LS Kinsinger

*Cancer Epidemiol Biomarkers Prev*; 19(9): 2164-71, Sept 2010

- Assessed trends on monthly new & total prescriptions for finasteride filled within the Veterans Health Administration (VHA) from Jan 2000 to Dec 2005.
- In July 2003, the initial positive findings from the “Prostate Cancer Prevention Trial” (PCPT) were published.
- There was no significant change in the prescribing pattern before vs. after that date ( $P = 0.45$ ).
  - 57% of urologists and 40% of PCPs endorsed prescribing finasteride more frequently in 2006 than 5 years prior.
  - However, among those who reported changing prescribing patterns, fewer than 2% reported being influenced by the PCPT.

# Knowledge and Use of Finasteride for the Prevention of Prostate Cancer

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- 64% of urologists and 80% of PCPs never prescribe finasteride for prostate cancer chemoprevention:
  - Although 55% of urologists cited concerns of inducing high-grade tumors, **these concerns should now be largely alleviated** with increasing dissemination of later analyses and publications about the PCPT indicating that finasteride selectively increases the ease of detection, not the occurrence, of high-grade tumors.
  - 52% of PCPs did not know finasteride could be used for chemoprevention.

**Trends after 2005 are not yet known.**

# Finasteride for the Prevention of Prostate Cancer

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**Conclusions:** The number of men starting finasteride in the VHA increased over time, but the change did not seem to be due to increased use of finasteride for chemoprevention.

Publication of the PCPT in July 2003 seemed to have little influence over the study period lasting until 2.5 years later.

## **Analysis: Physicians...**

- May not readily accept the use of chemopreventive agents for prostate ca,
- May have been awaiting further clarifications given concern over the initial report of an increase in high grade cancers,
- May be awaiting longer term studies to assess possible adverse effects, or
- Specific education may needed, focusing both on urologists & PCP

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# **Supplemental Slides**

# SELECT - some Q&A: SELENIUM

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**How much selenium was being used in SELECT?**

**What risks were involved with taking selenium?**

The amount of selenium (provided as *l*-selenomethionine) was 200 micrograms (µg) daily.

Since the start of SELECT, four studies have been published looking at the effect of selenium on **blood glucose and risk of diabetes**:

**two** studies suggested that higher levels of selenium taken from supplements or received naturally were associated with an **increased risk of diabetes**. **One** study showed **no** association between the two, and **one** showed that people with higher levels of selenium in their blood had a **reduced** risk of diabetes. Starting in early 2007, the SELECT DSMC was specifically asked to review the study data for cases of diabetes because of these findings.

# SELECT - some Q& A: SELENIUM

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## **What risks were involved with taking selenium? [continued]**

- ▶ The Nutritional Prevention of Cancer (**NPC**) study, first reported in 1996, included 1,312 men & women who had a history of non-melanoma skin cancer. Results of the trial showed that men who took selenium to prevent new non-melanoma skin cancers received no benefit from selenium in preventing that disease. However, approximately 60 percent fewer new cases of prostate cancer were observed among men who had taken selenium for six and one-half years than among men who took the placebo. In a 2002 follow-up report, the data showed that men who took selenium for more than seven and one-half years had about 52 percent fewer new cases of prostate cancer than men who took the placebo. **This trial was one of the reasons for studying selenium in SELECT.**
- ▶ Although the initial results of the NPC trial showed an overall decrease in cancer incidence from selenium, a 2003 **update** reported 17 percent **more** new non-melanoma skin cancers **in the selenium group** compared with the placebo group. It is not clear how these results would apply to men who did not already have skin cancer when they enrolled in SELECT, or to men who are not at increased risk for skin cancer.

# SELECT - some Q&A

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## **Why didn't the selenium supplement in SELECT prevent prostate cancer?**

Per the NCI, there are several possibly explanations for why selenium supplements did not prevent prostate cancer in men on SELECT. For example, the findings from the NPC study may not have been correct, and selenium may not affect prostate cancer risk; the participants on the NPC study were deficient in selenium compared with SELECT participants, and supplements given to the men in SELECT may have exceeded an optimum preventive range; or the formulation of selenium used in the NPC trial (high-selenium yeast) may have been more active than the l-selenomethionine used in SELECT.

Early tests showed that for the selenium yeast, the amount of selenium per dose was highly variable in the NPC trial and that was cause for concern and a reason why it was not used in SELECT. Also, the inorganic compounds present in the yeast can be toxic or lead to lower body stores of active selenium.

# SELECT - some Q&A: Vitamin E

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## **How much vitamin E was being used in SELECT? What risks were involved?**

The amount of vitamin E (provided as dl-alpha-tocopheryl acetate) was 400 milligrams (mg), which is equivalent to 400 International Units (IU) per day. This dose of vitamin E can thin the blood somewhat. **Men with uncontrolled high blood pressure were not eligible to take part in SELECT because taking this much vitamin E might have increased their risk of stroke.**

**Vitamin E has been shown to increase the risk of some cardiovascular conditions.**

In a 2005 study, men & women with vascular disease or diabetes who took 400 IU of vitamin E daily for 7 years had a 13 percent increased risk of heart failure compared with participants taking a placebo. Heart failure is a condition in which the heart's ability to pump blood is weakened. A 2005 analysis of several studies in which people with various medical problems took vitamin E suggested a link between high doses of vitamin E (400 IU or more) & increased mortality.

In the initial analysis of SELECT, there was no difference in the number of cardiovascular events, cardiovascular deaths, or overall deaths between the study groups.

# SELECT - some Q& A: Vitamin E

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## **Why didn't vitamin E supplements prevent prostate cancer in SELECT?**

Per the NCI, there are several possible explanations for why vitamin E supplements did not prevent prostate cancer in men on SELECT.

For example, the dose of vitamin E used (400 IU/day) may have been less effective than was the lower dose (50 IU/day) used in the ATBC study (the formulations were identical), vitamin E may be more protective against prostate cancer in smokers (of whom there were relatively few [7.5 percent] in SELECT compared to ATBC where smokers and former smokers were the participants), and the initial findings of the ATBC may have been due to chance.

# Published Results from SELECT:

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**Effect of Selenium and Vitamin E on Risk of Prostate Cancer and Other Cancers The Selenium and Vitamin E Cancer Prevention Trial (SELECT)** [Scott M. Lippman, MD et al](#)

**JAMA 2009;301(1):39-51.**

Also: Published online December 9, 2008  
(doi:10.1001/jama.2008.864)

**Results: As of October 23, 2008,** median overall follow-up was 5.46 years (range, 4.17-7.33 years).

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Hazard ratios (99% confidence intervals [CIs]) for prostate cancer were:

1.13 (99% CI, 0.95-1.35; n = 473) for vitamin E,

1.04 (99% CI, 0.87-1.24; n = 432) for selenium, and

1.05 (99% CI, 0.88-1.25; n = 437) for selenium + vitamin E

vs 1.00 (n = 416) for placebo.

There were no significant differences (all  $P > .15$ ) in any other prespecified cancer end points.

There were statistically nonsignificant increased risks of prostate cancer in the vitamin E group ( $P = .06$ ) and type 2 diabetes mellitus in the selenium group (relative risk, 1.07; 99% CI, 0.94-1.22;  $P = .16$ ) but not in the selenium + vitamin E group.

## ▶ **Conclusions:**

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Selenium or vitamin E, alone or in combination at the doses and formulations used, did **not** prevent prostate cancer in this population of relatively healthy men.

## AVODART: After Radical Therapy For Prostate Cancer Study

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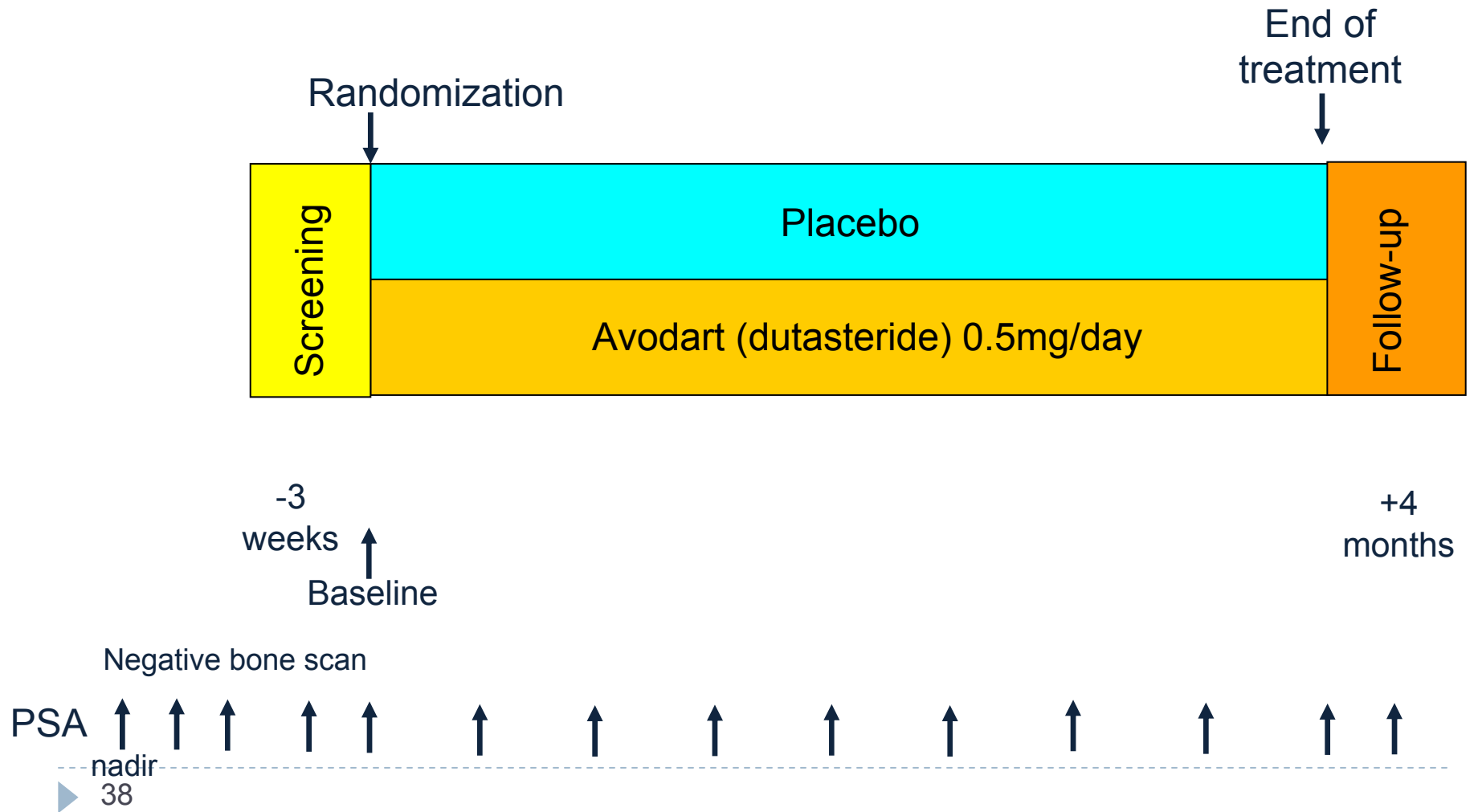
**ARTS:** double-blind, randomized, placebo-controlled trial conducted in Europe.

**Purpose:** to assess the efficacy & safety of dutasteride in extending time **to PSA doubling** in men who have been treated for clinically localised prostate cancer with a radical therapy (radical prostatectomy, primary radiotherapy or salvage radiotherapy) with curative intent **but** who experience a biochemical failure (PSA rise) afterwards **without** signs or symptoms of metastases.

**Design:** Subjects will be treated for 2 years with dutasteride or placebo. All patients will have a confirmatory negative bone scan before randomisation and will be **monitored every 3 months for PSA levels during the treatment phase**, followed by an additional PSA determination at the safety follow-up visit within 4 months of the end of the treatment period.

# ARTS Study Design

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# ARTS Endpoints

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- ▶ **Time to PSA doubling (primary endpoint)**
- ▶ Time to disease progression and percentage of patients with disease progression
- ▶ Percentage of patients with treatment response (any PSA decrease or an increase  $\leq 15\%$ )
- ▶ Changes in PSA including:
  - ▶ Time to PSA rise and percentage of patients with a PSA rise
  - ▶ Time to PSA progression and percentage of patients with PSA progression
  - ▶ Absolute and percentage PSA change from baseline and nadir PSA
- ▶ Changes in PSA doubling time during treatment
- ▶ Disease-related patient anxiety (MAX-PC)
- ▶ Safety outcomes