CHEMOPREVENTION OF HEAD AND NECK CANCER AND PROSTATE CANCER

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Definition

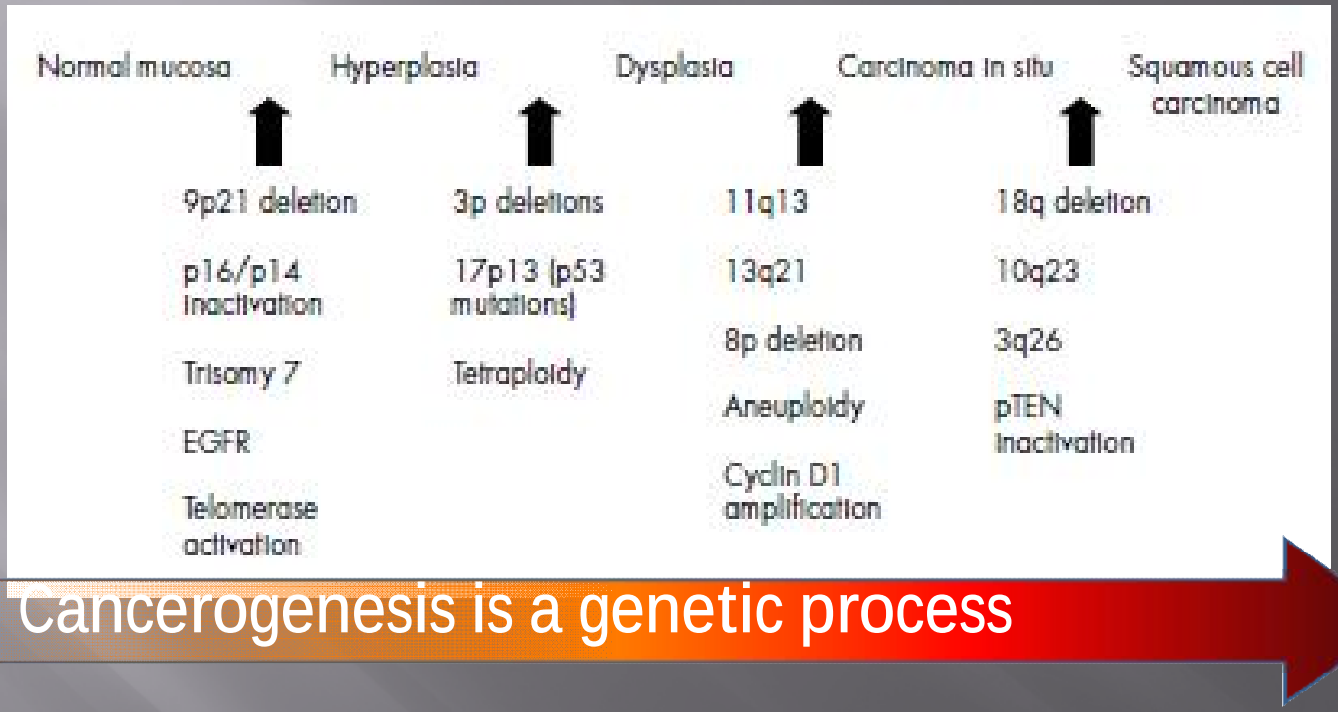
Cancer chemoprevention is

defined as the use of natural, synthetic, or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression to invasive cancer

Plan

- Basic Concepts
- Chemoprevention of Head and Cancer
  - Disease impact
  - Pathophysiology
  - Trials
- Chemoprevention of Prostate Cancer
  - Disease impact
  - Pathophysiology
  - Trials

Carcinogenesis



- Multistep process
  - Promotion
  - Progression
- Progressive Accumulation of genetic alterations in time
- Takes time (usually decades)

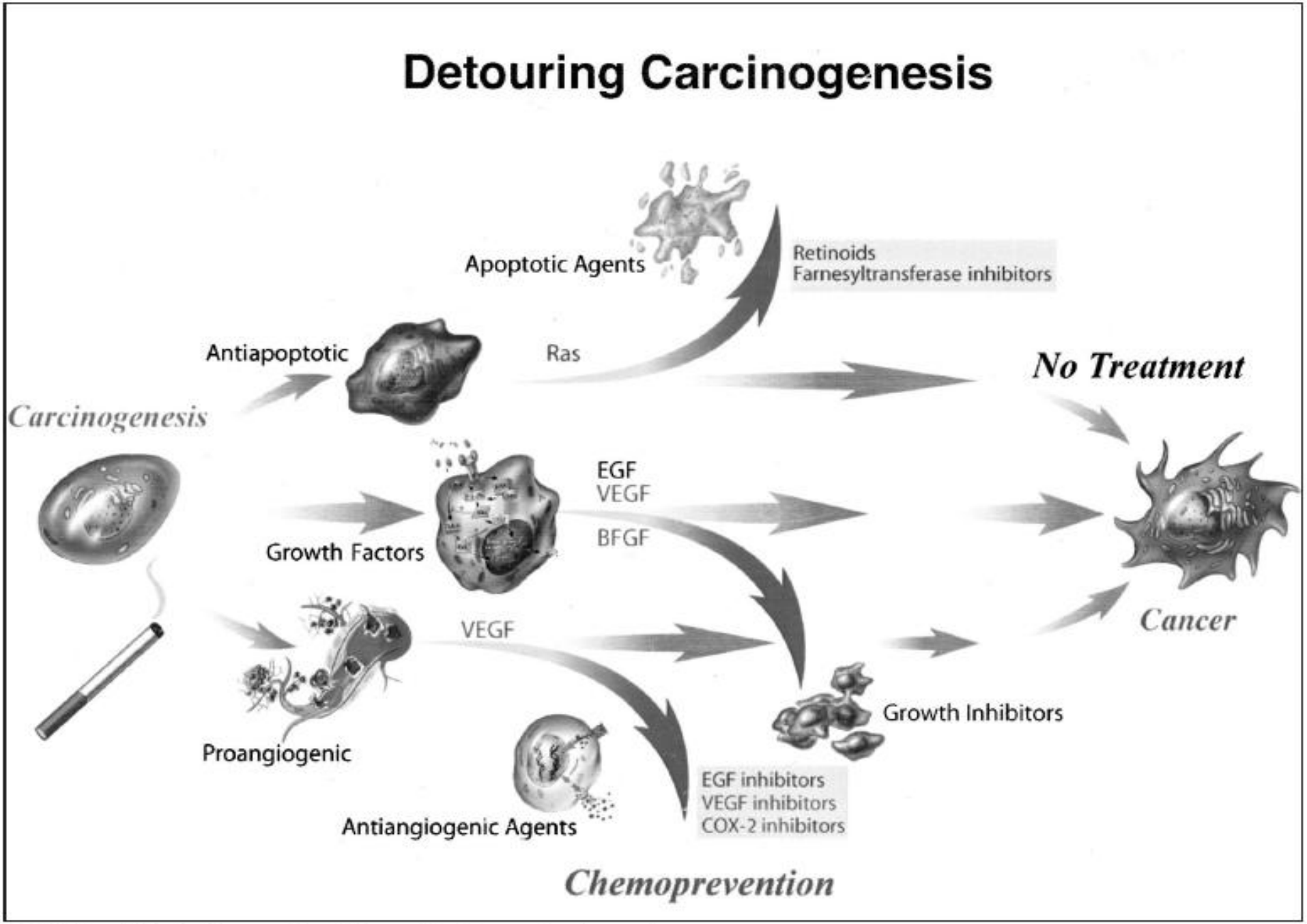


FIGURE 2 Biological Approaches to Preventing Cancer Development.
Adapted from Soria JC, Kim ES, Fayette J, et al.[19] with permission from Elsevier.

Difficulties of Trial Design in Chemoprevention

- To show mortality reduction
  - Large (and expensive) trials
  - Difficult to conduct
- Small and pragmatic trials
  - Less rigorous end points
    - Reversal of premalignant lesions
    - Prevention of invasive cancer
    - Other biomarkers

Biomarker

a characteristic,

measured and evaluated as an indicator

of normal biologic, pathogenic processes, or pharmacologic responses to therapeutic interventions.

- Clinical end—point
  - Survival
- Surrogate end-points
  - Intraepithelial neoplasia
- Global Assesment
  - Risk Benefit ratio

Examples of Intraepithelial Neoplasias

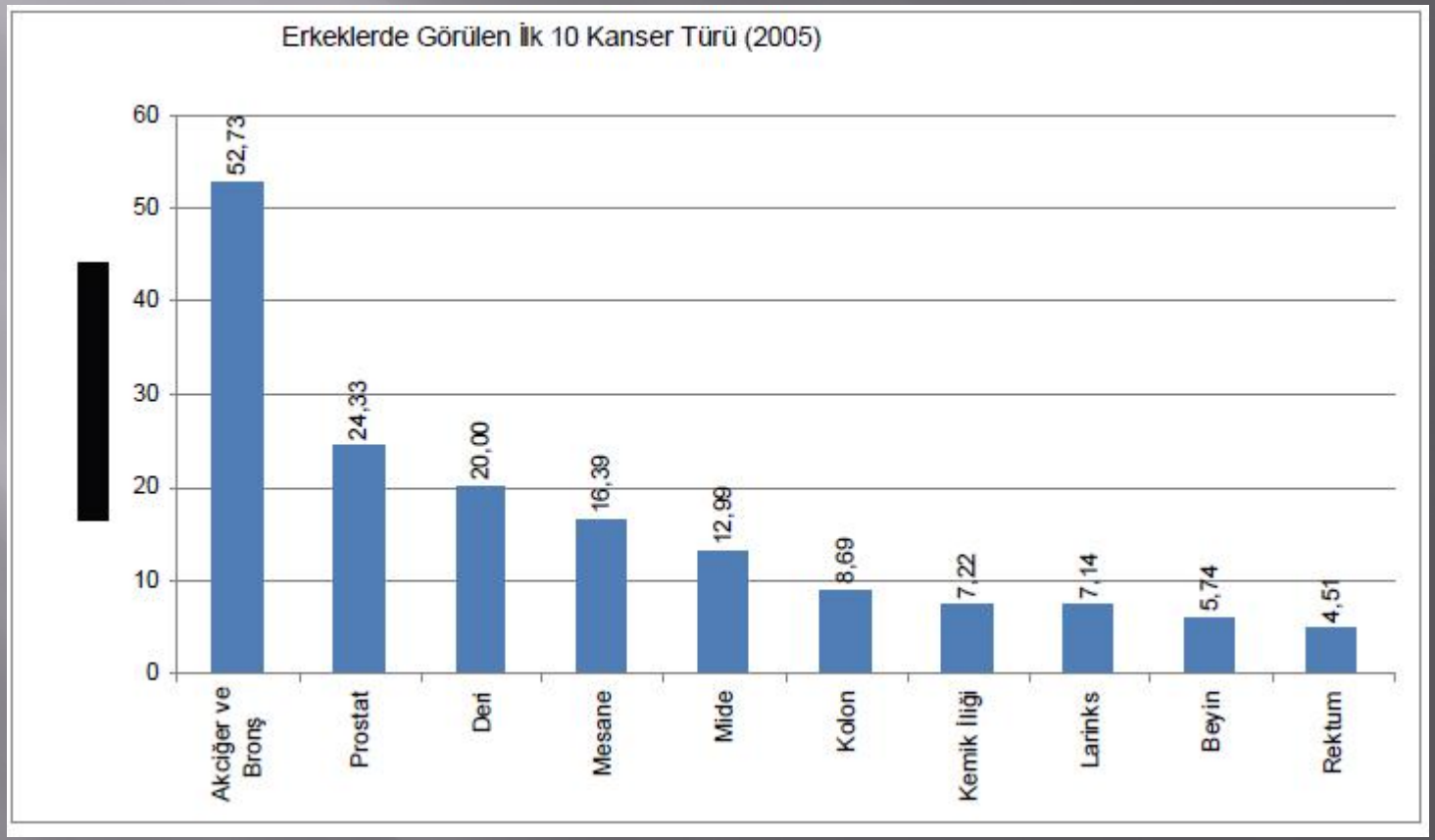
Epithelium	*Intraepithelial Neoplasia*
Colon and rectum	Adenoma
Lower esophagus	Barrett's esophagus
Upper esophagus	Squamous dysplasia
Skin-squamous/basal cell	Actinic keratosis
Skin-pigmented	Dysplastic nevus
Cervix	Cervical intraepithelial neoplasia
Head and neck	Leukoplakia
Lung	Bronchial dysplasia

Chemoprevention of Head Neck Cancer

Head Neck Cancer

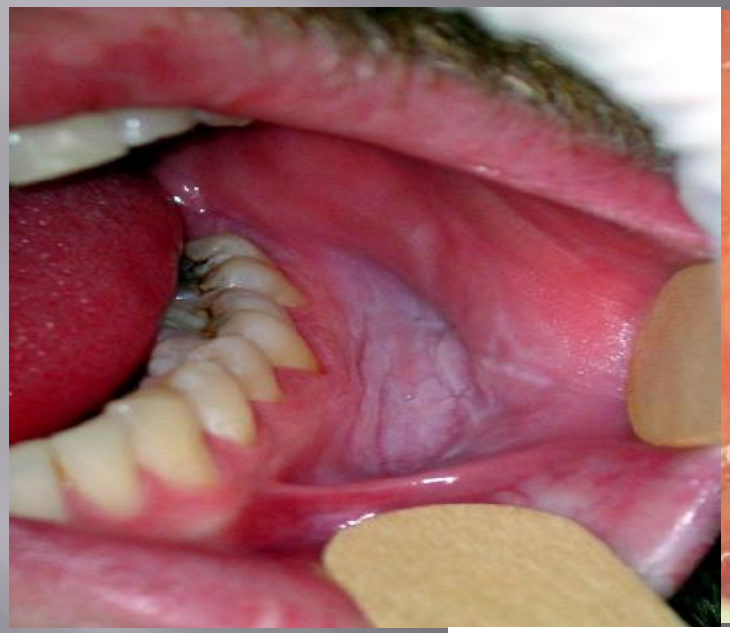
- Epidemiology
  - Sixth most frequent Cancer in the World
  - Eighth most frequent in men in Turkey
- Etiology
  - Smoking, alcohol and HPV
- Premalinant Lesion
  - Leukoplakia
  - Advanced
    - Erythroleukoplakia
    - Dysplatic leukoplakia
- One of most studied disease for chemoprevention

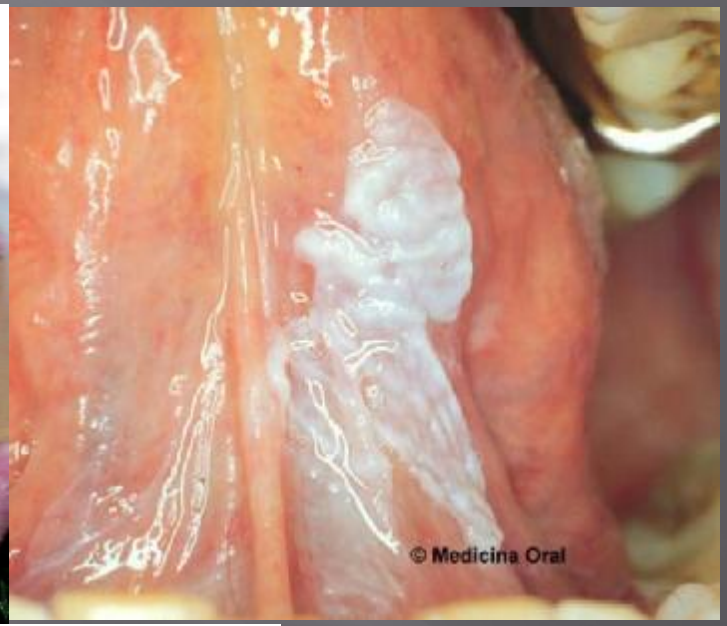
Top 10 Cancers in Turkiye

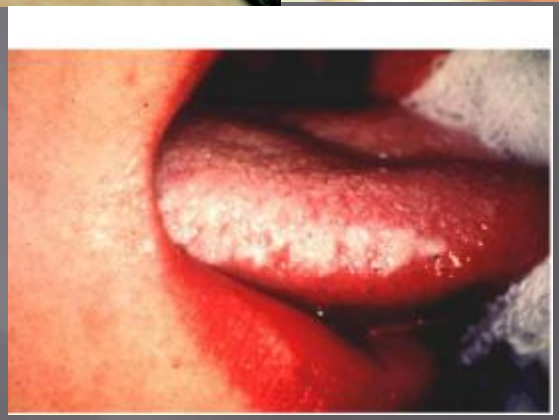


Kanserle Savaş Daire Başkalığı Web Site, accessed on January 15th, 2010

Leukoplakia







Head and Neck Cancer Field Carcinogenesis

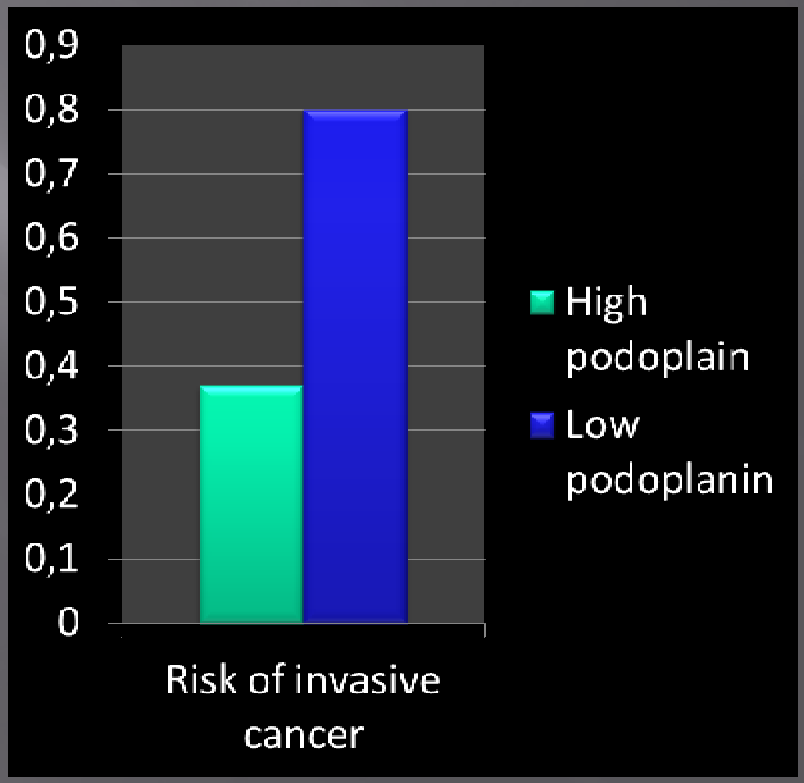
- Once carcinogenesis is initiated, it may do so everywhere affected by carcinogenic agent
  - E.g. Smoking and alcohol effet in upper aerodigestive tract
  - Supported by epidemiological data
  - Synchronous and metachronous tumors
- Individuals with (pre)malignant lesions are on increased risk of developing cancer related parts of body.

Not every patient with leukoplakia progress into invasive head and neck cancer

RISK FACTORS

- Continuing to smoke
- Continuing to drink alcohol
- High levels of podoplanin

IMPACT OF PODOPLANIN



Head Neck Cancer trials Chemoprevention

Naturraly Occuring Compunds

- Vitamin A
- Vitamin E
- Beta Carotene

Synthetic Compunds

- Synthetic Retinoids
  - 13-cis-retinoic acid (isotretinoin),
  - All-trans-retinoic acid,
  - Etretinate
- ONYX-015
- NSAIDS
- EGFR Inhibitors

Head Neck Cancer trials Chemoprevention

secondary chemo-prevention

- 5 trials

Before HN Cancer

tertiary chemo-prevention

- 4 trials

After HN and Lung Cancer

Head and neck cancer secondary chemo-prevention

The first trial (Vitamin A)

- First trial on 20 patients in 1957
  - Remarkable response (90%)
- Following 2 trials
  - lesser but signicant response rates

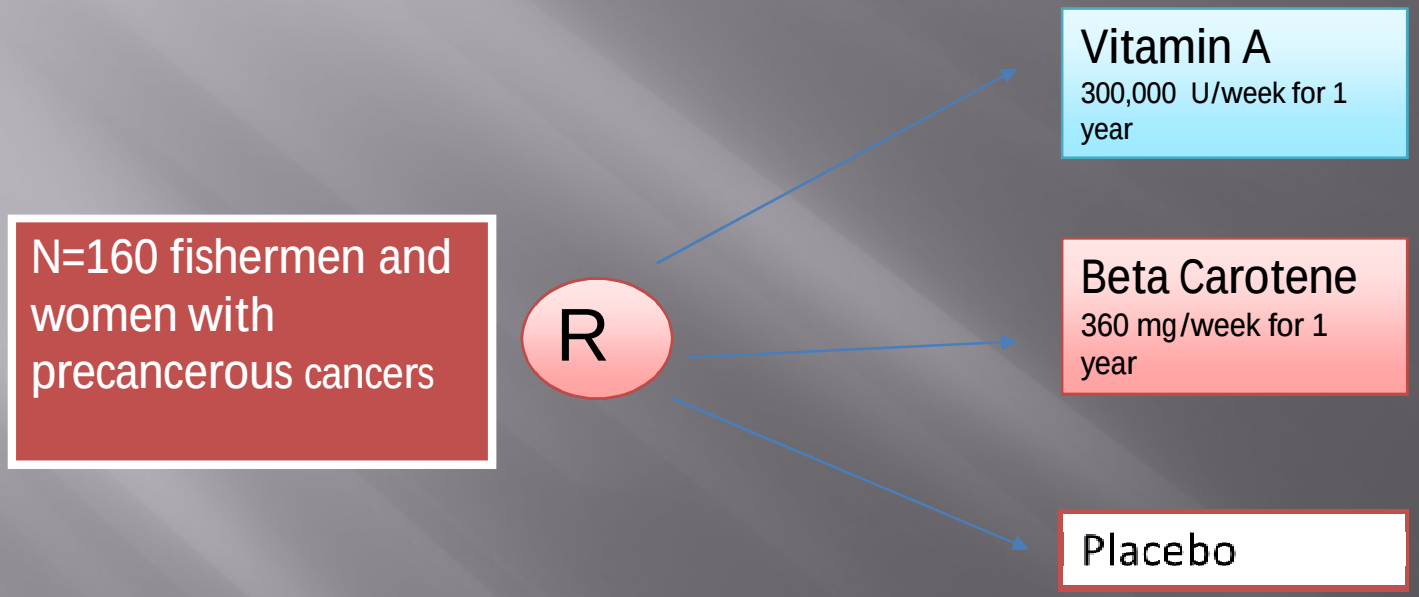
Uptodate 2009

Beta Carotene

- Precursor of vitamin A
- High response rates in patients with oral leukoplakia in small trials

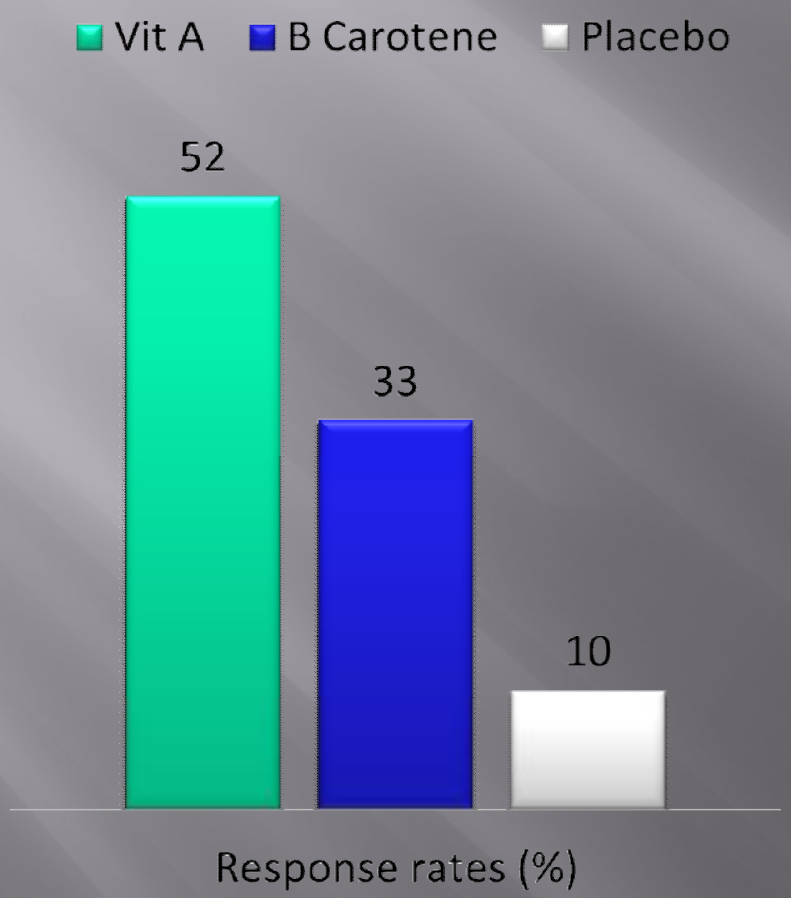
Garewal, HS, Meyskens, FL, Killen, D, et al. Response of oral leukoplakia to betacarotene. J Clin Oncol 1990; 8:1715.
Garewal, H. Chemoprevention of oral cancer: beta-carotene and vitamin E in leukoplakia.Eur J Cancer Prev 1994; 3:101.
Toma, S, Benso, S, Albanese, E, et al. Treatment of oral leukoplakia with beta-carotene.Oncology 1992; 49:77.

Vitamin A versus B Carotene versus Placebo
A randomized trial



Sankaranarayanan, R, Mathew, B, Varghese, C, et al. Chemoprevention of oral leukoplakia with vitamin A and beta carotene: An assessment. Oral Oncol 1997; 33:231.

Vitamin A versus B Carotene versus Placebo Results



- No major toxicities
- High relapse rate after discontinouation
  - Vit A
    - 2/3
  - B Carotene
    - 1/2

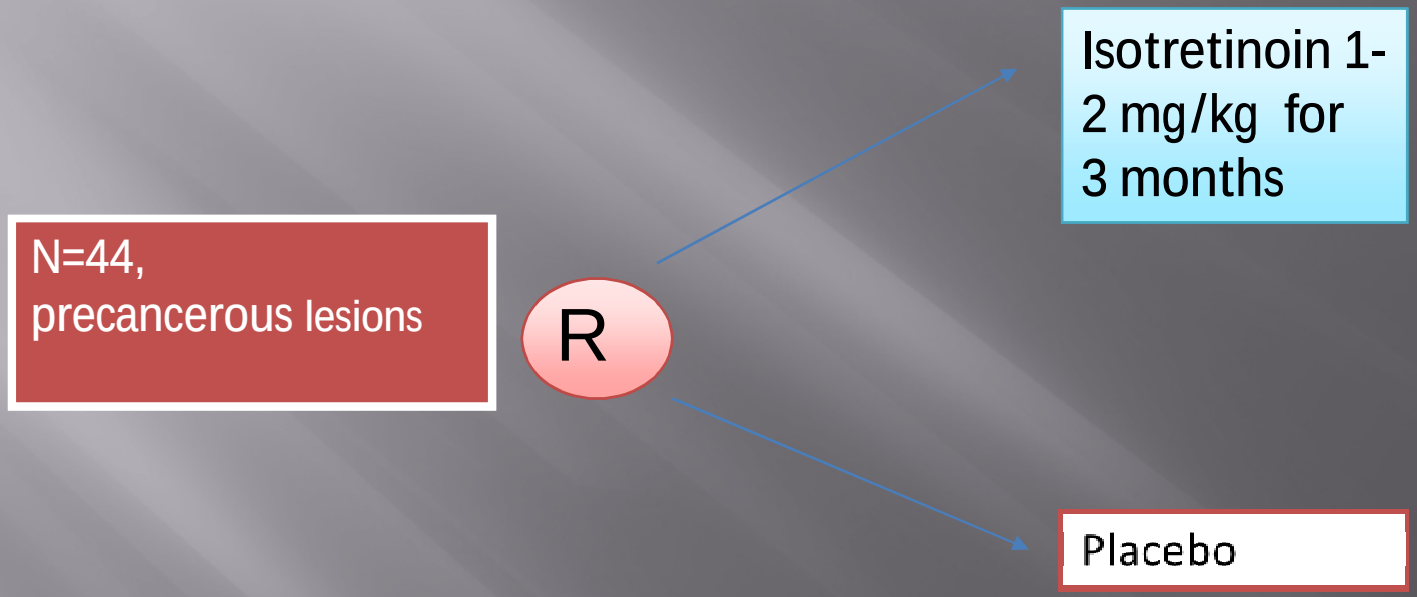
Sankaranarayanan, R, Mathew, B, Varghese, C, et al. Chemoprevention of oral leukoplakia with vitamin A and beta carotene: An assessment. Oral Oncol 1997; 33:231.

Synthetic retinoids

- One of the most studied compounds
- First trial in 1978
- Common compunds
  - Isotretinoin (13-cis-retinoic acid),
  - All-trans-retinoic acid,
  - Etretinate
- High response rates in intial studies
  - 50-90%

Khuri, FR, Lippman, SM, Spitz, MR, et al. Molecular epidemiology and retinoid chemoprevention of head and neck cancer. J Natl Cancer Inst 1997; 89:199.
Koch, HF. Biochemical treatment of precancerous oral lesions: The effectiveness of various analogues of retinoic acid. J Maxillofac Surg 1978; 6:59.
Koch, HF. Effect of retinoids on precancerous lesions of oral mucosa. In: Retinoids: Advances in Basic Research and Therapy, Orfanos, DE (Ed), Springer-Verlag, Berlin
1981. p.273

High Dose Isotretinoin versus placebo Randomized trial

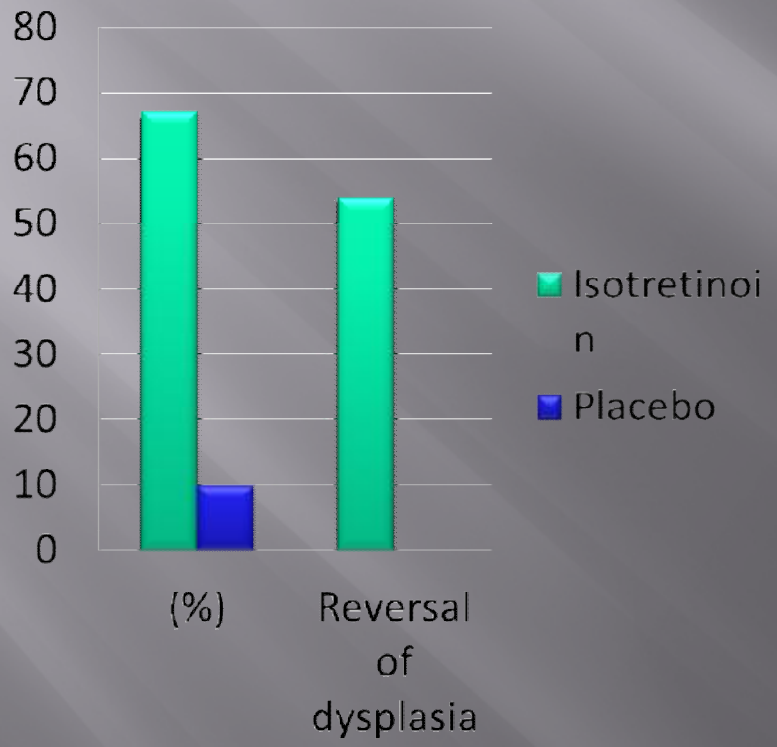


Drugs were given for 3 months
Then followed for 6months
Pre- and post-therapy biopsy

Hong, WK, Endicott, J, Itri, LM, et al. 13-cis-retinoic acid in the treatment of oral leukoplakia. N Engl J Med 1986; 315:1501.

High Dose Isotretinoin versus placebo Randomized trial-results

RESPONSES

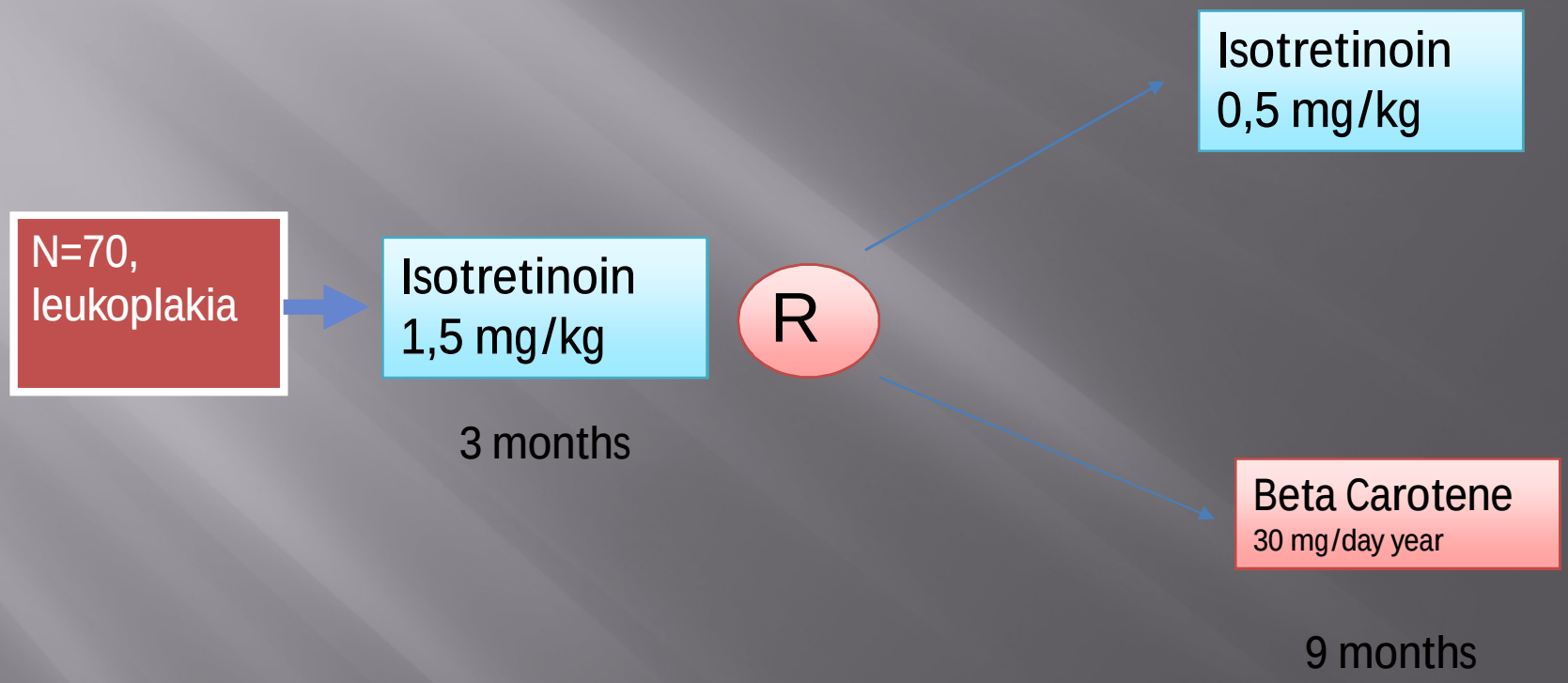


TOXICITY

- Common toxicities
  - Cheilitis,
  - facial erythema
  - dryness and peeling of the skin
  - Conjunctivitis
- Relapses
  - 50% in 3 months

Hong, WK, Endicott, J, Itri, LM, et al. 13-cis-retinoic acid in the treatment of oral leukoplakia. N Engl J Med 1986; 315:1501.

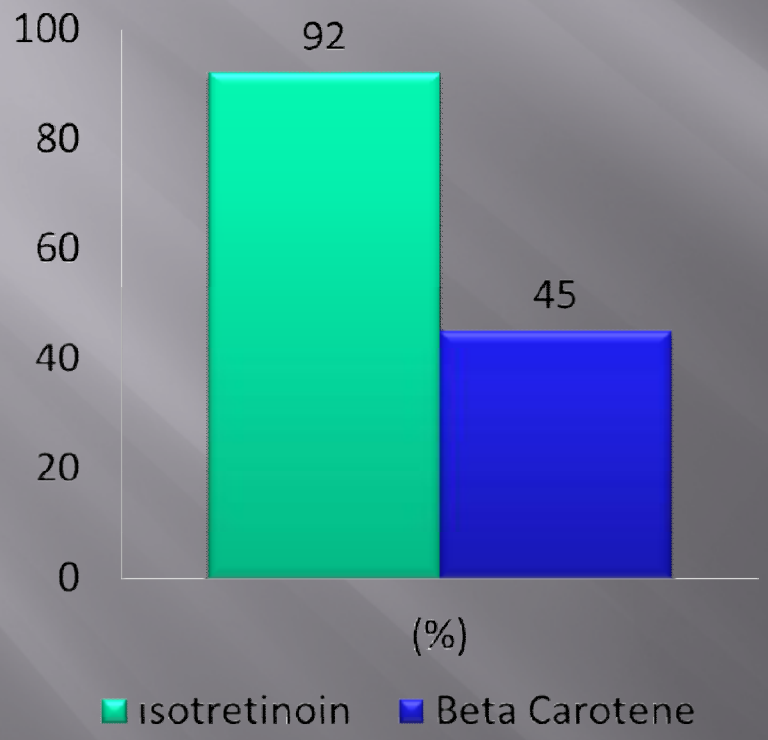
Maintanence after a high dose induction
Randomized trial



Lippman, SM, Batsakis. JG, Toth. BB, et al. Comparison of low-dose isotretinoin with beta carotene to prevent oral carcinogenesis. N Engl J Med 1993; 328:15.

Maintanence after a high dose induction Randomized trial

CONTINUED RESPONSE



TOXICITY

- Generally mild
- More with isotretinoin

Lippman, SM, Batsakis. JG, Toth. BB, et al. Comparison of low-dose isotretinoin with beta carotene to prevent oral carcinogenesis. N Engl J Med 1993; 328:15.

Head and neck cancer
Secondary prevention trials summary

- Small trials
- They (vitamin A, beta coretene, isotretinoin) work
  - In under-developed nations with vitamin deficiencies??
- İsotretinonin more successful, especially at high doses (2 mg/kg/day)

- But at a price
  - High toxicity (Xerostomia , conjunctivitis)
  - High relapse rate

Head and neck cancer tertiary chemo-prevention

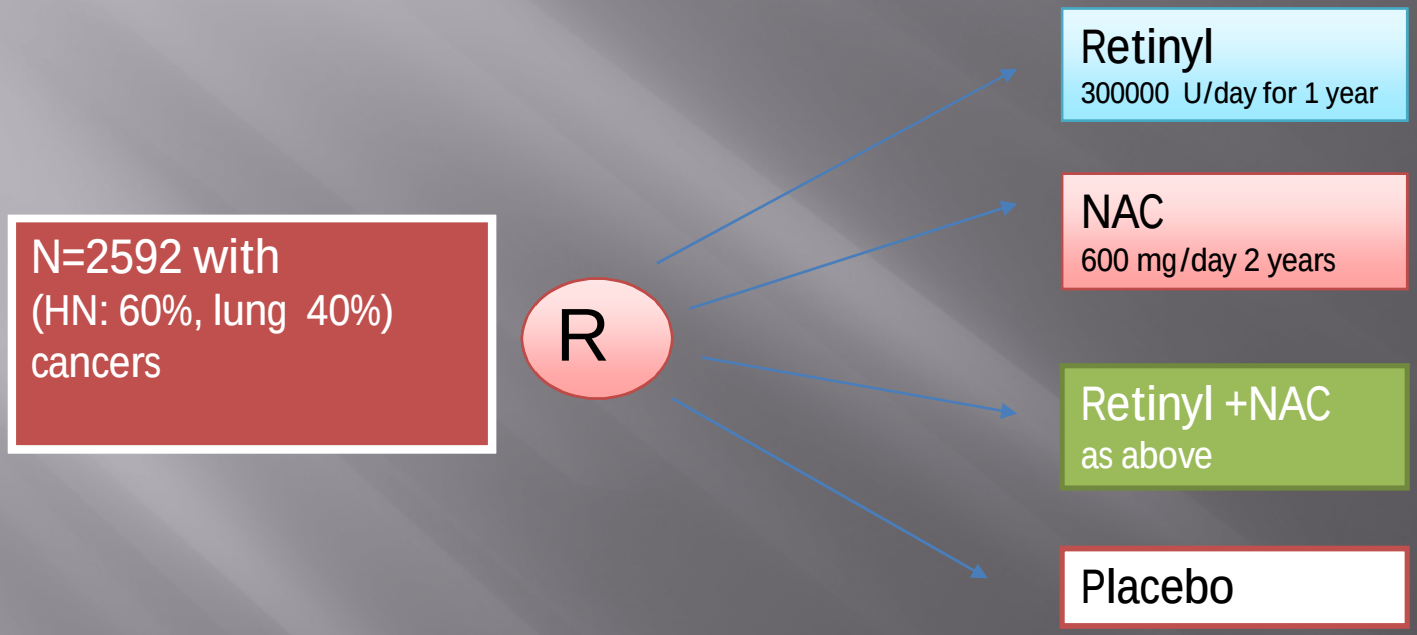
A placebo controlled randomized trial with high dose isotretinoin

- 103 patients with localized Hand and Neck Cancerafter curative therapy
- Isotretinoin (50-100 mg / m2) vs placebo for 12months

- No impact on loco-regional or distant relapses
- Significantly fewer new aerodigestive cancers (4 vs. 24)
- High toxicity
- High drop out rate

Hong, WK, Lippman, SM, Itri, LM, et al. Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. N Engl J Med 1990; 323:795.

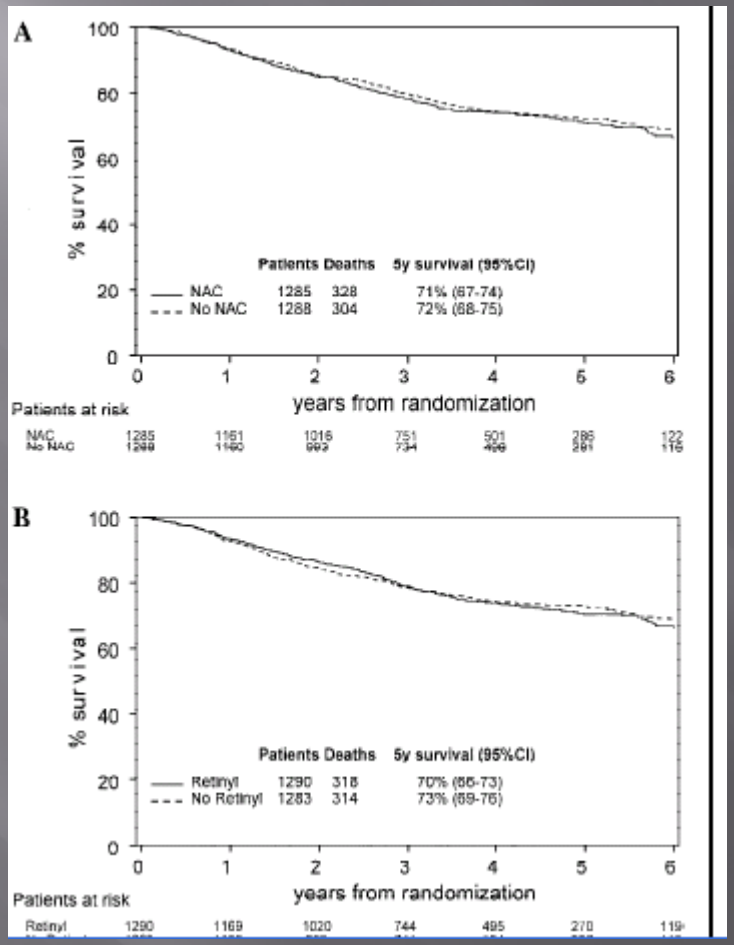
Euroscan trial
EORTC



- Primary end point: Second primary tumors
- 93.5% smoker, 25% continued
- High drop out rate (23%)
- Small number of locally advanced cancers

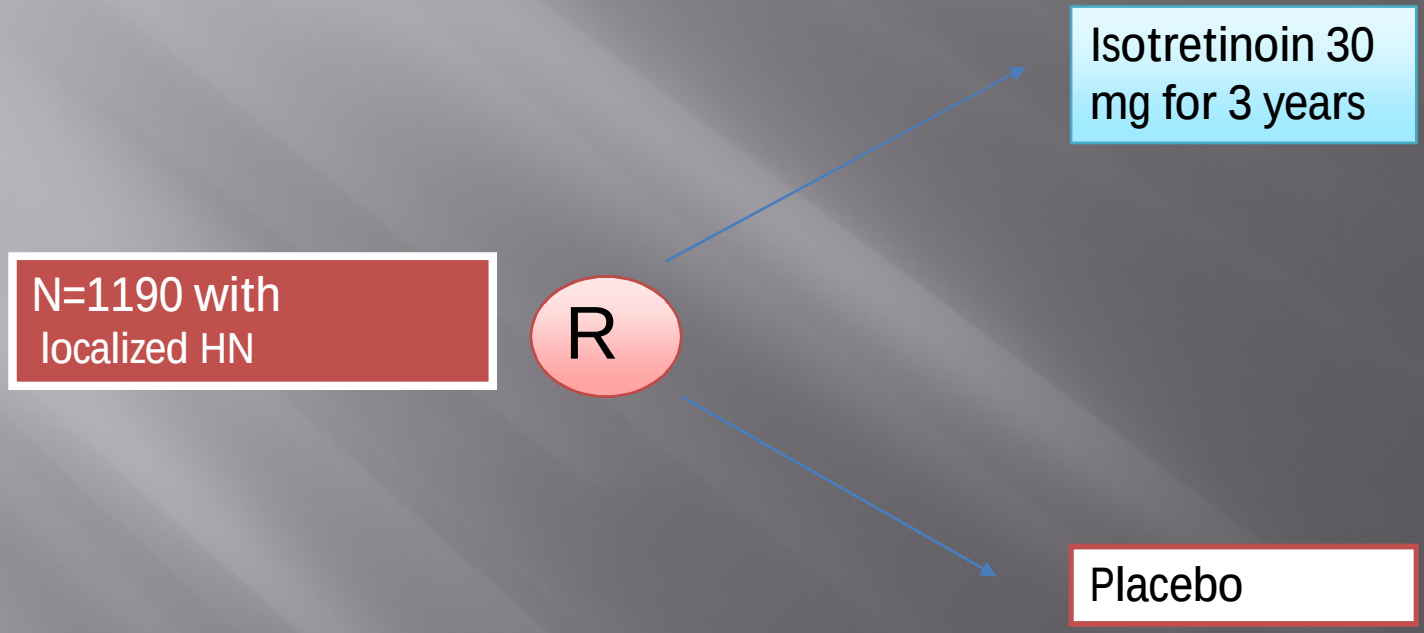
J Natl Cancer Inst 2000;92:977–86

EORTC trial over all survival



J Natl Cancer Inst 2000;92:977–86

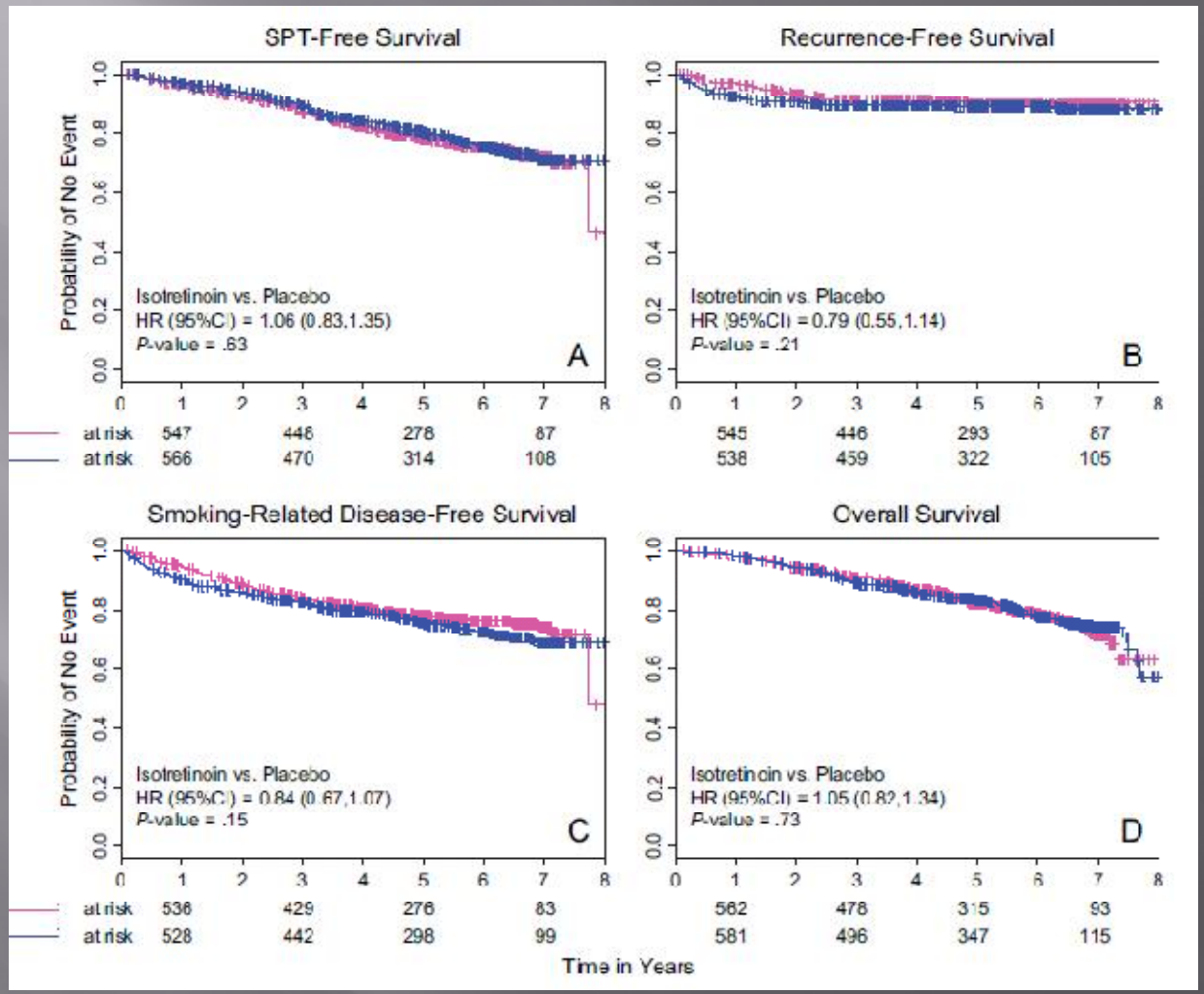
NCI C91-002



- Patients were followed for additinal 4 years
- Primary end point second primary tumors
- 15% drop out rate

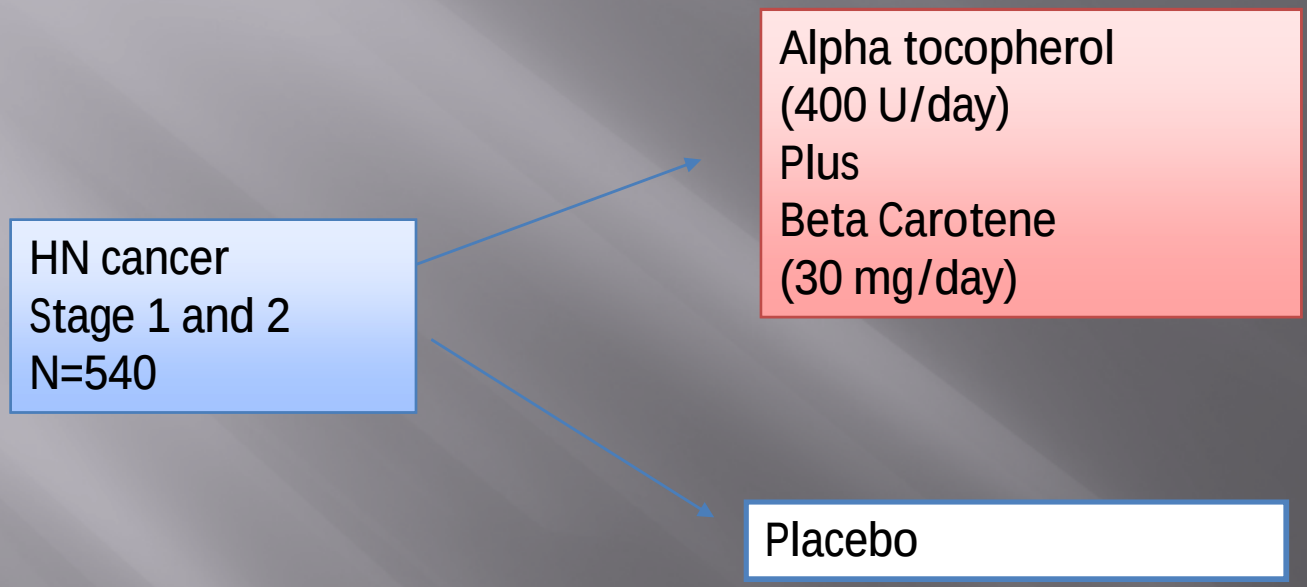
J Natl Cancer Inst 2006;98:441 – 50]

NCI C91-002



J Natl Cancer Inst 2006;98:441 – 50]

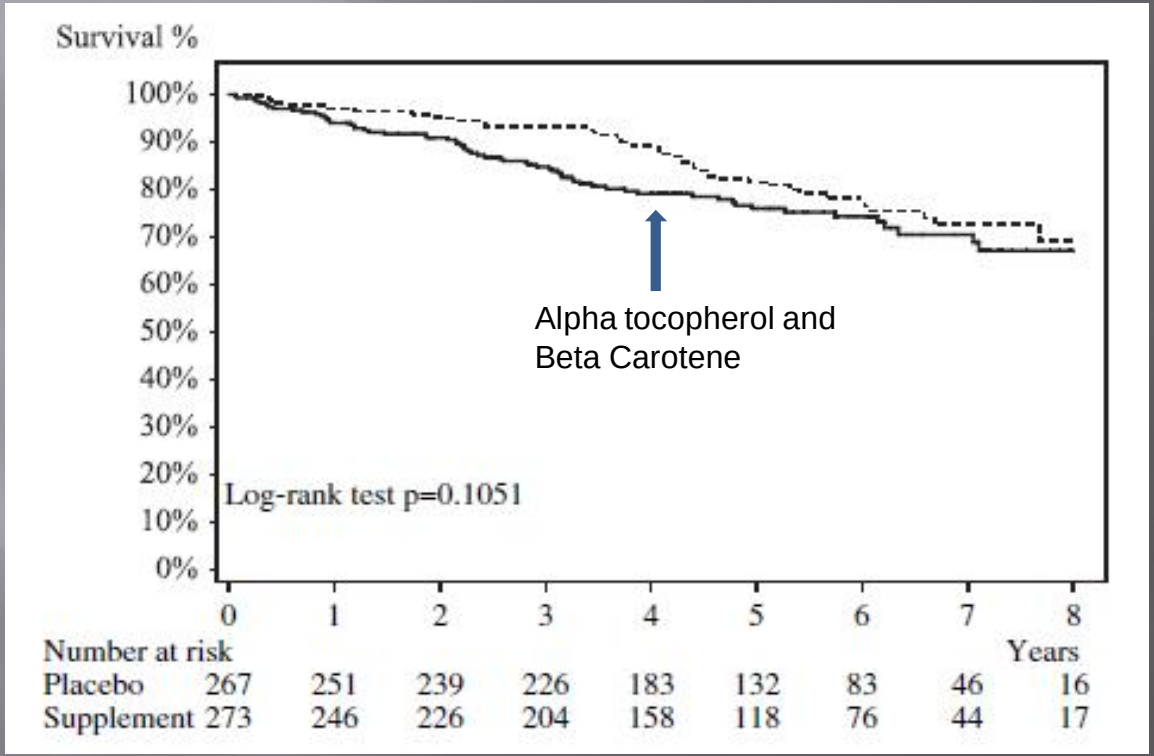
Alpha tocopherol and beta carotene in patients with HN cancer



- Supplemetation started with RT and lasted for 3 years
- 20-25% drop out rate

Journal of the National Cancer Institute, Vol. 97, No. 7, April 6, 2005

Combination had a detrimental effect



J Natl Cancer Inst 2000;92:977–86

HN Cancer Trials Summary

Positive, but at high doses with toxicity

Negative

Before invasive cancer

After invasive cancer

TABLE 5 Selected Head and Neck Chemoprevention Trials

Trial	Year	Patients (n)§§	Prevention	Population	Endpoint	Compounds*	End Result
High-risk Patients with Oral Leukoplakia							
Hong et al.[181]	1986	44	Secondary	Oral leukoplakia	Response	Isotretinoin (1–2mg/kg)	Positive
Lippman et al.[182]	1993	70	Secondary	Oral leukoplakia	Response	Isotretinoin (1.5 mg/kg)† Beta carotene (30 mg)	Positive‡
Stich et al.[188]	1988	65	Secondary	Oral leukoplakia from tobacco or betel nut use	Response	Vitamin A (100,000 IU) twice weekly	Positive
Chiesa et al.[189]	1993	137	Secondary	Oral leukoplakia	Recurrence	4-HPR (200 mg)§	Positive
Han et al.[190]	1990	61	Secondary	Oral leukoplakia	Response	4-HPR (40 mg)	Positive
Adjuvant Trials							
Hong et al.[191]	1990	103	Tertiary	Prior HNSCC	Recurrence SPT Survival	Isotretinoin (50 to 200 mg/m^2)	Positive
EUROSCAN[192]	2000	2,592	Tertiary	Prior lung or HNSCC¶	SPT Survival	Retinyl palmitate§ (300,000 IU)** N-Acetylcysteine (600 mg)	Negative††
Bolla et al.[193]	1994	316	Tertiary	Prior early-stage oral/oropharynx cancer	SPT‡‡ Survival	Etretinate (50 mg for one month, then 25 mg for 24 months)	Negative
NCI C91-002[194]	2003	1,384	Tertiary	Prior Stage I–II HNSCC	Recurrence SPT Survival	Isotretinoin (30 mg)	Negative
Biochemoprevention for Advanced Premalignant Lesions							
Papadimitrakopoulou et al.[195]	1999	36	Secondary	Advanced dysplasia	Response	Interferon-α (3 MU/m^2 twice weekly) α-Tocopherol (1200 IU) Isotretinoin (100 mg/m^2)	Positive for laryngeal lesions but not oral
Shin et al.[196,197]	2001	44	Tertiary	Prior head and neck cancer	Survival	Interferon-α (3 MU/m^2 three times weekly) α-Tocopherol (1200 IU) Isotretinoin (50 mg/m^2)	Positive

CA Cancer J Clin 2004;54:150–180.

HN Cancer
tertiary chemo-prevention

- High dose isotretinoin did not work except for
  - In one trial, incidence of second primary tumors (mostly HN, esophagus, lung) decreased
- Low doses did not work in 3 randomized trials
  - Including trials on 2592 and 1384 patients
- A detrimental effect was onserved in one study with beta carotene plus vitamin E
  - High relapse rate of HN cancer

Newer and Ongoing Trials

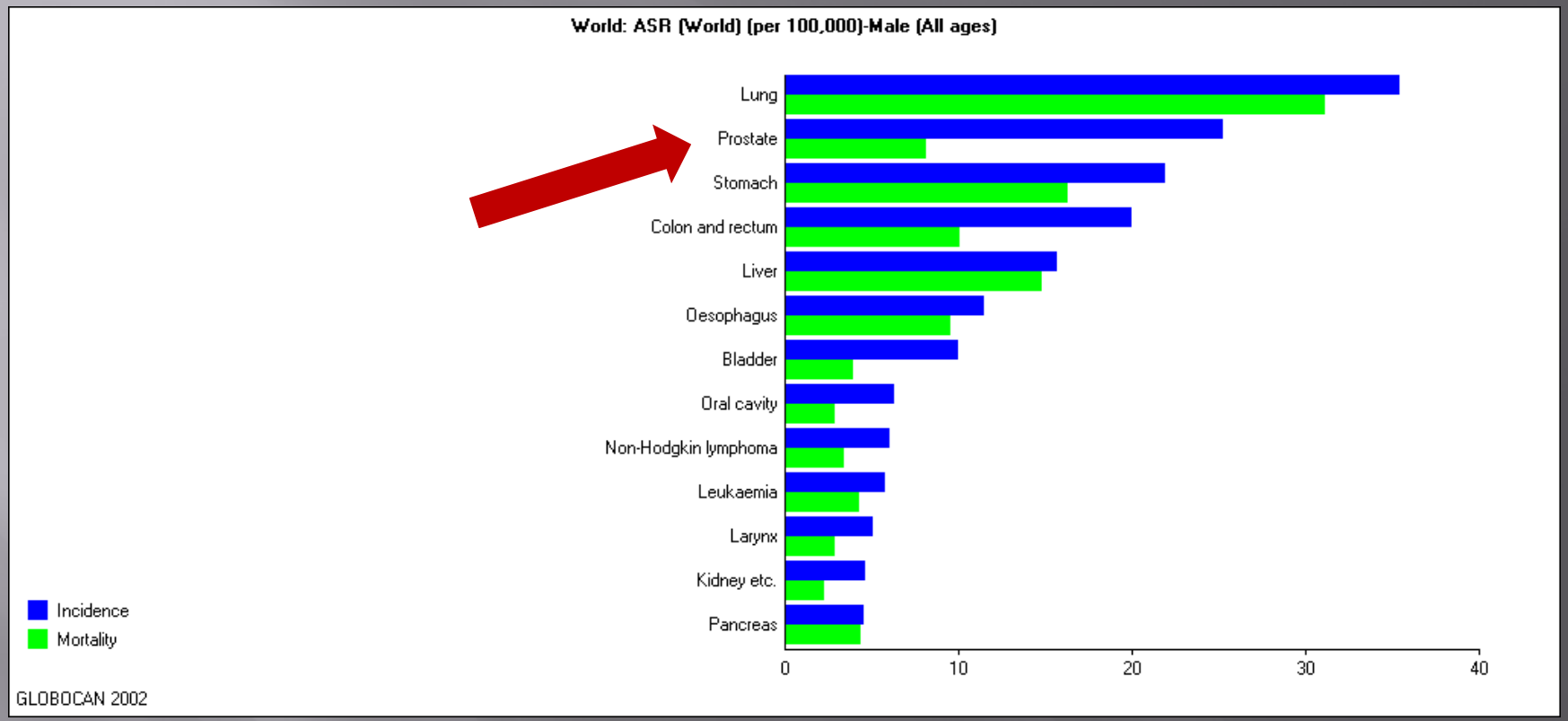
- ONYX–o15: An adenovirus selectively replicates in p53 deficient cells
  - Mouth washes, response 7/19
- EGFR inhibitors
  - Cetuximab (Ongoing)
- NSAIDS
  - Ketorolac mouth washes (Negative)
- Green tea extracts have some promising results

Prostate Cancer Chemo-prevention

Prostate Cancer

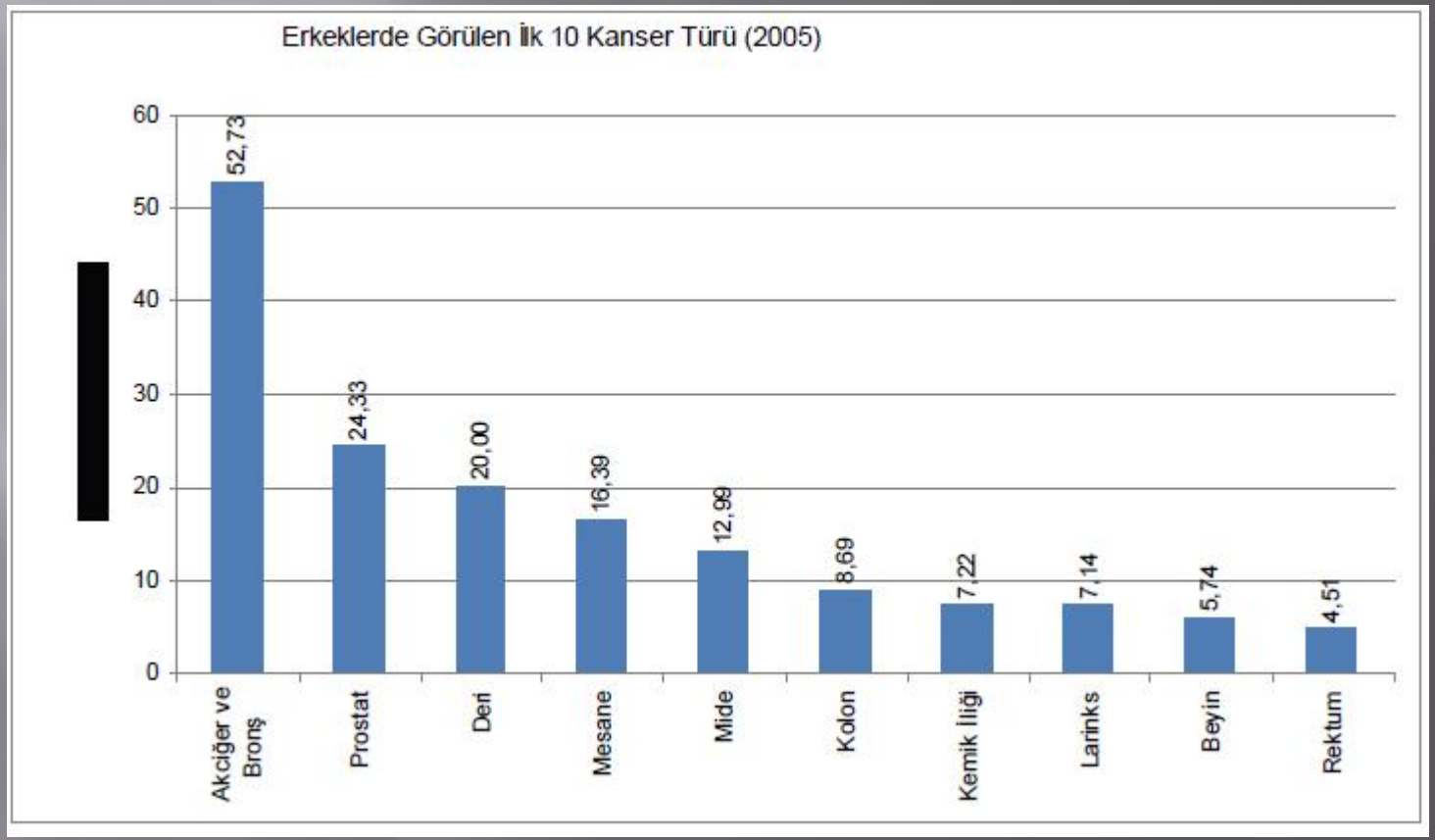
- The 2nd most frequently cancer in men in the world
- However, overall mortlity is relatively low compared to other cancers
- A long preclinical period

Prostate cancer statistics in the world



Around one – third is dying from it

Top 10 Cancers in Turkiye



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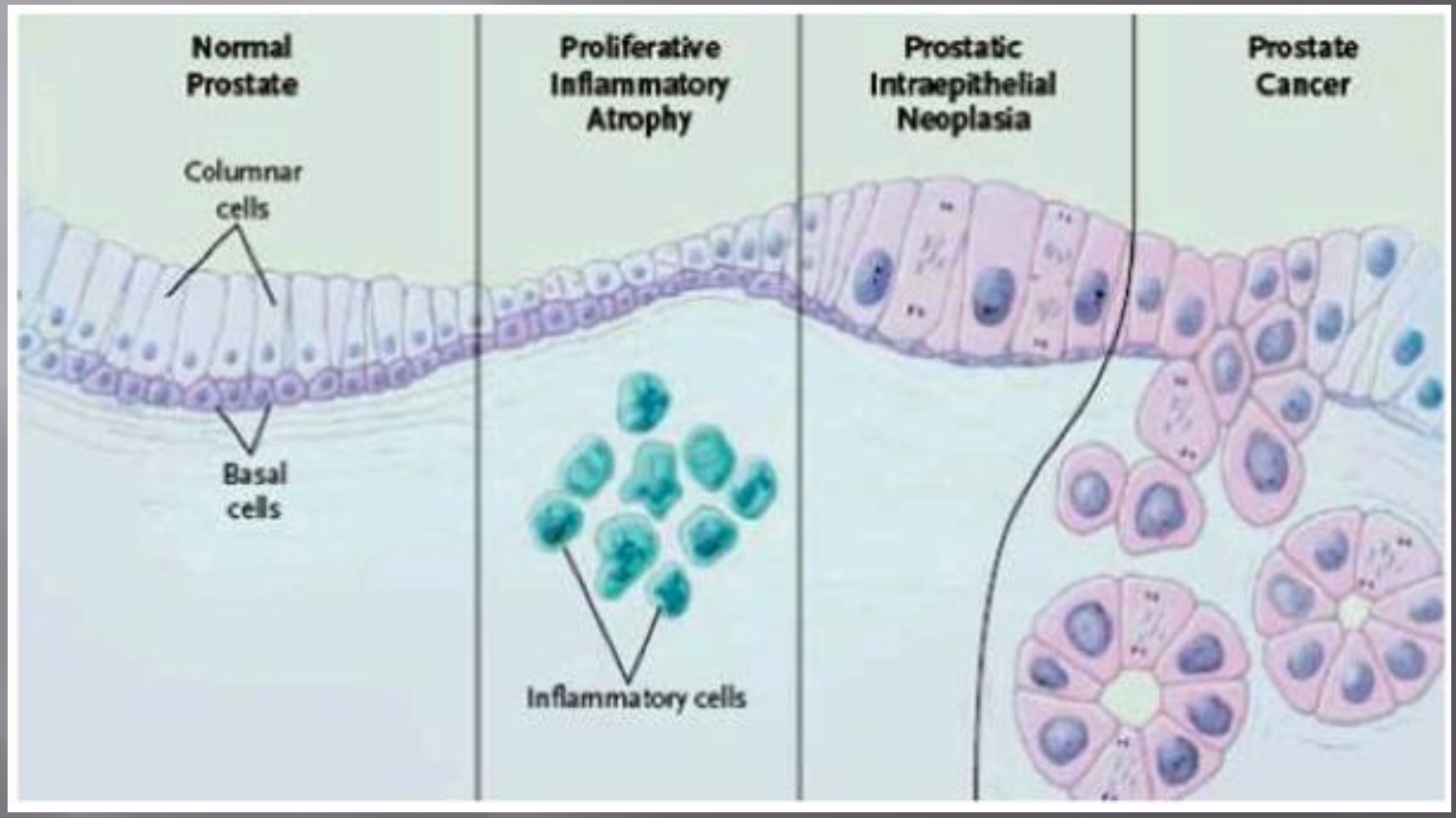
Prostate Cancer Pathophysiology



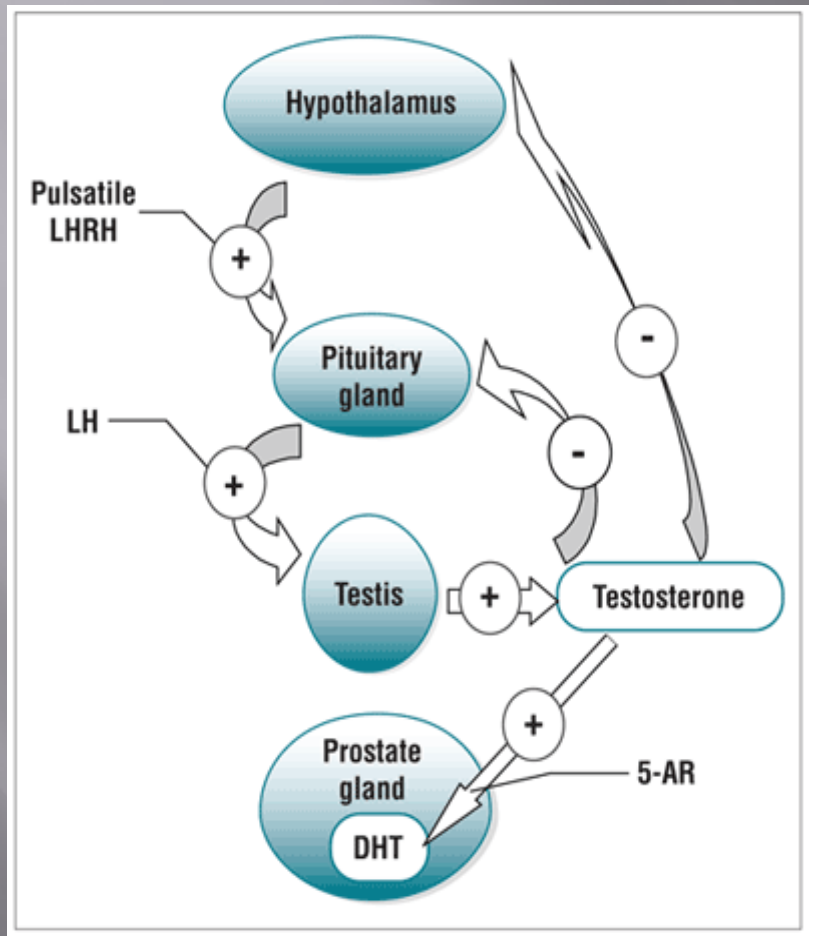
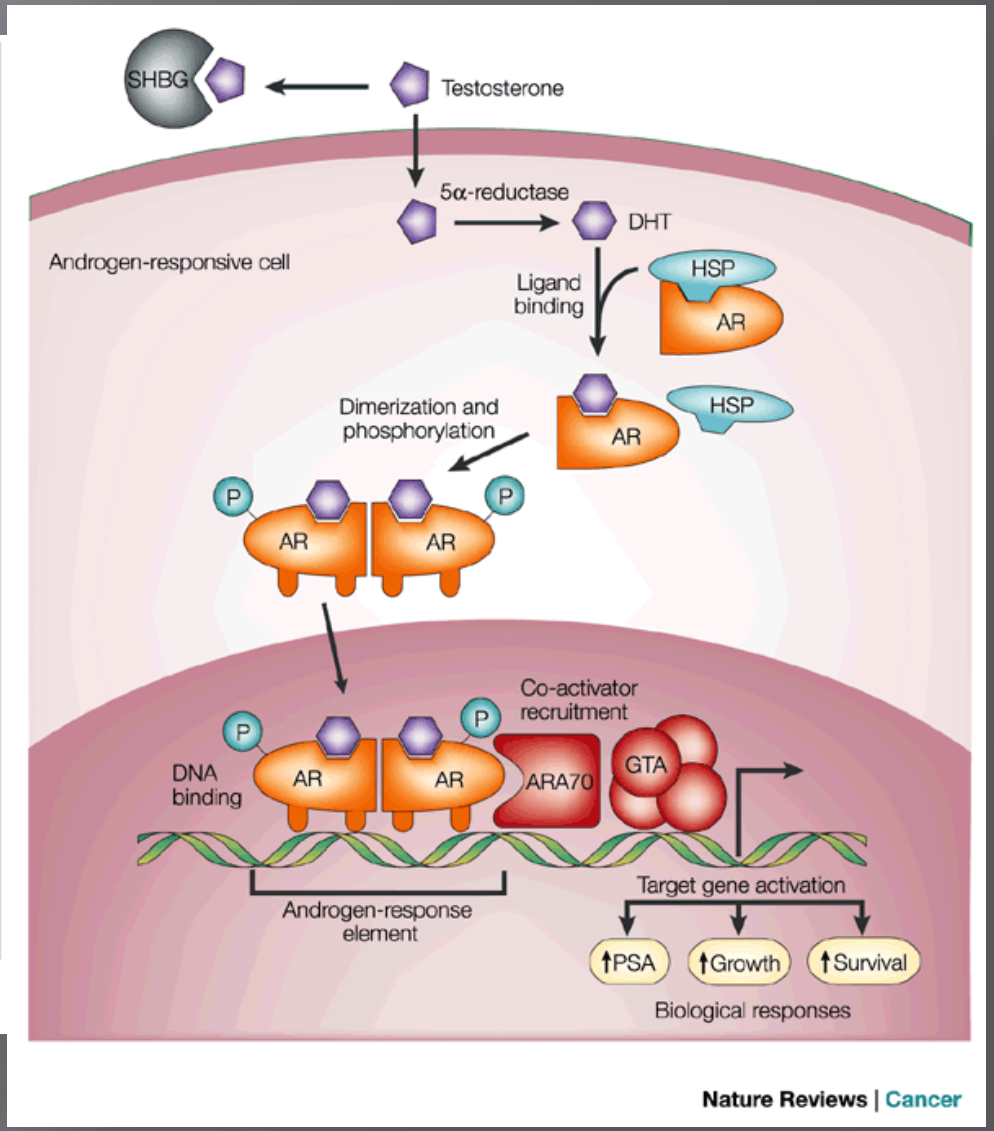


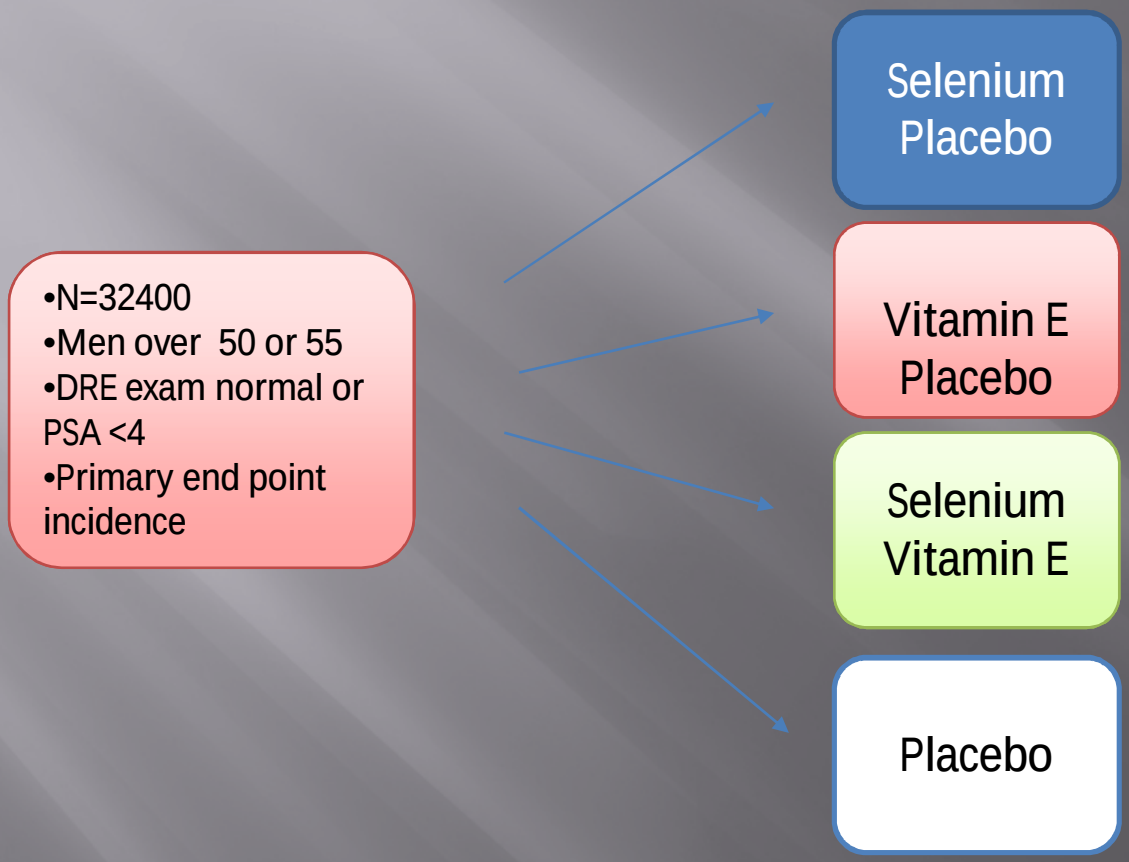
Figure 1. Hypothalamic-pituitary-testicular axis. DHT: dihydrotestosterone; 5-AR: 5-alpha reductase; LH: luteinizing hormone; LHRH: LH-releasing hormone.



3 large scale trials for prostate cancer

- SELECT
  - Selenium or vitamin E
- PCPT
  - Finasteride
- REDUCE
  - Dutasteride
- And smaller trials

SELECT trial



For 7-12 years

JAMA 2008; **301: 39**.

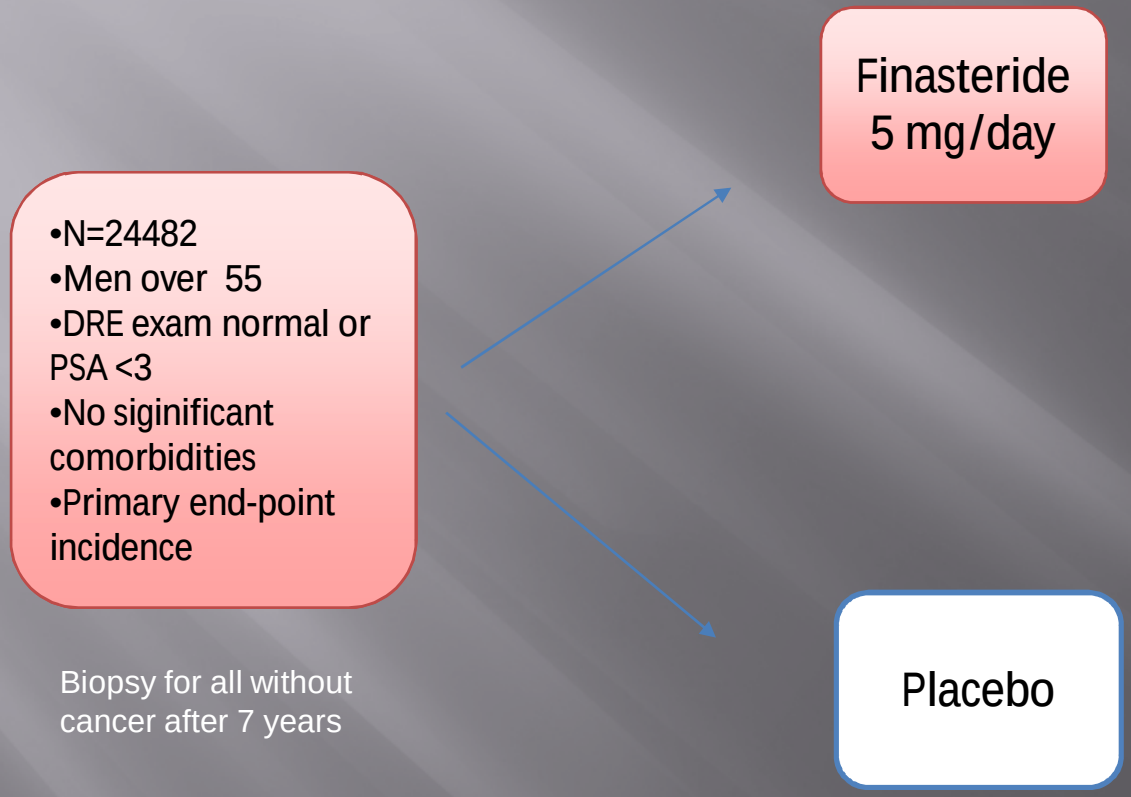
SELECT Trial

- Early stopped in 2008 by DSMC after second formal interim analysis
- No benefit
- No harm
  - Non-significant increased risk of DM
  - Slight increase in prostate cancer in subjects taking Vitamin E

JAMA 2008; **301: 39.**

PCPT trial

Type 2 5 alpha reductase inhibitor finasteride



For 7-12 years

N Engl J Med 2003; **349: 215.**

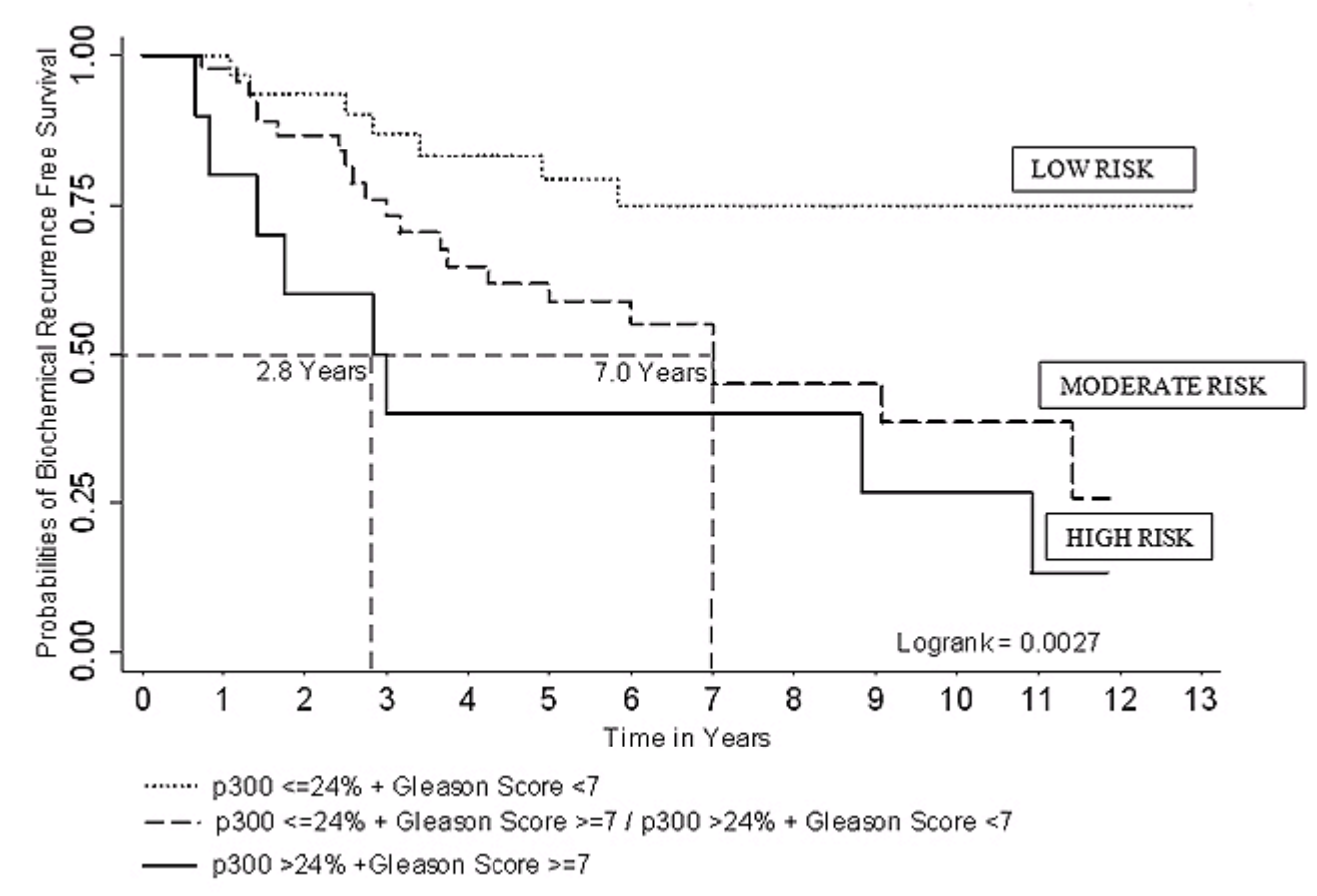
PCPTtrial

DSMC stopped it early in 2003

- It reached the primary end point after 9000 men
- 20% did not have biopsy
- About 25% risk reduction (p<0.001) with finasteride
- More high risk cancer (+15%) in finasteride arm
- Toxicity
  - More discontinuation in finasteride arm
  - More side effects in finasteride arm
  - More sexual problems
  - Prostatism symptoms were less

N Engl J Med 2003; **349: 215**.

Risk of reccurrence by Gleason Score



PCPT Trial Analysis
If those with PSA ≥ 2 taken

RISK REDUCTION BY PSA

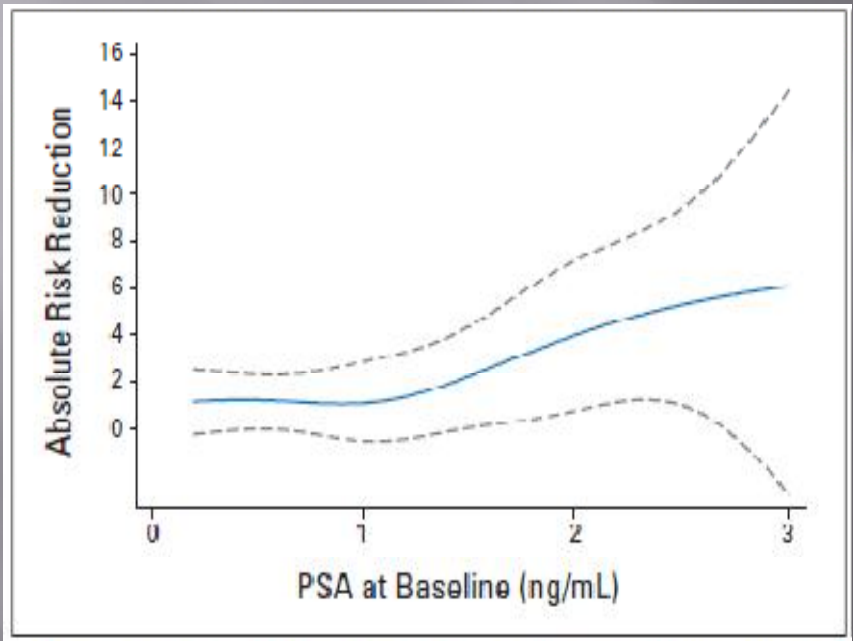
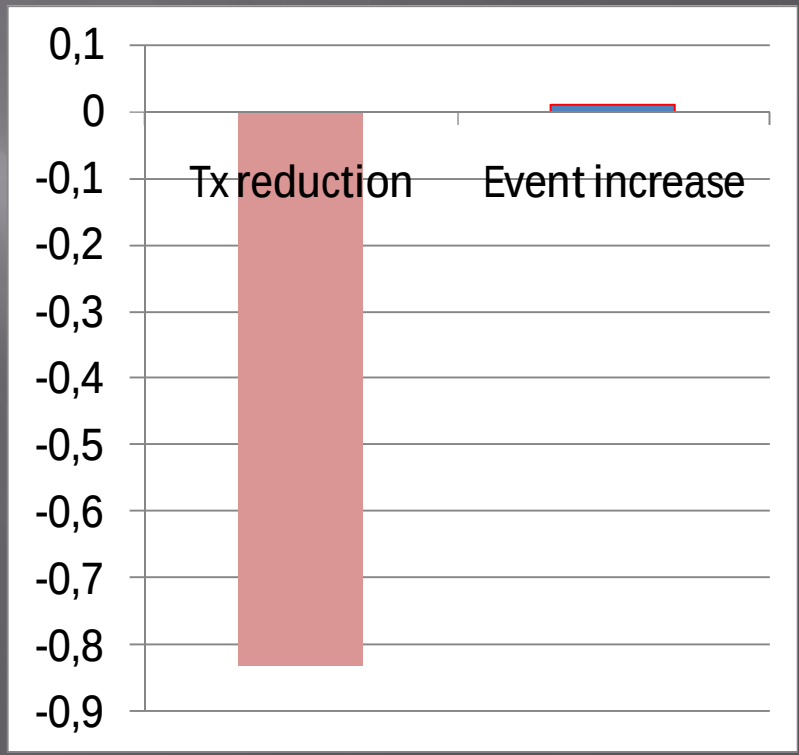


Fig 2. Absolute risk reduction of for-cause–detected cancers between placebo and finasteride groups predicted by prostate-specific antigen (PSA) at baseline.

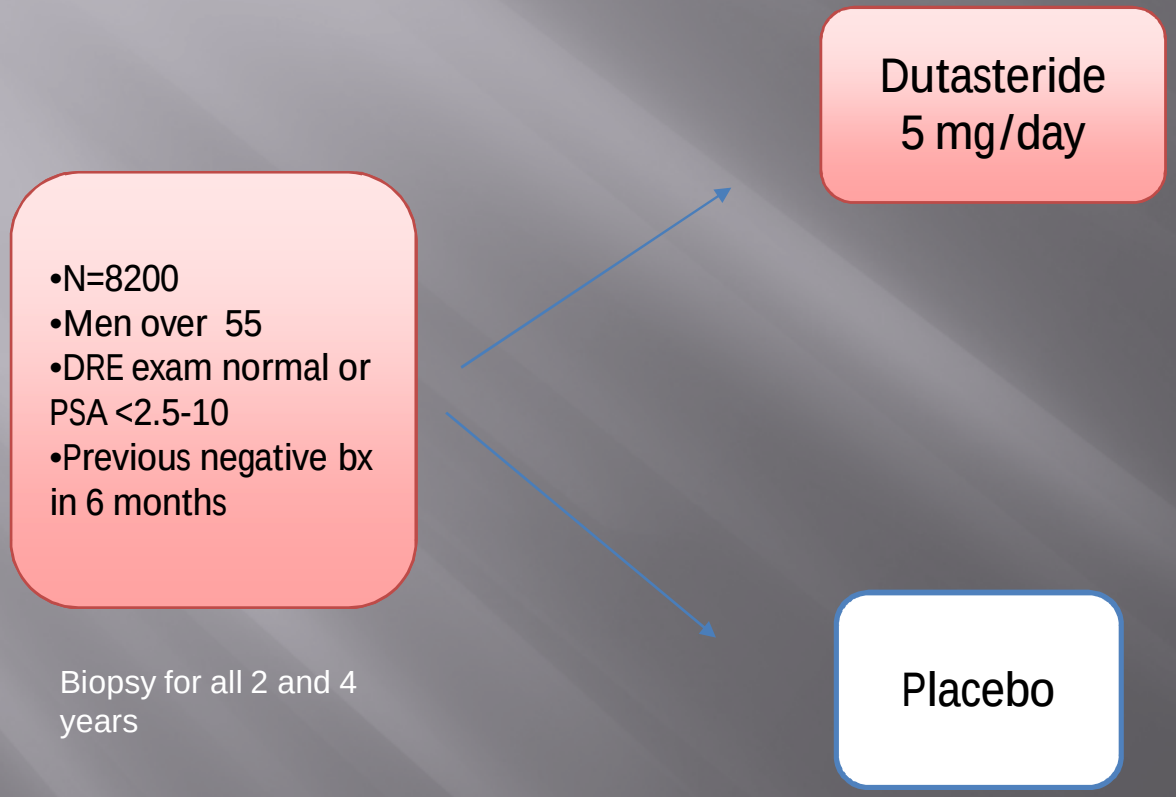
PSA ≥ 2 INDIVIDUALS TAKEN



Published Ahead of Print on February 1, 2010 as 10.1200/JCO.2009.23.5572

REDUCE trial

Type 2 5 alpha reductase inhibitor finasteride



For 4 years

REDUCE
Results

- 23% reduction in prostate cancer incidence
- No increase in high grade disease

Use of 5-α-Reductase Inhibitors for Prostate Cancer Chemoprevention: American Society of Clinical Oncology/ American Urological Association 2008 Clinical Practice Guideline

Barnett S. Kramer, Karen L. Hagerty, Stewart Justman, Mark R. Somerfield, Peter C. Albertsen, William J. Blot, H. Ballentine Carter, Joseph P. Costantino, Jonathan I. Epstein, Paul A. Godley, Russell P. Harris, Timothy J. Wilt, Janet Wittes, Robin Zon, and Paul Schellhammer

A B S T R A C T

Purpose
To develop an evidence-based guideline on the use of 5-α-reductase inhibitors (5-ARIs) for prostate cancer chemoprevention.

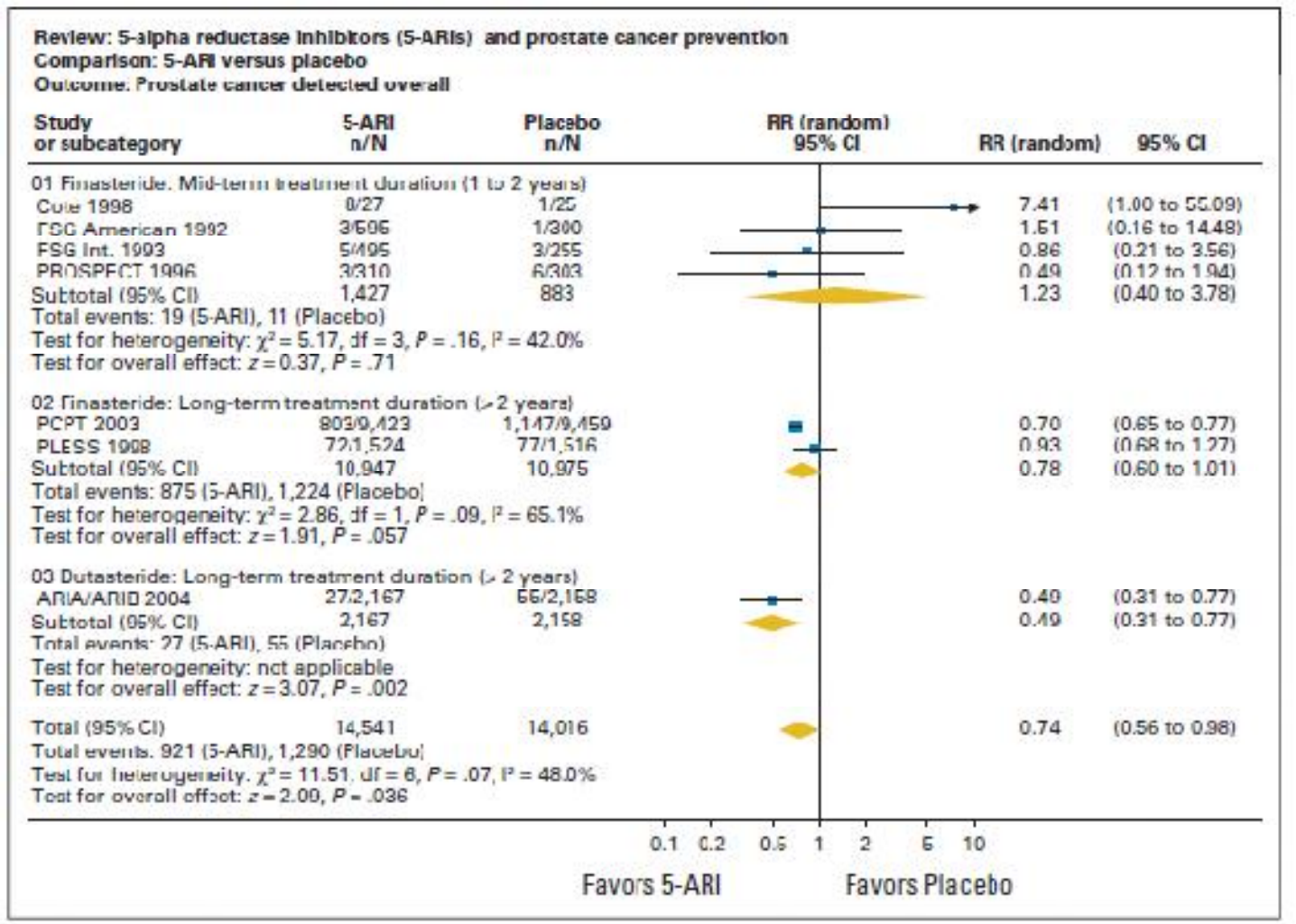
Methods
The American Society of Clinical Oncology (ASCO) Health Services Committee (HSC), ASCO Cancer Prevention Committee, and the American Urological Association Practice Guidelines Committee jointly convened a Panel of experts, who used the results from a systematic review of the literature to develop evidence-based recommendations on the use of 5-ARIs for prostate cancer chemoprevention.

Results
The systematic review completed for this guideline identified 15 randomized clinical trials that met the inclusion criteria, nine of which reported prostate cancer period prevalence.

Conclusion
Asymptomatic men with a prostate-specific antigen (PSA) ≤ 3.0 ng/mL who are regularly screened with PSA or are anticipating undergoing annual PSA screening for early detection of prostate cancer may benefit from a discussion of both the benefits of 5-ARIs for 7 years for the prevention of prostate cancer and the potential risks (including the possibility of high-grade prostate cancer). Men who are taking 5-ARIs for benign conditions such as lower urinary tract [obstructive] symptoms (LUTS) may benefit from a similar discussion, understanding that the improvement of LUTS relief should be weighed with the potential risks of high-grade prostate cancer from 5-ARIs (although the majority of the Panel members judged the latter risk to be unlikely). A reduction of approximately 50% in PSA by 12 months is expected in men taking a 5-ARI; however, because these changes in PSA may vary across men, and within individual men over time, the Panel cannot recommend a specific cut point to trigger a biopsy for men taking a 5-ARI. No specific cut point or change in PSA has been prospectively validated in men taking a 5-ARI.

J Clin Oncol 27:1502-1516. This guideline was developed through a collaboration between the American Society of Clinical Oncology and the American Urological Association and has been published jointly by invitation and consent in both the Journal of Clinical Oncology and Journal of Urology.

Meta-analysis



J Clin Oncol 2009; 27: 1502-1516

Small Trials for chemoprevention

- Supplement (Soy, isoflavones, lycopene, slymarin, antioxidant) after curative therapy for rising PSA slowed down the velocity

  Eur Urol. 2005 Dec;48(6):922-30

- Lycopene supplementation before surgery had positive effects on pathological correlates
  - Ömer Küçük, Exp Biol Med (Maywood). 2002 Nov;227(10):881-5
- Tomato products and soy protein had decreased PSA

  Nutr Cancer. 2008;60(2):145-54

Prostate cancer chemoprevention Concerns

- Alpha reductase inhibitors may reduce clinically insignificant (nonlethal, not requiring therapy) cancers in 34%
- No data to show reduction in the incidence clinically significant lethal cancers, or mortality from prostate cancer
- Question of increased rate of high grade neoplasia remains

The Question

So What?

Should I prescribe chemopreventive agents for “head and neck cancer and prostatic adenocarcinoma?

Head and Neck Cancer

NO

No trial provided conclusive evidence to support to use chemoprevention!

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Use of 5-α-Reductase Inhibitors for Prostate Cancer Chemoprevention: American Society of Clinical Oncology/ American Urological Association 2008 Clinical Practice Guideline

Barnett S. Kramer, Karen L. Hagerty, Stewart Justman, Mark R. Somerfield, Peter C. Albertsen, William J. Blot, H. Ballentine Carter, Joseph P. Costantino, Jonathan I. Epstein, Paul A. Godley, Russell P. Harris, Timothy J. Wilt, Janet Wittes, Robin Zon, and Paul Schellhammer

In summary, it is recommended that the physician:

1. inform the man who is considering a 5-ARI that these agents reduce the incidence of prostate cancer, and be sure to be clear that these agents do not reduce the risk of prostate cancer to zero;
2. discuss the elevated rate of high-grade cancer observed in the PCPT and inform men of the potential explanations;
3. make it known to men that no information on the long-term effects of 5-ARIs on prostate cancer incidence exists beyond approximately 7 years, and that whether or not a 5-ARI reduces prostate cancer mortality or increases life expectancy remains unknown;
4. inform men of possible but reversible sexual adverse effects; and
5. inform men of the likely improvement in lower urinary tract symptoms.

Prostate Cancer

- Alpha reductase inhibitors significantly reduced invasive cancer
- High grade cancer (the lethal one) may be increased
- Even early detection with PSA screening failed to show mortality reduction recently and is not recommended routinely

Prostate Cancer Chemoprevention

NO

No trial provided conclusive evidence to support to use chemoprevention!


THANK YOU