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
Cancerogenesis is a genetic process

- 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.
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 Assessment
  - Risk Benefit ratio
### Examples of Intraepithelial Neoplasias

<table>
<thead>
<tr>
<th>Epithelium</th>
<th>Intraepithelial Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon and rectum</td>
<td>Adenoma</td>
</tr>
<tr>
<td>Lower esophagus</td>
<td>Barrett's esophagus</td>
</tr>
<tr>
<td>Upper esophagus</td>
<td>Squamous dysplasia</td>
</tr>
<tr>
<td>Skin-squamous/basal cell</td>
<td>Actinic keratosis</td>
</tr>
<tr>
<td>Skin-pigmented</td>
<td>Dysplastic nevus</td>
</tr>
<tr>
<td>Cervix</td>
<td>Cervical intraepithelial neoplasia</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Leukoplakia</td>
</tr>
<tr>
<td>Lung</td>
<td>Bronchial dysplasia</td>
</tr>
</tbody>
</table>
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
• Premalignant Lesion
  – Leukoplakia
  – Advanced
    • Erythroleukoplakia
    • Dysplastic leukoplakia
• One of most studied disease for chemoprevention
Top 10 Cancers in Türkiye

Kanserle Savaş Daire Başkanlığı 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
Head Neck Cancer trials
Chemoprevention

Naturaly 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

- Before HN Cancer
  - 5 trials

- After HN and Lung Cancer
  - 4 trials

secondary chemo-prevention
tertiary chemo-prevention
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 significant response rates

Uptodate 2009
**Beta Carotene**

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

Vitamin A versus B Carotene versus Placebo
A randomized trial

N=160 fishermen and women with precancerous cancers

Vitamin A
300,000 U/week for 1 year

Beta Carotene
360 mg/week for 1 year

Placebo

Vitamin A versus B Carotene versus Placebo

Results

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

Synthetic retinoids

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

High Dose Isotretinoin versus placebo
Randomized trial

N=44, precancerous lesions

Isotretinoin 1-2 mg/kg for 3 months

Placebo

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

High Dose Isotretinoin versus placebo
Randomized trial-results

**RESPONSES**

<table>
<thead>
<tr>
<th>(%)</th>
<th>Reversal of dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td></td>
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<tr>
<td>60</td>
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<tr>
<td>50</td>
<td></td>
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<tr>
<td>40</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**TOXICITY**

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

Maintanence after a high dose induction
Randomized trial

N=70, leukoplakia

Isotretinoin 1,5 mg/kg
3 months

R

Isotretinoin 0,5 mg/kg

Beta Carotene 30 mg/day year
9 months

Maintainence after a high dose induction
Randomized trial

CONTINUED RESPONSE

TOXICITY

- Generally mild
- More with isotretinoin

Head and neck cancer
Secondary prevention trials summary

• Small trials
• They (vitamin A, beta coretene, isotretinoin) work
  – In under-developed nations with vitamin deficiencies??
• Isotretinoinin 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 Cancer after curative therapy
- Isotretinoin (50-100 mg/ m2) vs placebo for 12 months
- No impact on loco-regional or distant relapses
- Significantly fewer new aerodigestive cancers (4 vs. 24)
- High toxicity
- High drop out rate

Euroscan trial
EORTC

N=2592 with (HN: 60%, lung 40%) cancers

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

EORTC trial
over all survival

NCI C91-002

- N=1190 with localized HN

• Isotretinoin 30 mg for 3 years
• Placebo
• Patients were followed for additional 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

HN cancer
Stage 1 and 2
N=540

- Alpha tocopherol (400 U/day)
- Plus
- Beta Carotene (30 mg/day)
- Placebo

- Supplementation 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

Alpha tocopherol and Beta Carotene

## HN Cancer Trials Summary

### Table 5: Selected Head and Neck Chemoprevention Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Prevention</th>
<th>Population</th>
<th>Endpoint</th>
<th>Compounds*</th>
<th>End Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong et al.</td>
<td>1990</td>
<td>103</td>
<td>Tertiary</td>
<td>Prior HNSCC</td>
<td>Recurrence</td>
<td>Isotretinoin (50 to 200 mg/m²)</td>
<td>Positive</td>
</tr>
<tr>
<td>EUROSCAN</td>
<td>2000</td>
<td>2,592</td>
<td>Tertiary</td>
<td>Prior lung or HNSCC</td>
<td>Survival</td>
<td>Retinyl palmitate (300,000 IU)** N-Acetylcysteine (600 mg)</td>
<td>Negative††</td>
</tr>
<tr>
<td>Bolla et al.</td>
<td>1994</td>
<td>316</td>
<td>Tertiary</td>
<td>Prior early-stage oral/oropharynx cancer</td>
<td>Survival</td>
<td>Etilinate (50 mg for one month, then 25 mg for 24 months)</td>
<td>Negative</td>
</tr>
<tr>
<td>NCI C91-002</td>
<td>2003</td>
<td>1,384</td>
<td>Tertiary</td>
<td>Prior Stage I-II HNSCC</td>
<td>Survival</td>
<td>Isotretinoin (30 mg)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

### Biochemoprevention for Advanced Premalignant Lesions

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Prevention</th>
<th>Response</th>
<th>Compounds*</th>
<th>End Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papadimitrakopoulou et al.</td>
<td>1999</td>
<td>36</td>
<td>Secondary</td>
<td>Advanced dysplasia</td>
<td>Interferon-α (3 MU/m² twice weekly) α-Tocopherol (1200 IU) Isotretinoin (100 mg/m²)</td>
<td>Positive for laryngeal lesions but not oral</td>
</tr>
<tr>
<td>Shin et al.</td>
<td>2001</td>
<td>44</td>
<td>Tertiary</td>
<td>Prior head and neck cancer</td>
<td>Survival</td>
<td>Interferon-α (3 MU/m² three times weekly) α-Tocopherol (1200 IU) Isotretinoin (50 mg/m²)</td>
</tr>
</tbody>
</table>

*Compounds indicated with †, ‡, ††, ‡‡ are not discussed in the text.

**Retinyl palmitate is not discussed in the text.

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Before invasive cancer

Positive, but at high doses with toxicity

Negative

After invasive cancer

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 observed 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 mortality 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 Türkiye

Kanserle Savaş Daire Başkanlığı Web Site, accessed on January 15th, 2010
Prostate Cancer Pathophysiology

Normal Prostate
- Columnar cells

Proliferative Inflammatory Atrophy
- Basal cells
- Inflammatory cells

Prostatic Intraepithelial Neoplasia

Prostate Cancer
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

- N=32400
- Men over 50 or 55
- DRE exam normal or PSA <4
- Primary end point incidence

- Selenium
- Placebo
- Vitamin E
- Placebo
- Selenium
- Vitamin E
- Placebo

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

- N=24482
- Men over 55
- DRE exam normal or PSA <3
- No significant comorbidities
- Primary end-point incidence

Biopsy for all without cancer after 7 years

Finasteride 5 mg/day

Placebo

For 7-12 years

PCPT Trial
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

Risk of recurrence by Gleason Score

![Graph showing probabilities of biochemical recurrence free survival over time in years for different Gleason scores and PCa scores.

Legend:
- p300 <=24% + Gleason Score <7
- p300 <=24% + Gleason Score >=7 / p300 >24% + Gleason Score <7
- p300 >24% +Gleason Score >=7

Key:
- Low Risk
- Moderate Risk
- High Risk

Logrank = 0.0027

Time in Years
PCPT Trial Analysis
If those with PSA ≥ 2 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

- **N=8200**
- Men over 55
- DRE exam normal or PSA <2.5-10
- Previous negative bx in 6 months

Dutasteride 5 mg/day

Placebo

Biopsy for all 2 and 4 years

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


ABSTRACT

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. Copyright © 2009 American Society of Clinical Oncology and American Urological Association. All rights reserved. No part of this document may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without written permission by the American Society of Clinical Oncology or the American Urological Association.
### Meta-analysis

#### Comparison: 5-ARI versus Placebo

<table>
<thead>
<tr>
<th>01 Finasteride: Mid-term treatment duration (1 to 2 years)</th>
<th>02 Dutasteride: Long-term treatment duration (1 to 2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Subgroup</strong></td>
</tr>
<tr>
<td>ADT int. 1003</td>
<td>425</td>
</tr>
<tr>
<td>placebo</td>
<td>2,167</td>
</tr>
</tbody>
</table>

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**Note:** The above table and diagram are part of a meta-analysis comparing the efficacy of 5-ARI (5-alpha reductase inhibitors) versus placebo in the context of prostate cancer prevention. The outcomes are presented in terms of relative risk (RR) with 95% confidence intervals (CI) and statistical tests for heterogeneity and overall effect. The data are derived from various clinical trials, as indicated by the study labels (01, 02, ADT int. 1003, placebo).
Small Trials for chemoprevention

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

- Lycopene supplementation before surgery had positive effects on pathological correlates
  

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


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 reduce 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 trial provided conclusive evidence to support to use chemoprevention!
THANK YOU