

Updates in Cancer Prevention: *What's New*

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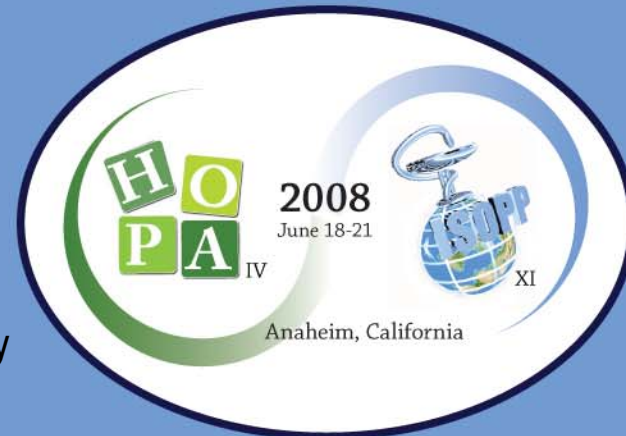
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Disclosure

- Judith Smith, PharmD, FCCP, BCOP has no real or apparent conflicts of interest to report

Learning Objectives

- Identify key characteristics for selection of optimal cancer prevention interventions
- Define and differentiate between prevention and screening for cancer
- Compare and contrast the benefits and concerns with cancer prevention interventions

Background
Where we have been

What is Cancer Prevention?

- To keep from happening or existing
 - Interventions:
 - Reduction in carcinogen exposure
 - Screening
 - Chemoprevention

Cancer Prevention

- Reduction in carcinogen exposure
 - Lifestyle choices
 - Tobacco cessation
 - Diet and exercise
 - Limit alcohol intake
 - Avoid unprotected exposure to sunlight
 - Reduce environmental exposures
 - Regular health check-ups

Cancer Prevention

■ Primary Prevention

● Prophylactic Surgeries

- Generally recommended for “high risk” populations only with family history
 - Oophorectomies
 - Tubal Ligation
 - Mastectomy

Cancer Prevention

- Cancer Screening Program:
 - High coverage of population at risk
 - Screen with accurate test
 - PAP smears
 - Mammograms
 - Colonoscopy
 - Skin exams
 - Ensure proper follow up and treatment for patients with positive test results

Cancer Prevention

- Chemoprevention

- Micronutrients/drugs used to prevent or delay the development of cancer in healthy population

- Delay or reverse carcinogenesis

- Initiation
- Promotion
- Progression

- Healthy population

- Significant toxicities not acceptable

Cancer Prevention Strategies

Chemoprevention

■ **Micronutrients**

- Folic acid
- Ascorbic acid
- Indole-3-carbinole
- Alpha-tocopherol
- Beta-carotene

■ **Drugs**

- Celecoxib
- Aspirin
- NSAIDs
- Finasteride
- Tamoxifen
- Oral contraceptives

***What's New in
Cancer Prevention***

Cancer Screening Guidelines

Updated Screening Guidelines

Colon Cancer

- American Cancer Society, US Multi-Society Task Force on Colorectal Cancer and American College of Radiology 2008 Consensus Guideline:
 - Annual fecal occult blood tests
 - 2 to 3 samples from consecutive bowel movements evaluated by gFOBT or FIT
 - Tests for detection of adenomas and CRC
 - Flexible sigmoidoscopy (FSIG) (every 5 years)
 - Double contrast barium enema (DCBE) (every 5 years)
 - CT-colonography (CTC) (every 5 years)
 - Colonoscopy (every 10 years)
 - Follow test for any abnormal results from FSIG, DCBE, or CTC

Updated Screening Guidelines

Prostate Cancer

- NCCN Guidelines:
 - Offer baseline DRE and PSA at age 40
 - If no risk, repeat every 5 years
 - Offer annual screening after age 50
 - African American or Family history need annual follow up
 - Digital rectal exam and PSA
 - Selective screening in men over age 80

- The Iowa Prostate Cancer Screening Consensus 2008:
 - Men > 75 years with caution
 - Family history
 - > 10 year expectancy
 - PSA done selectively
 - Age-based values
 - Discontinue screening in men > 75 years if:
 - Life expectancy of 5 to 10 years
 - Many co-morbidities

Updated Screening Guidelines

Prostate Cancer

- European Association of Urology Guidelines on Prostate Cancer:
 - Cannot support or discard population-based screening
 - Less controversial and widely used in clinical practice to screen well-informed patients
 - Digital rectal exam with PSA level

Updated Screening Guidelines

Breast Cancer

- ACS, NCI and NCCN Guidelines
 - Annual Mammogram
 - Changed from 50 to 40 years of age now in all women with normal risk
 - NCCN 2008 Guidelines:
 - Addition of MRI for screening tool in women at increased risk
 - BRCA mutation
 - First degree relative of BRCA carrier, but untested
 - Lifetime risk ~20-25% or >, as defined by BRCAPRO or other methods that are largely dependent on family history

Updated Screening Guidelines

Cervical Cancer

	ACOG	ACS
When to begin	3 years following onset of sexual activity, or age 21, whichever occurs first	
How often	Younger than 30 – annual Pap	Annually until 30. Every 2 years with liquid based techniques.
	Older than 30, Pap and HPV DNA every 3 years	
	If older than 30 with 3 negative cytologies, switch to every 2 years	
When to discontinue	Evidence inconclusive to establish upper age limit	70 yoa with 3 or more normal tests, and no abnormal tests in previous 10 years

Cox T. *Obstetrical and Gynecological Survey*. 2006;61:S15-S25.

Smith, R, et al. *CA A Cancer Journal for Clinicians*. 2007;57:90-104.

***Chemoprevention
Drugs***

Chemoprevention

Breast Cancer - Vogel et al

■ STAR trial, P2

● Study Design:

- Prospective, double-blind, randomized, multicenter trial

● Objective:

- To compare the relative effects and safety of raloxifene and tamoxifen on the risk of developing invasive breast cancer and other disease outcomes

● Inclusion criteria:

- 5-yr predicted breast cancer risk of 1.66% (based on the Gail model) \geq 35 yrs of age and postmenopausal

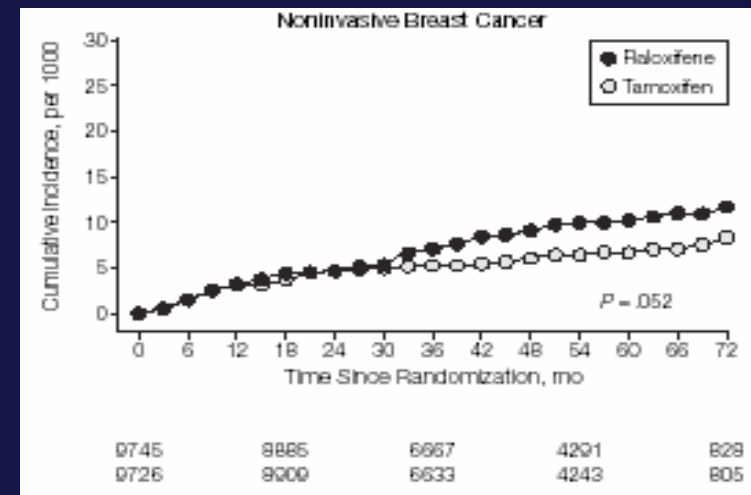
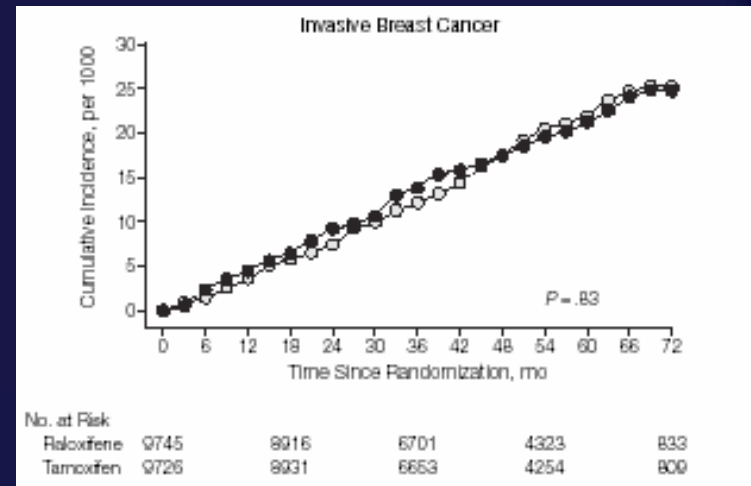
● Intervention:

- Tamoxifen 20 mg daily or raloxifene 60 mg daily x 5 yrs

Chemoprevention

Breast Cancer - Vogel et al

- Conclusion:
 - Raloxifene is as effective as tamoxifen in reducing risk of invasive breast cancer
 - Raloxifene has lower risk of thromboembolic events and cataracts compared to tamoxifen
 - Raloxifene has a non-statistically significant higher risk of noninvasive cancers



Chemoprevention

Breast Cancer - Fabian et al

■ Study Design:

- Multicenter, randomized, Phase I A/B study

■ Objective:

- Evaluate arzoxifene for prevention of breast cancer recurrence

■ Inclusion criteria:

- DCIS/ T1-T2 invasive cancers
- Pre and post menopausal women
- Likely to be ER+ or PR+
- HRT allowed prior to study entry

Chemoprevention

Breast Cancer - Fabian et al

■ Intervention:

- Phase IA
 - Randomized to arzoxifene 10, 20, or 50 mg/day x 6 weeks
 - Non-randomized no treatment controls
- Phase IB
 - Randomized to arzoxifene 20 mg/day or placebo x 6 weeks

■ Study Main Endpoint:

- Cell proliferation (Ki-67/PCNA)

■ Secondary endpoints:

- Tissue: Inhibition of ER, PR, EGFR, Her-2/*neu*, p53 expression
- Serum: Decrease levels of IGF-1, IGFBP-3, estradiol, progesterone, estrone, FSH < LH, SHBG, TBG

Chemoprevention

Breast Cancer - Fabian et al

■ Results:

- Decrease proliferations optimal at arzoxifene 20 mg/day
- Statistically significant decrease in ER expression compared to placebo
- Statistically significant decrease in insulin-like growth factor (IGF)-I ($p < 0.007$)

■ Conclusion:

- Favorable biomarker modulation
- Reasonable candidate for additional evaluation

Chemoprevention

Colon Cancer - Chan et al

- Long-term use of ASA and NSAIDs and risk of colon cancer
 - **Study Design:**
 - Prospective cohort study
 - **Objective:**
 - To examine the influence of aspirin and NSAIDs in the prevention of colorectal cancer
 - **Inclusion criteria:**
 - Women enrolled in the Nurses' Health Study
 - **Intervention:**
 - Standard ASA (325 mg) or non-ASA NSAID

Chemoprevention

Colon Cancer - Chan et al

■ Results:

- 82, 911 women over a 20-yr period
- 962 documented cases of colorectal cancer
- Relative Risk reductions
 - 0.77 (95%, CI 0.67-0.88) in regular users (> 2 tablets/week)
 - 5 years of use – no risk reduction:
 - RR= 1.04 (95%;CI0.88-1.24)
 - 10 years of use – significant benefit:
 - RR=0.67 (95% 0.54-0.85, $p < 0.001$)
 - 20 years of use- no additional benefit:
 - RR 0.68 (95%, CI 0.54-0.85)

Chemoprevention

Colon Cancer - Chan et al

■ **Conclusions:**

- Regular, long term aspirin use reduces the risk of colorectal cancer
- Non-aspirin NSAIDs appear to have a similar effect
- Significant effect from aspirin not seen until after 10 yrs of use, with maximal risk reduction at doses > 14 tablets / week

Chemoprevention

Colon Cancer - Alberts et al

■ Study Design:

- Double-blind, randomized, placebo-controlled trial

■ Objective:

- To test efficacy of ursodeoxycholic acid (UDCA) to prevent recurrence of colorectal adenomas.

■ Inclusion criteria:

- Removal of one or more colorectal adenomas (> 3 mm) within 6 months
- Between ages 40 to 80 years

■ Intervention:

- Randomized to:
 - UDCA 8-10 mg/kg (rounded to nearest 300 mg dose)
 - Matched placebo

Chemoprevention

Colon Cancer - Alberts et al

■ Results:

- 12% reduction in adenoma recurrence rate in UDCA treated patients
- Risk ratio for adenoma recurrence was 0.93 (95%, CI, 0.82 to 1.07) for the UDCA group
- UDCA group had 39% reduction in the incidence of high-grade dysplasia compare to placebo

■ Conclusion

- Observed statistically significant improvement in high- grade dysplasia
- Further chemoprevention trials of UDCA warranted

Chemoprevention

Prostate Cancer - Andriole et al

- REDUCE trial- *ongoing study*
 - **Study Design:**
 - International, multicenter, randomized, double-blind, placebo controlled, parallel group study
 - **Objective:**
 - To evaluate the efficacy and safety of oral once daily dutasteride in men at increased risk for prostate cancer
 - **Inclusion criteria:**
 - Men at increased risk for prostate cancer with no evidence of disease at baseline
 - Age 50 to 75 years
 - PSA between 2.5 to 10 ng/mL if 50 to 60 years or 3.0 to 10 ng/mL if > 60 years
 - **Intervention:**
 - Dutasteride 0.5 mg once daily x 4 years (or placebo)

Chemoprevention
Micronutrients

Antioxidants

■ History

- ATBC trial (*lung cancer prevention study*)
 - **Study design:** Randomized, double-blind, placebo-controlled, multicenter trial
 - **Objective:** To determine whether daily supplementation with alpha-tocopherol, beta carotene, or both will reduce the incidence of lung cancer
 - **Inclusion:** Male smokers aged 50-69
 - **Intervention:** Placebo, alpha-tocopherol 50 mg daily, beta-carotene 20 mg daily, or the combination daily x 5-8 yrs
 - **Outcome:**
 - Lung cancer not prevented by alpha-tocopherol
 - Lung cancer rates **INCREASED by 18%** in patients taking beta-carotene

Antioxidants

■ History

- CARET trial (*lung cancer prevention study*)
 - **Study design:** Randomized, double-blind, placebo-controlled trial
 - **Objective:** To determine whether daily supplementation with alpha-tocopherol, beta carotene, or both will reduce the incidence of lung cancer
 - **Inclusion:** asbestos-exposed workers 45-69 years OR Male smokers aged 50-69
 - **Intervention:** Placebo, alpha-tocopherol 50 mg daily, beta-carotene 20 mg daily, or the combination daily x 5-8 yrs
 - **Outcome:**
 - 28% increase incidence in lung cancer with beta-carotene vs. placebo
 - 17% more deaths with beta-carotene vs. placebo

Antioxidants

New Data - Head and Neck Cancers

- Toma et. al.
 - Study Design
 - Randomized study to evaluate 13-cis retinoic acid (13-cRA) alone or in combination with interferon a 2a (IFN-a2a)
 - Objective:
 - Determine if 13-cRA +/- IFN a2a improved relapse free survival and reduction of second malignancies.
 - Inclusion:
 - 18-75 years with documented III-IV HNSC achieving a CR to first-line treatment.

Antioxidants

New Data - Head and Neck Cancers

- Toma et. al.
 - Intervention:
 - 13-cRA 0.5 mg/kg/day alone or in combination with interferon 3,000,000 units IM TIW
 - Control (no treatment)
 - Results:
 - 126 patients in each group
 - 5 year survival 58.9% in 13-cRA compared to 57.2% in control group (p=0.94)
 - 5 year relapse rate was 55.6% in 13-cRA group compared to 48.9% in control group (p=0.62)
 - Conclusion:
 - 13-cRA ineffective as chemoprevention agent in HNSCC patients achieving CR to first line treatment
 - Confirmed in similar study by Perry et. al.

Antioxidants

New Data - Head and Neck Cancers

- Bairati et. al.
 - Study design: multicenter, double-blind, randomized, placebo controlled study
 - 540 patients with hx of stage I or II HNSCC
 - Supplementation with α -tocopherol (400 IU/day) and β -carotene (30 mg/day) x 52 months follow up
 - β -carotene stopped after enrollment for ethical concerns
 - Results:
 - During Supplementation period
 - α -tocopherol had higher rate second primary cancers (HR 2.88, 95%, CI 1.56-5.31)
 - α -tocopherol had higher rate recurrence (HR 1.86, 95%, CI 1.27-2.72)
 - Similar rates after supplementation discontinued
 - Conclusion: unexpected adverse effects of α -tocopherol on occurrence of second primary cancers and on cancer-free survival

Antioxidants

New Data - Prostate Cancer

■ SU.VI.MAX trial

- Study of 5,141 men randomized to take
 - Placebo or
 - Supplementation with capsule containing: Vitamin C 120 mg, α -tocopherol 30 mg, β -carotene 6 mg, selenium 100 μ g and zinc 20 mg daily
- 8 year follow up
- PSA and IGF monitored at baseline and follow up
- Endpoint: Incidence of prostate cancer

Antioxidants

New Data - Prostate Cancer

■ SU.VI.MAX trial

● Results:

- Overall moderate insignificant reduction in prostate cancer rate
- In men with normal baseline PSA (< 3 ng/mL)
 - HR = 0.52 (95%, CI= 0.29-0.92), p =0.009
- In men with elevated PSA at baseline
 - HR =1.54 (95%, CI=0.87-2.72), NS

● Conclusion:

- Supplementation may have beneficial effects, however patient selection important
 - In patients with pre-existing, not diagnosed cancer could increase risk

Primary Prevention
Cervical Cancer Vaccine

Primary Prevention

Prophylactic HPV Vaccines

■ Merck

- Recombinant L1 proteins using yeast
- 100% effective in preventing persistent HPV infection

■ Gardasil[®] (Merck & Co., Inc.)

- Quadrivalent Human Papillomavirus Vaccine
- Prepared from VLP of HPV types 6,11,16,18
- FDA approval June 2006

■ GSK

- Recombinant L1 proteins using baculovirus
- 100% effective in preventing persistent HPV infection

■ Cervarix[®] (GlaxoSmithKline)

- Protects against HPV types 16,18
- Phase III trials ongoing
- Anticipate approval in Spring 2008

Approval Clinical Trial -Gardasil®

Villa Trial – Preliminary Report

- Phase II RCT of quadrivalent vaccine (HPV types 6,11,16,18) vs placebo
- Females aged 16-23 from US, Brazil, Europe
 - 275 each received placebo or vaccine
 - Women with previous HPV infection not excluded
 - Followup 30 months
- Primary endpoints
 - Persistent infection with HPV 6,11,16,18
 - At 7 months, same HPV as next 2 visits (4 months apart)
 - 90% reduction in HPV persistent infection
 - 4 cases in vaccine group
 - 35 in placebo group

Approval Clinical Trial -Gardasil®

Limitations

- Immunogenicity reported at month 7 only
- Level of HPV antibodies that would provide protection against infection has not been defined
- HPV status not determined at baseline
- When events occurred not reported
- Large number of exclusions for HPV infection
- Designed to measure persistent HPV infection
 - Follow-up 30 months
 - Trial length insufficient to measure rate of progression to cervical cancer

Approval Clinical Trial -Gardasil®

Villa et al. - Five-year follow-up

- 18-month gap between end of Phase I and initiation of extension
- US participants in Phase I not included in extension
- Low participation
 - 47% of those completing initial (36 month efficacy evaluation)
- No new cases of HPV 16 or HPV 18 reported at month 54
- 2 of 3 HPV 16 cases at month 36 resolved.
 - 1 of 1 HPV 18 case persisted to month 54

Will revaccination be necessary?

- Level of protective antibody reported as geometric mean titer (GMT)
- GMT comparison
 - Vaccine recipients
 - Compared to placebo
 - Seropositive for HPV at baseline

Will revaccination be necessary?

	HPV 6	HPV 11	HPV 16	HPV 18
Month 7	560 31	624 324	3890 42	756 36
Month 36	88 30	78 219	441 21	50 24
Month 60	67 30	67 150	395 16	44 33

Will revaccination be necessary?

	HPV 6	HPV 11	HPV 16	HPV 18
Month 7	560 31	624 324	3890 42	756 36
Month 36	88 30	78 219	441 21	50 24
Month 60	67 30	67 150	395 16	44 33

How will the availability of the vaccine impact screening practices?

- HPV vaccines provide prophylaxis for a small number of known oncogenic types
- Only 70% of cervical cancers associated with HPV 16 or 18
- New screening model has been proposed:
 - Vaccinate females prior to age 12
 - Cytological screening every 3 years at 25

Do vaccinated women still need to be screened for cervical cancer?

■ YES

- Vaccine will NOT protect against all types of HPV that cause cervical cancer.
- If all vaccine doses are not received and/or at the correct intervals (1,2 and 6 months) vaccine is not effective
- Women may not get full benefit, may already be infected with one of the four HPV strains

Conclusions

Cancer Screening

- Emphasize early detection is “key” for prevention
- Cervical cancer screening still required
 - HPV testing after age of 30
- MRI has role for detection in high risk breast cancer patients
- Questionable benefits of continuing prostate cancer screening in men older than 75-80 years of age

Conclusions

Chemoprevention

- Raloxifene alternative to tamoxifen
- ASA/NSAIDs
 - Benefit vs. GI toxicity
- Dutasteride potential benefit over finasteride
- Antioxidants
 - Benefit in healthy patients with no risk factors
 - Potential harmful in patients with pre-existing/undiagnosed cancers!

■ HPV Vaccine

- Gardasil[®] was FDA approved based on efficacy in reduction in persistent HPV infection
- Gardasil[®] and Cervarix[®] are designed to protect against HPV types causing 70% of cervical cancers
- Durations of protection is not yet known.