Chemoprevention in Cervix and Colon Cancer

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Estimated new cases (incidence) and deaths (mortality) worldwide for the 15 most common cancers, 2000

- Lung
- Breast
- Colon/rectum
- Stomach
- Liver
- Prostate
- Cervix uteri
- Oesophagus
- Bladder
- Non-Hodgkin’s lymphoma
- Oral cavity
- Leukaemia
- Pancreas
- Ovary
- Kidney

Parkin et al 2001
PREVENTION

Cancer

Musculo-skeletal Disorders

Neuro-degenerative Diseases

Cardiovascular Disease
What causes cancer?

Familial cancer
- APC
- MYH
- MLH1
- SMAD4
- MSH2
- AXIN2
- MSH6
- LKB1
- BMPR1

Sporadic cancer
- p53
- k-Ras
- c-Myc
- CTTN
- BRAF

MLH1
- ER
- p16
- MGMT
- BAX
- TGFβR1

genes

environment
Understanding Risk
Cancer is a heterogeneous disease

- Who will get pre-malignant lesions?
- Which patients with pre-malignant lesions will develop cancer?
- Is each lesion in a given patient the same type of lesion?
Understanding Risk for Cancer

- Genetics:
  - Family history
  - Genetic testing

- Environment:
  - Toxic exposures
    - Radiation
    - Asbestos

- Lifestyle:
  - tobacco
  - diet
  - exercise

- Personal history:
  - cancer
  - pre-malignant disease
  - chronic inflammatory diseases
Understanding the biology of pre-malignant disease is the key to developing effective prevention methods

- Which individuals are at risk and for what type of cancer?

- What are the best methods of identifying and monitoring pre-malignant disease?

- How can we safely and effectively arrest the progression of pre-malignant disease?
Preventing cancer

• Eliminate or prevent pre-invasive disease before invasion develops

  • General health maintenance
    • Eat a healthy diet
    • Don’t smoke
    • Don’t drink too much
    • Exercise/ maintain optimal weight

• Surgery

• Chemoprevention
Chemoprevention of Cancer

**Definition**
- Chemoprevention is the use of medicines (including vitamins) to prevent disease.
- The term was coined by Sporn in 1976, who defined it as ‘the use of natural, synthetic or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression’.

**Rationale**
- A 15% decrease in epithelial cancers would prevent >100,000 deaths/yr and save $25 billion/yr

**Background**
- Epidemiology
  - Geographic/cultural differences
  - Genetics – 98% malignancies have somatic mutations rather than germ line mutations
  - Association of infections with cancer
Chemoprevention Drug Development

- How development differs from -
  - Cancer Therapy
    - Accepted surrogate of tumor/disease regression
    - Primary goal can be determined relatively quickly

- Vascular diseases
  - More similar than cancer therapy
  - Accepted surrogates
    - Hypertension
    - Hyperlipidemia
Chemoprevention Drug Development

- Similar to Vascular Health prevention, an accepted surrogate marker/endpoint would make chemoprevention drug development more efficient.

- Intraepithelial Neoplasia?
  - Colonic adenomas
  - Cervical Carcinoma in situ
  - Breast ductal carcinoma in situ
Chemoprevention

- Phenotypic surrogates
  - Skin – actinic keratoses, dysplastic nevi
  - Oral – leukoplakia, erythroplakia
  - Lung – bronchial dysplasia
  - Esophagus – Barrett’s (dysplasia)
  - Breast – DCIS, LCIS, atypical hyperplasia
  - Colon – adenomas
  - Cervix – cervical intraepithelial neoplasia (CIN)
  - Endometrium – atypical hyperplasia
  - Prostate – prostatic intraepithelial neoplasia (PIN)
  - Bladder – superficial bladder cancer
Chemoprevention of colon cancer
Cancer Chemoprevention

• The use of pharmacological compounds to prevent the development of malignancy

• Development of successful chemoprevention requires an understanding of early colorectal tumorigenesis
Colorectal Carcinogenesis

- **initiated**
- **adenomas**
- **invasive**

10-20 years

**VIEW 1:** Cancer is caused by
- Activation of oncogenes: K-ras, CTNNB1, c-myc
- Loss of tumor suppressor genes: APC, p53, TGFβRII, MLH1

**VIEW 2:** Cancer is caused by
- Abnormal stem cell activity

Suppression of the carcinogenic process by use of pharmacological or natural agents is the cornerstone of chemoprevention.
Colorectal Carcinogenesis: CRC has a natural history of transition from a precursor lesion, i.e., adenomatous polyp to cancer, that spans over 10 to 15 years providing an extended opportunity for intervention and cancer prevention.
Colon Cancer
Chemoprevention

Need/ Rationale

150,000 expected to be diagnosed with colorectal cancer in a year
>50,000 expected to die from colorectal cancer in a year
Colorectal Cancer Risk

- **Family history**
  - Familial cancer predisposition syndromes
  - Primary family member with colorectal cancer or adenomas

- **Age**

- **Personal history**
  - Identification of adenomas
  - Inflammatory bowel disease
  - History of treated colorectal cancer
Annual Age-adjusted Cancer Incidence Rates

Jemal et al. CA Cancer J Clin 2007
Identifying and monitoring pre-malignant disease
Candidate Agents

- COX-2 inhibitors, selective or non-selective
- Diet and Nutraceuticals
- Antioxidants/ Vitamins
- Statins
- Difluoromethylornithine (DFMO)
- Others
EXPRESSION OF ANTIOXIDANT AND PROOXIDANT ENZYMES CHANGES IN CANCER

- Manganese Superoxide Dismutase
  - ↓ in most cancers
  - Candidate Tumor Suppressor Gene
- Cu/Zn Superoxide Dismutase ↓
- Catalase ↓
- Glutathione Peroxidase-1 ↓
- Cyclooxygenase-2 ↑
- Nitric Oxide Synthase-2 ↑

→ A prooxidant state is common in human cancer
→ Most cancers poorly metabolize hydrogen peroxide

Oberley & Oberley, Histol Histopathol 1997
The Relation Between Cyclooxygenase-2 Expression and Colorectal Cancer

Katherine M. Sheehan,
JAMA 1999, 282, 1254 -1257
Selective COX-2 Inhibitors

• Celecoxib: FDA approved for adenomatous polyp prevention for individuals with Familial Adenomatous Polyposis
  – These data and retrospective data have led to extensive study of COX-2 inhibitors for sporadic adenomas as well
Selective COX-2 Inhibitors

**FAP Trial (phase IIb)**
- Phenotypic expression of APC mutation (n=81)
- 3 arms; duration = 6 mo.
  - celecoxib 100 mg bid
  - celecoxib 400 mg bid
  - placebo bid
- Change in polyp burden

Subject #5120

41 Polyps at Baseline 21 Polyps at Follow-Up

Images courtesy of Dr. E. Hawk, NCI
Change in Polyp Number

<table>
<thead>
<tr>
<th>% Change from Baseline</th>
<th>Placebo (N=15)</th>
<th>100 mg BID (N=32)</th>
<th>400 mg BID (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4.5</td>
<td></td>
<td>-11.9</td>
<td>-28.0%*</td>
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</table>

* p< 0.05; Steinbach, et al. - N Engl J Med 2000;342:1946-52
APC Trial

2035 Males or Females age ≥ 30 with adenomas (multiple or 1 > .5cm)

Endoscopic Polypectomy

Celecoxib 200mg bid
Celecoxib 400mg bid
Placebo

Followup Colonoscopy at 1 and 3 years
Detection of advanced adenomas on follow-up colonoscopy

"Advanced" = \( \geq 1 \) cm diameter, tubulovillous or villous histology, high grade dysplasia, intramucosal carcinoma or invasive carcinoma

- Placebo bid: 17.2%
- Celecoxib 200 mg bid: 57%
- Celecoxib 400 mg bid: 66%

\( \ast p<0.0001 \) compared to placebo

Bertagnolli, Hawk, Eagle DDW 2006
## APC: Cardiovascular Events

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (n = 679) (%)</th>
<th>Celecoxib 200 mg bid (n = 685)</th>
<th>Celecoxib 400 mg bid (n = 671)</th>
<th>Both Celecoxib Groups (n = 1356)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death</td>
<td>1 (0.1)</td>
<td>3 (0.4)</td>
<td>6 (0.9)</td>
<td>9 (0.7)</td>
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<tr>
<td></td>
<td>HR 3.0 (0.3–28.6)</td>
<td>HR 6.1 (0.7-50.3)</td>
<td>HR 4.5 (0.6-35.5)</td>
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<tr>
<td>CV Death or nonfatal MI</td>
<td>4 (0.6)</td>
<td>12 (1.8)</td>
<td>15 (2.2)</td>
<td>27 (2.0)</td>
</tr>
<tr>
<td></td>
<td>HR 3.0 (1.0-9.3)</td>
<td>HR 3.8 (1.3-11.5)</td>
<td>HR 3.4 (1.2-9.7)</td>
<td></td>
</tr>
<tr>
<td>CV Death, nonfatal MI, stroke, or heart failure</td>
<td>7 (1.0)</td>
<td>16 (2.3)</td>
<td>23 (3.4)</td>
<td>39 (2.9)</td>
</tr>
<tr>
<td></td>
<td>HR 2.3 (0.9-5.5)</td>
<td>HR 3.4 (1.5-7.8)</td>
<td>HR 2.8 (1.3-6.3)</td>
<td></td>
</tr>
<tr>
<td>CV Death, nonfatal MI, stroke, heart failure, or angina</td>
<td>11 (1.6)</td>
<td>18 (2.6)</td>
<td>25 (3.7)</td>
<td>43 (3.2)</td>
</tr>
<tr>
<td></td>
<td>HR 1.6 (0.8-3.4)</td>
<td>HR 2.3 (1.1-4.7)</td>
<td>HR 2.0 (1.0 – 3.8)</td>
<td></td>
</tr>
<tr>
<td>CV Death, nonfatal MI, stroke, heart failure, or angina, or need for a CV procedure</td>
<td>17 (2.5)</td>
<td>26 (3.8)</td>
<td>31 (4.6)</td>
<td>57 (4.2)</td>
</tr>
<tr>
<td></td>
<td>HR 1.5 (0.8-2.8)</td>
<td>HR 1.9 (1.0 – 3.3)</td>
<td>HR 1.7 (1.0-2.9)</td>
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</tr>
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Cardiovascular serious adverse events: Which adenoma patients are at greatest risk?

Prior History of CV Events = Past MI, Stroke, CHF, or Angina

Placebo bid

Celecoxib-treated patients (either dose)

RR = 3.0

Bertagnolli, Hawk, Eagle DDW 2006
Cardiovascular Toxicity

APPROVe study, blinded review with 3 yrs f/u, cardiac events 2.4% in 25 mg V vs 0.9% in placebo, comparing all cardiac (MI, sudden cardiac death, unstable angina), CV (fatal stroke, ischemic stroke, TIA) and peripheral vascular (thrombosis, PE) events

Bresalier et al. NEJM 2005
Celecoxib and Colon Cancer Prevention

• Psaty and Potter (NEJM 355:950, 2006)
  - Reviewed APC and PreSAP trials and concluded the following
  - Celecoxib decreases adenoma formation
  - Celecoxib increases the risk of cardiovascular adverse events
  - The potential increase in CV event/mortality outweighs the projected decrease in colon cancer incidence

Celecoxib has no role as a colon chemopreventive agent for people with a history of adenomas or the general population
Non-selective COX-2 inhibitors

- Retrospective data supporting potential preventive effects
- Cardiovascular issues appear less, but remain
- **Aspirin**
  - Sandler et al. NEJM 348:883, 2003
  - 635 subjects with previous colo-rectal CA randomized to ASA 325 mg/d or placebo
  - 1 or more adenomas in 27% of placebo vs 17% ASA
Calcium Polyp Prevention Study

Extended Follow-Up

- Self-reported surveys (n=822)
- Mean = 7 yrs post-intervention
- Histologic confirmation for adenomas
- 37% lower risk < 5 yrs

Calcium + Vitamin D

Women’s Health Initiative

• Postmenopausal women (n=36,282)
• 1000 mg elemental calcium + 400 IU vit. D₃ vs. placebo
• Mean duration = 7.0 yrs
• Incident CRC (sec. endpoint)
• HR=1.1; 95% CI=0.9-1.3

Postmenopausal female hormone supplements

- Chlebowski et al. NEJM 350:991, 2004; 16,600 postmenopausal women 0.625 mg estrogen + medroxyprogesterone 2.5 mg daily vs placebo

- Study stopped early with median of 5 yrs f/u due to increased breast CA

- However Hazard Ratio for colon cancer development was 0.61, 48/8506 with hormones and 74/8102 for placebo.

- This supports observational studies which note decreased colon cancer incidence with hormones. However, greater tendency toward higher stage on treatment arm.
Statins and Colon Cancer

• Lipid lowering agents have been associated with decreased incidence of various cancers

• Dale et al (JAMA 295:74, 2006) performed meta-analysis of randomized through 2005 and observed no effect on cancer incidence or death rate

• Poynter et al. (NEJM 352:2184, 2005) case control study in Israel of approx 2000 colon cancer patients vs 2000 controls; statin use of >5 yrs was associated with a 50% risk reduction
Chemoprevention of Colon Cancer

• Promising results with COX-2 inhibitors have been severely compromised by other organ toxicity

• Dietary measures or nutrient-based supplements have mainly been negative, potential exceptions include calcium ± vitamin D and selenium

• We continue to explore other options for the chemoprevention of colon cancer
Colorectal Cancer Chemoprevention: Results from Prospective Randomized Trials

- Dietary modification
  - Successful
  - 20-30% fewer advanced lesions

- Calcium supplements
  - ~30% fewer advanced lesions

- Aspirin
  - 57-74% fewer advanced lesions

- Selective Cox-2 inhibitors
Chemoprevention of cervical cancer
Cervical cancer

Cervix uteri: ASR (World) (per 100,000) (All ages)

- Romania: Incidence 20, Mortality 12
- Hungary: Incidence 15, Mortality 7
- Germany: Incidence 10, Mortality 4
- France: Incidence 8, Mortality 3
- Israel: Incidence 5, Mortality 2
- Turkey: Incidence 3, Mortality 1

GLOBOCAN 2002
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<tbody>
<tr>
<td>Total (3767)</td>
<td>Total (5171)</td>
<td>Total (1860)</td>
<td>Total (4047)</td>
<td>Total (423)</td>
<td>Total (2741)</td>
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<tr>
<td>Breast (25%)</td>
<td>Breast (37.6%)</td>
<td>Breast (36.2%)</td>
<td>Breast (42.3%)</td>
<td>Breast (31.5%)</td>
<td>Breast (10.9%)</td>
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<tr>
<td>Cervix (14%)</td>
<td>Lymphoma (9.6%)</td>
<td>Colorectal (9%)</td>
<td>Colorectal (7.4%)</td>
<td>Thyroid (8.7%)</td>
<td>Lymphoma (9.6%)</td>
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<tr>
<td>Colorectal (6.9%)</td>
<td>Leukemia (4.5%)</td>
<td>Leukemia (7.8%)</td>
<td>Ovarian (4.7%)</td>
<td>Cervix (6.2%)</td>
<td>Thyroid (9.3%)</td>
</tr>
<tr>
<td>GB etc (5.6%)</td>
<td>Ovarian (4.1%)</td>
<td>Thyroid (5.5%)</td>
<td>Lung (4.5%)</td>
<td>Stomach (5.9%)</td>
<td>Colorectal (7.8%)</td>
</tr>
<tr>
<td>Thyroid (5.3%)</td>
<td>Bladder (4%)</td>
<td>Endom. (4.7%)</td>
<td>Bladder (3.5%)</td>
<td>Lymphoma (5.9%)</td>
<td>Leukemia (6.5%)</td>
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<tr>
<td>Ovarian (5%)</td>
<td>Cervix (3.8%)</td>
<td>CNS (3.2%)</td>
<td>Endom. (2.8%)</td>
<td>Ovarian (5%)</td>
<td>Lung (5.9%)</td>
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<tr>
<td>Stomach (4.3%)</td>
<td>Larynx (3.1%)</td>
<td>Ovarian (2.7%)</td>
<td>Stomach (2.6%)</td>
<td>Leukemia (4.3%)</td>
<td>Endom. (3.8%)</td>
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<td>Lymphoma (3.7%)</td>
<td>CNS (3.1%)</td>
<td>Stomach (2.4%)</td>
<td>Thyroid (2.4%)</td>
<td>Bladder (3.4%)</td>
<td>Ovarian (3.7%)</td>
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<tr>
<td>Bladder (2.4%)</td>
<td>Endom. (2.4%)</td>
<td>Lung (2.4%)</td>
<td>Cervix (2.3%)</td>
<td>Skin (3.2%)</td>
<td>Skin Not-M (5.6%)</td>
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<tr>
<td>Endom. (2.3%)</td>
<td>Lung (2.4%)</td>
<td>Cervix (2%)</td>
<td>Kidney (1.5%)</td>
<td>Colorectal (3%)</td>
<td>Cervix (3.4%)</td>
</tr>
</tbody>
</table>
The greatest potential for the chemoprevention of cervical cancer is in women with human papillomavirus infection.

- Cervical cancer is caused by types of the human papillomavirus (HPV).
- HPV infection is essentially a sexually transmitted disease, and hence sexual practices and barriers contraception can play a major role in prevention.
Cancer prevention can be divided into primary, secondary and tertiary prevention.

Primary prevention refers to measures aimed at anyone who is at risk of the cancer.

Possible primary prevention strategies would include:

- Screening
- Prophylactic vaccination
- Altering sexual behaviour (reducing the numbers of sexual partners, increasing the use of condoms)
- Smoking cessation.
The Cervical Cancer Vaccine
Vaccination against human papilloma virus

• HPV infection is associated with development of cervical cancer and other anogenital tumors

• HPV infection rates are estimated as between 2-26%, depending upon the country

• Vaccination against HPV prevents cervical intraepithelial neoplasia in women at risk for cervical cancer
The Cervical Cancer Vaccine

- The cervical cancer vaccine (also called the Human Papillomavirus Vaccine or HPV vaccine) protects women from getting infected with the ‘High Risk’ HPV types that cause 70% of cervical cancer.
Vaccine Benefits

- The risk of HPV exposure increases with sexual activity.

- The benefits from the vaccine depend on prior HPV exposure.
  
- The more HPV exposure, the less likely the vaccine will work for the patients.
Effectiveness of the vaccine decreases with increasing sexual exposure

The patients can significantly decrease their chances of getting infected with the ‘High Risk’ HPV types if they get the vaccine before they have any sexual contact.

Even if they have been exposed to the HPV types this vaccine protects them from getting, the vaccine may still provide some benefit, but it is less.

This is why they still need their Pap tests and cervical cancer screening which may include HPV testing after vaccination.
Who should get the vaccine?

- The FDA has recommended the following groups of women get vaccinated:
  - **Girls 11–12**: Recommended Age Group (can be started as young as age 9).
  - **Women 13–26**: the benefit of the vaccine may be lower depending on prior HPV exposure.
Older than 26

- The vaccine is not FDA approved for women over the age of 26 nor is it approved for men.

- Regular Pap tests and gynecology visits will still effectively reduce their risk for cervical cancer.
Side Effects of the Vaccine

• The risks of receiving the vaccine are minimal and similar to other vaccines.

- The most common reported side effects are:
  - Redness and soreness where the shot is given.
  - Headaches (like when you have a cold or fever).
  - Fever.
  - If they become pregnant soon, there may be risks to their unborn fetus.
Severe Side Effects

Please seek emergency medical care if the following symptoms occur:
- Difficulty Breathing
- Severe Allergic Reaction (e.g. Severe Rash, High Fever)
Who should NOT receive the vaccine

- They should not receive the vaccine today if they are:
  - Very Sick
  - Allergic to Yeast
  - Pregnant
  - Trying to become pregnant
They must continue to get regular Pap test follow-up.
Additional Vaccinations

- The cervical cancer vaccination is given over 3 visits.
- Today, then in about 2 months and then in about 4 months.

- Today
  Vaccination 1
- Month 2
  Vaccination 2
- Month 6
  Vaccination 3
- Vaccination Complete
  Follow-up Pap tests
In cervix cancer potential chemopreventive agents:

• Micronutrients
• Antiviral agents
• Immune modifiers
REVIEW OF CHEMOPREVENTION TRIALS (I)

- **Beta-carotene**: Beta-carotene is a potent antioxidant and case-control studies have found a relative deficiency in beta-carotene in women with CIN compared to controls.

- **Folate**: At least three phase II or III clinical trials have investigated folic acid in women with CIN1 or CIN2. The trials used 5–10 mg folic acid (plus 10 mg vitamin C in one trial) versus placebo daily for 3–6 months. None of the trials had a statistically significant result. Between them the three trials recruited 555 patients. Meta-analysis shows no overall effect.

- **Retinoic acid**: Retinoids have antiproliferative effects and induce differentiation in epithelial cells, but have no specific anti-HPV activity. No association was found between topical all-trans retinoic acid and disease regression at 12 weeks in a more recent trial.
• **Indole-3-carbinol and diindolylmethane (DIM):** found in cruciferous vegetables and have been identified as compounds that could potentially prevent or halt carcinogenesis

• **ZYC101a:** ZYC101a is a novel therapeutic containing plasmid-DNA-encoding fragments derived from the E6 and E7 proteins of HPV

• **DMFO:** was carried out in women with CIN2 and CIN3 after encouraging results from a phase I trial.
What can we do to prevent cancer?

**Be good**
- healthy diet
- exercise regularly
- maintain healthy weight
- don’t smoke
- alcohol in moderation

**Know your risk**
- and seek appropriate evaluation or therapy for your risk level

**Support prevention research**
Ongoing Work

• Understand the mechanisms of cancer development to develop new treatments

• Individualize treatment, balancing risks and benefits of intervention
Thanks...